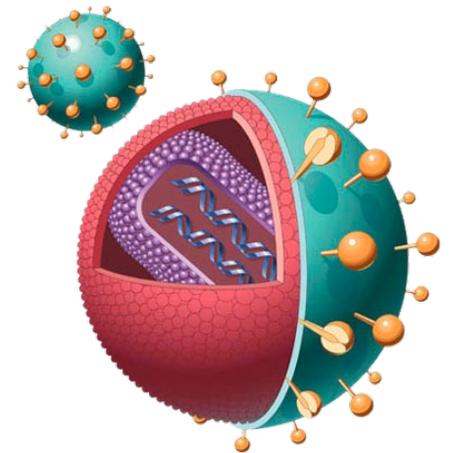


Neuropsychological Aspects of Aging with HIV Disease

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University of Houston



UNIVERSITY of HOUSTON

Disclosures

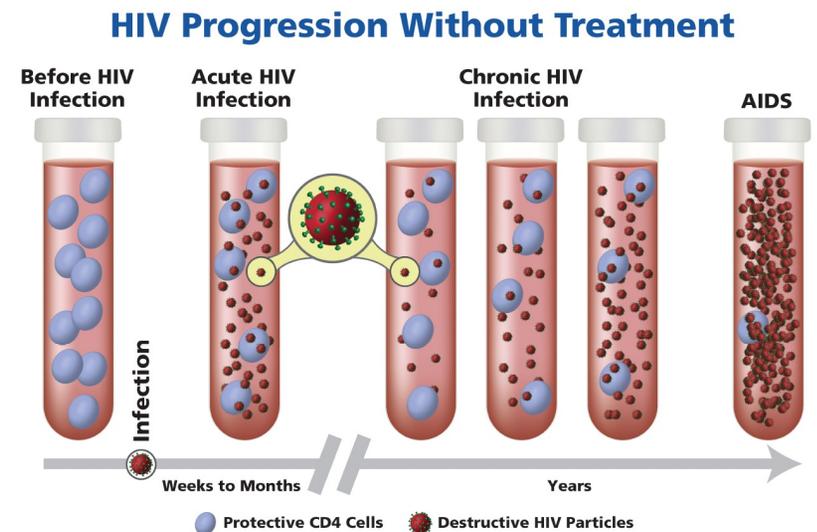
- No personal or financial conflicts to disclose
- Salary support
 - University of Houston
 - Professor, Director of Clinical Neuropsychology Training
 - Harris Health System
 - Director of Clinical Neuropsychology Service, Quentin Mease
Thomas Street Health Clinic
 - Research
 - Investigator on grants funded by the National Institute on Aging and Texas Alzheimer's Research and Care Consortium
 - American Psychological Association
 - Editor-in-Chief, *Neuropsychology*

Outline of Today's Talk

- Primer on HIV Disease and HIV-associated Neurocognitive Disorders
- Aging of the HIV epidemic in the United States
- Brain-behavior aspects of aging and HIV disease
 - Neurobiological
 - The “cortical” hypothesis
 - Neurocognitive
 - Everyday functioning
 - Successful cognitive aging

HIV: The Basics

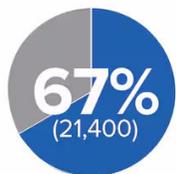
- **HIV = Human Immunodeficiency Virus**
 - ◆ DNA retrovirus that targets white blood cells (e.g., CD4+)
- **AIDS = Acquired Immune Deficiency Syndrome**
 - ◆ Low CD4 count (<200 cells mL) and/or opportunistic infections
- **Viral loads = HIV RNA**
 - ◆ Measure of viral replication in plasma and/or cerebrospinal fluid
- **ART = antiretroviral therapy**
 - ◆ A medication that dampens HIV RNA replication (undetectable)
 - ◆ cART = Multiple drugs that affect different aspects of the virus



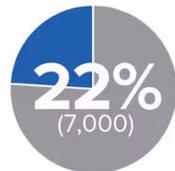
HIV Transmission and Prevalence

- Approximately 1.2 million people in the U.S. have HIV disease

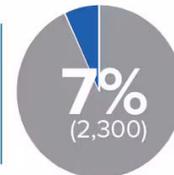
There were **31,800** estimated new HIV infections in the US in 2022. Of those:



were among gay, bisexual, and other men who reported male-to-male sexual contact*



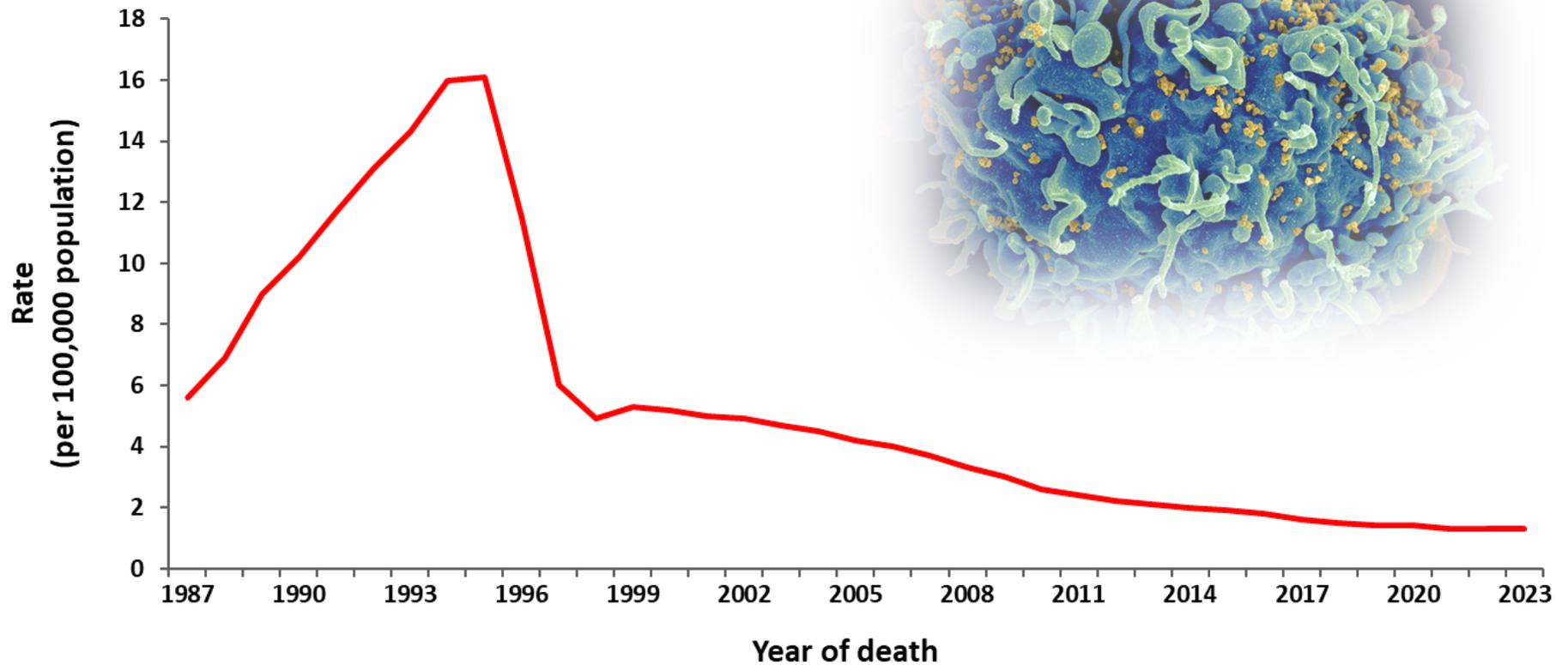
were among people who reported heterosexual contact



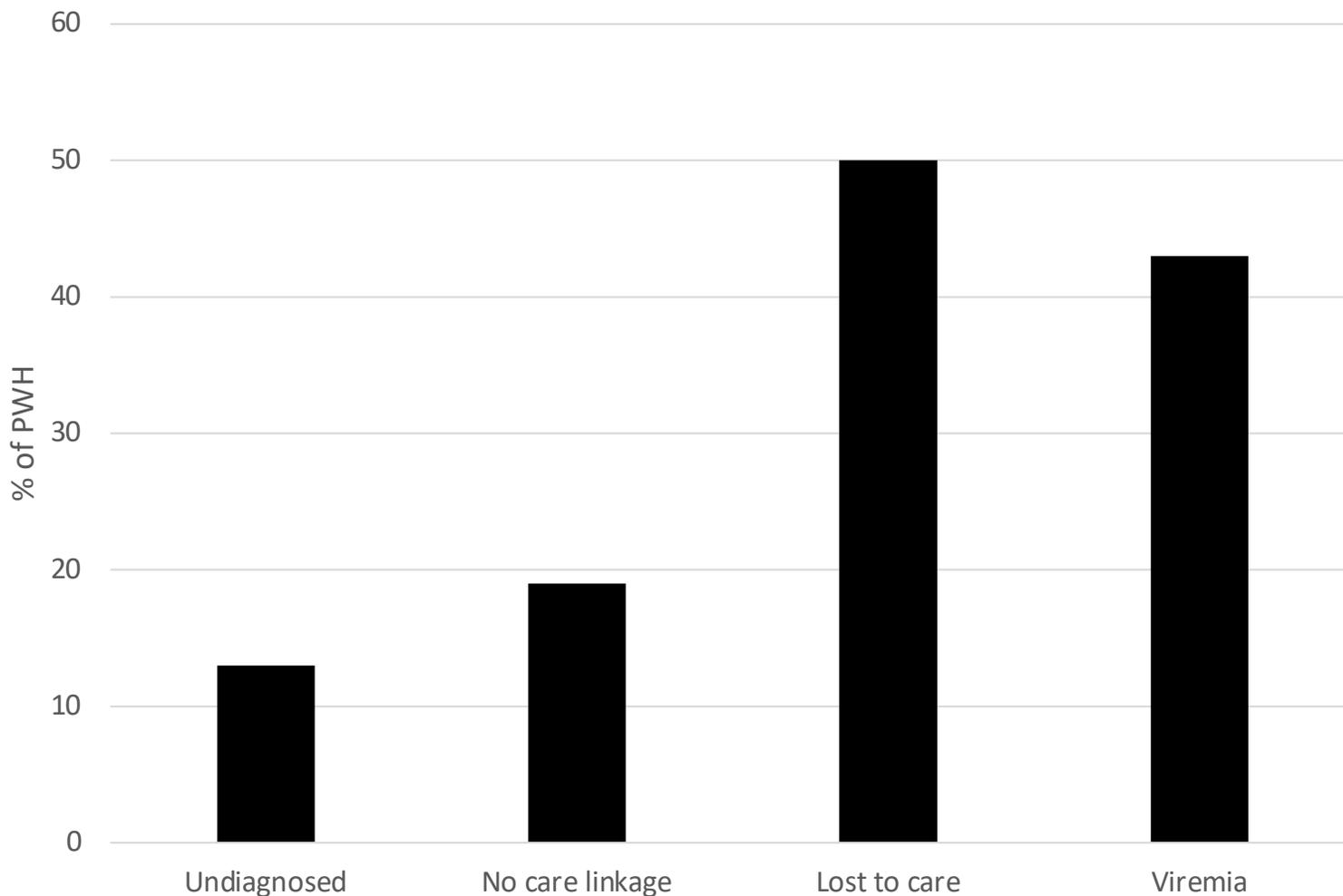
were among people who inject drugs

- Incidence of HIV is down ~12% in the past few years
 - Young Black and Hispanic/Latin American MSM in the Southern U.S. are at highest risk of incident HIV

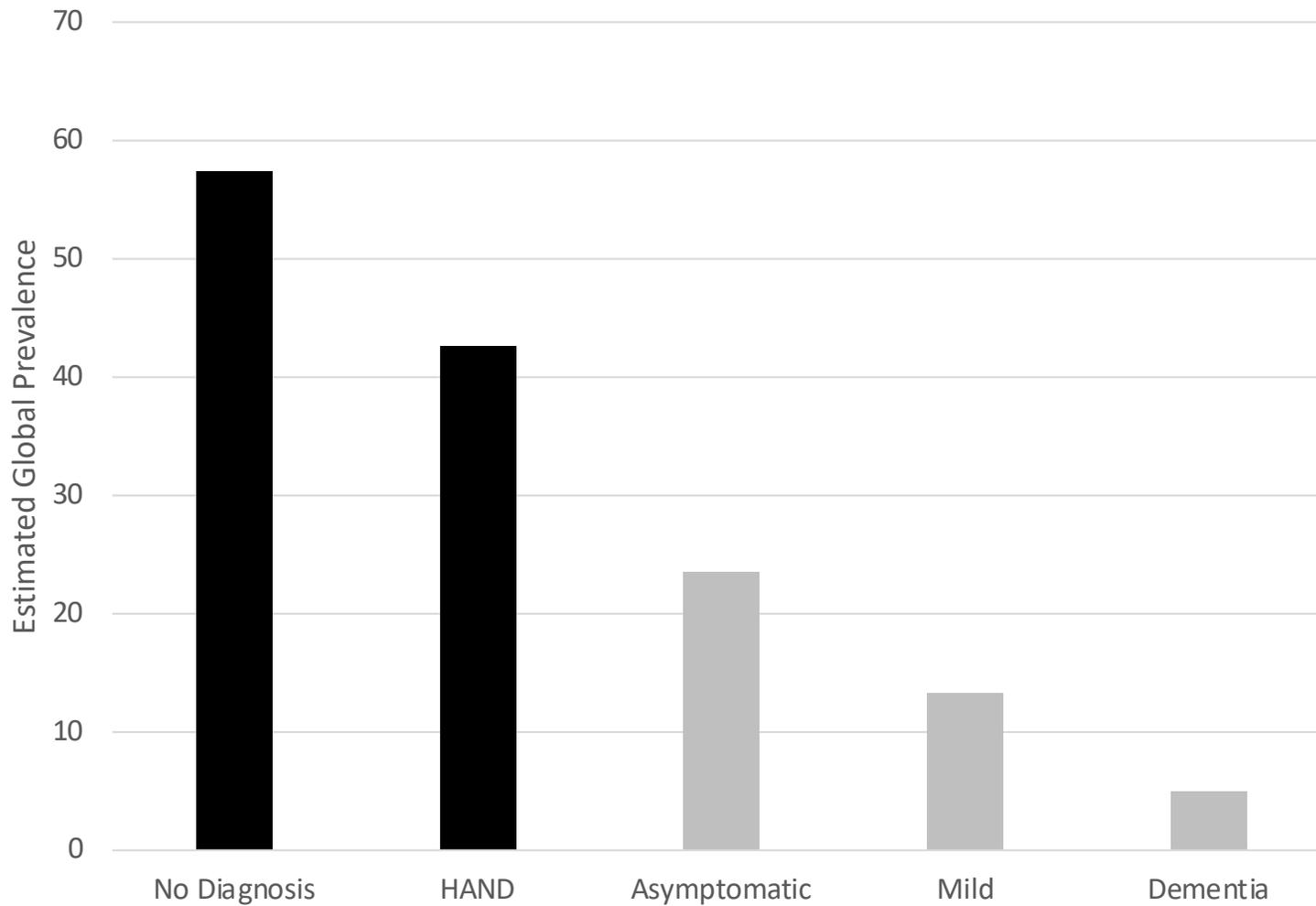
HIV as a Chronic Disease: *cART Reduced Mortality in the Mid-1990s*



Major Gaps in PWH Healthcare: *The Treatment Cascade*



HIV-associated Neurocognitive Disorders Persist in the cART era

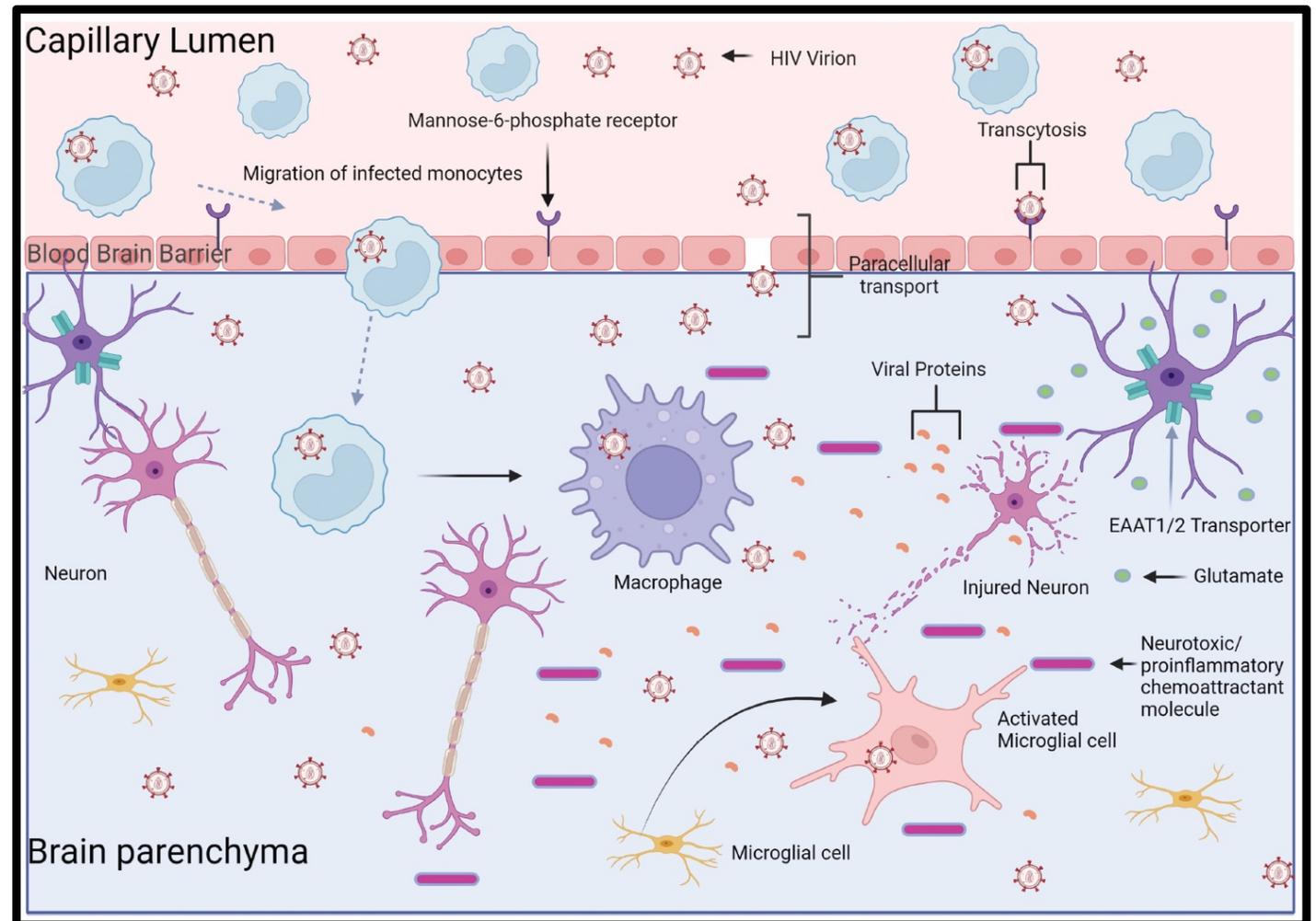


Estimated >16 million cases of HAND worldwide

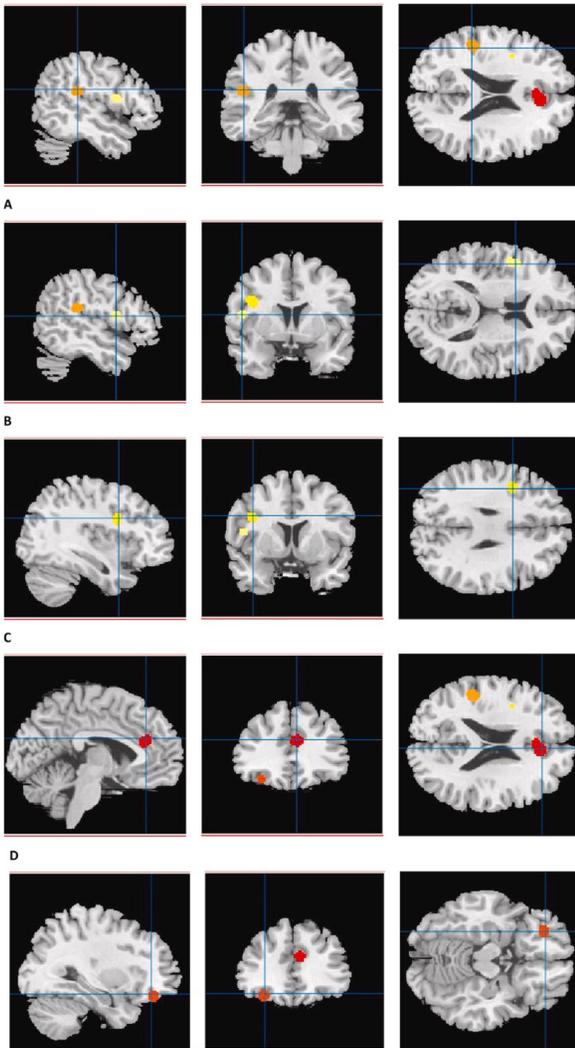
(>11 million in sub-Saharan Africa)

HIV and the Brain

- HIV can cross the blood-brain barrier in the early stage of infection
- HIV primarily infects glial cells
 - Microglia
- HIV can trigger inflammation
- Vascular injury



Brain Systems Affected in HAND

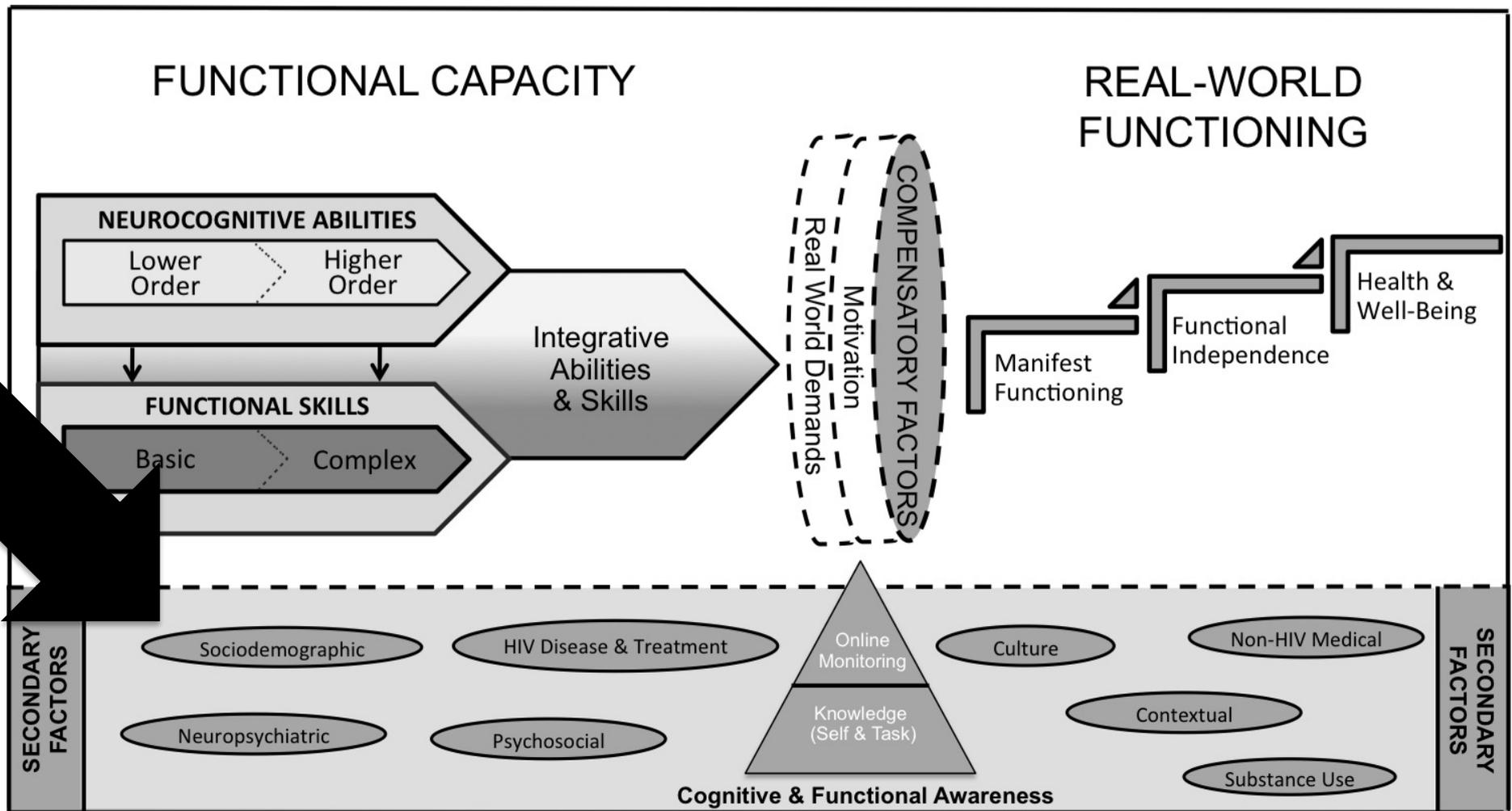


- HIV can affect the integrity of grey and white matter in multiple brain systems
- HIV tends to affect fronto-striatal systems more so than others
 - Hippocampus/MTL
- Mild-to-moderate (and often spotty) deficits in related neuropsychological ability areas
 - Executive functions
 - Strategic encoding and retrieval
 - Psychomotor

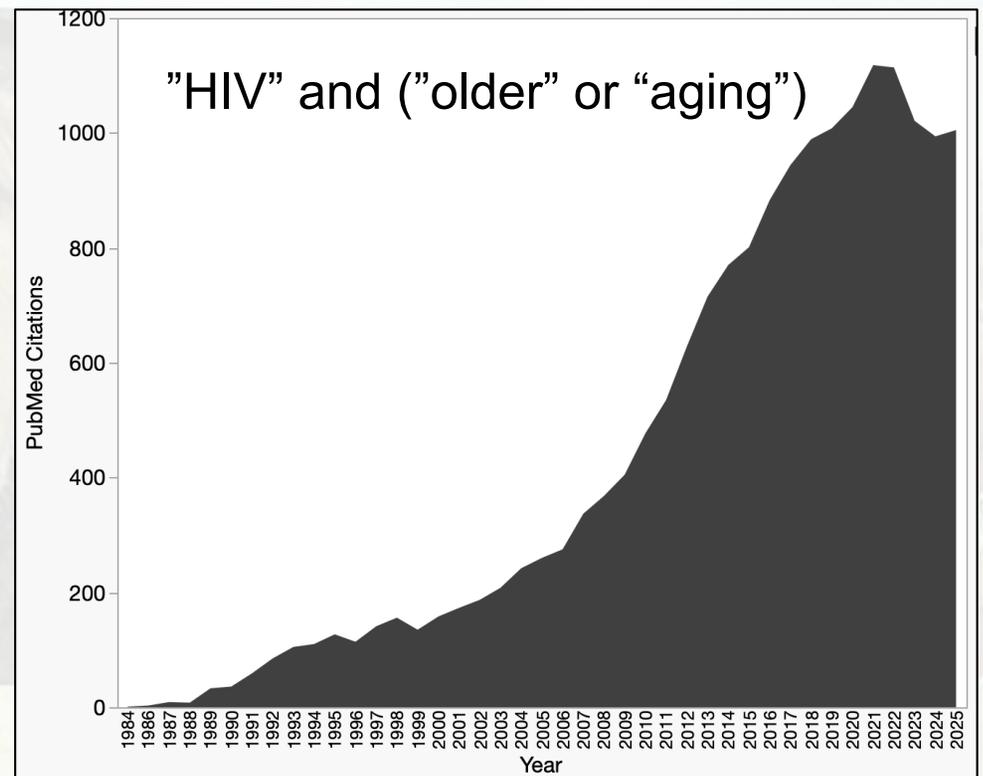
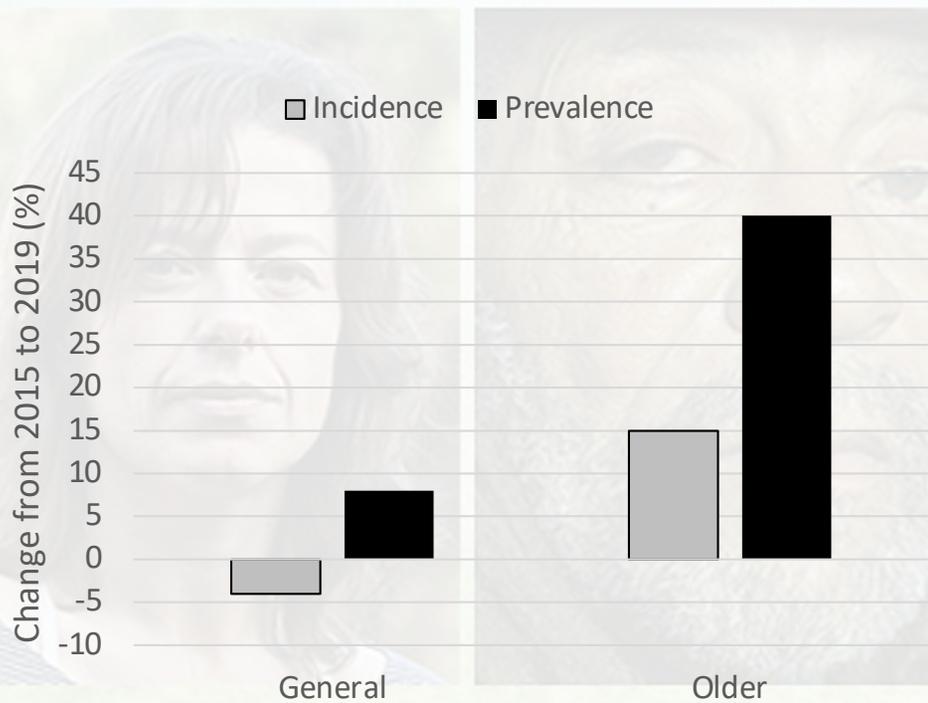
HAND Adversely Affects Daily Life

- Activities of Daily Living
 - Vocational functioning
 - Financial management
 - Household management
 - Shopping
 - Cooking
 - Transportation
- Health Factors
 - Health literacy
 - Medication adherence
 - Retention in care
- Cognitive Symptoms
- Quality of life

Many Clinico-demographic Factors Can Influence the Expression of HAND and its Functional Impact



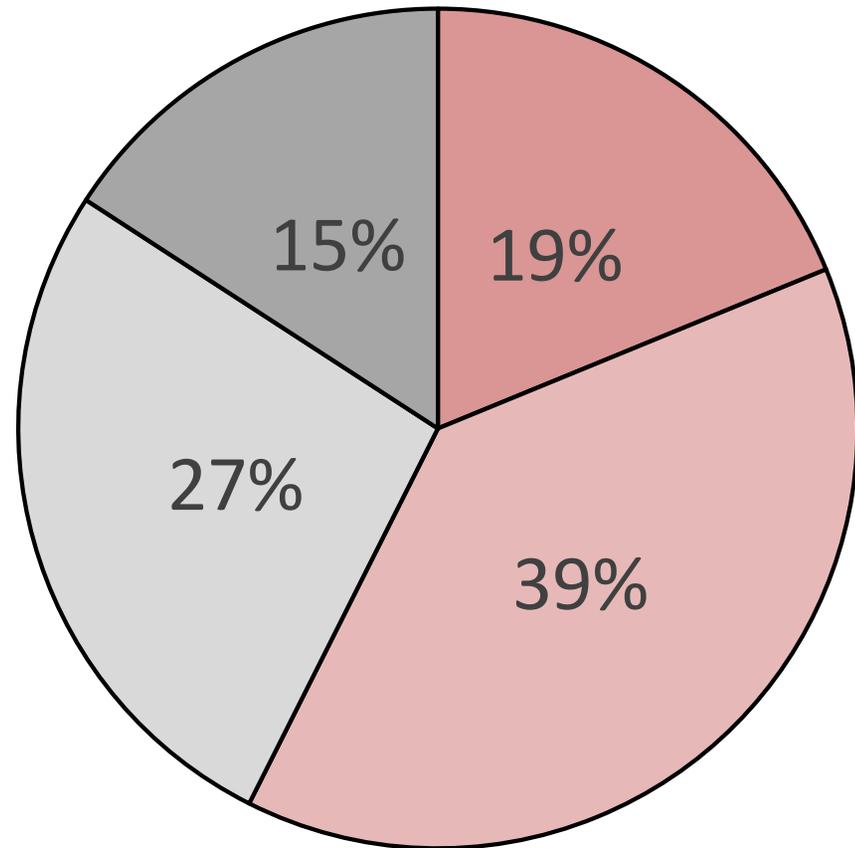
The Greying of the HIV Epidemic



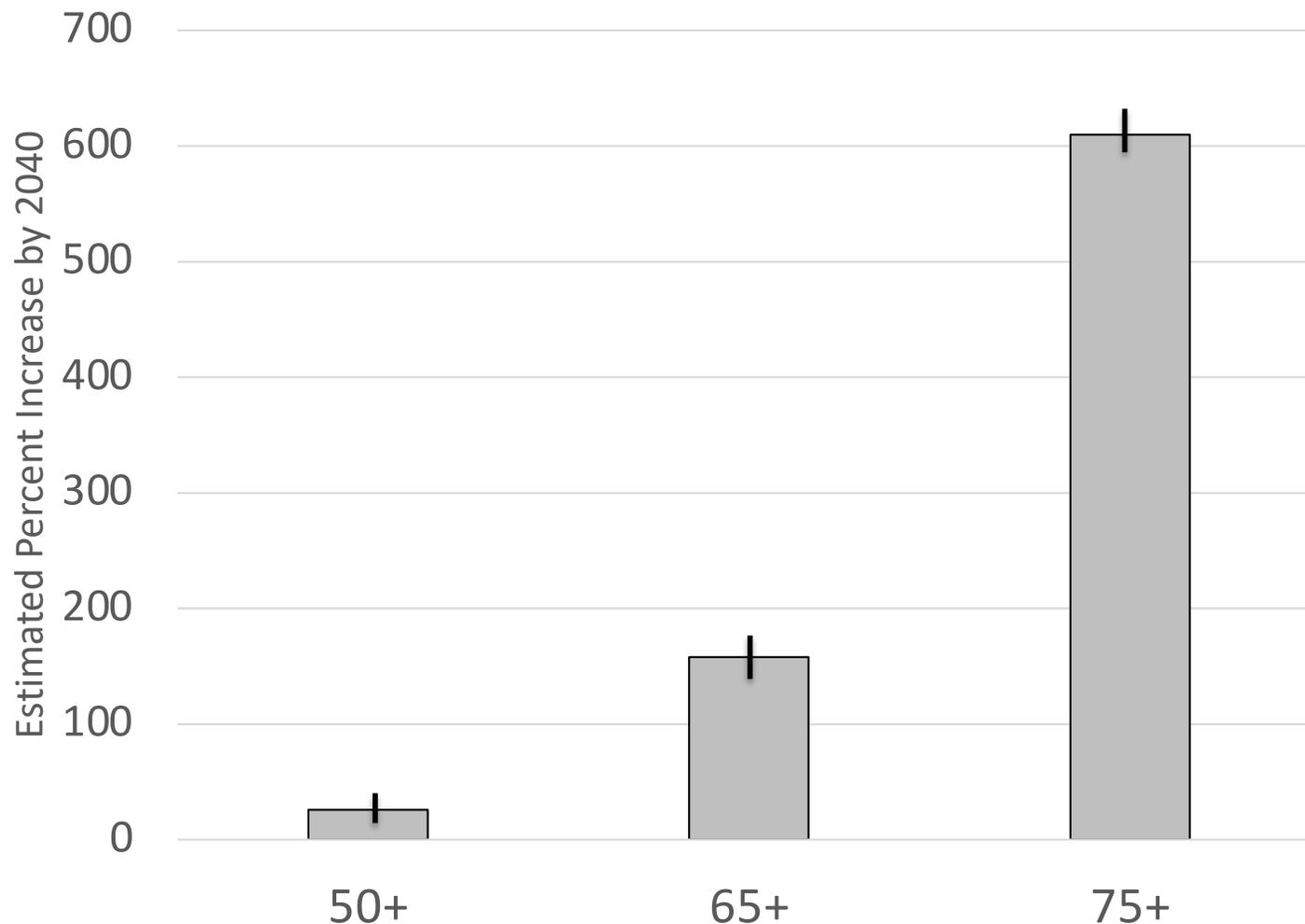
Aging & HIV

■ <35yo ■ 35-54 yo ■ 55-64 yo ■ 65+ yo

- Approximately 42% of PWH are 55 and older
- Older adults less likely to be tested for HIV and more likely to have AIDS



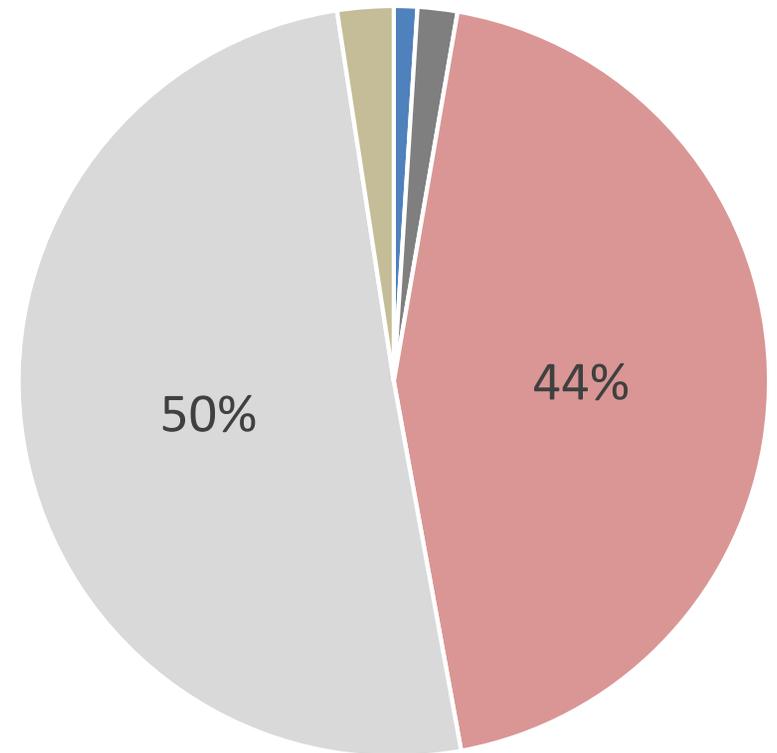
The Prevalence of Older PWH Will Likely Increase in the Coming Years



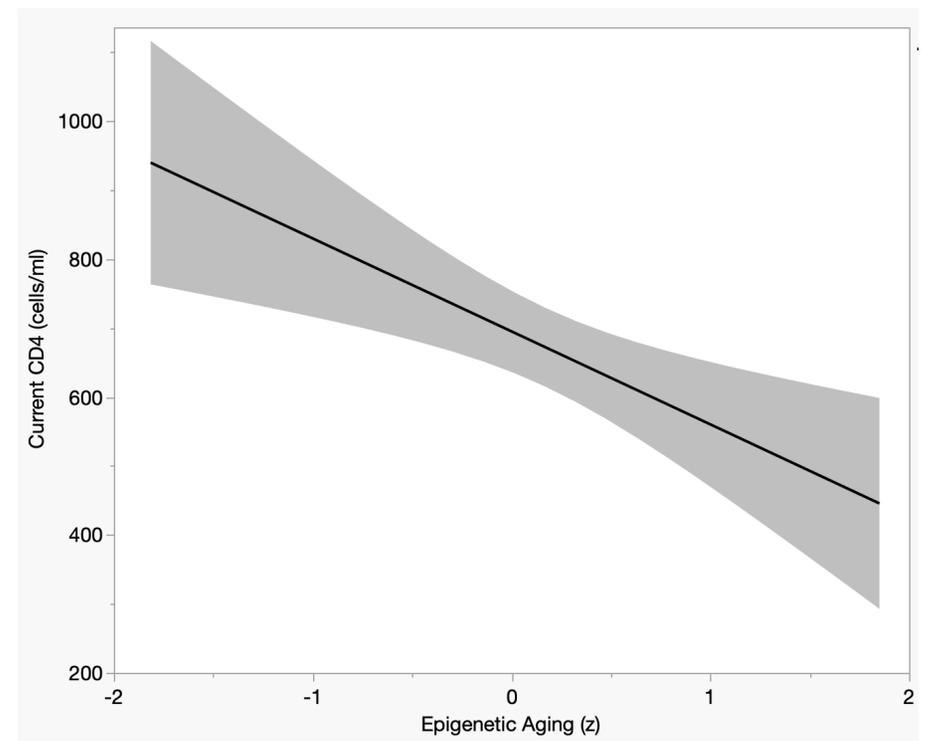
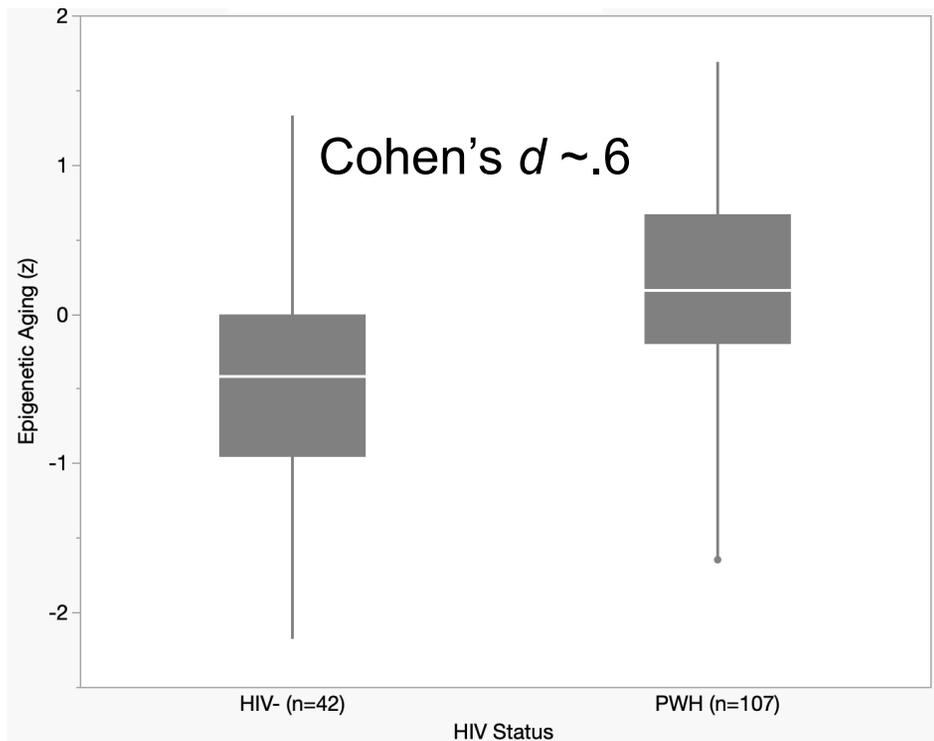
Characteristics of Older PWH

- Mix of incident cases and people with chronic HIV
- 25% women, 35% H/L
- Better medication adherence and higher viral suppression
- Immunosenescence
- Highest mortality
 - 8-32% of HIV deaths
 - 3x higher than younger

■ AN/PI ■ Asian ■ Black ■ White ■ Multiple

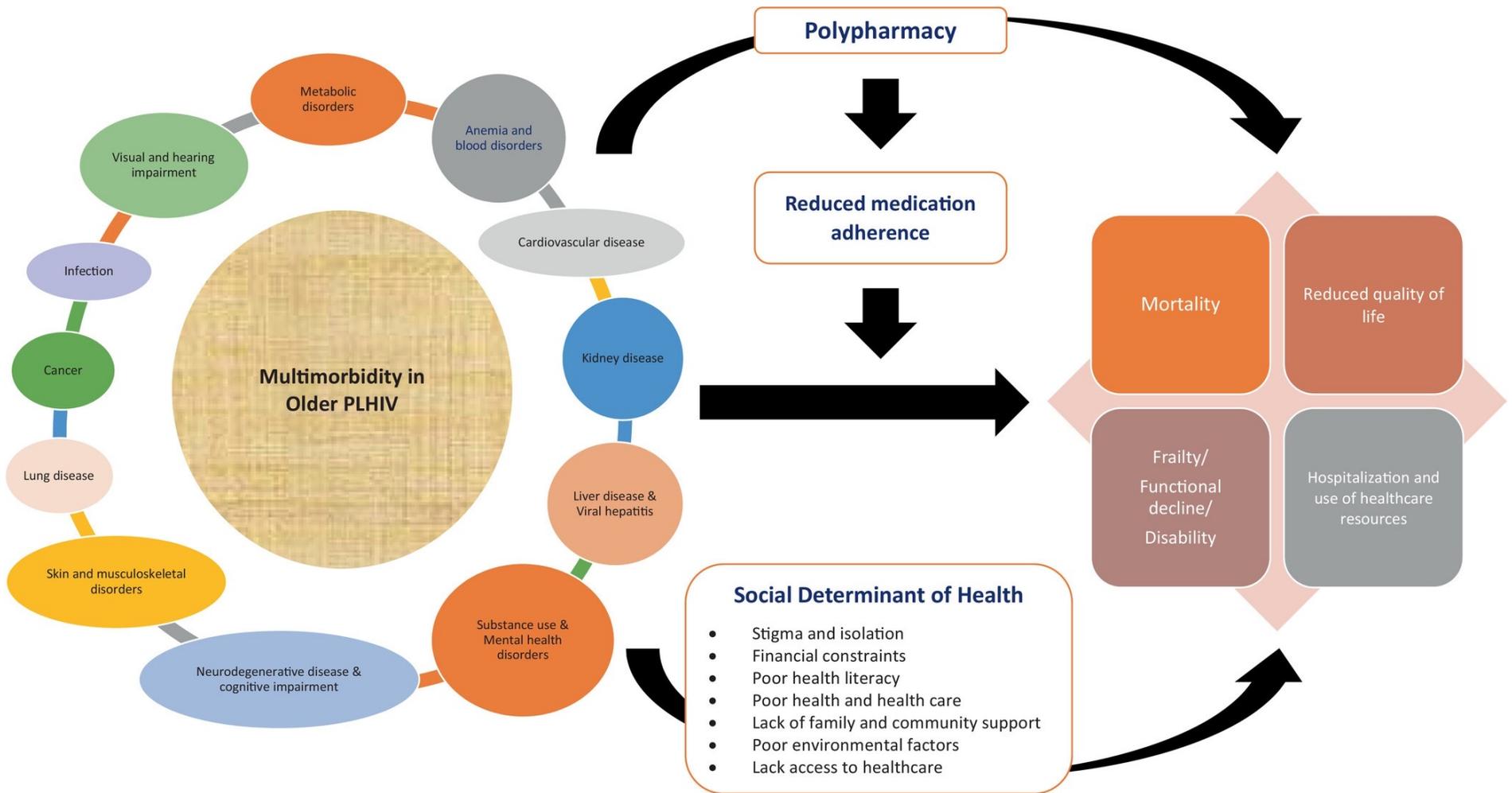


Advanced Biological Aging in PWH



1st and 2nd generation epigenetic clocks that measure age-related changes to DNA (i.e., blood-based marker of methylation, which is the addition of methyl groups to DNA)

Comorbidities and Polypharmacy



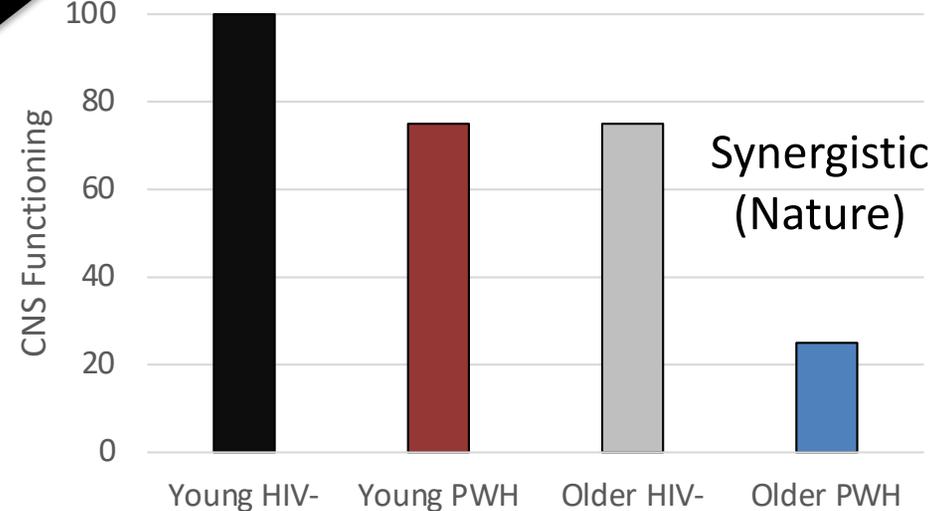
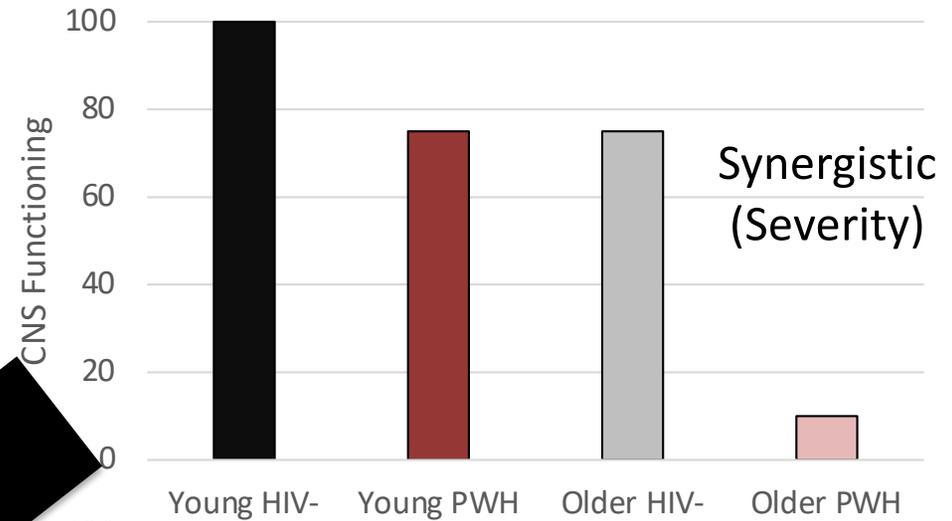
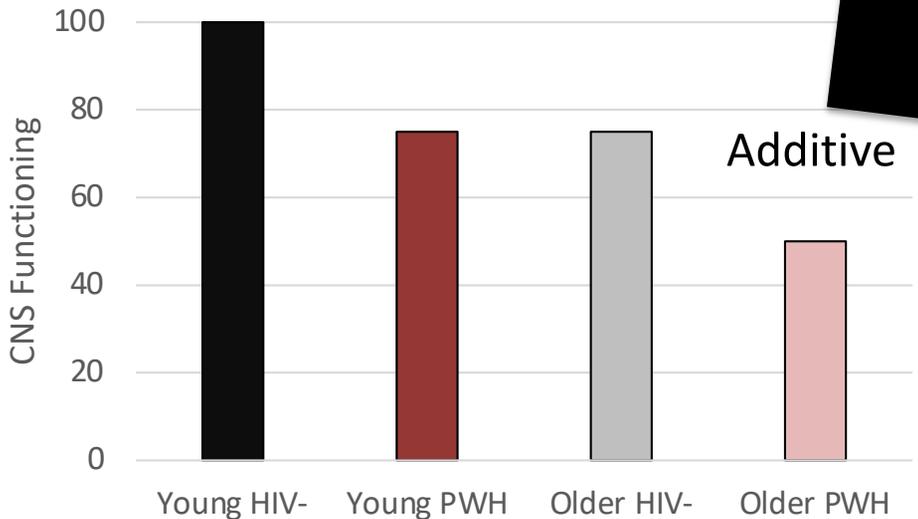
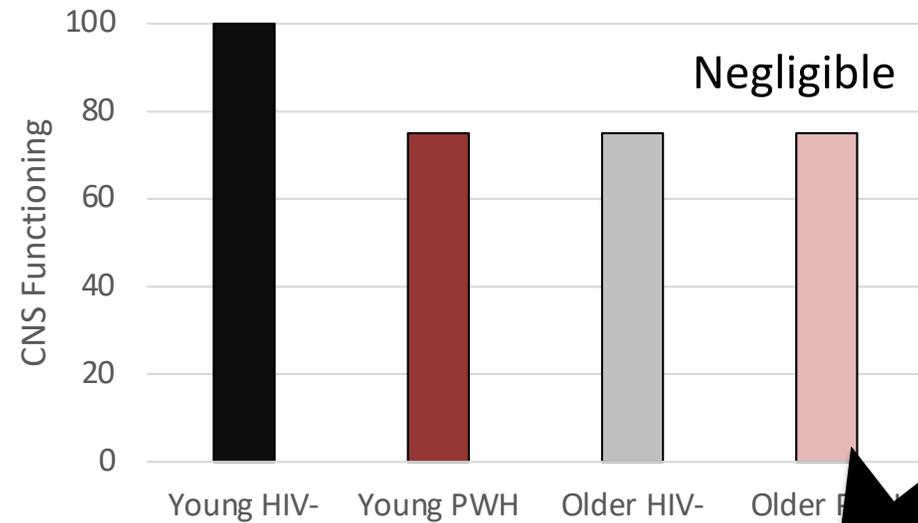
HIV Disease and Aging: Possible Mechanisms of CNS Injury

- Duration of HIV infection
 - ◆ Cumulative HIV-induced neural injury
 - Neurotoxic viral proteins
 - ◆ Increased exposure to ARVs
 - Toxicity from ART
 - Metabolic syndrome
- Vulnerability to age-related factors
 - ◆ Hormonal changes
 - ◆ Diabetes
 - ◆ Cerebrovascular disease
 - ◆ Atherosclerosis
 - ◆ Progressive dementias



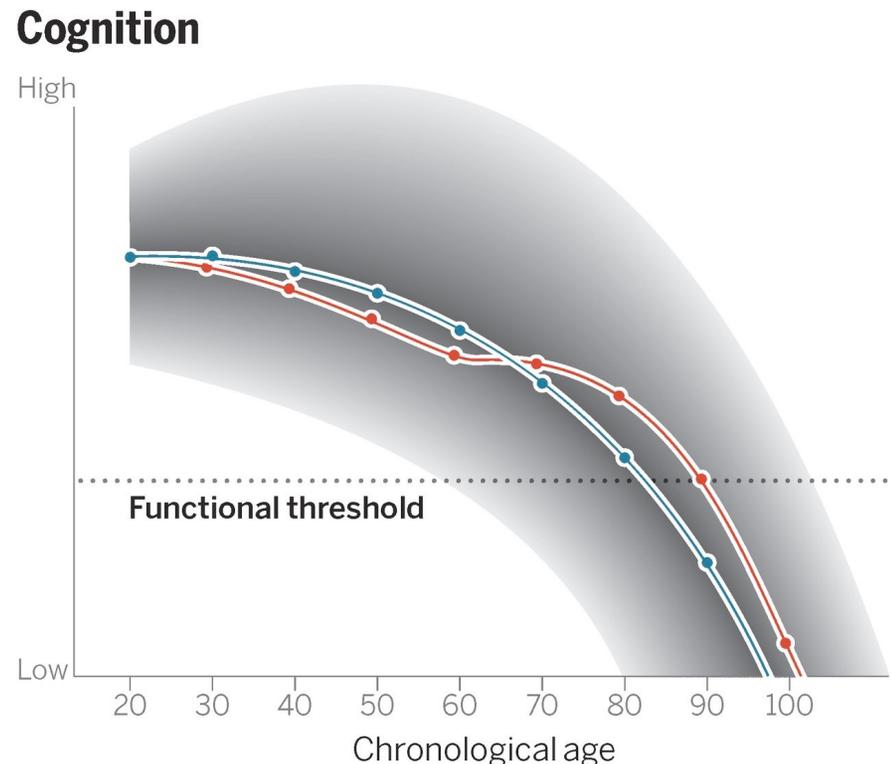
The Well Project

Combined Brain Effects of HIV and Aging: *Negligible, Additive, or Synergistic?*



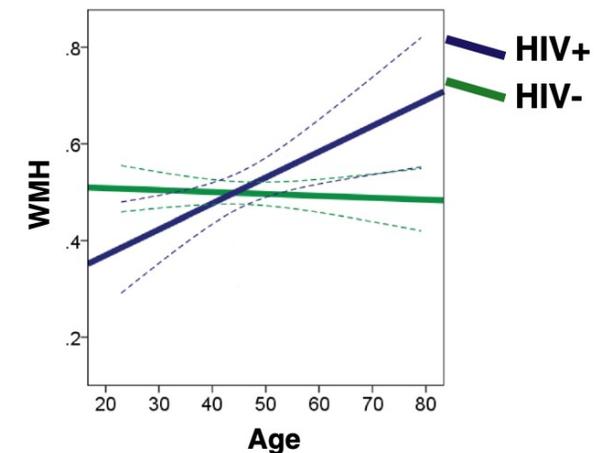
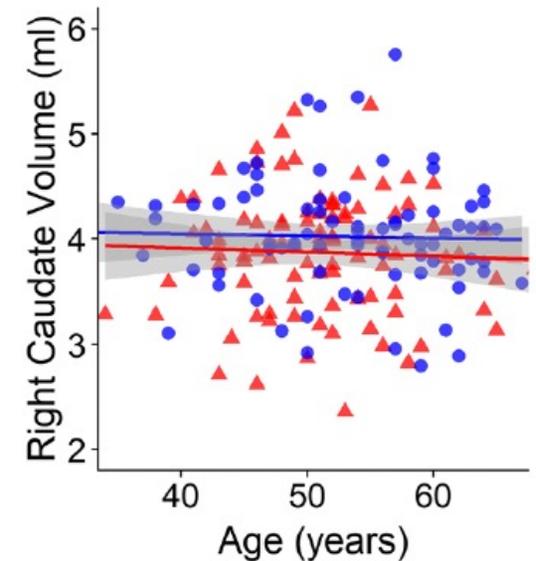
The Aging Brain

- HIV and aging are independently associated with:
 - ◆ Neuropathological changes
 - Reduced synaptodendritic complexity
 - Inflammation
 - Cerebrovascular disease
 - Altered structure and function of fronto-striatal systems
 - Medial temporal cortex also affected
 - ◆ Neurocognitive decline
 - Executive dysfunction
 - Episodic memory loss
 - Psychomotor slowing

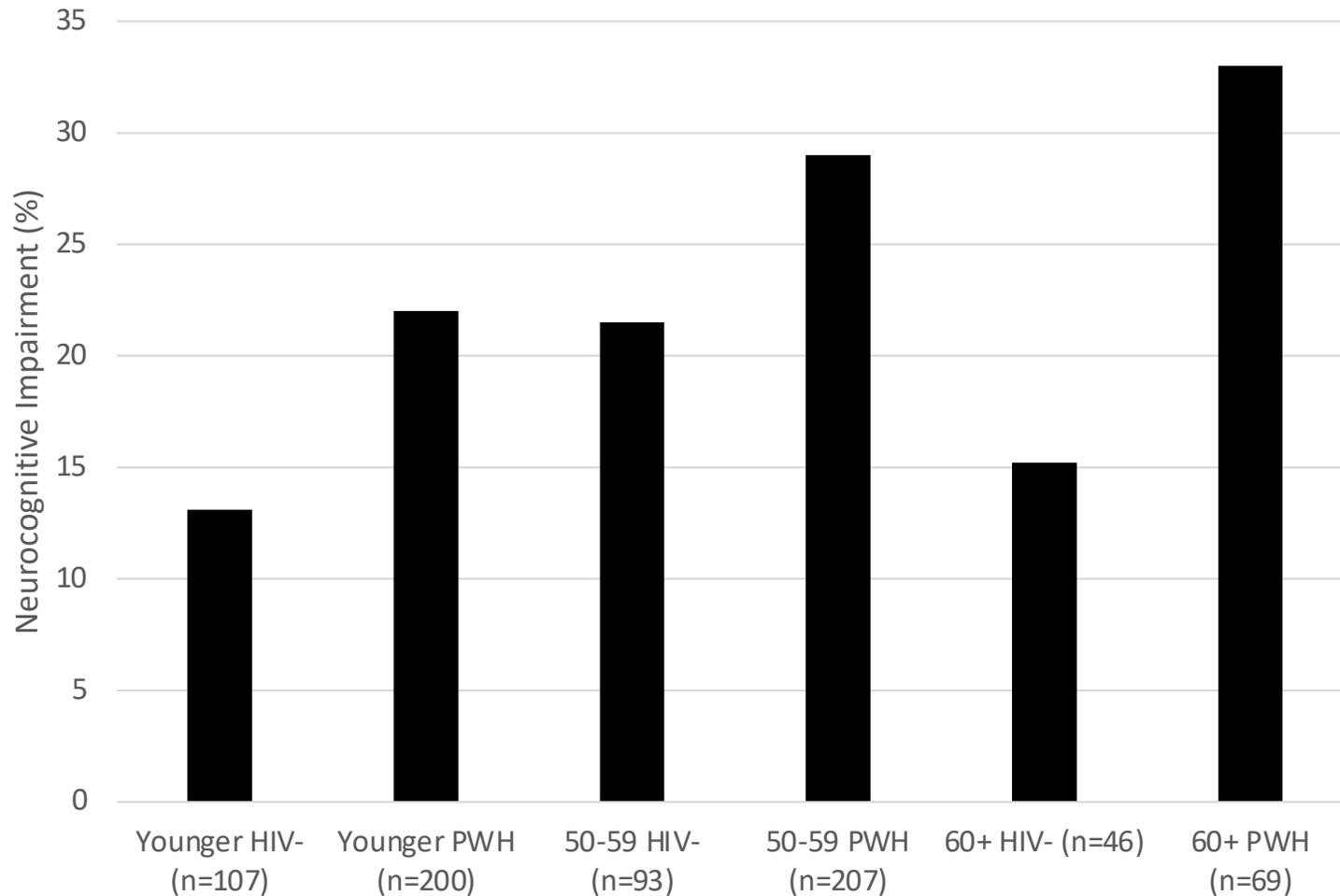


HIV and Aging: Neuroimaging Findings

- Cross-sectional evidence largely points to additive, independent effects of HIV on brain structure and blood flow in fronto-striatal systems (e.g., O'Connor et al., 2019; Peterson et al., 2021; Pluta et al., 2019)
 - ◆ Some evidence for interactions in white matter microstructure (e.g., Kuhn et al., 2019; Seider et al., 2016)
 - ◆ Some evidence for accelerated longitudinal decline in brain structure in PWH (e.g., Clifford et al., 2017; Jakabek et al., 2022)
 - ◆ Comorbidities (e.g., vascular disease, substance use) are important contributors (e.g., Jakabek et al., 2022; Pfefferbaum et al., 2024; Saloner et al., 2019)

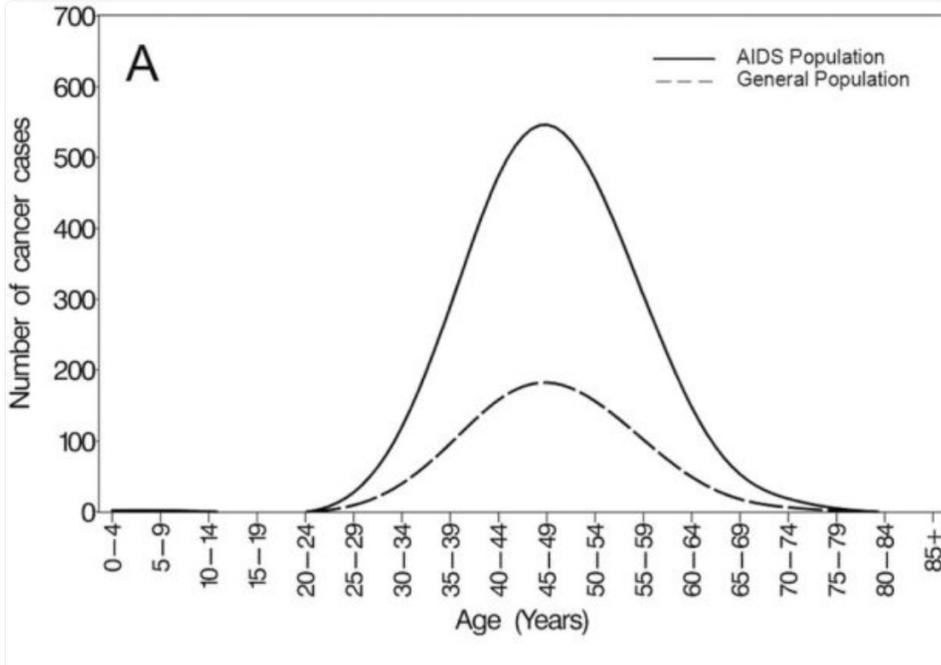


HIV and Age Confer Additive Risk of Neurocognitive Impairment

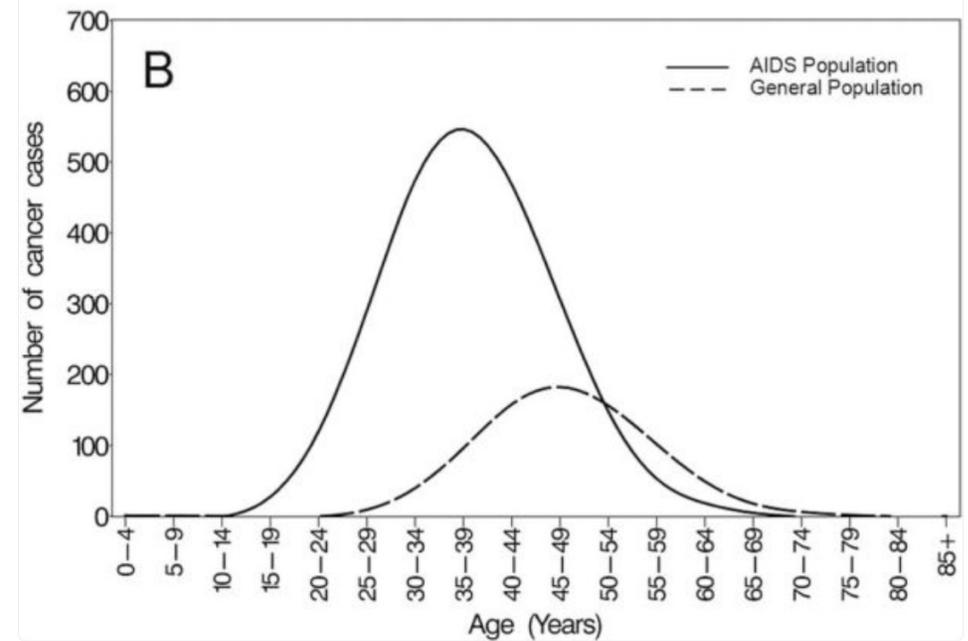


Is HIV Associated with Accentuated or Accelerated Cognitive Aging?

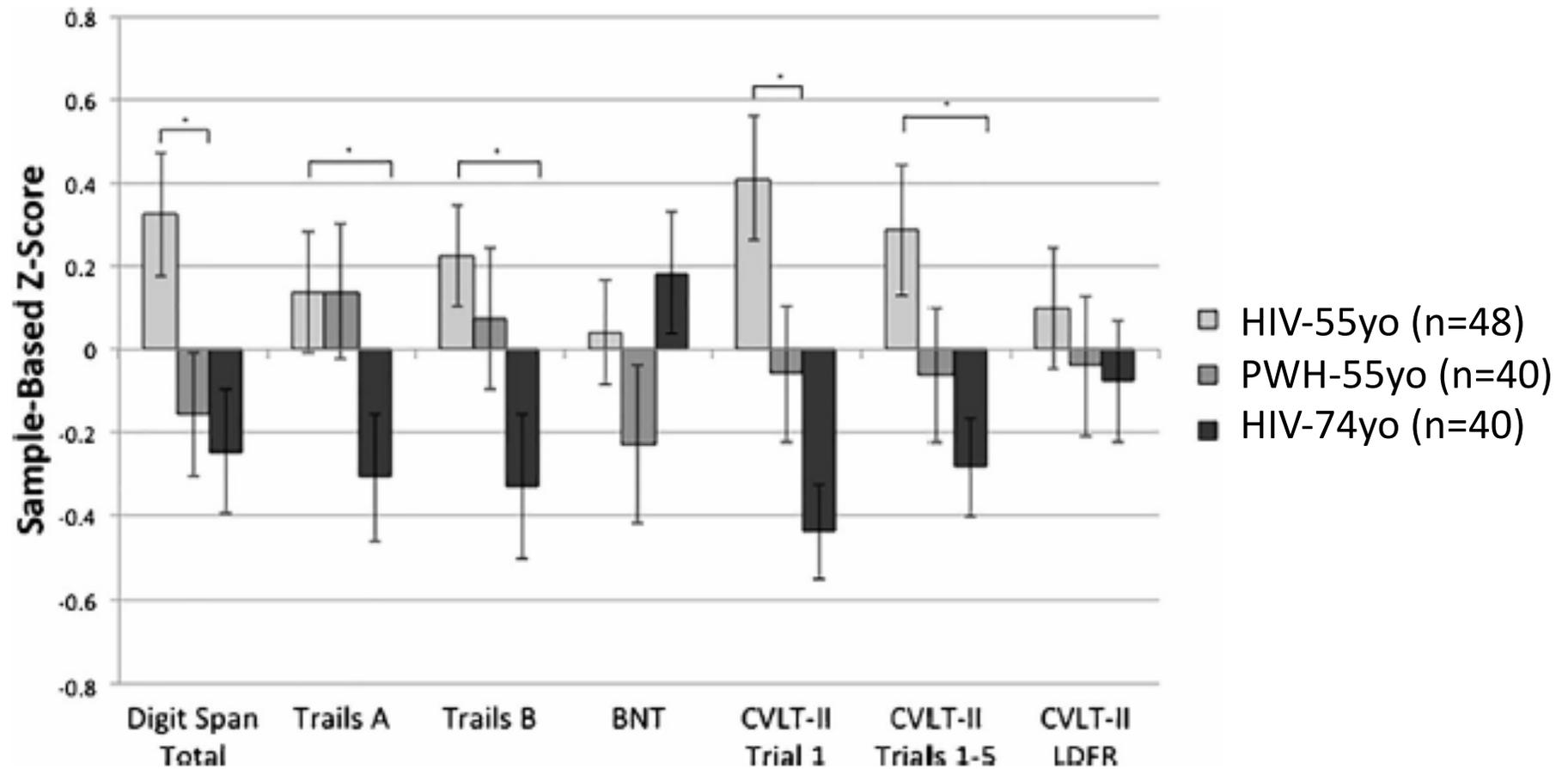
Accentuated



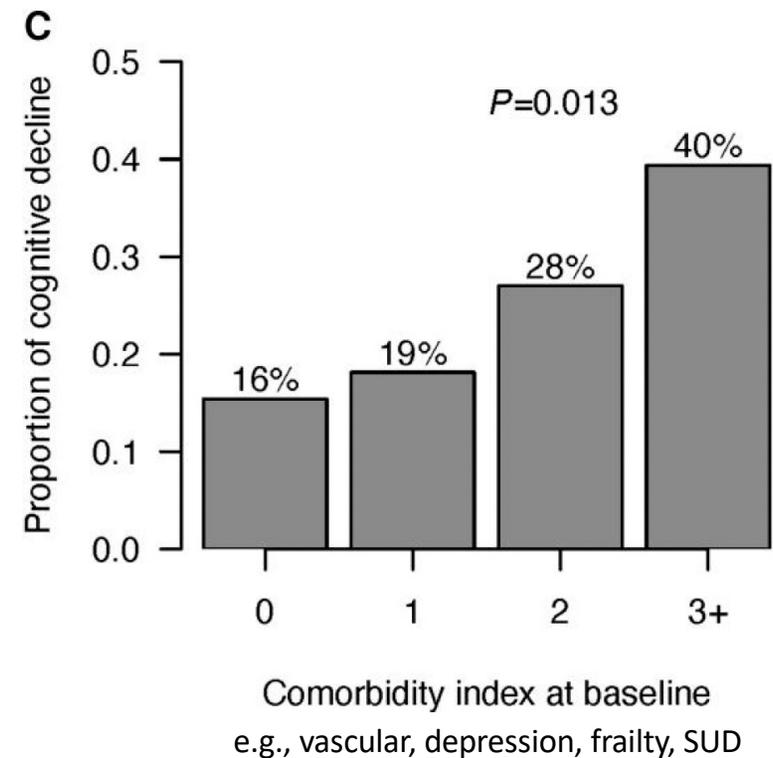
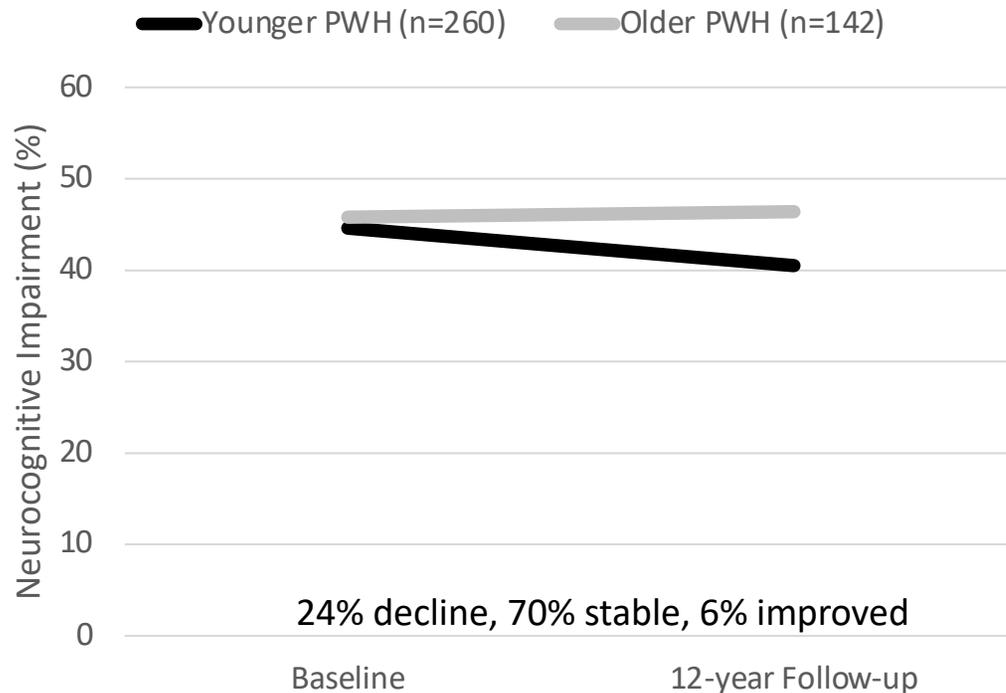
Accelerated



Accelerated (auditory-verbal) and Accentuated Cognitive Aging Occur in HIV Disease

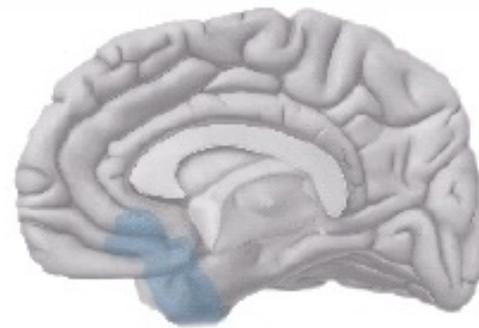


Neurocognitive Change Over 12 Years in Younger (<40) and Older (50+) PWH

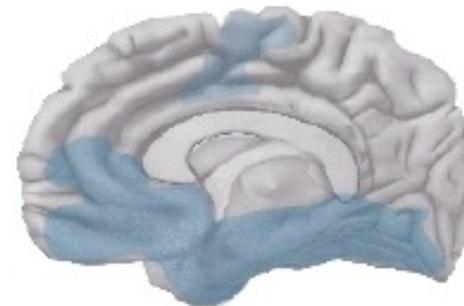


The Alzheimer's Disease ("Cortical") Hypothesis of Aging and HAND

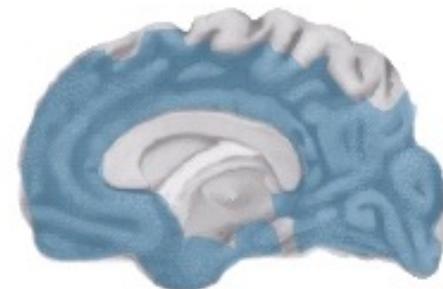
- Alzheimer's disease
 - ◆ Most common cause of dementia among older adults
 - ◆ Progressive dementia
 - Amyloid plaques and neurofibrillary tangles
 - Especially in the medial temporal lobes
 - ◆ Neurocognitive profile
 - Rapid forgetting, semantic memory failures, visuoperceptual changes, aphasia, dyspraxia



**Very Early
Alzheimer's**



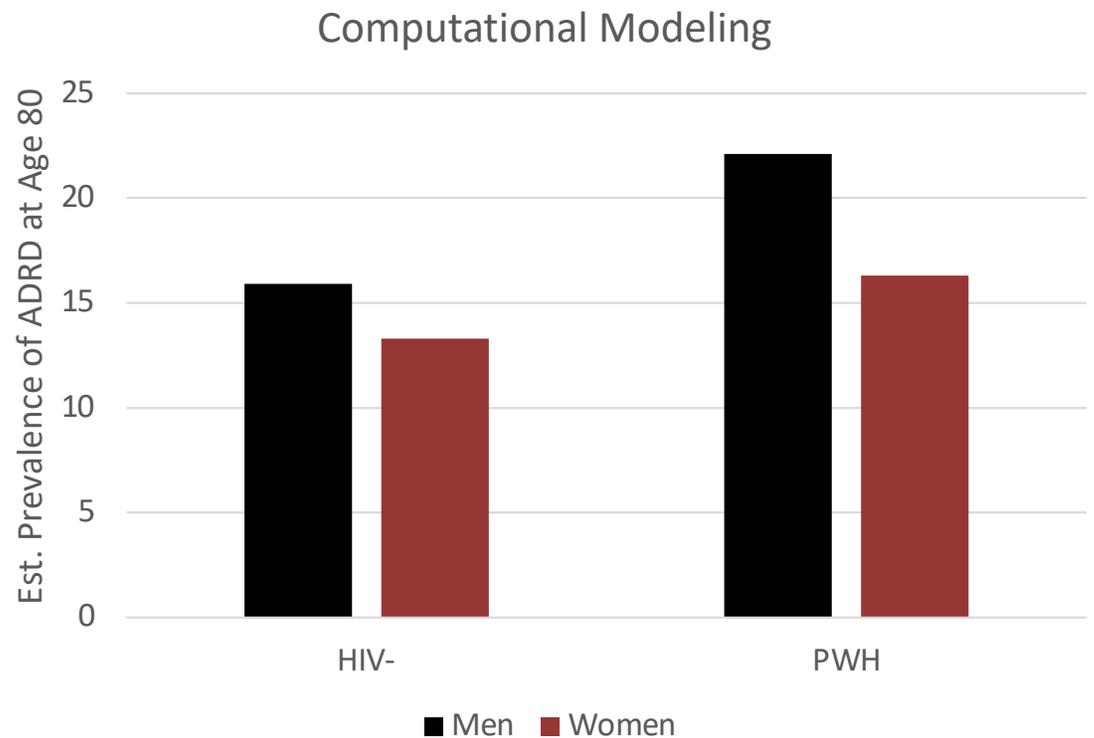
**Mild to
Moderate
Alzheimer's**



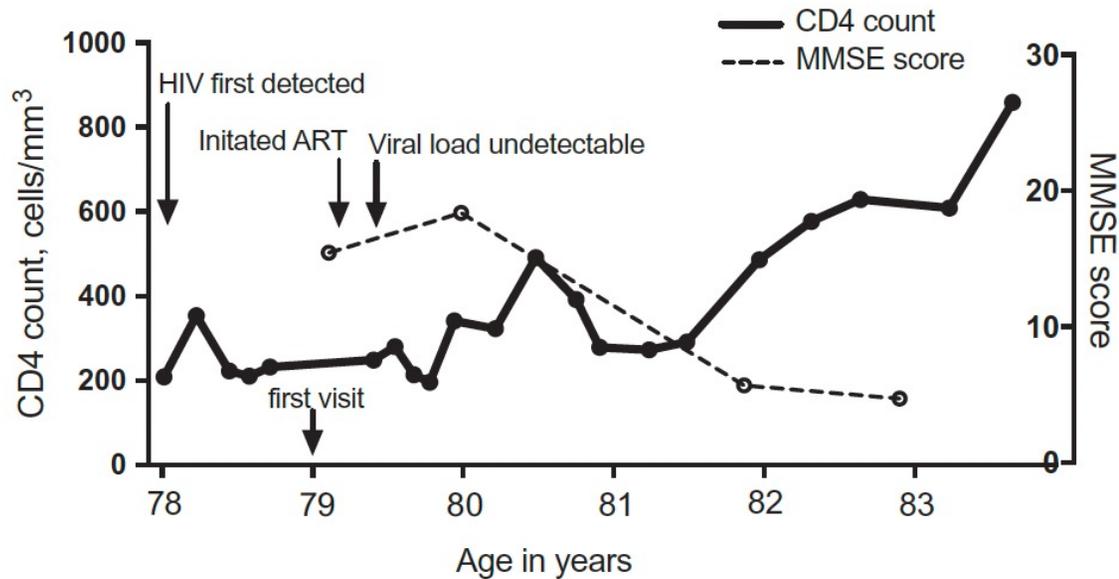
**Severe
Alzheimer's**

Arguments *for* the AD Hypothesis of HAND

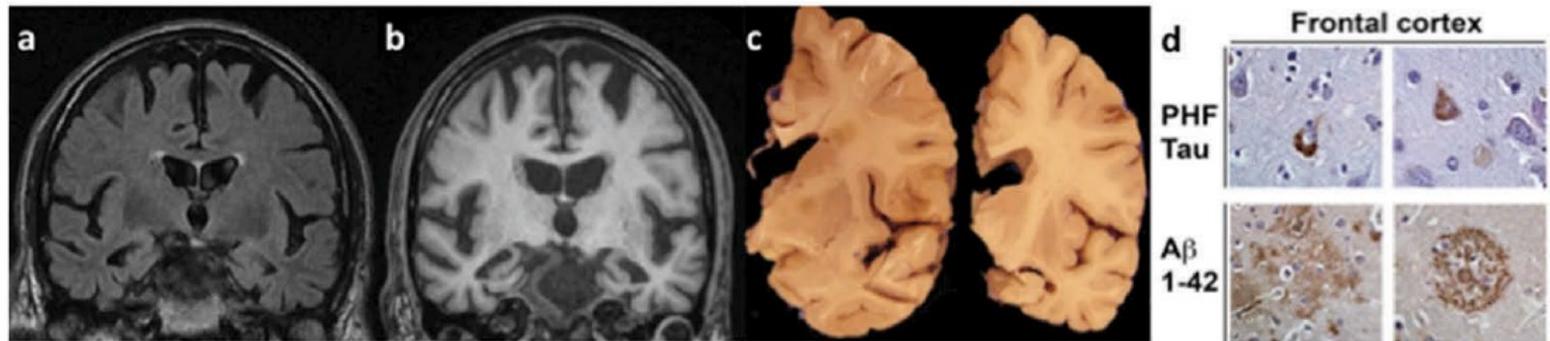
- Common risk factors
 - ◆ Age
 - ◆ APOE-e4
 - ◆ Lipid metabolism
 - ◆ Vascular disease
 - ◆ Health behaviors
- Neuroanatomy
 - ◆ Hippocampus
- Neuropathology
 - ◆ Amyloid plaques



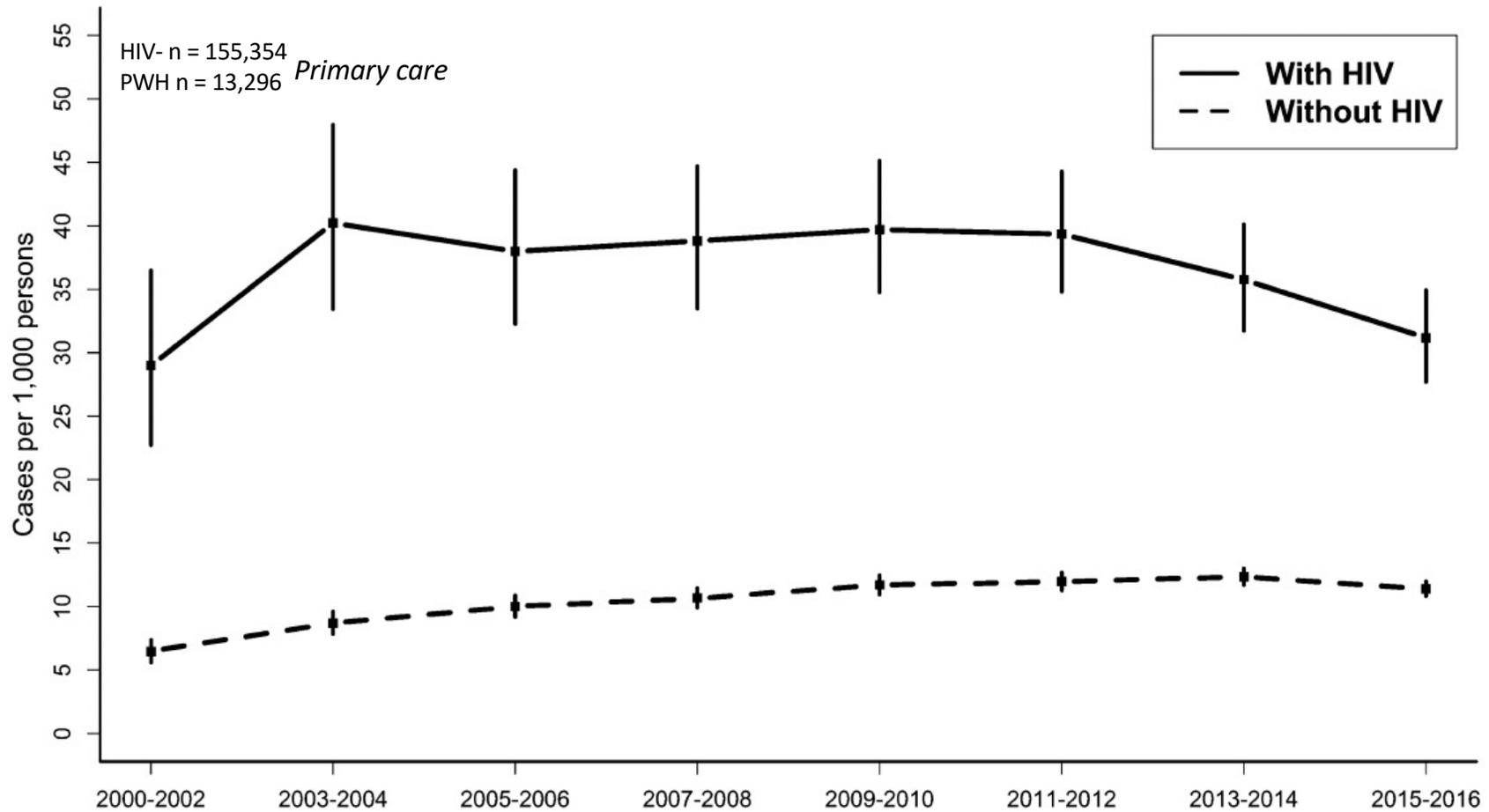
PWH Are Unlikely to Avoid Age-Related Risk of Alzheimer's Disease



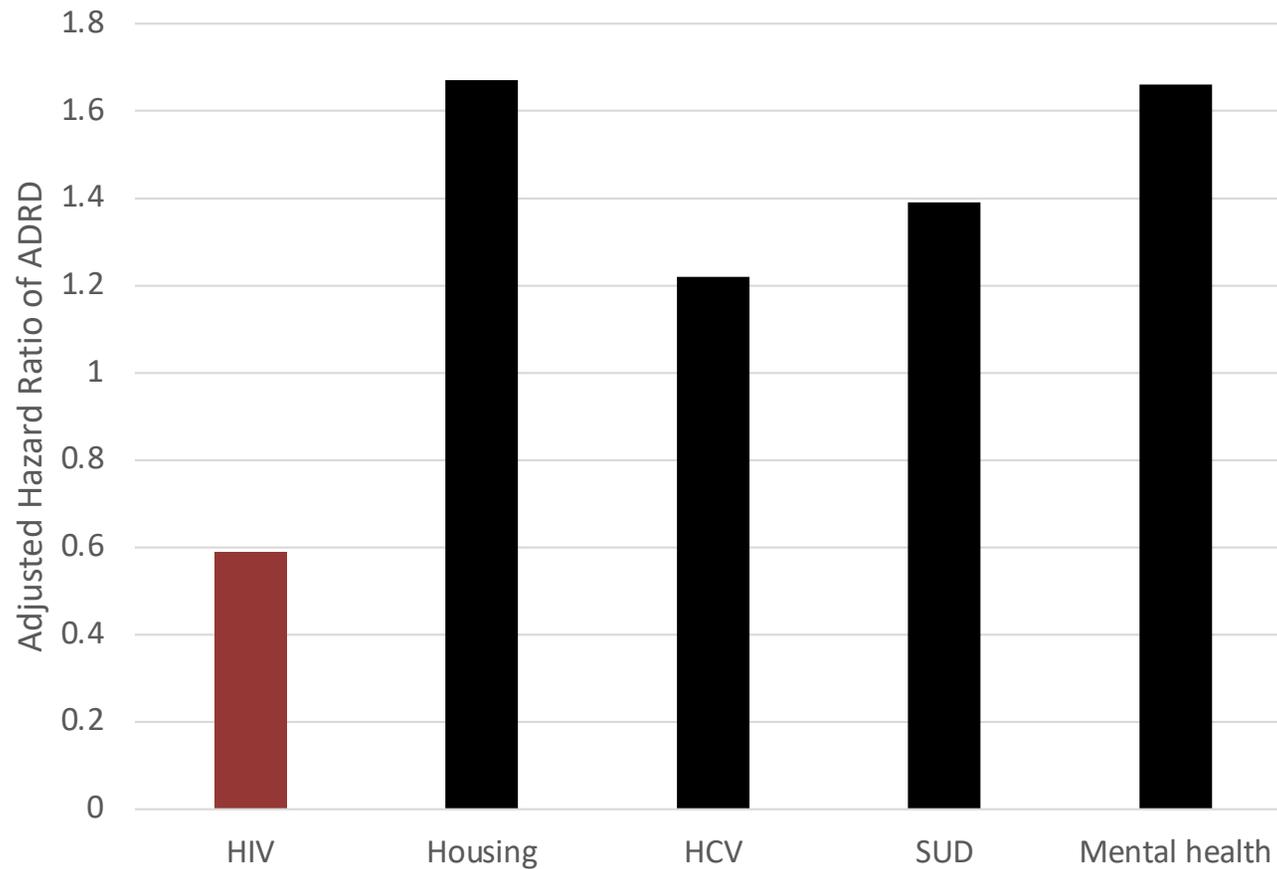
Draw CLOCK (Ten past eleven)
(3 points)



Older PWH Will Likely Also be at Risk for Other Age-Related Major Neurocognitive Disorders



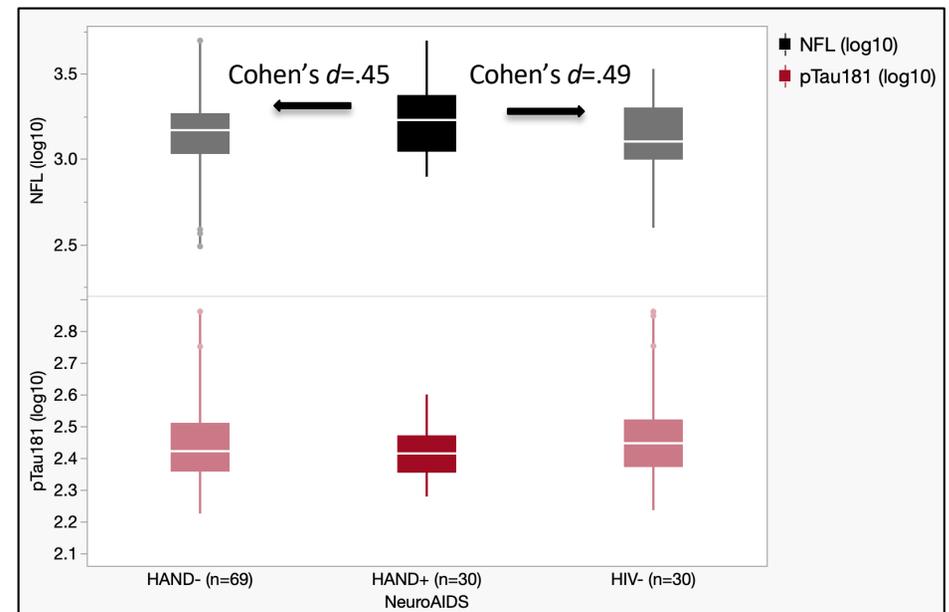
Large Epidemiological Studies



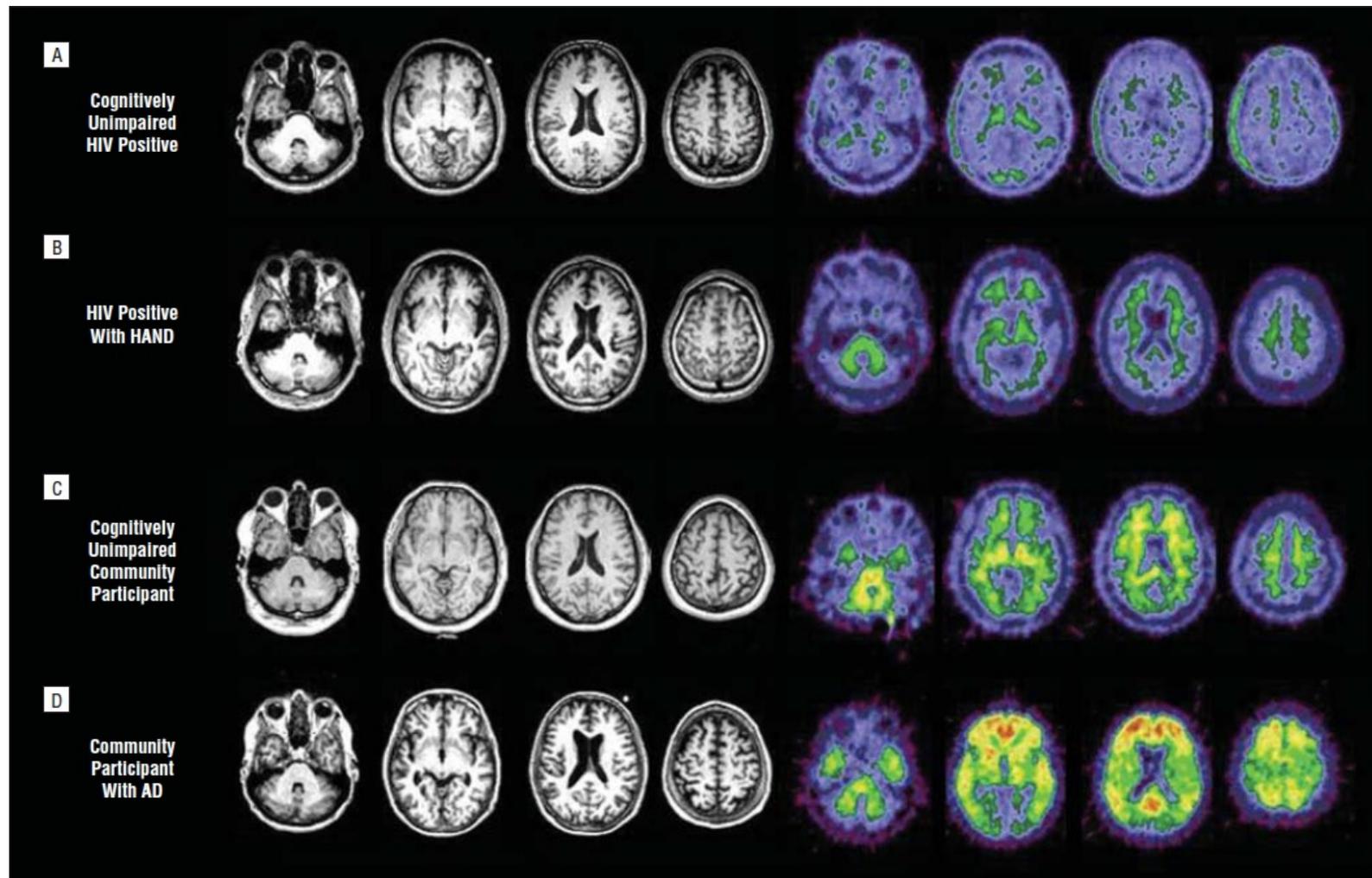
N=3,275,098 veterans

Peripheral Biomarkers of AD in PWH: *A/T/N Framework*

- Neurofilament light (NFL; neuroaxonal) may be higher in HAND?
- AB (plaques) findings are largely mixed
 - May be lower in HAND?
 - Higher than ADRD
- Tau (neuroaxonal) findings are mixed
 - May be higher in HAND?



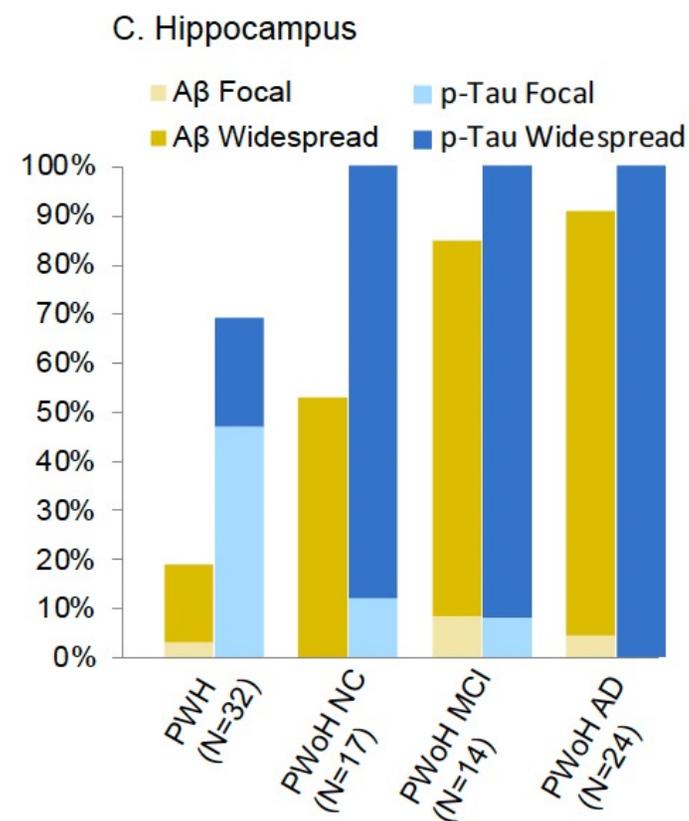
In Vivo Amyloid Imaging in HAND Is *Not* Generally Consistent with the AD Hypothesis



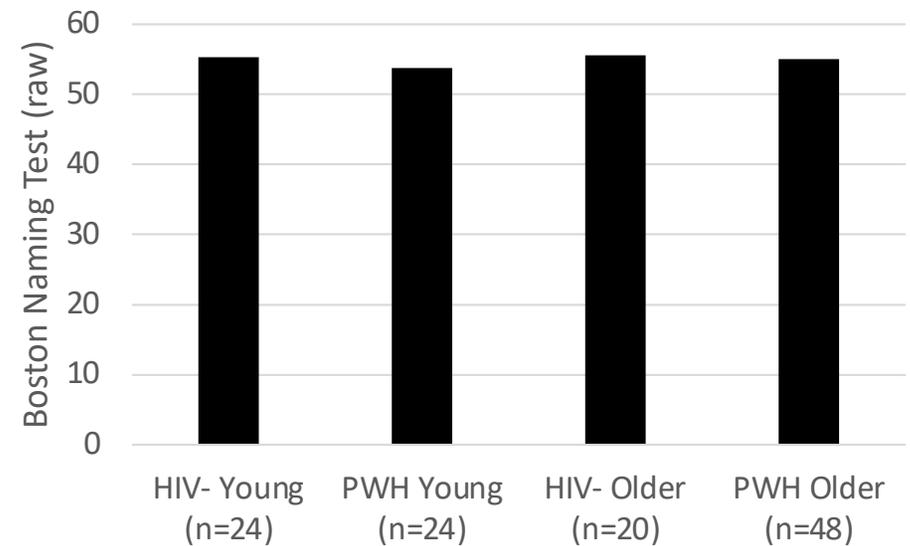
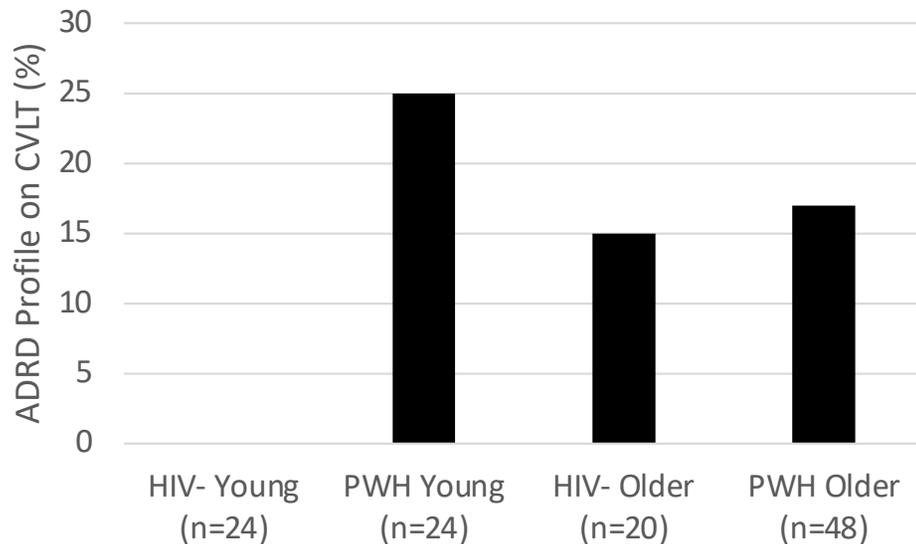
PIB on PET

The Neuropathology Data Are Compellingly Null So Far

- Magaki et al. (2022) found no difference in microglial or astrocyte activation between 9 older PWH and 7 HIV-
- Nader et al. (2023) found no association between HIV and hippocampal tauopathy in 71 PWH and 25 HIV-
- Sundermann et al. (2023) found lower rates of ADRD pathology in 49 PWH versus 20 HIV-
- Umlauf et al. (2019) found a 3% higher rate of cerebral β -amyloid plaques in the frontal cortex of 279 PWH vs 1,110 HIV-

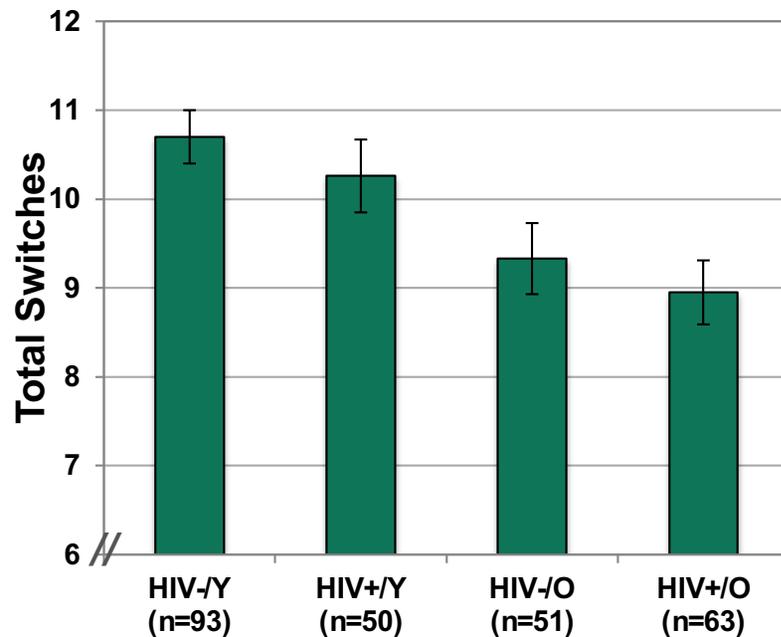


Cognitive Studies Generally Do *Not* Support the AD Hypothesis



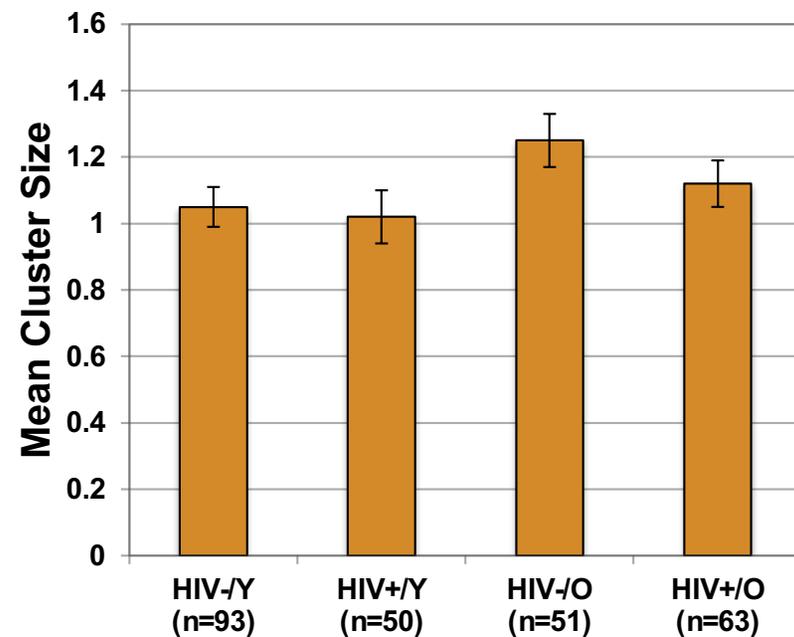
Cognitive Studies Generally Do *Not* Support the AD Hypothesis

Switching



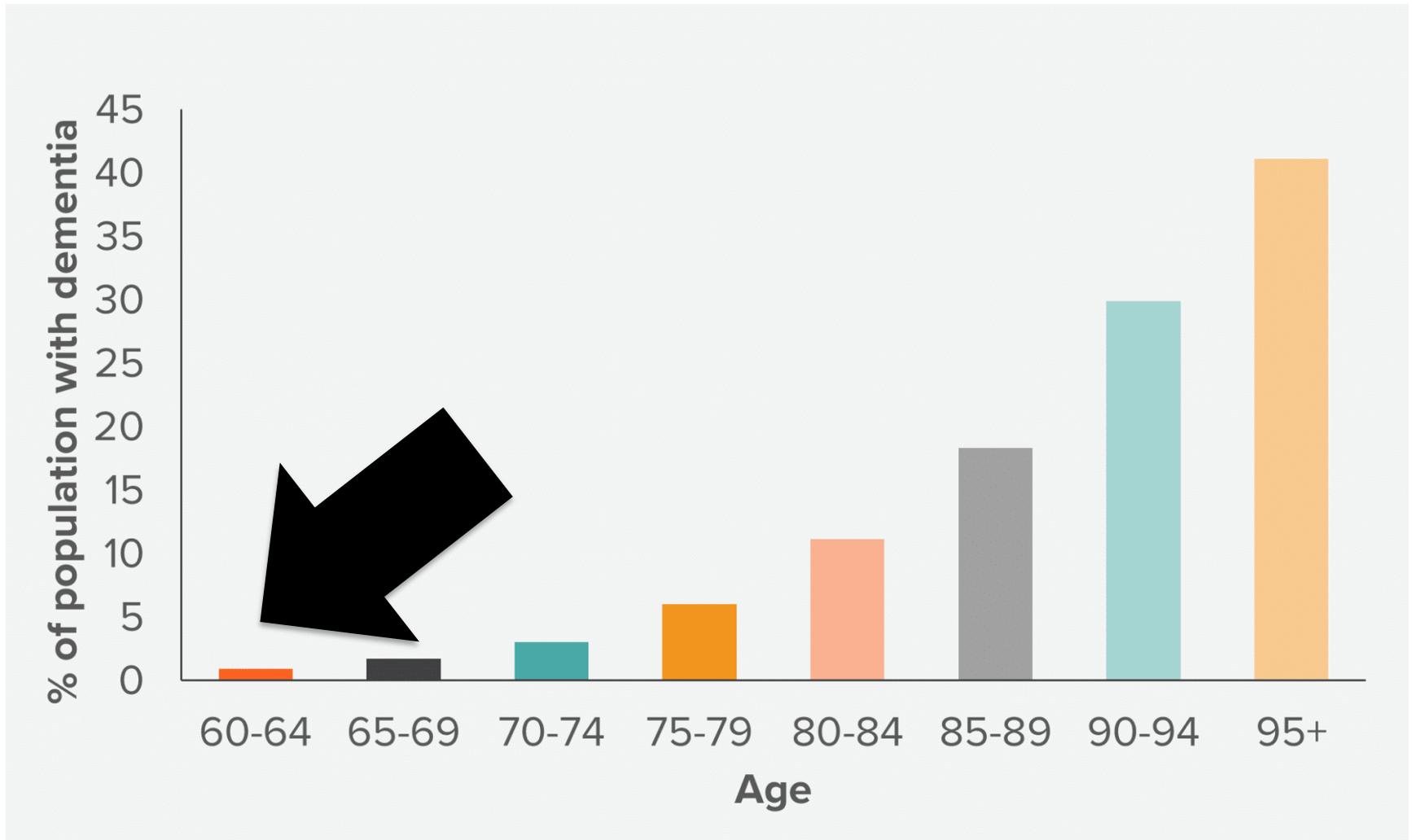
J-T Statistic = 2.16
 $p = 0.015$

Mean Cluster Size

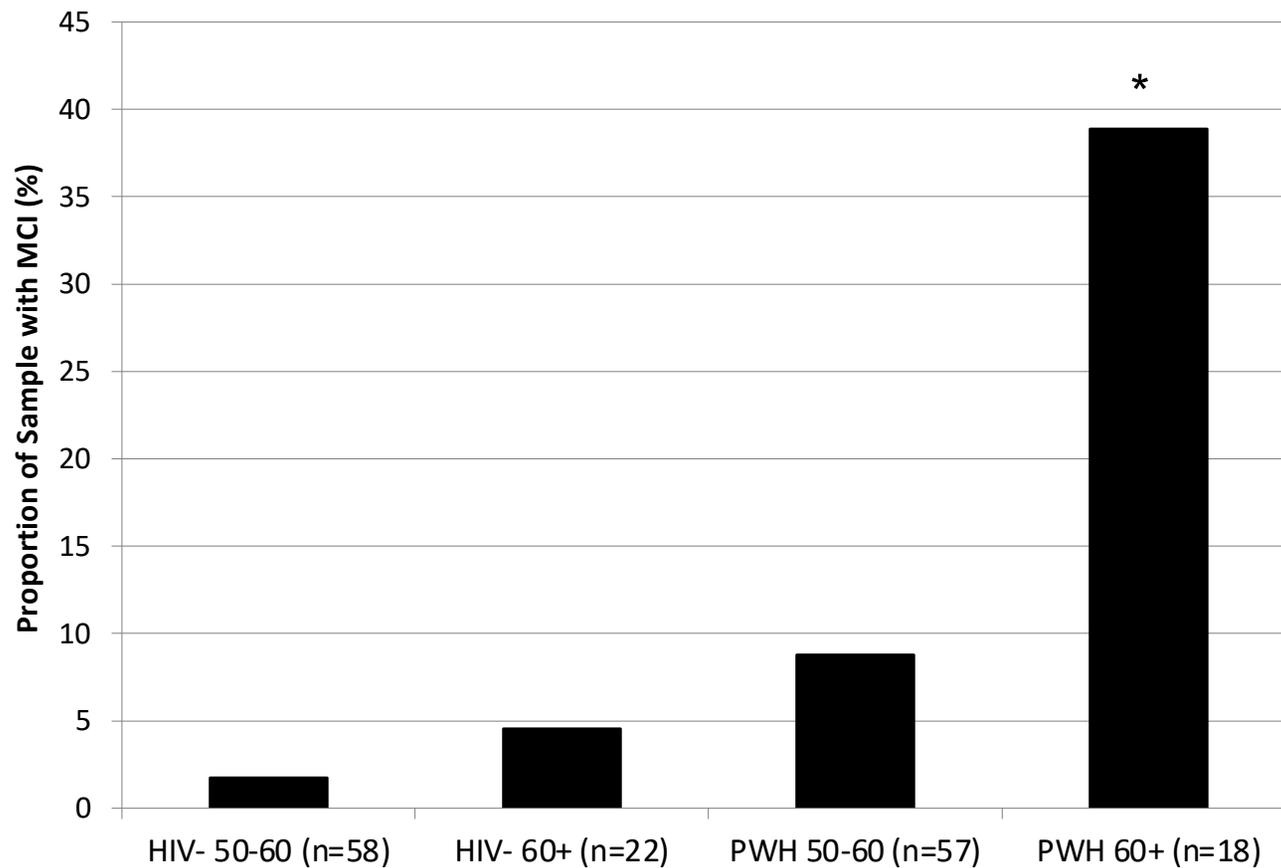


J-T Statistic = -1.37
 $p = 0.915$

Reason for Cautious Interpretation: *Base Rates of AD Across the Lifespan*

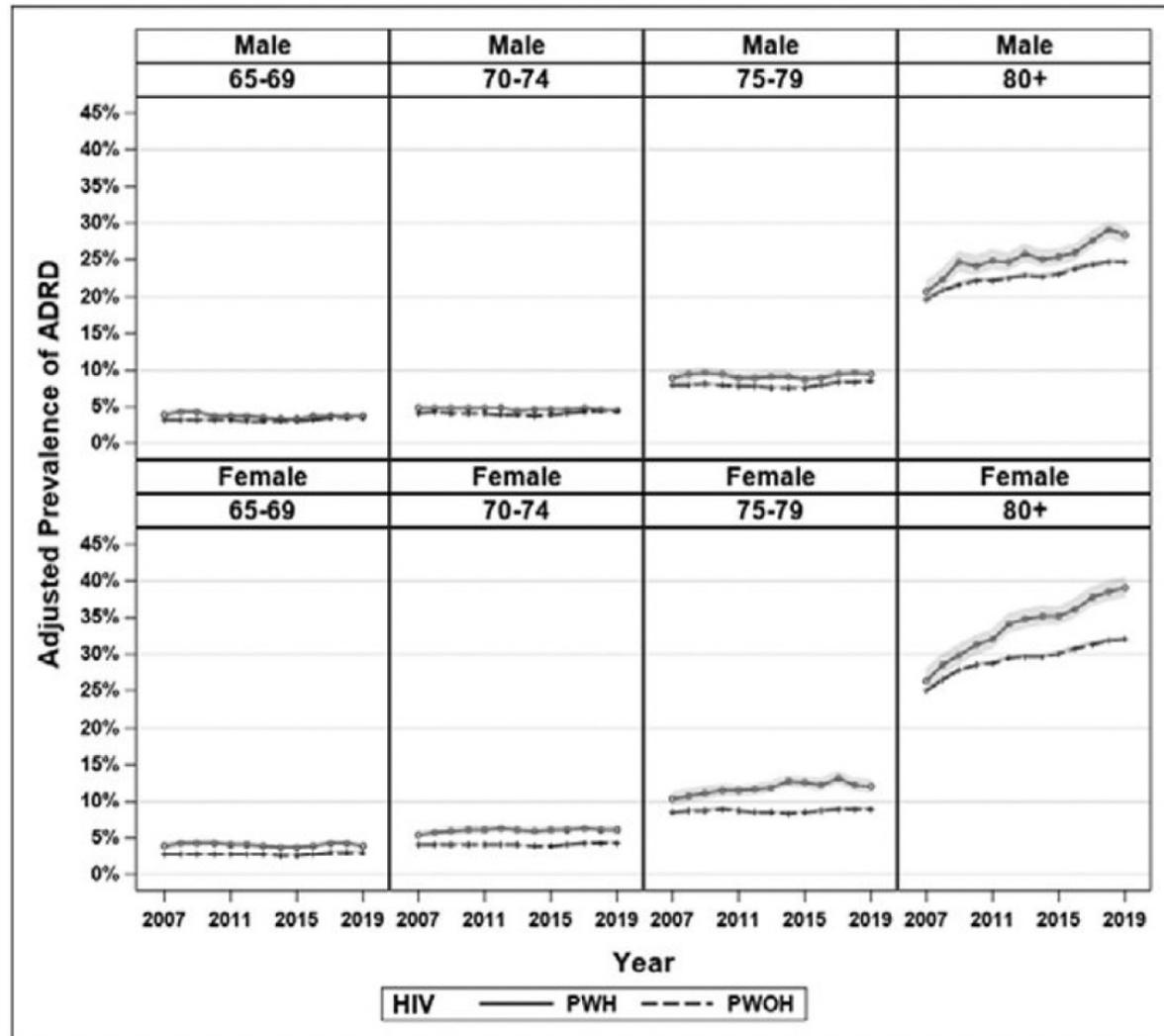


Risk of Mild Cognitive Impairment (MCI) in HIV Disease Increases with Age



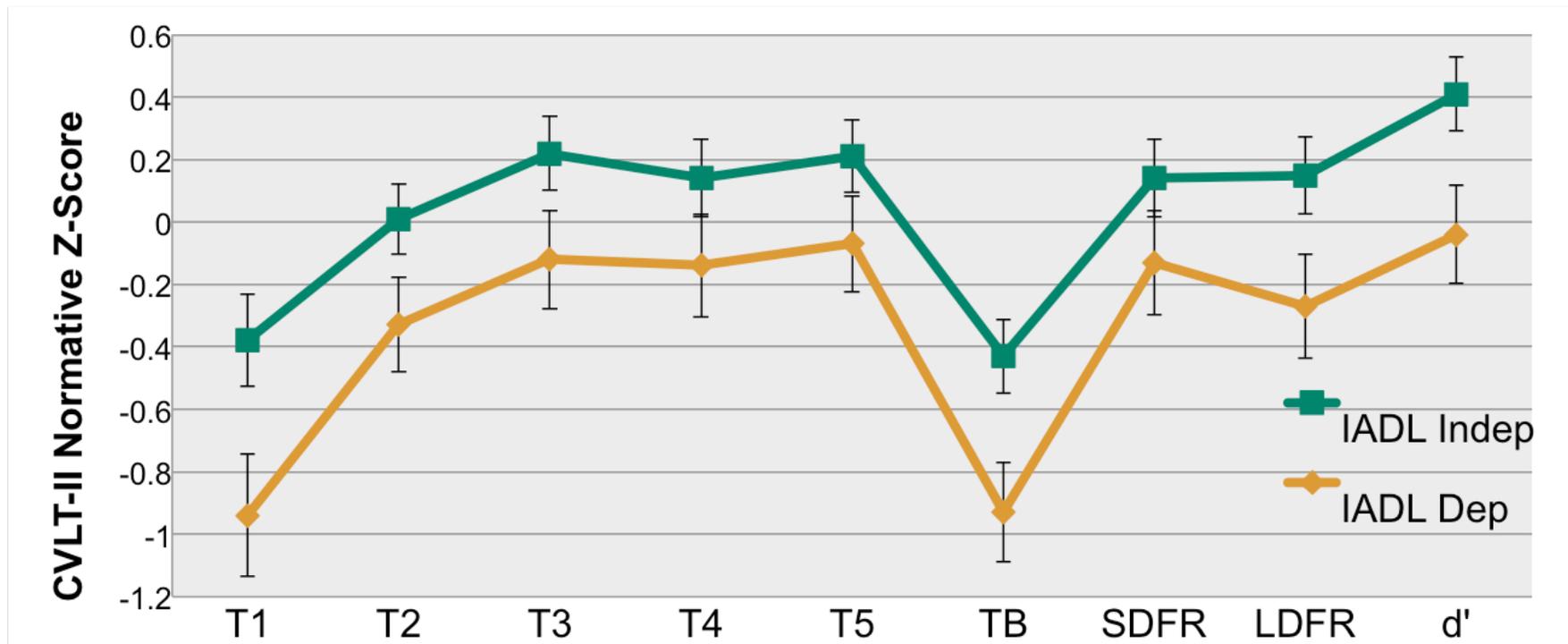
* $p < 0.01$

The Future Will Tell the Tale



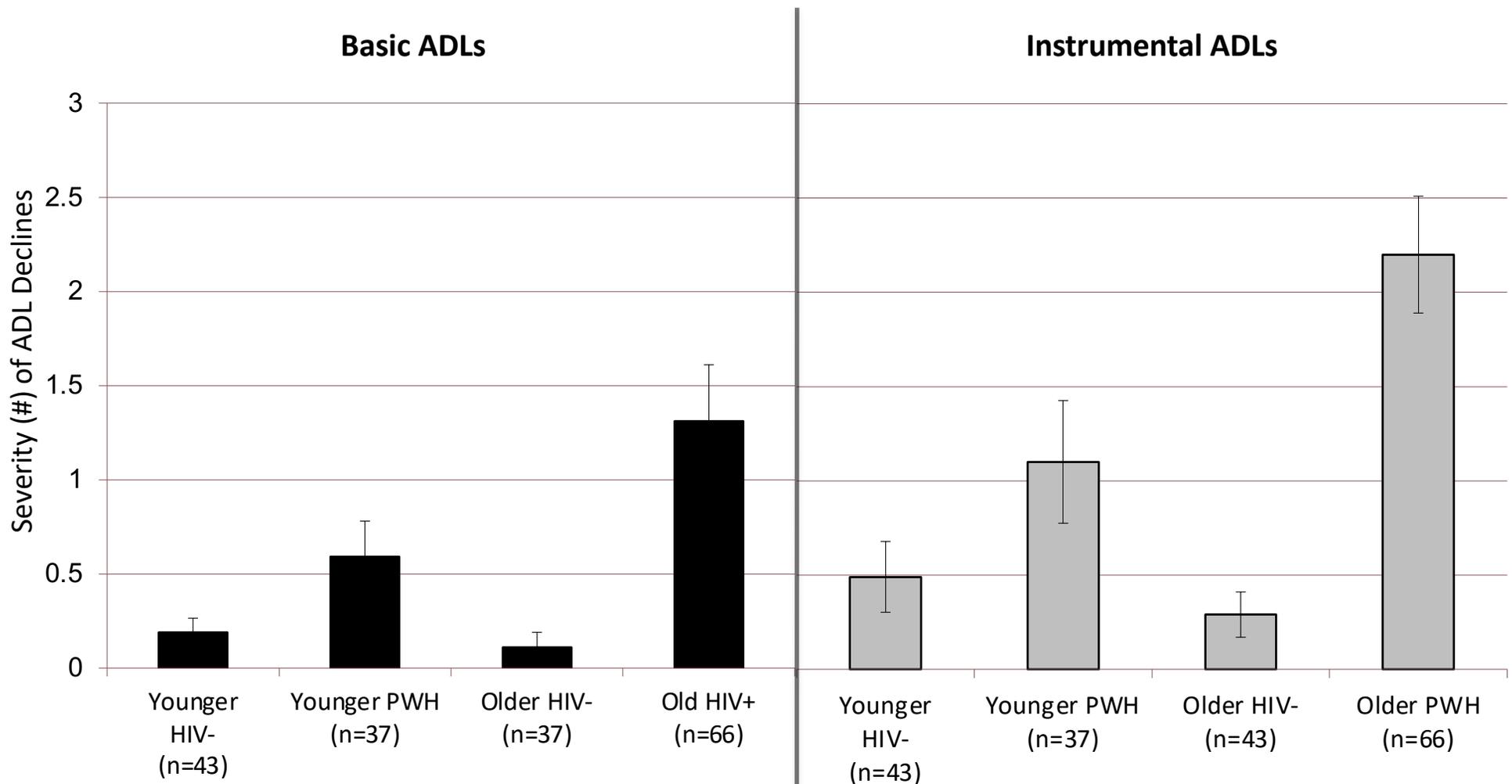
HIV- n= 2,289,831
 PWH n = 87,216

Shallow Encoding (Recency) and Mild Forgetting Predict IADL Declines in Older PWH

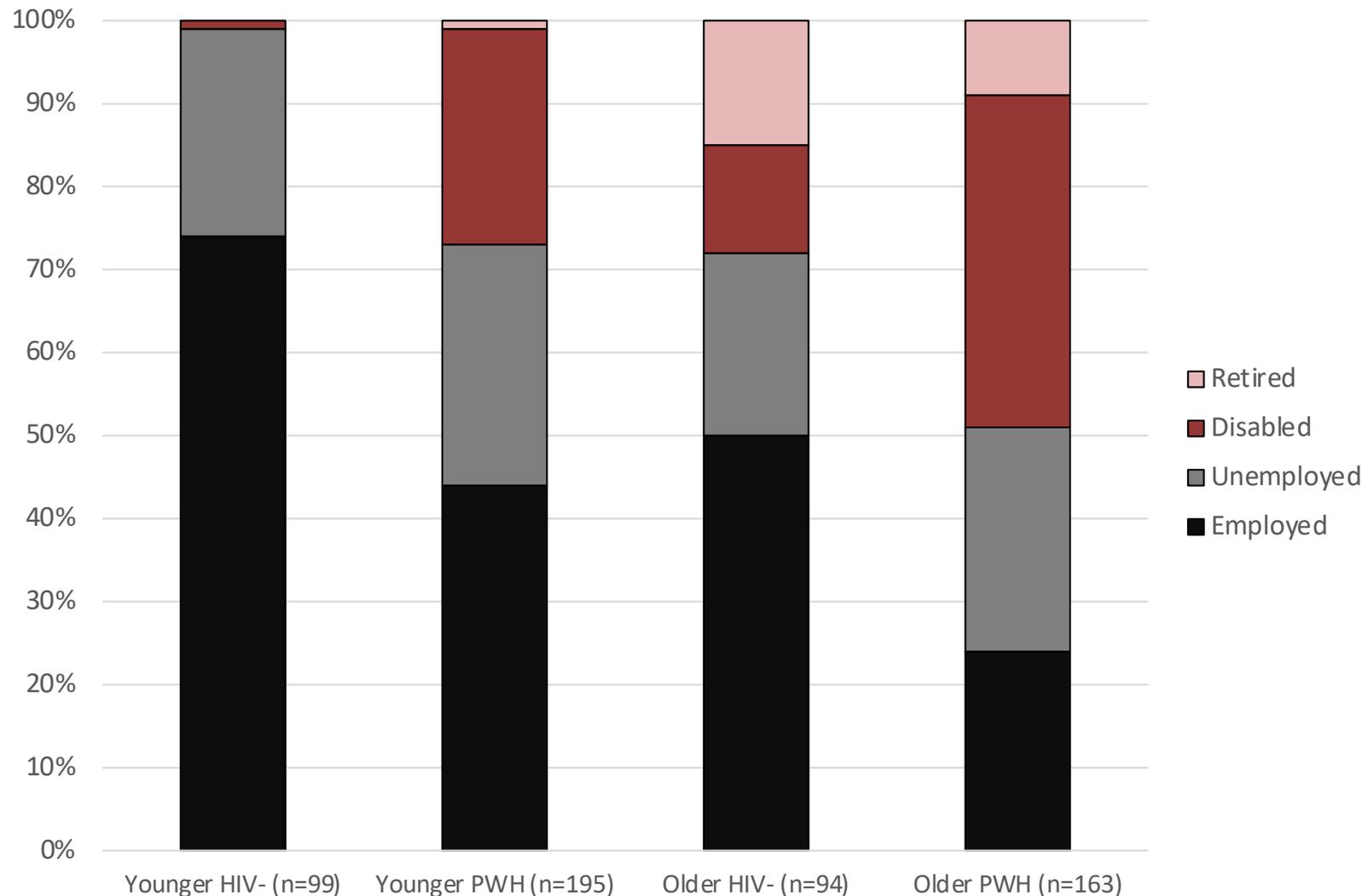


N=119 Older PWH

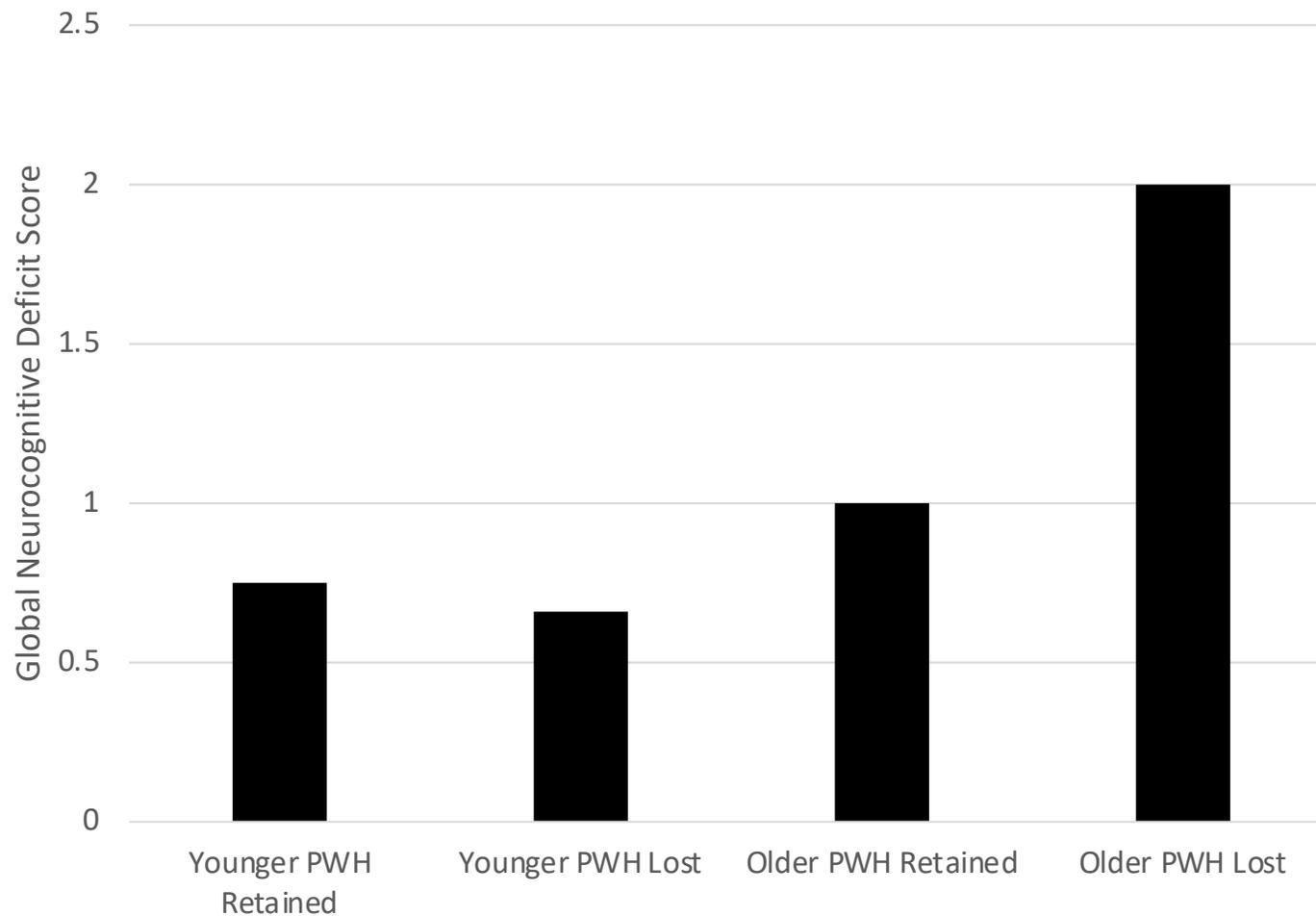
Aging, HIV, and Daily Functioning



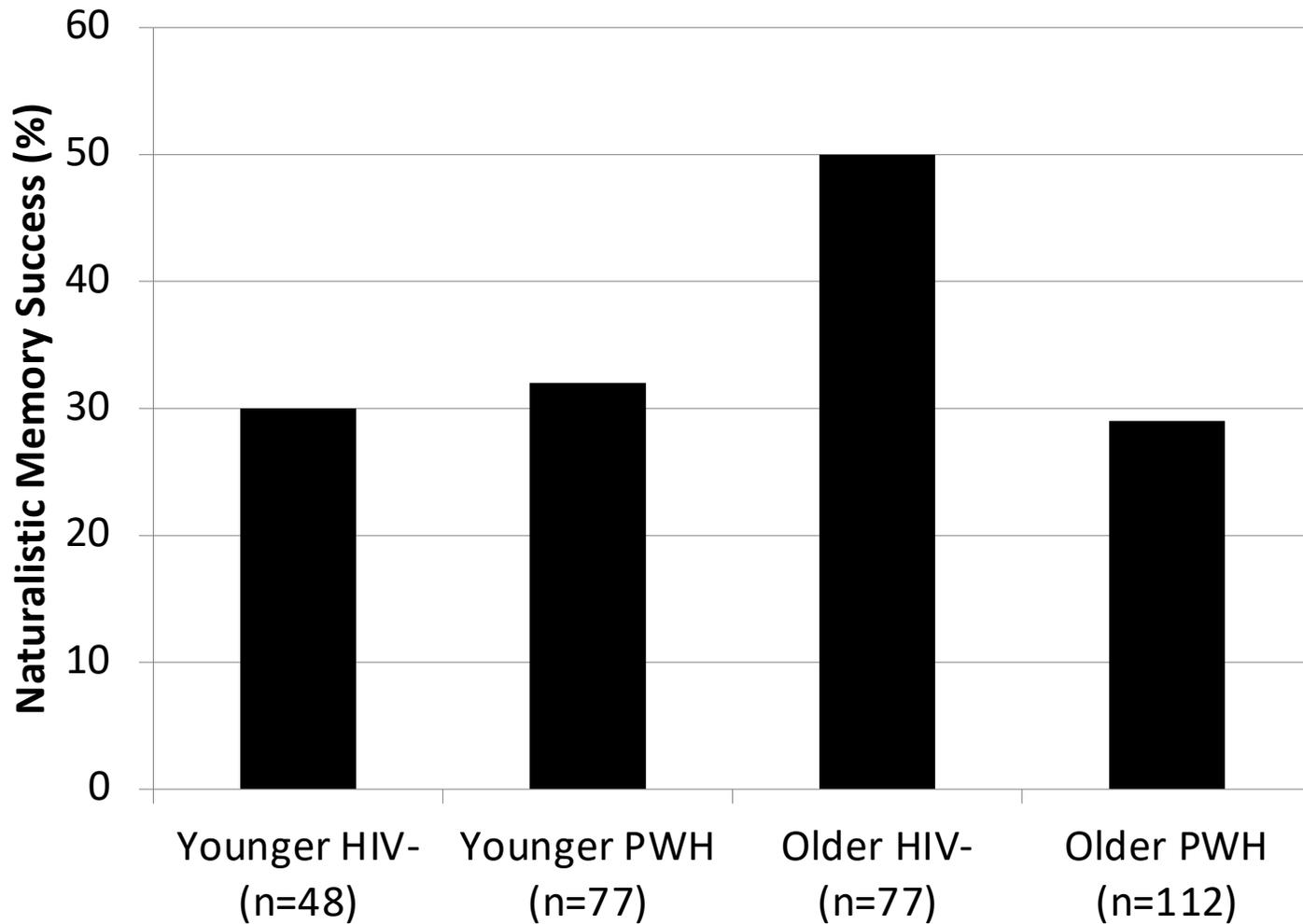
Worse Vocational Functioning in Older PWH



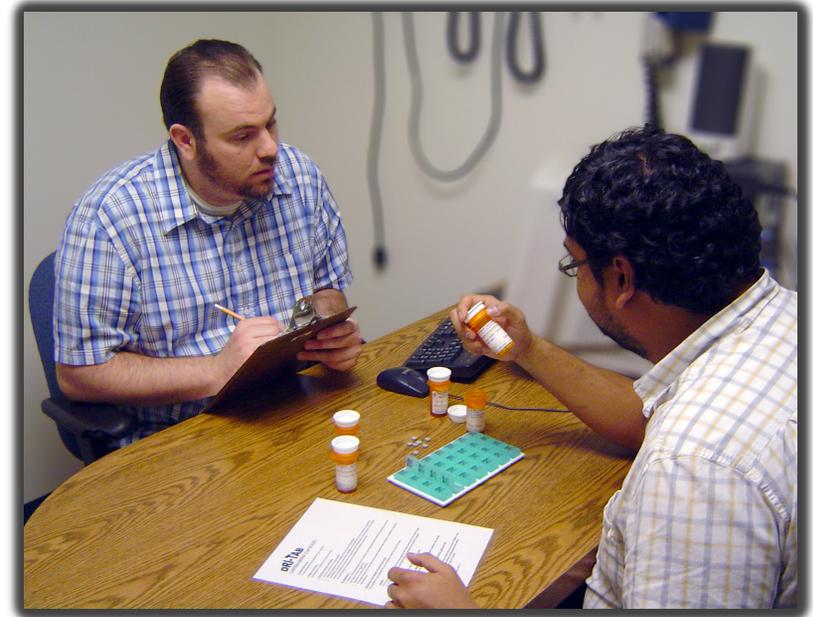
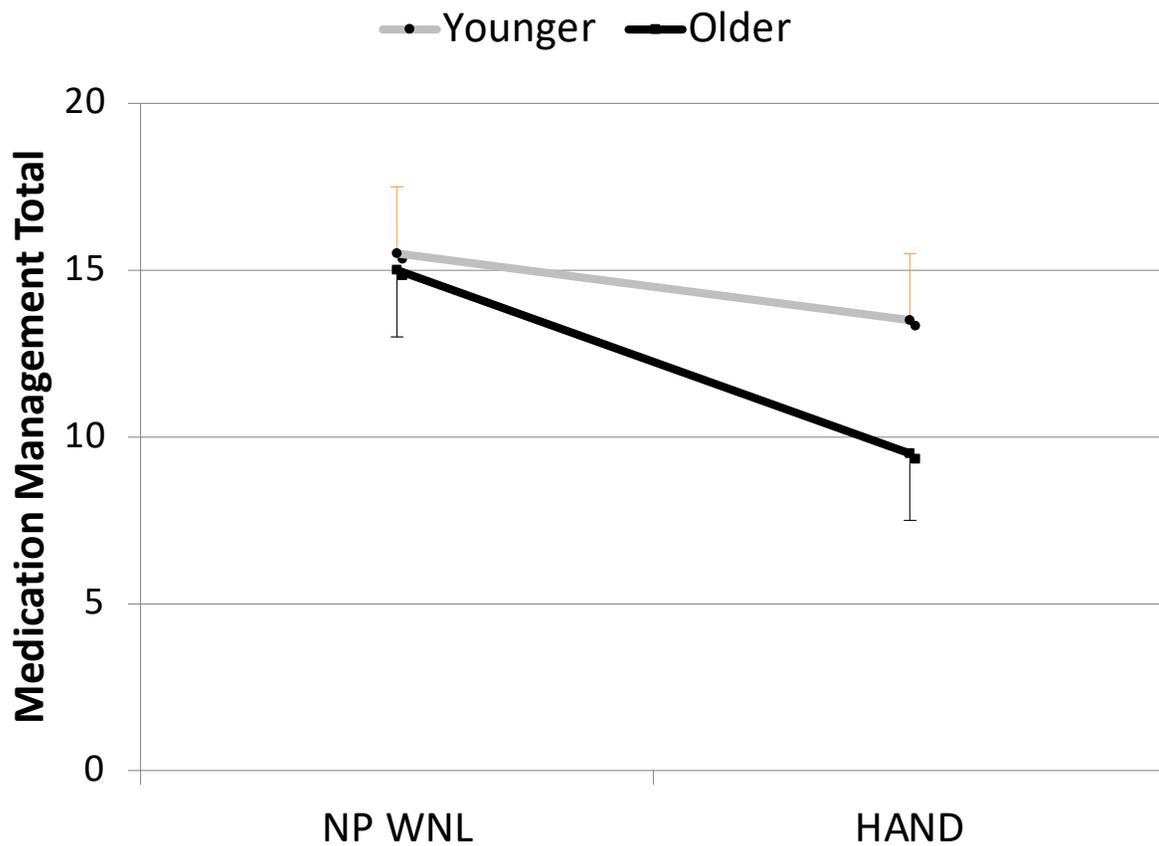
HAND Hinders Retention Care Among Older PWH



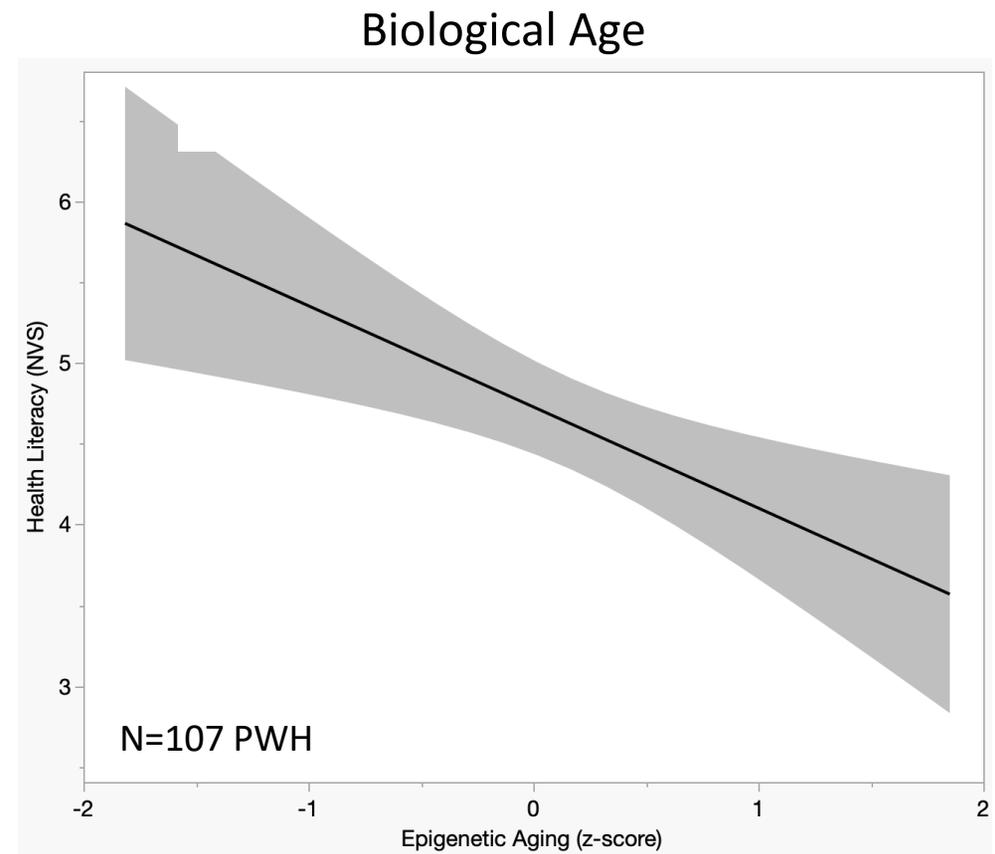
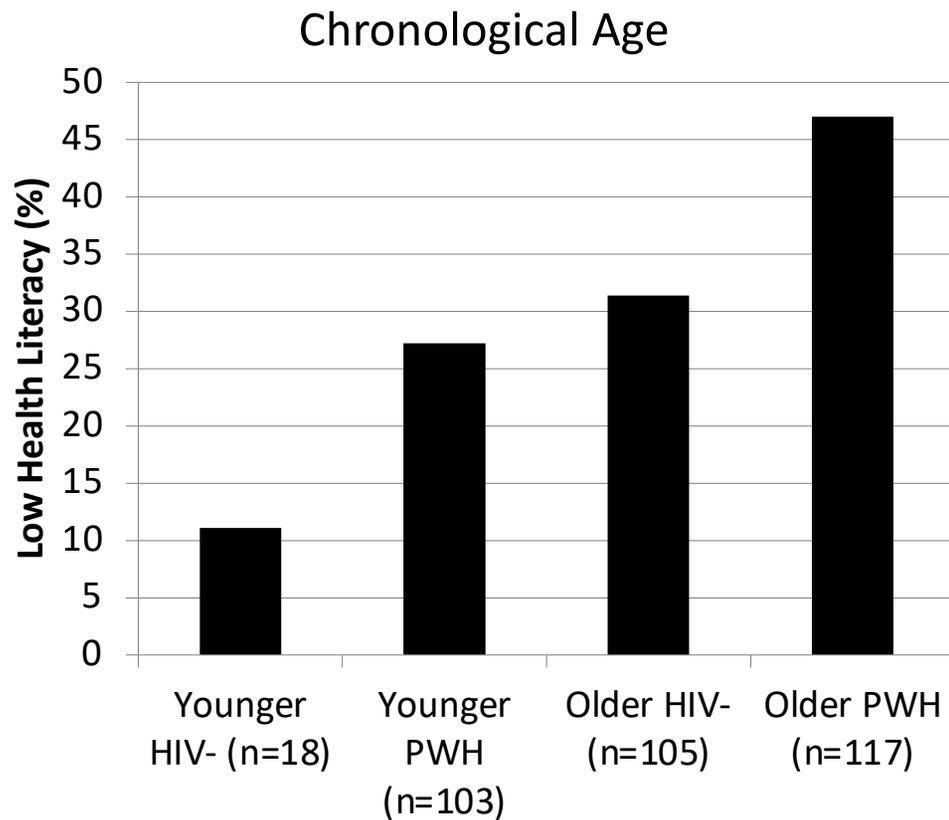
Age-Memory Paradox in Older PWH



HAND Exacerbates Age-Associated Deficits in Medication Management Capacity

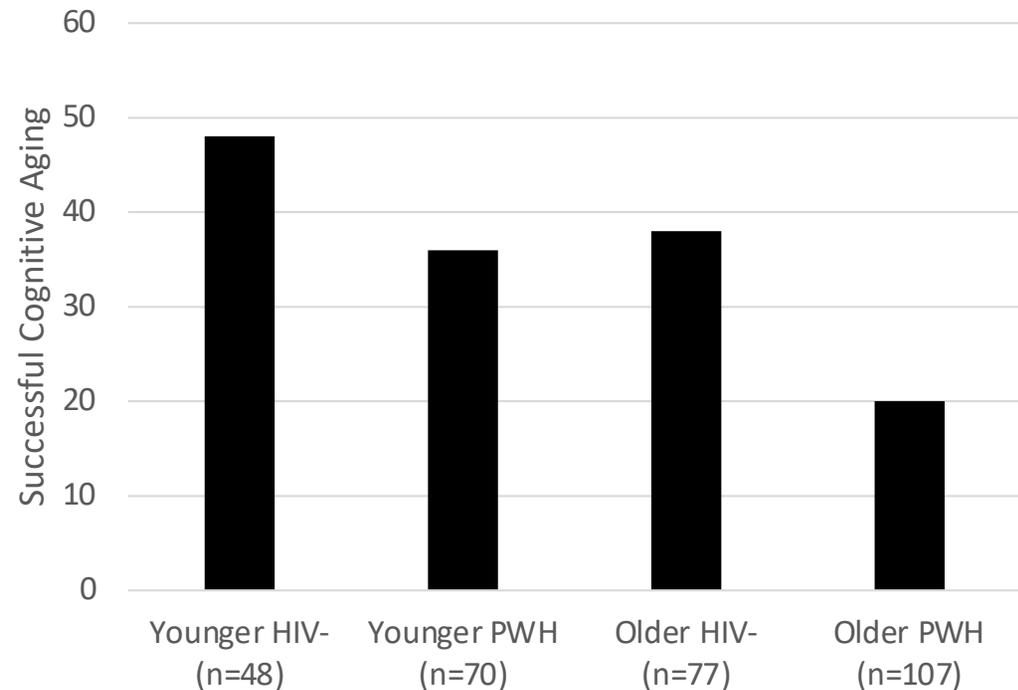


Additive Effects of HIV and Aging on Health Literacy



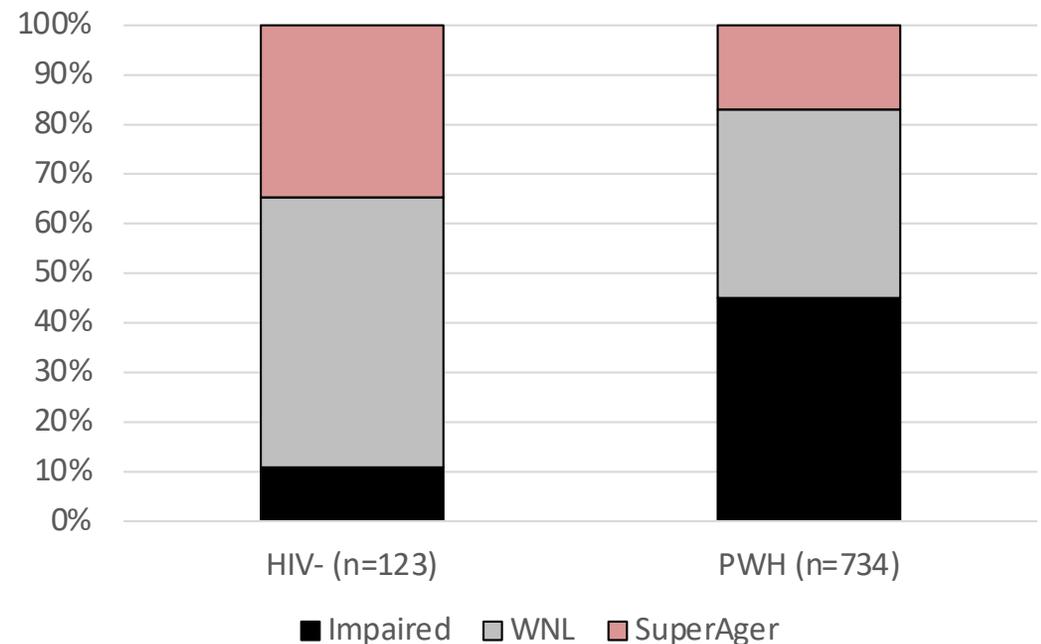
Successful Cognitive Aging in HIV Disease

- HIV infection is associated with ~3-fold decrease in successful cognitive aging among older adults
- Successful cognitive aging in PWH is associated with
 - Mental quality of life
 - Medication adherence
 - Better healthcare provider relationships
 - Positive psychological factors
 - Lower risk of frailty and vascular depression



SuperAging is Possible Among PWH

- SuperAging (i.e., older adults with normal cognition for individuals who are much younger)
- SuperAging in PWH is associated with
 - Higher cognitive reserve
 - Fewer medical and psychiatric comorbidities
 - Better everyday functioning



Summary of Age Effects on HIV-associated Neurocognitive Disorders (HAND)

- The number of older PWH is growing
- Age and HIV show generally additive effects on brain structure and function, with some exceptions
- Comorbidities (e.g., vascular, psychiatric) are important
- There is limited support for the AD hypothesis
 - Rising prevalence of PWH 65+yo may change the landscape
- Older adults with HAND are at risk for poor functional and health outcomes
- Much work left to be done on mediators and moderators
- Effective pharmacological, cognitive, and behavioral interventions are needed

Many thanks for your
attention today!

Questions?
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