Neurocognitive screening and behavioural interventions for HIV-Associated Neurocognitive Disorders (HAND)

International Forum on HIV and Rehabilitation Research

Translating Research Evidence from the Canada-UK HIV and Rehabilitation Research Collaborative and the Canadian Working Group on HIV and Rehabilitation

Li Ka Shing Knowledge Institute, Toronto, ON Canada
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Director, Universities Without Walls (CIHR STIHR)
Centre for Brain Health in HIV/AIDS

Main Foci

1) Natural history / epidemiology / validation (including screening) of HAND in Canada - building foundational work to support multidisciplinary investigations
2) Understand the “lived experience” of HAND
3) Build and Evaluate Interventions for HAND – Cognitive / Behavioural / Medical (smoking / CVD) / CNS Penetration
4) Build Models of Care for HAND in the Health System
5) Education and KTE – Ensure knowledge and evidence is available in useful ways for decision-making – for patient care, health care providers and policy-makers
Approximately 30-50% of people with HIV develop neuropsychological impairments (NPI) - generally in mild / mild to moderate in severity) - Previous work by our group at St. Michael’s Hospital has shown similar rates of neuropsychological impairment by CDC-93 staging

Risk factors for NPI include: older age, reduced cognitive reserve, history of immune suppression (low CD4 nadir), and a host of mental health and medical comorbidities, including HCV

Incidence of NPI in HIV is estimated to be 10-25% in the US

But is this neuropsychological impairment important to assess? What does it mean to a person’s everyday life?

YES – increases in NPI related to reduced ability to function in everyday activities (work, managing medications, driving), social functioning, confidence and sense of self, quality of life, and survival.
Updated Nosology for HIV-Associated Neurocognitive Disorders

**Frascati Criteria – 3 Diagnostic HAND Categories**

1. **Asymptomatic Neurocognitive Impairment (ANI)**
   Presence of NP impairment in at least 2 NP ability domains, but no functional impairment in everyday life.

2. **Mild Neurocognitive Disorder (MND)**
   Presence of neurocognitive impairment in at least 2 NP ability domains with mild functional impairment in everyday life.

3. **HIV Associated Dementia (HAD)**
   Presence of neurocognitive impairment in at least 2 NP ability domains with marked functional impairment in everyday life.

Introduction and Rationale for Current Study

Decision Tree For Frascati Criteria: HIV-Associated Neurocognitive Disorder

PubMed Search Results on “HAND” = 217 Hits (April 10, 2013)
Publication Date from January 2006 to present

<table>
<thead>
<tr>
<th>Year</th>
<th>PubMed Results</th>
<th>2013 Year Projection</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>0</td>
<td>31 so far</td>
</tr>
<tr>
<td>2007</td>
<td>1</td>
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<td>2008</td>
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<td>2010</td>
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<tr>
<td>2011</td>
<td>50</td>
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<tr>
<td>2012</td>
<td>76</td>
<td>62 more</td>
</tr>
<tr>
<td>2013</td>
<td>93</td>
<td>for a total of 93</td>
</tr>
</tbody>
</table>
Rehabilitation Context

The US CHARTER Study (Heaton et al. 2010): Learning more about cognitive complications in the real world
Risk of cognitive impairment increases with lower CD4 and as presence of medical / mental health/addiction conditions increase.
Recent research is emphasizing the importance of cardiovascular / cerebrovascular risks and complications for cognitive impairments in HIV-positive persons.
CVD, HIV and the Brain

Recent research is emphasizing the importance of cardiovascular / cerebrovascular risks and complications for cognitive impairments in HIV.

Vascular risk factors, HIV serostatus, and cognitive dysfunction in gay and bisexual men

ABSTRACT

Background: The purpose of this study was to evaluate the relationship between cognitive performance, risk factors for cardiovascular and cerebrovascular disease (CVD), and HIV infection in the era of highly active antiretroviral therapy.

Methods: We evaluated the cognitive functions of men enrolled in the cardiovascular disease substudy of the Multicenter AIDS Cohort Study who were aged ≥40 years, with no self-reported history of heart disease or cerebrovascular disease. Results from comprehensive neuropsychological evaluations were used to construct composite scores of psychomotor speed and memory performance. Subclinical CVD was assessed by measuring coronary artery calcium and carotid artery intima-media thickness (IMT), as well as laboratory measures, including total cholesterol, fasting glucose, glycylated hemoglobin, glomerular filtration rate (estimated), and standardized blood pressure and heart rate measures.

Results: After accounting for education, depression, and race, carotid IMT and glomerular filtration rate were significantly associated with psychomotor speed, whereas IMT was associated with memory test performance. HIV serostatus was not significantly associated with poorer cognitive test performance. However, among the HIV-infected individuals, the presence of detectable HIV RNA in plasma was linked to lower memory performance.

Conclusions: These findings suggest that HIV infection may not be the most important predictor of cognitive performance among older gay and bisexual men in the post-HIV therapy era, at least among those with access to medical care and to appropriate medications. Medical factors associated with normal aging are significantly associated with performance on neuropsychological tests, and good clinical management of these factors both in HIV-infected individuals and those at risk for infection may have beneficial effects in the short term and could reduce the risk of subsequent cognitive decline. Neurology® 2009;73:1292-1299

Role of obesity, metabolic variables, and diabetes in HIV-associated neurocognitive disorder

ABSTRACT

Objective: To evaluate relationships between HIV-associated neurocognitive disorder and metabolic variables in a subgroup of HIV+ participants examined in a prospective, observational multicenter cohort study.

Methods: In a cross-sectional substudy of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, 130 HIV+ participants provided fasting blood samples. Neurocognitive impairment (NCI) was defined by performance on neuropsychological tests adjusting for age, education, gender, and race/ethnicity. Global ratings and global deficit scores were determined. Demographics, biomarkers of HIV disease, metabolic variables, combination antiretroviral therapy (cART) history, other drug exposures, and self-reported diabetes were examined in multivariate models predicting NCI. Separate models were used for body mass index (BMI) alone (n = 50) and BMI and waist circumference (WC) together (n = 55).

Results: NCI (global impairment rating >5) was diagnosed in 40%. In univariate analyses, age, longer duration of HIV infection, obesity, and WC, but not BMI, were associated with NCI. Self-reported diabetes was associated with NCI in the substudy and in those >55 in the entire CHARTER cohort. Multivariate logistic regression analyses demonstrated that central obesity (as measured by WC) increased the risk of NCI and that greater body mass may be protective if the deleterious effect of central obesity is accounted for.

Conclusions: As in HIV-uninfected persons, central obesity, but not more generalized increases in body mass (BMI), was associated with a higher prevalence of NCI in HIV+ persons. Diabetes appeared to be associated with NCI only in older patients. Avoidance of antiretroviral drugs that induce central obesity might protect from or help to reverse neurocognitive impairment in HIV-infected persons. Neurology® 2012;78:485-492.
OHTN Cohort Study (OCS)

- Ongoing observational, open dynamic cohort of HIV-positive persons in care in Ontario
  - HIV Infrastructure Information Program (2000-2006)
  - Renamed OCS in 2007
- Over 5,900 participants recruited from 11 specialized HIV clinics & primary care practices throughout Ontario
- Neuropsychological assessments are conducted at two sites in Toronto (since October 2007)

Measures

• **Brief NP test battery administered (baseline and 1-year follow up):**
  

  WAIS-R Digit Symbol Test  (Heaton et al, 2002; The Psychological Corporation, 1997)

  Grooved Pegboard Test  (Klove, 1963)


• **Self-reported cognitive complaints** were assessed with the 4-item version of the Medical Outcomes Study (MOS) Cognitive Functioning scale  (Wu et al, 1991; Stewart et al, 1992)

• **Adherence to ARVs** (past 4 days) was assessed using one item from the Adults AIDS Clinical Trials Group (AACTG) Adherence Follow Up Questionnaire  (Chesney et al, 2000)

• **Clinical / medical data** (e.g., CD4 count) obtained from clinical charts

• **Determinants of health data** - Other non-clinical data obtained through interviewer-administered quantitative questionnaire that included measures for mental health status (CES-D), alcohol use (AUDIT-10) and drug use (DAST-20)
Methods – Generating NP Status and HAND Categories

- **Conversions** - Participants’ raw NP scores on each test were first converted into scaled scores and then into z-scores. Z-scores of ability domains were computed by averaging z-scores of individual tests.

- **Corrections for demographics** - Published age/gender/education/race norms were used to convert raw scores into T-scores (Heaton et al, 2002; Heaton et al, 2004; Norman et al, 2011).

- **Calculating NP Impairment** - Global Deficit Scores (GDS) were computed from T-scores using previously published cut-off scores; “Norma” NP functioning GDS < 0.5; “Impaired” NP ≥ 0.05 (Carey et al, 2004).

- Following the Antinori et al., criteria, GDS score and self-reported cognitive complaints were used to determine HAND status.

<table>
<thead>
<tr>
<th>NP Status</th>
<th>No self-reported complaint</th>
<th>≥ 1 self-reported complaint (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDS &lt; 0.5</td>
<td>NP-normal</td>
<td>NP-normal</td>
</tr>
<tr>
<td>0.5 ≤ GDS ≤ 1.5</td>
<td>ANI</td>
<td>MND</td>
</tr>
<tr>
<td>GDS &gt; 1.5</td>
<td>HAD</td>
<td>HAD</td>
</tr>
</tbody>
</table>
Prevalence of HAND at Baseline and 1-year Follow Up (N=375)

Overall – 58% have Neuropsychological Impairment (NPI); Approximately 60% of persons with NPI have ANI

Estimating HAND in Canada: ANI = 22,750 persons; MND / HAD = Each 7,800 persons
At 1-year follow up

<table>
<thead>
<tr>
<th></th>
<th>NP-Normal</th>
<th>ANI</th>
<th>MND</th>
<th>HAD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP-Normal</td>
<td>110</td>
<td>33</td>
<td>8</td>
<td>5</td>
<td>156</td>
</tr>
<tr>
<td>ANI</td>
<td>33</td>
<td>73</td>
<td>11</td>
<td>16</td>
<td>133</td>
</tr>
<tr>
<td>MND</td>
<td>13</td>
<td>10</td>
<td>17</td>
<td>7</td>
<td>47</td>
</tr>
<tr>
<td>HAD</td>
<td>2</td>
<td>12</td>
<td>6</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>158</strong></td>
<td><strong>128</strong></td>
<td><strong>42</strong></td>
<td><strong>47</strong></td>
<td><strong>375</strong></td>
</tr>
</tbody>
</table>

HAND status remained stable (n=219, 58%)
HAND status improved (n=76, 20%)
HAND status worsened (n=80, 22%)

ANI, Asymptomatic Neurocognitive Impairment
MND, Mild Neurocognitive Disorder
HAD, HIV-associated Dementia
Change in HAND Status Comparable to US CHARTER Study

Examined neurocognitive changes over 18 to 42 months (N=436)

Changes in NP Status:
- 23% declined (n=98)
- 61% stable (n=266)
- 17% improved (n=72)

NP Decline predicted by:
- neurological comorbidities
- Lower CD4 count
- being off ART

Clinical Implications:
- benefit of ART and management of CNS complications
Asymptomatic HIV-associated Neurocognitive Disorder (ANI) Increases Risk for Future Symptomatic Decline: A CHARTER Longitudinal Study

Robert Heaton, PhD¹, Donald Franklin, BS¹, Steven Woods, PsyD¹, Christina Marra, MD², David Clifford, MD³, Benjamin Gelman, MD,PhD⁴, Justin McArthur, MBBS⁵, Susan Morgello, MD⁶, Allen McCutchan, MD¹, and Igor Grant, MD¹ for the CHARTER Group

¹ University of California, San Diego; ² University of Washington, Seattle; ³ Washington University, St. Louis; ⁴ University of Texas Medical Branch, Galveston; ⁵ Johns Hopkins University, ⁶ Mount Sinai School of Medicine

Heaton et al. (2012). CROI
Examined risk of NP decline according to HAND (N= 347)

ANI predicts decline

- Relative risk of 3-5 for development of HAND compared to those persons who are neurocognitively normal
- ANI remained significant predictor after controlling education, reading score, comorbidity status

Implication: Evidence for risk of progression of HAND

Heaton et al. (2012) - CROI
Overall Neurocognitive Impairment by VACS Index (N=317)

*Chi-square trend test ; **p < 0.05    M=Median

NOTE: For Lower risk in Quartile 2: See Slides 9, 19, and 20
# VACS index as a Predictor of Overall NPI (N=317)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Bivariate</th>
<th>Multivariate 1</th>
<th>Multivariate 2</th>
<th>Multivariate 3</th>
<th>Multivariate 4</th>
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<td><strong>VACS Index</strong></td>
<td></td>
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<tr>
<td>Quartile 4</td>
<td><strong>2.53 (1.32, 4.85)</strong></td>
<td><strong>2.17 (1.07, 4.40)</strong></td>
<td><strong>2.07 (1.03, 4.15)</strong></td>
<td><strong>2.06 (1.02, 4.15)</strong></td>
<td></td>
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<tr>
<td>Quartile 3</td>
<td>1.39 (0.74, 2.59)</td>
<td>1.40 (0.72, 2.72)</td>
<td>1.35 (0.70, 2.61)</td>
<td>1.35 (0.70, 2.61)</td>
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<tr>
<td>Quartile 2</td>
<td><strong>0.51 (0.27, 0.98)</strong></td>
<td>0.51 (0.26, 1.03)</td>
<td>0.52 (0.26, 1.04)</td>
<td>0.52 (0.26, 1.04)</td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>(Ref)</td>
<td>(Ref)</td>
<td>(Ref)</td>
<td>(Ref)</td>
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<tr>
<td><strong>Demographic characteristics</strong></td>
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<tr>
<td>Language spoken at home (English)</td>
<td>0.63 (0.37, 1.08)</td>
<td>0.57 (0.32, 1.02)</td>
<td>0.63 (0.35, 1.14)</td>
<td>0.62 (0.34, 1.11)</td>
<td>0.62 (0.34, 1.110)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>1.03 (0.95, 1.12)</td>
<td>1.06 (0.98, 1.17)</td>
<td>1.07 (0.98, 1.18)</td>
<td>1.07 (0.97, 1.17)</td>
<td>1.07 (0.97, 1.17)</td>
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<tr>
<td><strong>Substance use and mental health</strong></td>
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<tr>
<td>Alcohol use (AUDIT ≥ 8)</td>
<td>0.61 (0.35, 1.04)</td>
<td>0.58 (0.32, 1.05)</td>
<td>0.63 (0.35, 1.16)</td>
<td>0.63 (0.34, 1.14)</td>
<td>0.63 (0.34, 1.15)</td>
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<tr>
<td>Used illicit drugs (yes)</td>
<td>0.98 (0.58, 1.64)</td>
<td>1.15 (0.64, 2.03)</td>
<td>1.19 (0.66, 2.15)</td>
<td>1.22 (0.68, 2.20)</td>
<td>1.23 (0.68, 2.21)</td>
</tr>
<tr>
<td>Depression (CESD ≥ 16)</td>
<td>1.44 (0.91, 2.29)</td>
<td>1.63 (0.99, 2.64)</td>
<td>1.51 (0.91, 2.50)</td>
<td>1.49 (0.90, 2.45)</td>
<td>1.48 (0.90, 2.45)</td>
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<tr>
<td><strong>ARV therapy</strong></td>
<td></td>
<td></td>
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<tr>
<td>On ARV Therapy (yes)</td>
<td>1.40 (0.83, 2.35)</td>
<td>1.37 (0.79, 2.36)</td>
<td>1.23 (0.68, 2.22)</td>
<td>1.17 (0.65, 2.10)</td>
<td>1.17 (0.65, 2.10)</td>
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<td><strong>Comorbidities</strong></td>
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<tr>
<td>Current smoker (yes)</td>
<td>0.99 (0.62, 1.57)</td>
<td>1.35 (0.78, 2.29)</td>
<td>1.19 (0.68, 2.10)</td>
<td>1.15 (0.66, 2.00)</td>
<td>1.15 (0.66, 2.02)</td>
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<tr>
<td>Hypertension (yes) a</td>
<td>1.54 (0.74, 3.21)</td>
<td>1.72 (0.55, 5.94)</td>
<td>2.04 (0.61, 6.82)</td>
<td>-</td>
<td>1.09 (0.47, 2.55)</td>
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<tr>
<td>Diabetes (yes) b</td>
<td><strong>4.43 (1.46, 13.47)</strong></td>
<td><strong>4.93 (1.49, 16.36)</strong></td>
<td><strong>4.23 (1.19, 15.03)</strong></td>
<td><strong>3.84 (1.16, 12.71)</strong></td>
<td><strong>3.69 (1.05, 12.99)</strong></td>
</tr>
<tr>
<td>CVDs (yes) ** a b</td>
<td>1.28 (0.72, 2.28)</td>
<td>0.63 (0.24, 1.63)</td>
<td>0.49 (0.18, 1.31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other comorbidities (yes) **</td>
<td>1.85 (0.72, 4.75)</td>
<td>1.93 (0.71, 5.29)</td>
<td>1.74 (0.62, 4.87)</td>
<td>1.50 (0.56, 4.07)</td>
<td>1.50 (0.55, 4.07)</td>
</tr>
</tbody>
</table>

a Correlation between hypertension and CVD was significant (r=0.77, p<0.01)
b Correlation between CVD and Diabetes was significant (r=0.27, p<0.01)
c CVDs include Angina, Angioplasty, Bypass surgery, Congestive heart failure, Coronary artery disease, Dyslipidemia, Myocardial Infarction, Peripheral Vascular Disease, or Stroke.
d Includes Asthma, COPD, emphysema, meningitis, Epilepsy, B12 deficiency, or Progressive Multifocal Leukoencephalopathy (PML)
Screening Tools for HAND:

HIV Dementia Scale (HDS)
Montreal Cognitive Assessment (MoCA)
Computerized Assessment of Cognitive Impairment (CAMCI)
Cogstate
Montreal Cognitive Assessment - MoCA

- Paper based, 30-item test (10min)
- Originally designed to screen geriatric patients at risk of early dementia for mild cognitive impairment
- Domains assessed: orientation, attention, language, executive functions, visuo-construction, and memory
- A score of ≥ 26 out of a possible 30 is considered “unimpaired”
CAMCI: Computer Assessment of Mild Cognitive Impairment

- Tablet based (20 mins)
- Initially designed to evaluate mild changes in cognitive function among geriatric populations
- A percentile score of ≥ 40 out of a possible 100 is considered low risk for cognitive impairment
- A series of modified neuropsychological tasks designed to measure attention, executive abilities, working memory, and visual and verbal memory; and one virtual reality exercise.
- Laptop based (10 mins)
- A score of ≥ 80 on any of the tasks is considered unimpaired
- Brief battery measures attention/vigilance, processing speed, working memory, and visual learning
- can be used to detect change in cognitive function over very brief intervals (minutes), and longer intervals (weeks or months)
Systematic Review of Screening Tools for HAND

Study funded by the Ontario Ministry of Health and Long-term Care

Short Title: Systematic Review of Screening Tools for HAND

Amy R. ZIPURSKY¹,², David GOGOLISHVILI¹, Sergio RUEDA¹,², Maggie ATKINSON¹; Jason BRUNETTA³; Adriana CARVALHAL²,³; Evan COLLINS²,⁴; Jennifer A. MCCOMBE⁵; M. John GILL⁶; Anita RACHTIS²,⁷; Ron ROSENES¹; Gordon ARBESS²,⁴; Thomas MARCOTTE⁸; Sean B. ROURKE¹,²,⁴

Ontario HIV Treatment Network¹; University of Toronto²; Maple Leaf Clinic³; St. Michael’s Hospital⁴; University Health Network⁵; Southern Alberta HIV Clinic and University of Alberta⁶; Sunnybrook Hospital⁷; University of California, San Diego⁸
Results: Search Review and Evaluation

• Title and abstract review of 1,696 articles – 1,368 were excluded because not relevant to research questions

• Full article appraisal completed on 316 papers - 265 of these did not meet full inclusion criteria)

• 51 studies met inclusion criteria and fell into 2 categories:
  (1) studies evaluating screening tools by comparing them to a reference or “gold” standard (31 of 51 or 61%); and
  (2) studies that evaluated screening tools by other methods

Our review focused on those compared to reference standard in (1)
Results: Main Findings

• Most studies focused on “neurocognitive impairments” or “deficits” (55%) or screening for HIV-Associated Dementia (35%); Few studies focused on milder forms of HAND (ANI or MND)

• Only 23% used gold standard battery of NP tests as criterion

• Functional status assessed in minority of studies (< 30%)

• Quality appraisal – some key aspects rated as poor in quality

• **15 of 31 studies had adequate sensitivity (≥ 0.75):**
  HIV Dementia Scale; Cogstate; Hopkins Verbal Learning Test / Grooved Pegboard or WAIS-III Digit Symbol; Screening Algorithm
Figure 3a. Forest Plot:

Utility of the HIV Dementia Scale in Detecting HIV-Associated Neurocognitive Disorders

- Power 1995 (Small): 0.81 (0.65 - 0.92)
- Wojna 2007 (Medium): 0.87 (0.66 - 0.97)
- Smith 2003 (Medium): 0.39 (0.24 - 0.55)
- Simioni 2010 (Medium): 0.82 (0.72 - 0.90)
- Richardson 2005 (Medium): 0.55 (0.32 - 0.77)
- Carey 2004 (Large): 0.09 (0.03 - 0.20)
- Morgan 2008 (Large): 0.17 (0.09 - 0.29)
- Rourke 2013 (Large): 0.12 (0.01 - 0.36)

Pooled Sensitivity = 0.48 (0.42 to 0.53)
Chi-square = 146.05; df = 7 (p = 0.0000)
Inconsistency (I-square) = 95.2%
Evaluation of Screening Tools for HAND: Preliminary Results

Study funded by the Canadian Institutes of Health Research
PURPOSE: To examine the clinical utility of four short screening tools in detecting HAND.

The 5 tools are:
(1) HIV Dementia Scale (HDS);
(2) Montreal Cognitive Assessment (MoCA);
(3) Combination of Hopkins Verbal Learning Test /WAIS-III Digit Symbol,
(4) Computer Assessment of Mild Cognitive Impairment (CAMCI), and
(5) Cogstate

METHODS:
Participants (n=500) will complete the “gold standard” of neuropsychological testing (3-4 hours), functional status battery, and the 5 short screening tools, and then be classified according the HAND (ANI, MND, and HAD) according to Antinori et al., 2007.
### Performance of HAND Screening Tests to Detect Neuropsychological Impairment Using Comprehensive NP Testing and Clinical Diagnosis (Antinori et al., 2007)

<table>
<thead>
<tr>
<th>Case</th>
<th>Criterion</th>
<th>Clinical Dx</th>
<th>MoCA</th>
<th>CAMCI</th>
<th>Cogstate</th>
<th>HDS</th>
<th>HDS - Adjusted</th>
</tr>
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<tbody>
<tr>
<td>001</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild</td>
</tr>
<tr>
<td>002</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild</td>
</tr>
<tr>
<td>003</td>
<td>ANI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>004</td>
<td>ANI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
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</tr>
<tr>
<td>005</td>
<td>ANI*</td>
<td>MCI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild</td>
</tr>
<tr>
<td>006</td>
<td>MND*</td>
<td>MCI</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Moderate</td>
</tr>
<tr>
<td>007</td>
<td>MND*</td>
<td>Normal</td>
<td>Severe</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Moderate</td>
</tr>
<tr>
<td>008</td>
<td>MND*</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>HAD</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>009</td>
<td>MND</td>
<td>MCI</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>010</td>
<td>HAD</td>
<td>MCI</td>
<td>Moderate</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

*Comorbid conditions – based on Frascati criteria:*
“Contributing”: 005 (daily marijuana use); 006 (learning disability); 007 (traumatic brain injury)
“Confounding”: 008 (cerebral event)

HDS – Adjusted – Morgan et al., J Clin Exp Neuropsychology (2008) – Age and education adjustments to HDS
### Performance of HAND Screening Tests to Detect Neuropsychological Impairment Using Comprehensive NP Testing and Clinical Diagnosis (Antinori et al., 2007)

<table>
<thead>
<tr>
<th>Case</th>
<th>Criterion</th>
<th>Clinical Dx</th>
<th>MoCA</th>
<th>CAMCI</th>
<th>Cogstate</th>
<th>HDS</th>
<th>HDS - Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>011</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>012</td>
<td>ANI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Mild</td>
</tr>
<tr>
<td>013</td>
<td>MND</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Moderate</td>
</tr>
<tr>
<td>014</td>
<td>MND</td>
<td>MCI</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>015</td>
<td>MND</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>016</td>
<td>MND</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>017</td>
<td>MND</td>
<td>MCI</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>018</td>
<td>MND</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>019</td>
<td>MND</td>
<td>Normal</td>
<td>Normal</td>
<td>Impaired</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
<tr>
<td>020</td>
<td>HAD</td>
<td>Normal</td>
<td>Moderate</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

**HDS – Adjusted** – Morgan et al., J Clin Exp Neuropsychology (2008) – Age and education adjustments to HDS
Using “Gold Standard” – Classification of “NP Normal” vs. “NP Impaired / HAND” (n=20)

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Hit rate</th>
<th>PPP</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td>35.0</td>
<td>100.0</td>
<td>45.0</td>
<td>100.0</td>
<td>21.4</td>
</tr>
<tr>
<td>CAMCI</td>
<td>17.6</td>
<td>100.0</td>
<td>30.0</td>
<td>100.0</td>
<td>17.6</td>
</tr>
<tr>
<td>Cogstate</td>
<td>41.2</td>
<td>100.0</td>
<td>50.0</td>
<td>100.0</td>
<td>23.1</td>
</tr>
<tr>
<td>HIV Dementia Scale</td>
<td>11.8</td>
<td>100.0</td>
<td>25.0</td>
<td>100.0</td>
<td>16.7</td>
</tr>
<tr>
<td>HIV Dementia Scale - Adjusted</td>
<td>82.4</td>
<td>33.3</td>
<td>75.0</td>
<td>87.5</td>
<td>25.0</td>
</tr>
</tbody>
</table>

HIV Dementia Scale – Adjusted: Used Morgan et al., 2008 (J Clin Exp Neuropsych) to adjust HDS scores for age and education
### Pilot / Preliminary Results: Evaluation of HAND Screening Tools

#### Using “Gold Standard” – Classification of “NP-normal” vs. “ANI or MND” (n=18)

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Hit rate</th>
<th>PPP</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td>33.3</td>
<td>100.0</td>
<td>44.4</td>
<td>100.0</td>
<td>23.1</td>
</tr>
<tr>
<td>CAMCI</td>
<td>6.7</td>
<td>100.0</td>
<td>22.2</td>
<td>100.0</td>
<td>17.6</td>
</tr>
<tr>
<td>HIV Dementia Scale</td>
<td>13.3</td>
<td>100.0</td>
<td>27.8</td>
<td>100.0</td>
<td>18.8</td>
</tr>
</tbody>
</table>

#### Using “Gold Standard” – Classification of “NP-normal” vs. “ANI” (n=7)

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Hit rate</th>
<th>PPP</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td>25.0</td>
<td>100.0</td>
<td>57.1</td>
<td>100.0</td>
<td>50.0</td>
</tr>
<tr>
<td>CAMCI</td>
<td>0.0</td>
<td>100.0</td>
<td>42.9</td>
<td>0.0</td>
<td>42.9</td>
</tr>
<tr>
<td>HIV Dementia Scale</td>
<td>0.0</td>
<td>100.0</td>
<td>42.9</td>
<td>0.0</td>
<td>42.9</td>
</tr>
</tbody>
</table>

#### Using “Gold Standard” – Classification of “NP-normal” vs. “MND” (n=14)

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Hit rate</th>
<th>PPP</th>
<th>NPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MoCA</td>
<td>36.4</td>
<td>100.0</td>
<td>50.0</td>
<td>100.0</td>
<td>30.0</td>
</tr>
<tr>
<td>CAMCI</td>
<td>9.1</td>
<td>100.0</td>
<td>28.6</td>
<td>100.0</td>
<td>23.1</td>
</tr>
<tr>
<td>HIV Dementia Scale</td>
<td>18.2</td>
<td>100.0</td>
<td>35.7</td>
<td>100.0</td>
<td>25.0</td>
</tr>
</tbody>
</table>
Centre for Brain Health in HIV/AIDS

Main Foci

1) Natural history / epidemiology / validation (including screening) of HAND in Canada - building foundational work to support multidisciplinary investigations
2) Understand the “lived experience” of HAND
3) Build and Evaluate Interventions for HAND – Cognitive / Behavioural / Medical (smoking / CVD) / CNS Penetration
4) Build Models of Care for HAND in the Health System
5) Education and KTE – Ensure knowledge and evidence is available in useful ways for decision-making – for patient care, health care providers and policy-makers
What are learning from studying the brains of people living with HIV as they age?

Recent brain imaging studies suggest that the brains of people living with HIV can look like HIV-negative persons who are 15-20 years older.

The Journal of Infectious Diseases (2010); 201: 336-340
Processing Speed in Normal Controls: How fast it takes to do a mental task

$R^2 = 0.45$
Working Memory in Normal Controls: How well a person can multi-task

\[ R^2 = 0.24 \]
What we are learning from aging can help us in HIV rehabilitation interventions

A Cognitive Training Program Based on Principles of Brain Plasticity: Results from the Improvement in Memory with Plasticity-based Adaptive Cognitive Training (IMPACT) Study

Glenn E. Smith, PhD, Patricia Housen, PhD, Kristine Yaffe, MD, Ronald Ruff, PhD, Robert F. Kemison, PhD, Henry W. Mabonke, PhD, and Elizabeth M. Zelinski, PhD

OBJECTIVES: To investigate the efficacy of a novel brain plasticity–based computerized cognitive training program in older adults and to evaluate the effect on untrained measures of memory and attention and participant-reported outcomes.

DESIGN: Multisite randomized controlled double-blind trial with two treatment groups.

SETTING: Communities in northern and southern California and Minnesota.

PARTICIPANTS: Community-dwelling adults aged 65 and older (N = 487) without a diagnosis of clinically significant cognitive impairment.

INTERVENTION: Participants were randomized to receive a broadly-available brain plasticity–based computerized cognitive training program (intervention) or a novelty- and intensity-matched general cognitive stimulation program modeling treatment as usual (active control). Duration of training was 1 hour per day, 5 days per week, for 8 weeks, for a total of 40 hours.

MEASUREMENTS: The primary outcome was a composite score calculated from six subtests of the Repeatable Battery for the Assessment of Neuropsychological Status that use the auditory modality (RBANS Auditory Memory/Attention). Secondary measures were derived from performance on the experimental program, standardized neuropsychological assessments of memory and attention, and participant-reported outcomes.

RESULTS: RBANS Auditory Memory/Attention improvement was significantly greater (P = .02) in the experimental group (3.9 points, 95% confidence interval [CI] = 2.7–5.1) than in the control group (1.8 points, 95% CI = 0.6–3.0). Multiple secondary measures of memory and attention showed significantly greater improvements in the experimental group (word list total score, word list delayed recall, digits backwards, letter-number sequencing; P < .05), as did the participant-reported outcome measure (P = .001). No advantage for the experimental group was seen in narrative memory.


Key words: clinical trial; cognitive decline; computerized cognitive training; participant-reported outcomes; brain plasticity
Figure 2. Pretraining and posttraining estimated means with 95% confidence intervals in the intention-to-treat group. For each outcome measure, the P-value and Cohen $d$ effect size estimate is from the training group (experimental treatment (ET) vs active control (AC)) × time interaction, corrected for the significantly different sex distribution between groups. In (A) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and (B) overall memory, higher scores are better; in (C) processing speed and (D) Cognitive Self-Report Questionnaire -25 Total, lower scores are better.
Table 3. Percent of Participants Showing Reliable Improvement in the Fully Evaluable Group (0.2 Standard Deviations of the Mean Criterion for Reliable Improvement)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Experimental Training n = 223</th>
<th>Active Control n = 213</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeatable Battery for the Assessment of Neuropsychological Status</td>
<td>56</td>
<td>43</td>
</tr>
<tr>
<td>Auditory Memory/Attention, index score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Processing speed, ms</td>
<td>79</td>
<td>32</td>
</tr>
<tr>
<td>Neuropsychological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall memory, index score</td>
<td>57</td>
<td>46</td>
</tr>
<tr>
<td>Rey Auditory Verbal Learning Test, raw score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>48</td>
<td>36</td>
</tr>
<tr>
<td>Word list delayed recall</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>Rivermead Behavioral Memory Test, raw score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate recall</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>Delayed recall</td>
<td>50</td>
<td>46</td>
</tr>
<tr>
<td>Wechsler Memory Scale III, raw score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digits backwards</td>
<td>49</td>
<td>42</td>
</tr>
<tr>
<td>Letter-number sequencing</td>
<td>48</td>
<td>43</td>
</tr>
<tr>
<td>Participant-reported outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Self-Report Questionnaire-25, total, raw score</td>
<td>48</td>
<td>40</td>
</tr>
</tbody>
</table>
Cognitive Rehabilitation in HIV/AIDS: A Case Study Demonstrating the Benefits of the Brain Fitness Program

Our Approach
- We evaluated the potential benefits of the Brain Fitness Program (BFP), a computerized and self-administered cognitive rehabilitation intervention.
- The case study involved a 52-year-old, well-educated gay man with a previously documented diagnosis of HIV-Associated Cognitive Impairment (mild cognitive impairment).
- Cognitive rehabilitation testing and symptom questionnaires were administered prior to and after eight weeks of the BFP intervention.
- The BFP intervention consisted of one hour of exercises five days per week for a total of 40 sessions. The BFP uses computer-based exercises for use on a PC or Mac that are designed to be very easy to use, even for computer novices. It is designed to speed up auditory processing, improve working memory, and encourage efficiency of neural networks involved in memory processing. The exercises adapt to individual level, and give constant feedback about progress.

The Challenge
30% to 50% of people with HIV/AIDS experience cognitive impairments in attention (particularly multi-tasking), memory (particularly efficiency in learning new information), speed of cognitive processing (how fast a person conducts cognitive tasks), and fine motor skills. Cognitive impairments can have a significant effect on day-to-day functioning, and quality of life, and can disrupt a person’s self-confidence in his abilities and everyday performance.

HAART has dramatically improved health outcomes and survival and reduced AIDS dementia, but as many as 50% of people on HAART continue to experience mild neurocognitive disorder (HIV-Associated Minor Cognitive-Motor Disorder or MCMID) -- even when markers of HIV disease are controlled and stable.

Antiretroviral agents that cross into the brain have some benefit in cognitive functioning but they are not likely to fully reverse (or prevent) cognitive impairments. Future avenues for treatment need to be explored to address these issues.

Our Findings
Intervention Improves Cognitive Ability
We observed clinically significant improvements -- beyond expected practice effects -- were observed following the 8-week Brain Fitness Program intervention in the following cognitive ability areas:
- Complex attention and working memory (multi-tasking ability)
- Learning efficiency (ability and quickness in learning new information)
- Verbal fluency (increased ease with finding words to express oneself)
- Complex psychomotor efficiency (cognitive processing under time pressure).

Participants also noted substantial improvements in:
- Subjective ratings of cognitive processing: efficiency
- Efficiency in day-to-day activities and tasks.

Clinical Implications for Practice
- The Brain Fitness Program (BFP) may offer a potentially beneficial cognitive intervention tool for people with HIV experiencing cognitive impairments related to HIV/AIDS.
- If the cognitive benefits also translate into significant and lasting impacts on the ability to perform complex everyday functioning tasks and activities, the intervention may offer real potential for those who want to continue working and those who want to return to work.
- Our multidisciplinary team is currently involved in other case studies to explore potential support for an evaluation of a larger rigorous intervention trial to formally test the effectiveness of the Brain Fitness Program in people with HIV.
Cognitive Interventions for HAND Underway in Toronto
Mindfulness-Based Cognitive Behaviour Treatment Pilot Study
(To Start June 17, 2013)
Led by Dr. Evan Collins and Pat Rockamn

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.
A Mind of Her Own

Long-term survivor Maggie Atkinson adds cognitive problems to her list of HIV-related issues. Here she takes a walk down memory lane and shares what she's learned about protecting her brain.

ILLUSTRATION BY PHIL
Thank you

Sean.rourke@utoronto.ca

Sean B. Rourke, Ph.D.
Professor of Psychiatry, University of Toronto
Scientific and Executive Director, Ontario HIV Treatment Network
Scientist, Li Ka Shing Knowledge Institute of St. Michael’s Hospital
Director, CIHR Centre for REACH in HIV/AIDS and Collaborative CBR Centre
Director, Universities Without Walls (CIHR STIHR)