AMERICAN ACADEMY OF HIV MEDICINE

Neurocognitive Functioning among Persons with HIV

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This activity is jointly provided by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine.

This activity is supported by an independent educational grant from Gilead Sciences.

Target Audience

This activity has been designed to meet the educational needs of physicians, physician assistants, nurse practitioners, and pharmacists; other healthcare providers, such as nurses, nutritionists, social workers, and case managers are also encouraged to attend.

Statement of Need/Program Overview

Academy-credentialed providers, clinicians, members, and guest participants will gain a broader perspective on the intersection neurocognitive disorders and HIV. People with HIV are more likely to suffer from neurocognitive disorders than their HIV negative counterparts. This is exacerbated by the lack of mental health provider. This webinar is designed to give an overview of neurocognitive disorders and treatment, for HIV clinicians so they can address patient quality of life issues and treatment efficacy.

Joint Accreditation Statement

In support of improving patient care, this activity has been planned and implemented by the Partners for Advancing Clinical Education (PACE) and the American Academy of HIV Medicine. Partners for Advancing Clinical Education is accredited by the American Council for Continuing Medical Education (ACCME), Accreditation Council for Pharmacy Education (ACPE) and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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INTERPROFESSIONAL CONTINUING EDUCATION

Physician Continuing Medical Education

CREDIT DESIGNATION

- PACE designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Pharmacist Continuing Education

CREDIT DESIGNATION

- PACE designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of the Accrediting Council for Pharmacy Education.
- (Universal Activity Number #JA4008073-9999-24-070-L02-P

- Type of Activity: Knowledge

Upon completion of the online evaluation, your credit will be submitted to CPE Monitor.Pharmacists have up to thirty (30) days to complete the evaluation and claim credit. Please check your NABP account within thirty (30) days to make sure the credit has posted.

Nursing Continuing Professional Development

CREDIT DESIGNATION

- The maximum number of hours awarded for this Nursing Continuing Professional Development Activity is 1.0 contact hours.

Disclosure Information

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Faculty Disclosures:

Dr. David Moore, faculty for this program, has nothing to disclose.

Planners and Managers Disclosures

American Academy of HIV Medicine (AAHIVM)

The Academy planners and others have no relevant financial relationship(s) to disclose with ineligible companies.

Partners for Advancing Clinical Education (PACE)

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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Fee Information

There is no fee for this educational activity.

Learning Objectives

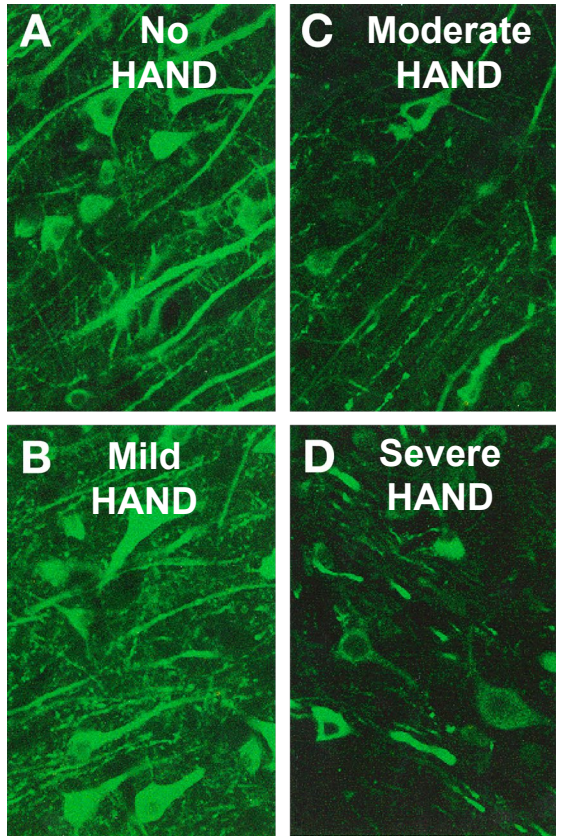
- To show standard methods for determining cognitive functioning among persons with HIV (PWH)
- To describe levels of neurocognitive functioning impairment cross sectionally and longitudinally among PWH
- To describe how co-occurring conditions impact neurocognitive functioning among PWH
- To discuss everyday functioning outcomes among PWH
- To identify the oncoming challenge of distinguishing neurocognitive difficulties among PWH who are aging

HIV in the Central Nervous System

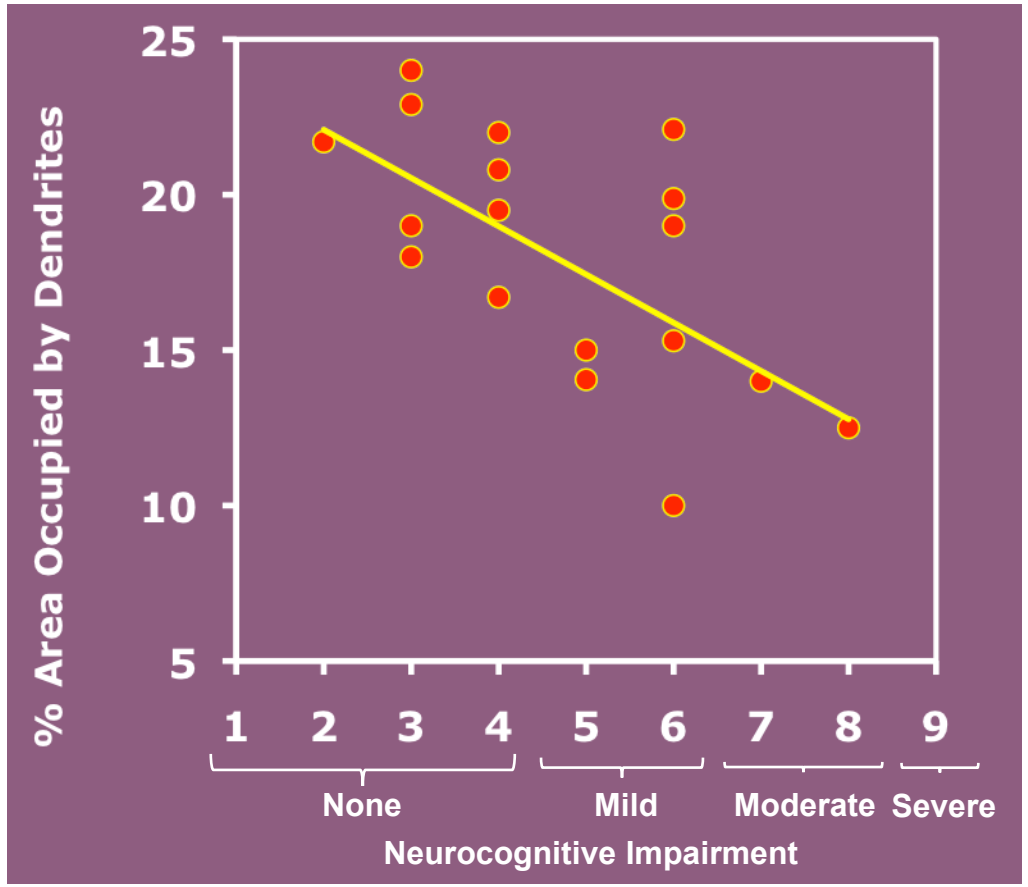
- HIV enters CNS soon after infection
- CNS infected cells: Blood-derived macrophages, resident microglia, astrocytes
- Neurologic disease: Eventually affects 25--50+% of people with HIV (PWH), depending upon ascertainment methods
- Neuronal loss, reduced synapto-dendritic complexity correlate w/ antemortem neurocognitive impairment

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

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

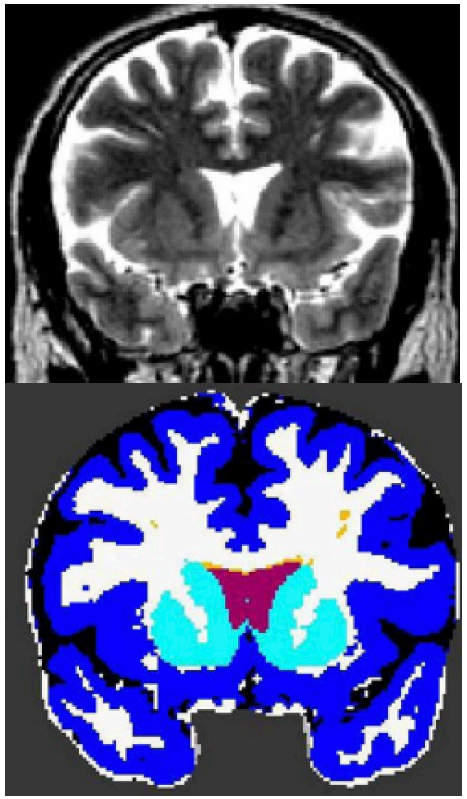


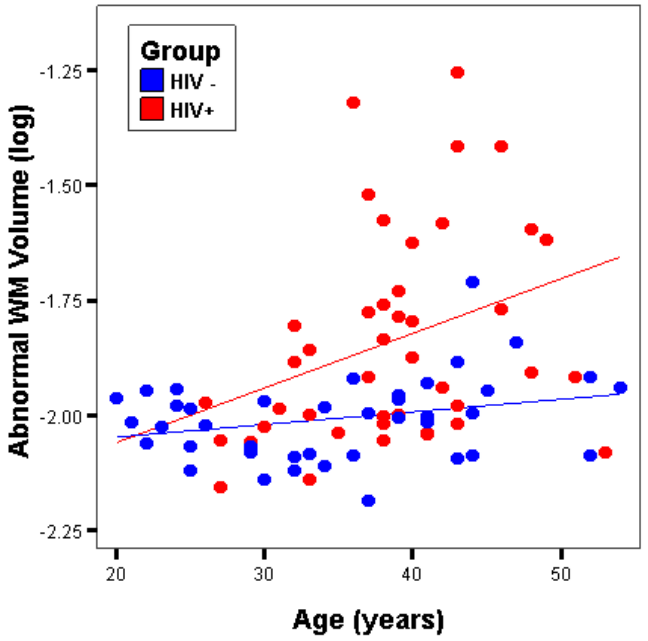
Greater Cognitive Impairment Before Death Corresponds to Greater Dendritic Loss



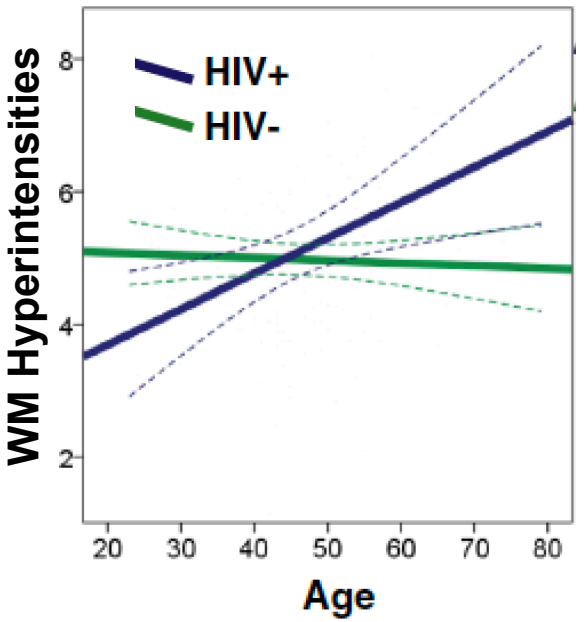
Masliah, et al. Ann Neurol.1997, 42(6): 963-72

HIV May Accelerate White Matter Injury

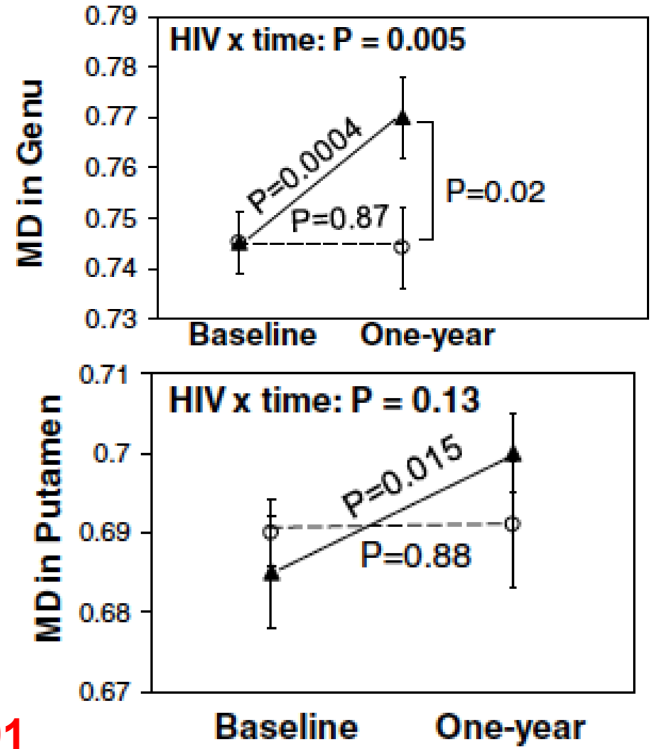




HIV x Age Interaction p = 0.003



HIV x Age Interaction p = 0.01



Archibald et al, J. Neurovirol. 2014. 20: 603–611

Fennema-Notestine et al, J Neurovirol, 2013. 19 (4), 393-401

Seider et al, J. Neurovirol. 2016. 22:201–212

Holt et al, J. Neurovirol. (2012) 18:291–302

Aims of Neuropsychological Assessment among PWH

- Detecting and classifying Neurocognitive Impairment (NCI)
- Determining if NCI is associated w/ co-occurring factors
  - Psychiatric illnesses, co-infections, other medical conditions
- Explore relations between NCI & HIV disease variables
  - Current & nadir CD4 count, VL, biomarkers, neuroimaging
- Evaluate relation between NCI & everyday functioning in populations around the world
- Determining implications for treatment
  - Adherence, drug regimen CNS penetration profiles

CHARTER Neurocognitive (NC) Test Battery: 7 Ability Domains

- Verbal Fluency
  - Animals
  - Letter
- Attn/Working Memory
  - PASAT-50
  - Letter-Number Sequencing
- Processing Speed
  - WAIS-III Digit Symbol
  - WAIS-III Symbol Search
  - TMT A

15 individual NC measures

- Executive Functioning
  - WCST-64 PR
  - TMT B
- Learning
  - Verbal (HVLT-R) Total
  - Visual (BVMT-R) Total
- Memory
  - Verbal (HVLT-R) Recall
  - Visual (BVMT-R) Recall
- Motor
  - Grooved Pegboard DH
  - Grooved Pegboard NDH

Updated research nosology for HIV-associated neurocognitive disorders

	Acquired Impairment in ≥ 2 Cognitive Abilities	Affects Daily Functioning	Onset After HIV	No Current Strongly Confounding Condition
Asymptomatic Neurocognitive Impairment (ANI)	✔	**No**	✔	✔
Mild Neurocognitive Disorder (MND)	✔	**Mild**	✔	✔
HIV-Associated Dementia (HAD)	**Marked**	**Marked**	✔	✔

- Impairment must be attributed to HIV, at least in part.
- "Minimal" or "Moderate" comorbidities allowed, but "Severe" conditions preclude diagnosis of HAND
- Supplementary materials outline how co-occurring conditions should be handled

Symptomatic HAND

Antinori et al, Neurology 2007, 69: 1789-99

Described an approach to categorizing the severity of comorbid conditions other than HIV that could affect cognition

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Frascati Comorbid Conditions

- **MINIMAL:** Could have minor effects on NP test results, but unlikely to cause even mild global impairment (does not preclude diagnoses of HAND).

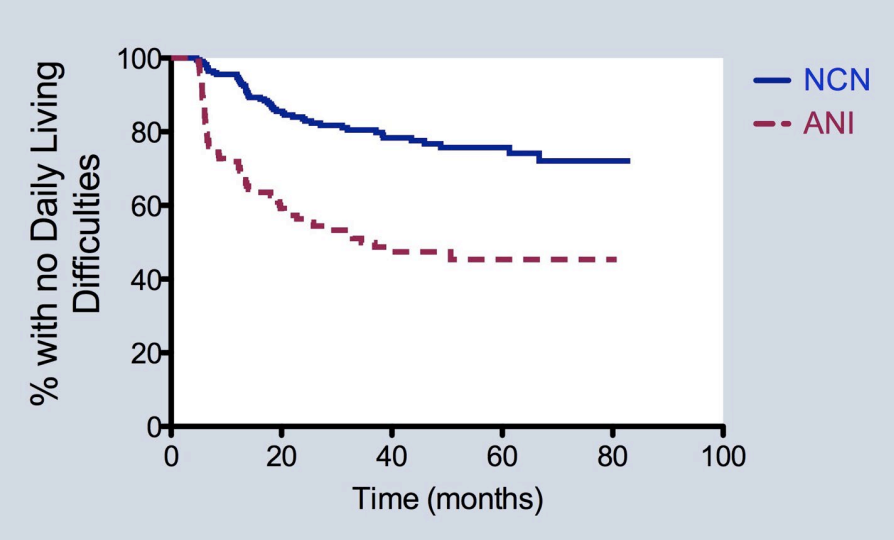
- **MODERATE:** Likely to have at least mild effects on NP test results but cannot fully explain the nature and/or timing of observed impairment or disability (does not preclude diagnoses of HAND).

- **SEVERE:** Likely to have major effects on NP test results, with significant neurocognitive impairment and functional disability, or NP results invalid due to poor effort (precludes diagnoses of HAND at baseline assessment).

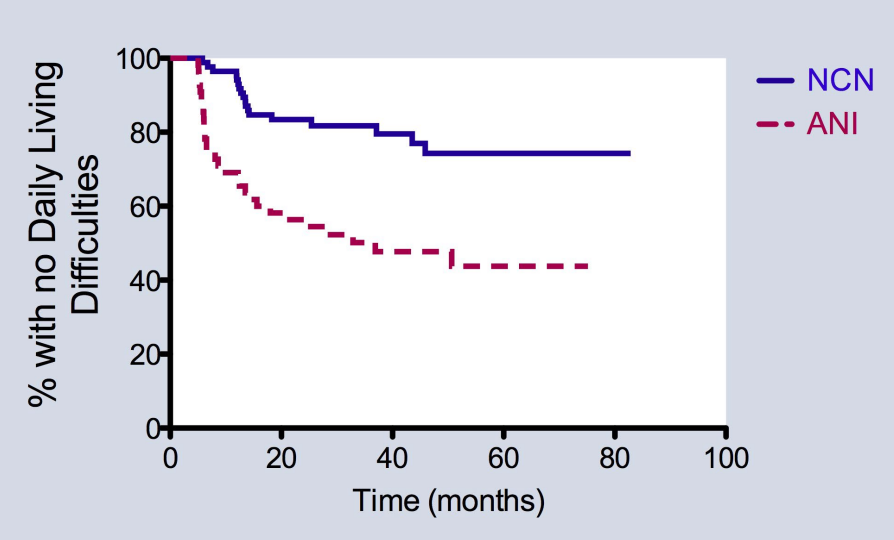
Even "Asymptomatic" NCI may increase risk of developing difficulties in everyday functioning

Over time those initially with ANI developed functional difficulties more often than those who were cognitively normal

Total Sample



Virologically Suppressed

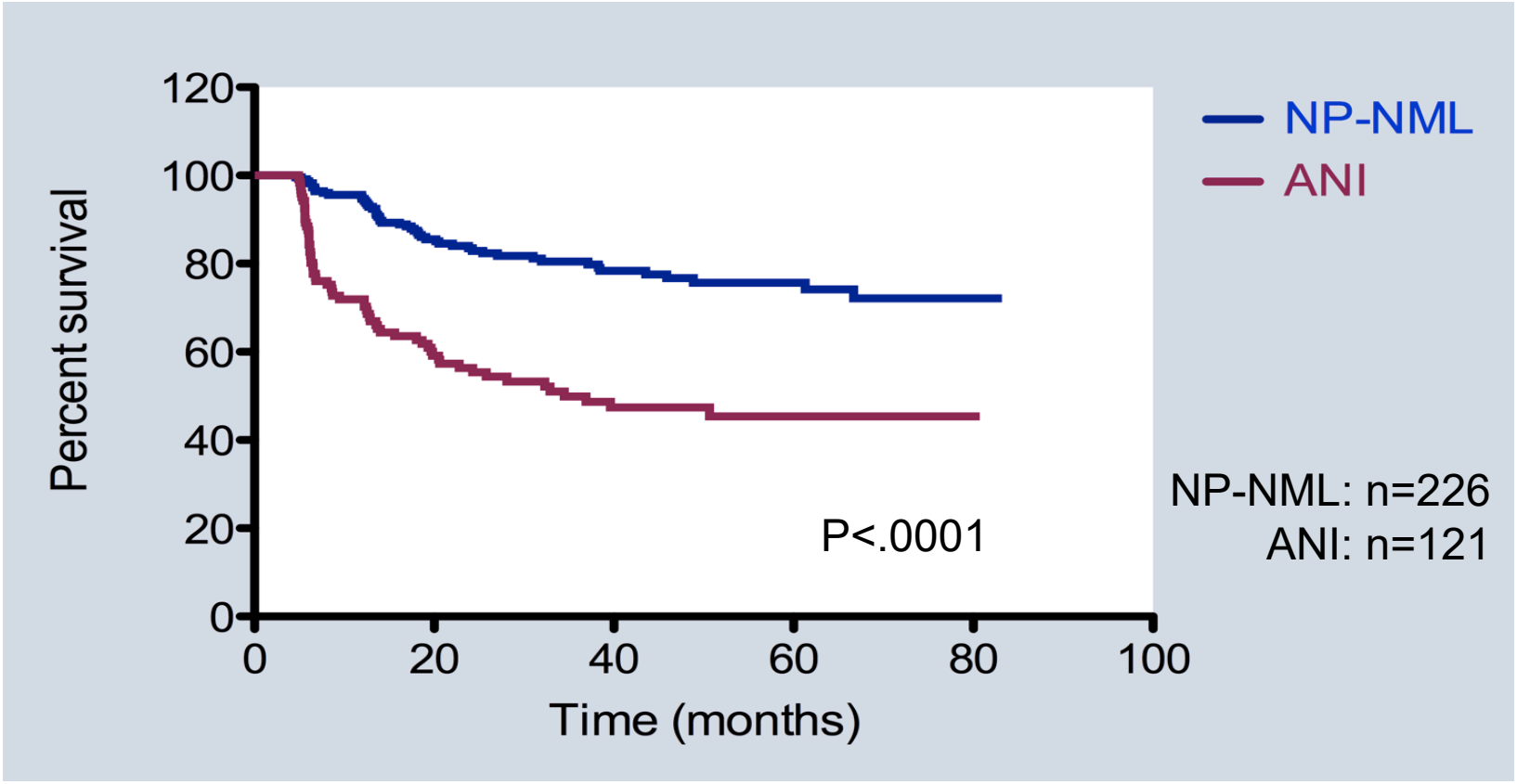


NML:	n=226	Relative Risk: 3.02
ANI:	n=121	CI: 2.08, 4.42

NML:	n=85	Relative Risk: 3.1
ANI:	n=55	CI: 1.7, 5.7

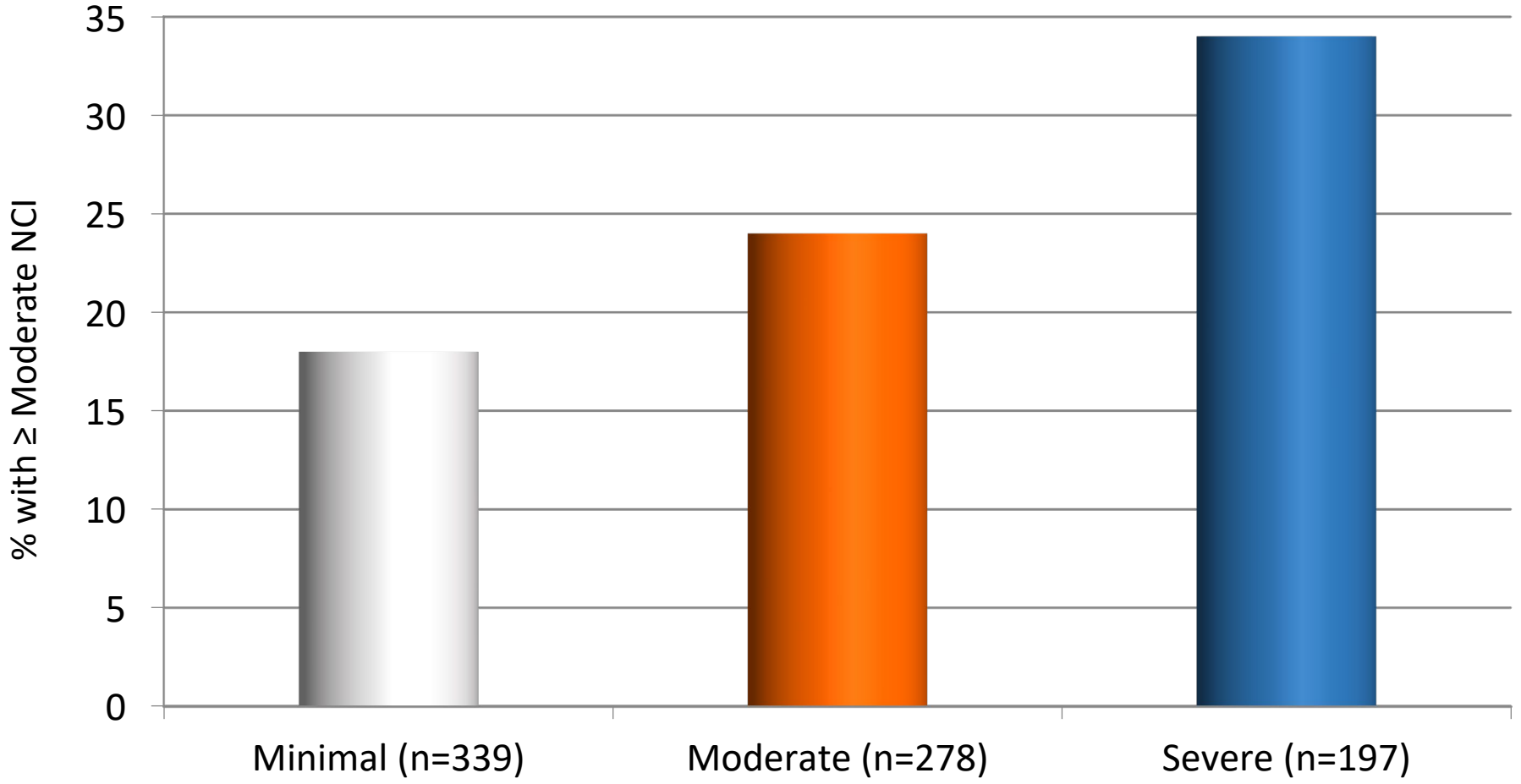
Grant I, et al., Neurology, 2024 in press

ANI Increases Risk for Change to MND

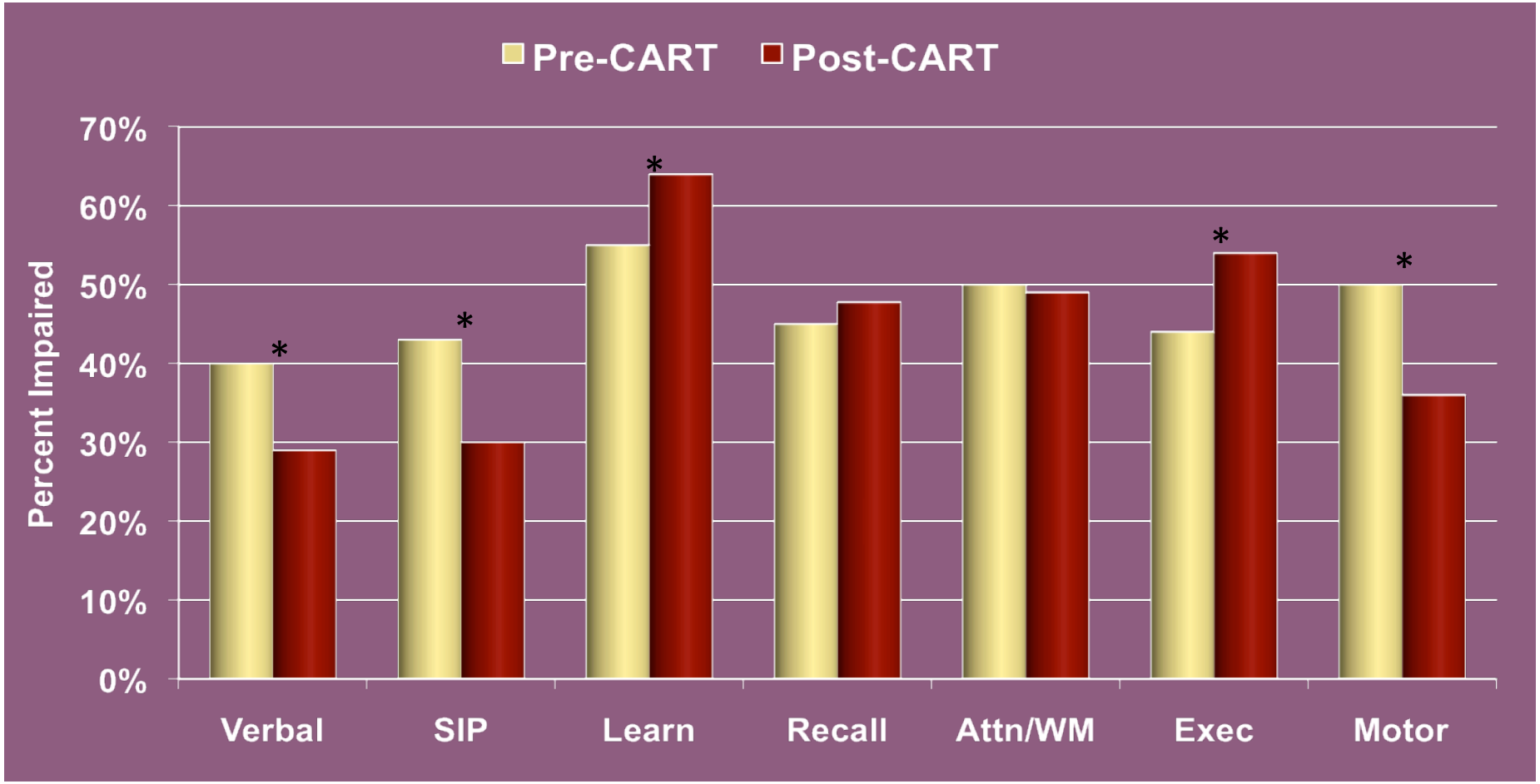


Relative Risk for Symptomatic Status: 3.23 CI [2.16-4.84]; p<.0001

Increasing Severity of Impairment with Increasing Comorbidity (NCI only)



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



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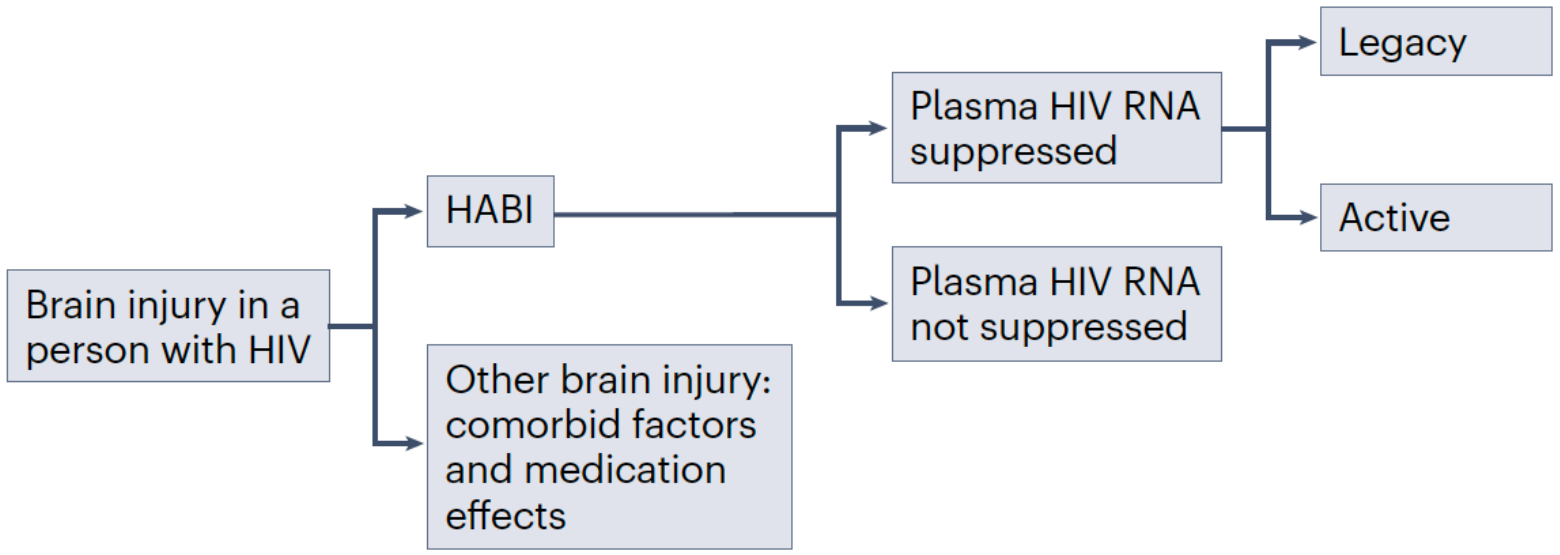
* p<.05; ** p<.01; ***p<.001

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

Alternative Approaches to Classifying NCI in PWH

HIV-Associated Brain Injury: Focusing on Conditions of Greatest Clinical Concern



Potential causes of brain injury in people living with HIV

This is not an exhaustive list, as any neuropathological process can potentially affect people living with HIV.

HIV-associated brain injury (HABI) (Fig. 1)

- Legacy HABI: inactive brain injury from pretreatment damage
- Active HABI: ongoing brain injury leading to clinical or radiological progression

Other causes of brain injury

- Previous or ongoing CNS infections (for example, neurosyphilis, CNS tuberculosis, CNS toxoplasmosis, CNS cryptococcosis and progressive multifocal leukoencephalopathy)
- Cerebrovascular disease
- Traumatic brain injury
- Neurodegenerative disorders such as Alzheimer disease
- Other non-HIV-related neurological condition (for example, multiple sclerosis or uncontrolled epilepsy)
- Developmental disability
- Nutritional deficiencies (for example, vitamin B_{12} or niacin deficiency)
- Coinfections (for example, syphilis or hepatitis C)
- Hazardous alcohol use
- Substance misuse
- Antiretroviral CNS neurotoxicity

NeuroHIV
NAPLES, ITALY
GRAND HOTEL ORIENTE

Nightingale et al, Nature Reviews Neurology, 2023.
https://doi.org/10.1038/s41582-023-00813-2

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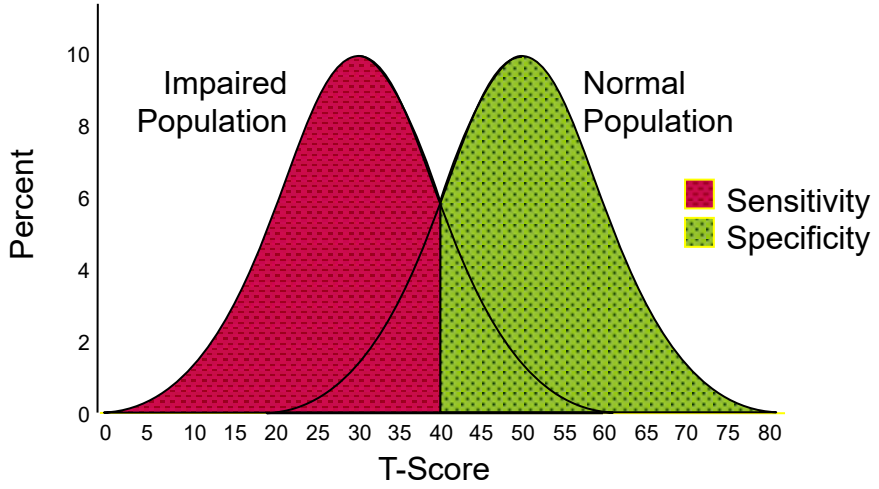
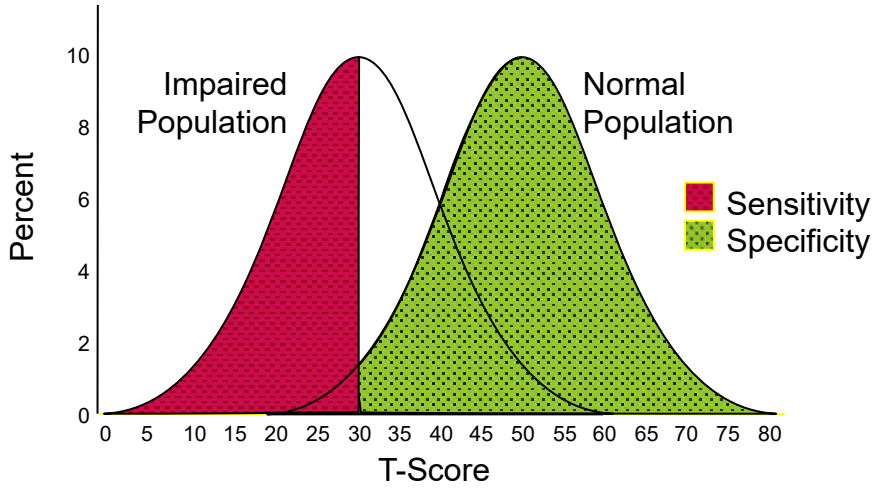
Inverse Relationship Between Specificity and Sensitivity





Increasing specificity will lead to fewer false positives, but at the risk of missing those with problems.

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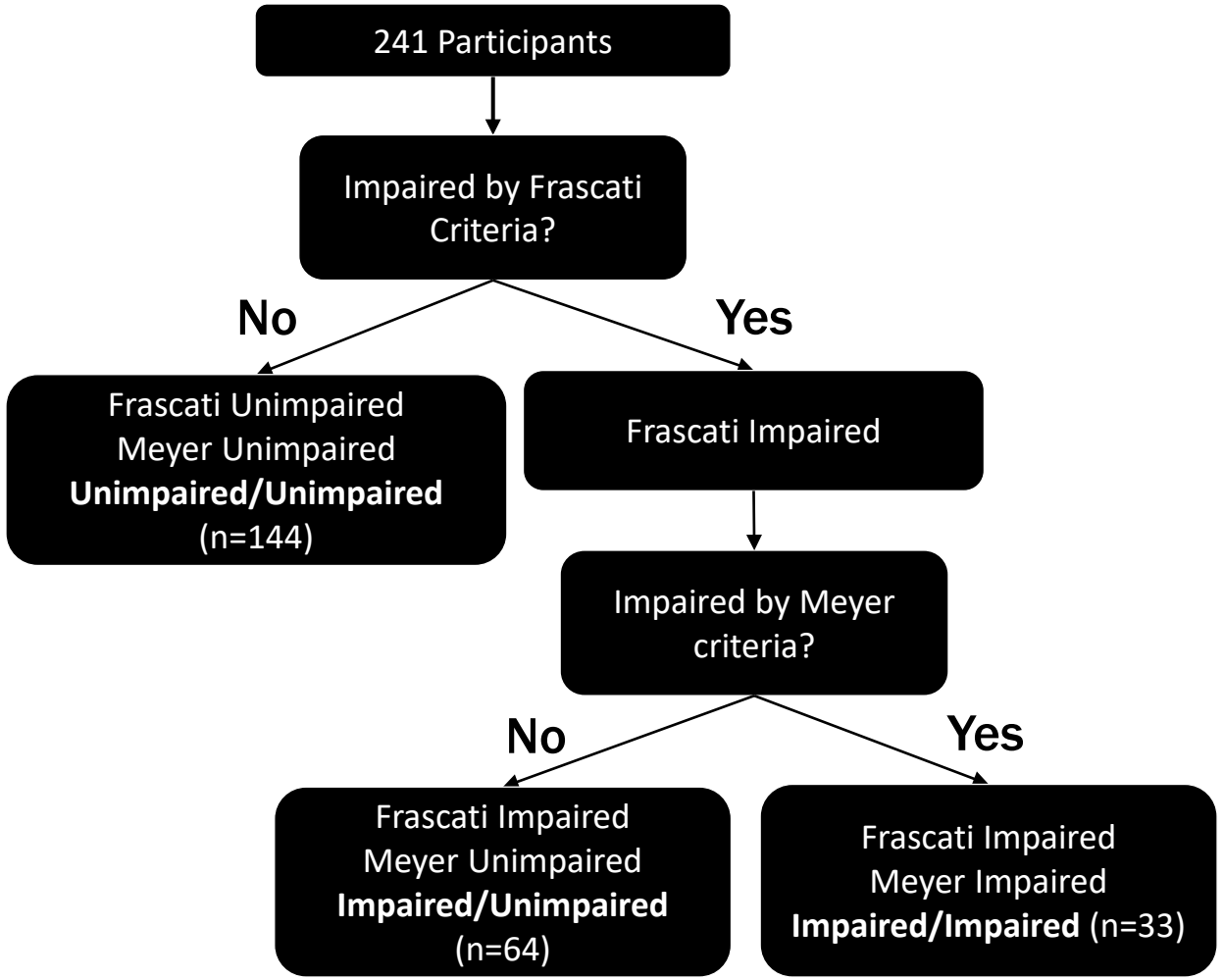
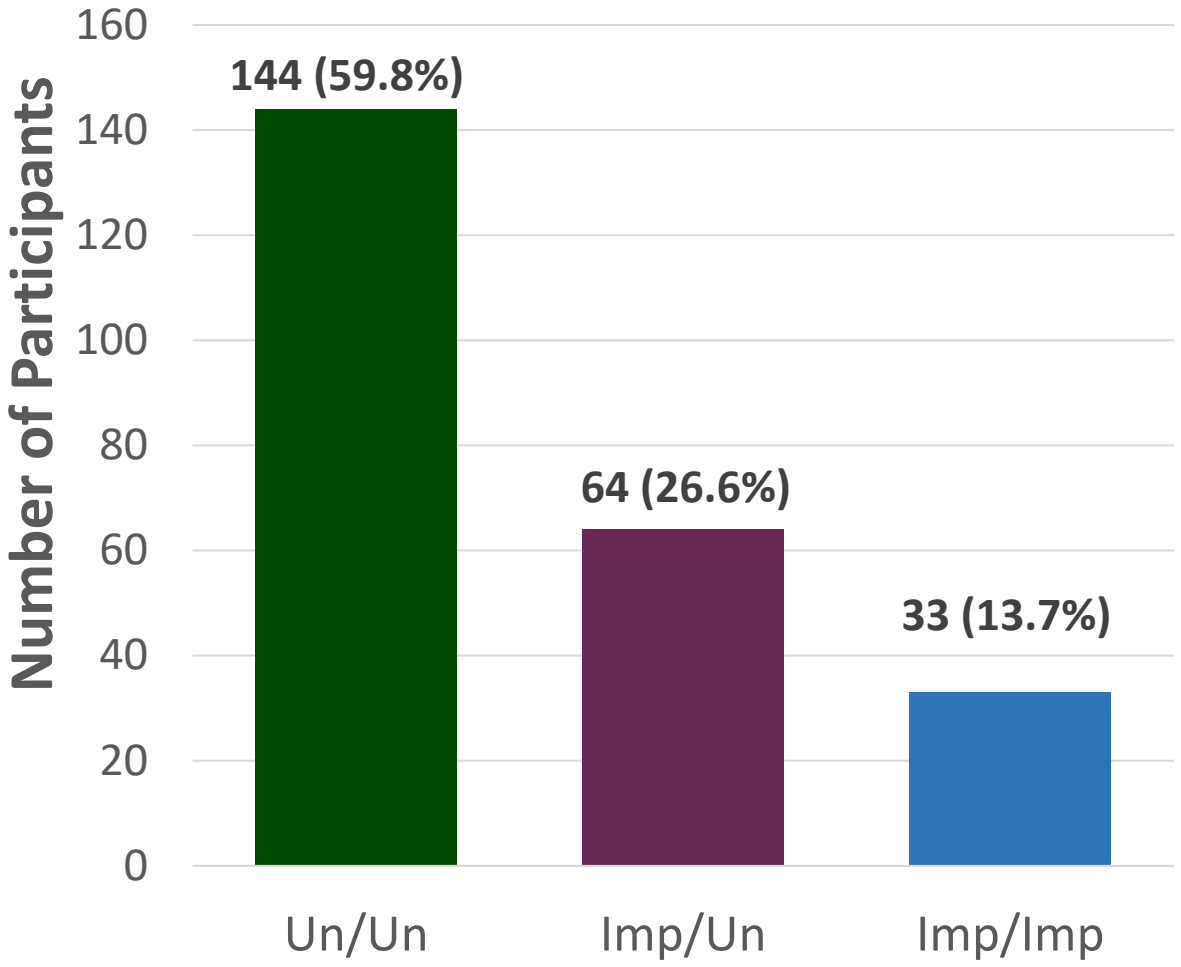
Meyer et al. (2013) Conclusions

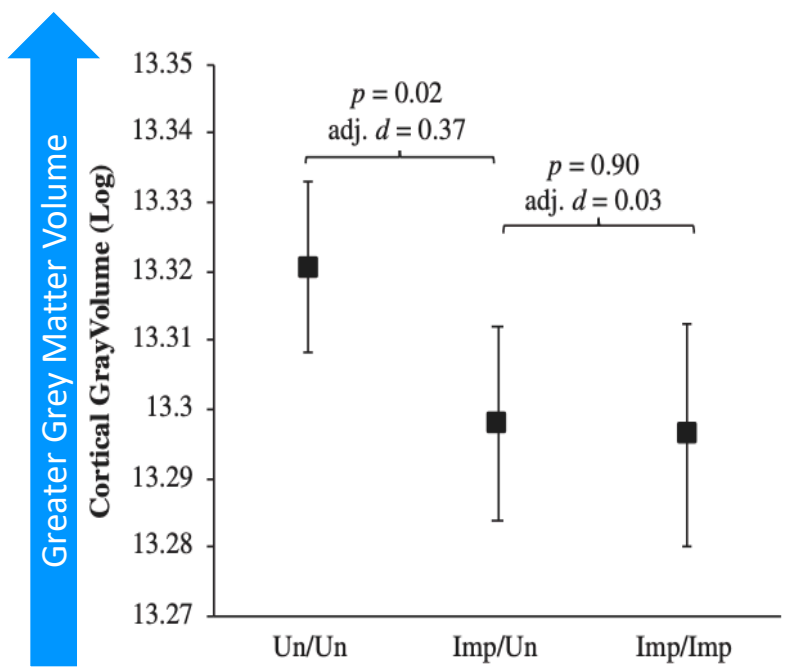
- Meyer et al. suggest Frascati criteria for ANI & MND have high false-positive frequencies
- “Minimizing false-positive frequencies is critical to decrease bias in prevalence estimates and minimize reductions in power in studies of association, particularly for mild forms of HAND.”
- Recommend:
  - limiting analysis to 3-5 cognitive domains
  - changing the Z score threshold to ≤-1.5 for mild impairment
  - using the average Z score to define an abnormal domain.
  - Meyer et al. does not address comorbidities

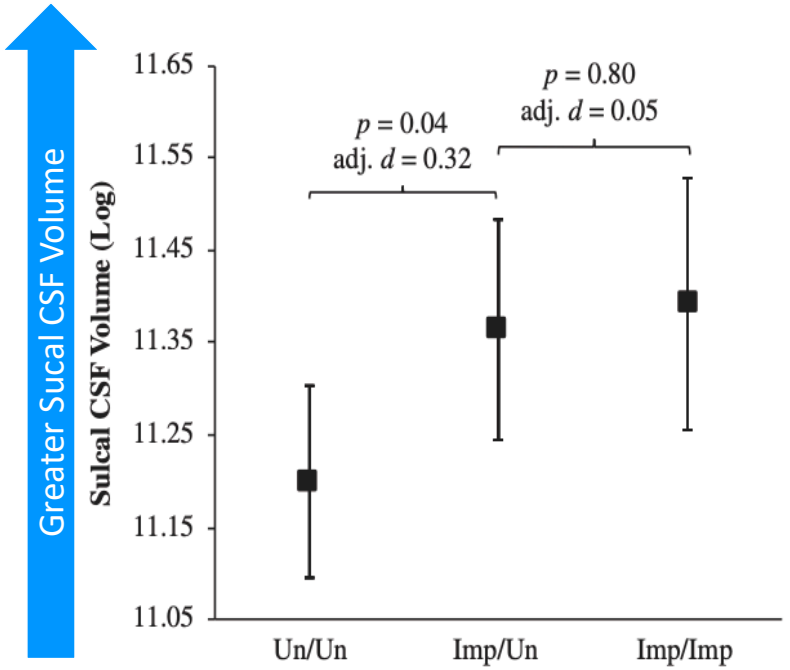
Participant Groups

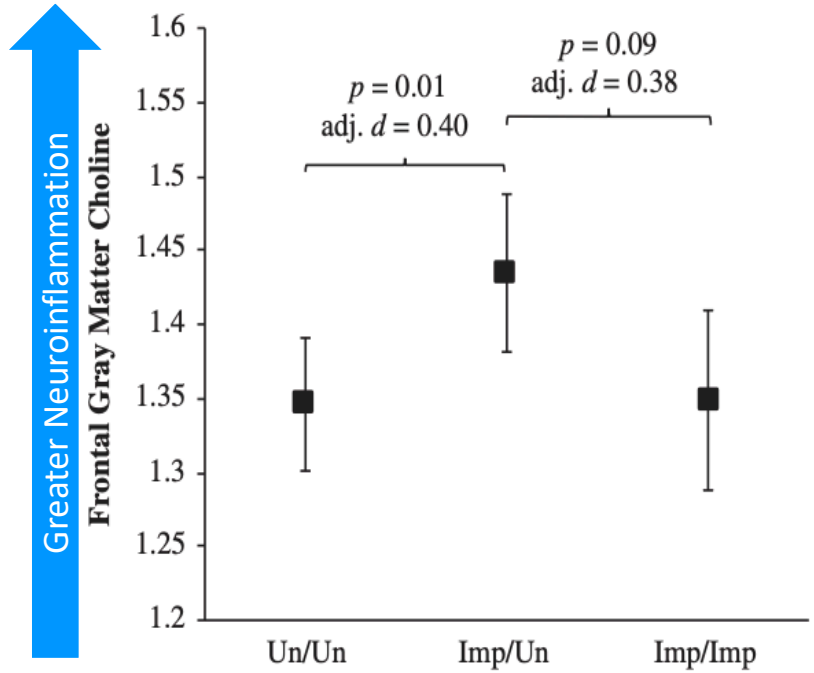




The Meyer criteria fails to capture a substantial portion of PLWH with brain abnormalities





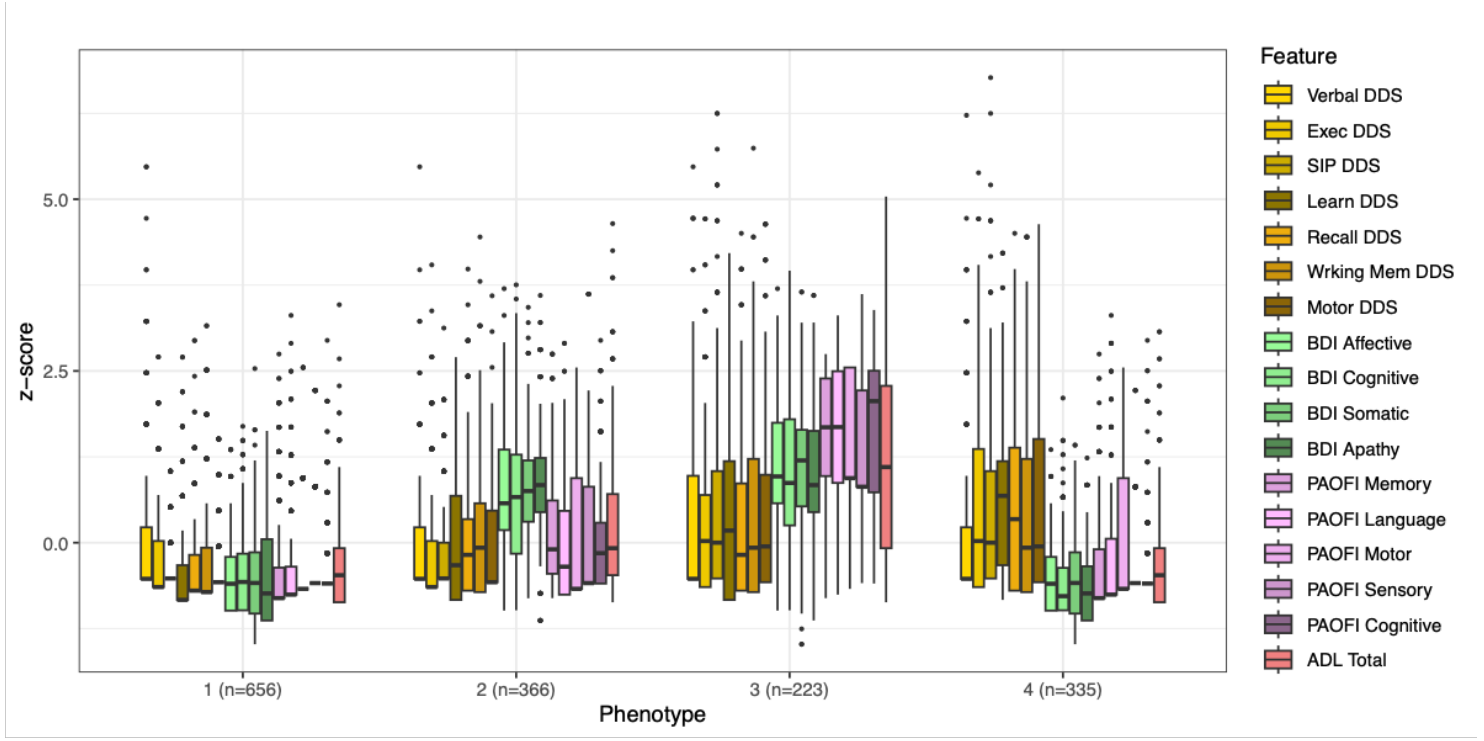


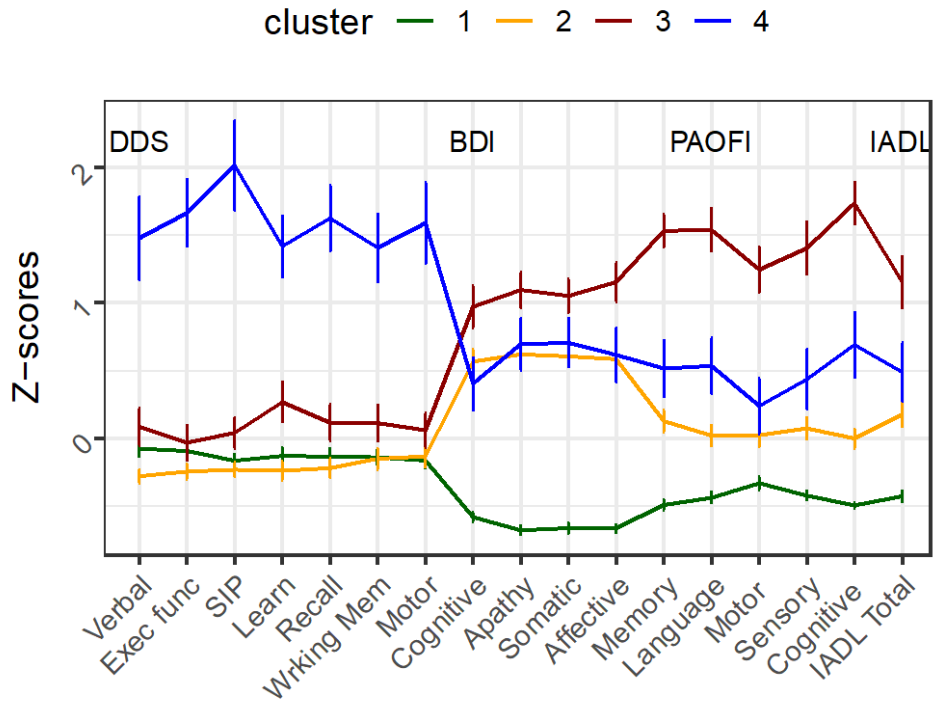
Un/Un = unimpaired via Frascati and Meyer criteria
Imp/Un = Impaired via Frascati criteria, unimpaired via Meyer criteria
Imp/Imp = impaired via Frascati and Meyer criteria

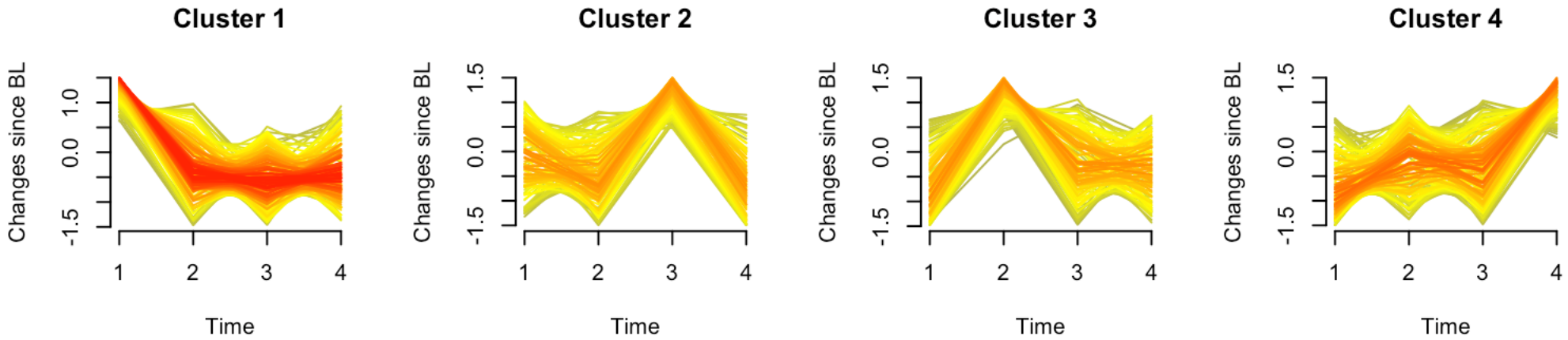
Campbell et al., 2019

Conclusions

- Those that are classified as impaired using Frascati criteria but do not meet criteria for impairment using the Meyer recommendations differ neuroanatomically from those with normal cognition.
- Meyer criteria appear to under-classify HAND by failing to identify a large (26.5%), clinically relevant group of individuals with brain abnormalities.
- These findings support continued use of Frascati criteria to detect HIV-associated CNS dysfunction.







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Tang et al, CROI 2023, Abstract 474

CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER):

Multi-Site Study (1555 HIV+ Participants):

- Johns Hopkins University
- Mount Sinai School of Medicine
- University of California San Diego
- University of Texas Medical Branch
- University of Washington Seattle
- Washington University, St. Louis

MH22005/HHSN27120100036C NIMH/NINDS

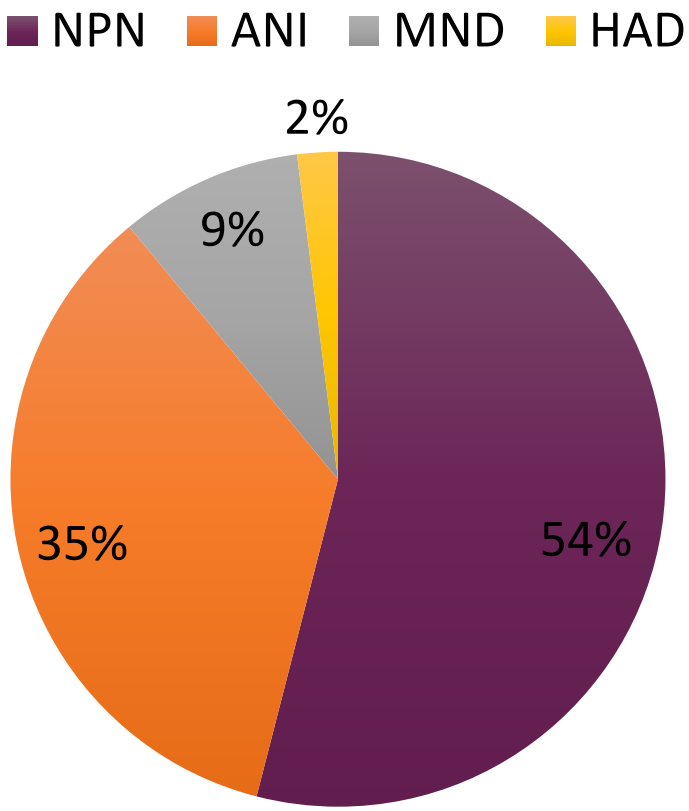
Prevalence of Specific HAND Diagnoses in CHARTER (N=1555 HIV+)

NPN = neurocognitive unimpaired

ANI = asymptomatic neurocognitive impairment

MND = mild neurocognitive disorder

HAD – HIV associated dementia

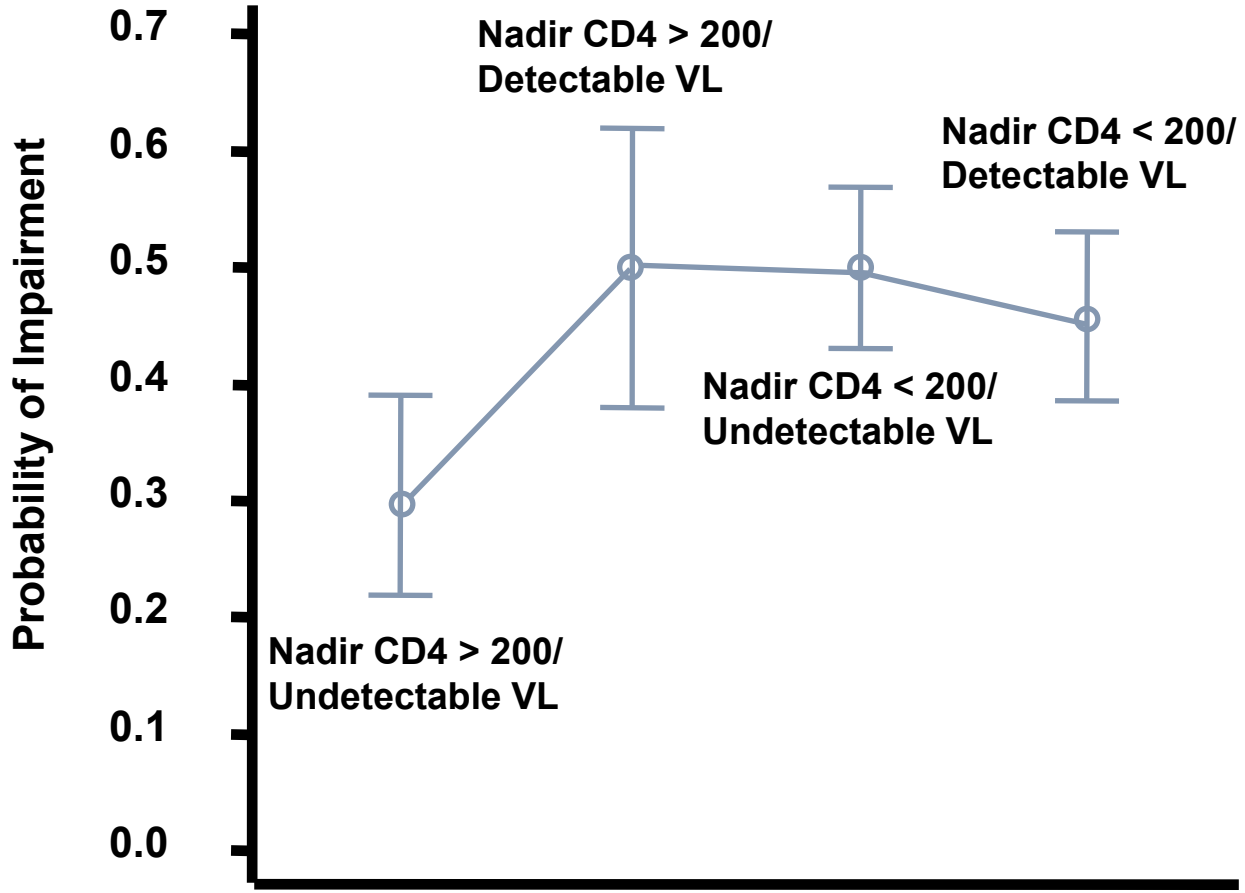


Heaton et al., Neurology 2010, 75(23): 2087-96

CHARTER Comorbidity Group Comparisons

	Minimal 843 (54%)	Moderate 473 (31%)	Severe 239 (15%)	
% AIDS	62.9%	64.1%	70.%	
Known Duration HIV+ (months)	116.6 (77.1)	129.2 (89.3)	124.5 (102.2)	Min<Mod
Nadir CD4	216.2 (200.4)	203.8 (199.3)	181.8 (169.2)	Min>Sev
% On CART	69.9	71.7	74.1	
Current CD4	467.0 (278.4)	452.8 (300.6)	448.9 (279.6)	
% Detectable Plasma VL	60.0%	55.9%	60.0%	
% Detectable CSF VL (n=1205)	35.2%	32.0%	33.0%	
% NC Impaired	41%	59%	84%	Min<Mod<Sev

HIV treatment implications: lower neurocognitive impairment risk when immuno-suppression is avoided and virologic control is good

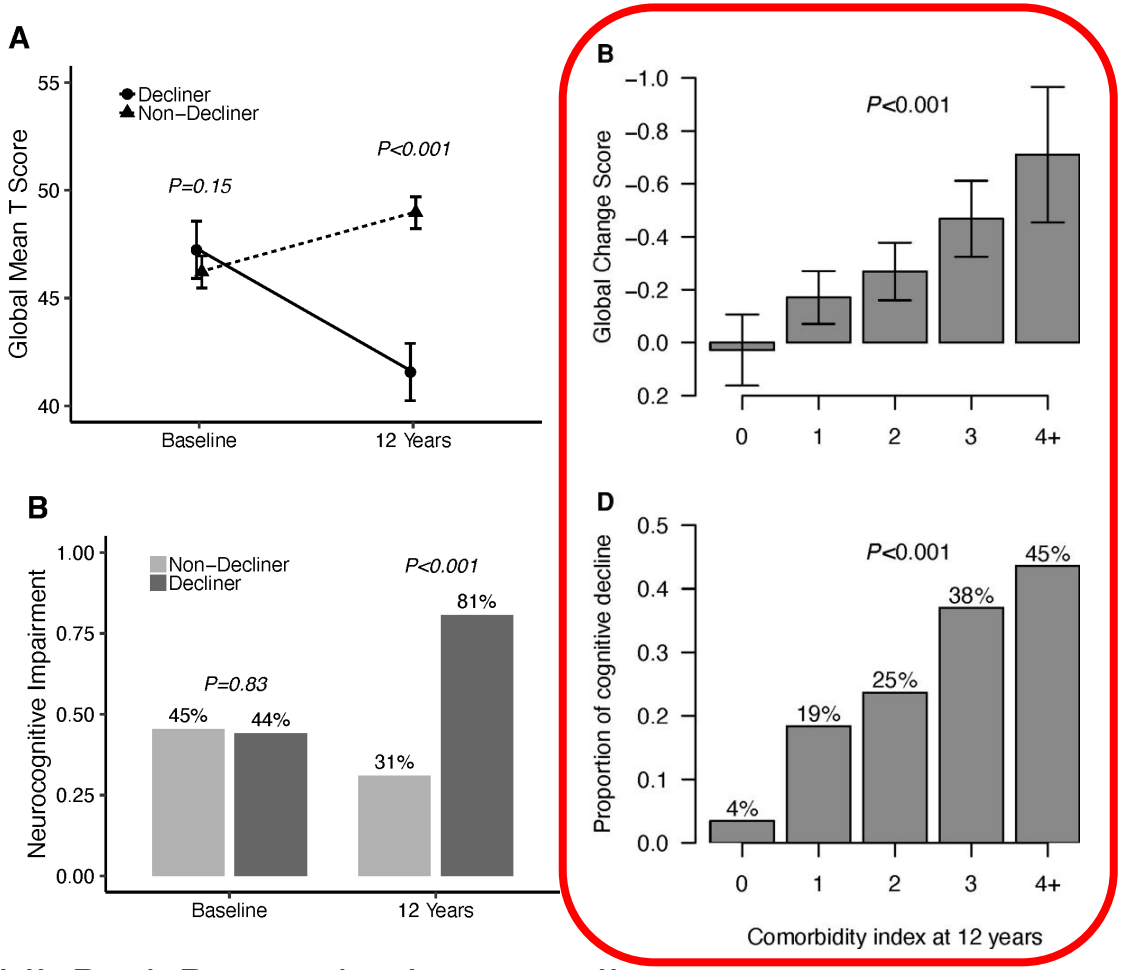


Heaton RK, et al. (2010). Neurology, 75, 2087-2096

Twelve-Year Neurocognitive Decline in PWH is Associated with Comorbidities, Not Age

- 402 PWH who were comprehensively assessed twice 12 years apart at six sites in the US
- Using Global Change Score and normative data, **23.7% declined, 70.0% remained stable, and 6.2% improved**

	Risk	Baseline	12 Years
Hypertension	Present	√	
Chr. Pulmonary Dis.	Present	√	√
Diabetes	Present		√
BDI-II	> 13	√	√
Lifetime Cannabis Use Disorder	Present	√	√
Serum AST	Higher	√	
Serum Protein	Lower	√	
Hematocrit	Lower		√
Prefrail/Frail	Present		√



BDI-II=Beck Depression Inventory-II

Heaton et al, Brain 2023, PMID: 36477867

Co-Occurring Conditions

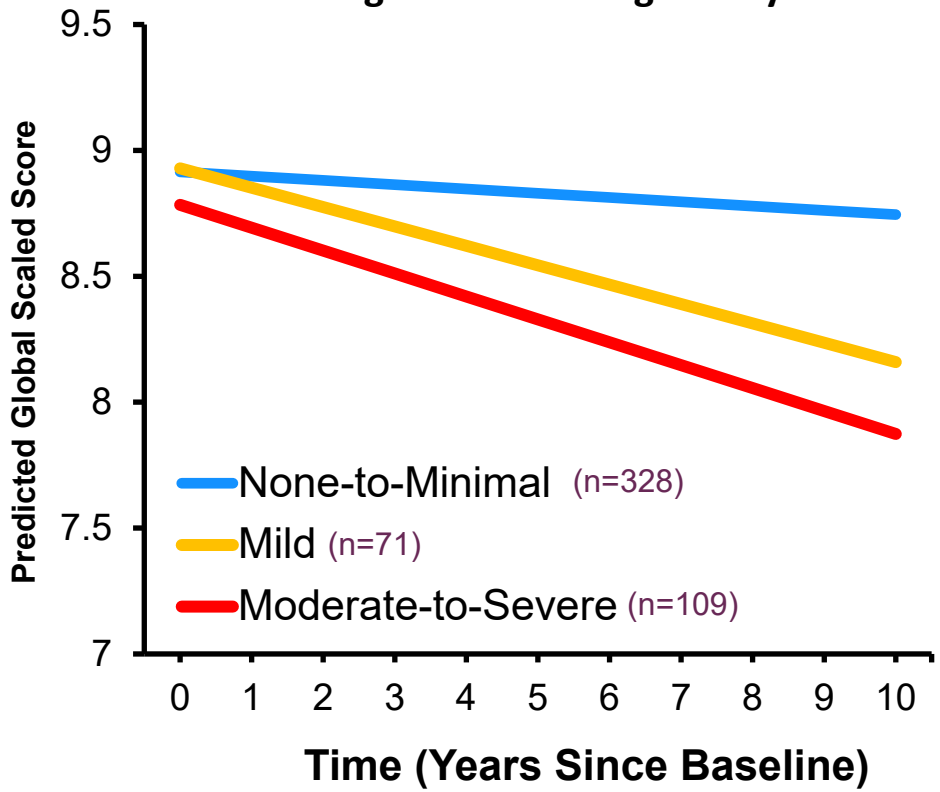
Comorbidities: Why do we care?

Major risk factors for:

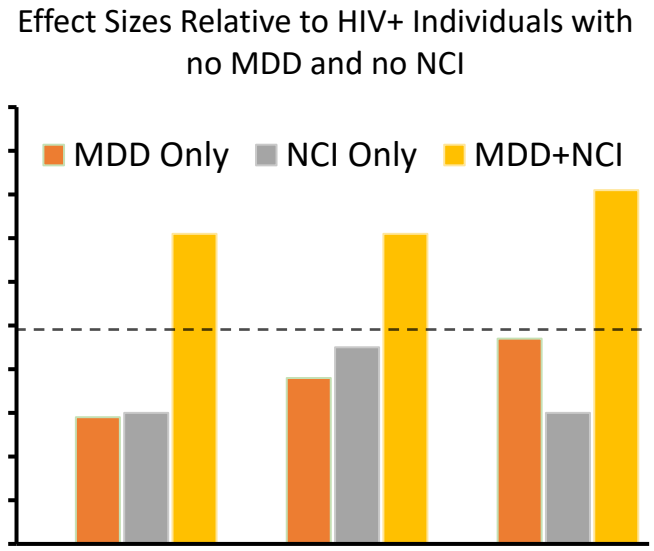
- death
- disability
- need for dialysis
- need for supplemental oxygen
- polypharmacy
- Stroke, MI

Relationships between depression, cognitive decline and functional outcomes in HIV

Higher mean depressive symptom severity associated with greater decline in cognitive functioning over an average of 4 years

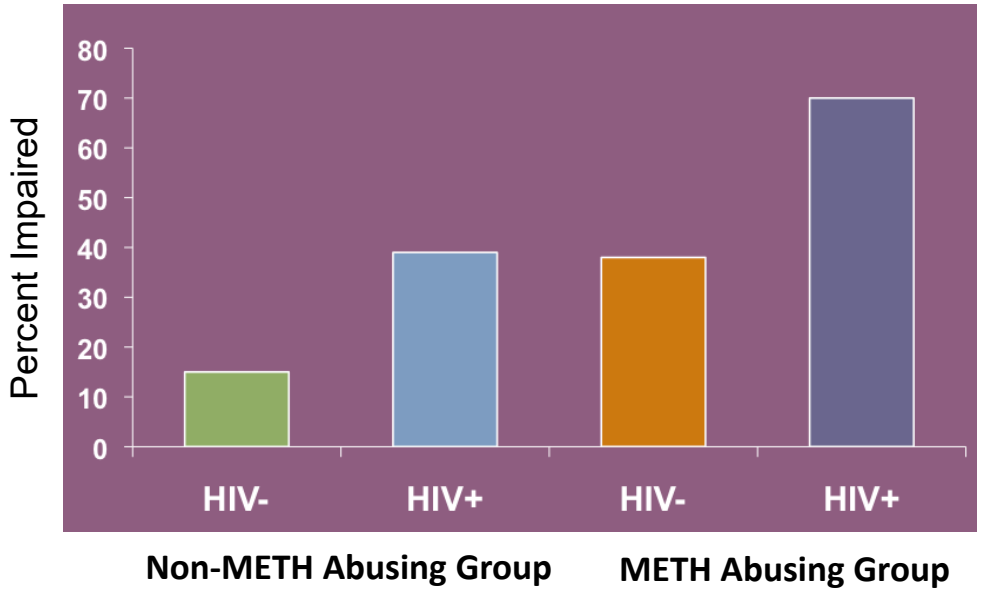


Synergistic effects of LT MDD and neurocognitive impairment (NCI) on everyday functioning

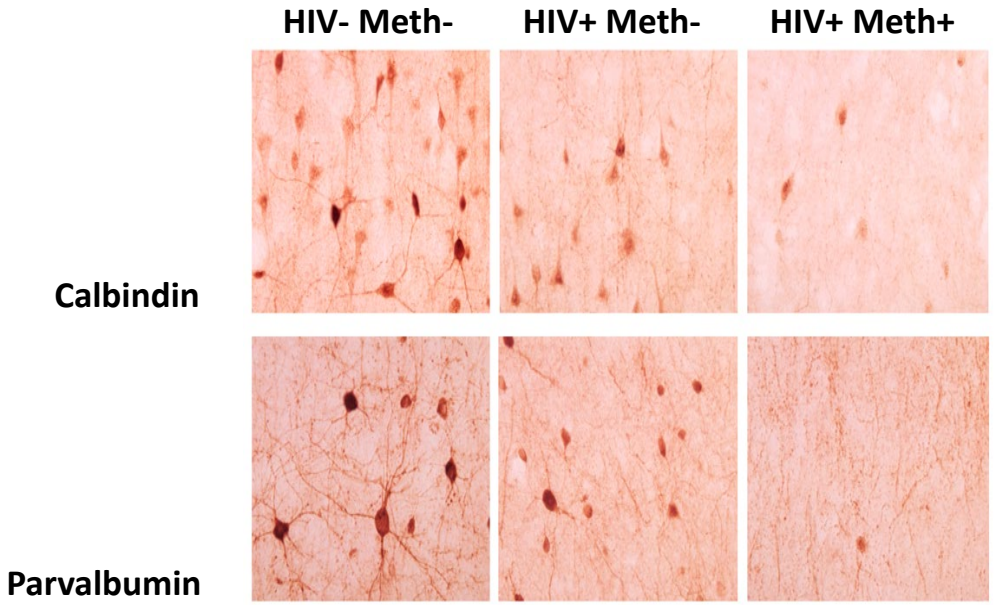


HIV and METH enhance each other's neurotoxicity

Rippeth, et al. 2004



Increased rates of neurocognitive impairment in HIV+ METH+



Chana et al (2006)

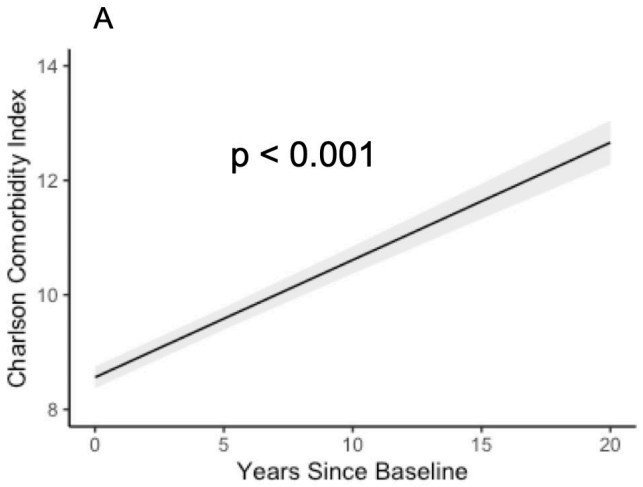
Marked reduction in interneurons in HIVE+ METH+

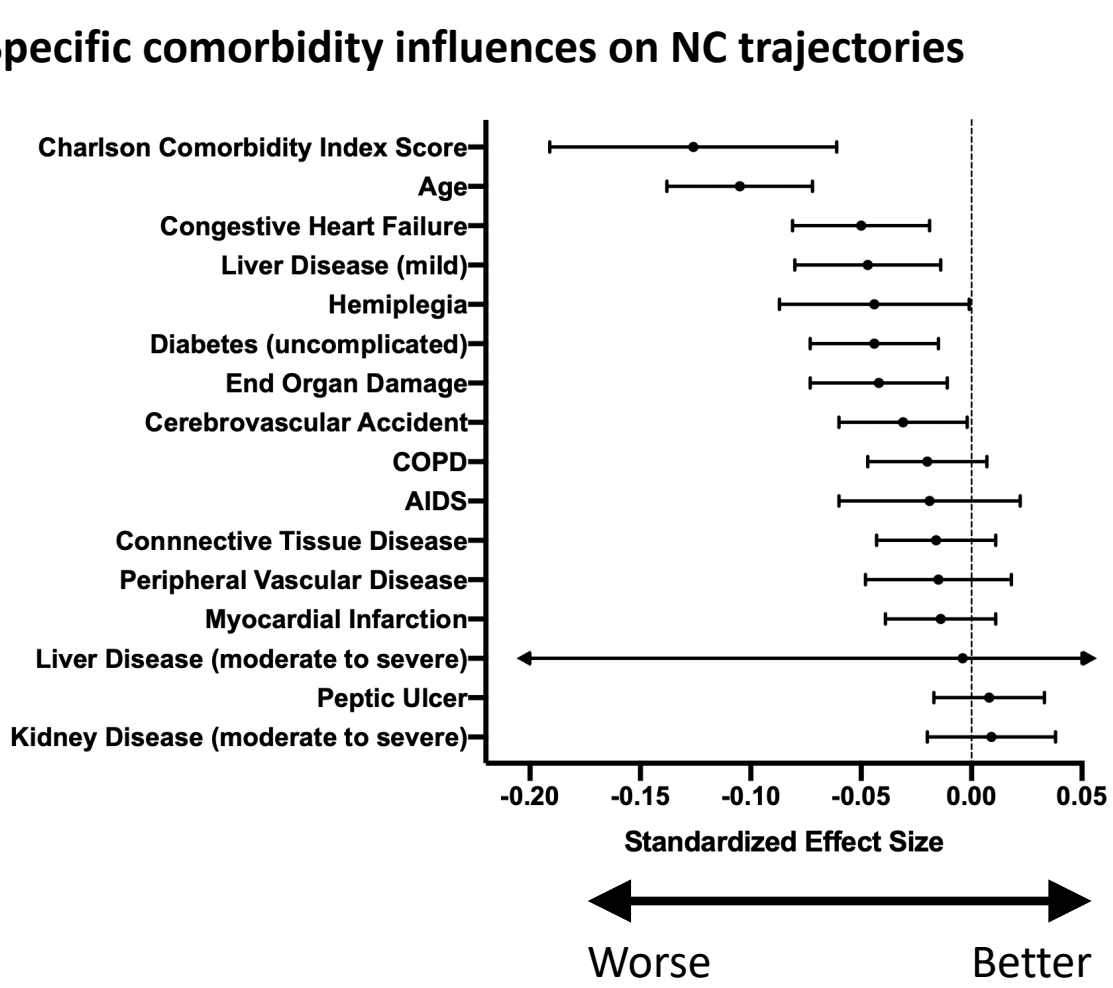
Multimorbidity and poor neurocognitive trajectories

- Objective
- Evaluate whether a validated multimorbidity index predicts neurocognitive (NC) trajectories in PWH
- Hypothesis
- Cumulative comorbidities will associate with worse neurocognitive trajectories in PWH

Ellis et al. Higher Comorbidity Burden Predicts Worsening Neurocognitive Trajectories in People with Human Immunodeficiency Virus. CID 2021.

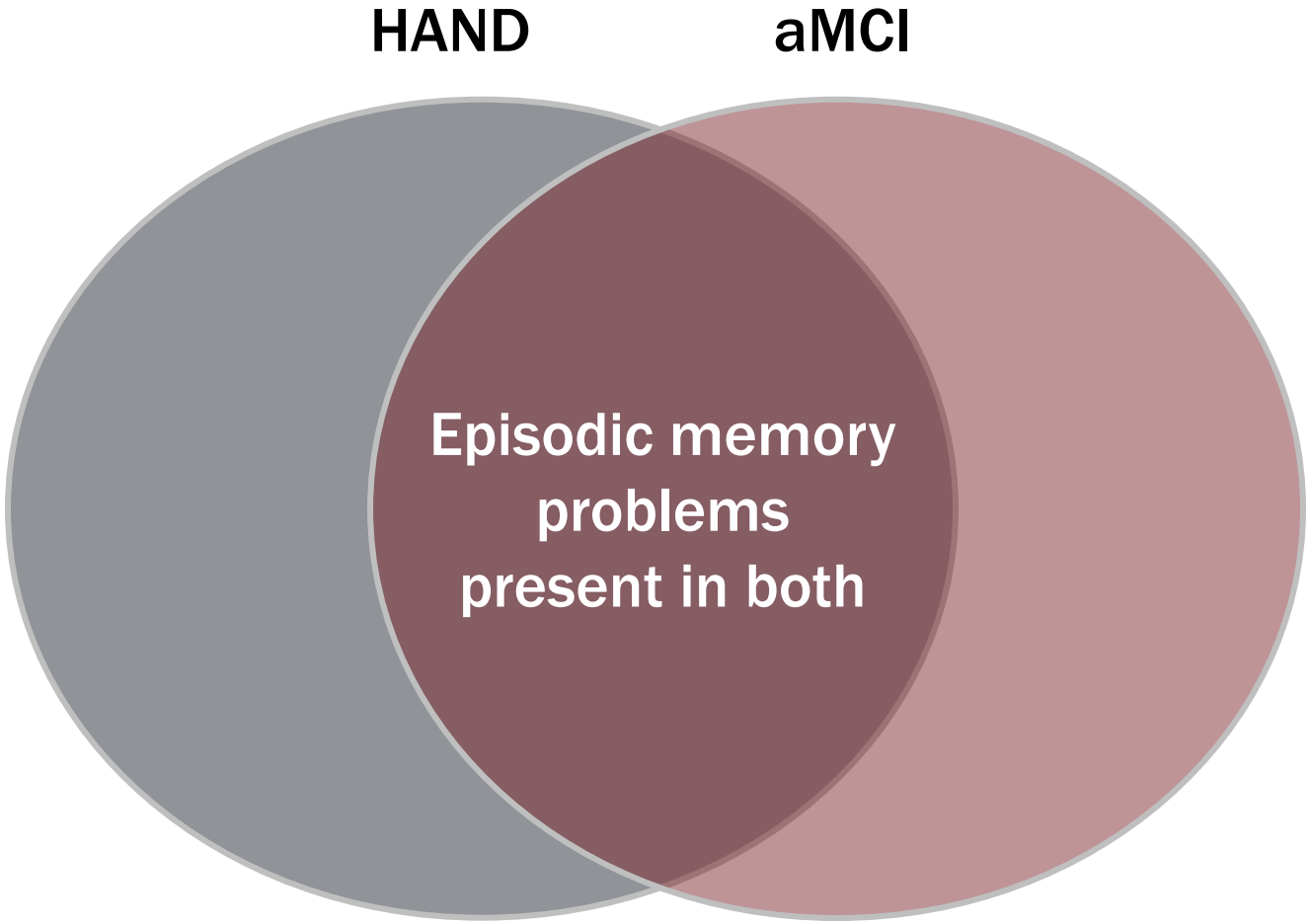
Results: Accumulation of multi-morbidity and association with more rapid decline in neurocognition during follow-up





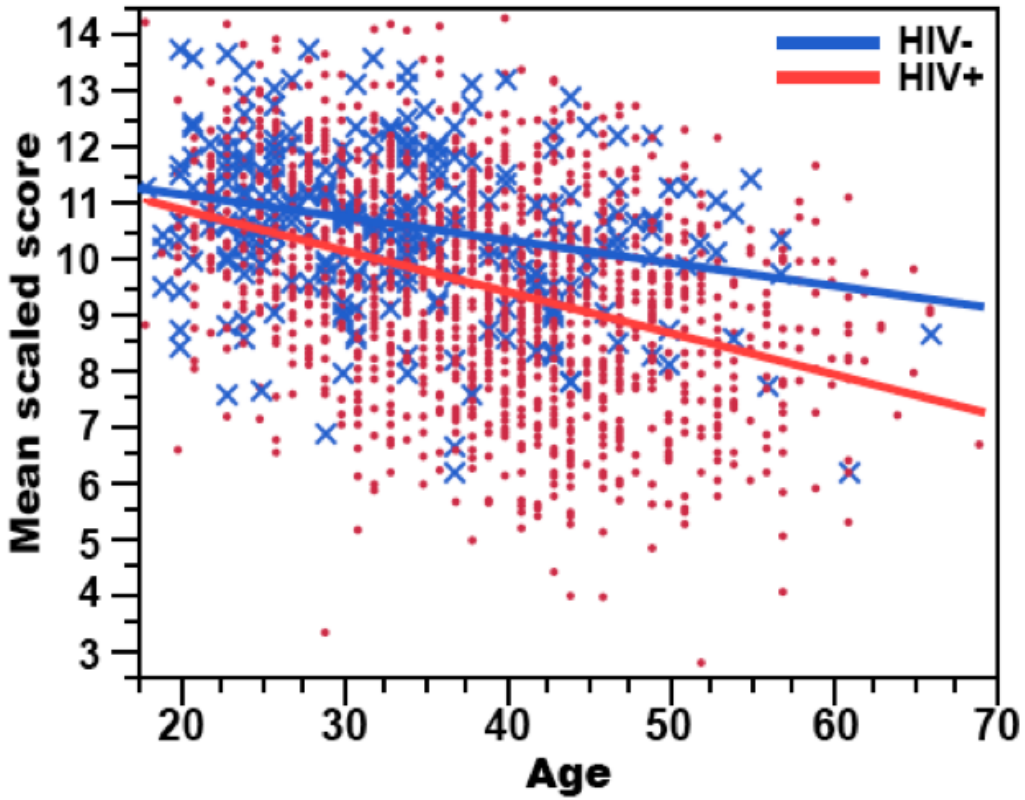
HIV and Aging

Challenges in Disentangling AD Precursor (aMCI*) vs HAND

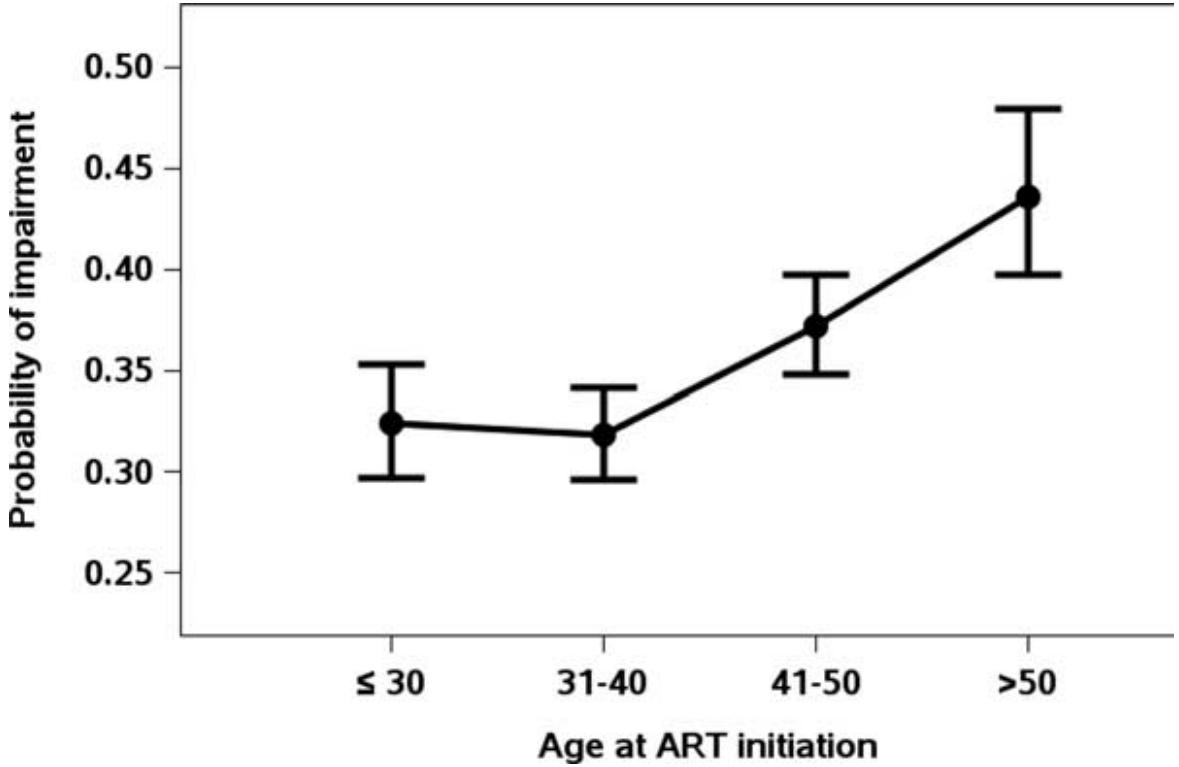


*aMCI – amnestic mild cognitive impairment

Worsening cognition with age in PWH vs PWoH

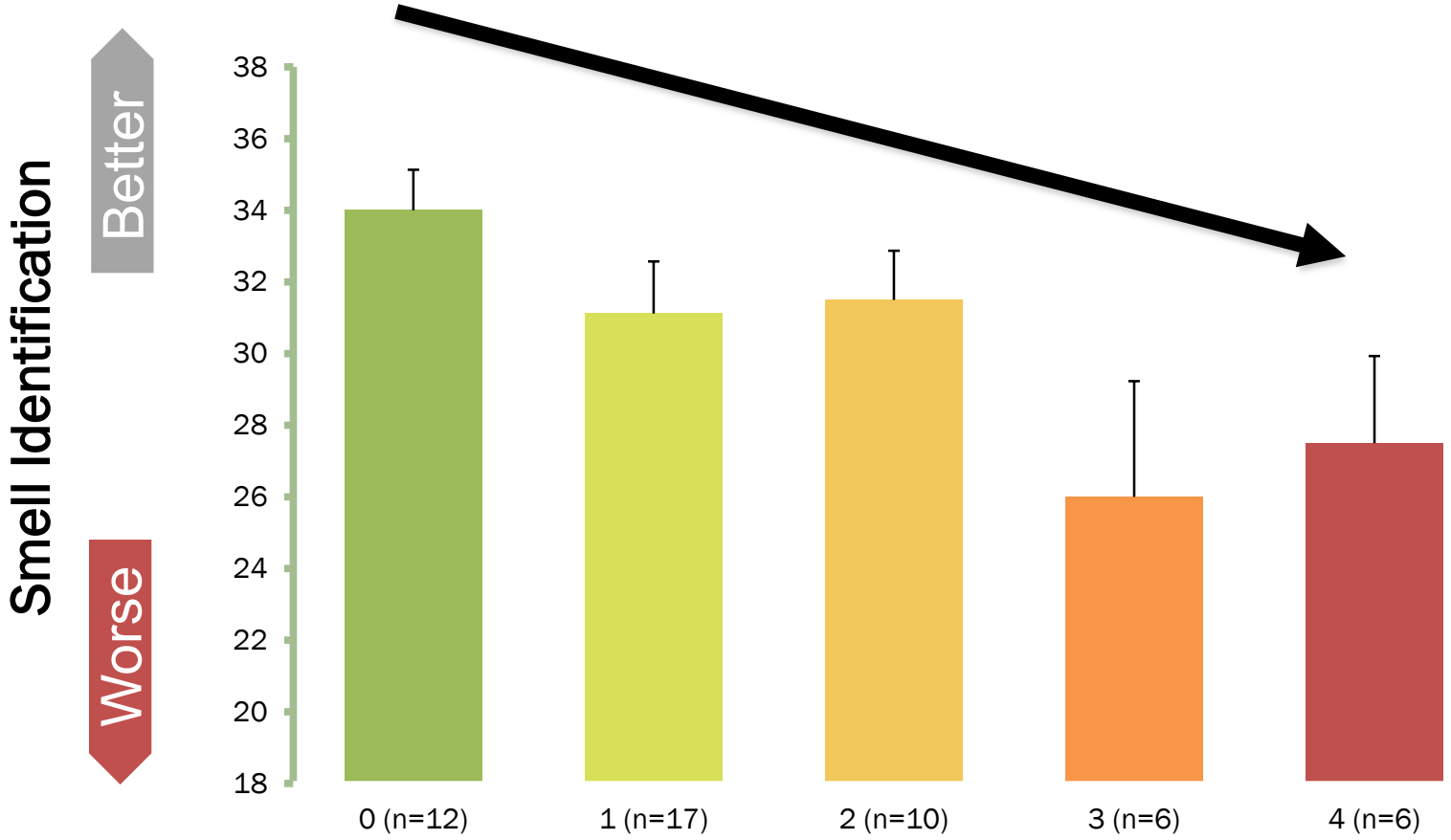


HNRC, unpublished



Coban et al AIDS 2017

Sense of Smell – Distinguishing aMCI vs. HAND



Sense of Smell – Distinguishing aMCI vs. HAND

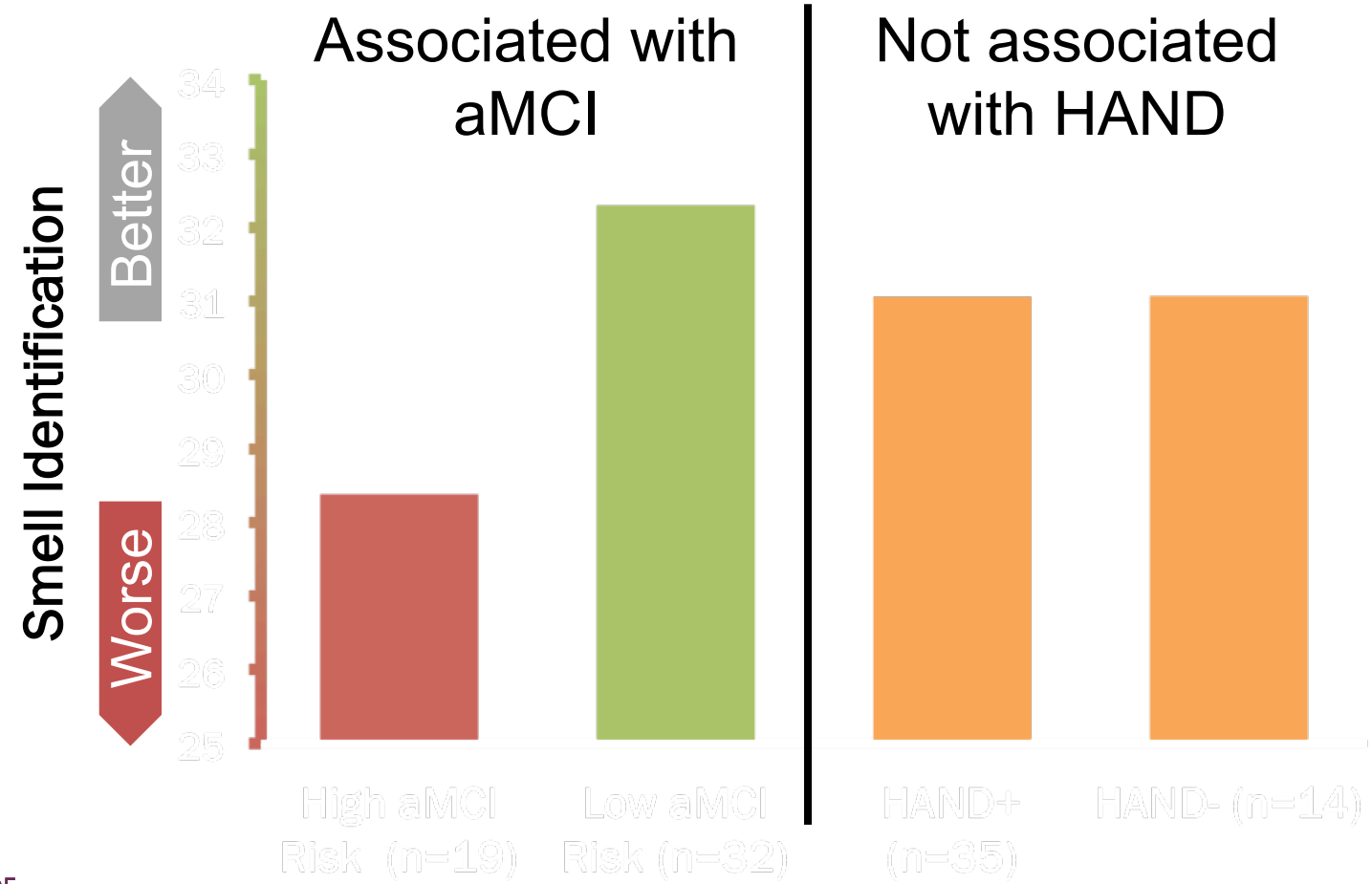
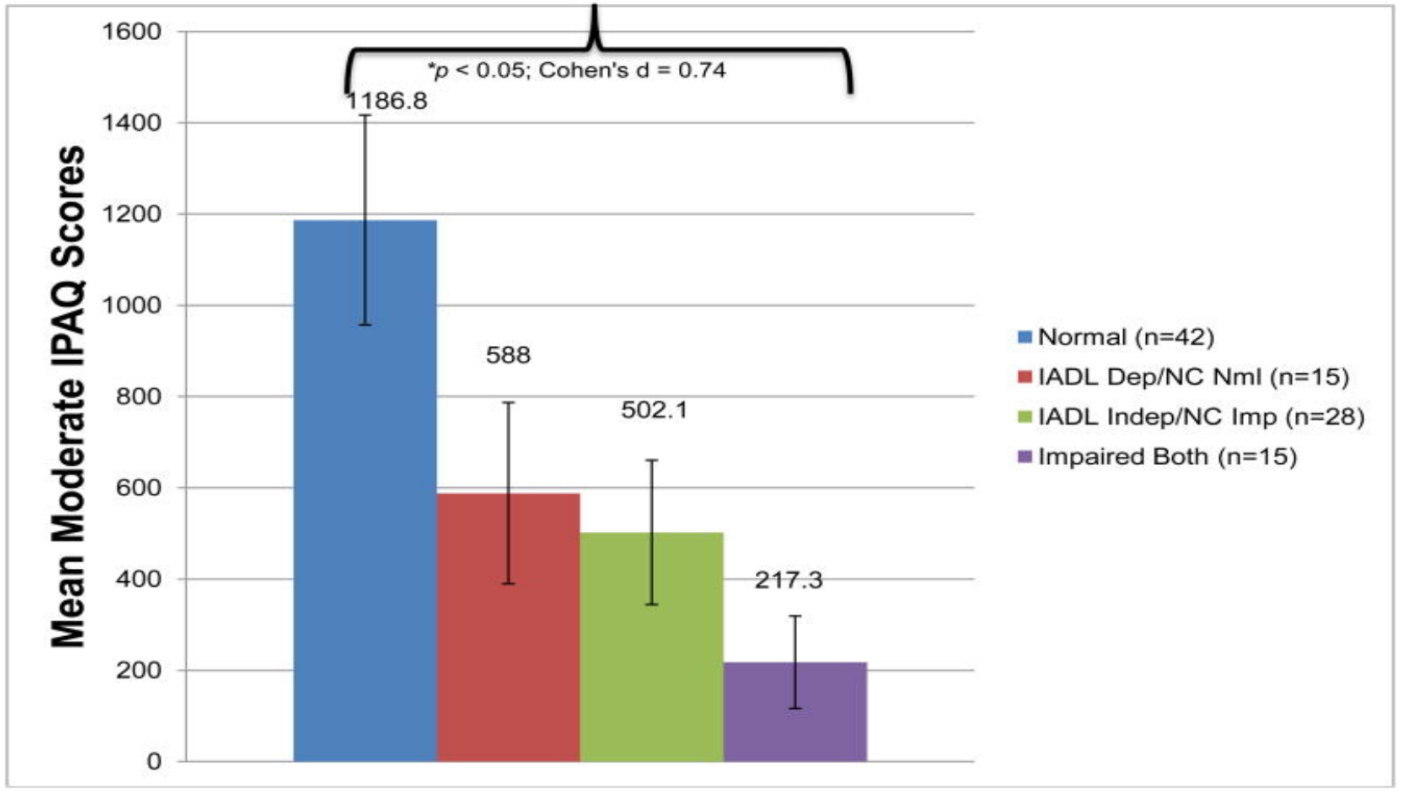


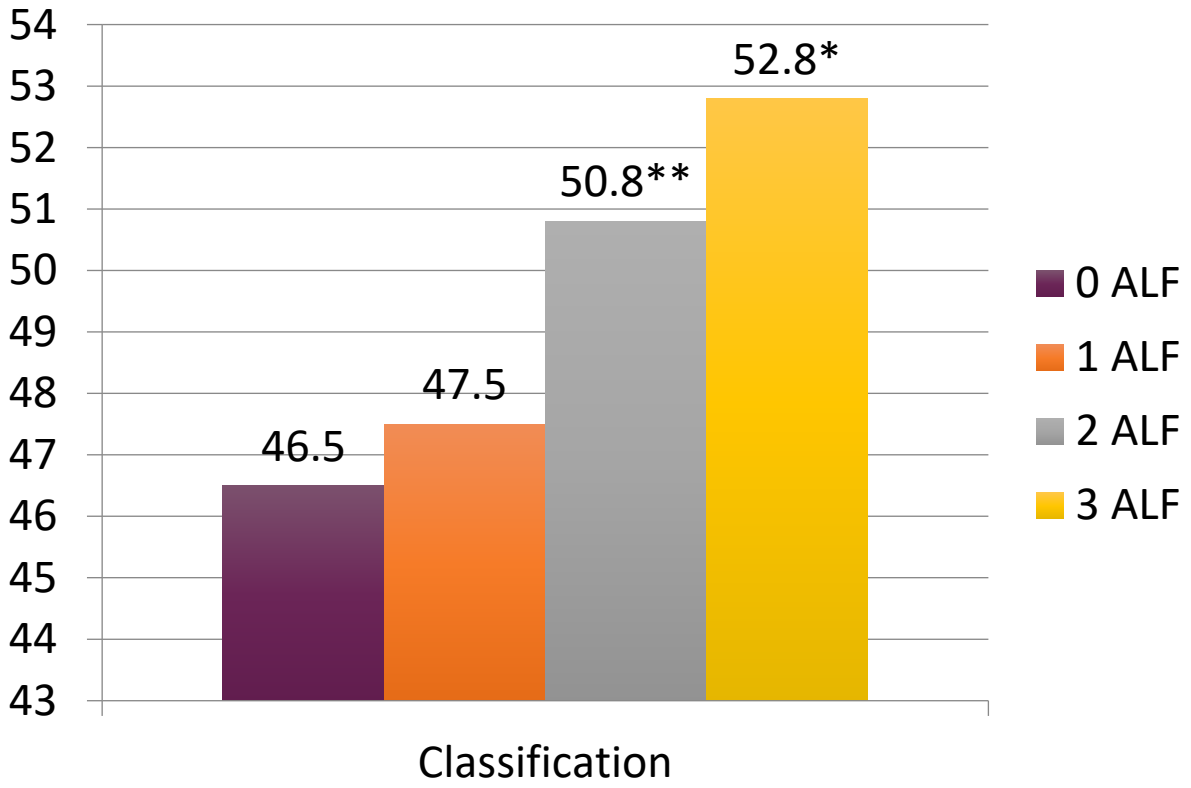
Figure 2. Older PWH with both cognitive and functional impairment report the lowest levels of physical activity



Note. IPAQ=international physical activity questionnaire; IADL Dep/Indep = dependent or independent in instrumental activities of daily living; NC Imp/Nml = neurocognitively normal or impaired.

Fazeli et al., 2015, AIDS & Behavior

A Greater Number of Active Lifestyle Factors Related to Better Neurocognition



ALF=Active Lifestyle Factors (social, mental, physical)

Fazeli et al, 2014, J of Neurovirology

General Exercise Guidelines for Positive Aging

Why should I exercise? Exercise may help you to:

- Improve mood & physical health
- Sleep better
- Decrease medications
- Improve overall quality of life

Is it safe? Yes! YES!
Studies show that moderate exercise (exercise that raises your heart rate, makes you break a sweat, but not so hard that you cannot talk) is generally safe for people with any chronic condition. Regardless of your starting point, gradually work toward a long-term exercise goal.

What's a good long-term exercise goal?
The basic exercise recommendations for all adults include either:

- At least 150 minutes of moderate aerobic activity per week and muscle-strengthening activities on 2 or more days per week, or
- 75 minutes of vigorous-intensity aerobic activity a week and muscle-strengthening activities on 2 or more days per week

TIP: You can add up exercise time in short periods throughout the day. Walking for 10 minutes morning, noon, and evening equals 30 minutes of walking.

How should I start exercising?
Try a step-by-step approach:

Step 1: Pick an exercise
- What kind of exercise do I enjoy, or would be willing to do?
- What kind of exercise fits into my day?

Step 2: Set a short-term goal that you can accomplish
- "This week, I will walk for 10 minutes on 3 days."

Step 3: Set a long-term goal
- "Six months from now, I will be able to take a brisk walk for 20 minutes, 5 days of the week."

Step 4: Develop an action plan!
- Set a specific plan for how you will accomplish your short and long-term goals.

Step 5: Monitor your activity
- This could include a paper log, a pedometer, wrist monitor (such as FitBit), a smart phone program, or inexpensive hip-worn pedometer.

Step 6: Schedule time for activity!
- Block the time you plan to exercise on your calendar. Set an alert on your phone to remind you. Pick a time of the day that you are less likely to cancel because of fatigue or other commitments.

Step 7: Recruit a buddy or a group or tell a friend about your plan!

Rx for Health:
Get Up and Get Moving

Congratulations on deciding to increase your physical activity! Here is the plan we discussed to start you on your way.

Name: _____ Date:_____

Aerobic Activity

Type: Walk Run Swim Bike Other _____

Days per Week							
start with:	1	2	3	4	5	6	7
gradually increase to:	1	2	3	4	5	6	7

Intensity			
start with:	Light (a casual walk)	Moderate (a brisk walk)	Vigorous (jogging or running)
gradually increase to:	Light (a casual walk)	Moderate (a brisk walk)	Vigorous (jogging or running)

Minutes per Day					
Start with:	10	20	30	45	60+
Gradually increase to:	10	20	30	45	60+

Steps per Day:					
Start with:	2,500	5,000	7,500	10,000	12,500+
Gradually increase to:	2,500	5,000	7,500	10,000	12,500+

For next week, only change one thing at a time

Strength Training

- There are benefits to muscle strengthening done two days per week.
- It is best to do exercise to strengthen all major muscle groups: legs, hips, back, chest, abdomen, shoulders, arms.
- For each exercise, 8-12 repetitions is optimal.
- Examples include resistance exercises using body weight (e.g., push-ups, lunges) or resistance bands, sit-ups, and heavy gardening.

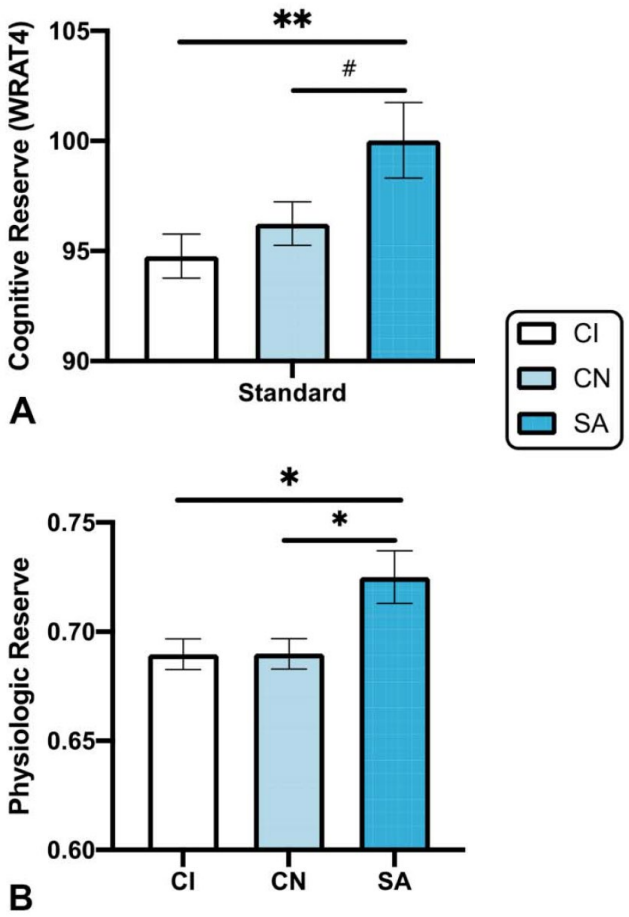
We will review this plan at your next visit.

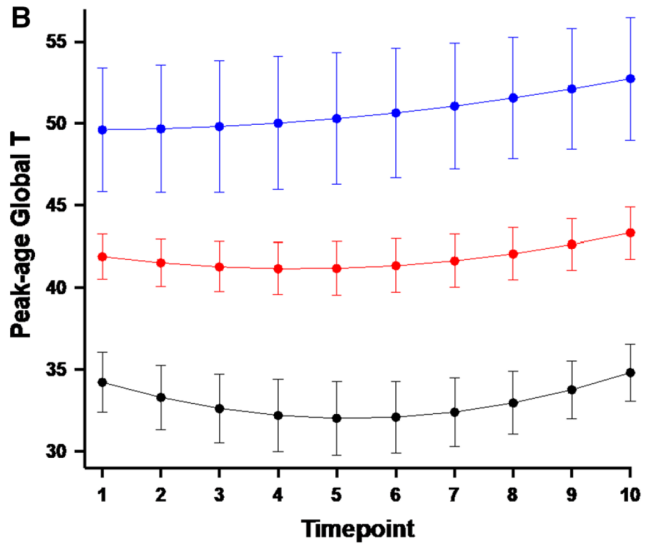
Health Care Provider : _____

Patient's Signature:_____

Montoya et al., AIDS 2019

Cognitive SuperAging and Youthful Trajectory in PWH





Up to 5 Years Follow-up

Predictor	Class 2 *Quadratic Average*			Class 3 *Quadratic Low*		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.06	0.88–1.26	0.540	1.20	0.99–1.45	0.058
PAOFI	1.07	1.01–1.14	0.020	1.14	1.06–1.22	<0.001
Physiologic reserve	0.83	0.49–1.39	0.470	0.48	0.27–0.86	0.014
Cognitive reserve	0.33	0.16–0.68	0.002	0.12	0.06–0.28	<0.001

Saloner et al, JAIDS 2022, PMID: 35364601
Saloner et al, AIDS Behav, 2022. PMID: 34878634

Summary

- HAND persists despite combination antiretroviral therapy (CART)
- Even milder HAND produces behavioral and functional impairments that are significant to the individual and society, thus of public health importance
- Synaptodendritic injury is one of the substrates of HAND.
- Causes of neuronal injury are likely multiple, including viral products, inflammatory molecules, disruption in trophic factors, disturbed protein management, brain small vessel pathology; these processes, incl. expression of viral products may persist despite apparent control of viral replication
- Comorbidities (e.g. drug abuse) may increase risk of HAND, and its progression

Summary (cont.)

- HAND amplified by age related neurologic, vascular and metabolic changes. Comorbidities may further accelerate age related neurocognitive declines
- Neurocognitive health best preserved in those who never have CD4 nadirs <200 and are currently virologically suppressed (implication: treat HIV as soon as possible)
- While continuous virologic suppression is associated with least likelihood of neurocognitive decline over time, ART neurotoxicity or vascular toxicity need to be considered
- No currently accepted neurotherapeutics; need new concepts, and possibly novel delivery systems to brain
- Non-pharmacologic (e.g., physical activity) strategies may have promise

Early Identification is Important

- All can agree that early detection leads to better outcomes in many diseases:
  - Heart disease, cancer, cerebrovascular disease, depression, Alzheimer's Disease
  - Why should HAND identification be any different?
- Relying exclusively on clinical judgement and patient self report are likely to miss people at the earliest stages of cognitive impairment
- New treatments are being evaluated and these are not just anti-amyloid therapies (e.g., synolytics, LM11A-31)

Challenges & Opportunities

- **Longstanding Challenges**
  - Prioritization of limited clinical resources
  - Legacy effects
  - Mild or equivocal or fluctuating disease
  - Many conditions can contribute to neuropsychiatric disease
  - Multimorbidity, polypharmacy, and neurotoxicity
  - Health and research equity for women & low-and-middle-income countries
- **More Recent Challenges**
  - Premature aging
  - Persistent production of viral RNA and proteins
  - Persistent inflammation
  - Very long duration of HIV infection and ART in some
  - Greater diversity of the clinical population
  - Continuing evolution of ART and cure-focused interventions
  - Advances in molecular and analytical methods

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Much of the Data Presented was with thanks to all our Study Participants and to Collaborating Investigators and Sponsors

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- NIA
- NINDS

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- Laura Campbell
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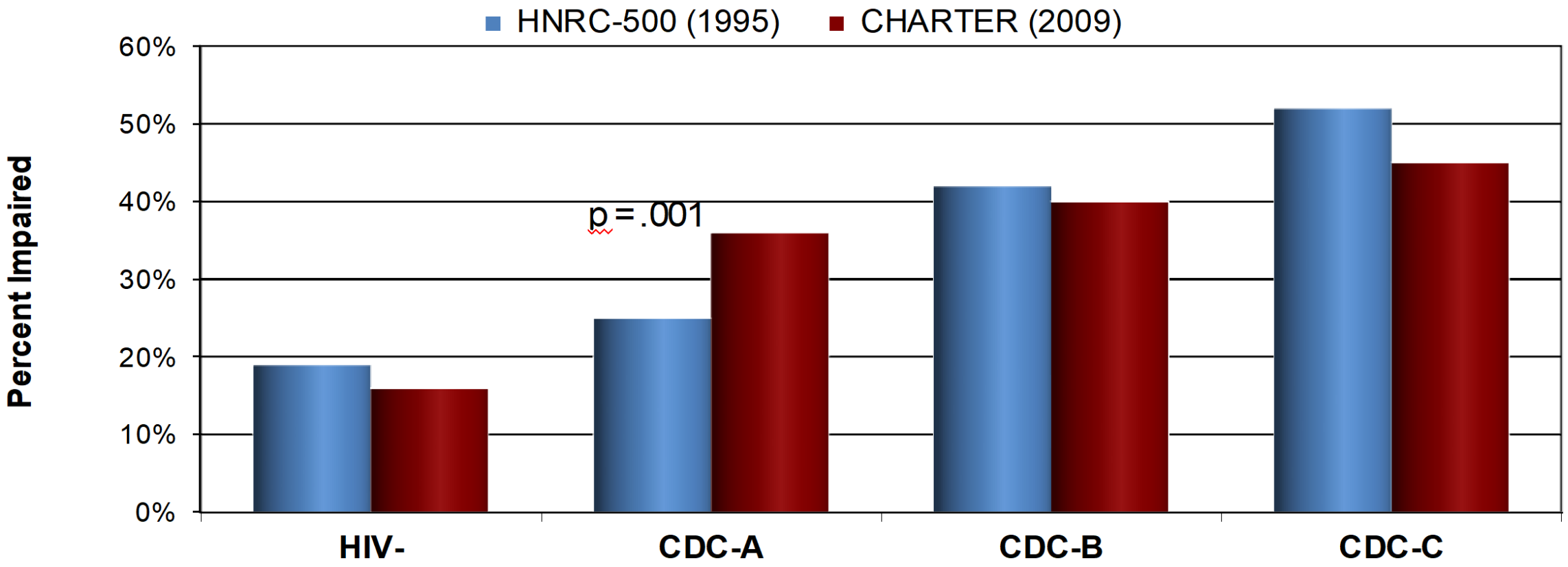
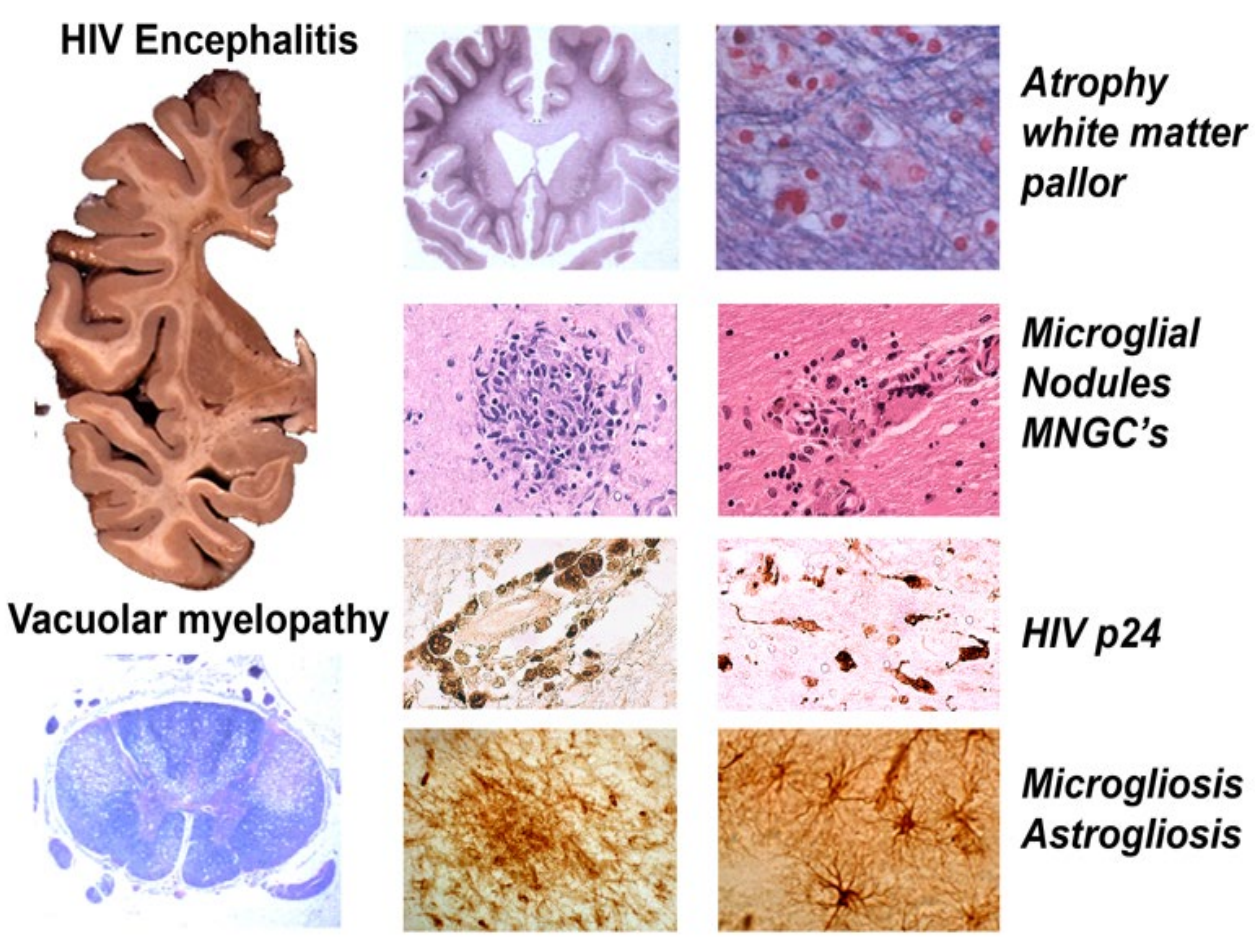
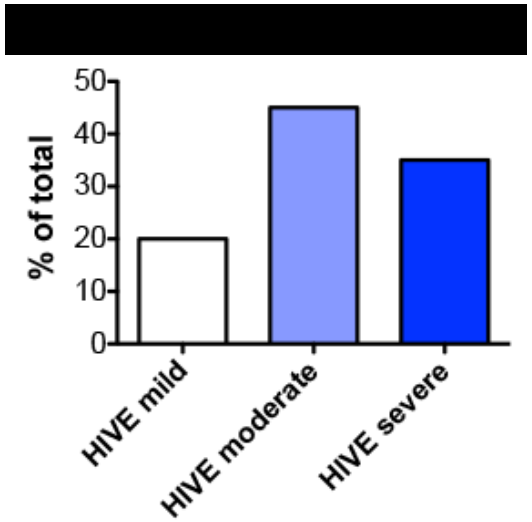
- Emily Paolillo
- Rowan Saloner

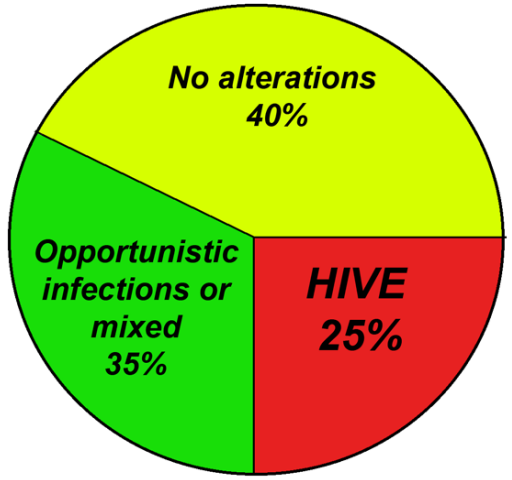
NC Impairment in the Pre-CART and CART Eras



Neuropathology of HIV in the pre-HAART era







Courtesy Eliezer Masliah, HNRP UCSD

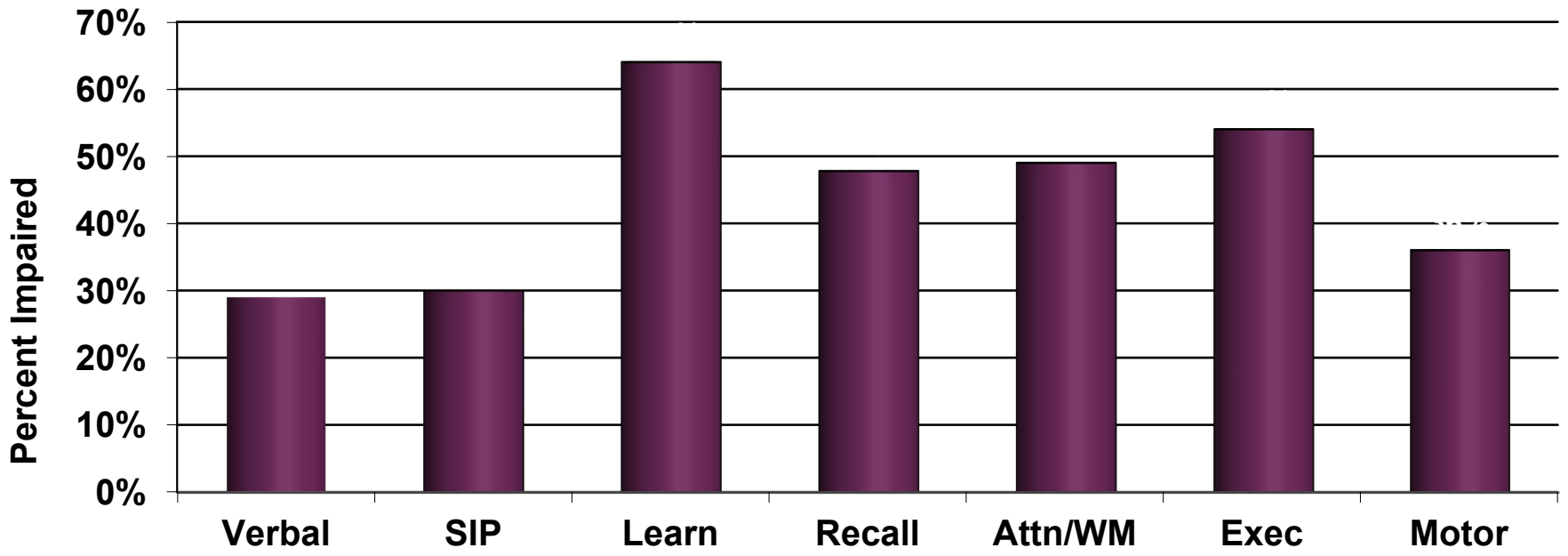
Has the prevalence of HAND changed since the introduction of CART (1996)?

N = 1794*	HIV-	Non-AIDS	AIDS
Pre-CART Era n's	179	516	162
CART Era n's	94	336	507
Total	273	852	669

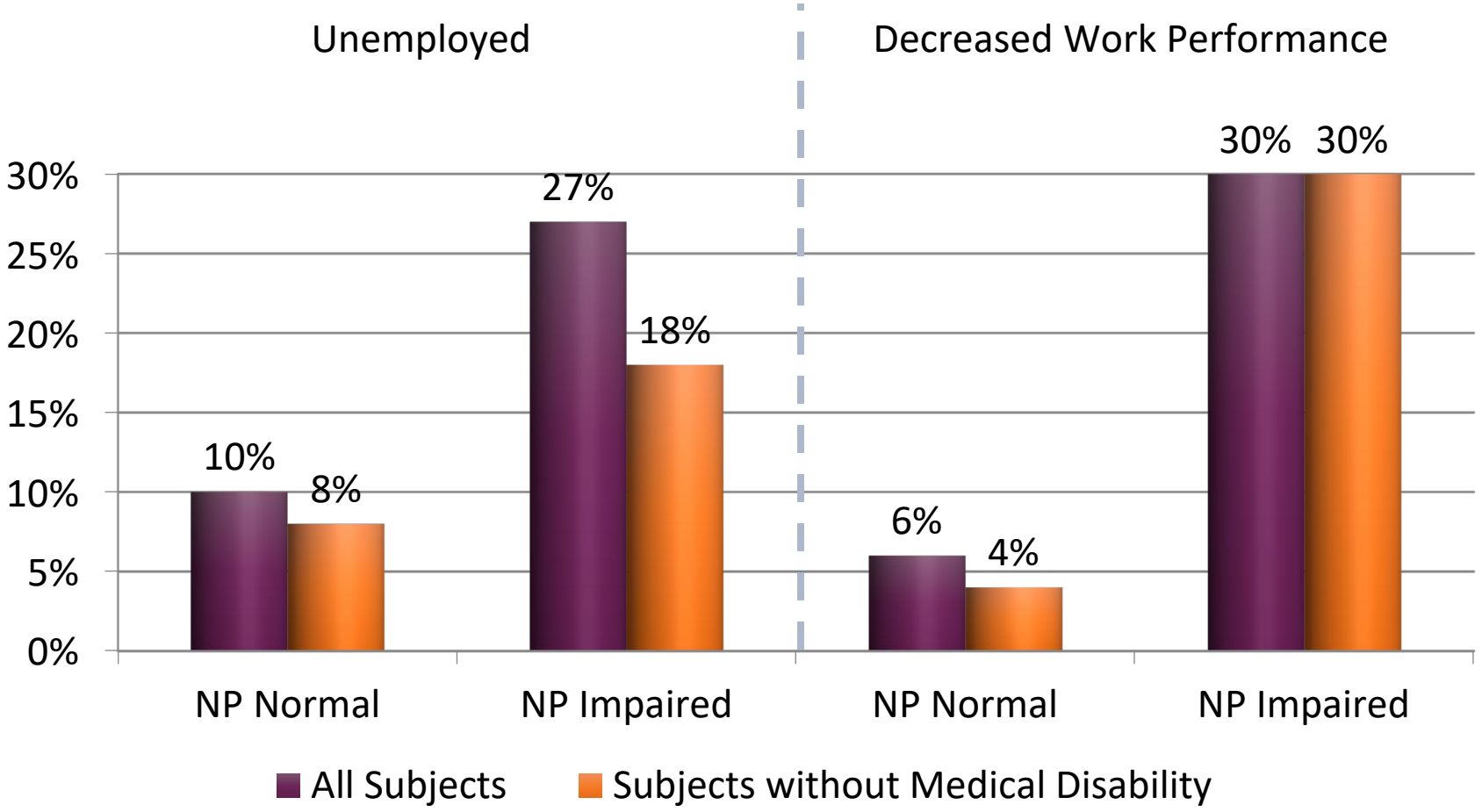
* Only minimal comorbidity participants included

HIV Associated Neurocognitive Disorders (HAND) remain highly prevalent (~50%) in the CART era, even with suppressive therapy

Typically mild to moderate in severity and non-progressive, although some cognitive fluctuations can occur (e.g., with changes in treatment)



HIV and Vocational Functioning



Heaton et al., 1994

ANI relates to neuroimaging

Use of Neuroimaging to Inform Optimal Neurocognitive Criteria for Detecting HIV–Associated Brain Abnormalities

Laura M Campbell [1 2], Christine Fennema-Notestine [2 3], Rowan Saloner [1 2], Mariam Hussain [1 2], Anna Chen [2], Donald Franklin [2], Anya Umlauf [2], Ronald J Ellis [2], Ann C Collier [4], Christina M Marra [5], David B Clifford [6], Benjamin B Gelman [7], Ned Sacktor [8], Susan Morgello [9], J Allen McCutchan [10], Scott Letendre [2 10], Igor Grant [2], Robert K Heaton [2]; CHARTER Group

- Compared Frascati to Meyer Criteria (more stringent Z-score threshold to ≤ -1.5 for ANI)
- ***"The Meyer criteria failed to capture a substantial portion of PLWH with brain abnormalities. These findings support continued use of Frascati or GDS criteria to detect HIV-associated CNS dysfunction. "***

What factors are associated with HAND?

- Viral factors
  - Clade? Probably not
  - Higher molecular viral diversity in circulating HIV?
  - Shift in viral tropism, eg., to dual tropism? Maybe
  - Specific neurotropic/neuropathogenic variants? Unclear
  - ARV resistance?
  - Viral molecules, eg., Tat; gp120: contribute to abnormal intracellular signaling, protein mismanagement, and dendritic injury
- Host vulnerability
  - Unknown if specific host genetic factors confer neuro-vulnerability. Possibly APO E4
  - Co-morbidities may amplify HIV effects: substance abuse; HCV; head injuries; aging; metabolic syndrome
- Treatment factors
  - Treatment not begun early enough to prevent lasting brain injury?
  - Ineffective: not sustained suppression, particularly in CNS; persisting viral reservoirs?
  - Neurotoxicity of ARV?

Complete the Evaluation for Your CME

To obtain CME for this live webinar, please visit:

https://www.paceducation.com/HIVMH3