HIV Neuropsychiatric Issues

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Columbia University

The Columbia University HIV Mental Health Training Project, with funding from the New York State Department of Health AIDS Institute, now offers the Warmline. Mental health and primary care providers with HIV clients can access assistance from a psychiatrist who specializes in the relationship between HIV and mental health. All calls will be returned within 48 business hours.
32nd Year of AIDS

World AIDS Day
Dec 1, 2013

Twenty-Five year trends in HIV and AIDS cases 1984-2007

Reported AIDS Cases, Persons Living with HIV, Persons Living with AIDS, and Deaths: 1984 through 2007
New York State

* HIV annual reporting began in NY in 2000
Good News and Bad News

Steven Deeks MD IAS-USA May 2009

- Poor life expectancy
- 10-30 years less
- “Patients receiving long term antiretroviral therapy are at increased risk of age associated non-AIDS related morbidity/mortality…”

Higher rates of non-AIDS dx

- Cardiovascular disease
- Cancers
- Osteopenia
- LV Dysfunction
- Liver Failure
- Kidney Failure
- Cognitive Decline
- Accelerated aging/chronic inflammation

New York Magazine 11-9-09
The New HIV Scare
Another Kind of AIDS Crisis

- CHARTER (CNS HIV antiretroviral therapy effects research)
  - Started in 2002
  - >$38 million in NIMH NIND grants
  - Follows 1555 patients living with HIV/AIDS
  - CHARTER Neurology 2010, Heaton et al
- Manhattan HIV Brain Bank
  - 250 volunteers
  - Persistent inflammation, little viral replication
  - High rates of psychiatric/substance abuse disorders

HIV and the Brain/CNS

- HIV is a neurovirulent virus and affects more than just the immune system
- The neuropsychiatric effects of HIV on the Central Nervous System (CNS) can be difficult to assess
- Other diseases appear similar to neuropsychiatric issues
- It is important to rule out treatable causes
Assessing Neuropsychiatric issues

Look for underlying biological cause

1. Medications: HIV, psychiatric, other
2. Substances: Alcohol, drugs, herbal, other
3. Non-HIV medical problems
4. HIV-related illnesses:
   • CNS lesions, infections
   • Non-CNS medical problems

Psychiatric Syndromes

HIV-neuropsychiatric manifestations:
• MCMD
• HAD

Screening tools

- Substance Abuse Mental Illness Symptom Screener (SAMISS)
- Client Diagnostic Questionnaire (CDQ)

Specifically designed to assess mental health problems in people who are living with HIV/AIDS
- Brief, structured interview, immediately scored, reliable predictor of disorder
- Developed for primary care settings.
- Indicates which clients need to be referred to a mental health professional for further assessment and treatment
- The interview can be conducted by a lay interviewer with no formal training in mental health assessment

Adapted by Angela Aidala PhD at the Mailman School of Public Health
Most common rule out diagnosis: Depression

- Mood disorders are the most frequent psychiatric complication associated with HIV disease.
- Depression significantly worsens ARV adherence and HIV viral control. Compliant SSRI use is associated with improved HIV adherence and laboratory parameters.
- Those with symptomatic HIV disease are more likely to experience a major depressive episode than asymptomatic HIV+ and HIV- individuals.
- Suicide risk is elevated across the trajectory of HIV disease.
- Common Co-morbid diagnosis of depression with loss of abilities.

Atkinson 2007; Horberg 2007

What’s Unique to Depression and Neuropsychiatric manifestations of HIV?

- Psychomotor retardation or apathy of HIV associated dementia may be confused with depression.
- Other common physical symptoms of depression can overlap with HIV associated dementia (e.g., fatigue, eating disturbance).
- Depressive symptoms can often be the first sign of dementia.
- HIV Assoc Dementia ABC+M (affect/behavior/cognitive+ motor).
Initial Approach to Management

- General Neuropsychiatric workup
- Exclude other treatable causes
  - a. neuroimaging: MRI to exclude OI's: toxoplasmosis, PML or lymphoma
  - b. Labs: thyroid TSH, B12, anemia, testosterone
  - c. Lumbar Puncture: CSF for OI or VL
  - d. toxicology: Rule out substance abuse issues- meth, ETOH
  - e. R/O delirium
  - f. HCV infection
- Neuropsychological screeners- cognitive
- Functional assessment

Neuroimaging studies

- Pre ARV- subcortical & Periventricular White Matter Changes
- Post ARV- mixed cortical and subcortical features
  - + More neuronal loss in hippocampus, basal ganglia, caudate nucleus

Volumetric MRI=cognitive motor dysfunction
Quantitative MRI=cerebral atrophy=NP performance
### Hepatitis C / Liver Disease

- Chronic hepatitis C
- It is estimated that 30% of HIV-infected patients nationally and 40% in New York State are co-infected with HCV
- 55-85% will progress to chronic HCV infection
- Co-infected people with <200 CD4 cells/mL are at greatest risk for end-stage liver disease
- Worse Neurocognitive status

- Hepatic Encephalopathy
- “Brain Fog” of HCV Tx
- HALT-C group 2007 32%
  HCV 198 pts= cognitive impairments
- Aronow 2008 et al compared
  HIV/HCV and MSK ADC score
  HIV/HCV-coinfected subjects were statistically
  significantly more impaired neurocognitively than
  HIV-infected subjects without coinfection (using
  ANOVA).

### HIV-Neuropsychiatric Manifestations

![Image of a woman with her head in her hands]
HIV Associated Neurocognitive Disorders (HAND)
NIMH, NINDS Panel 2005

Asymptomatic neurocognitive impairment (ANI)

Minor Cognitive Motor Disorder/
Mild Neurocognitive Disorder

HIV Associated Dementia/
Moderate Neurocognitive Disorder

Prevalence of HIV Associated Neurocognitive Disorders – HAND
Charter 2011, Heaton et al

NP Normal ➔ ANI Asymptomatic Neurocognitive Impairment 33%

NP – Neuro-Psychological

Minor Cognitive Motor Disorder –
MCMD/HIV Assoc Mild Neurocognitive Disorder

MND 12% HIV+

≠

HAD 2% AIDS

HIV Associated Dementia – HAD/Moderate-Severe ND)

← Functional Impairment →
HIV and the CNS (Trojan Horse)

- HIV enters the central nervous system (CNS) soon after initial infection and is responsible for a range of neuropsychiatric complications (HIV-1 Associated Encephalitis)
- Although HIV is neuroinvasive, it does not directly infect neurons
- The major brain reservoirs for HIV infection and replication are microglia and macrophages. Astrocytes can be infected without replication
- HIV-associated neurological complications are indirect effects of viral neurotoxins (viral proteins gp120, vpr, tat) and HIV chemokines (CXCR), and inflammatory cytokines (NO, TNF, IL-1, quinolinic acid, arachidonic acid, PAF)

HIV-1 neuroinvasion
Mechanism of neuropathogenesis

Nomenclature of HIV-1 CNS Disorders 1

Mild Manifestations
- Minor Cognitive/Motor Disorder (MCMD)
- HIV Associated Mild Neurocognitive Disorder (MND)

Diagnostic Criteria
1. At least 2 symptoms (1SD): impaired attention, concentration, memory, mental/psychomotor slowing, impaired coordination, personality change
2. >1 month
3. Mild functional impairment
Minor Cognitive-Motor Disorder / HIV Assoc Mild Neurocognitive Disorder (MND)

Clinical Features
- Mild impairment in functioning
- Impaired attention or concentration
- Memory/concentration problems
- Low energy/slowed movements
- Impaired coordination
- Personality change, irritability or emotional lability

Patient Complaints/Symptoms
- Patients may not recognize the problem since their is mild functional impairment
- Has difficulty with complex tasks
- Mild memory problems
- Distractibility/confusion
- Needs to make lists
- Adherence problems
- May make excuses for forgetting

Overview
Prevalence pre ARV
- 20-30% for asymptomatic clients
- 60%-90% for late stage clients

Prevalence post ARV
- CHARTER 2011: 12%
- 5%, 15% & 25% in asymptomatic, early or late stage

Possible Risk Factors
- Age, late stage disease, viral load
**Minor Motor-Cognitive Disorder / Mild Neurocognitive Disorder (MND)**

Often does not present for any treatment and not recognized nor diagnosed

Differential Diagnosis: Diagnosis of Exclusion

Treatment

- Antiretroviral medications -adherence

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**Nomenclature of HIV-1 CNS Disorders 2**

<table>
<thead>
<tr>
<th>Severe Manifestations</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-Associated Dementia (HAD)</td>
<td>1 Acquired cognitive abnormality in 2 or more domains (2SD)</td>
</tr>
<tr>
<td>Moderate to severe neurocognitive disorder</td>
<td>1 <em>mod-severe functional impairment</em></td>
</tr>
<tr>
<td></td>
<td>2 Acquired abnormality in motor performance or behavior</td>
</tr>
<tr>
<td></td>
<td>3 No clouding of consciousness or other confounding etiology (e.g. CNS OIs, drug use, psychopathology)</td>
</tr>
<tr>
<td></td>
<td>&gt;1 month</td>
</tr>
</tbody>
</table>
### HIV-Associated Dementia (HAD)/Moderate-Severe Neurocognitive Disorder

**Clinical Features**
- Cognitive, motor, and behavioral problems
- Attention/concentration problems
- Slowed decision-making
- Abstraction/reasoning problems
- Visuospatial skill problems
- Memory/learning impairment
- Speech/language problems

**Patient Complaints, Symptoms**
- Memory problems/“I’m very forgetful”
- Distractibility/“I lose track of conversations”
- “I can’t keep up with work”
- Anger/irritability
- Fatigued/slow
- “I am depressed”/sadness
- Complains of poor balance, clumsiness

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### HIV-Associated Dementia (HAD)/Moderate to Severe Neurocognitive Disorder

**Overview**
- Prevalence pre ARV
  - Early studies estimated 15-20%
  - Current studies estimate 5-10% AIDS
- Prevalence post ARV
  - 50% reduction; not as prominent as other CNS OIs
  - CHARTER 2011 2% prevalence

**Possible Risk Factors**
- Older age, low CD4 count, high viral load, drug interactions, co-infections, gender, previous delirium
HIV-Associated Dementia (HAD)/Moderate to Severe Neurocognitive Disorder

Differential Diagnosis: Diagnosis by Exclusion
Treatment
Primary: Antiretroviral medications
Secondary: neuroprotective agents
(immunostimulants/inflammatory mediators)
Palliative:
- Neurotransmitter manipulation
- Non-pharmacological treatments
  - Environmental engineering
  - Education
  - Supportive Therapy

Neurocognitive Disorder Screeners

- HIV Dementia Scale (requires training)
- International HIV Dementia Scale (req training)
- Modified Dementia Scale (non-neurologists)
- Mental Alternation Test (early dementia)
- Memorial Sloan Kettering Scale (severity)
- Trail Making Tests Part A/B (requires neuropsychologist interpretation)
- Montreal Cognitive Assessment (MOCA) (earlier disease)
HIV Dementia Scale Screening Test

<table>
<thead>
<tr>
<th>Score</th>
<th>Memory-Registration</th>
<th>Give four words to recall (dog, hat, green, peach) - 1 second to say each. Then ask the patient all 4 after you have said them.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
<td><strong>Attention</strong> Anti-saccadic eye movements(^1): 20 (twenty) commands. ___ errors of 20 trials. (less than or equal to 3 errors = 4; 4 errors = 3; 5 errors = 2; 6 errors = 1; &gt; 6 errors = 0).</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td><strong>Psychomotor Speed</strong> Ask patient to write the alphabet in upper case letters horizontally across the page (use back of this form) and record time: ___ seconds. (less than or equal to 21 sec = 6; 21.1 - 24 sec = 5; 24.1 - 27 sec = 4; 27.1 - 30 sec = 3; 30.1 - 33 sec = 2; 33.1 - 36 sec = 1; &gt; 36 sec = 0).</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td><strong>Memory - Recall</strong> Ask for 4 words from Registration above. Give 1 point for each correct. For words not recalled, prompt with a &quot;semantic&quot; clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). Give 1/2 point for each correct after prompting.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td><strong>Construction</strong> Copy the cube; record time: ___ seconds. (&lt; 25 sec = 2; 25 - 35 sec = 1; &gt; 35 sec = 0).</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>(10 or less ~ HIV dementia)</td>
</tr>
</tbody>
</table>

\(^1\) Hold both hands up at patient's shoulder width and eye height, and ask patient to look at your nose. Move the index finger of one hand, and instruct patient to look at the finger that moves, then look back to your nose. Practice until patient is familiar with task. Then, instruct patient to look at the finger which is NOT moving. Practice until patient understands task. Perform 20 trials. An error is recorded when the patient looks towards the finger that is moving.
International HIV Dementia Scale  Saktor 2005

- Memory-Registration – Give four
  words to recall (dog, hat, bean, red) – 1 second to say each. Then
  ask the patient all four words after
  you have said them. Repeat
  words, if the patient does not
  recall them all immediately. Tell
  the patient you will ask for recall of
  the words again a bit later.

- 1. Motor Speed: Have the patient
  tap the first two fingers of the non-
  dominant hand as widely and as
  quickly as possible.
  - 4 = 15 in 5 seconds
  - 3 = 11-14 in 5 seconds
  - 2 = 7-10 in 5 seconds
  - 1 = 3-6 in 5 seconds
  - 0 = 0-2 in 5 seconds
  - maximum possible score is 12 points. A
    patient with a score of ≤ 10
    should be evaluated further for possible
    dementia.

- 2. Psychomotor Speed: Have the
  patient perform the following
  movements with the
  non-dominant hand as quickly as
  possible: 1) Clench hand in fist on flat
  surface. 2) Put hand flat on surface
  with palm down. 3) Put hand
  perpendicular to flat surface on
  the side of the 5th digit. Demonstrate
  and have patient perform twice for
  practice.
  - 4 = 4 sequences in 10 seconds
  - 3 = 3 sequences in 10 seconds
  - 2 = 2 sequences in 10 seconds
  - 1 = 1 sequence in 10 seconds
  - 0 = unable to perform

- 3. Memory-Recall: Ask the patient to recall
  the four words. For words not recalled,
  prompt with a semantic clue as follows:
  animal (dog); piece of clothing (hat);
  vegetable (bean); color (red). Give 1 point
  for each word spontaneously recalled. Give
  0.5 points for each correct answer after
  prompting
  - Maximum – 4 points.

Montreal

- Cognitive
- Assessment

- MOCA
  - 8 sections
  - Normal >-
    26/30

- Z. Nasreddine
Potential Neuropsychological Battery

**Information Processing Speed**
- Coding, Color-Word Interference (Color Naming and Word Reading)

**Executive Functioning**
- D-KEFS Trail Making, Color-Word Interference (Inhibition/ Switching)

**Verbal & Non-Verbal Memory**
- WRAML-2 specifically assesses 2 areas of memory — verbal and visual.

**Attention/Concentration**
- Digit Span Total, Color-Word Interference (Inhibition)

**Motor**
- Grooved pegboard

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Functional Status Assessment

- Self report
- MOS HIV Cognitive Functional Scale
- Cognitive Difficulties Scale
- Sickness Impact Profile
  - Objective report
- Direct Assessment of Functional Status
- UCSD Performance Based Skills Assessment
Screening for HIV Associated Neurocognitive Disorders – HAND:
MOS HIV Cognitive Functional Status Scale

1. Difficulty reasoning and solving problems?
2. Forget things that happened recently?
3. Trouble keeping your attention on any activity?
4. Difficulty doing activities involving concentration and thinking?

Validated against NP overall performance
Knippels et al., AIDS 2002

Mainstay of Treatment ARVs

Primary: Antiretroviral medications
Secondary: neuroprotective agents
(immunostimulants/
inflammatory mediators)

Palliative:
- Neurotransmitter manipulation
- Non-pharmacological treatments
  - Environmental engineering
  - Education
  - Supportive Therapy
NP Improvement with ARV

- Greater numbers of CSF-penetrating drugs showed greater reduction in CSF viral load
- CSF virological suppression demonstrated greater global deficit score (GDS) improvement
- NP improvement was greater in ART-naive versus treatment-experienced subjects.
- Including CSF-penetrating drugs in the ART regimen and monitoring CSF viral load
- If CD4 <200 CSF VL correlates with cognitive dysf
- CSF viral load is a research tool rather than routine standard of care

Letendre et al., Ann Neurol 2004

CNS penetration-effectiveness (CPE) Rank

CHARTER Study
(CNS HIV Antiretroviral Therapy Effects Research)

- 0 Low
- 0.5 Intermediate
- 1 High
  - Based on chemical properties (large molecular weight)
  - Concentrations in CSF (measurable animal/human)
  - Effectiveness in CNS in clinical studies

Letendre et al., 2008
Conceptualization of CNS Treatment Strategies

Antiretroviral medications with higher CPE
- stavudine (D4T)
- zidovudine (ZDV)
- abacavir (ABV)
- efavirenz (EFV)
- nevirapine (NVP)
- indinavir (IDV)
- lamivudine (3TC)

Subjects who had lower CNS Penetration-Effectiveness (CPE) ranks were more likely to have detectable cerebrospinal fluid (CSF) viral load when CPE rank was analyzed as a continuous variable (A) or as a categorical variable (B)
CNS penetration–effectiveness (CPE) score to estimating HAART ability to improve cognition

<table>
<thead>
<tr>
<th>CPE scores</th>
<th>Zidovudine, abacavir, delavirdine, nevirapine, amprenavir-ritonavir, fosamprenavir-ritonavir, atazanavir-ritonavir, indinavir-ritonavir, lopinavir-ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 high</td>
<td>Stavudine, lamivudine, emtricitabine, efavirenz, amprenavir, fosamprenavir, atazanavir, indinavir</td>
</tr>
<tr>
<td>0.5 intermediate</td>
<td>Remaining antiretrovirals</td>
</tr>
<tr>
<td>0 low</td>
<td>Remaining antiretrovirals</td>
</tr>
</tbody>
</table>

n = 92 at risk for, and n = 93 with HIV-associated neurocognitive disorders underwent neuropsychological (NP) testing before HAART initiation and at follow-up

- Higher CPE scores correlated with greater improvements in NP testing
- The correlation was stronger among NP-impaired patients.
- No association was seen between CD4 and plasma viral load changes with both scores.


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How important is CPE?

- In theory, this is an important issue since the use of “neuroactive” HAART regimens appears promising
- Lack of standardized CPE ratings and specific clinical guidelines for antiretroviral medications
- At this time, the selection of antiretroviral regimens must be based on
  - sensitivity/resistance patterns
  - Adherence issues
  - quality of life considerations
Adjunctive strategies

Current research has focused on:
- Interfering with the inflammatory cascade
- Reducing viral replication
- Reducing neurotoxin release
- Reducing oxidative stress, and apoptotic effects
- Providing neuroprotection

Conclusion

- HIV Neuropsychiatric Manifestations
  - Disease of the immune system and CNS
- HIV Assoc Neurocognitive Disorders (HAND) and new terms ANI, Mild-severe ND
- Increasingly prevalent with advancing age
- Primary focus of treatment is ARVs
  - Neuroactive HAART regimens
  - ARV Adherence is critical
  - Symptomatic improvement is secondary
Subscribe to HIV Guidelines????

- To get new and regular updates of guidelines, go to:
  - www.hivguidelines.org
    - Click the subscribe to hivguidelines.org tab in top right corner and follow instructions

To schedule a Psychiatric Consultation please contact James Satriano, PhD, at
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OR 212/543-5591

To schedule a Training Activity, please contact Veronica Pinho at
VAP2112@COLUMBIA.EDU
OR 212/543-6028

OR visit us on the web at:
http://www.columbia.edu/cu/hivmentalhealthtraining
TOPICS

1. DIAGNOSTIC ASSESSMENT AND TREATMENT RECOMMENDATIONS
2. MEDICATION EVALUATION
3. OTHER CLINICAL/PSYCHIATRIC ASPECTS OF PRIMARY CARE
4. LEGAL/ETHICAL ISSUES
5. CARE OF THE TRIPLY DIAGNOSED
6. CROSS-CULTURAL PROFICIENCY IN PSYCHIATRIC DIAGNOSIS AND TREATMENT
7. MOTIVATIONAL INTERVIEWING IN PRIMARY CARE SETTINGS
8. COGNITIVE-BEHAVIORAL THERAPIES IN PRIMARY CARE SETTINGS
9. NEUROPSYCHIATRIC ASPECTS OF HIV INFECTION
10. HIV TESTING FOR PEOPLE WITH MENTAL ILLNESS