

A person in dark clothing stands on a wooden pier, looking out at a misty sea with mountains in the background. The scene is dimly lit, suggesting dawn or dusk.

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

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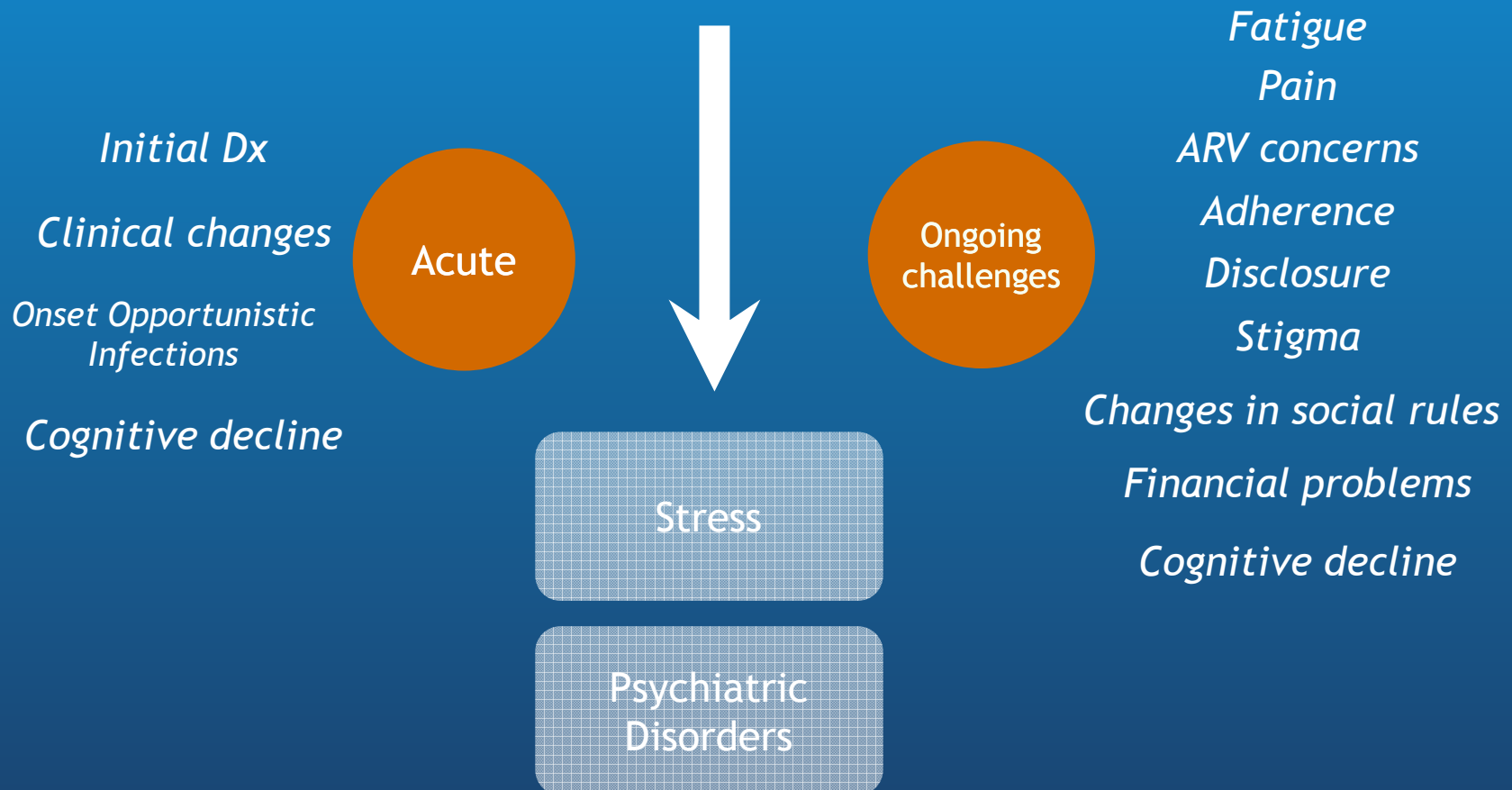
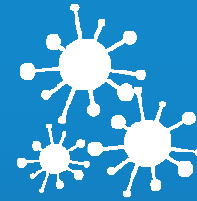
D – Relationship is considered directly relevant to the presentation.
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Introduction



- 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



HIV and Psychiatric Disorders



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

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...

A person in dark clothing stands on a wooden pier, looking out at a misty sea and mountains. The scene is dimly lit, suggesting dawn or dusk. The word "Depression" is overlaid in white text.

Depression

Prevalence of depression

- 20-30% of patients with HIV suffer from depression¹
- Depression is more common in patients with the following characteristics:
 - Women²
 - Non-Caucasian ethnicity³
 - Progressed to AIDS⁴
 - Unemployed³
 - Have dependants who are minors³
 - Hepatitis C co-infection⁵

1. Coughlin SS. *Am J Epidemiol* 2013;177:126–130; 2. Nyirenda *et al. J Affect Disord* 2013; Epub ahead of print. doi: 10.1016/j.jad.2013.05.005;

3. Shacham E *et al. AIDS Patient Care STDs* 2009;23:949–55; 4. Ramasubbu R *et al. Ann Clin Psychol* 2012;24:82–90;

6. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010.

Available at: <http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf>. Last accessed July 2013.

Depression

- Depression in patients with HIV is associated with:^{1,2}
 - Lower quality of life
 - Reduced adherence to ART
 - Poorer self-care
 - Worse treatment outcomes
 - Impairment in social and vocational functioning
 - Social isolation
 - High-risk behaviour and substance abuse
- Patients with HIV and depression may be less likely to receive ART^{3,4}

ART, antiretroviral therapy.

1. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010.

Available at: <http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf>. Last accessed July 2013;

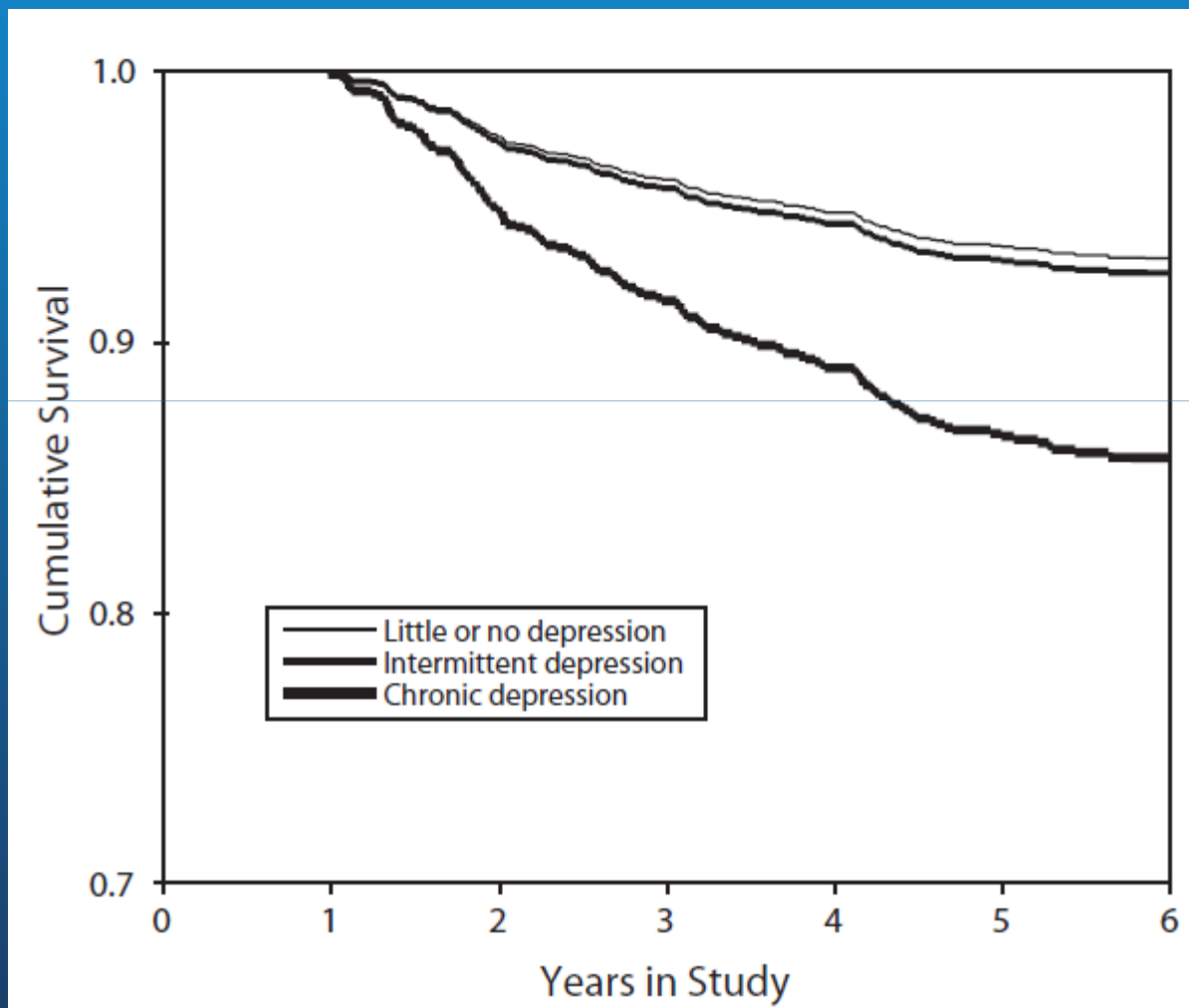
2. Relf MV *et al.* *J Assoc Nurses AIDS Care* 2013;24(1 Suppl):S15–28;

3. Tegger MK *et al.* *AIDS Patient Care STDS* 2008;22:233–43; 4. Bhatia R *et al.* *AIDS Behav* 2011;15:1161–70.

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 affect adherence to ART

Patients with depression have a higher mortality risk

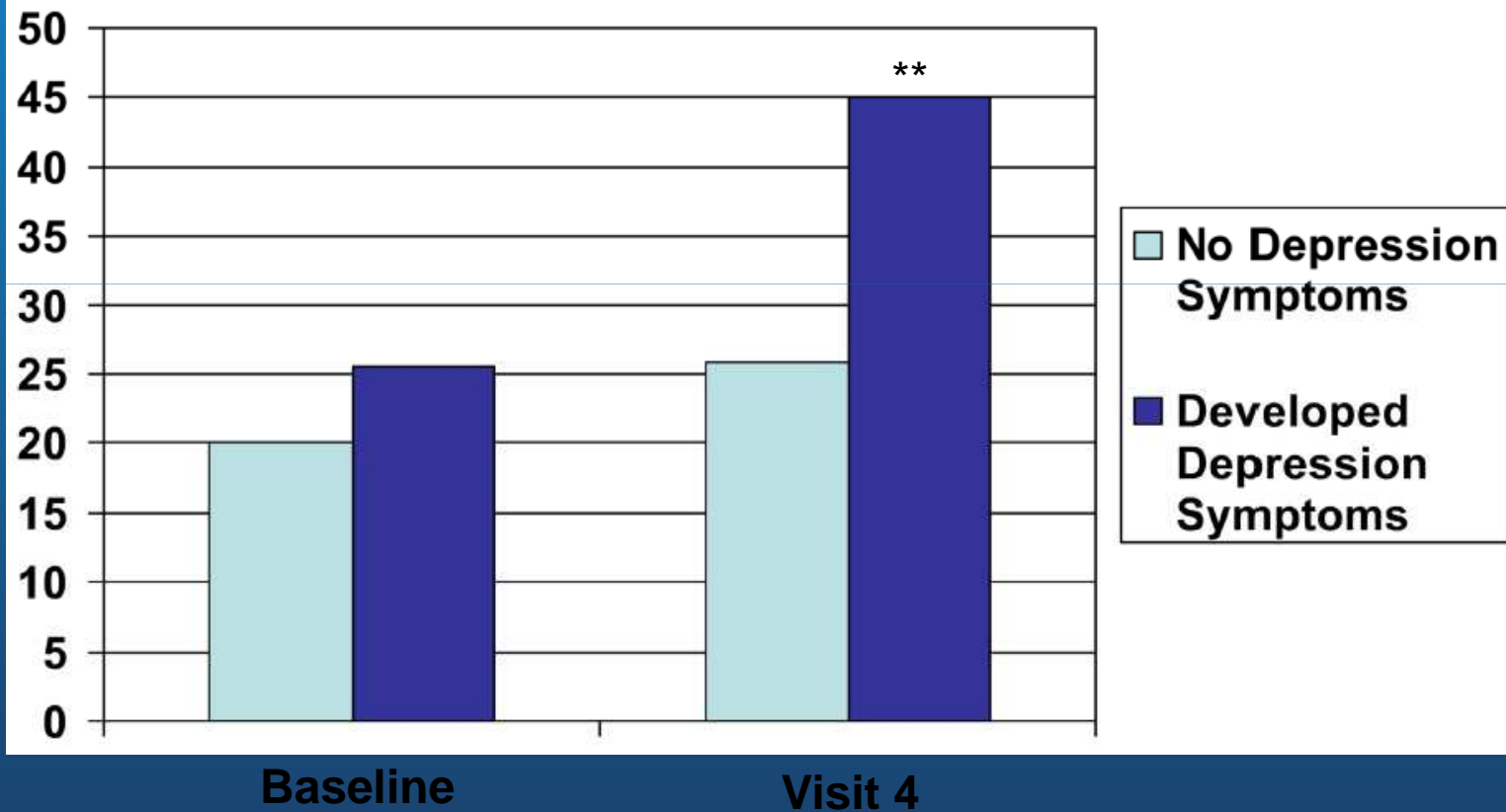


Patients with depression have lower treatment adherence

- Depression is negatively correlated with treatment adherence in patients with HIV¹
 - Adherence decreases as the severity of depression increases¹
 - Patients are more likely to discontinue treatment²
- Cognitive symptoms of depression are particularly correlated with non-adherence¹
- Lower treatment adherence in patients with HIV and depression leads to an increased viral load²

The relationship between adherence and depression is dynamic

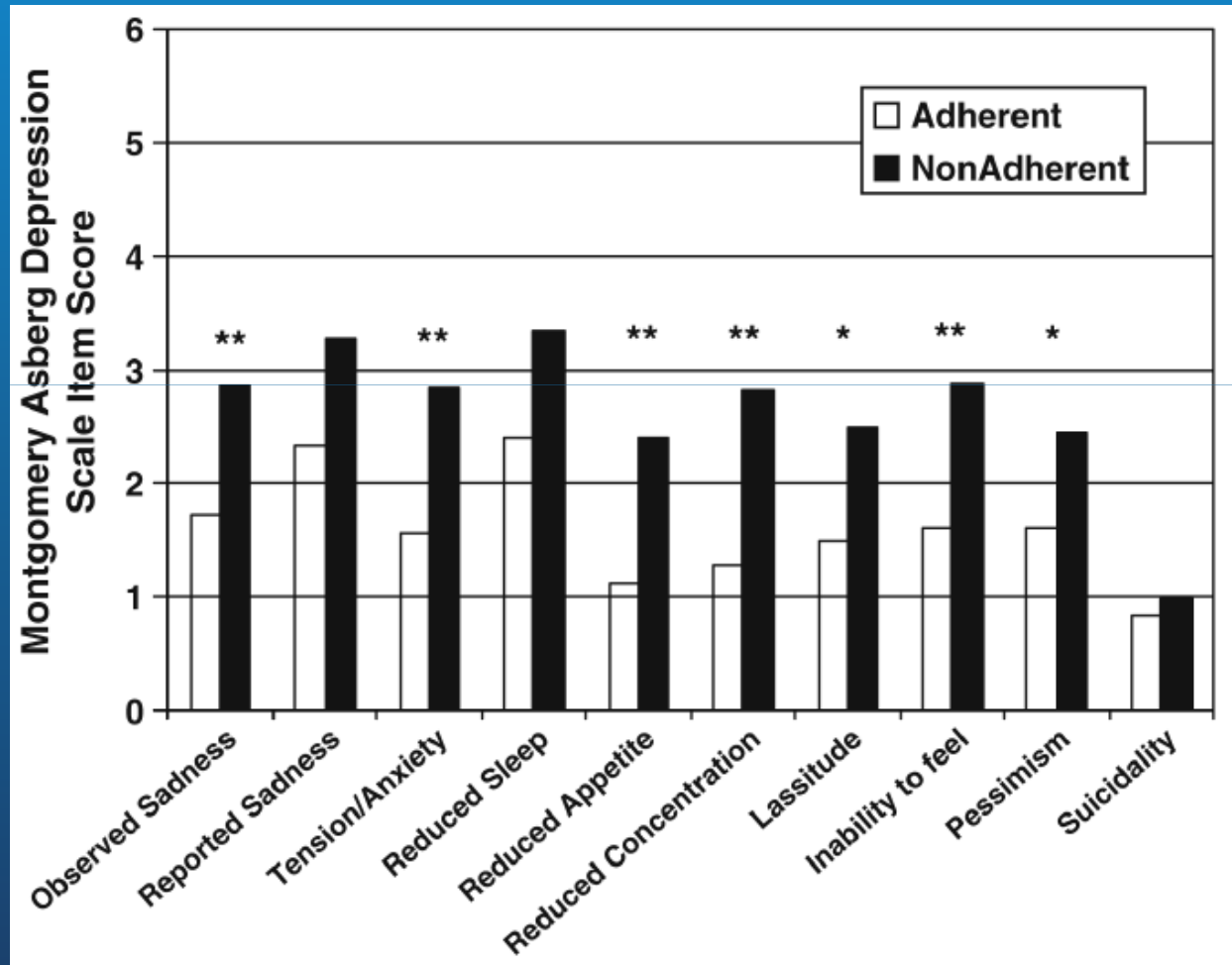
Proportion of patient population with suboptimal adherence (%)



**p<0.01

Kacanek et al. *J Acquir Immune Defic Syndr* 2010;53:266–72.

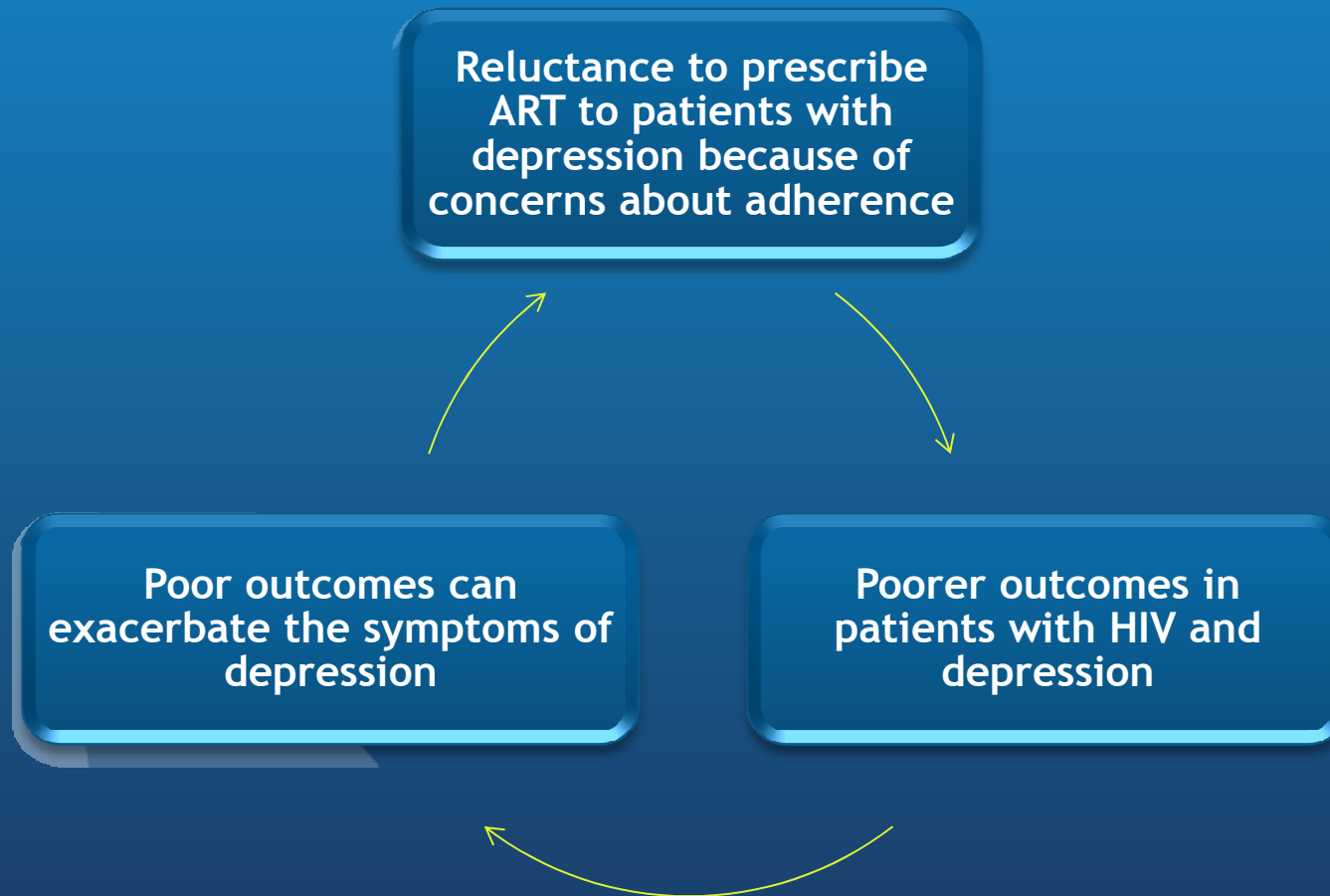
Patients with depression have lower treatment adherence



*p<0.05; **p<0.01

Gonzalez JS et al. *Ann Behav Med* 2011;42:120–6.

Adherence in patients with depression



ART: antiretroviral therapy.
Hartzell et al. 2008

Screening for depression

Screening

- Patients may not recognise or self-report symptoms of depression¹
 - Some physicians may also be afraid to ask questions about psychological health

Diagnosis

- A wide variety of depression screening techniques are available²
 - Most rely on self-reporting
 - Some tools focus in physical symptoms
 - Most diagnose the severity rather than presence of depression

Monitoring

1. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010. Available at: <http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf>. Last accessed July 2013.

2. Ramasubbu R *et al.* *Ann Clin Psychiatr* 2012;24:82–90.

Screening for depression

- Many screening techniques can be performed in ≤ 10 minutes¹
 - Screening methods as short as two questions have been recommended²
 - Questionnaire length does not impact accuracy³

Screening instruments used for evaluating comorbid depression in patients with medical illness			
Screening instrument	Method of administration	Administration time	Assessment
Hamilton Depression Rating Scale (HAM-D)	Clinician administrated	20 to 30 minutes	Severity of depression
Montgomery-Åsberg Depression Rating Scale (MADRS)	Clinician administrated	5 to 10 minutes	Severity of depression
Symptom Check List 90-Revision (SCL-90-R)	Self report	15 minutes	Screens depression/other psychiatric comorbidity
Brief Symptom Inventory (BSI) (Abbreviated SCL-90-R)	Self report	10 minutes	Screens depression/other psychiatric comorbidity
Illness Distress Scale (IDS)	Self report	5 to 10 minutes	Severity of physical and emotional distress
Psychological Distress Inventory (PDI)	Self report	5 minutes	Severity of distress
Carroll Depression Rating Scale (CDRS)	Self report	5 minutes	Severity of depression
Geriatric Depression Scale (GDS)	Self report	5 minutes	Severity of depression
Zung Depression Scale (Zung)	Self report	5 minutes	Severity of depression
Beck Depression Inventory for Primary Care (BDI-PC)	Self report	5 minutes	Severity of depression
Beck Depression Inventory–Fast Screen for Medical Patients (BDI-FS)	Self report	<5 minutes	Severity of depression
Depression in the Medically Ill scale (DMI-10)	Self report	5 minutes	Severity of depression
General Health Questionnaire (GHQ)	Self report	Dependent on the version	Severity of depression
Patient Health Questionnaire (PHQ-9)	Self report	<5 minutes	Presence of depression
Medical Outcomes Study Depression Questionnaire (MOS-DQ)	Self report	<5 minutes	Presence of depression
Hospital Anxiety and Depression Scale (HADS)	Self report	<5 minutes	Severity of depression
Centre for Epidemiological Studies Depression Scale (CES-D)	Self report	10 minutes	Severity of depression

Source: Reference 45.

1. Ramasubbu R *et al.* *Ann Clin Psychiatr* 2012;24:82–90;

2. New York State Department of Health. Depression and mania in patients with HIV/AIDS. New York (NY): New York State Department of Health; 2010. Available at: <http://cdn.hivguidelines.org/wp-content/uploads/depression-and-mania-posted-10-19-2010.pdf> Last accessed July 2013;

3. Akena D *et al.* *BMC Psychiatry* 2012;12:187.

Screening for depression

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

	Rarely or none (less than 1 day)	Some or a little (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most or all the time (5-7 days)
I was bothered by things that usually don't bother me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I felt hopeful about the future	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Confounding factors for the diagnosis of depression

Screening

Diagnosis

Monitoring

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

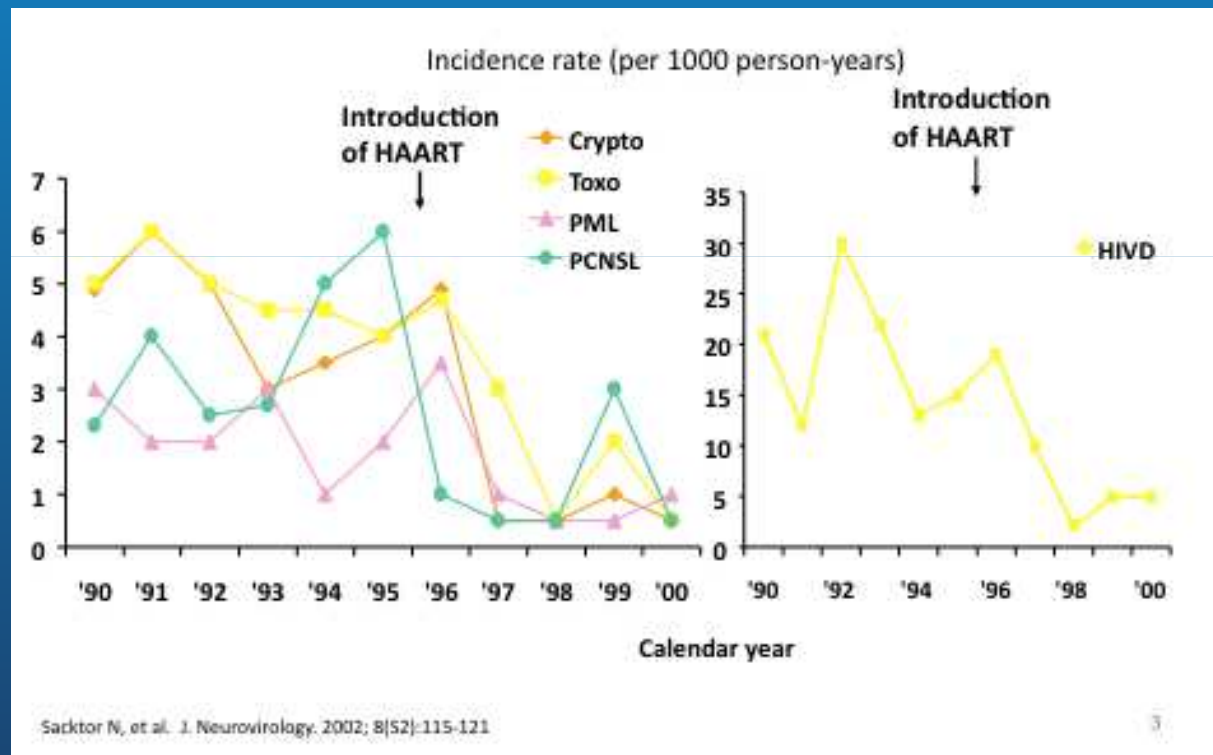


- Psychopharmacological management is complicated:
 - Broad differential diagnoses
 - Potential for adverse effects to increase somatic distress
 - Possibility of drug interaction with ARV
- Psychosocial interventions:
 - Training for specific interventions
 - Multidisciplinary teams

A person is standing on a wooden pier, looking out at a misty sea and mountains. The person is wearing dark clothing and is seen from behind. The scene is atmospheric and somewhat somber, with a blue and grey color palette. The text "Cognitive Disorders" is overlaid in the center of the image in a white, serif font.

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

Mild

Moderate

Functional
Impairment

None

Mild

Moderate

Assessment, Diagnosis, and Treatment of HIV-Associated Neurocognitive Disorder: A Consensus Report of the Mind Exchange Program

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?

Disease

- Low CD4 nadir
- High plasma, CSF VL
- Low current CD4
- Hx HIV-related CNS disease
- Longer HIV duration

Treatment

- Poor adherence
- ARV interruptions
- non-optimal ARV regimen
- low ARV duration-related to treatment failure
- Potential neurotoxicity
- lower CPE

Co-morbidities

- HCV +
- Hx acute CV event
- CV risk factors
- Psychiatric disorder
- Brain injury
- Substance use

Demographic

- older individuals
- low education
- lower socio-economic status
- lack of access to care
- poverty

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

Memory: give 4 words: dog, hat, bean, red

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

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

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Role of chronic depression and
neurocognitive dysfunction

Depression and neurocognitive impairment

- 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”

Cysique LA et al *J Neurovirol* 2016; 22:56-65

Dubé B et al. *J Psychiatry Neurosci* 2005;30:237–46;. Cysique LA et al. *J Int Neuropsychol Soc* 2007;13:1–11;

Millikin CP et al. *J Clin Exp Neuropsychol* 2003;25:201–15; Gibbie T et al. *HIV Med* 2006;7:112–21; 4..

How can depression confound the diagnosis of HAND?

Suggested flow for screening / diagnosis of HAND



1. Sacktor NC et al. AIDS 2005;19:1367–1374; 2. Cysique LA, Brew BJ. The assessment of HIV-associated neurocognitive disorders: new challenges in the HAART era. Paul RH et al., editors. HIV and the Brain, New Challenges in the Modern Era. Humana Press, 2009; 3. Antinori A et al. Neurology 2007;69:1789–1799; 4. Owe-Larson et al. Afr J Psychiatry (Johannesbg) 2009;12:115–128; 5. Cysique et al. J Int Neuropsychol Soc 2007;13:781–790; 6. Thames AD et al. J Clin Exp Neuropsychol 2011;33:200–209.

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

**Muchmas
Gracias**

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