

HIV Associated Neurocognitive Disorders in the era of modern CART

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Points to be covered

- HIV associated neurocognitive disorder (HAND) is common in HIV
- HAND persists even where combination antiretroviral therapy (CART) is available
- Significance of HAND: biological and functional correlates
- Cofactors (comorbidities) increase likelihood of HAND, and may influence progression
- Virologic control in CNS helps ameliorate HAND, but may not be fully effective in many cases
- ARV with higher CNS penetration-effectiveness (CPE) have some value, but must be balanced vs neurotoxicity
- Non pharmacologic (eg., cognitive rehabilitation) strategies may have promise

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

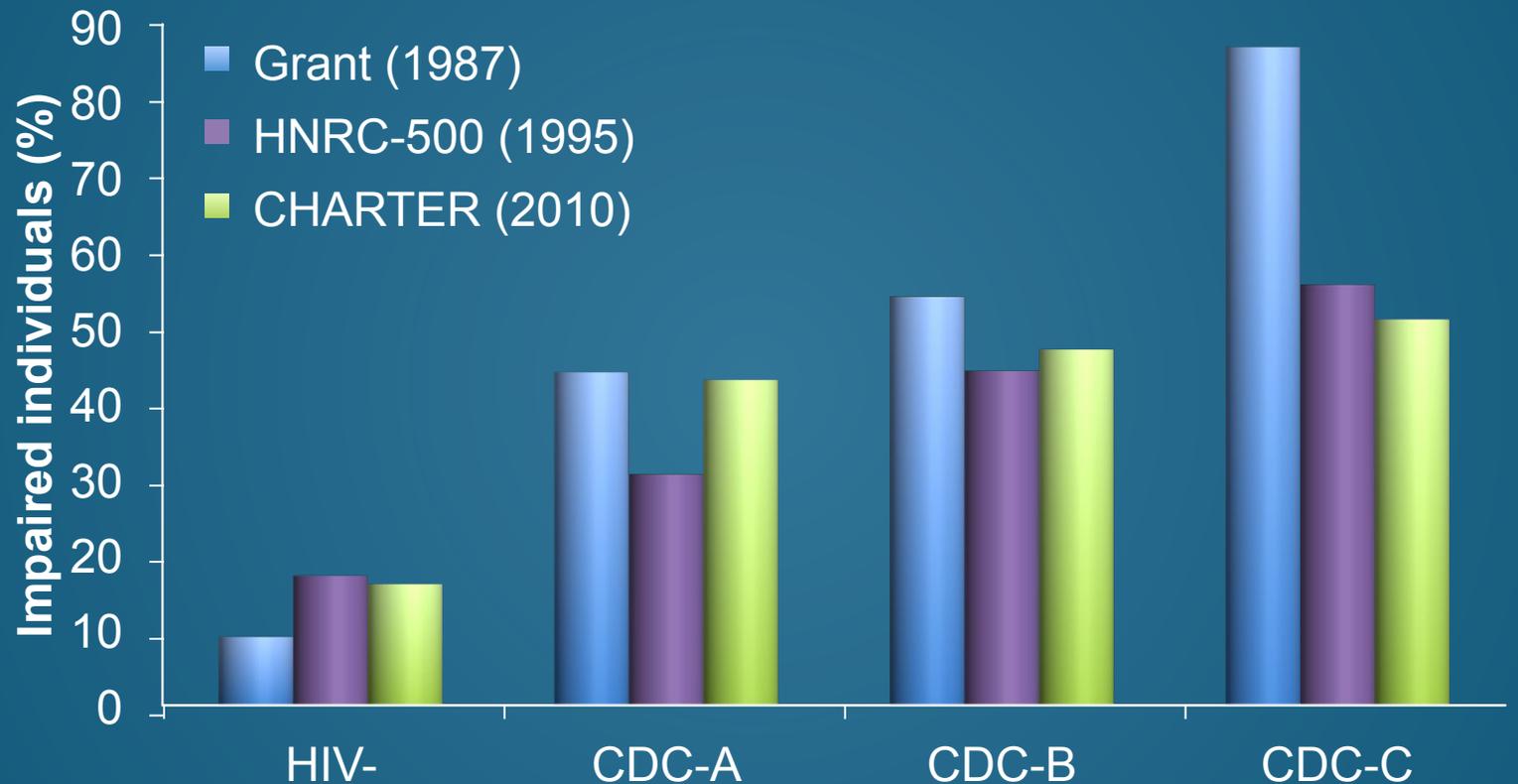
New Onset

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

Pre-exist / recurrent / comorbid

- Mood disorders
- Substance use disorders
- Other mental disorders

Despite ARV benefits on morbidity and mortality HAND remains prevalent



ARV, antiretroviral; CDC, Centers for Disease Control; HAND, HIV-associated neurocognitive disorders

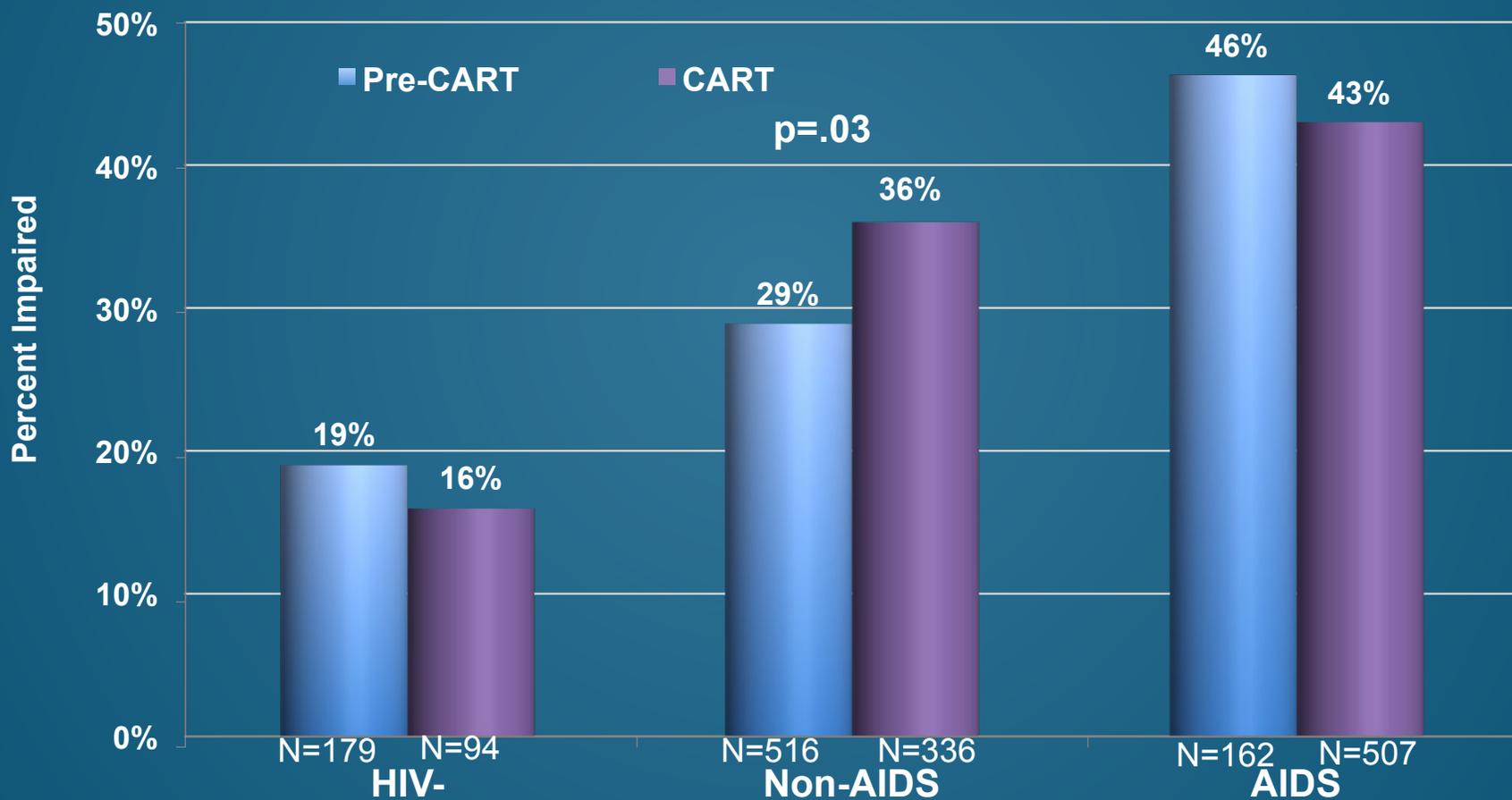
Grant I, et al., *Ann Intern Med* 1987;107:828-36.

Heaton RK., et al. *J Int Neuropsychol Soc* 1995;1:231-51.

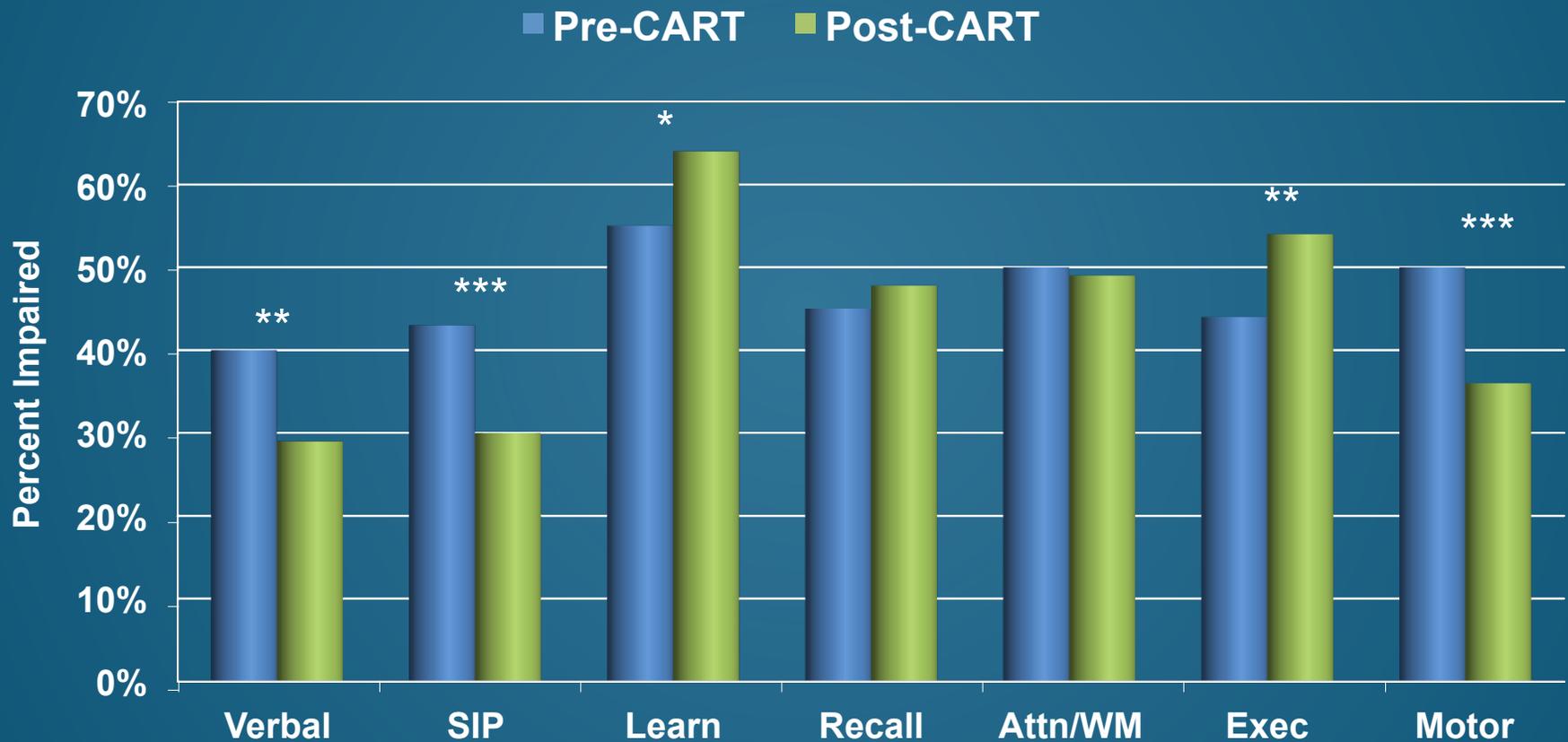
Heaton RK, et al., *Neurology* 2010;75:2087-2096.

Prevalence of HAND in nonAIDS HIV+ has increased as people remain medically asymptomatic longer

Heaton, et al, (2011) *Journal of Neurovirology*, 17(1), 3-16.



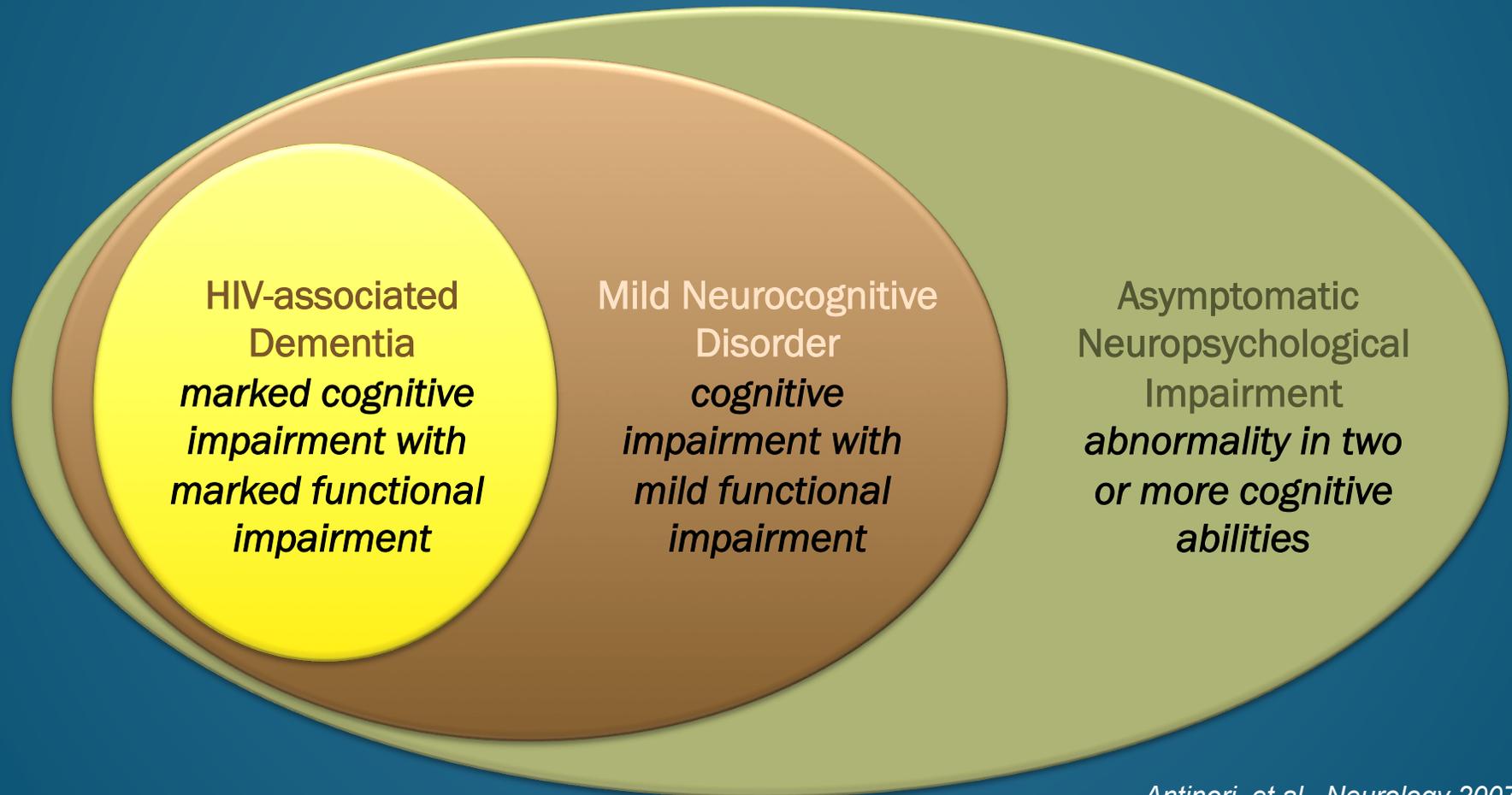
NC Impairment by Domain in HIV+ Samples from Pre-CART and Post-CART Eras (NCI only)



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

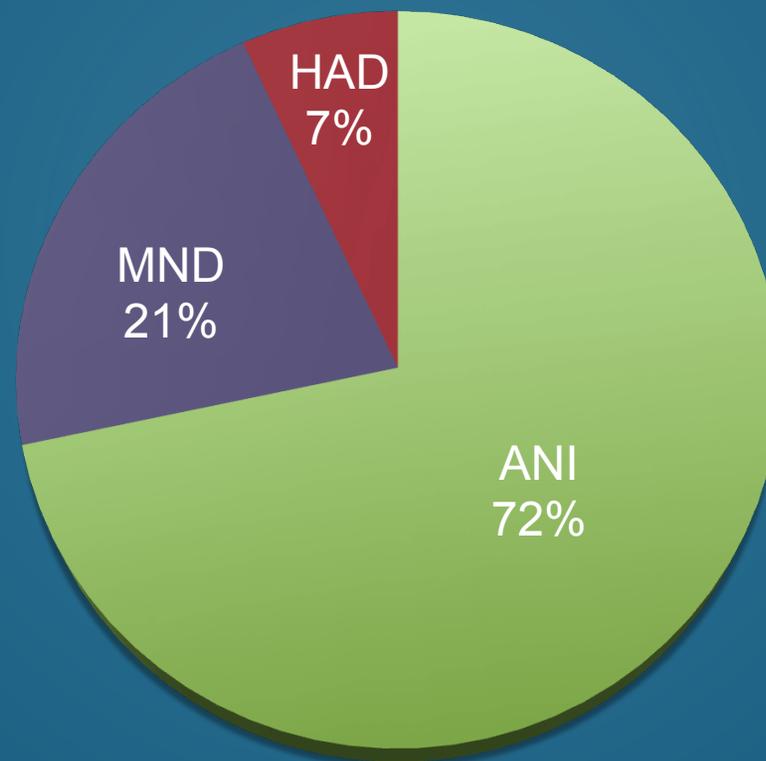
Heaton, et al, (2011) *Journal of Neurovirology*, 17(1), 3-16.

HIV Associated Neurocognitive Disorders (HAND): Frascati Criteria



Antinori, et al., Neurology 2007

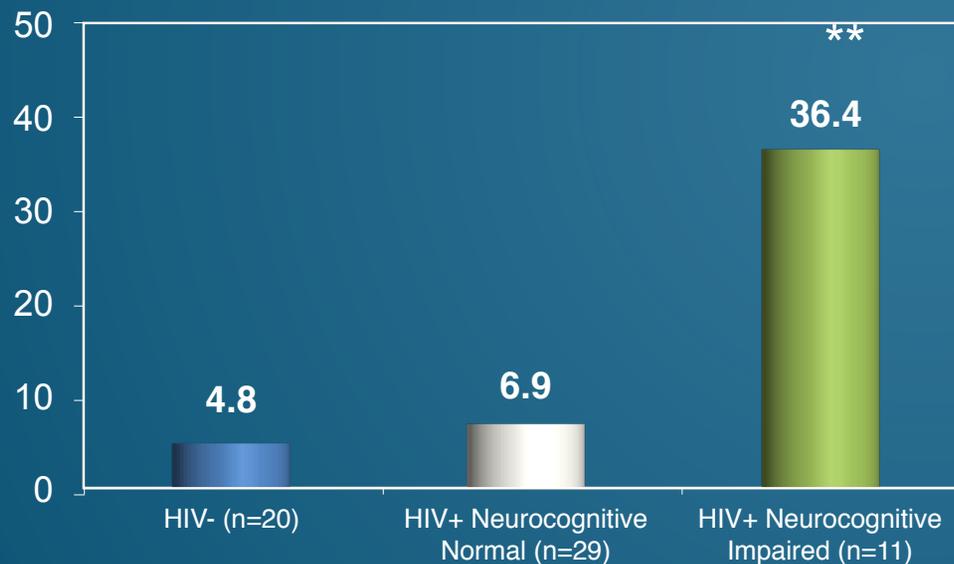
Frequency of Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV Associated Dementia (HAD) (from CHARTER Cohort)



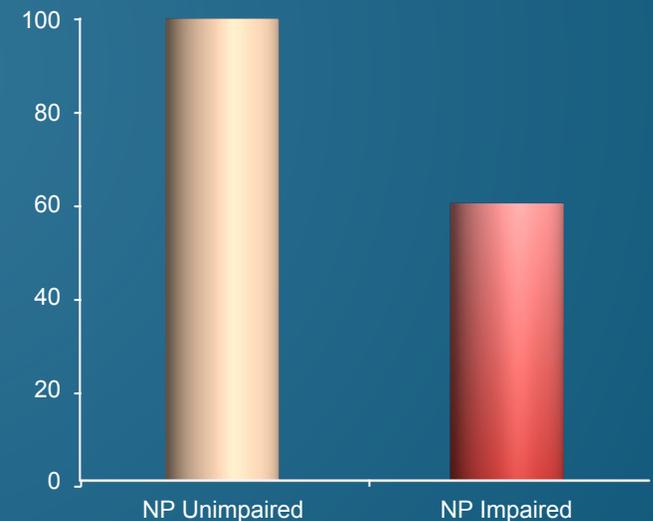
Neurocognitive Impairment Matters

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

Driving Errors Noted by On-road Observation

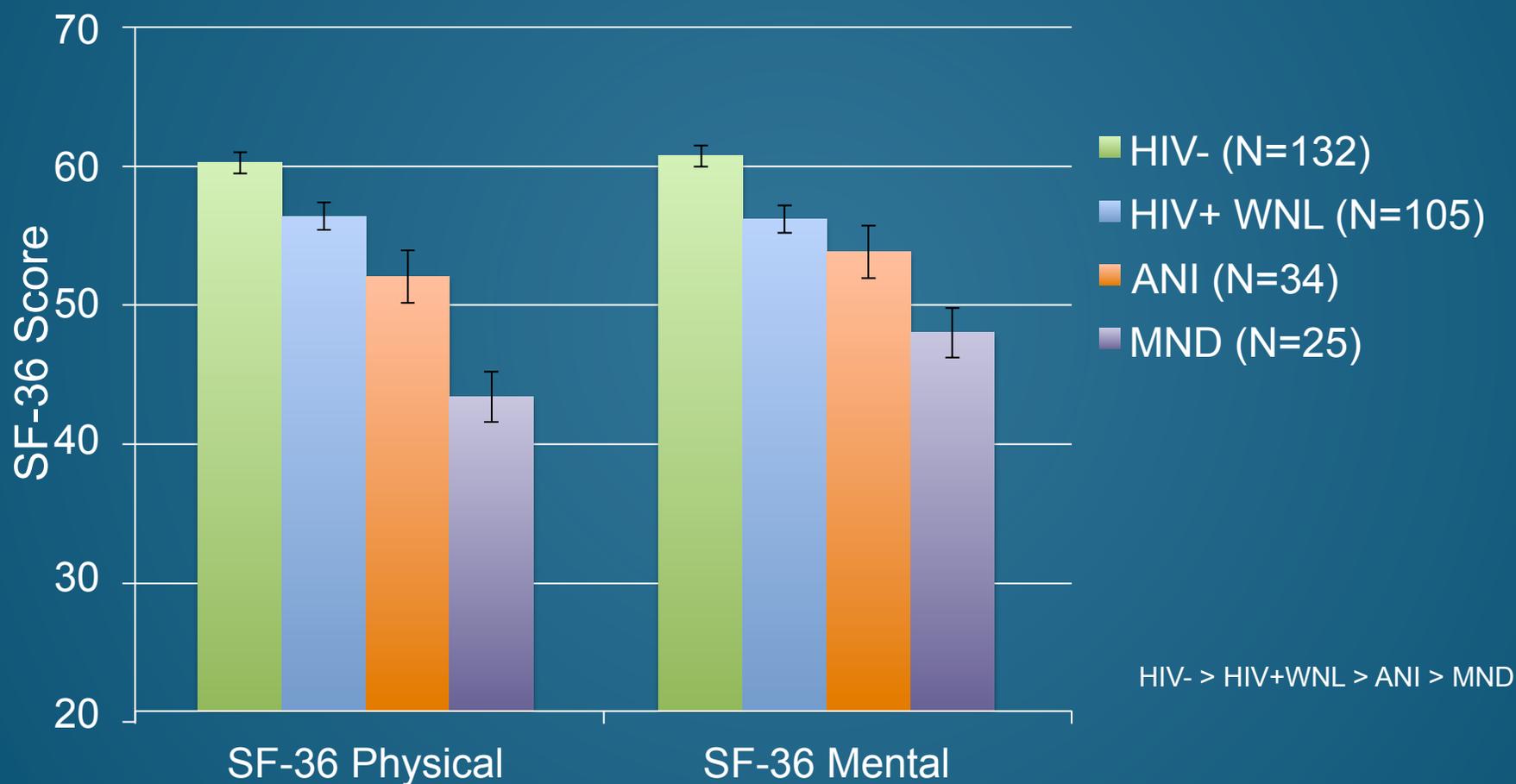


% That Followed Schedule "Most of the Time"



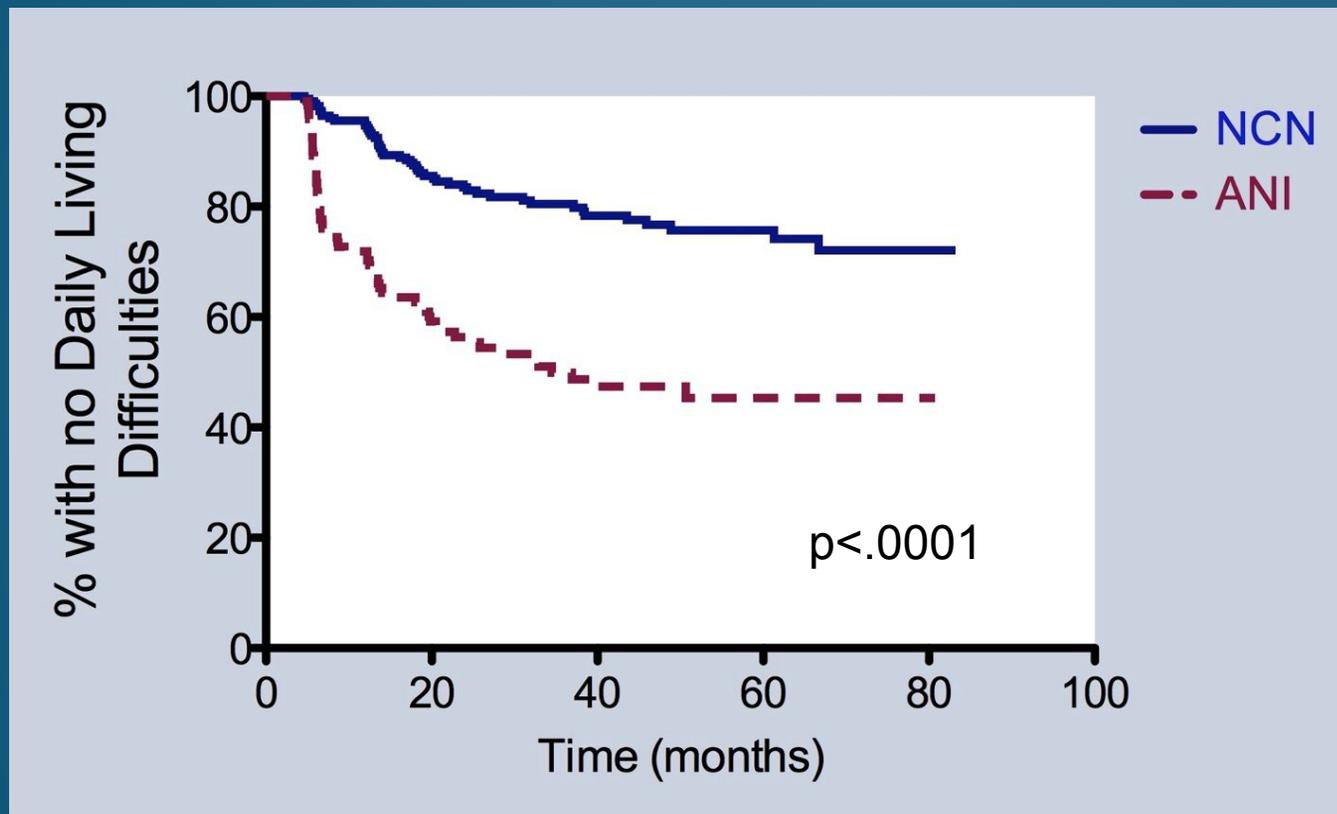
Marcotte et al., 2004

Severity of NCI is Associated With Lower Health-related Quality of Life



Woods SP : R01 MH73419

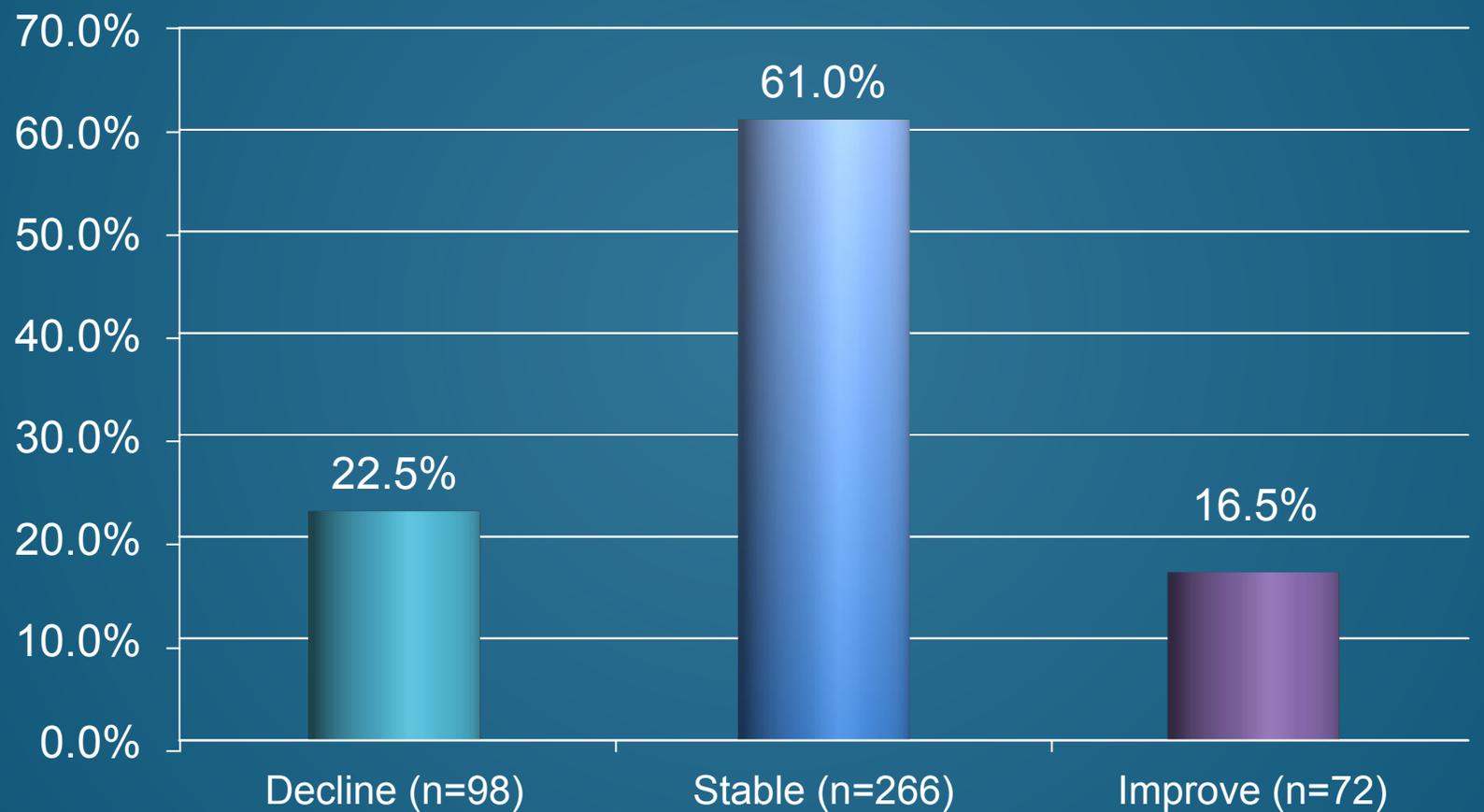
Compared to Neurocognitively Normal (NCN) ANI Increases Risk for progression to Symptomatic HAND



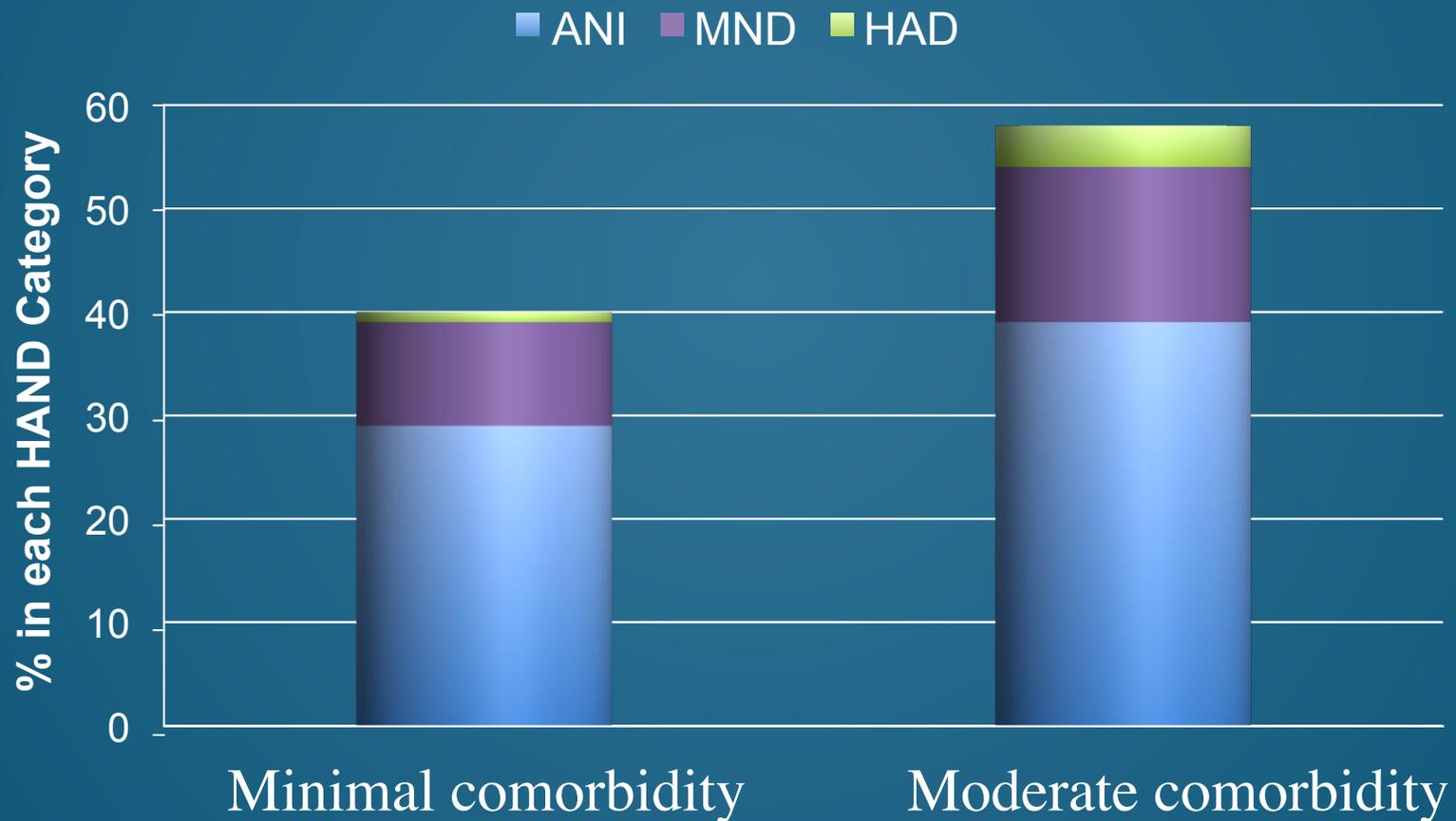
NML: n=226
ANI: n=121

Relative Risk:
3.02
CI: 2.08, 4.42

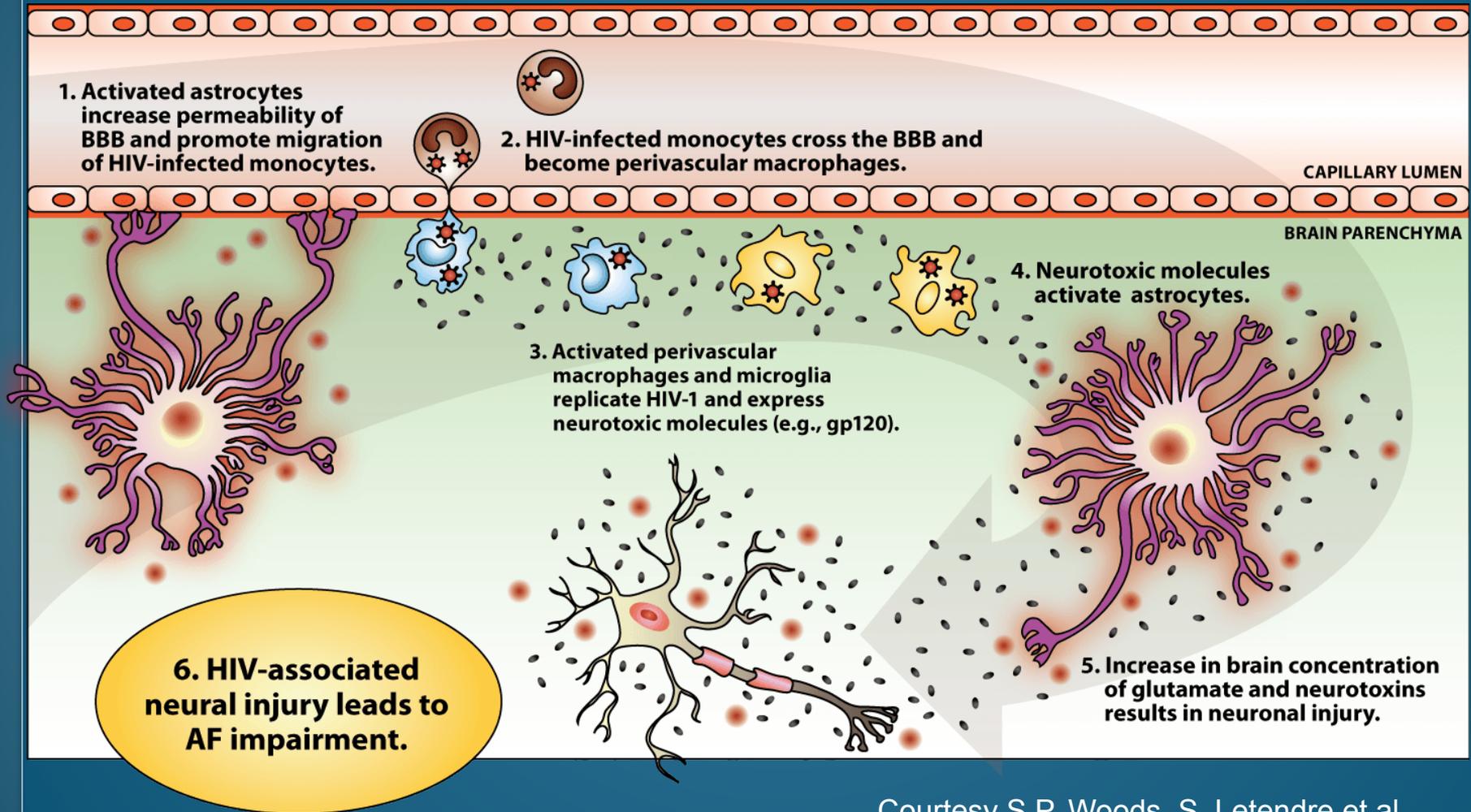
Neurocognitive Change Status in CHARTER Sample with ≥ 4 visits (n=436)



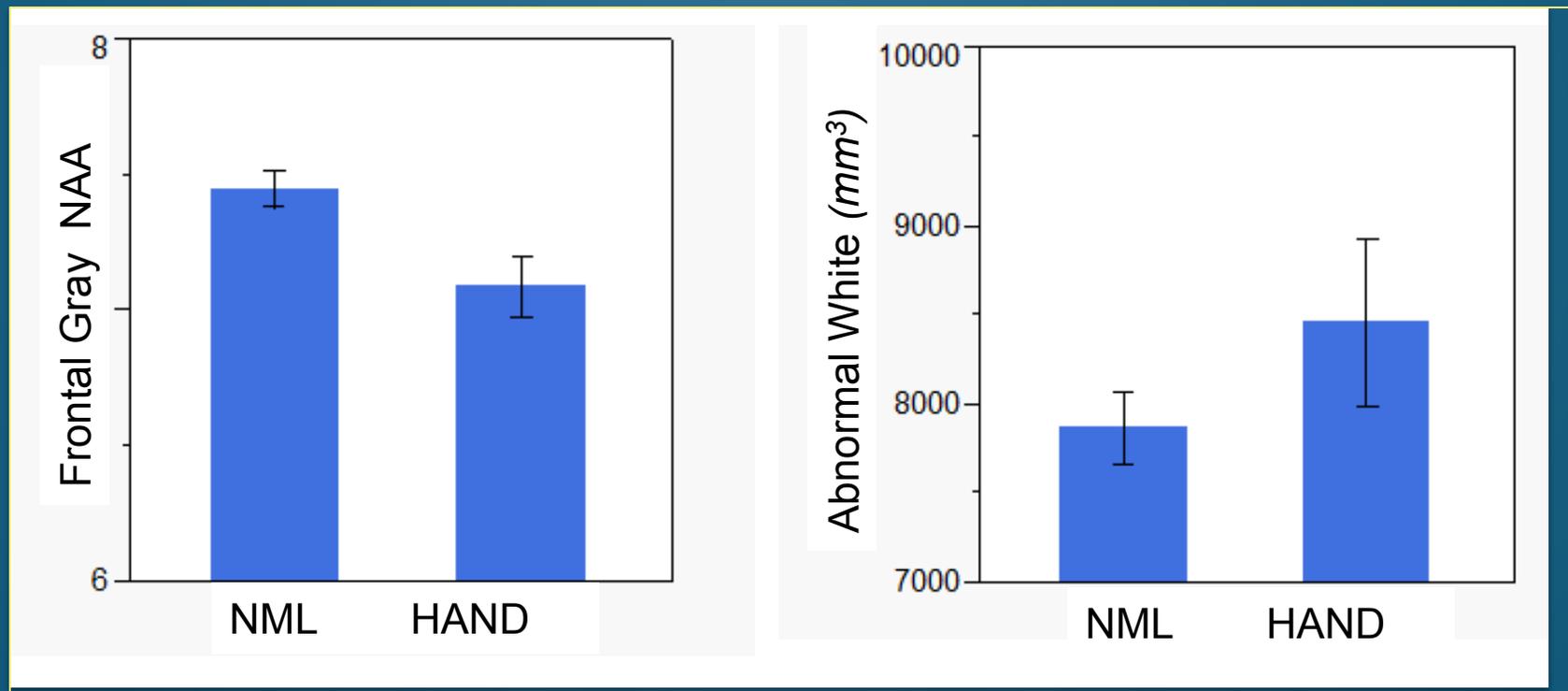
**HIV+ persons often have “comorbidities”,
eg., HCV coinfection; drug abuse; prior head injuries,
which can compound HIV effects on brain:
Frequency and Severity of HAND rise with Comorbidities**



Pathogenesis of HAND

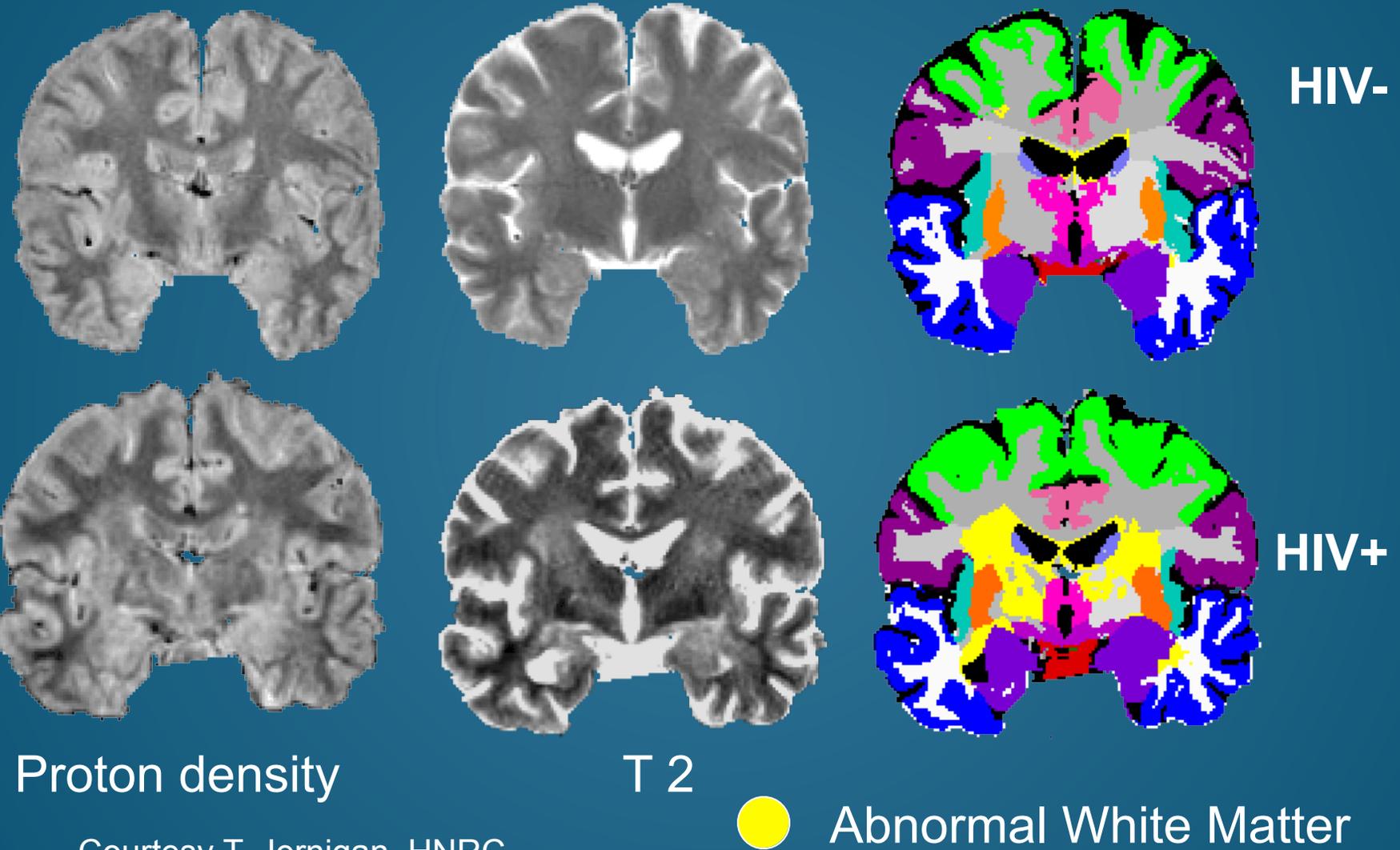


HAND associated with reduced N acetyl aspartate (NAA: an indicator of neuronal integrity) signal on MR spectroscopy and more white matter abnormalities on quantitated MRI



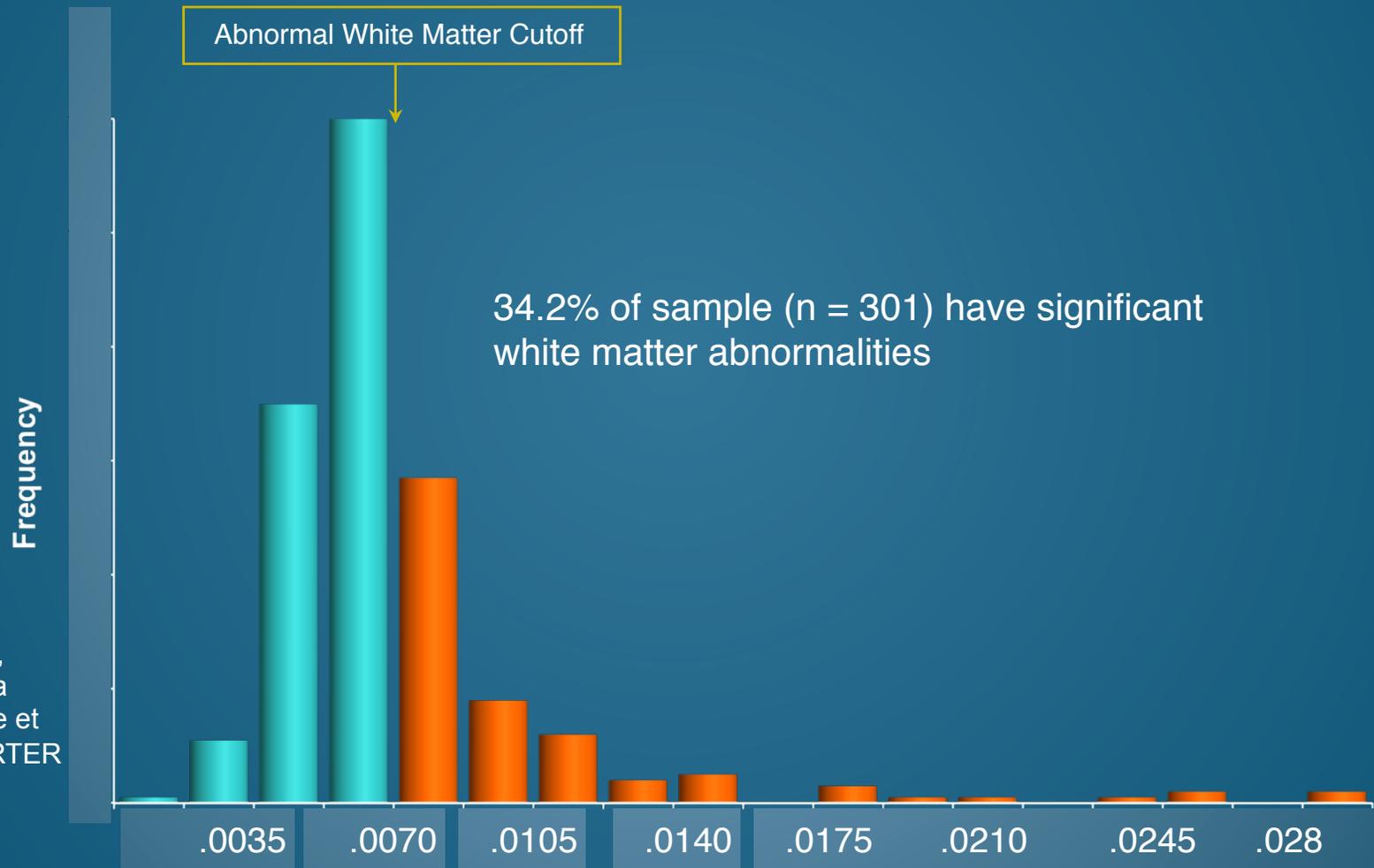
Fennema-Notestine et al. CROI 2013

Abnormal white matter signal is associated with HIV

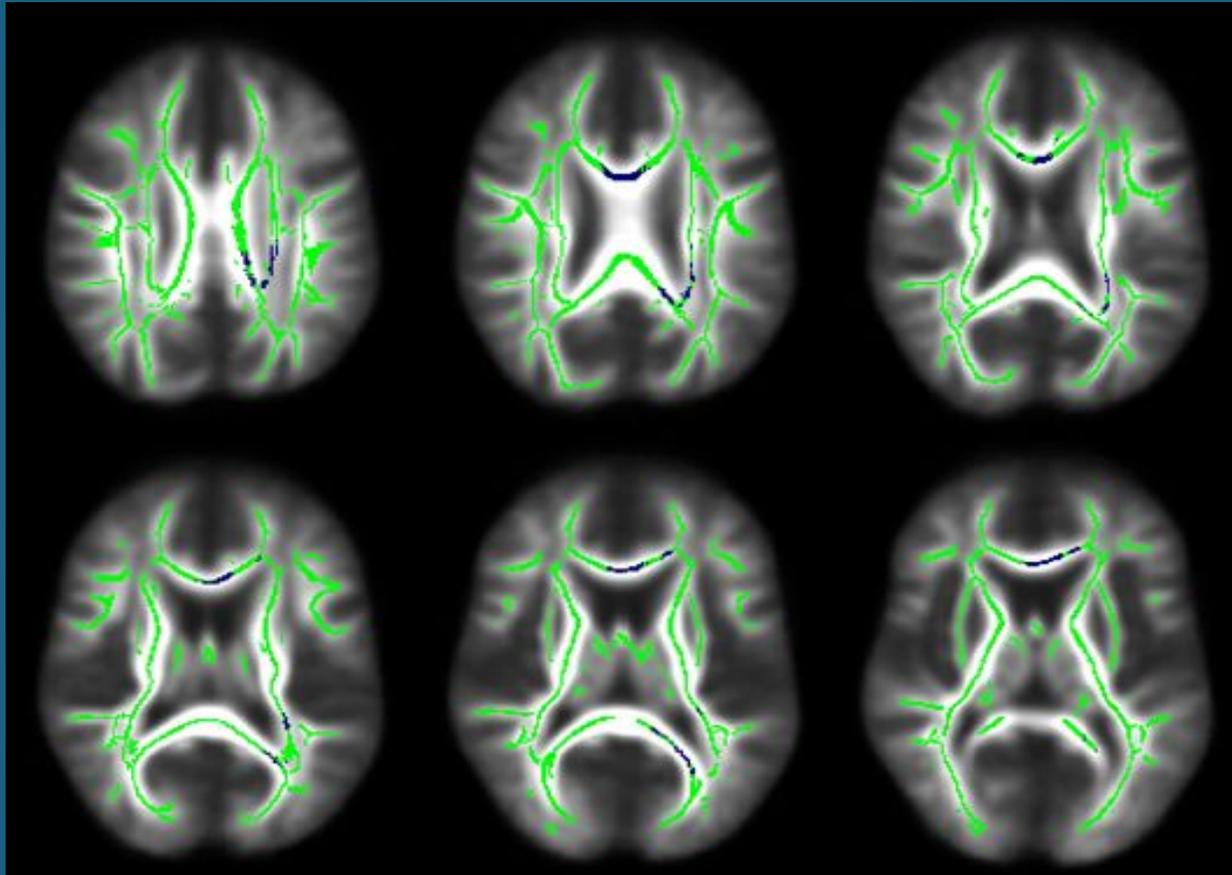


Courtesy T. Jernigan, HNRC

Abnormal white matter signal seen on quantitated MRI in about 1/3 of HIV+ cases

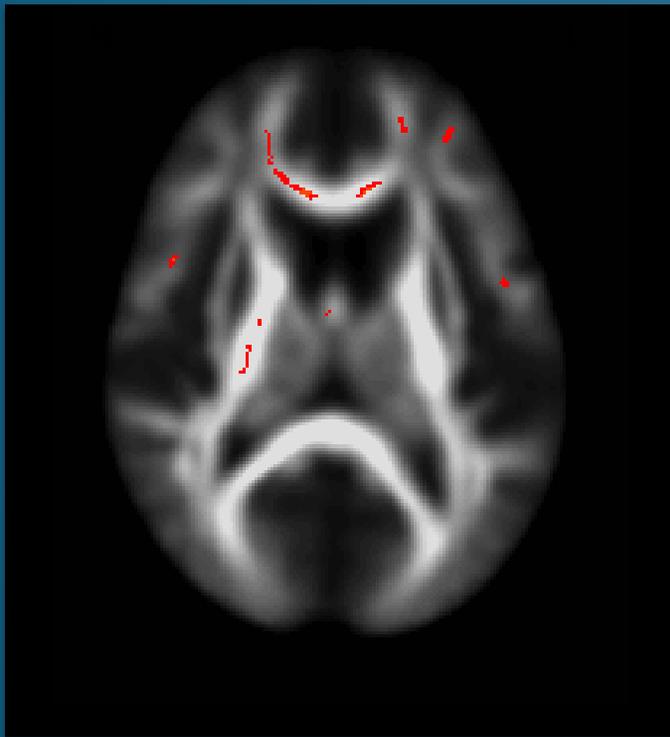


Increased mean diffusivity, suggesting injury to white matter tracts in NCI HIV+



Sample consecutive 5-mm slices showing voxels with significantly increased MD (in blue) in neurocognitively impaired (NCI) relative to unimpaired HIV+ participants, overlaid on white matter tract skeleton (green), and averaged FA image (grayscale). (Gongvatana, et al. INS 2008)

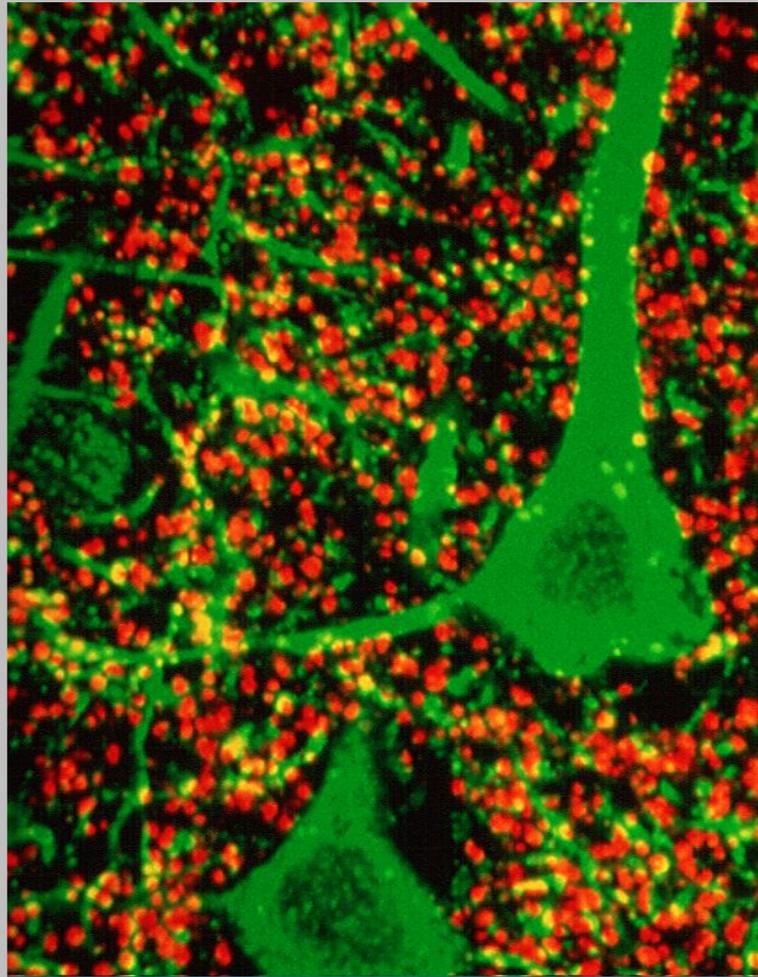
Reduced fractional anisotropy associated with more executive dysfunction



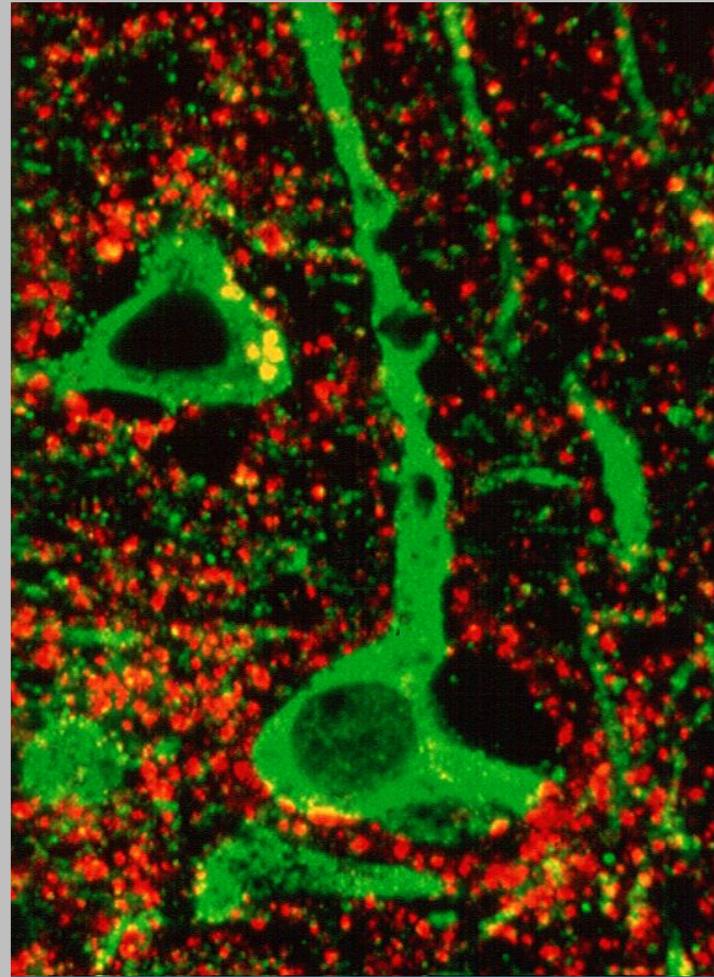
- Red highlights indicate significant positive, partial correlation clusters between executive domain T-score and fractional anisotropy (independent of age)
- Significant regions shown are genu, frontal association fibers, posterior limb of internal capsule

Jacobus et al., INS 2008

Loss of synapses and dendrites in HIV+



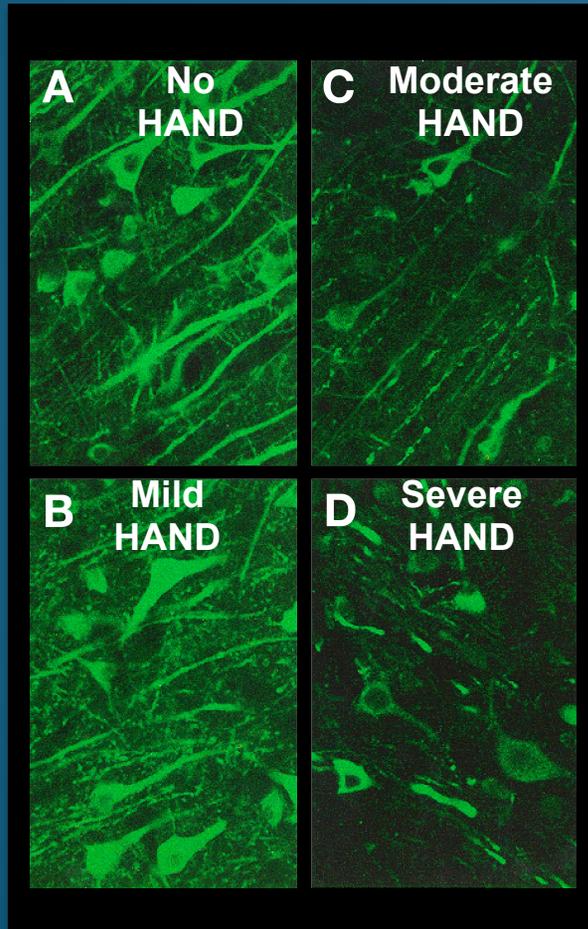
HIV-



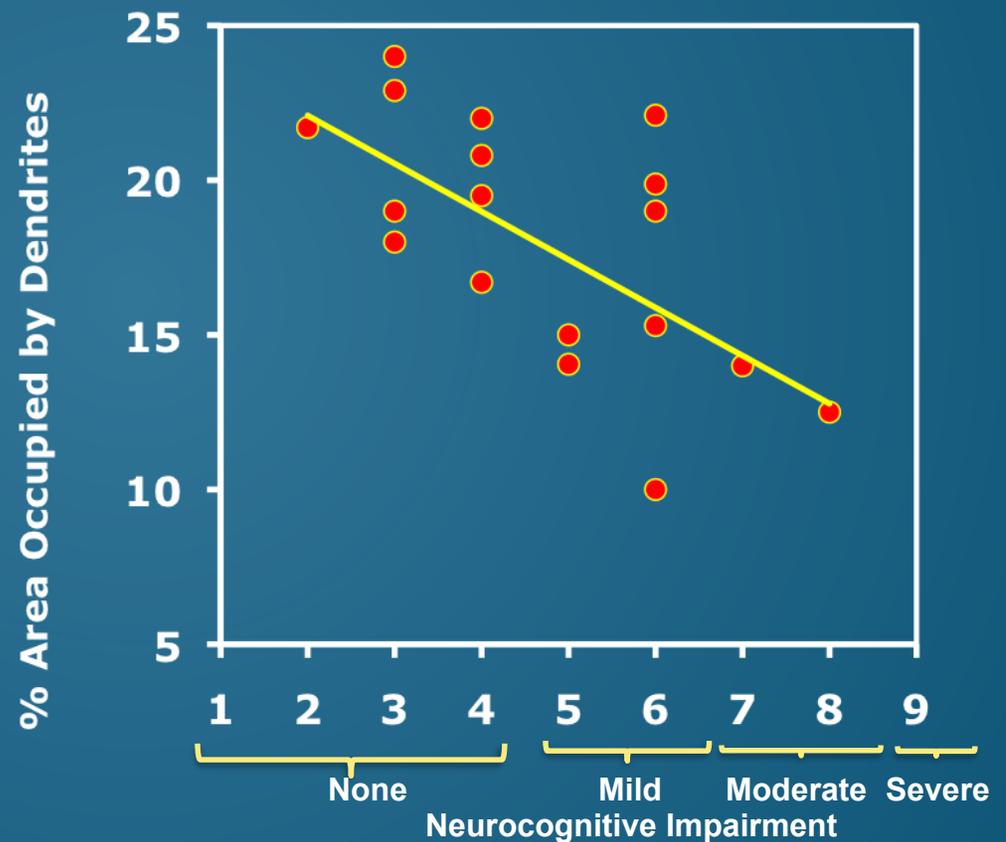
HIV+

Injury to synapses and dendrites may form a basis of HIV neurocognitive impairment

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

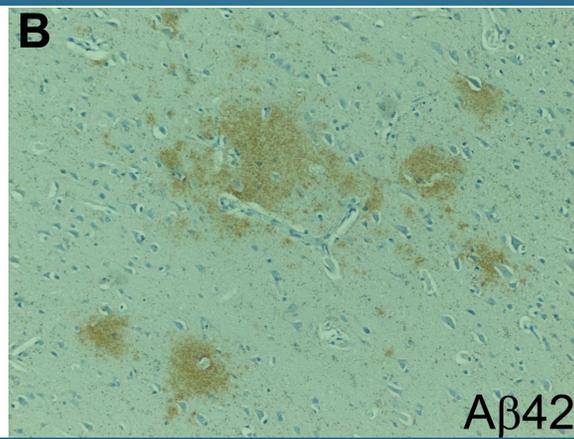
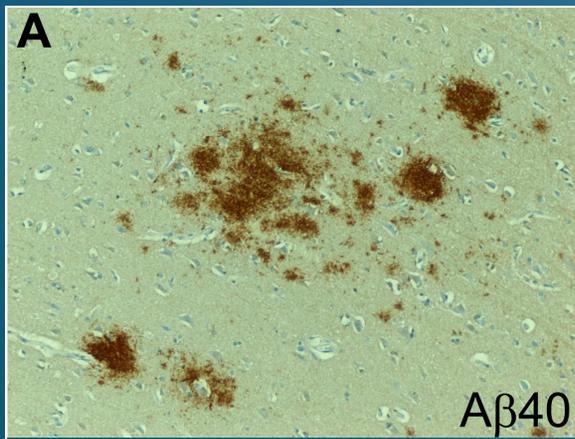
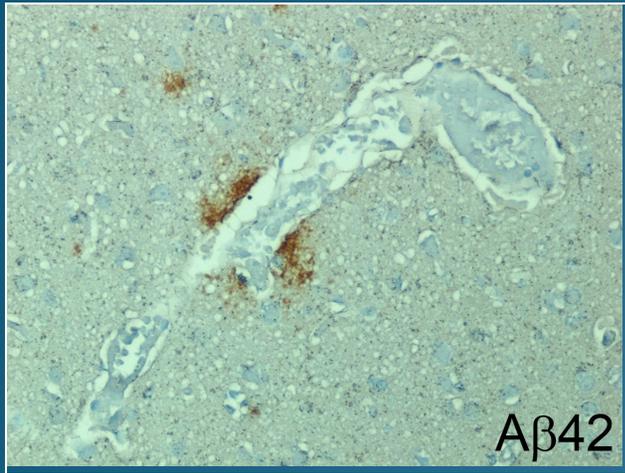


Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



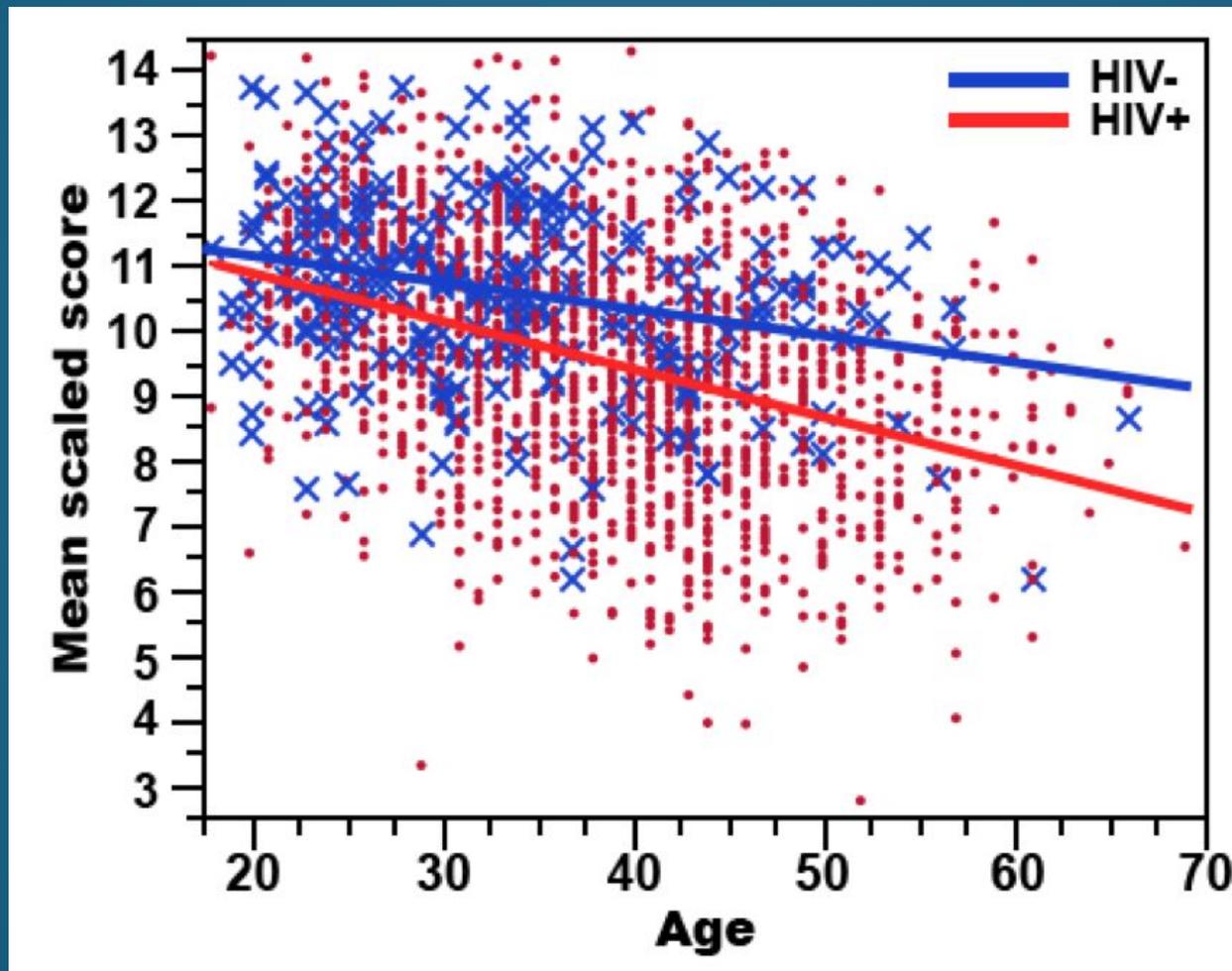
Masliah, et al. *Ann Neurol.* 1997, 42(6): 963-72

**Disordered protein management
may be another substrate of HIV
neuropathogenesis:
Perivascular and diffuse A β and
neuritic plaques in brains**



Soontornniyomkij and Achim, CNTN data

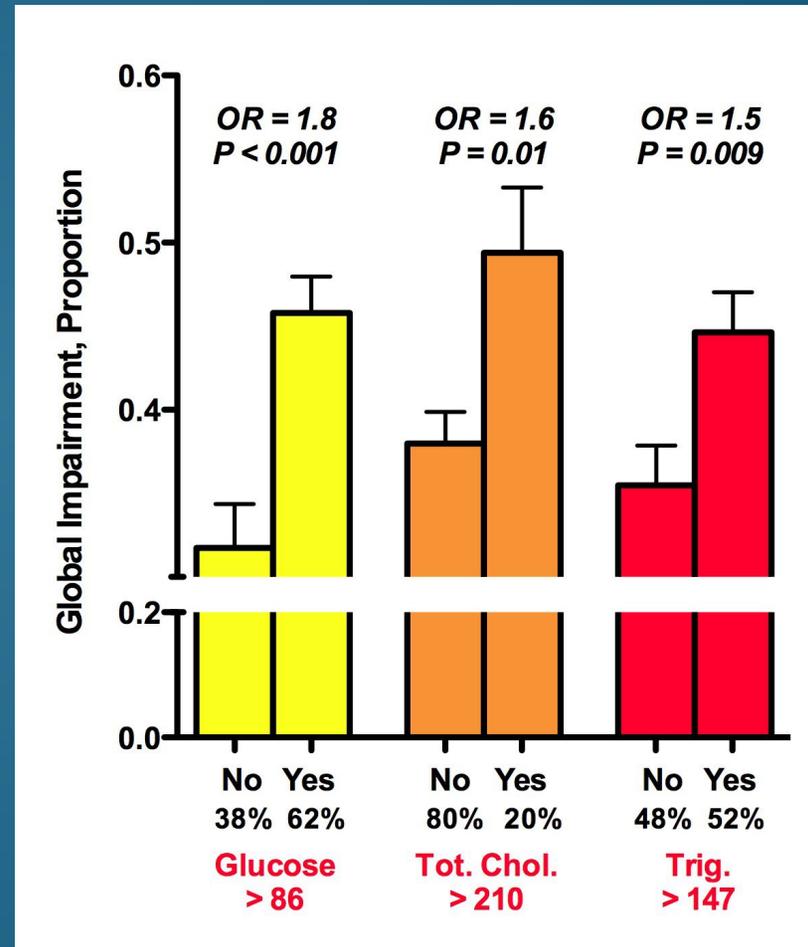
Comorbid factors: Greater neurocognitive impairment with age in HIV+ vs HIV- persons



Grant et al
CHARTER
& HNRP
data

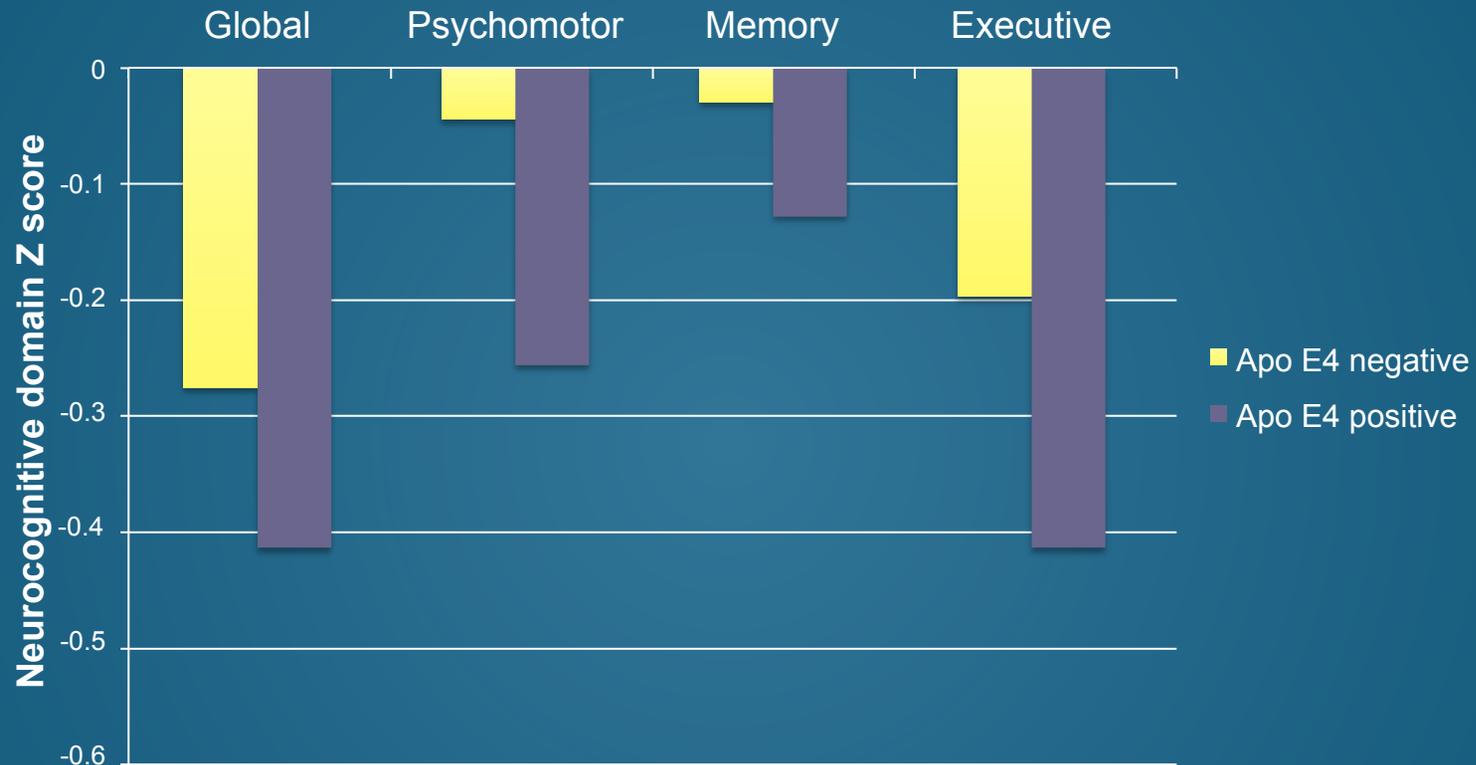
Comorbid factors: Markers associated with metabolic syndrome are related to neurocognitive impairment

- Cross-sectional visits with “minimal” comorbidities
- Biomarkers of metabolic syndrome compared to global NP performance
- ROC curves identified thresholds associated with global NP impairment



Courtesy J.A McCutchan and S. Letendre

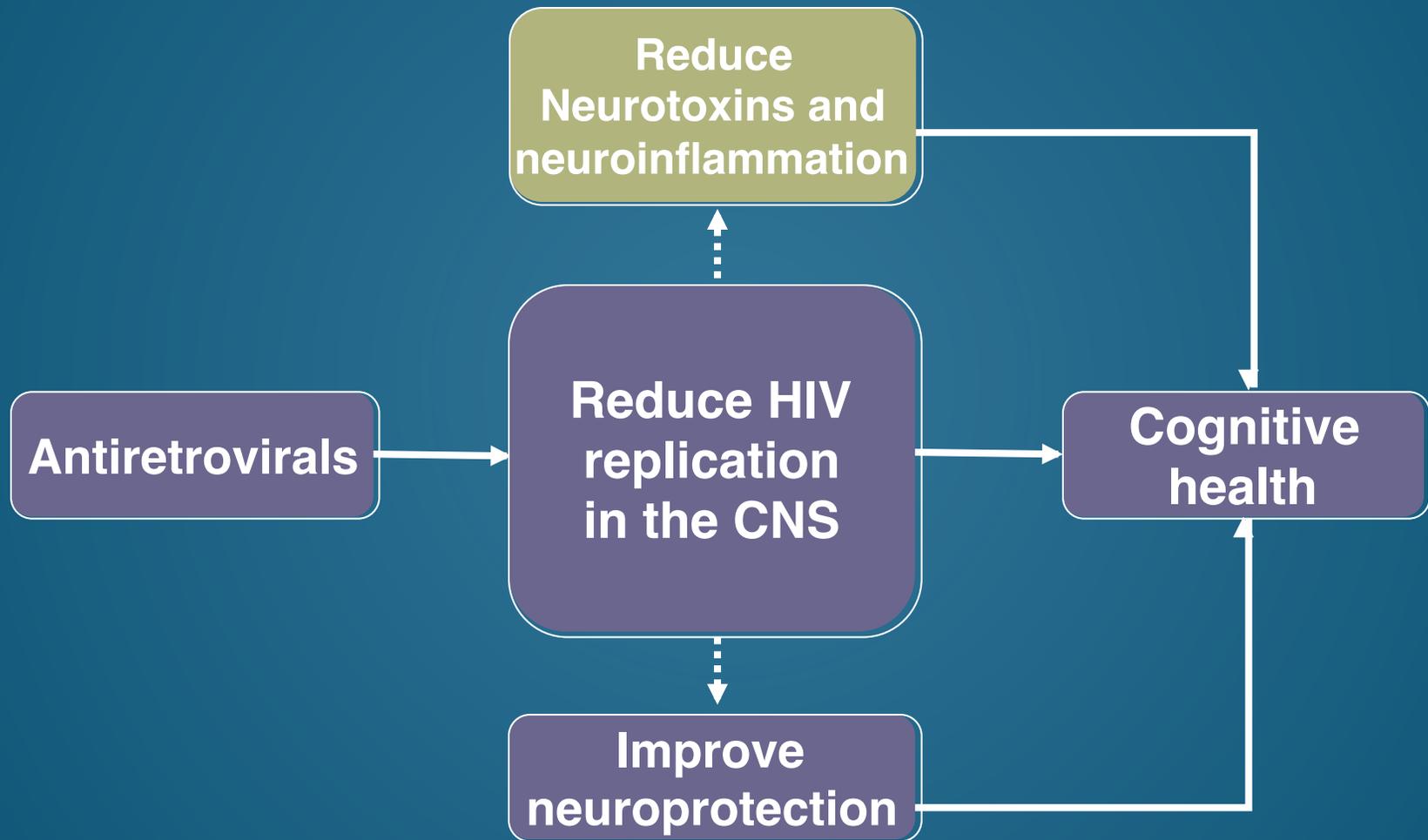
Comorbid factors: APO E4 HIV+ have worse neurocognition



Association of apolipoprotein (Apo) E4 with poorer neuropsychologic testing performance shown by Z scores in patients in the University of California San Francisco (UCSF) HIV Over 60 Cohort (adjusted for CD4+ cell count, nadir CD4+ cell count, years HIV seropositive, and plasma HIV RNA level). Adapted with permission from Atputhasingam et al 2013, Poster presented at Annual Scientific Meeting of Am Geriatrics Soc May 2-5.

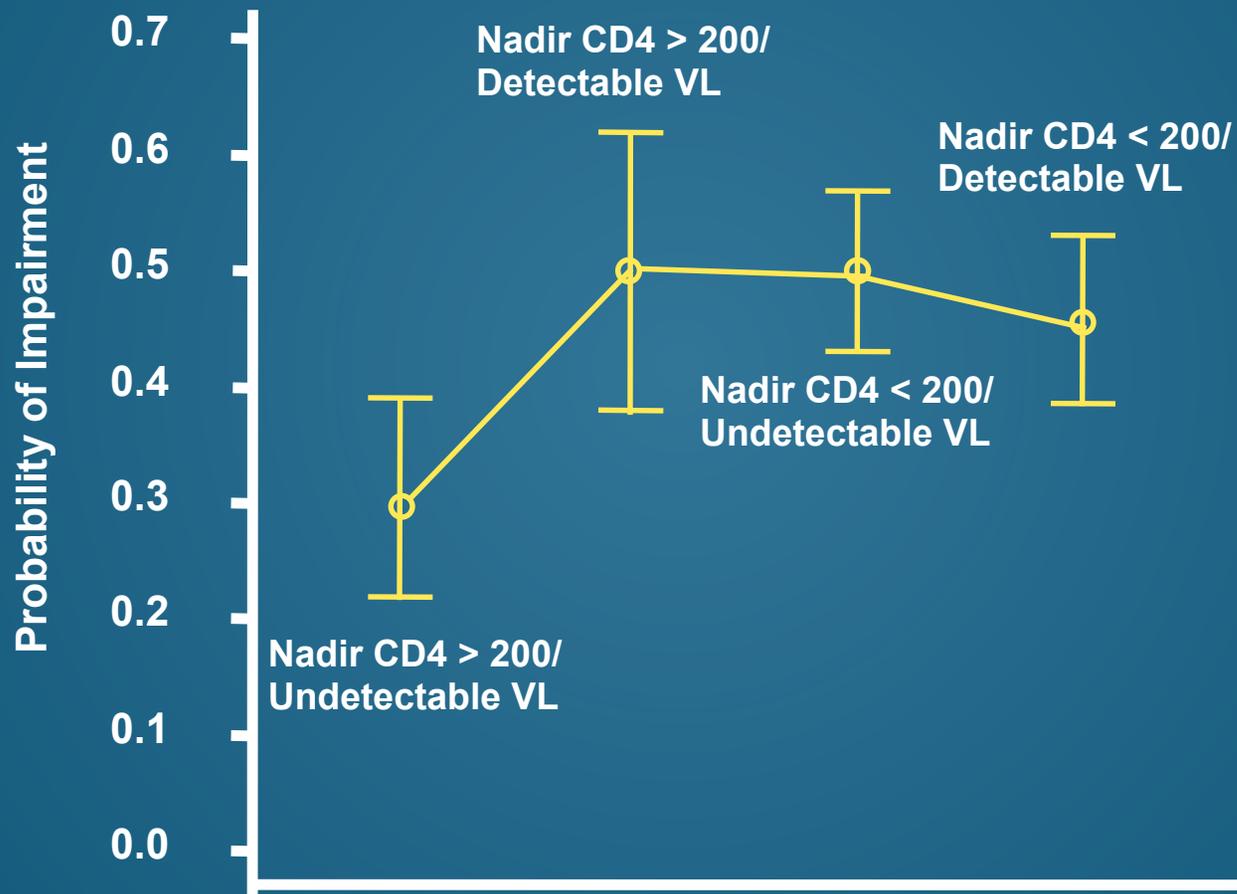
Valcour VG, 2013. Top Antivir Med, 21(3):119-23.

Management of HAND requires consideration of multiple mechanisms: controlling HIV is 1st step



Modified from S.Letendre

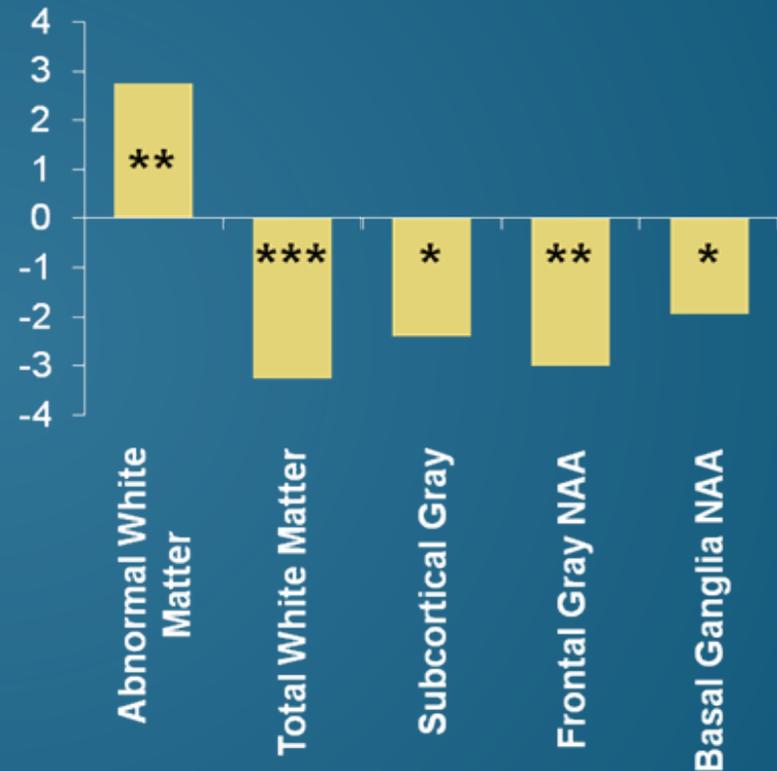
Lower neurocognitive impairment risk when immunosuppression is avoided and virologic control is good



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

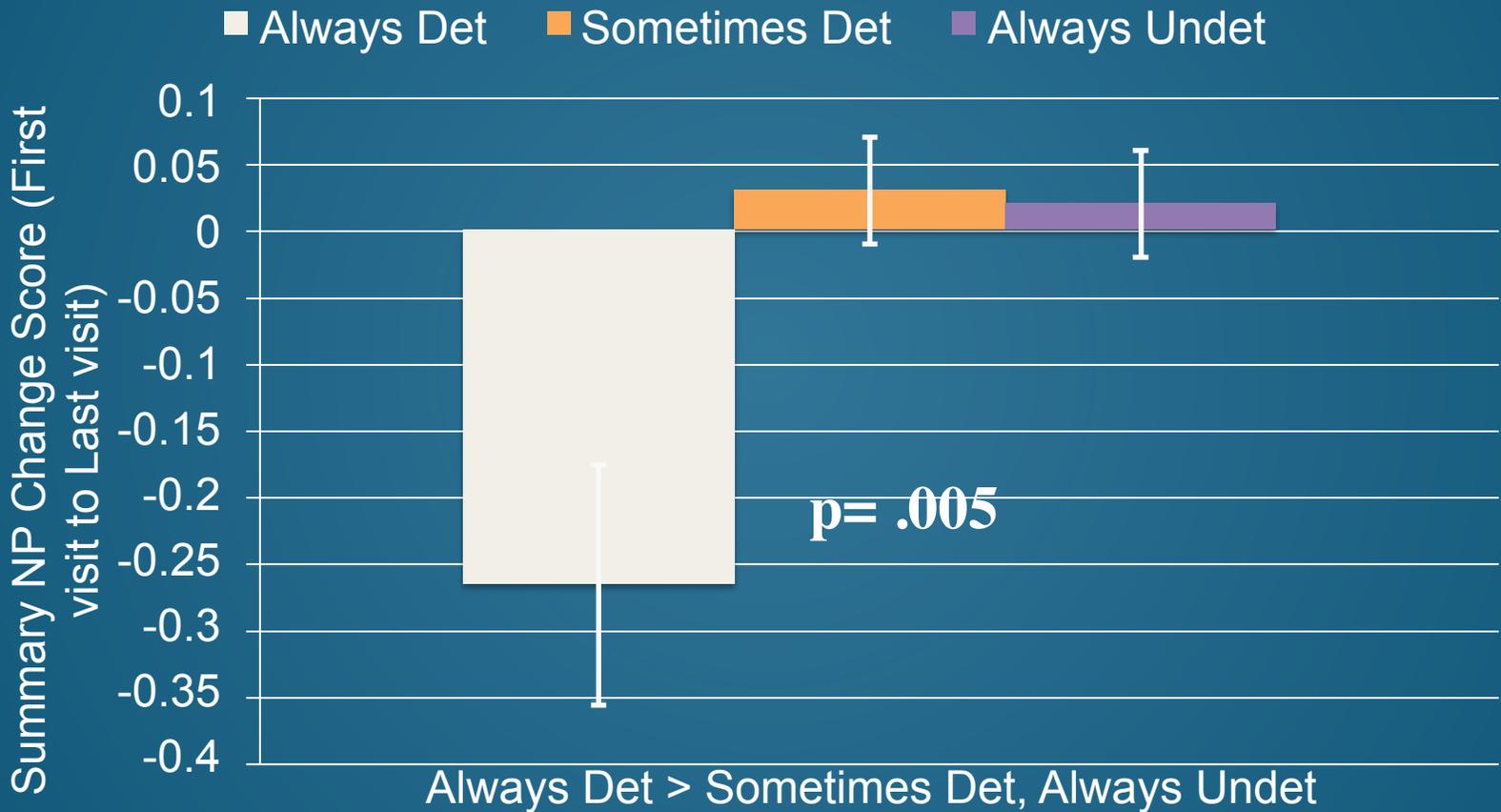
Historical HIV neuromedical factors associated with white matter and gray matter damage

- Lower nadir CD4
 - ↑ abnormal white matter
 - ↓ white matter volume
 - ↓ subcortical gray matter
 - ↓ neuronal integrity (NAA)
- Longer exposure to ART
 - ↓ white matter, controlling for duration of HIV infection



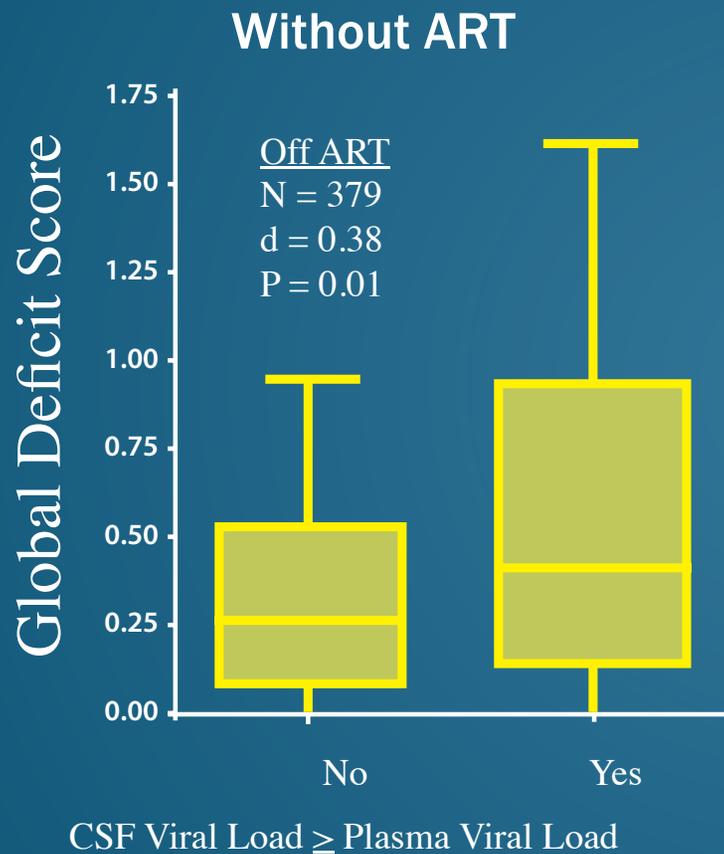
Jernigan et al. JNV 2011;
Fennema-Notestine et al. CROI 2013

Plasma VL Over Time vs. Summary NP Change Score

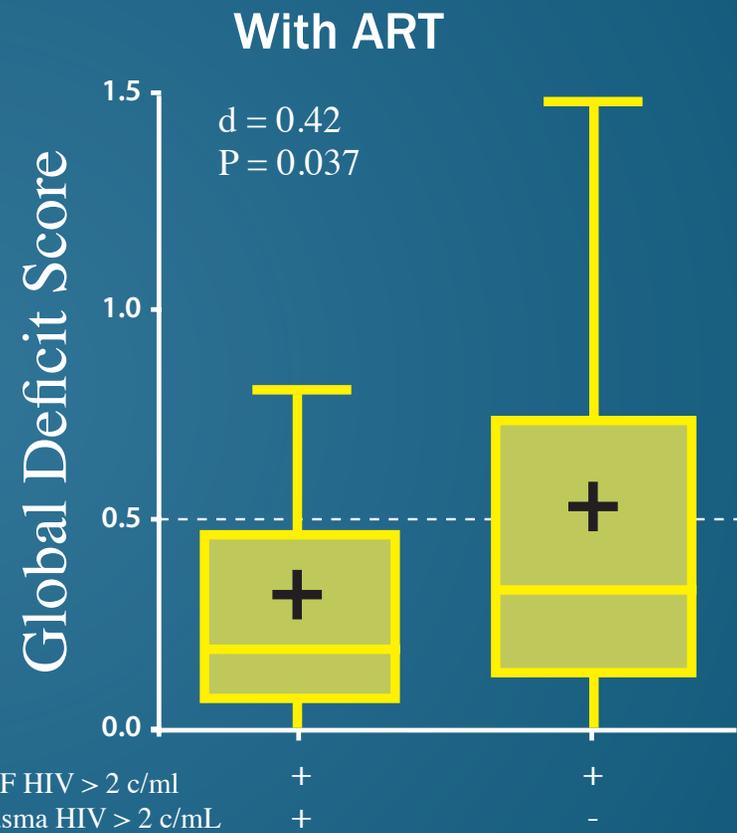


Heaton et al. CHARTER data

CSF Viral Loads Are Associated with HAND When Compared to Plasma Viral Loads



Letendre et al, 17th CROI 2010, Abstract 172



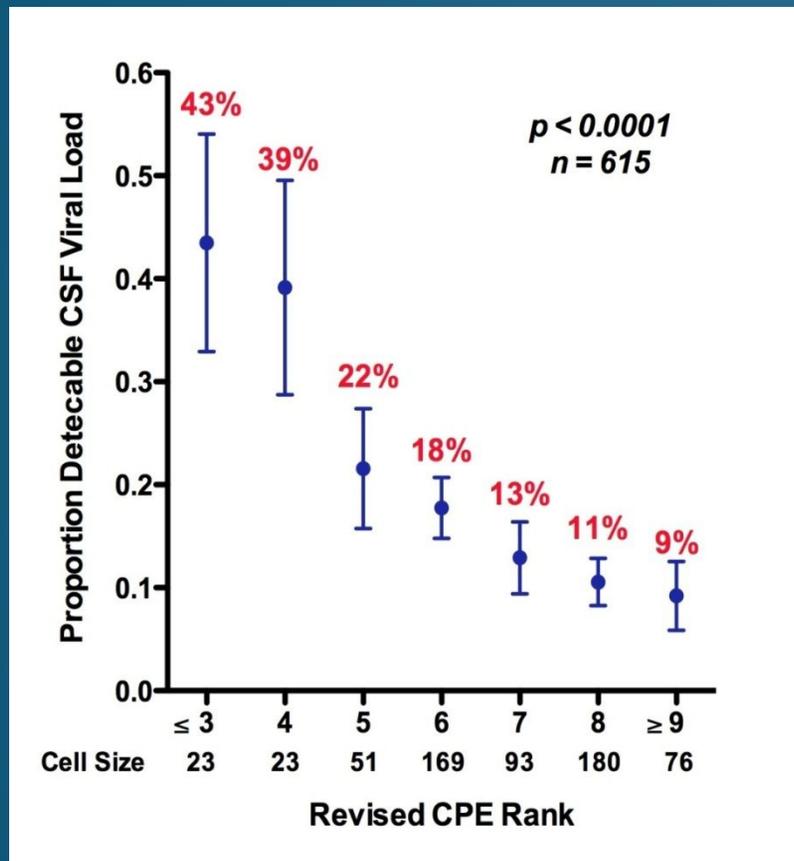
Letendre et al, 16th CROI 2009, Abstract 484b

CNS Penetration Effectiveness Ranks 2010

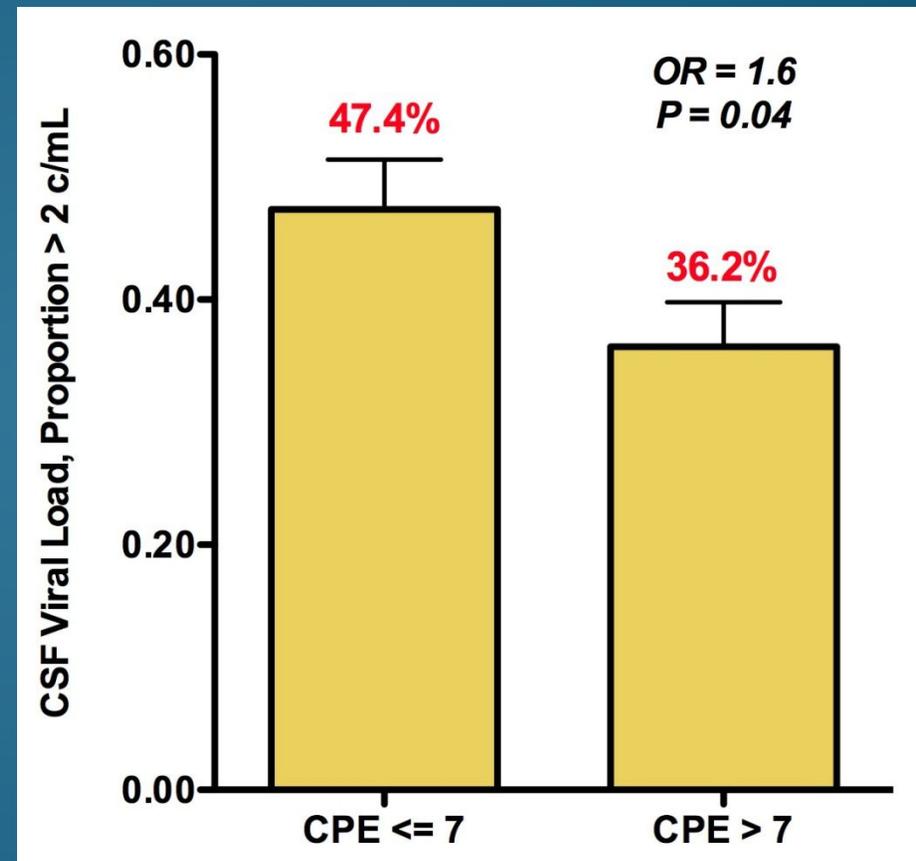
	4	3	2	1
NRTIs	Zidovudine	Abacavir Emtricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-r	Darunavir-r Fosamprenavir-r Indinavir Lopinavir-r	Atazanavir Atazanavir-r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-r Tipranavir-r
Entry/Fusion Inhibitors		Maraviroc		Enfuvirtide
Integrase Inhibitors		Raltegravir		

Letendre SL, et al. 17th CROI 2010, Abstract 172

Higher CPE values are associated with lower HIV RNA levels in CSF



Letendre S et al, 17th CROI 2010, Abstract 172

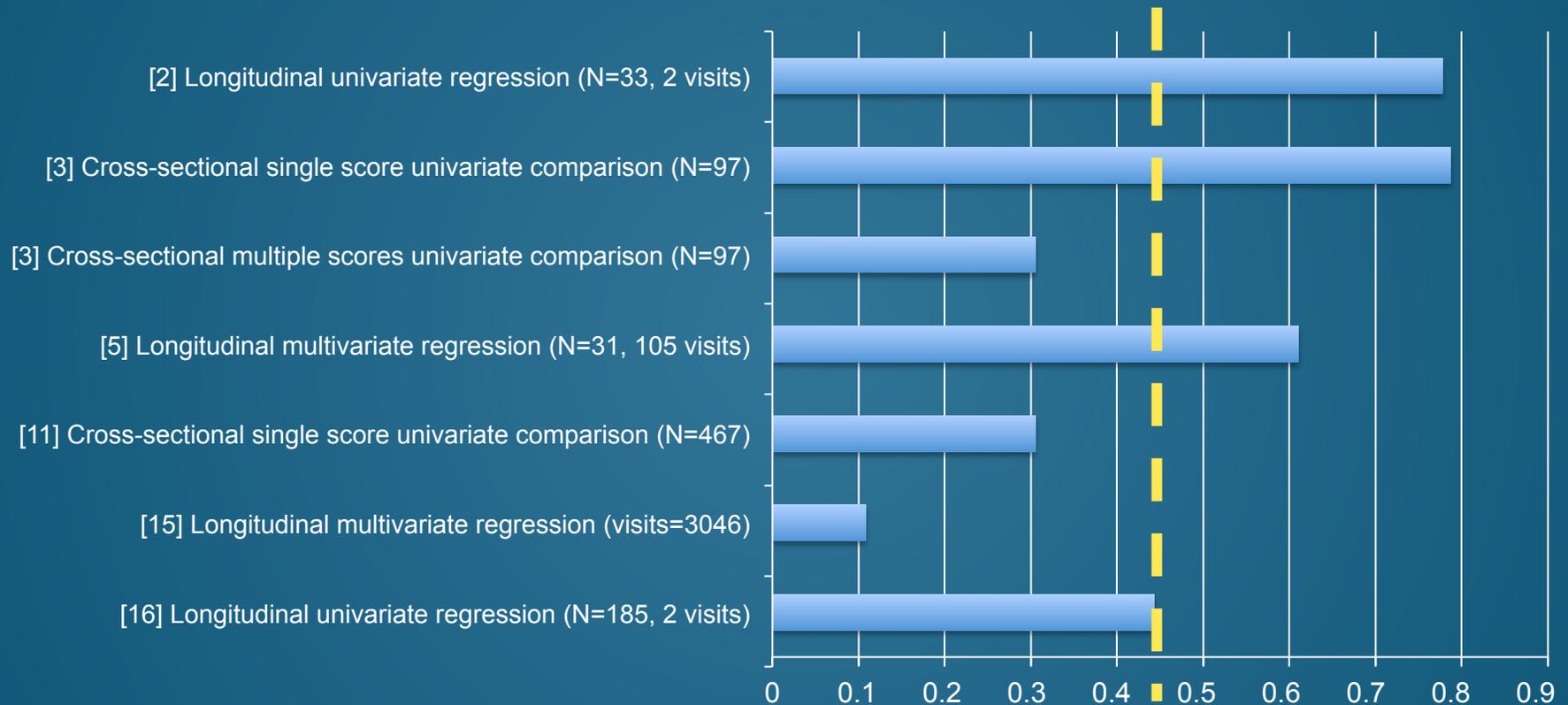


Letendre et al, 16th CROI 2009, Abstract 484b

Copyright S. Letendre, 2011

Well designed studies indicate higher CPE regimens benefit neurocognition

Median effect size



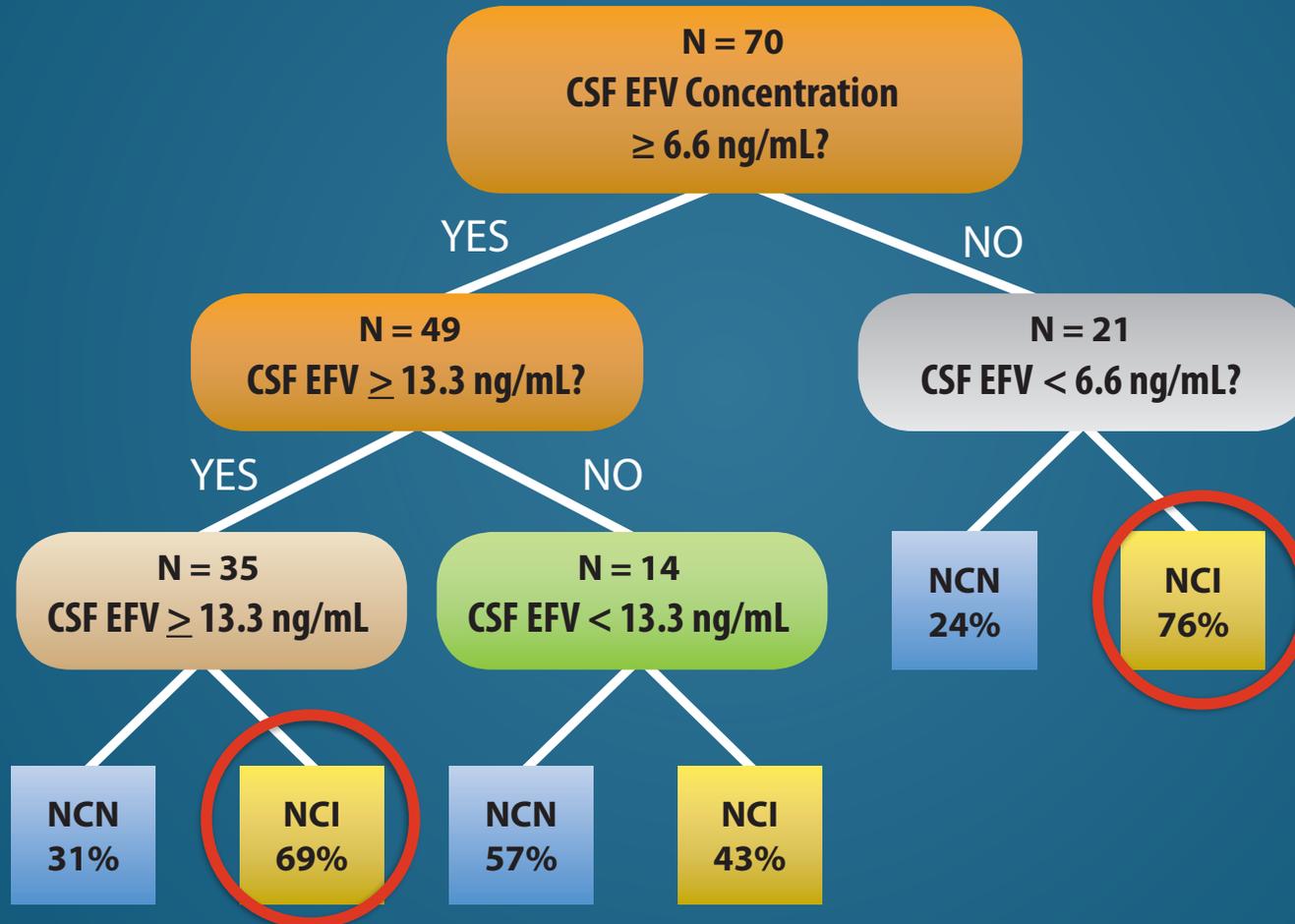
CPE, CNS Penetration-Effectiveness

From Cysique, Waters & Brew (Central Nervous System Antiretroviral Efficacy in HIV infection: A Qualitative and Quantitative Review. *BMC Neurology*: provisionally accepted).

Presented with permission of the author

Is there a “neurotherapeutic window”?

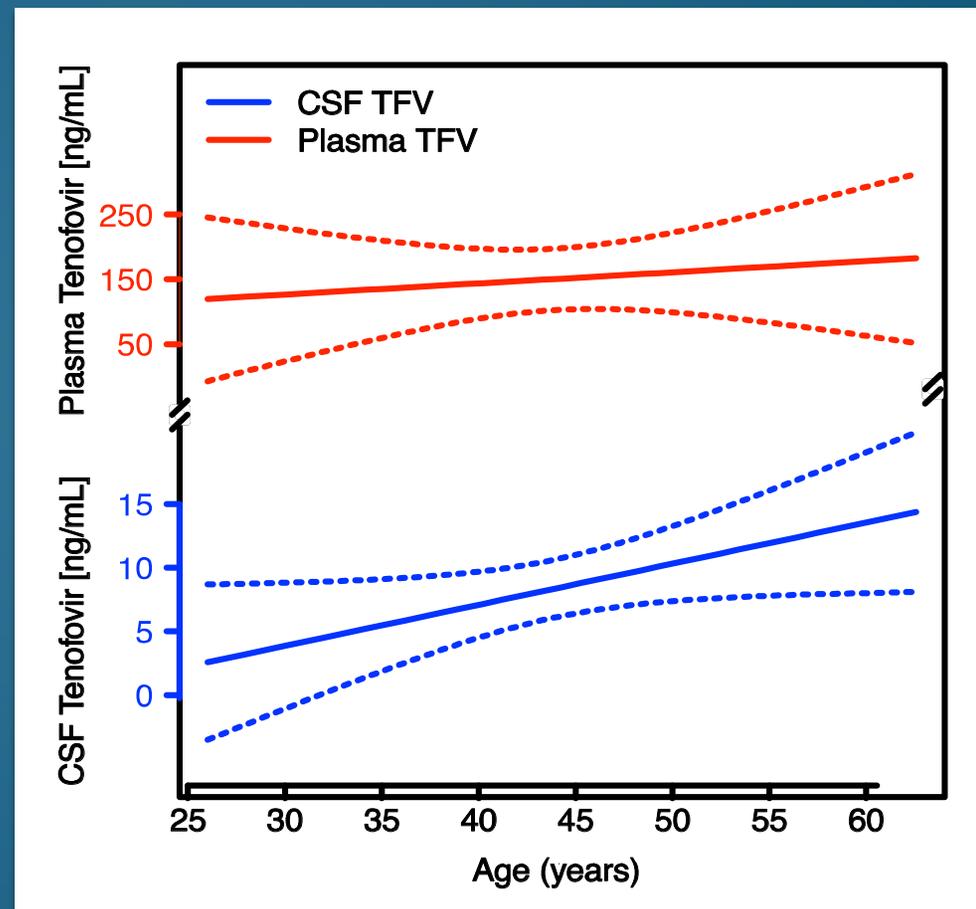
Both high and low CSF EFV associated with more neurocognitive impairment



Letendre S, et al., HNRP data 2011:Unpublished.

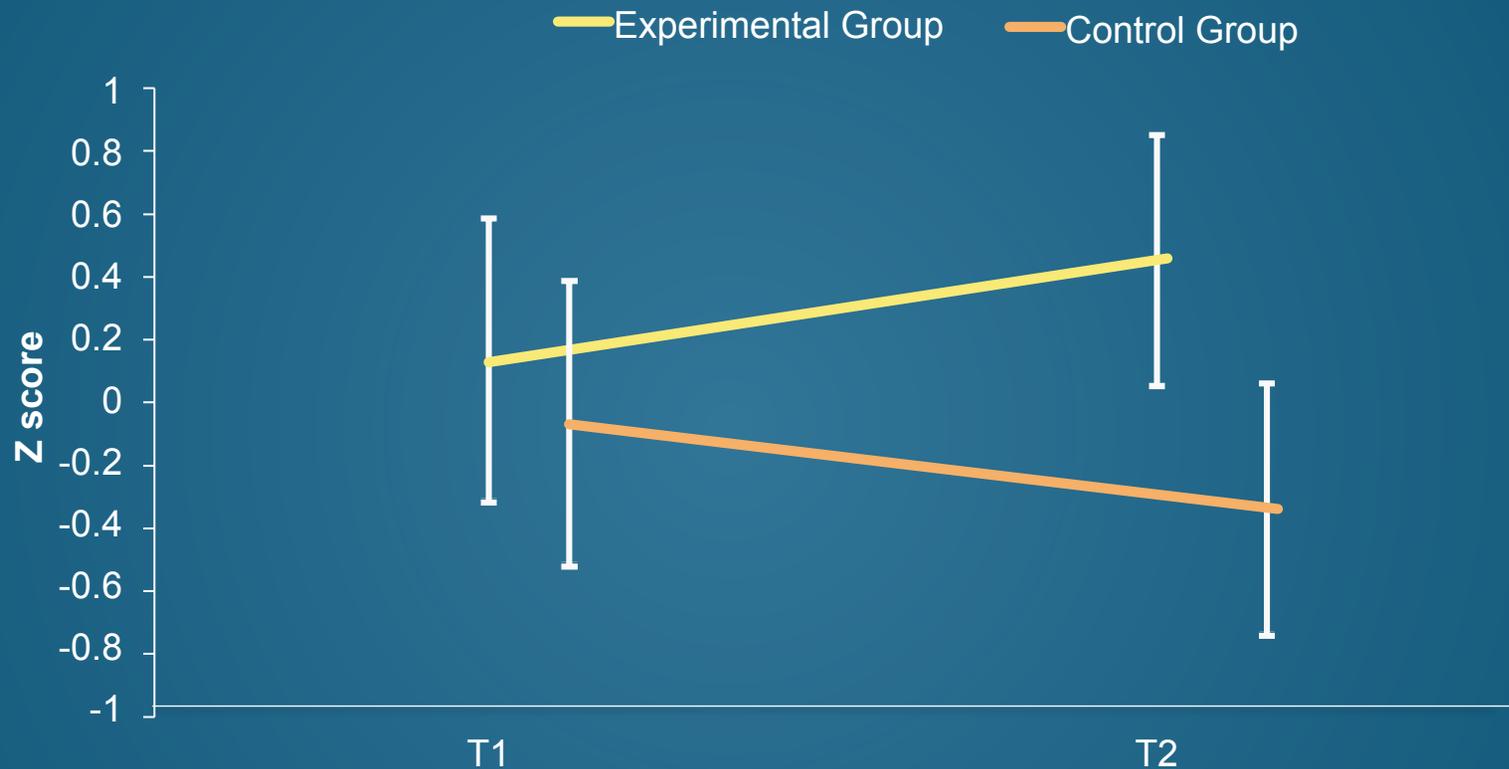
How should neuroeffective therapy be modified in aging HIV population?

- Age related changes in plasma and cerebrospinal fluid (CSF) pharmacokinetics of Tenofovir (TFV)



Letendre S, et al., HNRP data 2011:Unpublished.

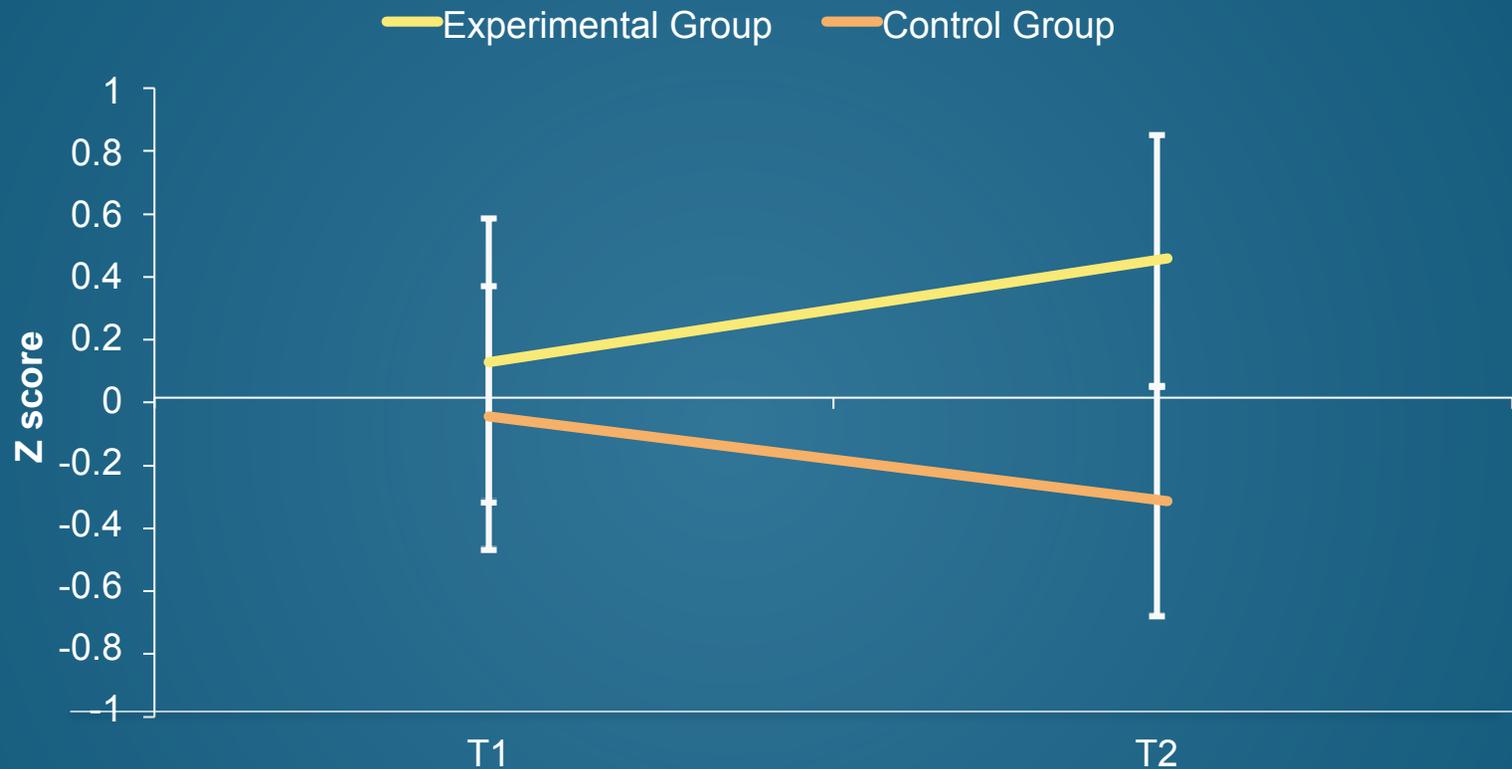
Non Pharmacologic approaches to HAND? ANI improves after 3 months of cognitive rehabilitation



LEGEND: clinical evolution discordant between the two groups: the experimental group showed an improvement differential at T1, this improvement does not occur in the control group, which instead show a worsening of neurocognitive performance compared to T0 to T1.

Livelli, et al., CROI 2013

Non Pharmacologic approaches to HAND? ANI improves after 3 months of cognitive rehabilitation



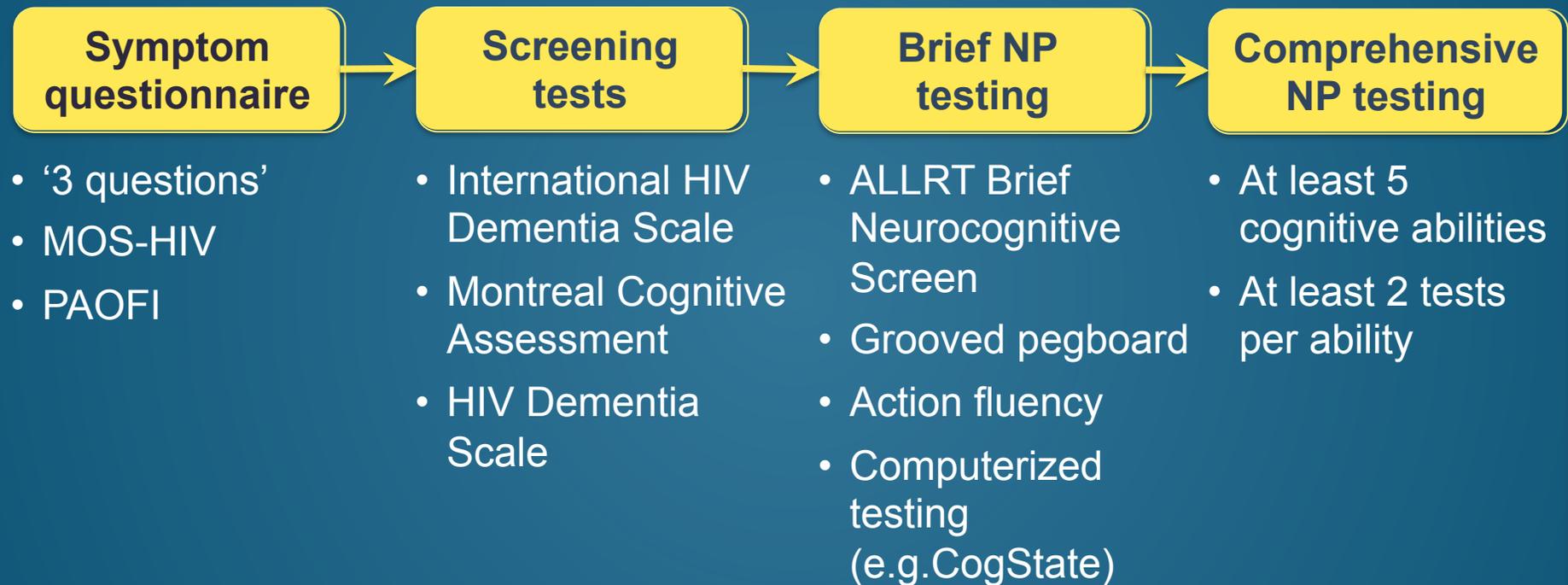
LEGEND: clinical evolution discordant between the two groups: the experimental group showed an improvement differential at T1, this improvement does not occur in the control group, which instead show a worsening of neurocognitive performance compared to T0 to T1.

Livelli, et al., CROI 2013

HNRP Recommendations for Evaluating and Managing Suspected HAND

- **Question** patients about cognitive symptoms and activities of daily living at routine visits and before initiating ART
 - » **Brief testing** improves the ability to correctly identify HAND
 - » **Screen for and treat other conditions** that could account for nervous system complaints (e.g. co-infections, substance use, mood disorders, vascular disease, metabolic disorders)
 - » Consider lumbar puncture and neuroimaging
- **Consider using ART with higher CPE** since accumulating data support that it better reduces HIV in CSF and leads to neurocognitive improvements
- **Continue to monitor** effectively treated patients
 - » Cognitive impairment might persist or even occur for the first time in treated individuals: drug resistance and/or drug neurotoxicity?

Examples of assessment methods for HAND



NP = Neuropsychological; MOS-HIV = Medical Outcome Study HIV Health Survey;
PAOFI = The Patients Assessment of Own Functioning Inventory;
ALLRT = AIDS Clinical Trials Group Longitudinal Linked Randomized Trials

Revised EACS Guidelines: 3 questions

Patients are considered to have an “abnormal” result when answering “yes, definitely” on at least one question

	Never	Hardly ever	Yes, definitely
Do you experience frequent memory loss? (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)			
Do you feel that you are slower when reasoning, planning activities, or solving problems?			
Do you have difficulties paying attention? (e.g. to a conversation, a book, or a movie)			

Simoni et al. AIDS 2009

International HIV dementia scale

- **Memory:**
 - » Word Recall
- **Motor speed:**
 - » Finger tapping
- **Psychomotor speed:**
 - » Alternating hand movements

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

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).

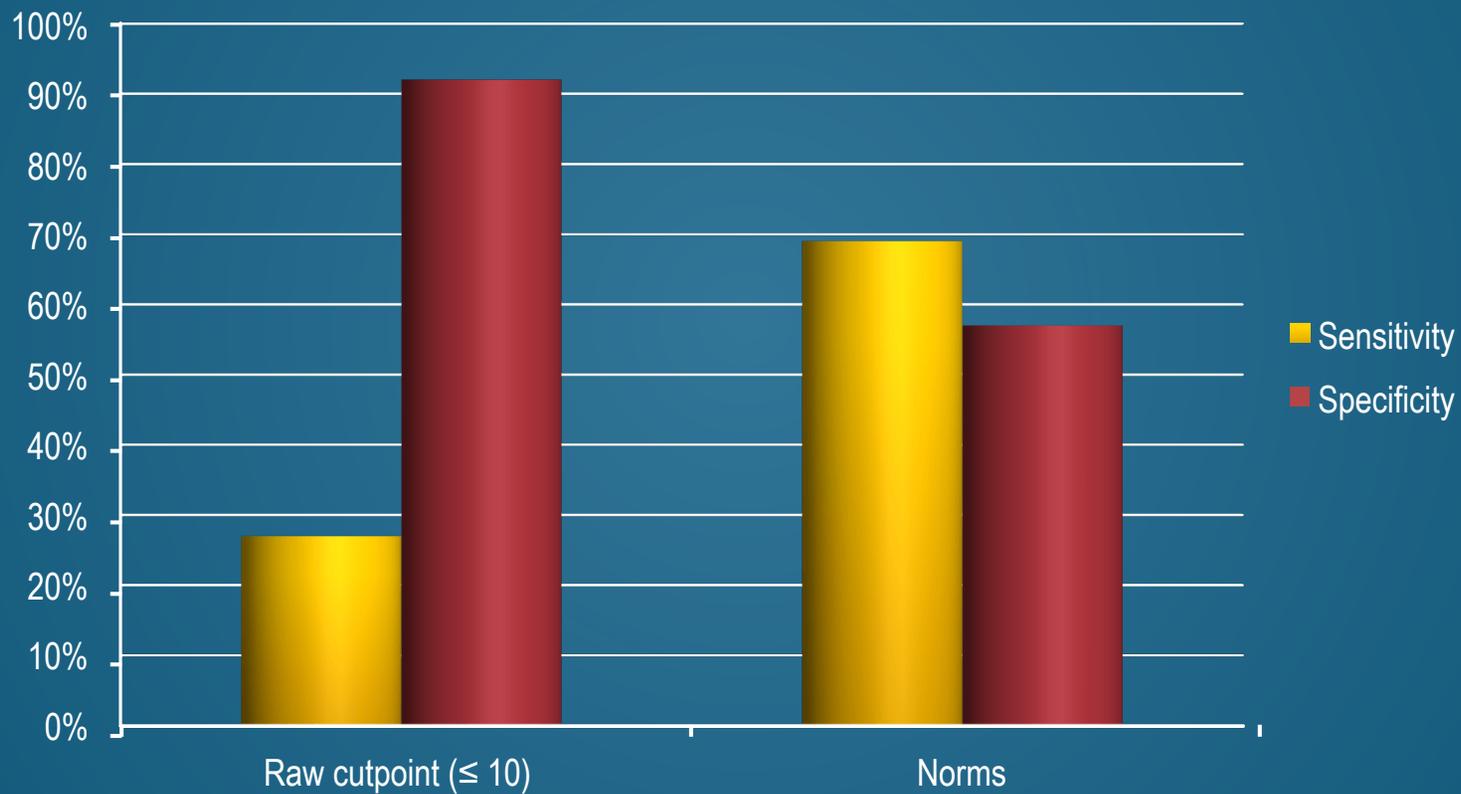
Give 1 point for each word spontaneously recalled.

Give 0.5 points for each correct answer after prompting

Maximum – 4 points.

-74

Classification accuracy of the HIV Dementia Scale (HDS)

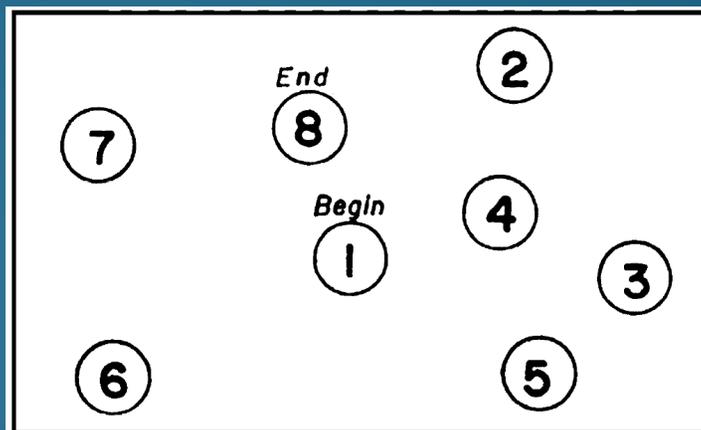


CHARTER study, N=1580

Letendre S, et al., HNRP data 2011:Unpublished.

Brief neuropsychological testing

- Brief neurocognitive screen (ALLRT)
 - » Trailmaking A & B
 - » Digit symbol test
 - Sensitivity up to 65%
 - Specificity up to 84%
- Grooved pegboard
- Paced auditory serial addition test
- CogState

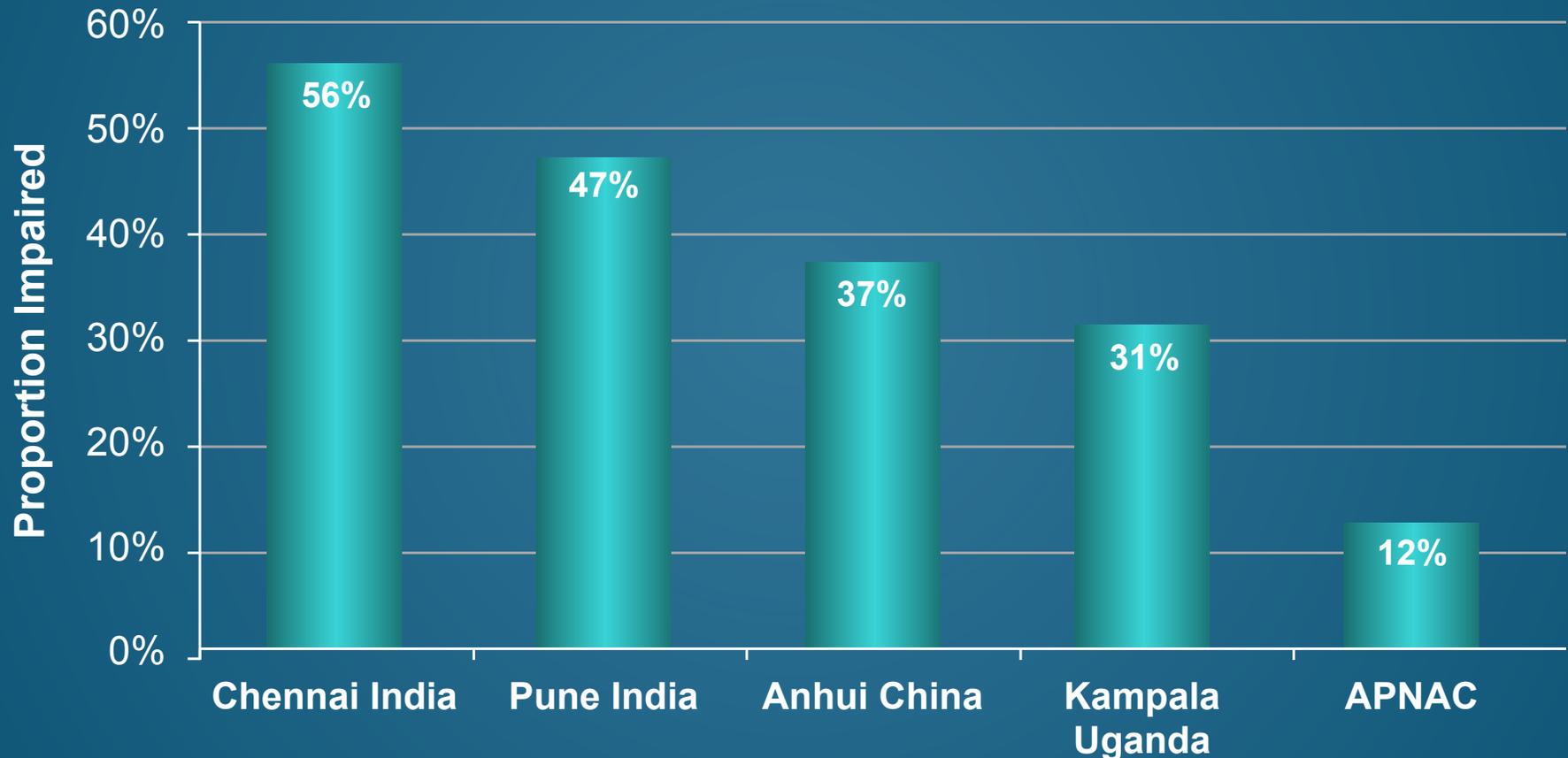


1	2	3	4	5	6	7	8	9
-	⊥	⊐	L	⊏	O	^	x	=

SAMPLES																			
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

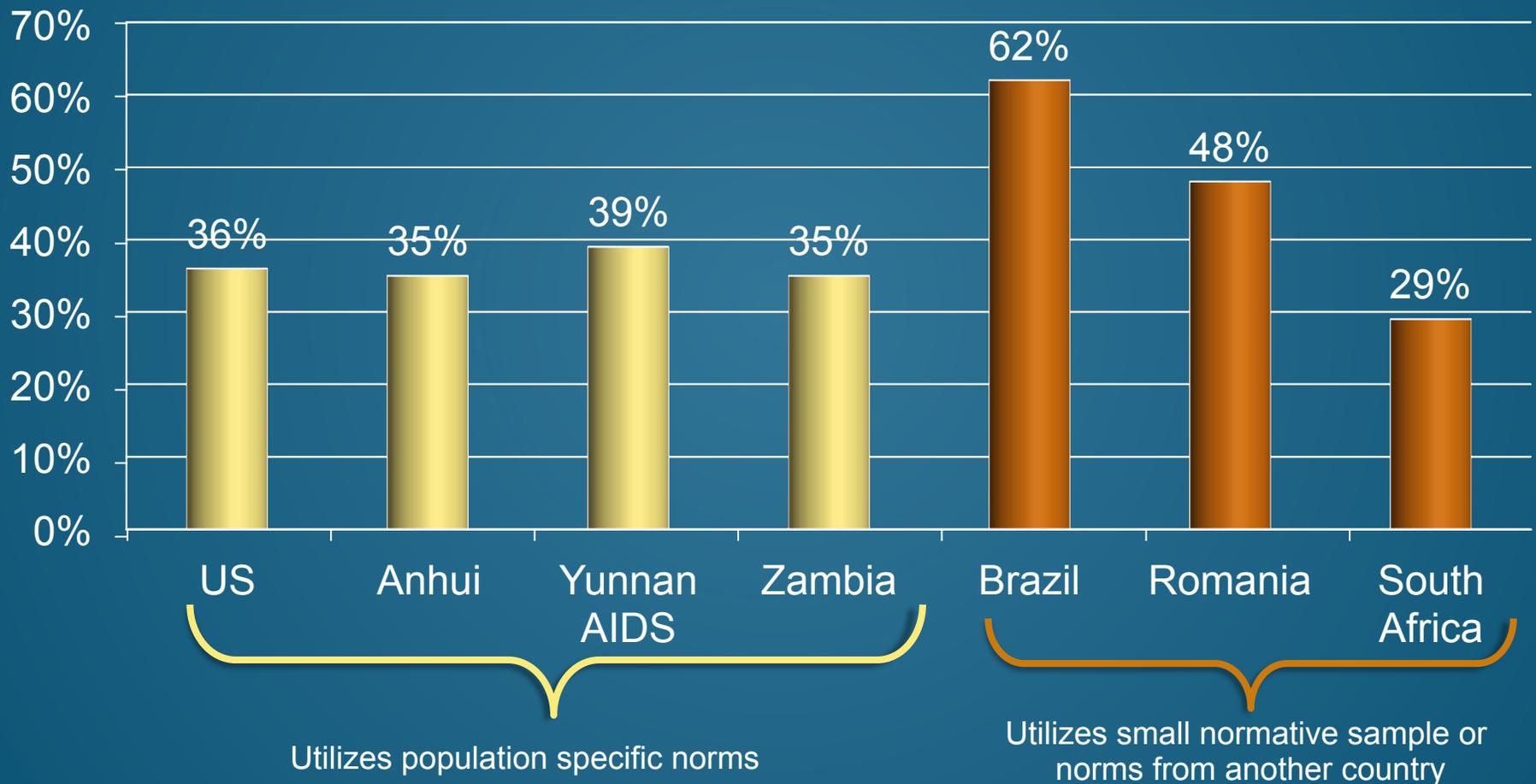
Ellis RJ, et al. J Neurovirol 2005;11:503-11

Lack of Comparable, Reliable Diagnostic Methods Impedes International NeuroAIDS Research and Treatment

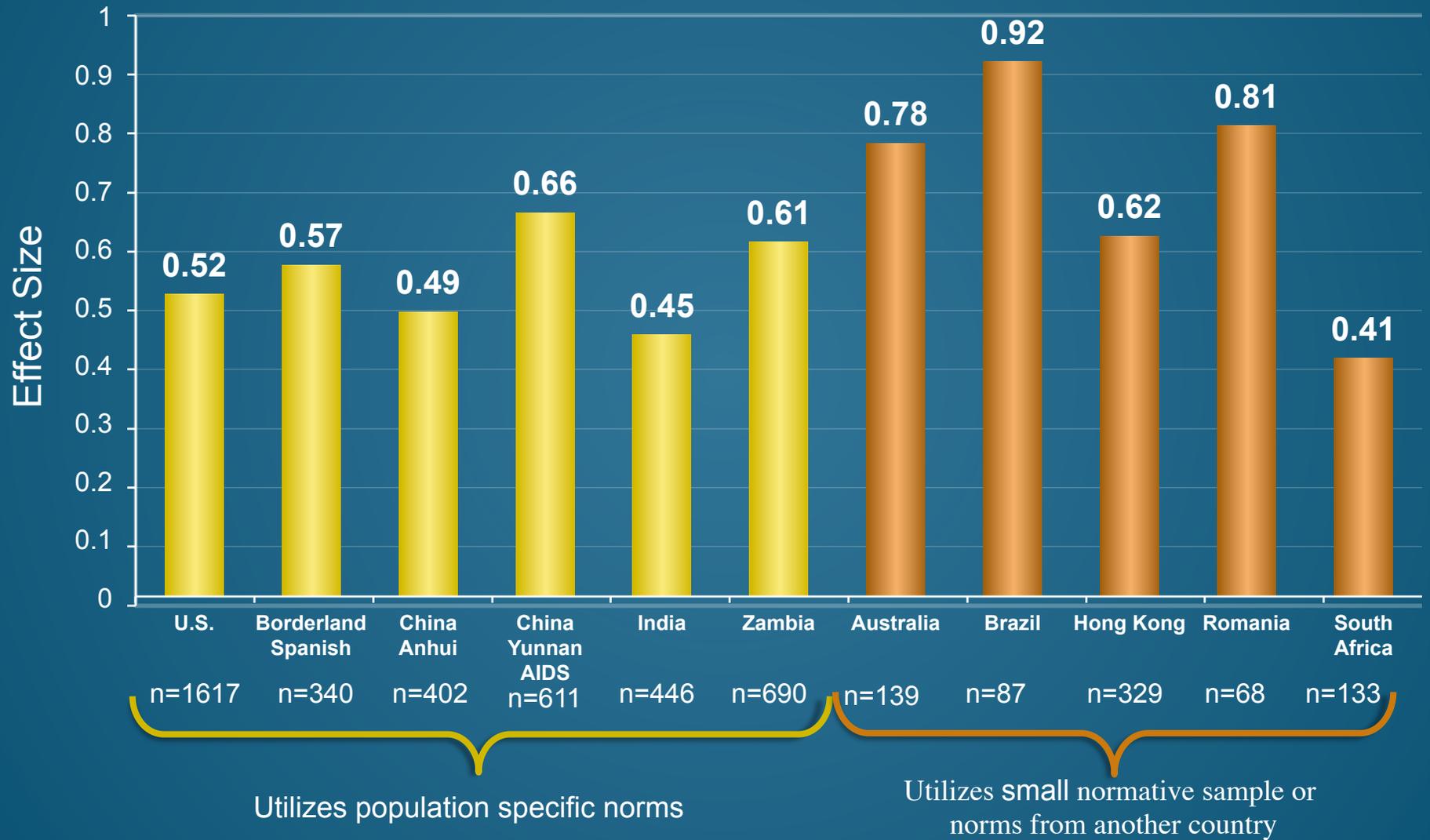


Yeptomhi, J., International Neuropsychological Society, 2006; Unpublished Data, NARI-UCSD Collaboration, 2006; Unpublished Data, China CDC-UCSD Collaboration, 2007; Wong et al, Neurology, 2007; Wright et al, XVI International AIDS Conference, 2006

NC Impairment in International HIV+ Cohorts



HIV Effect Size Across Countries



Summary

- HIV associated neurocognitive disorder (HAND) is common in HIV
- HAND persists even where combination antiretroviral therapy (CART) is available
- Significance of HAND: biological and functional correlates
- Cofactors (comorbidities) increase likelihood of HAND, and may influence progression
- Virologic control in CNS helps ameliorate HAND, but may not be fully effective in many cases
- ARV with higher CNS penetration-effectiveness (CPE) have some value, but must be balanced vs neurotoxicity
- Non pharmacologic (eg., cognitive rehabilitation) strategies may have promise

Priorities and Future Directions

- *HIV Reservoirs in the CNS:* research into timing, location and quantification of nervous system infection; whether viral evolution is compartmentalized, and whether it can be transmitted or eliminated.
- *Pathophysiology:* research into systemic and neurological inflammation and neurodegeneration; cerebrovascular disease; effects of aging and drug use.
- *Biomarkers:* research into imaging of viral reservoirs and ongoing disease activity; CSF-based biomarkers including state of the art “omics”; and the movement of biomarkers into clinical practice.
- *Clinical Studies:* research in acute and early infection; psychiatric manifestations; the development of specialized cohorts (e.g, women, children, drug abusers, other comorbidities); research into peripheral neuropathy; the integration of neurological and psychiatric complications with medical complications of HIV infection; pediatric studies to include children exposed to HIV but not infected; research into unique vulnerabilities in international settings, eg., effects of systemic inflammation due to TB, malaria, etc.
- *Development of CNS Specific Therapeutics:* research into targets for neuroinflammation; neuroprotection; antiretrovirals and elimination of CNS viral reservoirs; palliative care of persons with HAND or neuropathic pain; and CNS specific opportunistic infections (PML and TB). Development of cognitive remediation and other behavioral strategies

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And to Collaborating Investigators and Sponsors

UCSD HNRP (I. Grant, Director)

- Scott Letendre
- Ron Ellis
- Bob Heaton
- Edmund Capparelli
- Brookie Best
- David Moore
- Hamp Atkinson
- Davey Smith
- Tom Marcotte
- Cris Achim
- Steven Woods
- Eliezer Masliah
- Mariana Cherner
- Allen McCutchan

CHARTER (I. Grant, PI)

- David Clifford
- Justin McArthur
- Ned Sacktor
- Ann Collier
- Allen McCutchan
- Christina Marra
- Susan Morgello
- David Simpson
- Ben Gelman

National Institutes of Health

- ...Mental Health
- ...Drug Abuse
- ...Neurological Disorders and Stroke

Pharma

- Abbott Laboratories

Special Thanks to Dr. Scott Letendre

Thank You for Your Attention!

**HIV Associated Neurocognitive
Disorders in the era of modern CART**

Igor Grant, MD, FRCP(C)

Director

HIV Neurobehavioral Research Program

University of California, San Diego

