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Neuropsychological Aspects of HIV Infection

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Overview

- HIV and AIDS
  » Basic Definitions
  » Epidemiology

- HIV-associated Neurocognitive Impairment
  » Diagnosis, Epidemiology and Profile
  » Neurobiology/Biomarkers
  » Comorbidities
  » Functional Consequences
  » Treatments

HIV/AIDS: Basic Definitions

- HIV = Human Immunodeficiency Virus
  » Retrovirus that destroys white blood cells (i.e., CD4 cells)

- AIDS = Acquired Immune Deficiency Syndrome
  » Decline in CD4 cell count (<200) and/or opportunistic infection

- Viral loads = HIV RNA
  » Measure of viral replication in plasma and/or cerebrospinal fluid

- ARV = antiretroviral
  » A medication that is designed to treat a retrovirus

- HAART = Highly Active Antiretroviral Therapy
  » A combination of multiple drugs that work via different mechanisms
  • Now referred to as combination antiretroviral therapy (CART)
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Course of HV Infection and Disease

Fauci et al., 1996

HIV: History

- 1981: Clinical syndrome described in CDC report
- 1983: First cases of AIDS-related dementia reported
- 1984: HIV identified as the agent
- 1987: First antiretroviral drug (zidovudine - AZT) approved by the FDA
- 1987: First published report of subtle neurocognitive deficits in HIV (Grant et al.)
- 1996: HAART introduced


Adults Living with AIDS in the US

HIV Surveillance Report (2016), CDC
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http://www.who.int/gho/hiv/en/

Rates of Adults and Adolescents Living with Diagnosed HIV (2011)
N = 896,652; Total Rate (per 100,000 population) = 342.1

Adults/Adolescents Living with Diagnosed HIV Infection by Race/Ethnicity (2015—United States)
Note: Data include persons (adults and adolescents) with a diagnosis of HIV infection
+Heterosexual contact with a person known to have, or to be at high risk for, HIV infection.
+Includes hemophilia, blood transfusion, perinatal exposure, and risk factor not reported or not identified.

Diagnoses of HIV Infection by Sex/Transmission Category (2012)

HIV/AIDS Today

- The development of HAART for HIV infection is one of modern medicine’s most dramatic success stories.
- HIV/AIDS continues to be prevalent and has been transformed into a chronic disease.
- Ethnic/racial minorities are disproportionally affected by HIV/AIDS.

HIV-Associated Neurocognitive Impairment

Focus on Brain Health

- Many changes with HIV
  - Physical
  - Social
  - Emotional
  - Neurocognitive

HIV-Associated Neurocognitive Disorders (HAND) Criteria

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

- NCI must be attributed to HIV (at least in part)
- Neurocognitive impairment required in 2 domains in at least 2 tests (DSM-V criteria for neurocognitive disorders - 1 domain required)
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Pattern of HIV-Associated NCI

- NCI is observed in approximately half of HIV+ persons


** p<.05; *** p<.01; **** p<.001

Marquine et al (2018)

NCI by Hispanic Subgroup

Non-White (p<.01)
Hispanic (p<.001)

Marquine et al (2018)
Logistic regression on global NCI showed:
• Significant main effects of Hispanic ethnicity (OR = 2.31, p < .001) and NY site (OR = 2.83, p < .001), and no significant interaction (p = .35).

With the advent of cART HIV+ individuals are living longer.
• Older adults with HIV are at an increased risk for NCI.
  • Additive or synergistic?
  • Predictors of neurocognitive decline: non-HIV comorbidity, being off ART, lifetime methamphetamine use diagnosis, Hispanic ethnicity.
  • Predictors of neurocognitive improvement: No lifetime Major Depressive Disorder, higher premorbid cognitive functioning.

Marquine et al. 2018.

Heaton et al. 2014. CID.
In a model adjusting for characteristics that differed significantly between groups:

Hispanic - NH White: OR = 2.8, CI = 1.4-5.6, p < .001
Hispanic - NH Black: OR = 3.2, CI = 1.6-6.3, p < .001

Baseline Predictors of Subsequent Neurocognitive Decline by Ethnic/Racial Group

<table>
<thead>
<tr>
<th></th>
<th>NH White (n=185)</th>
<th>NH Black (n=184)</th>
<th>Hispanic (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid status</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Current Major Depression</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detectable plasma RNA</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Baseline Neurocognitive Impairment</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

"Frontal Systems Behaviors" in HIV infection

- Data from early as well as chronically infected cohorts suggest that apathy and other "frontal" behaviors increase following HIV infection.

Prevalence rate of apathy is 30–50% in chronically infected HIV cohorts

Karnat et al., (2016). Cognitive and Behavioral Neurology

HAND Diagnosis, Epidemiology, and Profile

- Milder forms of HAND continue to be common.
- Neuropsychological profile: Problems with learning/ memory, executive dysfunction and attention/working memory.
- Other neurobehavioral problems are also common (e.g. apathy).
Neurobiology

- HIV infiltrates the CNS early in the course of infection (Davis et al., 1992; Gonzalez-Scarano & Martin-Garcia, 2005)
- HIV does not directly infect neurons, but unleashes an excitotoxic cascade that can greatly affect neurons and neurobehavioral functioning

The Neuropathogenesis of HIV/AIDS

Regionality of HIV Neuropathologies

- HIV neuropathologies occur throughout the brain parenchyma, especially in frontostriatal circuits
Blood and CSF Biomarkers

- **CD4 count**
  - Clinical marker of immune competence, but generally poor indicator of CNS status
  - Nadir (i.e., lowest) CD4 count is a better marker of CNS functioning
  - Perhaps reflecting the vulnerability of the CNS
- **HIV viral load**
  - Plasma viral load does not accurately reflect current CNS status
  - CSF viral load provides a clearer window on the CNS (viral compartmentalization)
  - Composite of biomarkers is likely to better capture complexity of CNS effects of HIV, especially as HIV+ persons reach older age.

The Veterans Aging Cohort Study (VACS) Index and NCI

The VACS Index combines:
- Age
- Traditional HIV biomarkers (current CD4 count and HIV-1 plasma RNA)
- Non-HIV biomarkers (renal and liver function, anemia and hepatitis C)

The VACS Index combines:

Changes in VACS Index and Neurocognitive T Scores Over Time

VACS Index and NCI by Ethnic/Racial Group
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Psychiatric Comorbidities and HAND

- **Depression**
  - Major depression is among the most common comorbid psychiatric disorders in HIV (~50% lifetime prevalence rate)
  - Associated with increased cognitive complaints and IADL declines
  - Does not confer additive risk of HAND

- **Substance Use Disorders**
  - Risk factor for acquiring HIV infection and use is common among the infected.
  - Impact on CNS varies by type of substances, duration and patterns/severity of use.

Functional Impact

- Approximately 50% of HIV-infected persons with cognitive impairment experience daily functioning problems.
- Deficits range in severity and cover a variety of domains: driving problems, medication nonadherence, unemployment, activities of daily living.

Activities of Daily Living by Neurocognitive Status

- % Failed
- Money Management, Household Finances, Shopping, Cooking, Restaurant, Medication Management, Work

Treatment of HAND

- HAART
  - Initiation of HAART (esp. in treatment naïve patients) improves HAND
  - Cross-sectional findings are mixed and are complicated by Rx practices
- Non-HAART medications:
  - Psychostimulants (e.g., methylphenidate); NMDA agonists (e.g., memantine); Mood stabilizers (e.g., lithium); Antidepressants (e.g., SSRIs)
- Cognitive Rehabilitation/Behavioral Interventions

Letendre et al. (2004); Hinkin et al. (2001); Schiffel et al. (2007); Schiffel et al (2009)

Pre-exposure Prophylaxis (PrEP)

- Medication to prevent HIV (Truvada) in persons at increased risk of infection
- Risk of getting HIV infection up to 92% lower for those who took the medicines consistently than for those who didn’t.
- Guidelines on PrEP Use

Exercise and NCI in HIV

<table>
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<tr>
<th></th>
<th>Exercisers (n=83)</th>
<th>Non-Exercisers (n=252)</th>
</tr>
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<tbody>
<tr>
<td>% with NCI</td>
<td>15.66</td>
<td>30.95</td>
</tr>
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Dufour et al., JNV, 2013

Personalized Texting for Adherence

CONVERSATION: Reminder, Didn’t

Message: Edit

[Example: 8:00 AM: Smith, ur health is key, remember to take ur pill.
Response: As usual]

[Example: 8:10 AM: B]

[Example: 8:16 AM: Was there a reminder for ur small white pill in your phone? (Yes/No)]

[Example: 8:17 AM: A]

[Example: 8:17 AM: Thanks for responding. Ur current small white pill adherence is 100%. Add 1 more.]
Summary/Conclusions

- Milder forms of HAND continue to be common and impactful.
- Neuropsychological profile: Problems with learning/memory, executive dysfunction and attention/working memory.
- Other neurobehavioral problems are also common (e.g. apathy).
- Underlying mechanisms of HAND are yet to be understood.
- Nadir CD4 best predictor of HAND, yet composite of biomarkers is likely to better capture complexity of CNS effects of HIV.
- Important to consider comorbidities in diagnosis and tx of HAND.

Thank you!

Questions?

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Opportunistic Infections

- Candidiasis of bronchi, trachea, esophagus, or lungs
- Invasive cervical cancer
- Coccidioidomycosis
- Cryptococcosis
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (particularly CMV retinitis)
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, multiple forms
- Mycobacterium avium complex
- Pneumocystis carinii pneumonia
- Pneumococcal pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella enteritidis, recurrent
- Tuberculosis
- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella enteritidis, recurrent
- Tuberculosis

Extra slides
**Common CNS Opportunistic Infections**

<table>
<thead>
<tr>
<th>Region</th>
<th>Infections</th>
</tr>
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<tbody>
<tr>
<td>Europe and North America</td>
<td>PML, toxoplasmic encephalitis, cryptococcal meningitis</td>
</tr>
<tr>
<td>South America</td>
<td>Cerebral toxoplasmosis, tuberculosis meningitis, cryptococcal meningitis, Chagas disease</td>
</tr>
<tr>
<td>Asian and Pacific Regions</td>
<td>Cryptococcal meningitis, cerebral toxoplasmosis, tuberculosis meningitis, Japanese encephalitis B</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>Tuberculosis meningitis, cryptococcal meningitis, cytomegalovirus, malaria</td>
</tr>
</tbody>
</table>

PML = Progressive multifocal encephalitis