#CHAIR2019

11TH ANNUAL

CHAIR SUMMIT

CME Outfitters

Master Class for Neuroscience Professional Development

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HIV-Associated Neurocognitive Disorders

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Learning Objective 1

Describe the epidemiology and pathogenesis of HIV-associated neurocognitive disorders (HAND).

Learning Objective 2

Recognize the clinical manifestations and the use of biomarkers in the diagnosis of HAND.

Learning Objective 3

Evaluate the recent advances in the management of HAND.

HIV Neurobehavioral Disturbances

HIV-associated Neurocognitive Disorders (HAND)

Primary HAND

- Asymptomatic neurocognitive impairment
- Mild neurocognitive disorder
- HIV-associated dementia

Secondary HAND

- Infection
- Neoplasia
- Cerebrovascular
- Nutritional
- Treatment related

Emotional & Other Behavioral

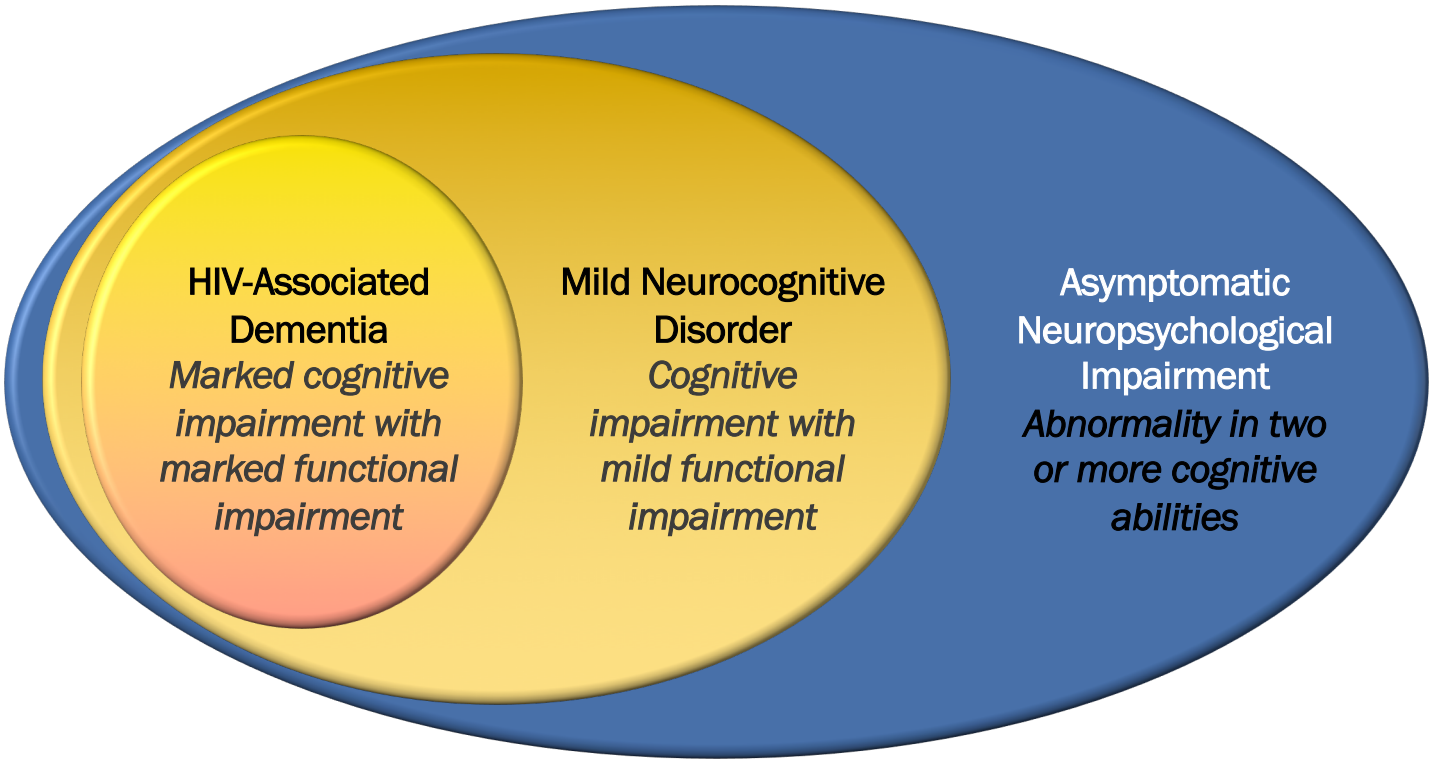
New Onset

- Depression
- Anxiety
- Adjustment disorders
- HIV mania
- HIV psychosis

Pre-existing / recurrent / comorbid

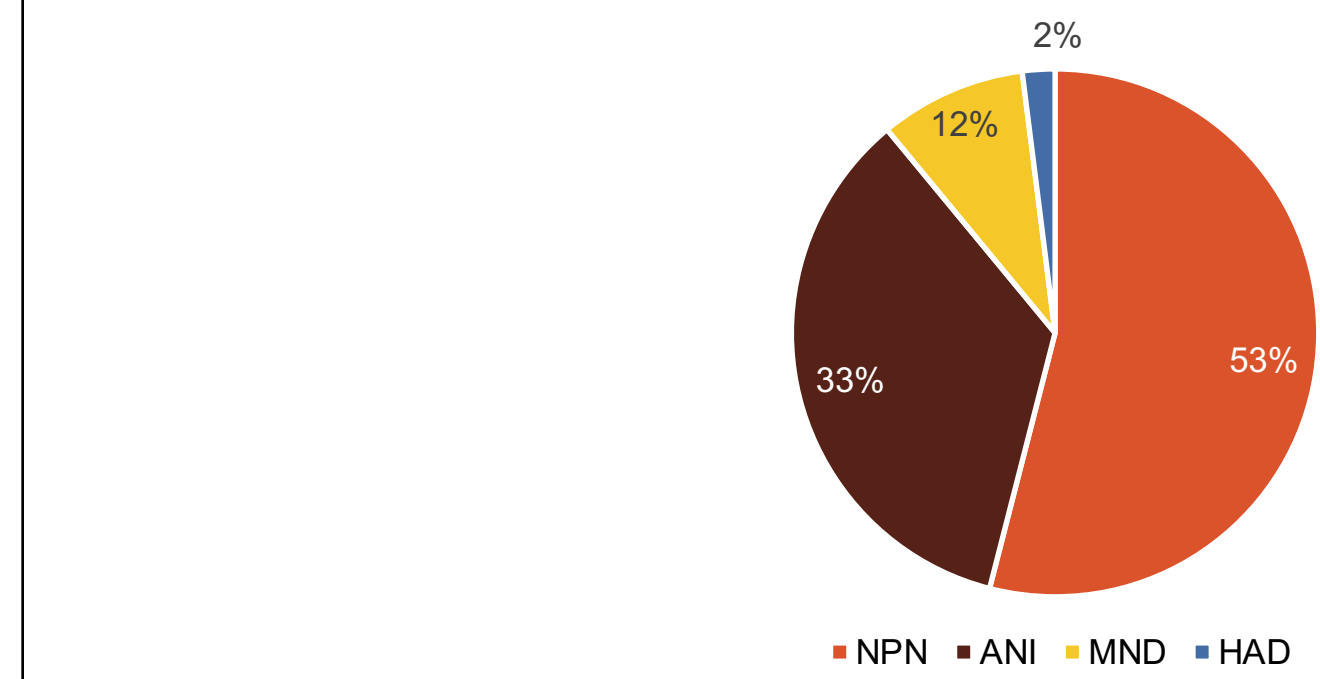
- Mood disorders
- Substance use disorders
- Other mental disorders

HAND: Frascati Criteria



Antinori A, et al. *Neurology*. 2007;69(18):1789-1799.

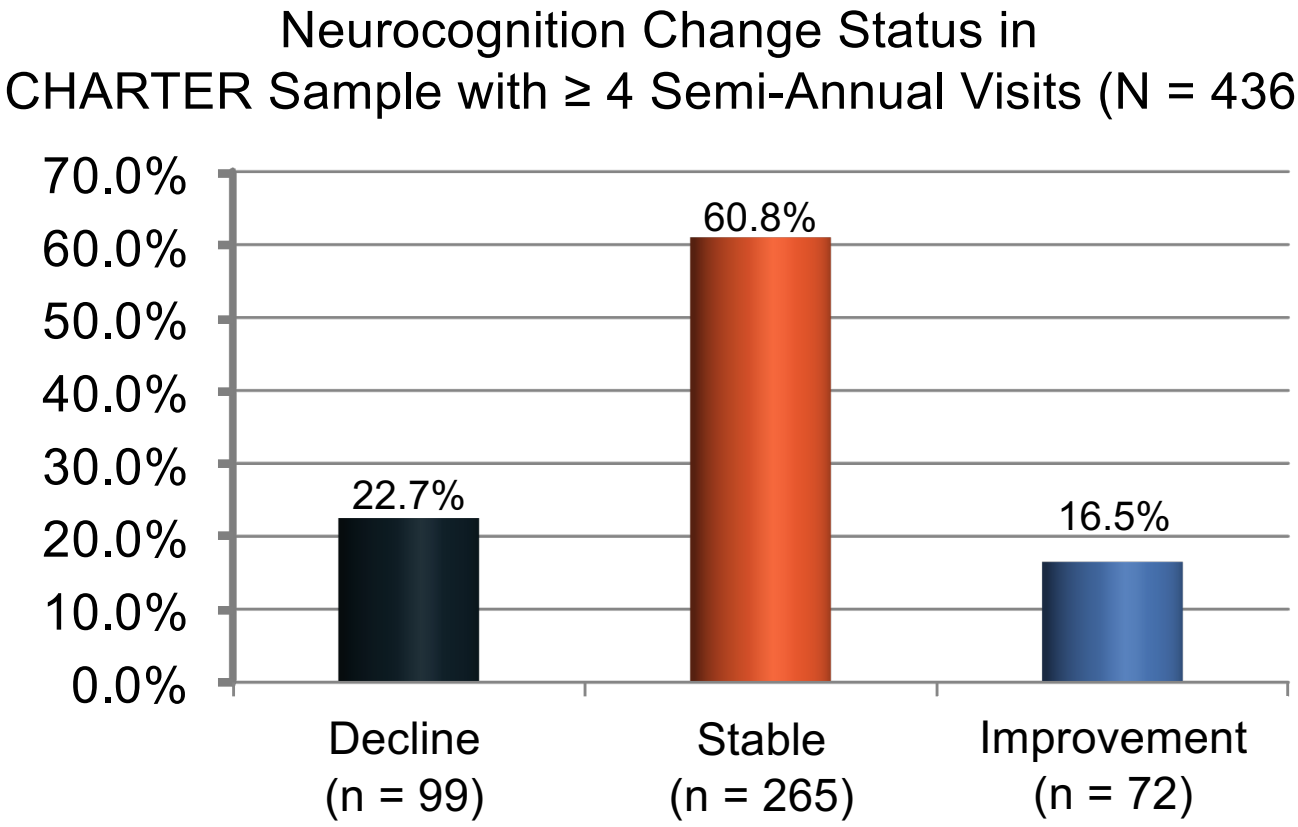
Prevalence of Specific HAND Diagnoses in CHARTER (N = 1,555 HIV+)



ANI = asymptomatic neurocognitive impairment; HAD = HIV-associated dementia; MND = mild neurocognitive disorder; NPN = neurocognitive normal.

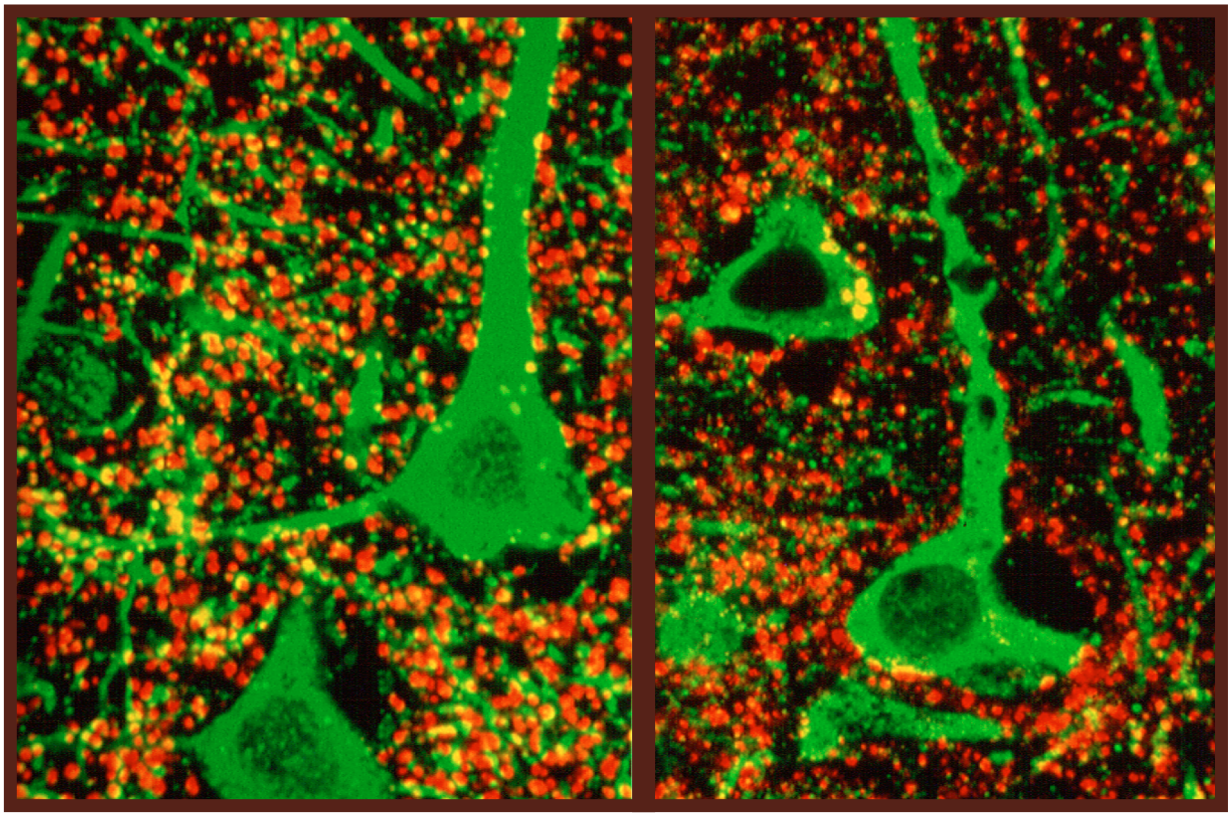
Heaton RK, et al. *Neurology*. 2010;75(23):2087-2096.

How Does Neurocognition Change Over Time?



Heaton RK, et al. *Clin Infect Dis*. 2015;60:473-480.

Loss of Synapses and Dendrites in HIV+



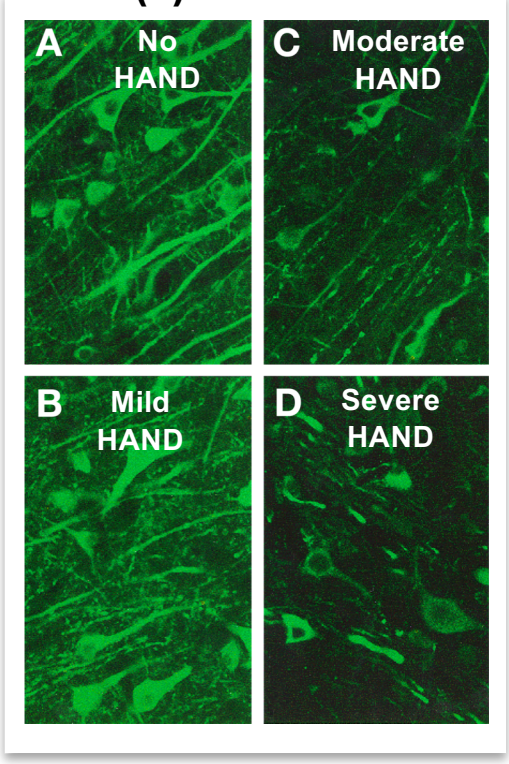
HIV-

HIV+

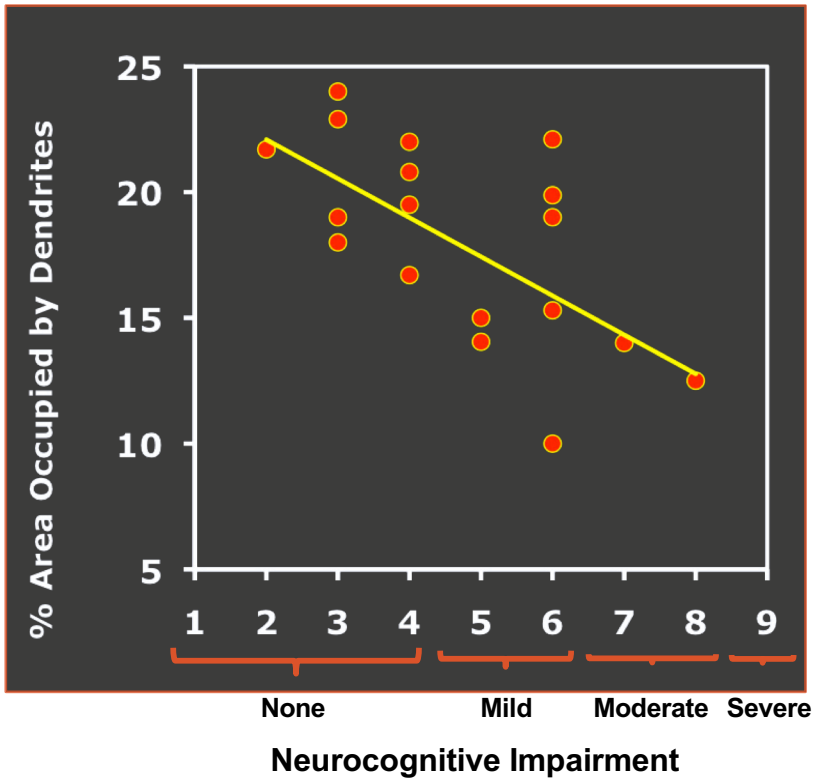
Courtesy Eliezer Masliah. UCSD HNRP.

Injury to Synapses and Dendrites May Form a Basis of HIV Neurocognitive Impairment

Progressive Dendritic Loss from No HAND (A) to Severe HAND (D)



Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



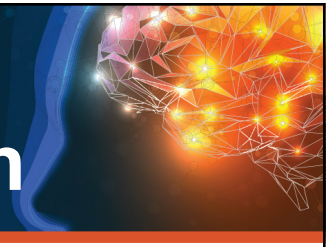
Masliah E,, et al. *Ann Neurol.*1997;42(6):963-972.

Biomarkers of HAND

- Cerebral spinal fluid (CSF) viral load
- Monocyte biomarkers
  - CD16+
  - CD163
  - sCD14
- Tat
- CCR5
- HIV RNA expression in CSF
- CSF neurofilament light chain

Carroll A, Brew B. *F1000Res.* 2017;6:312.

Does HAND Matter?
Yes, It Affects Everyday Function and Health

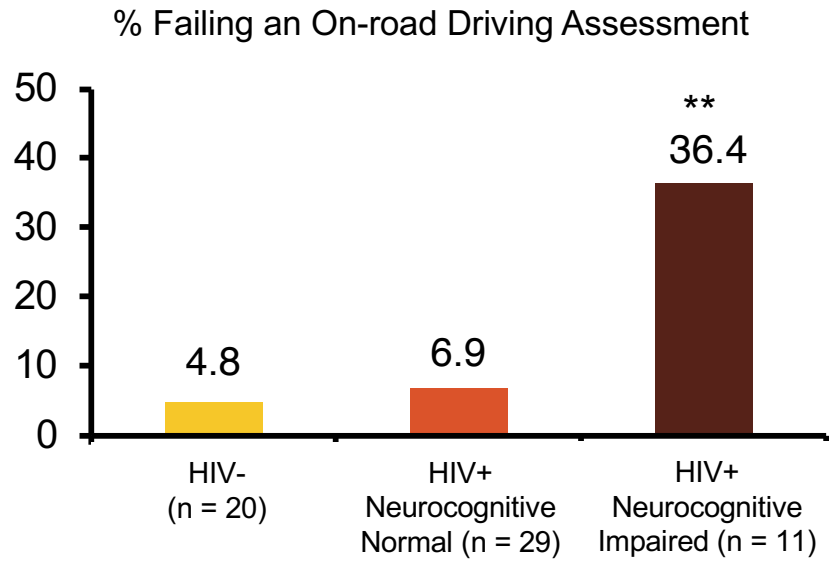


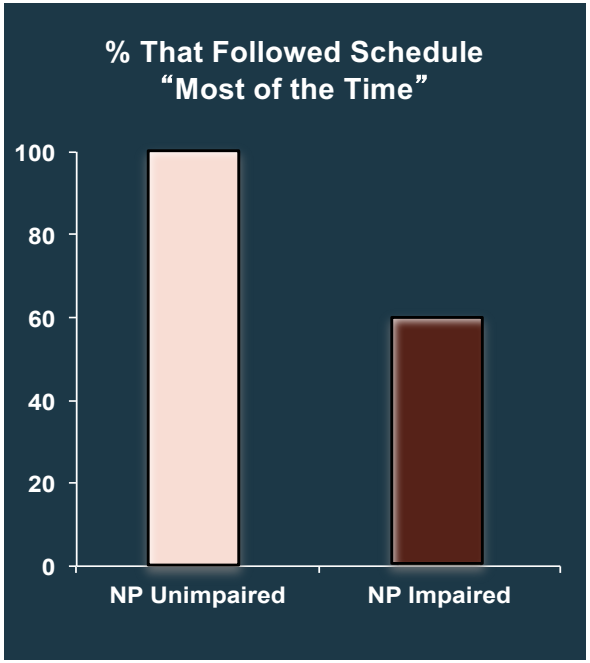
- Worse work-related function
- Twice as likely to be unemployed
- May impair driving
- Worse medication adherence
- ? May be associated with impaired risk assessment and/or impulsivity: more risk behavior
- ? May benefit less from interventions to reduce risk
- Independently predicts earlier mortality

Heaton RK, et al. *Psychosom Med*. 1994;56:8-17.

Neurocognitive Impairment Matters

It can lead to problems in everyday functioning such as work inefficiency, driving impairment, and worse adherence to treatment





HNRC Data

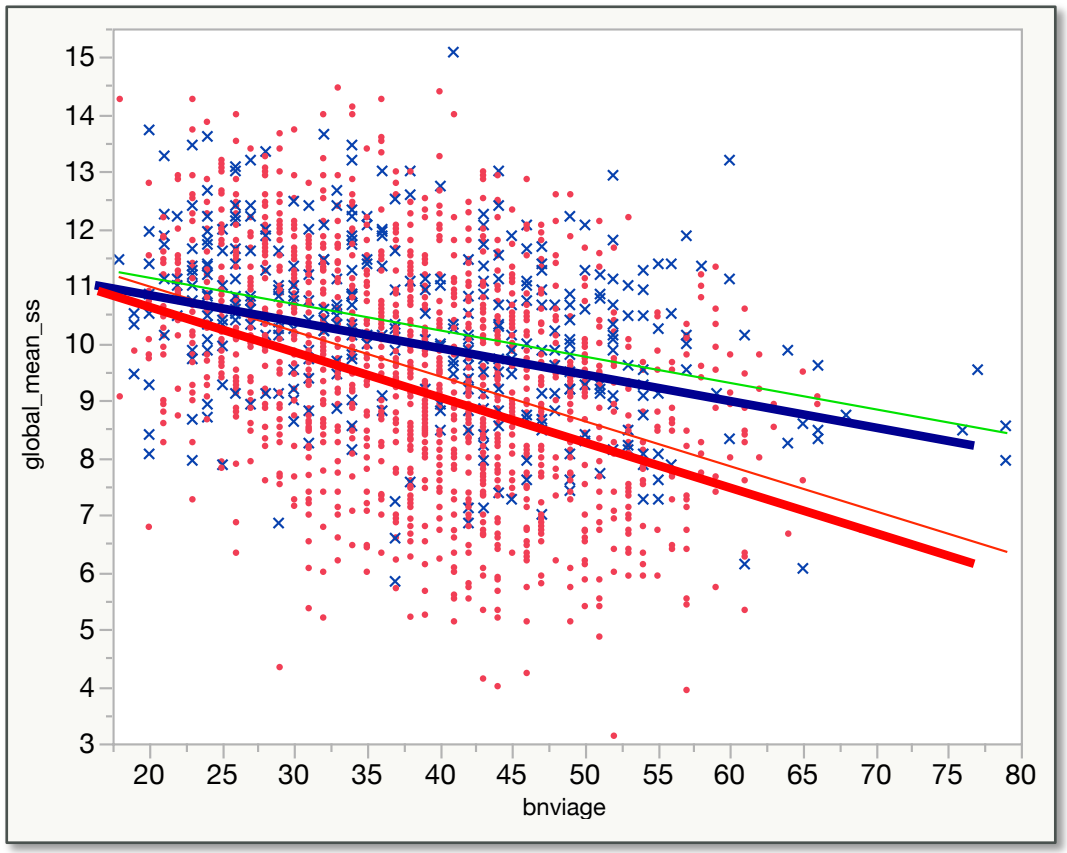
NP = neuropsychological.

Marcotte TD, et al. *Neurology.* 2004;63(8):1417-1422.

Persistence of Neurocognitive Complications May Be Driven Partly by Comorbid Factors

- Aging
- Metabolic syndrome
- Drug and alcohol abuse
- Coinfections (e.g., hepatitis C, cytomegalovirus, toxoplasma, tuberculosis)
- Neurotoxicity of treatments
- History of neurologic insults (e.g., head injury that may increase vulnerability to neuroAIDS)

Neurocognitive Performance Declines Faster with Age in HIV+ Compared to HIV-

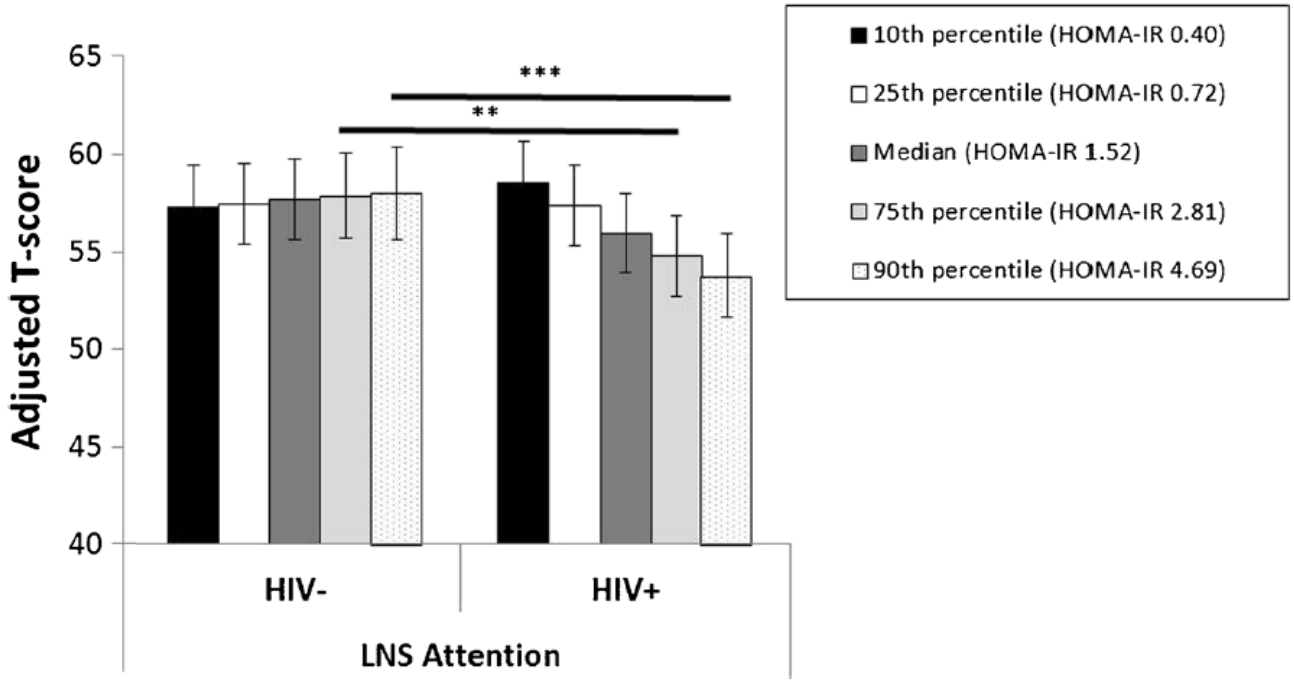


HIV-
HIV+

Age Effect: $p < .0001$
HIV Effect: $p < .0001$
Interaction: $p < .0001$

Data from UCSD HIV Neurobehavioral Research Program.

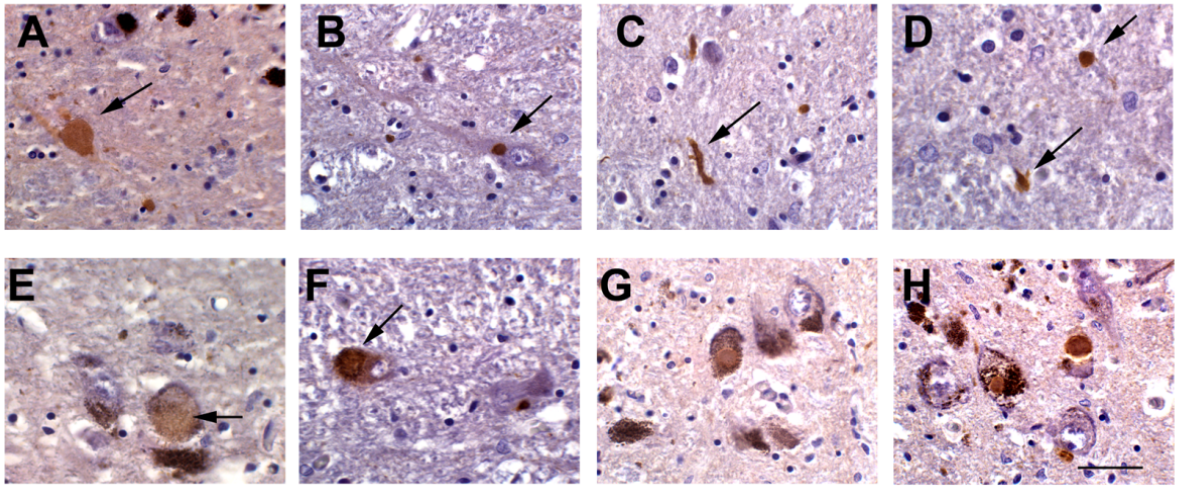
Example of HIV and Medical Morbidity Interaction on Cognitive Performance: Attentional Function Worsens with Greater Insulin Resistance in HIV+ but Not HIV-



The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function.
LNS = letter-number sequencing.
Valcour V. *J Neurovirol*. 2015;21:415-421.

Increased Neuritic α-Synuclein Expression in the Brains of Patients Age 55-65; Accelerated Age-Related "Protein Mismanagement" in the Brains of Patients Who Are HIV+?

- Neuritic α-synuclein expression (arrows) was found in 16% of the substantia nigra studied (12/73)



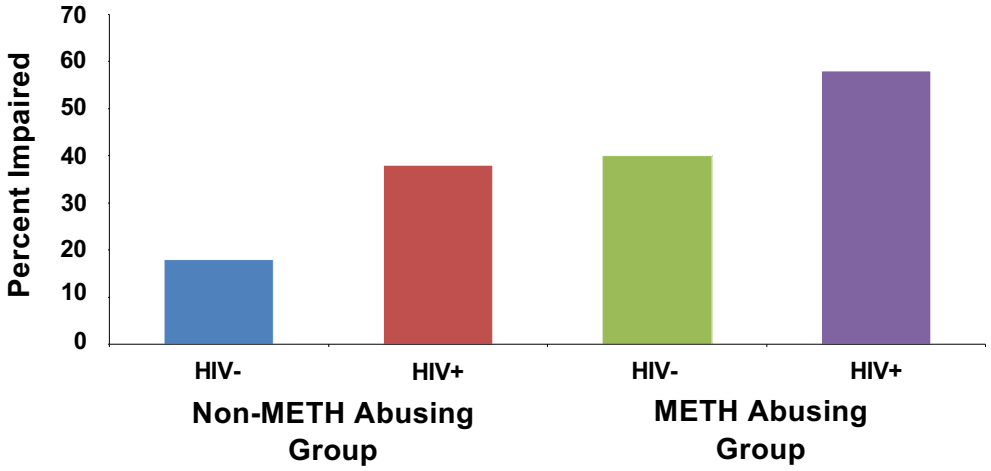
Khanlou N, et al. *J Neurovirol*. 2009;15(2):131-138.

Do Drugs of Abuse Cause Brain Damage? Do These Drugs Potentiate NeuroAIDS?

Drug	Evidence for Brain Damage? Neurocognitive Impairment (NCI)?	HIV X Drug?
Alcohol	Well documented in long-term alcoholics	Maybe
Methamphetamine	Well documented in extensive users	Yes
Cocaine	Data are mixed	Uncertain
Heroin/opioids	Contradictory findings; no systematic evidence for neurocognitive impairment	Unknown
Sedative/hypnotics	NCI in chronic heavy users	Unknown
Hallucinogens	Data too fragmentary	Unknown
Cannabis	Mixed neuroimaging findings; meta-analyses report weak to null NCI in those who are not using at time of testing	No effect or possibly protective?

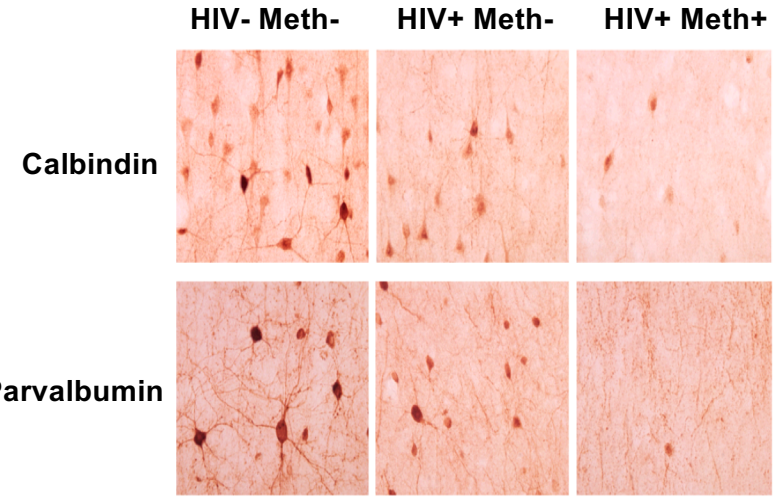
Rosenblom MJ, et al. *Alcohol Res Health*. 2010;33(3):247-257; Chana G, et al. *Neurology*. 2006;67(8); Martin-Thormeyer EM, Paul RH. *Neuropsychol Rev*. 2009;19(2):215-231; Meyer VJ, et al. *J Acquir Immune Defic Syndr*. 2013;63(1):67-76; Grant I, et al. *J Int Neuropsychol Soc*. 2003;9(5):679-689; Chang l, et al. *J Neuroimmune Pharmacol*. 2006;1(1):65-76.

HIV and METH Enhance Each Other's Neurotoxicity



Increased rates of neurocognitive impairment in HIV+ METH+

Marked reduction in interneurons in HIVE+ METH+



Rippeth JD, et al. *J Int Neuropsychol Soc*. 2004;10:1-14; Chana G, et al. *Neurology*. 2006;67(8).

Have Modern ARV Regimens Affected HAND?

- Yes: CNS opportunistic disease markedly reduced (e.g., toxoplasmosis, progressive multifocal leukoencephalopathy)
- Yes: Severe dementia has dropped from estimated 15% pre combination ART to < 5% now
- BUT: Moderate and mild forms of neurocognitive impairment remain prevalent

Heaton RK, et al. *Neurology*. 2010;75(23):2087-2096.

Pharmacological Management: Are We There Yet?

Trials of various antioxidants, anti-inflammatory drugs, etc, have been largely negative.

Drug	Report	Finding
Selegiline	Schifitto, et al. 2007	+/-
Thioctic Acid	Dana Consortium. 1998	No effect
Peptide T	Heseltine. *Arch Neurol*. 1998	-/+
Lithium	Letendre. *AIDS*. 2006	+
Memantine	Schifitto. *AIDS*. 2007	No effect
Minocycline	Nakasujja. *Neurology*. 2013	No effect
Rivastigmine	Simioni. *Neurology*. 2013	No effect

Emerging Therapies:

Nitromemantine (N-methyl-D-aspartate–type glutamate receptor antagonist)

Sunitinib (CDK5 inhibitor)

Schifitto G, et al. *Neurology*. 2007;69(13):1314-1321; Dana Consortium. *Neurology*. 1998;50(3):645-651; Heseltine PN, et al. *Arch Neurol*. 1998;55(1):41-51; Letendre SL, et al. *AIDS*. 2006;20(14):1885-1888; Schifitto G, et al. *AIDS*. 2007;21(14):1877-1886; Nakasujja N, et al. *Neurology*. 2013;80(2):196-202; Simioni S, et al. *Neurology*. 2013;80(6):553-560.

Non-Pharmacological Management of HAND

- Behavioral techniques
  - Cognitive retraining
  - Exercise-based interventions

Summary

- HAND persists despite combination antiretroviral therapy (CART)
- HAND causes a decline in everyday function and health
- Synaptodendritic injury is one of the substrates of HAND
- Comorbidities may increase the risk of HAND and its progression
- No currently approved neurotherapeutics; non-pharmacologic strategies may have promise

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Accurately diagnose patients with HAND
- Stay up-to-date with emerging therapies for the treatment of HAND

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- …Neurological Disorders and Stroke
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Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.