Differential diagnosis between depression and neurocognitive impairment in HIV-infected persons

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## Disclosure

Research: Canadian Institute Health Research (CIHR) - I  
Ontario HIV Treatment Network (OHTN) - I  

<table>
<thead>
<tr>
<th>Company</th>
<th>Abbvie Laboratories</th>
<th>Bristol-Myers Squibb Canada</th>
<th>Janssen Biotech</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consulting</td>
<td>I</td>
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<tr>
<td>Speaking &amp; Teaching</td>
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<tr>
<td>Advisory Board</td>
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</tbody>
</table>

D – Relationship is considered directly relevant to the presentation.  
I – Relationship is NOT considered directly relevant to the presentation.
Introduction

- Evolution from an untreatable condition to a chronic disease
- Challenges have changed with the advances in the treatment
- HIV-positive patients continue to face:
  - Extensive social challenges
  - Stigma and discrimination
  - Social isolation
HIV/AIDS

Initial Dx
Clinical changes
Onset Opportunistic Infections
Cognitive decline

Acute

Fatigue
Pain
ARV concerns
Adherence
Disclosure
Stigma
Changes in social rules
Financial problems
Cognitive decline

Ongoing challenges

Stress

Psychiatric Disorders
HIV and Psychiatric Disorders

Risk
Poor QoL

HIV ↔ Psychiatric Disorders

Severity
Poor self-care
Adherence
Worse treatment outcomes
Impairment in social and vocational functioning
Social isolation
Use of health services

Ref, MV et al. 2013.
When psychiatric illness...

- Difficulties trusting and relating to health care providers
- Worsening of cognitive complaints
- Coexistence of different psychiatric comorbidities
- Medication adherence
- Difficulties maintaining appointments
They can be the most challenging and frustrating patients for the HIV team...
Depression
20–30% of patients with HIV suffer from depression

Depression is more common in patients with the following characteristics:

- Women
- Non-Caucasian ethnicity
- Progressed to AIDS
- Unemployed
- Have dependants who are minors
- Hepatitis C co-infection

Depression in patients with HIV is associated with:

1. Lower quality of life
2. Reduced adherence to ART
3. Poorer self-care
4. Worse treatment outcomes
5. Impairment in social and vocational functioning
6. Social isolation
7. High-risk behaviour and substance abuse

Patients with HIV and depression may be less likely to receive ART.

ART, antiretroviral therapy.

Why make the diagnosis of depression?

- Patients with HIV diagnosed with depression can have:
  - Declining CD4+ counts
  - Higher activated CD8 T-lymphocyte counts
  - Higher viral loads
  - Slower virological response

- Depression affects adherence to ART

Patients with depression have a higher mortality risk.

Depression is negatively correlated with treatment adherence in patients with HIV\(^1\):
- Adherence decreases as the severity of depression increases\(^1\)
- Patients are more likely to discontinue treatment\(^2\)

Cognitive symptoms of depression are particularly correlated with non-adherence\(^1\)

Lower treatment adherence in patients with HIV and depression leads to an increased viral load\(^2\)

The relationship between adherence and depression is dynamic.


**p<0.01
Patients with depression have lower treatment adherence

*p<0.05; **p<0.01
Adherence in patients with depression

- Reluctance to prescribe ART to patients with depression because of concerns about adherence
- Poorer outcomes in patients with HIV and depression
- Poor outcomes can exacerbate the symptoms of depression

ART: antiretroviral therapy.
Hartzell et al. 2008
Patients may not recognise or self-report symptoms of depression. Some physicians may also be afraid to ask questions about psychological health.

A wide variety of depression screening techniques are available. Most rely on self-reporting. Some tools focus in physical symptoms. Most diagnose the severity rather than presence of depression.

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Many screening techniques can be performed in ≤10 minutes\(^1\)

- Screening methods as short as two questions have been recommended\(^2\)
- Questionnaire length does not impact accuracy\(^3\)

### Screening instruments used for evaluating comorbid depression in patients with medical illness

<table>
<thead>
<tr>
<th>Screening Instrument</th>
<th>Method of administration</th>
<th>Administration time</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamilton Depression Rating Scale (HAM-D)</td>
<td>Clinician administered</td>
<td>20 to 30 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Montgomery-Åsberg Depression Rating Scale (MADRS)</td>
<td>Clinician administered</td>
<td>5 to 10 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Symptom Check List 90-Revision (SCL-90-R)</td>
<td>Self report</td>
<td>15 minutes</td>
<td>Screens depression/other psychiatric comorbidity</td>
</tr>
<tr>
<td>Brief Symptom Inventory (BSI) (Abbreviated SCL-90-R)</td>
<td>Self report</td>
<td>10 minutes</td>
<td>Screens depression/other psychiatric comorbidity</td>
</tr>
<tr>
<td>Illness Distress Scale (IDS)</td>
<td>Self report</td>
<td>5 to 10 minutes</td>
<td>Severity of physical and emotional distress</td>
</tr>
<tr>
<td>Psychological Distress Inventory (PDI)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of distress</td>
</tr>
<tr>
<td>Carrol Depression Rating Scale (CDRS)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Geriatric Depression Scale (GDS)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Zung Depression Scale (Zung)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Beck Depression Inventory for Primary Care (BDI-PC)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Beck Depression Inventory-Fast Screen for Medical Patients (BDI-FS)</td>
<td>Self report</td>
<td>&lt;5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Depression in the Medical Illness scale (DMM-9)</td>
<td>Self report</td>
<td>5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>General Health Questionnaire (GHQ)</td>
<td>Self report</td>
<td>Depend on the version</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Patient Health Questionnaire (PHQ-9)</td>
<td>Self report</td>
<td>&lt;5 minutes</td>
<td>Presence of depression</td>
</tr>
<tr>
<td>Medical Outcomes Study Depression Questionnaire (MOS-DO)</td>
<td>Self report</td>
<td>&lt;5 minutes</td>
<td>Presence of depression</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale (HADS)</td>
<td>Self report</td>
<td>&lt;5 minutes</td>
<td>Severity of depression</td>
</tr>
<tr>
<td>Centre for Epidemiological Studies Depression Scale (CES-D)</td>
<td>Self report</td>
<td>10 minutes</td>
<td>Severity of depression</td>
</tr>
</tbody>
</table>

Source: Reference 4.

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Screening for depression

- Centre Epidemiological Studies - Depression - CES-D
- Simple, quick and easy to interpret
- Screening tools assess several somatic symptoms
- Scoring > 16

Radloff 1977
When diagnosing HIV patients with depressive symptoms, it may be necessary to exclude the following possible causes:

| Other neuropsychiatric disorders | • Bipolar disorder  
| • Post-traumatic stress disorder  
| • HIV-associated dementia  
| • Alcohol and substance abuse |
| HIV-related medical conditions and treatments | • Endocrinological abnormalities  
| • HIV-related treatments  
| • Opportunistic and other infections (e.g. syphilis)  
| • HIV-associated dementia |
Treatment

- Psychopharmacological management is complicated:
  - Broad differential diagnoses
  - Potential for adverse effects to increase somatic distress
  - Possibility of drug interaction with ARV

- Psychosocial interventions:
  - Training for specific interventions
  - Multidisciplinary teams

Carvalhal et al. 2012.
Cognitive Disorders
Declining incidence of neurologic complications
What changes can be experienced?

- Slowing (cognitive operations)
- Concentration/paying attention
- Multi-tasking ability ("working memory")
- Word finding
- Memory ability (particularly short-term)
- Motor coordination
HAND: Functional Impairment

- **Activities of daily living:**
  - *Medication adherence*
  - Driving (2-3 time as likely to fail tests)
  - Problem solving
  - Complex tasks

- **Vocational functioning:**
  - 5 times more likely to complain of problems performing their jobs
  - twice as likely to be unemployed

Definition of HAND

- Asymptomatic Neurocognitive Impairment (ANI)
- Mild Neurocognitive Disorder (MND)
- HIV-Associated Dementia (HAD)

Neurocognitive Impairment:
- Mild
- Moderate

Functional Impairment:
- None
- Mild
- Moderate


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.
Which patients should be screened for HAND, and when? How often should patients be screened?

Who to screen:
- In all patients with HIV - assist treatment decisions and detect changes before symptoms arise

When to screen:
- within 6 months of diagnosis, as soon as clinically appropriate
- before the initiation of ARV, if possible
- insufficient data to establish best time for follow up - cognitive reserve and natural history of the disease
  - 6-12 months in high risk patients
  - 12 - 24 months in lower risk patients
  - evidence of deterioration
How can clinicians identify patients at risk of HAND?

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment</th>
<th>Co-morbidities</th>
<th>Demographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Low CD4 nadir</td>
<td>• Poor adherence</td>
<td>• HCV +</td>
<td>• older individuals</td>
</tr>
<tr>
<td>• High plasma, CSF VL</td>
<td>• ARV interruptions</td>
<td>• Hx acute CV event</td>
<td>• low education</td>
</tr>
<tr>
<td>• Low current CD4</td>
<td>• non-optimal ARV regimen</td>
<td>• CV risk factors</td>
<td>• lower socio-economic status</td>
</tr>
<tr>
<td>• Hx HIV-related CNS disease</td>
<td>• low ARV duration-related to treatment failure</td>
<td>• Psychiatric disorder</td>
<td>• lack of access to care</td>
</tr>
<tr>
<td>• Longer HIV duration</td>
<td>• Potential neurotoxicity</td>
<td>• Brain injury</td>
<td>• poverty</td>
</tr>
<tr>
<td></td>
<td>• lower CPE</td>
<td>• Substance use</td>
<td></td>
</tr>
</tbody>
</table>
Which tools should be used to screen for HAND?

- Several screenings are available, choice depend on:
  - expertise of neuropsychology is available
  - if we want to screen for HAD or MND/ANI
  - time and costs
- Not be used in isolation of clinical factors
- No single screening is suitable for use across all settings
- HDS and IHDS are the most widely used
Evaluation of brief screening tools for neurocognitive impairment in HIV/AIDS: a systematic review of the literature

Amy R. Zipursky\textsuperscript{a, b}, David Gogolishvili\textsuperscript{a}, Sergio Rueda\textsuperscript{a, b}, Jason Brunetta\textsuperscript{c}, Adriana Carvalhal\textsuperscript{b, d}, Jennifer A. McCombe\textsuperscript{e}, M. John Gill\textsuperscript{f}, Anita Rachlis\textsuperscript{b, f}, Ron Rosenes\textsuperscript{a}, Gordon Arbess\textsuperscript{b, d}, Thomas Marcotte\textsuperscript{g} and Sean B. Rourke\textsuperscript{a, b, d}

Objective(s): To systematically review literature on brief screening tools used to detect and differentiate between normal cognition and neurocognitive impairment and HIV-associated neurocognitive disorders (HANDs) in adult populations of persons with HIV.

Design: A formal systematic review.

Methods: We searched six electronic databases in 2011 and contacted experts to identify relevant studies published through May 2012. We selected empirical studies that focused on evaluating brief screening tools (<20 min) for neurocognitive impairment in persons with HIV. Two reviewers independently reviewed retrieved literature for potential relevance and methodological quality. Meta-analyses were completed on screening tools that had sufficient data.

Results: Fifty-one studies met inclusion criteria; we focused on 31 studies that compared brief screening tools with reference tests. Within these 31 studies, 39 tools were evaluated and 67% used a comprehensive neuropsychological battery as a reference. The majority of these studies evaluated HIV-associated dementia (HAD). Meta-analyses demonstrated that the HIV Dementia Scale (HDS) has poor pooled sensitivity (0.48) and the International HIV Dementia Scale (IHDS) has moderate pooled sensitivity (0.62) in detecting a range of cognitive impairment. Five newer screening tools had relatively good sensitivities (>0.70); however, none of the tools differentiated HAND conditions well enough to suggest broader use. There were significant methodological shortcomings noted in most studies.

Conclusion: HDS and IHDS perform well to screen for HAD but poorly for milder HAND conditions. Further investigation, with improved methodology, is required to understand the utility of newer screening tools for HAND; further tools may need to be developed for milder HAND conditions.

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AIDS 2013, 27:2385–2401
International HIV Dementia Scale – IHDS

Paper based (3-5 min)

3 domains assessed: motor and psychomotor speed; memory-recall

A score of ≥10 is considered “unimpaired”

1. Motor Speed:
   tap 2 fingers non-dom hand (in 5 sec)
   4 = 15  2 = 7-10  0 = 0-2
   3 = 11-14  1 = 3-6

2. Psychomotor Speed: n sequences 10 sec
   a) Clench hand
   b) Hand flat with palm down
   c) Hand perpendicular on the side

3. Memory-recall: ask 4 words
   Memory: give 4 words: dog, hat, bean, red

Differential Diagnosis

- Psychiatric disorders
- Prescription drugs - anticholinergic effects
- Syphilis, OI and other HIV-related CNS disorders
- Alzheimer’s disease
- Cerebrovascular disease and metabolic syndrome
- Aging
- Other chronic neurologic disorders - Traumatic brain injury (TBI) and seizures
- Vitamin or hormone deficiency - folate, B12, testosterone, thyroid
Role of chronic depression and neurocognitive dysfunction
Depression and HAND are independent
- Treatment for depression before neuropsych assessment

Depression is not a systematic driver of neurocognitive decline
- Response to treatment is key in confirming or not if depression impact HAND

Testing for HAND may be confounded by the presence of depression
- Because depression could manifest itself as cognitive impairment, it must be ruled out before diagnosing HAND
- HAND may initially present itself as “resistant depression”
HIV diagnosis

• Assessment of history and risk factors for HAND/NCI
• Screening for NCI

NP assessment

• Assess comorbidities to judge degree of impairment caused by HIV
• Functional assessment
• Diff diagnosis in older pts

Diagnosis of ANI, MND or HAD

• Initiate cART or consider changing regimen
• Ensure viral suppression

• Some screening tests may be influenced by symptoms of depression

A brief assessment of emotional state of patient is advisable regardless of the NP screening tool used2

Unresolved depression is a key confounding etiology in identification of neurocognitive impairment3
• Depression can affect NP test performance4

Depression can result in overestimate of self-reporting of cognitive difficulties5

Take home messages...

- Despite many advances in the treatment of HIV infection, psychiatric disorders remain a challenge.
- A significant proportion of patients with HIV suffer from depression.
- Depression may be associated with a negative impact on patient outcomes and treatment adherence.
- Screening for depression and HAND can be done quickly, but it is important to consider alternative diagnoses following preliminary investigations.
Now I challenge you...

• It is important **early detection** of any psychiatric disorder - Think about include screenings in your clinical practice

• Take serious if a patient complaint of cognitive impairment and **think in common conditions** first (e.g. Depression and Substance use)

• There are conditions with great **evidence for treatment** (e.g. Depression) and these treatment may improve cognition
Muchas Gracias
Differential diagnosis between depression and neurocognitive impairment in HIV-infected persons

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