

# The Impact of HIV and Aging on the Brain: Challenges and Opportunities



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**National AIDS Treatment Advocacy Project**

*Dr. Ances has no disclosures*



# Educational Objectives

- To understand the changes seen with HIV associated neurocognitive disorder (HAND) and Alzheimer's disease (AD).
- To identify biomarkers for assessing HAND and AD.
  - A role for neuroimaging, cerebrospinal fluid (CSF), and plasma markers
- To understand the effects of detectable HIV viral load, co-morbidities, cannabis, gender, aging, and social determinants of health on neuroimaging measures in persons living with HIV (PLWH)
- To evaluate adjunctive therapies for HAND.



# 1<sup>st</sup> PLWH in Saint Louis: 1968

- 1968- Patient RR, a 16 year old male, presented with lymph edema, shortness of breath, and impaired immune system
- 1969- At autopsy he was noted to have Kaposi sarcoma, chronic wasting, and diagnosed with an unknown illness
- 1973- Original case report written by Dr. Robert Drake (pathology at WUSTL) and colleagues
- 1987- Blood sample retrieved from RR by Dr. Memory Elvin-Lewis (ID at WUSTL ) and was confirmed to have HIV using Western blot



# PLWH in Saint Louis in 2022

- ◆ A 64 year old Caucasian male presents with mild cognitive changes over the past few years.
- ◆ For the past 2-3 years he has had slowed mentation, mild forgetfulness (cannot remember why he has walked into the room), more problems remembering taking his medications (prospective memory), and poor concentration.
- ◆ His friends have noticed that he more frequently misplaces objects (e.g. keys), sometimes gets lost, has slowed gait and appears to be somewhat frail.

# The HIV+ Patient In 2022- Part 2

Past Medical History: HIV (diagnosed in 1990's), PCP (1990's), previous drug abuse (1990's), peripheral neuropathy (2002), hypertension, and elevated cholesterol (2010)

Medications: Biktarvy [has been on several combination antiretroviral therapy (cART) regimens in the past], Neurontin, and Lipitor

Exam: Male who was in no apparent distress

Mental Status: Alert and oriented x 3, MoCA: 24

Cranial nerves: 2-12 intact

Motor: Normal tone and bulk, 5/5 throughout

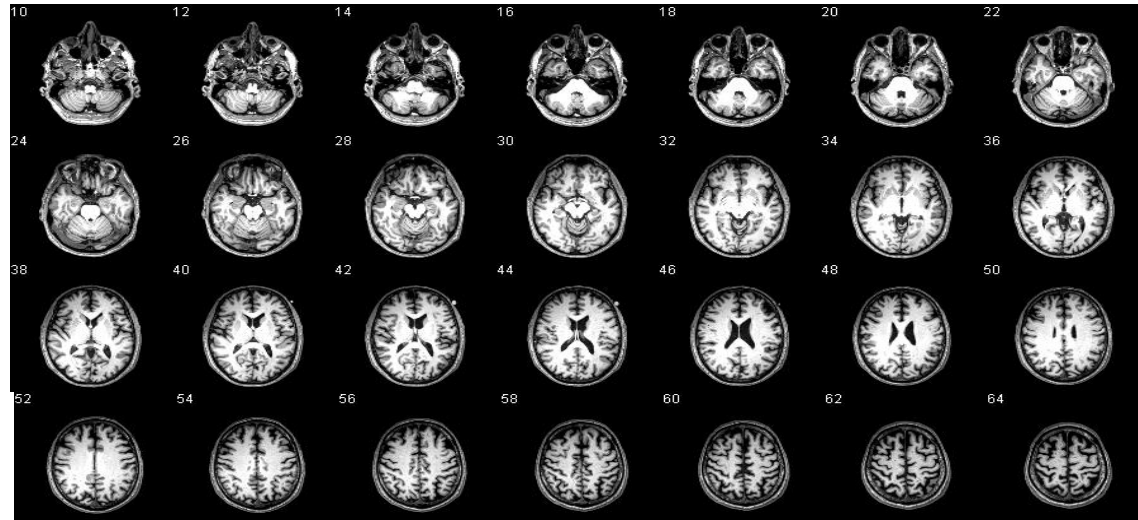
Sensory: Diminished sensation below the knees

Reflexes; 2+ upper extremities, 1+ patellar, 0 at ankles

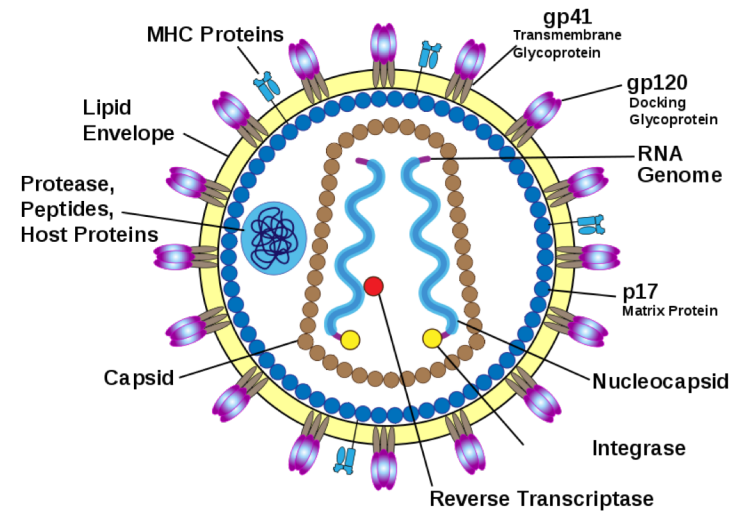
Coordination/ Gait: Slowed

# Diagnostic Tests For Older PLWH In 2022

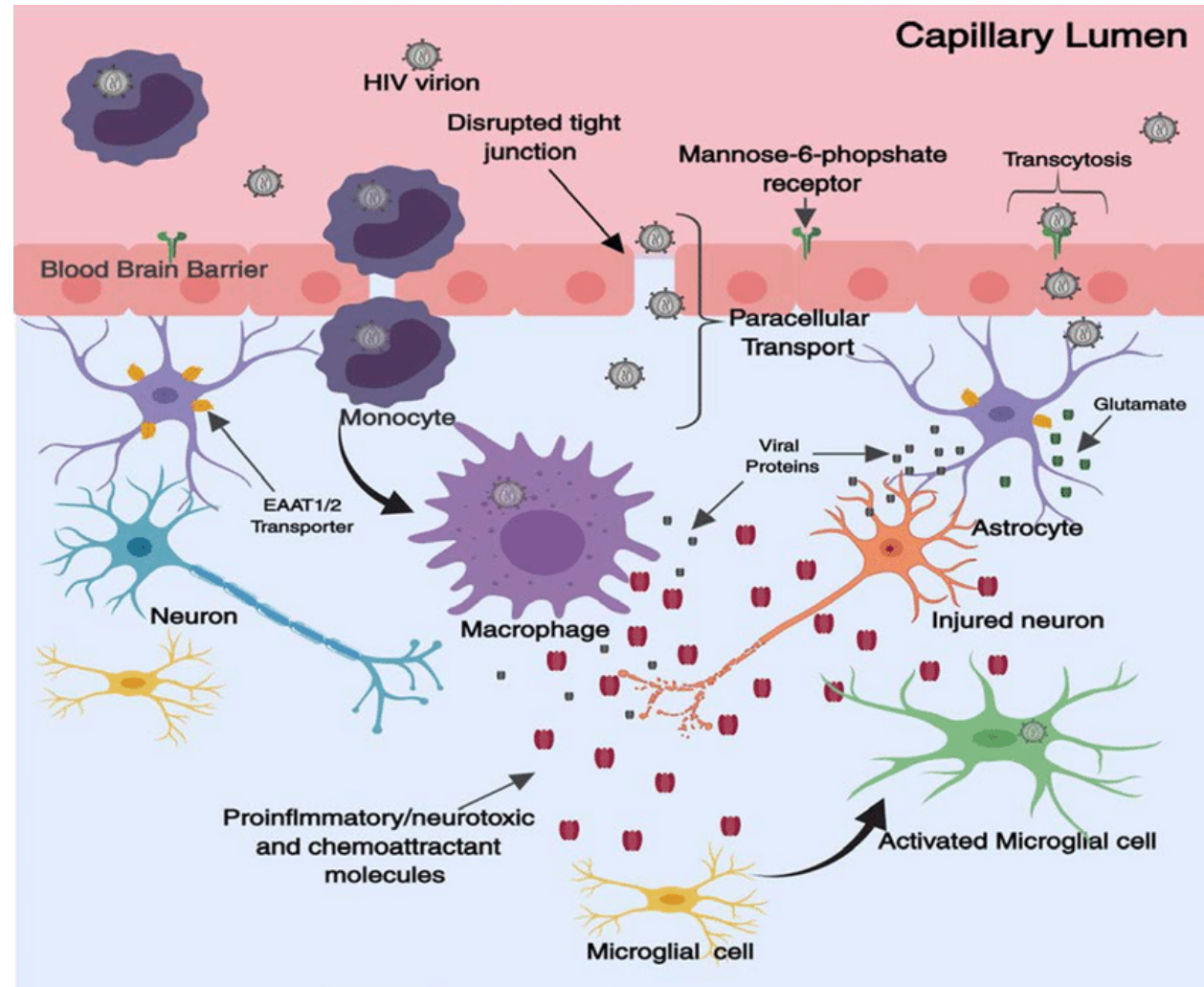
- ◆ CMP and CBC: normal
- ◆ Thyroid panel: normal
- ◆ Ammonia: 35
- ◆ UA: negative
- ◆ UDS: negative
- ◆ B12: 937
- ◆ Folic acid: 8.1
- ◆ RPR: negative
- ◆ CD4 cell count = 502 (Nadir: 54)
- ◆ Plasma HIV Viral Load= undetectable
- ◆ Structural imaging with and without contrast: unremarkable



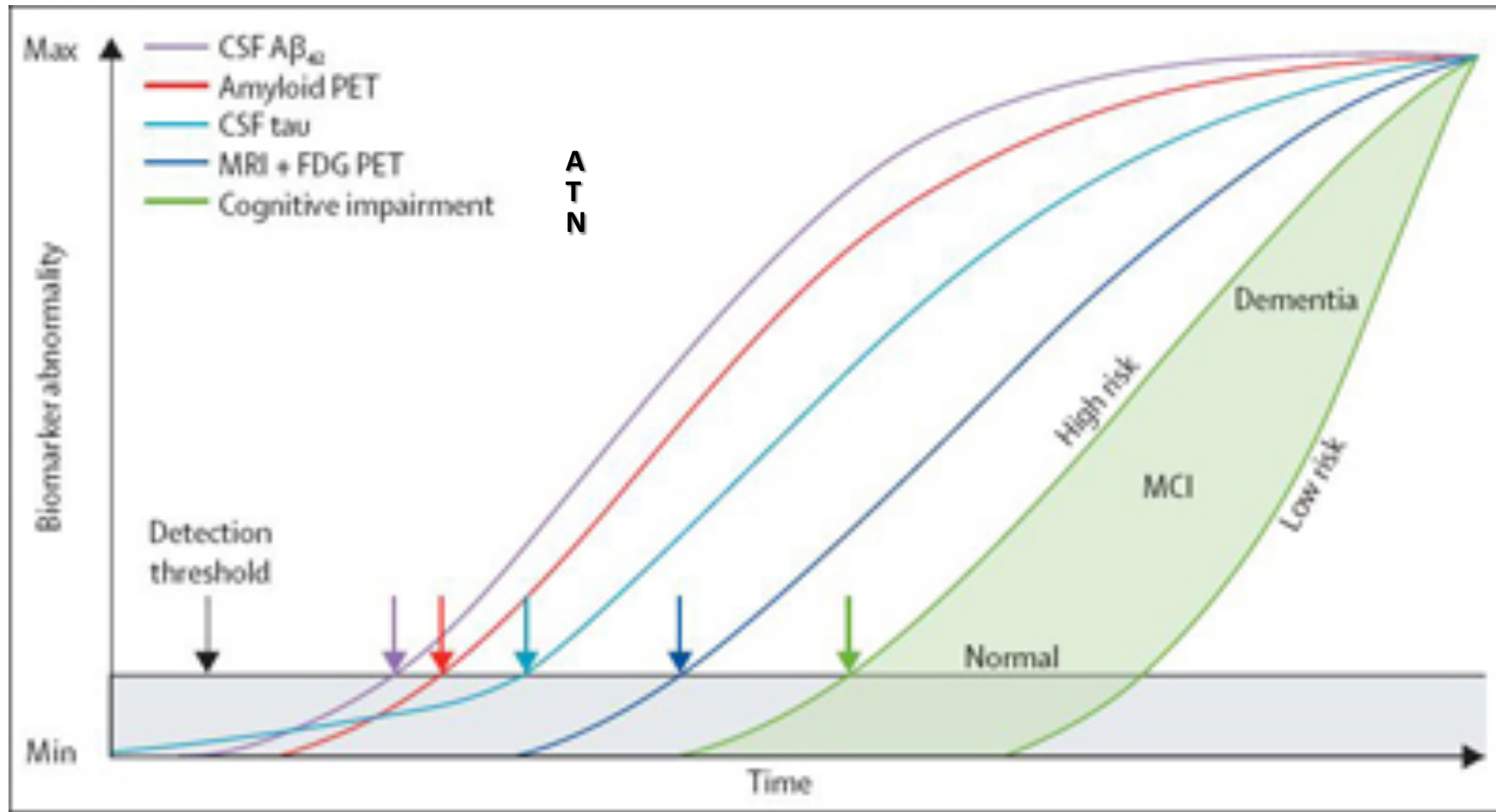
# HAND and AD Pathology



# HIV Reservoirs Develop In The Brain Soon After Seroconversion

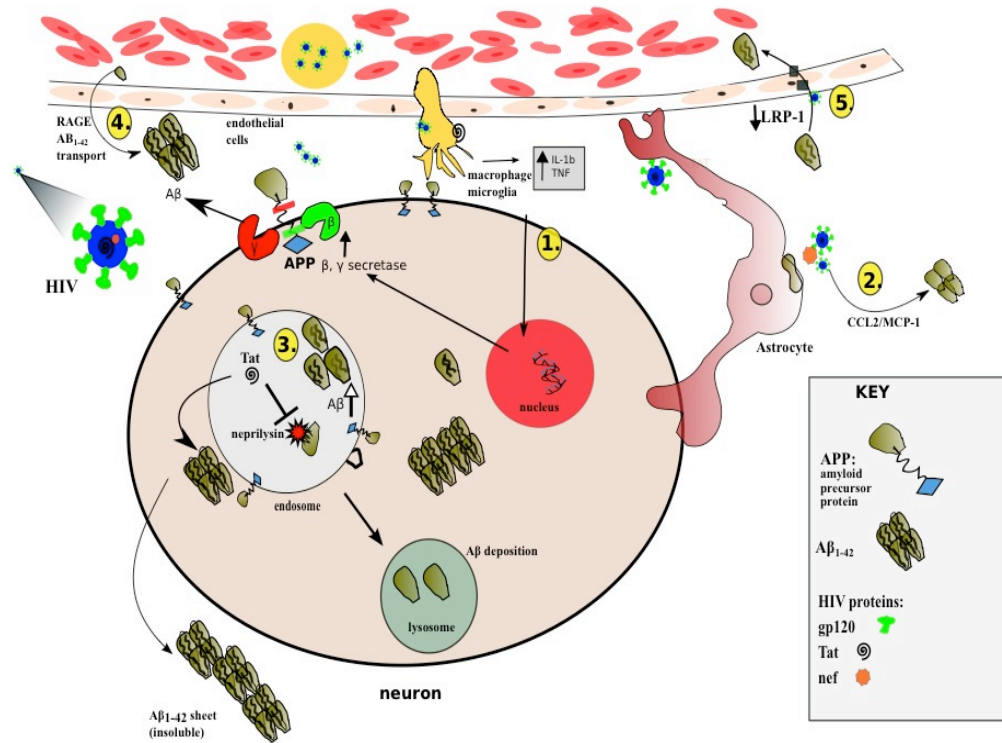


# Hypothesized Cascade for AD

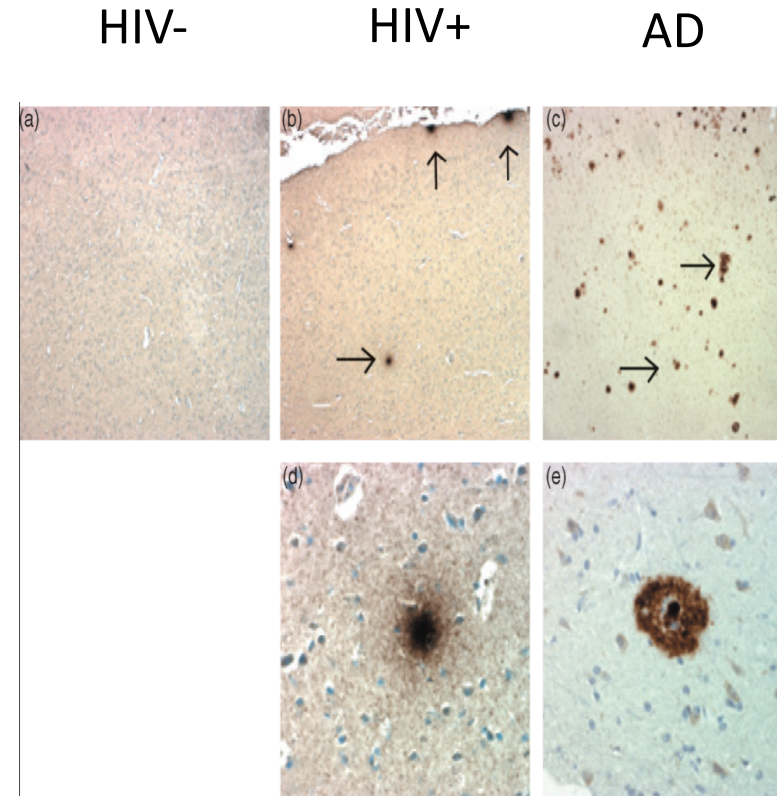




# HIV Affects Amyloid Metabolism



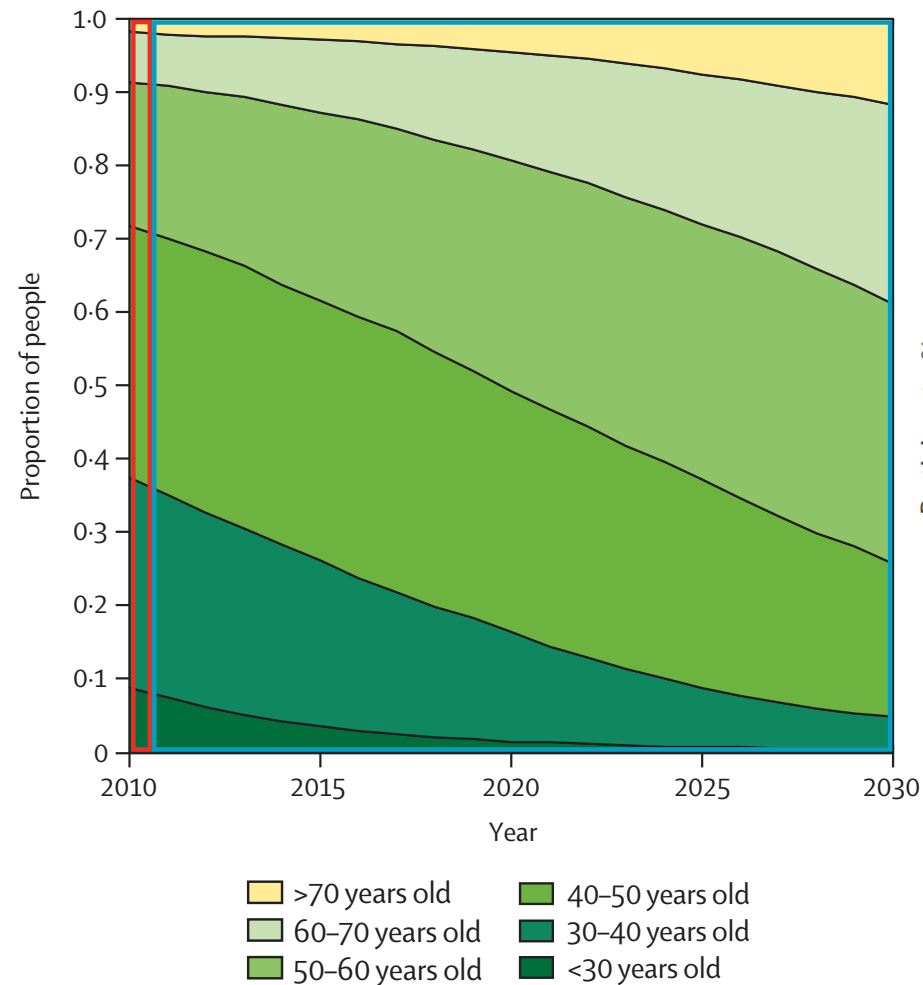
Ortega and Ances, *J Neuroimmune Pharmacol*, 2014



Rempel and Pulliam, *AIDS*, 2005

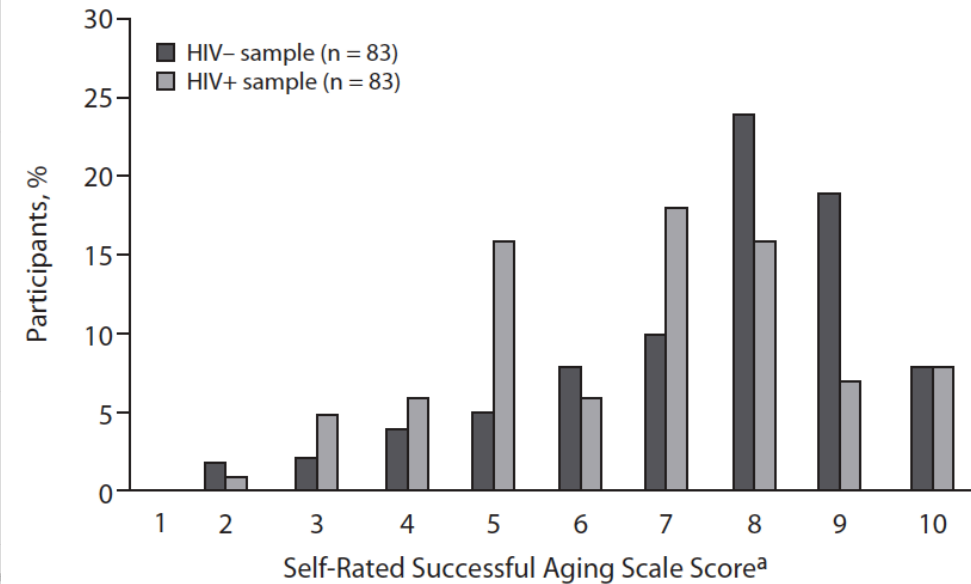


# Older PLWH Are Getting Older But Often Not Successfully



Smit, *Lancet Inf Dis*, 2015

In HIV- Adults: The most common correlates of successful aging were not smoking and absence of disability, arthritis, and diabetes

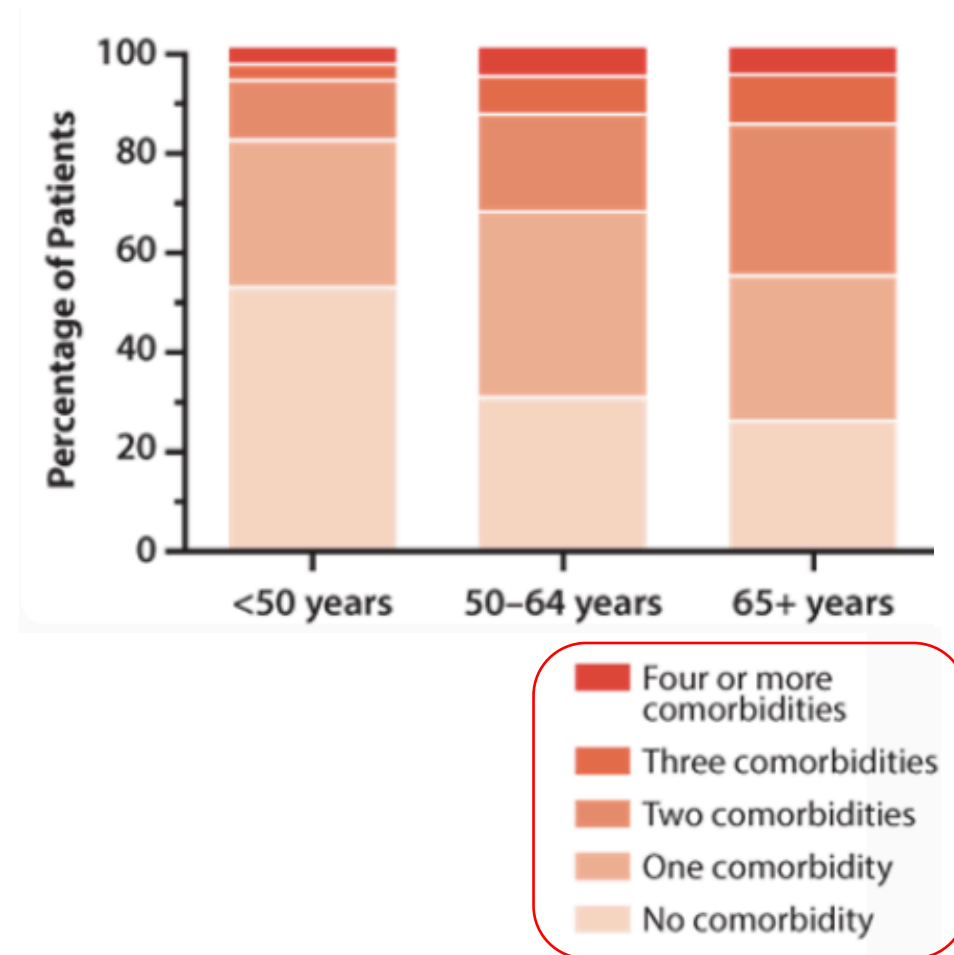


In PLWH: Successful aging was associated with greater physical activity, more social contacts, better self-rated health, absence of depression and cognitive impairment, and fewer medical conditions.

Depp & Jeste, *Am J Geriatric Psychiatry*, 2006  
Moore et al, *J Clinical Psychiatry* 2013

# Older PLWH Often Have Several Comorbidities

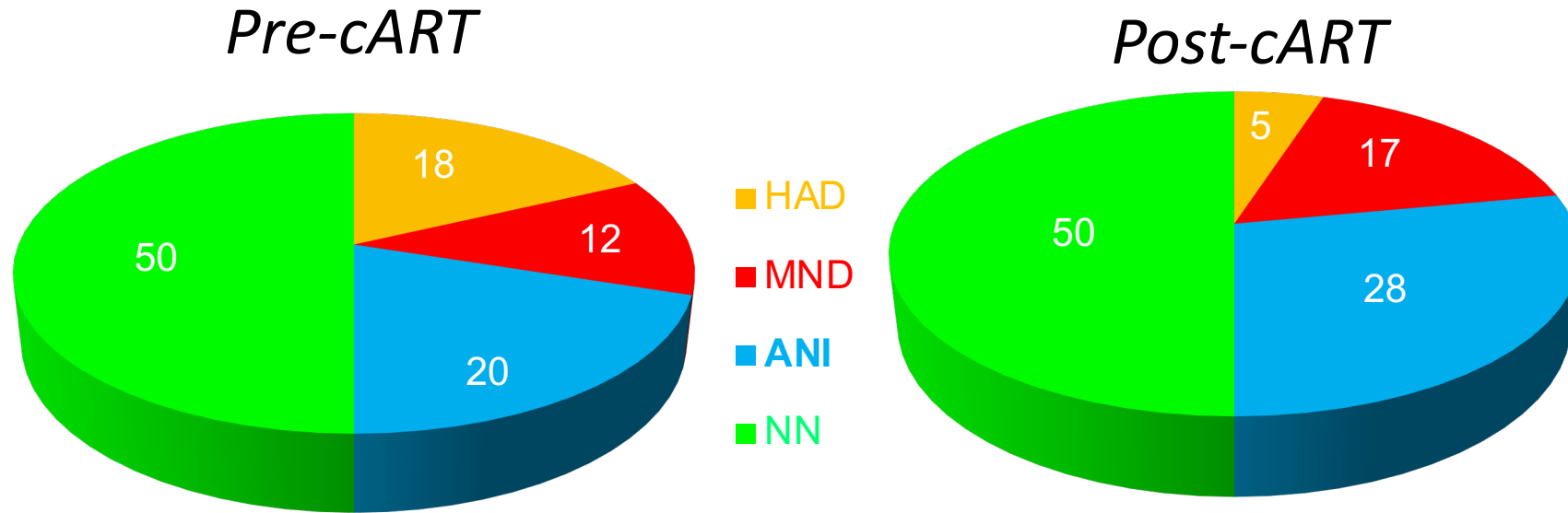
- Older PLWH are more likely to have multiple comorbidities (e.g. cardiovascular disease, chronic kidney disease, metabolic syndrome and diabetes, etc.) compared to HIV- adults
- Prevalence of comorbidities in PLWH approaches those seen among HIV- adults who are 5 years older



Hasse et al, *CID*, 2011

McMillan et al., *CMAJ*, 2018

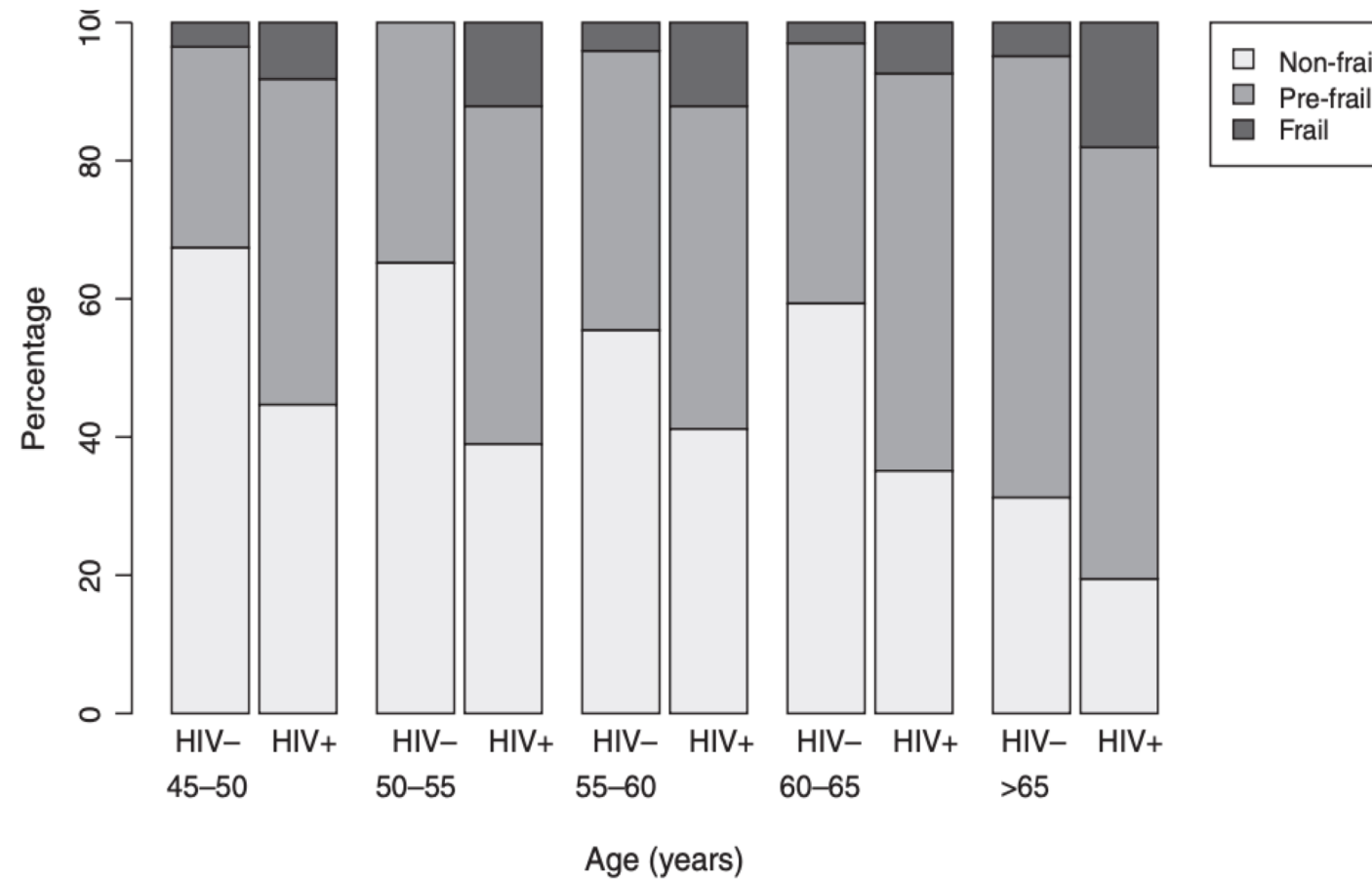
# HAND Still Occurs In The Combination Anti-Retroviral Therapy (cART) Era



Adapted from: Heaton, et al. *Neurology* 2010. Also: Robertson, et al. *AIDS* 2007; Simioni, et al. *AIDS* 2010; Garvey *HIV Clin Trials* 2011; Cysique & Brew, *Journal of Neurovirology* 2011; Meyer et al. *Neuroepidemiology* 2013, Grant et al., *Neurology*, 2014

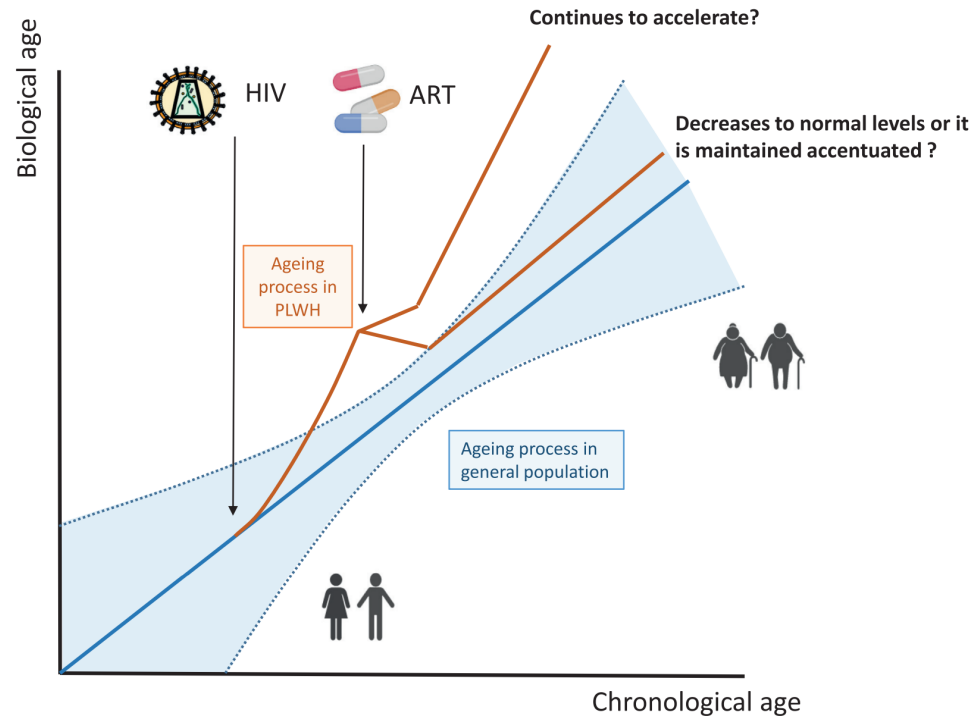
- Incidence but not prevalence of HAND has declined with cART
- A three fold increase in mortality risk exists for individuals with HAND compared to individuals without HAND

# Frailty Occurs Earlier in PLWH

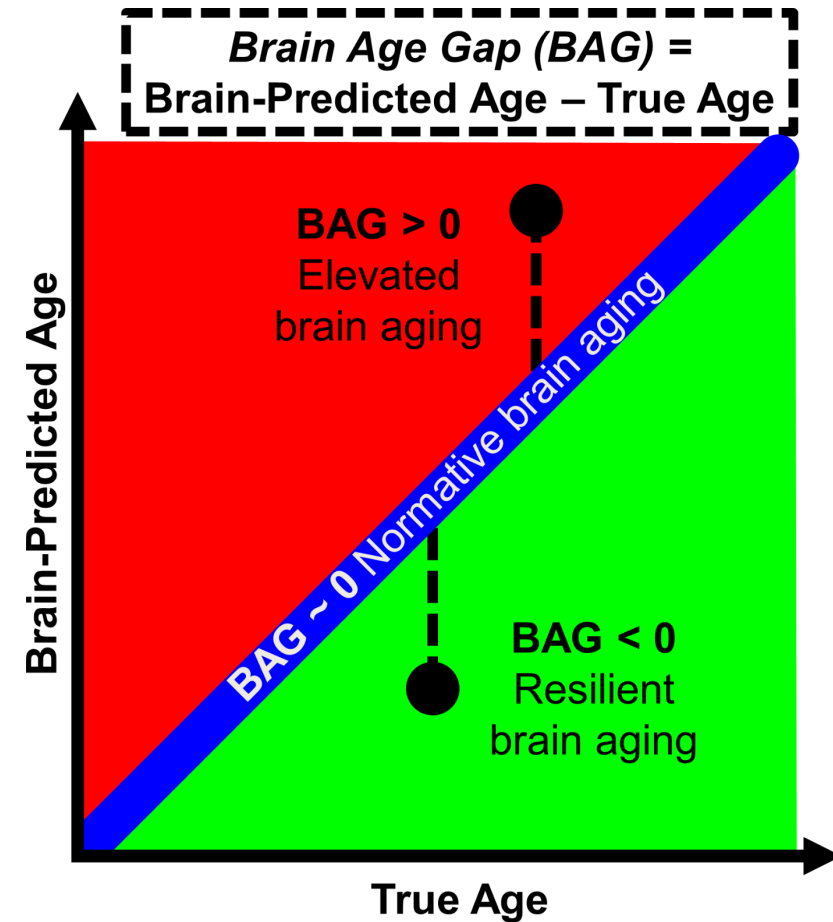


# Interactions Among HIV, Aging, and CART:

## Chronological vs Biological Age



Rodes et al. *eBiomedicine*, 2022

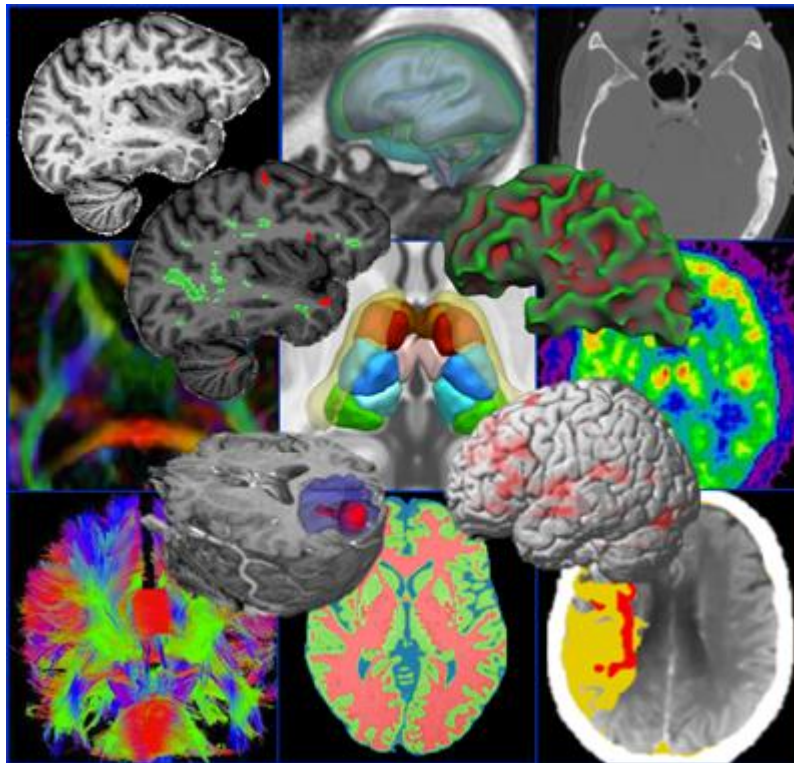


Cole & Franke, *Trends Neurosci*, 2017

# Section Summary

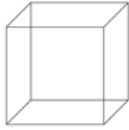
- PLWH are aging into their 60s and 70s due to virological suppression with cART
- Survival of older PLWH is approaching that seen in the general population
- Older PLWH are more likely to have multiple comorbidities compared to general population
- HAND and AD need to be disentangled in older PLWH
- Chronological age  $\neq$  biological age in older PLWH

# Biomarkers of the Brain



# How to Evaluate for HAND in Persons with HIV (PWH) in the Outpatient Clinic

## International HIV Dementia Scale

Maximum score	Score	Subtests
—	—	<b>Memory: registration</b> Give the patient four words to recall (dog, hat, green, peach)—one second to say each. Then ask the patient to recall all four after you have said them.
4	( )	<b>Attention</b> Antisaccadic eye movements: 20 commands. _____ errors of 20 trials. [≤ three errors = 4; four errors = 3; five errors = 2; six errors = 1; > six errors = 0] <i>Instructions for attention score: Hold both hands up at the patient's shoulder width and eye height, and ask the patient to look at your nose. Move the index finger of one hand, and instruct the patient to look at the finger that moves, then look back to your nose. Practice until the patient is familiar with the task. Then, instruct the patient to look at the finger that is NOT moving. Practice until the patient understands the task. Perform 20 trials. An error is recorded when the patient looks toward the finger that is moving.</i>
6	( )	<b>Psychomotor speed</b> Ask patient to write the alphabet in uppercase letters horizontally across the page and record time: _____ seconds. [≤ 21 seconds = 6; 21.1 to 24 seconds = 5; 24.1 to 27 seconds = 4; 27.1 to 30 seconds = 3; 30.1 to 33 seconds = 2; 33.1 to 36 seconds = 1; > 36 seconds = 0]
4	( )	<b>Memory: recall</b> Ask for the four words from memory registration (above). Give one point for each correct recall. For words not recalled, prompt with a semantic clue, as follows: animal (dog); piece of clothing (hat), color (green), fruit (peach). [one-half point for each correct recall after prompting]
2	( )	<b>Construction</b> Copy the cube below; record time: _____ seconds. [< 25 seconds = 2; 25 to 35 seconds = 1; > 35 seconds = 0] 
<b>Total score</b>	___/16*	

NOTE: This scale requires training to administer and may not be preferable for use in a clinical setting. The Modified HIV Dementia Scale<sup>11</sup> omits the attention category and may be more suitable for administration by a physician. In the modified scale, the maximum possible score would be 12; < 7.5 points indicates possible HIV-associated dementia.

HIV = human immunodeficiency virus.

\*—A score of less than 10 points indicates possible HIV-associated dementia.

## Montreal Cognitive Assessment

NAME: \_\_\_\_\_ Date of birth: \_\_\_\_\_  
 Education: \_\_\_\_\_ Sex: \_\_\_\_\_ DATE: \_\_\_\_\_

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**

**ORIENTATION / EXECUTIVE**

Draw a cube (1 point)

Trace cube (1 point)

Draw 5 lines (1 point)

**NAMING**

Identify the animals: Lion (1 point), Rhino (1 point), Camel (1 point)

**MEMORY**

Read list of words; subject must repeat them. Do not repeat after 5 minutes.

FACE NAME CHURCH GARDEN BED

**ATTENTION**

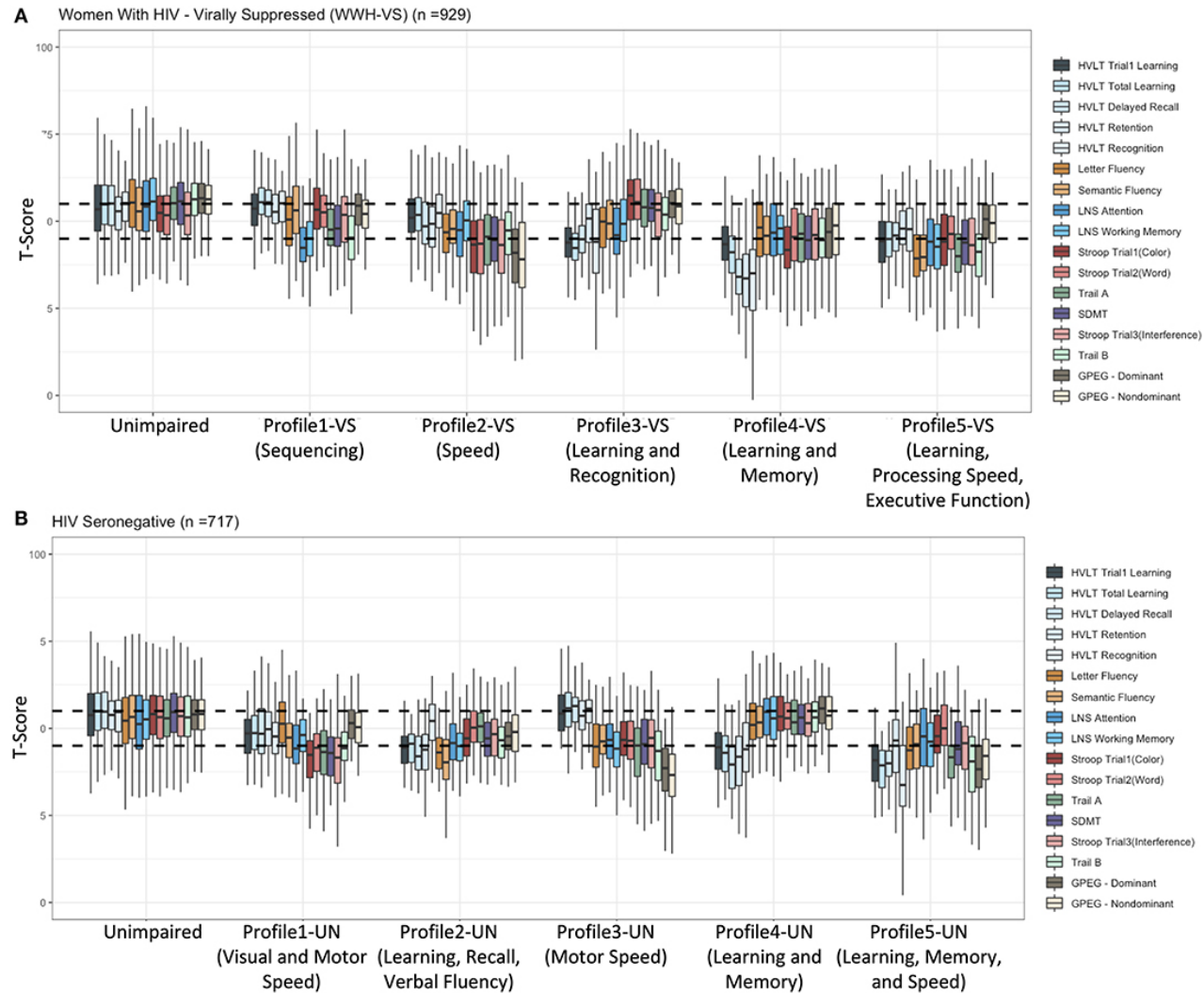
Read list of digits (5 digits set). Subject has to repeat them in the forward order. Subject has to repeat them in the backward order.

Read list of letters. The subject must tap with his hand at each letter (1 point for each letter).

Serial 7 subtraction starting at 100: 100 - 7 = 93, 93 - 7 = 86, 86 - 7 = 79, 79 - 7 = 72, 72 - 7 = 65, 65 - 7 = 58, 58 - 7 = 51, 51 - 7 = 44, 44 - 7 = 37, 37 - 7 = 30, 30 - 7 = 23, 23 - 7 = 16, 16 - 7 = 9, 9 - 7 = 2, 2 - 7 = -5, -5 - 7 = -12, -12 - 7 = -19, -19 - 7 = -26, -26 - 7 = -33, -33 - 7 = -40, -40 - 7 = -47, -47 - 7 = -54, -54 - 7 = -61, -61 - 7 = -68, -68 - 7 = -75, -75 - 7 = -82, -82 - 7 = -89, -89 - 7 = -96, -96 - 7 = -103, -103 - 7 = -110, -110 - 7 = -117, -117 - 7 = -124, -124 - 7 = -131, -131 - 7 = -138, -138 - 7 = -145, -145 - 7 = -152, -152 - 7 = -159, -159 - 7 = -166, -166 - 7 = -173, -173 - 7 = -180, -180 - 7 = -187, -187 - 7 = -194, -194 - 7 = -201, -201 - 7 = -208, -208 - 7 = -215, -215 - 7 = -222, -222 - 7 = -229, -229 - 7 = -236, -236 - 7 = -243, -243 - 7 = -250, -250 - 7 = -257, -257 - 7 = -264, -264 - 7 = -271, -271 - 7 = -278, -278 - 7 = -285, -285 - 7 = -292, -292 - 7 = -299, -299 - 7 = -306, -306 - 7 = -313, -313 - 7 = -320, -320 - 7 = -327, -327 - 7 = -334, -334 - 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# Heterogeneity Exists in Cognitive Deficits Seen in PLWH: One Size Does Not Fit All



- Learning and Memory: ability to learn and retain new verbal information.
- Executive function: ability to plan, remember, learn, and adapt to changes
- Processing Speed: speed needed to understand and react to information received

# How to Evaluate for AD in the Outpatient Clinic

## AD-8

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	YES, A change	NO, No change	N/A, Don't know
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. <b>Daily</b> problems with thinking and/or memory			
<b>TOTAL AD8 SCORE</b>			

## Clinical Dementia Rating (CDR) Scale

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

- 0 – 1: Normal cognition 0.0 0.2 0.4 0.6 0.8 1.0
- 2 or greater: Cognitive impairment is likely to be present
- Sensitivity > 84%
- Specificity > 80%
- It is important to have a collateral sources who knows the individual
- Need to evaluate if there is change from an individual's baseline

# HAND In The Research Setting: Additional Biomarkers Are Needed

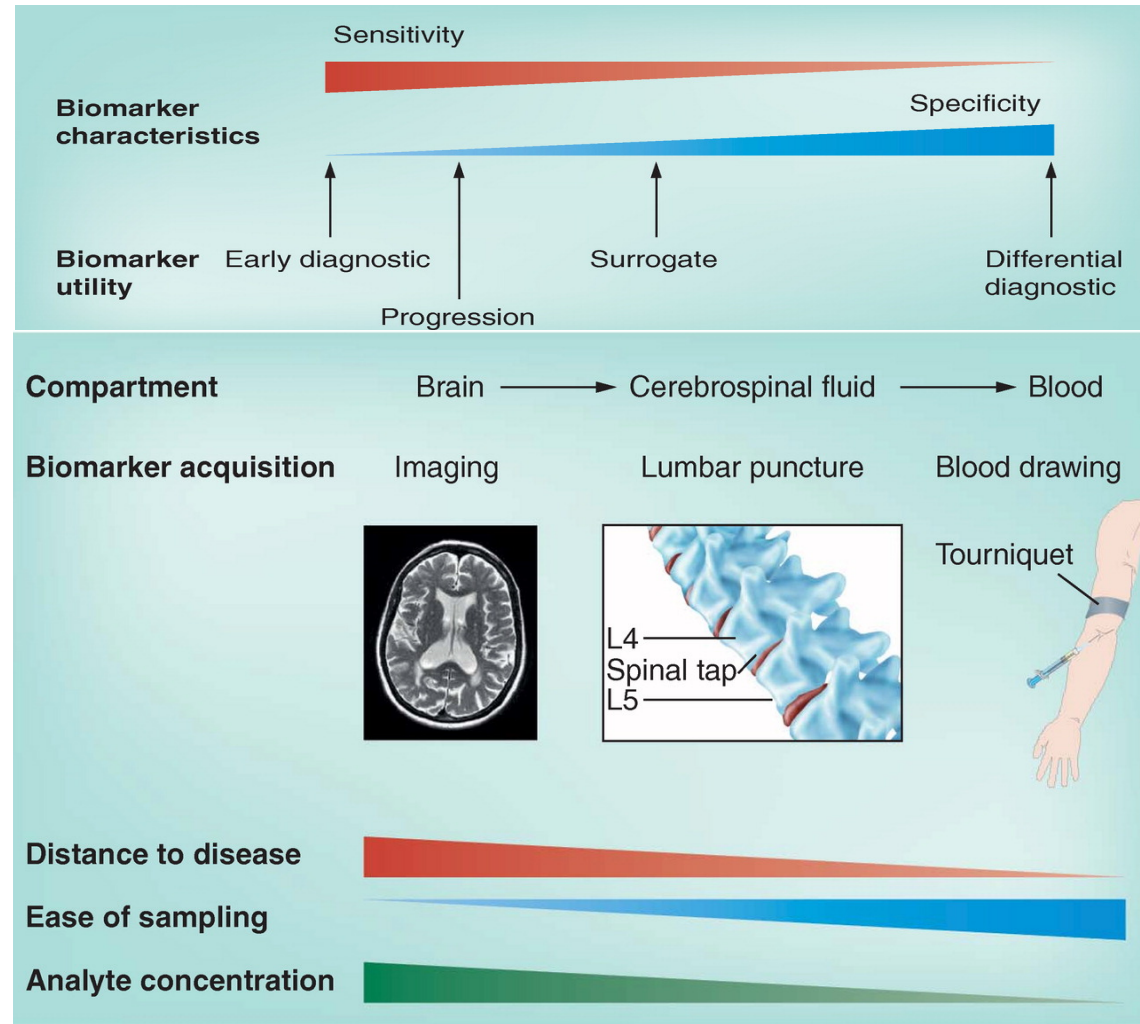
	Neurologically Normal (NN)	Asymptomatic Neurocognitive Impairment (ANI)	Mild Neurocognitive Disorder(MND)	HIV Associated Dementia (HAD)
Global Deficit Score (GDS)	0	0.5	0.5	>1
Impairment in $\geq 2$ Cognitive domains ( $> 1SD$ )	No	Yes	Yes	Yes ( $> 2 SD$ )
Impairment in Activities of Daily Living	No	No	Yes- Mild	Yes- Marked

Antinori et al., *Neurology*, 2007

- The role of the collateral source is not included in the HAND diagnosis.
- Neuroimaging, CSF, or plasma measures are **NOT** included in HAND criteria.
- HAND needs to be evaluated like other neurodegenerative disorders [Alzheimer's disease (AD), multiple sclerosis (MS), or Parkinson's disease (PD)].

# Biomarkers for Disease

Biomarker- a measurable substance in an organism whose presence is indicative of a disease, infection, or environmental exposure



# Section Summary

- Cognitive impairment can be initially evaluated in the clinic with referral for additional work-up.
- Significant heterogeneity exists in the cognitive profile of PLWH
- Additional biomarkers should be considered in the evaluation of HAND. This is used in other neurodegenerative diseases.

# Mechanisms of Central Nervous System (CNS) Injury In Our PLWH Living in Saint Louis in 2022

**Time:** Effects of acute and early HIV (AEH) infection in the CNS



Co-morbidities and social determinants of health

Aging

cART: the effects of polypharmacy

**Virus:** Ongoing viral replication

# Mechanisms of CNS Injury In Our PLWH Living in Saint Louis in 2022

## AEH affects the CNS

Initially infected in 1990s and  
is regularly followed  
“the initial hit”



Co-morbidities and  
social determinants of  
health

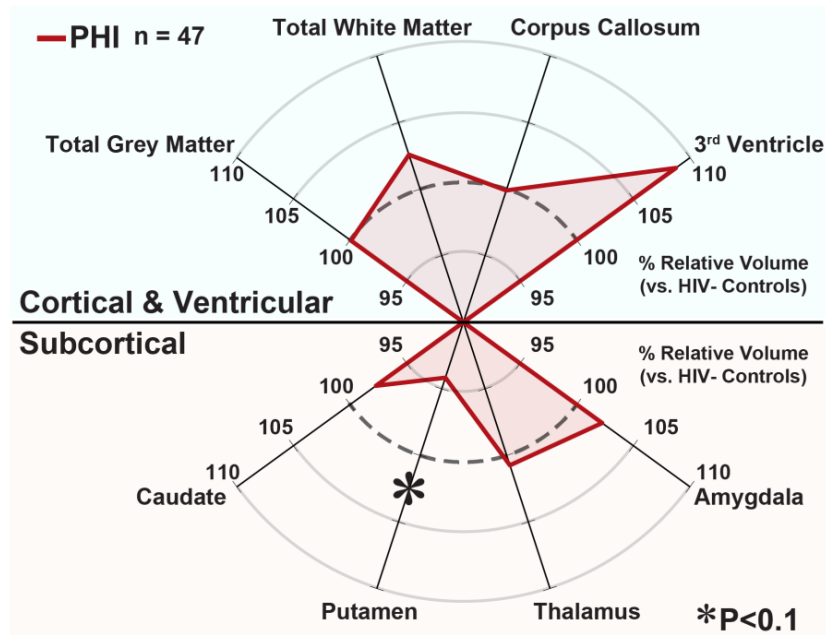
Aging

Viral replication

cART

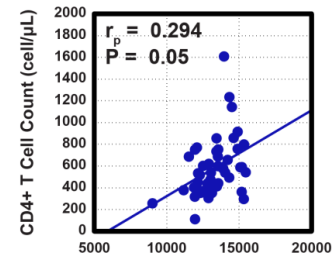


# Early HIV Infection Affect the Brain Structure

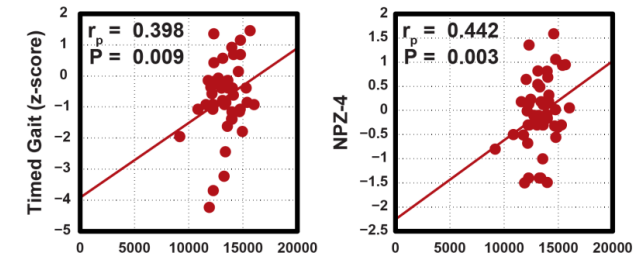


18 HIV-  
47 AEH

*Immune System Health*

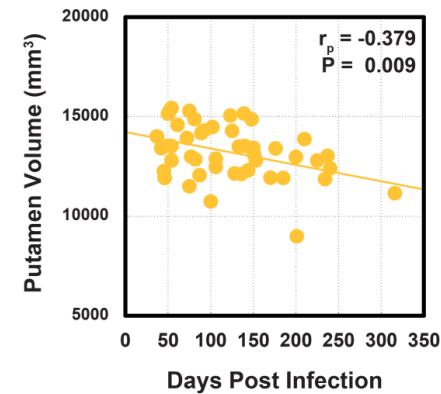


*Neuropsychological Performance*



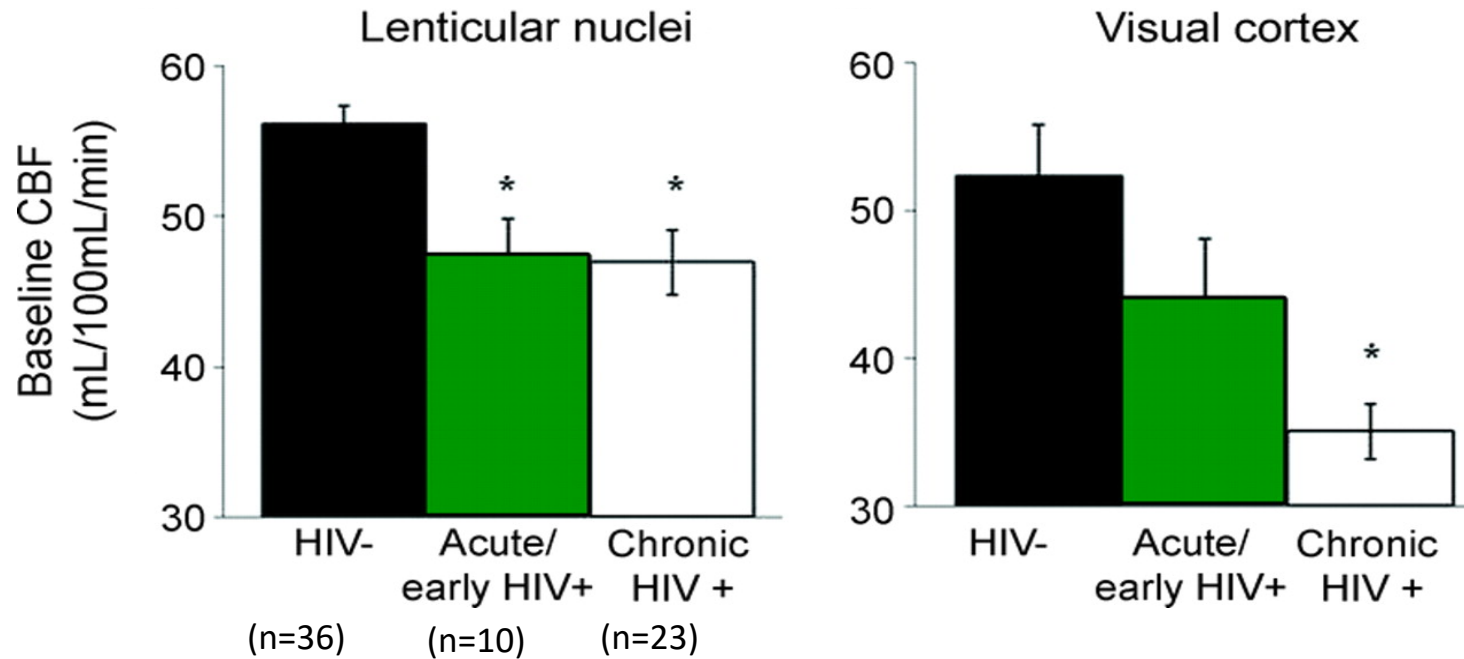
*Putamen Volume (mm<sup>3</sup>)*

*Duration of Infection*





# Early HIV Infection Reduces Blood Flow to the Brain

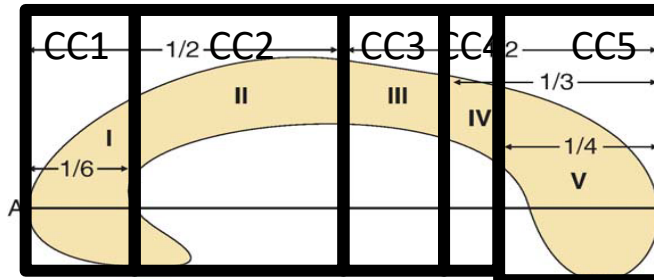


AEH= Acute and Early HIV Infected Patients  
CHI= Chronic HIV Infected Patients

# Duration of Infection Affects Brain Tracts:

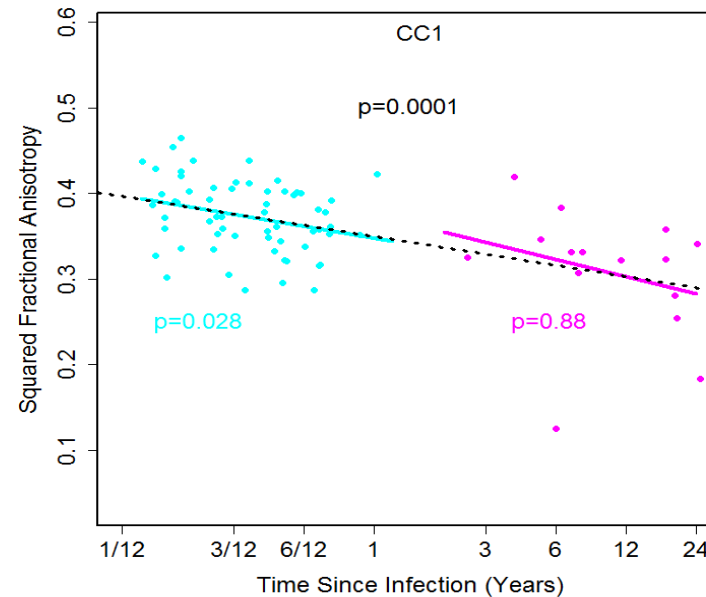
## Time = Brain

Corpus Callosum- super highway



All PLWH were untreated

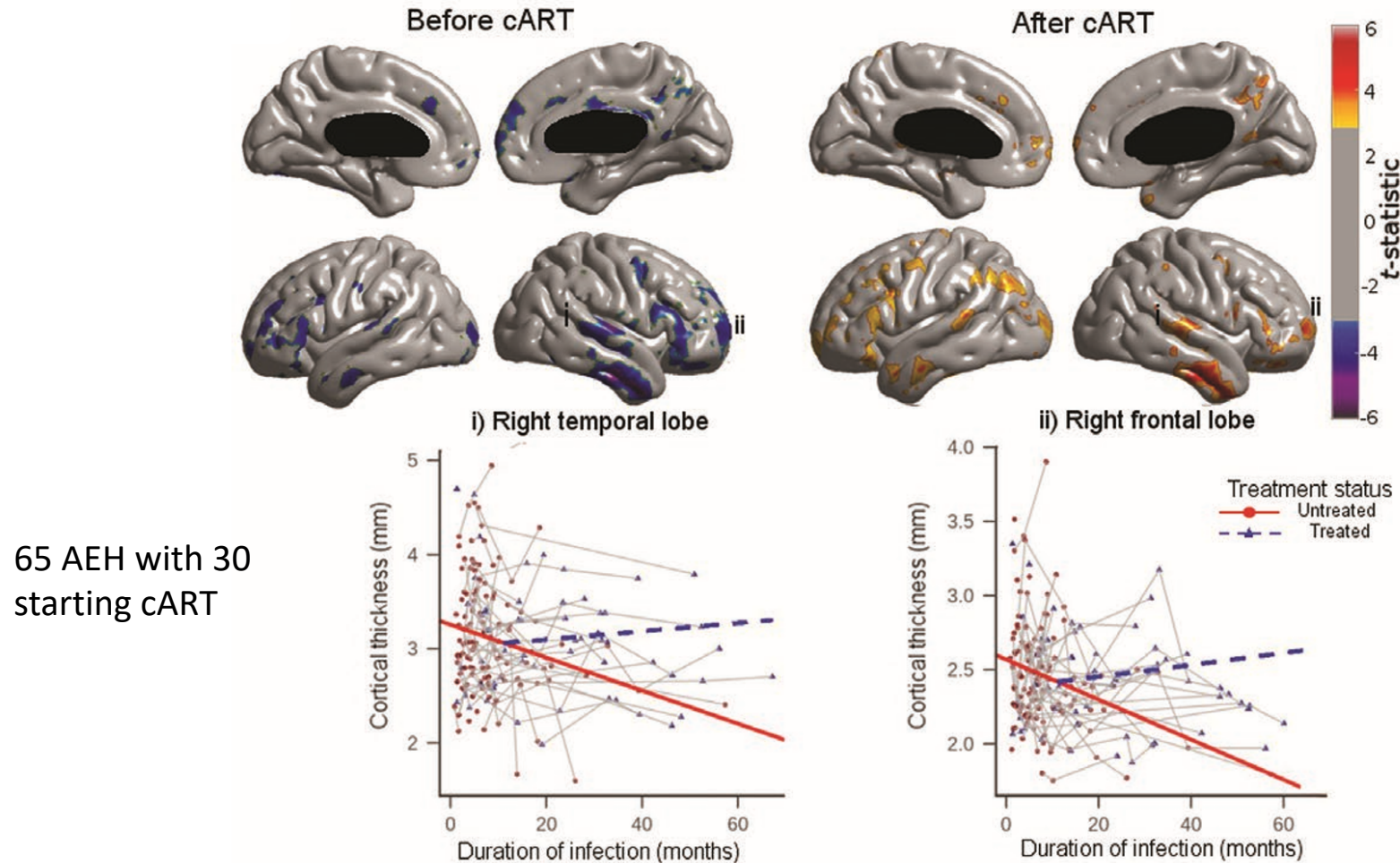
19 HIV-  
62 AEH  
16 CHI



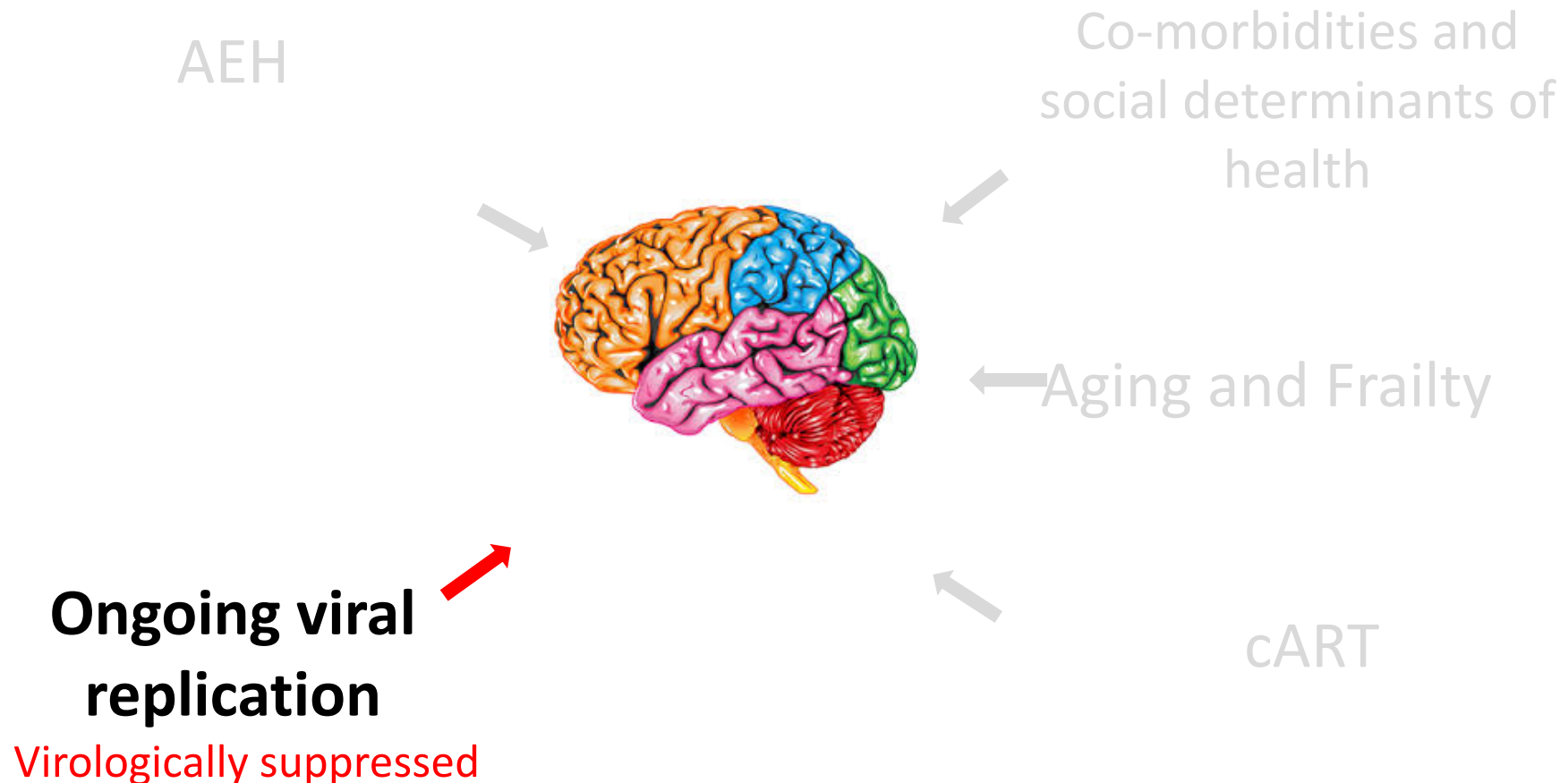
Wright et al., *JAIDS*, 2015

- The longer an individual remains untreated the more changes occur in the brain

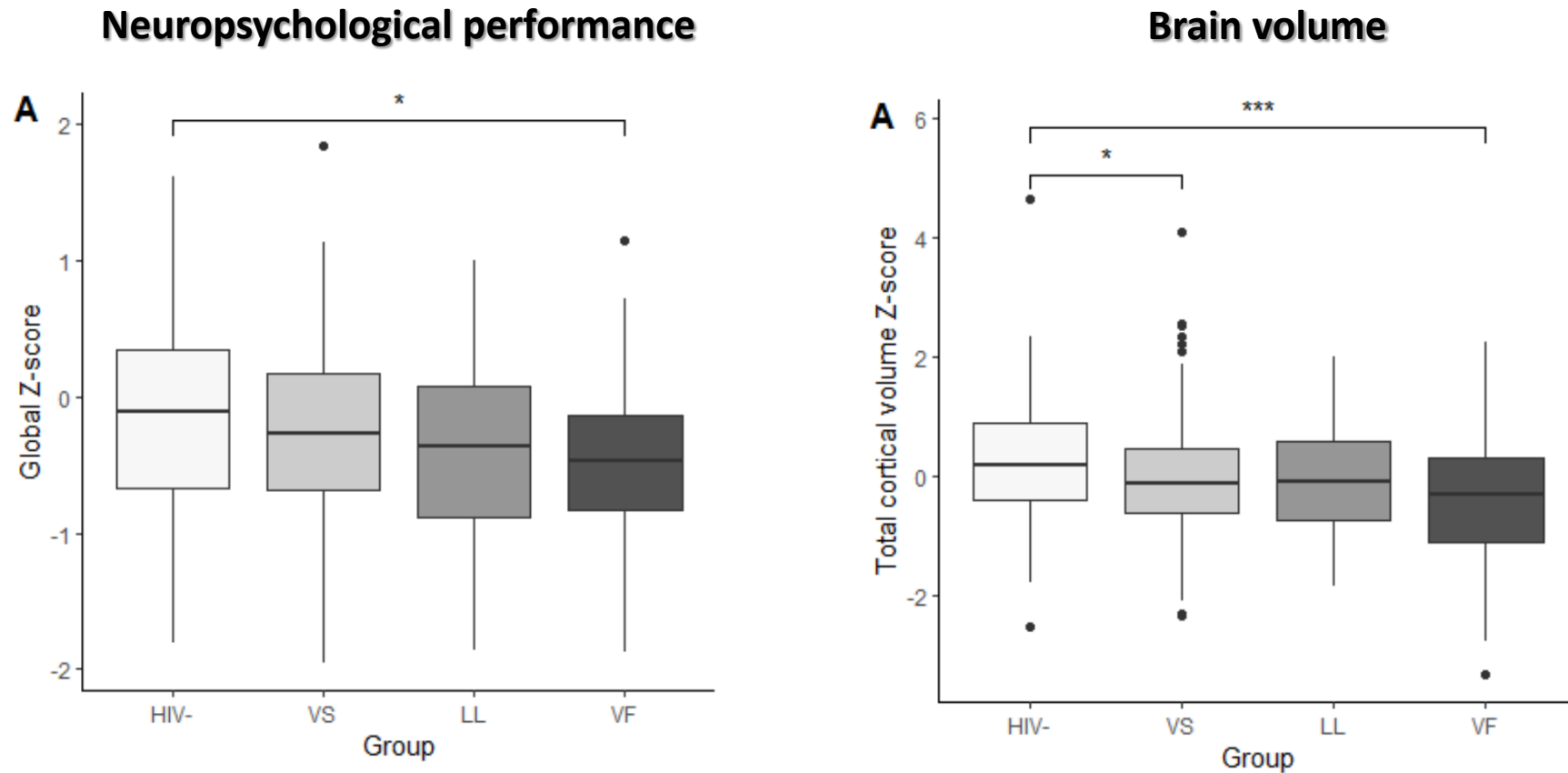
# Initiating CART Stabilizes Brain Loss



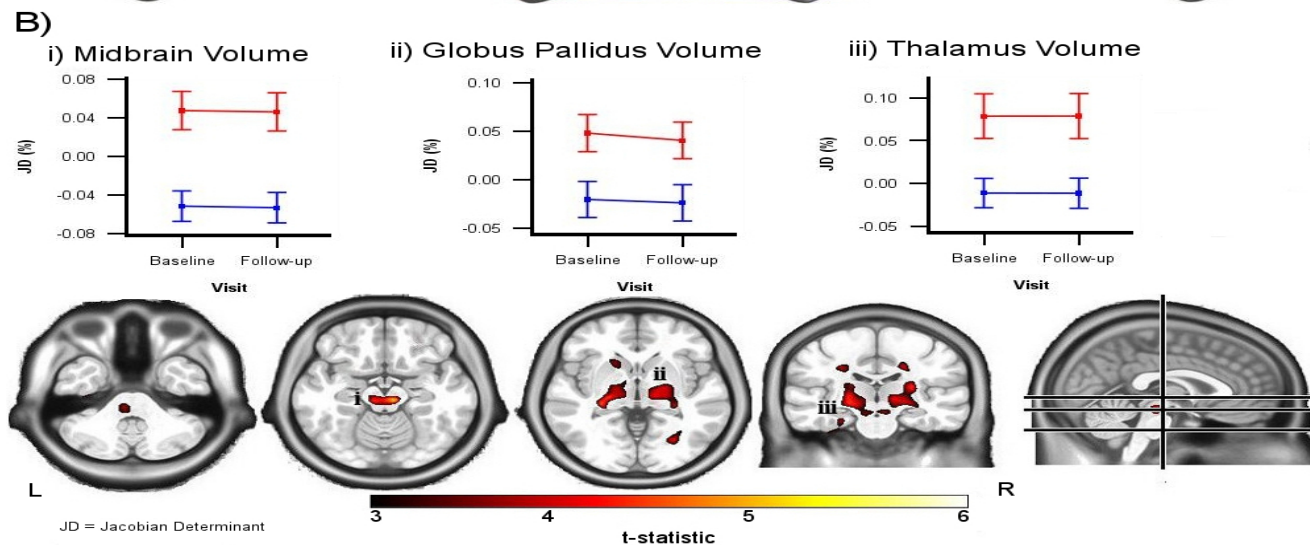
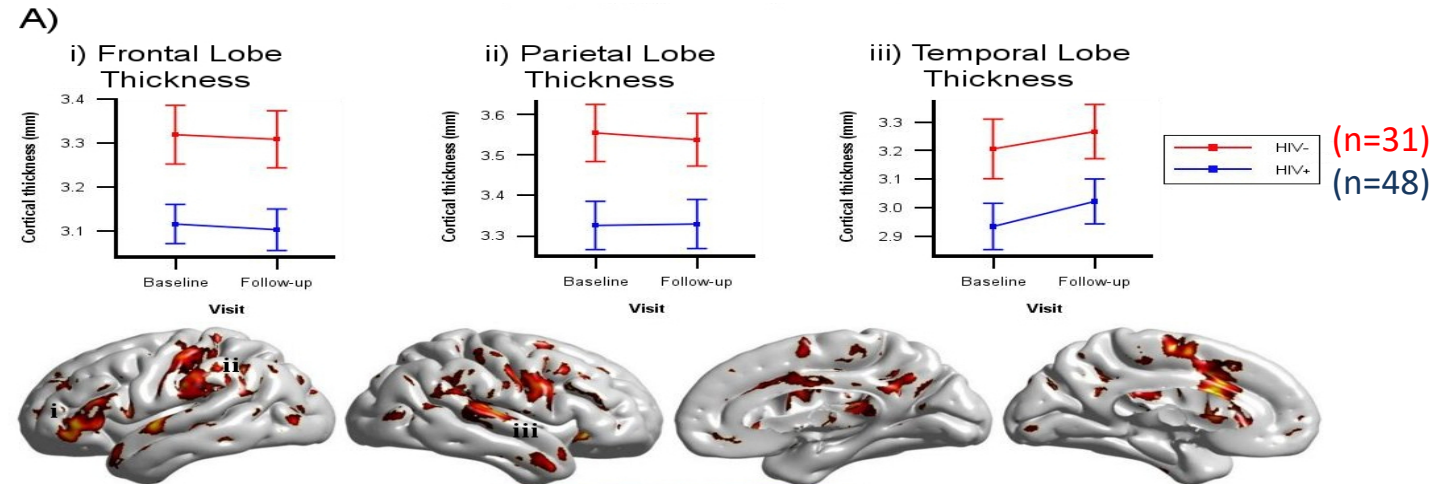
# Mechanisms of Central Nervous System (CNS) Injury In Our PLWH Living in Saint Louis in 2022



# Virological Failure is Associated With Worse Cognitive Performance and Smaller Brain Volumes

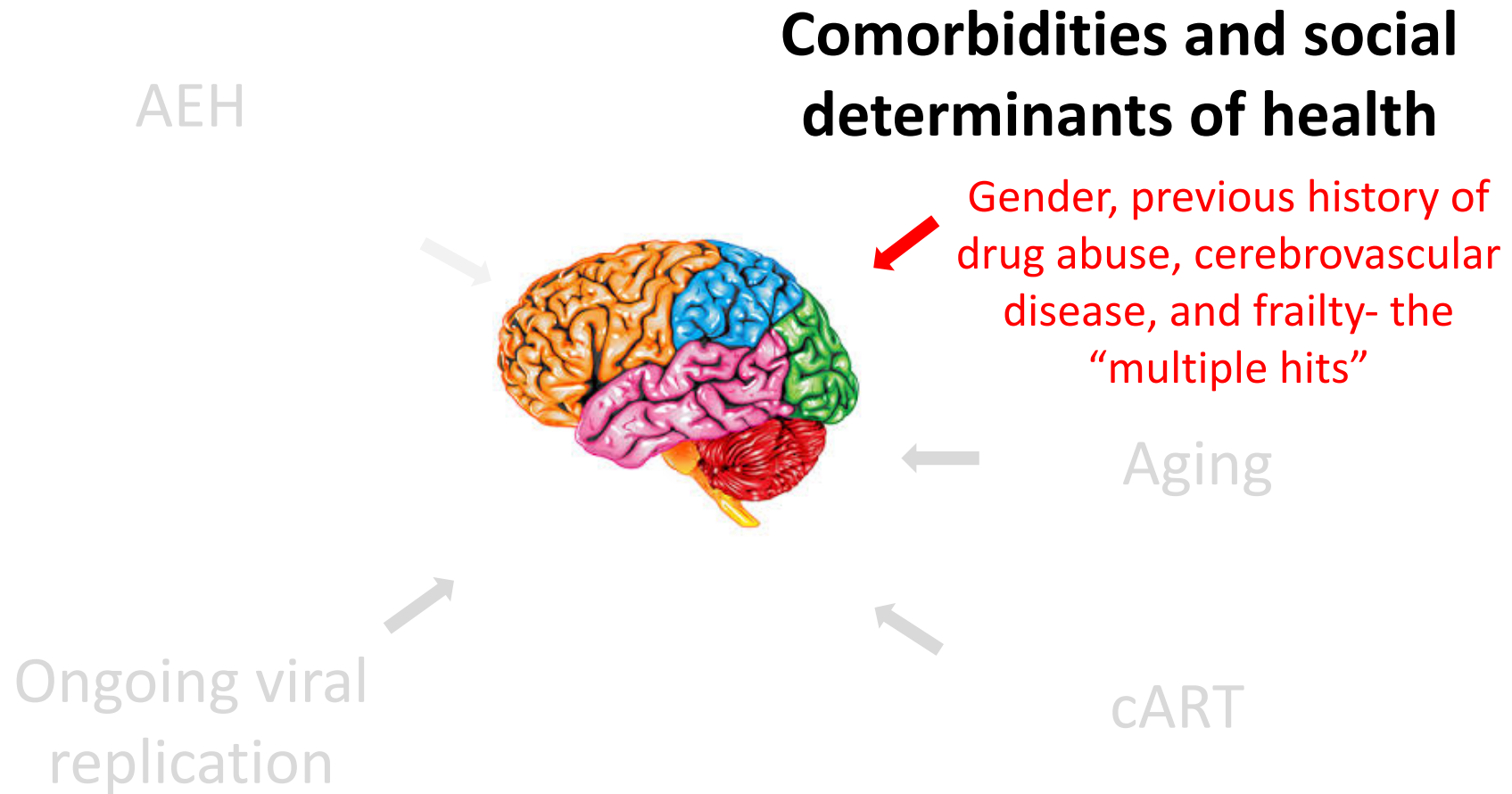


# Virologically Suppressed PLWH Have Volumetric Loss Similar To HIV- Individuals

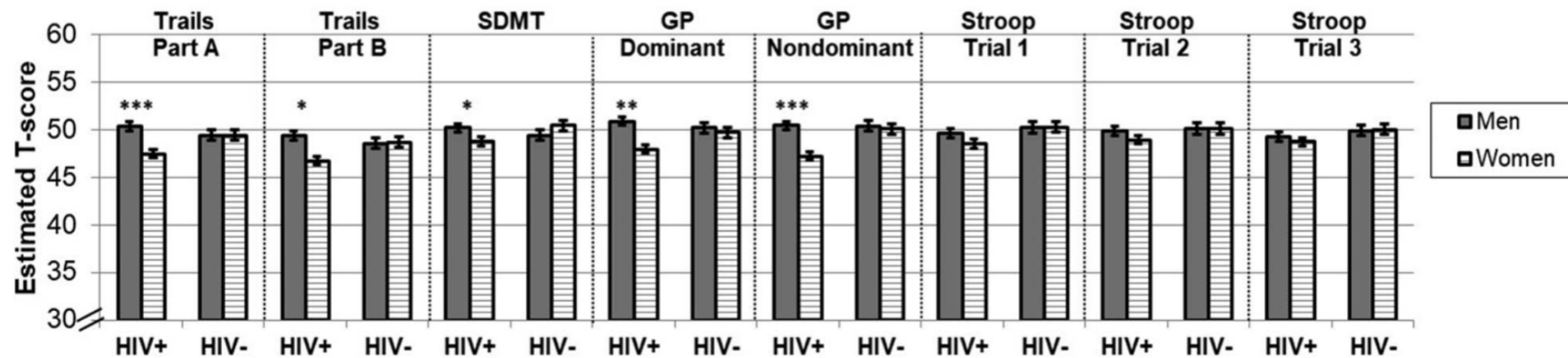


- Initial hit and then stabilized with cART

# Mechanisms of CNS Injury In Our PLWH Living in Saint Louis in 2022



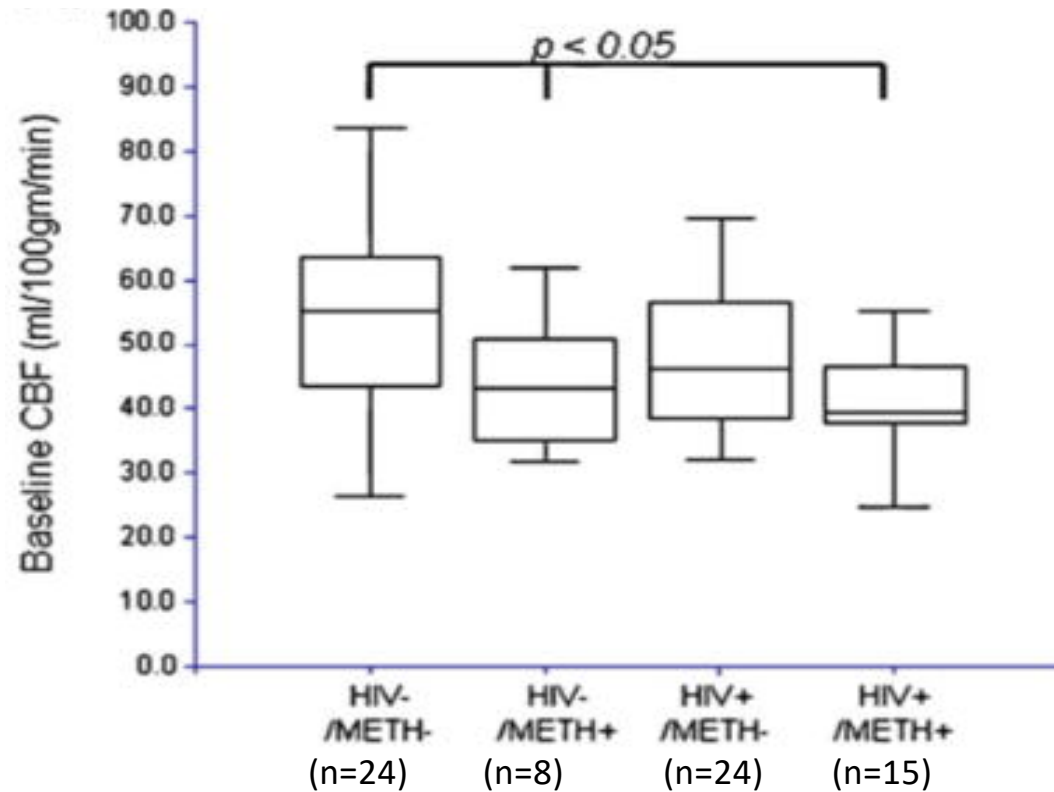
# Cognitive Impairment is More Prevalent in Female vs Male PLWH



Maki et al., *JAIDS*, 2018

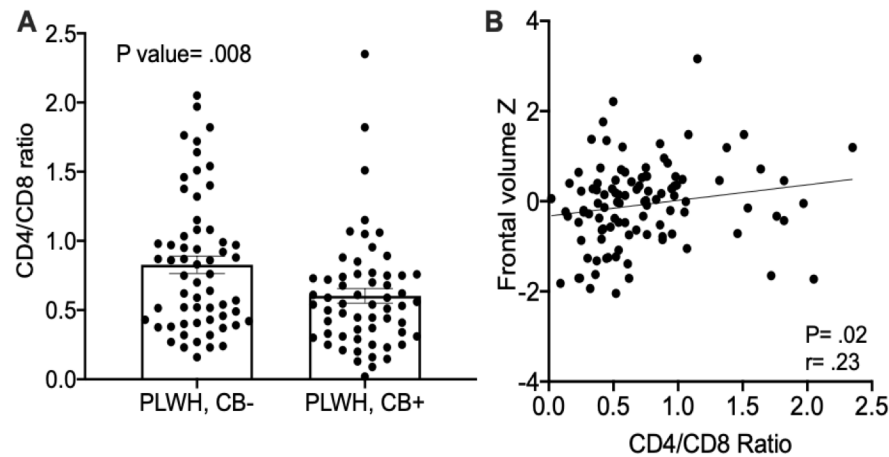


# HIV Infection and Previous Methamphetamine Use Independently Reduce CBF

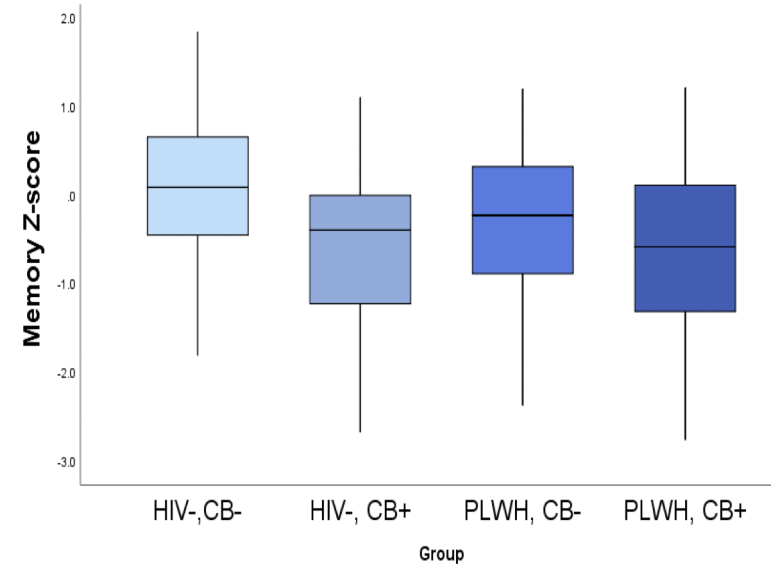


# Cannabis Is Associated With Worse Immune Health and Cognition

## Immune Function

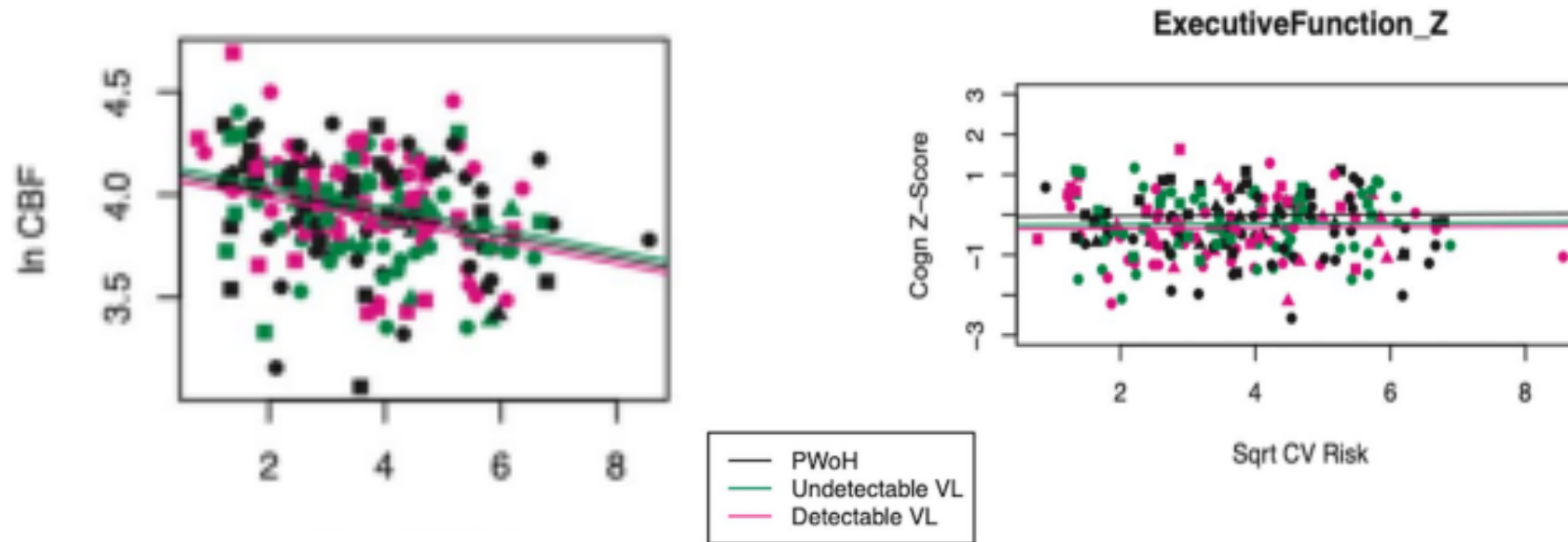


## Cognition



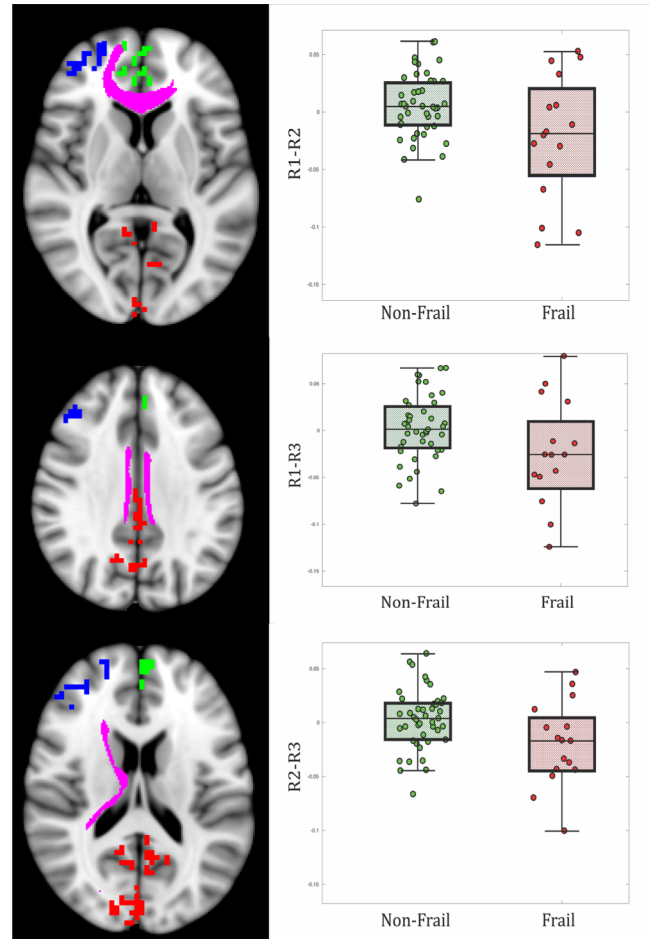
Burdo et al., in progress

# Effects of Cardiovascular Risk on Neuroimaging and Neuropsychological Performance in PLWH



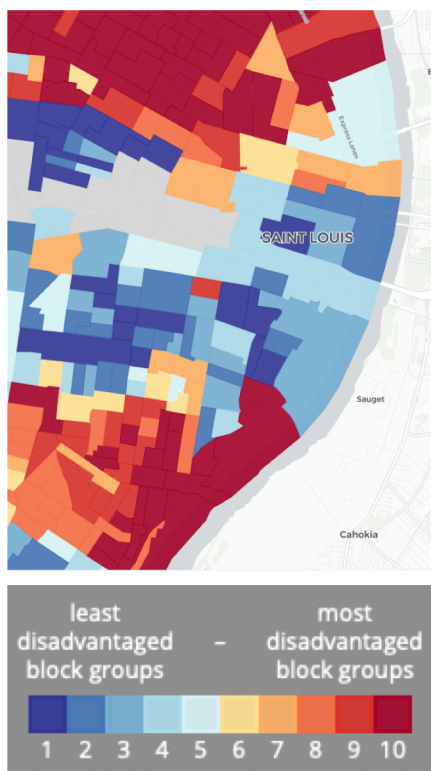
- Neuroimaging, but **not** cognitive, measures were associated with elevated cardiovascular risk
- HIV serostatus was associated with diminished brain volumes and worse cognition
- Blood flow in the brain remained unchanged between PLWH and HIV- controls reflecting potential protective effects of cART.

# Frailty is Associated with Reductions in Brain Tracts in PLWH

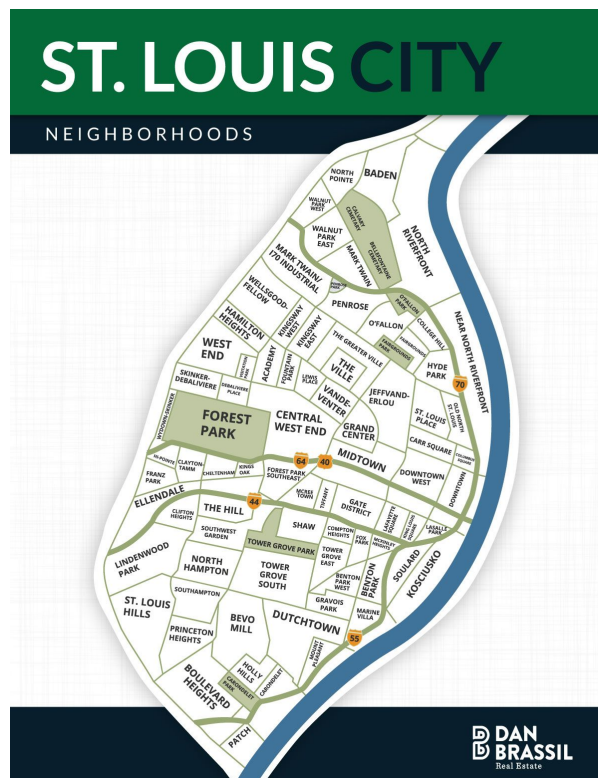


## Relationship Between Place of Residence and Brain Structure

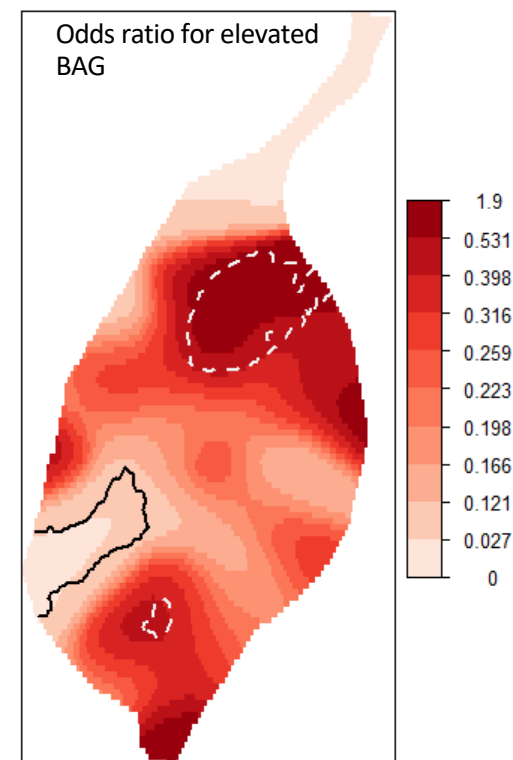
## Area Deprivation Index (ADI)



## Neighborhoods of St. Louis



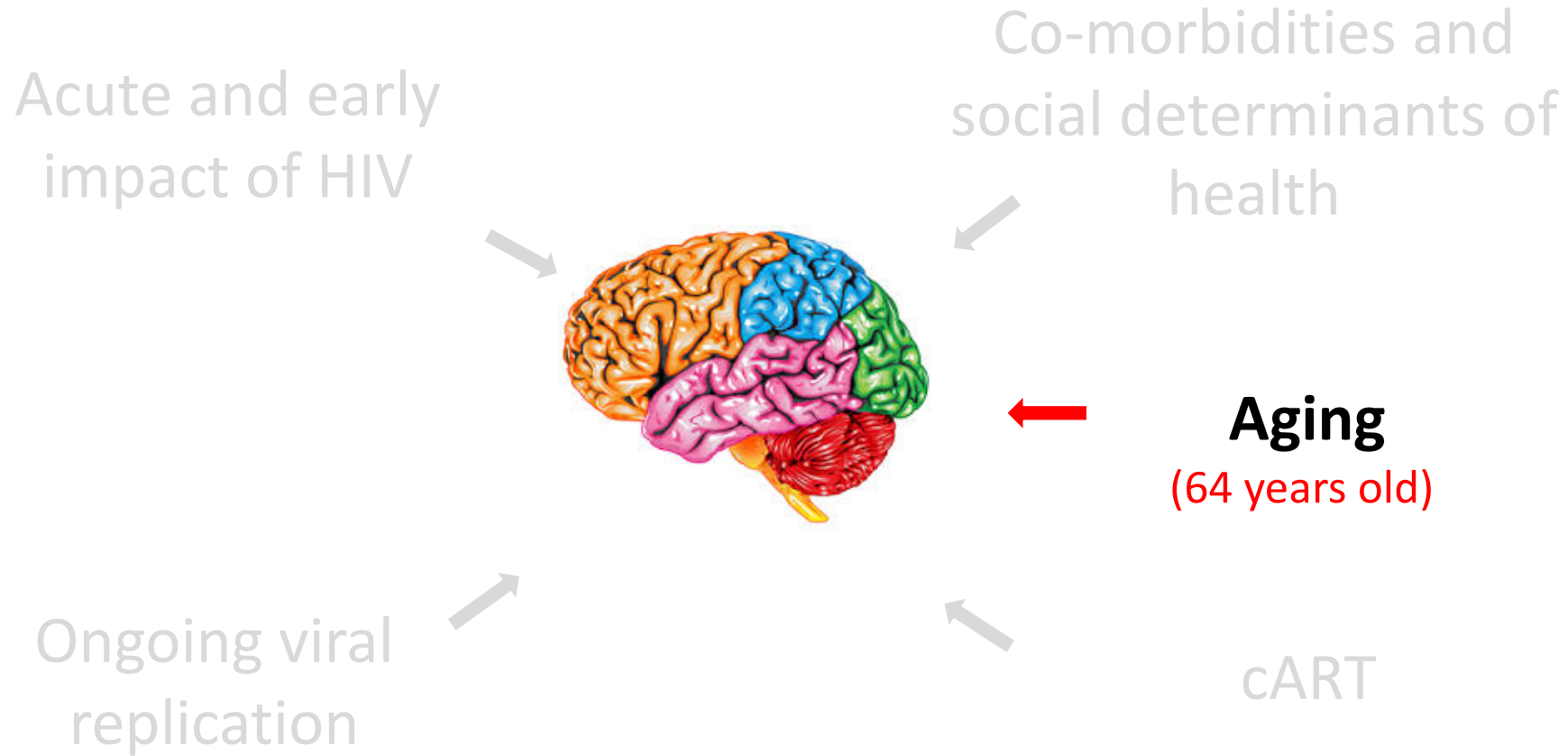
## Brain Age Gap (BAG)



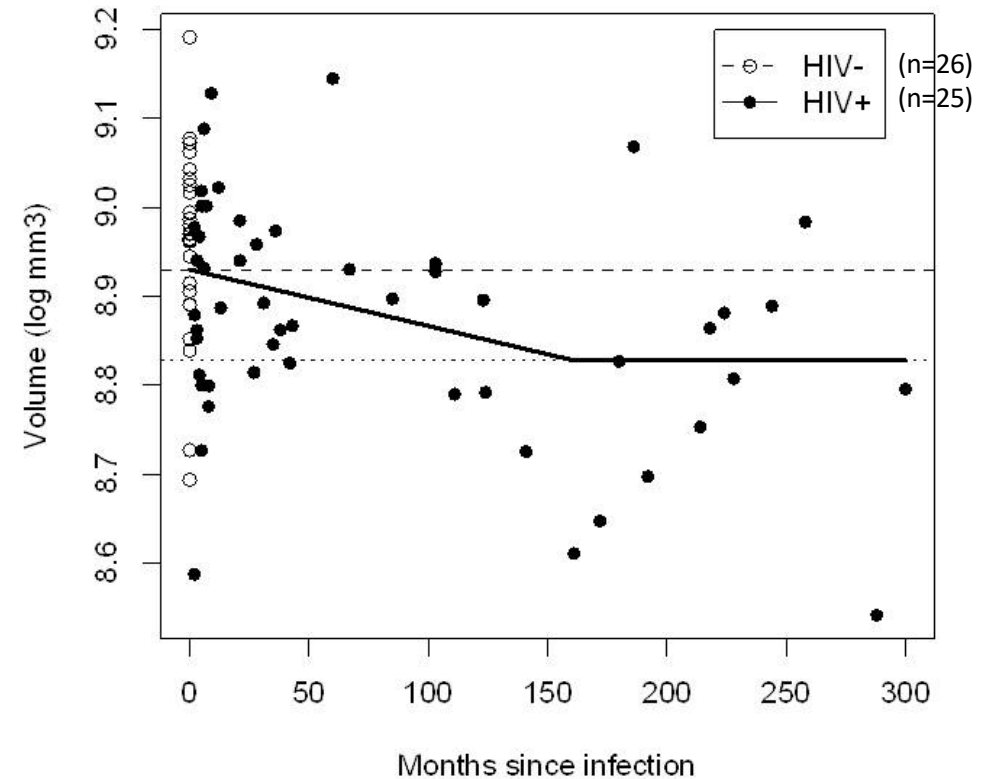
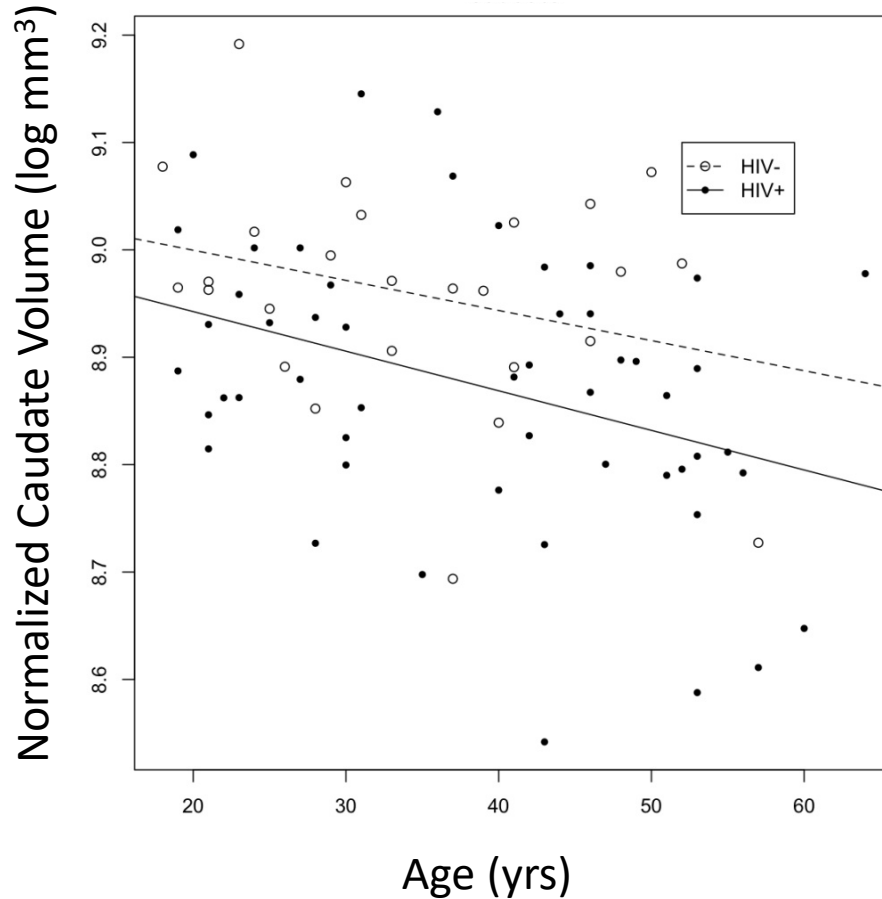
Wisch et al., in progress

- Worse ADI associated with elevated BAG

# Mechanisms of CNS Injury In Our PLWH Living in Saint Louis in 2022

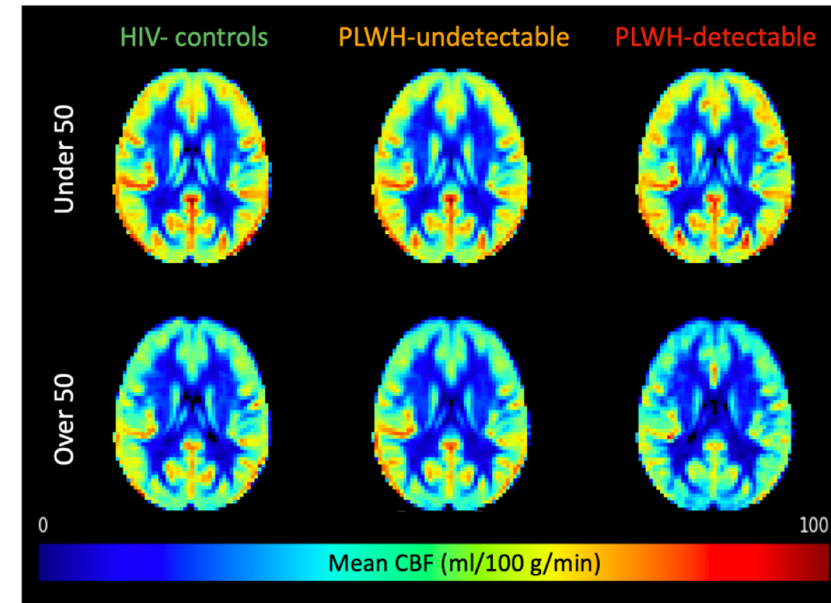
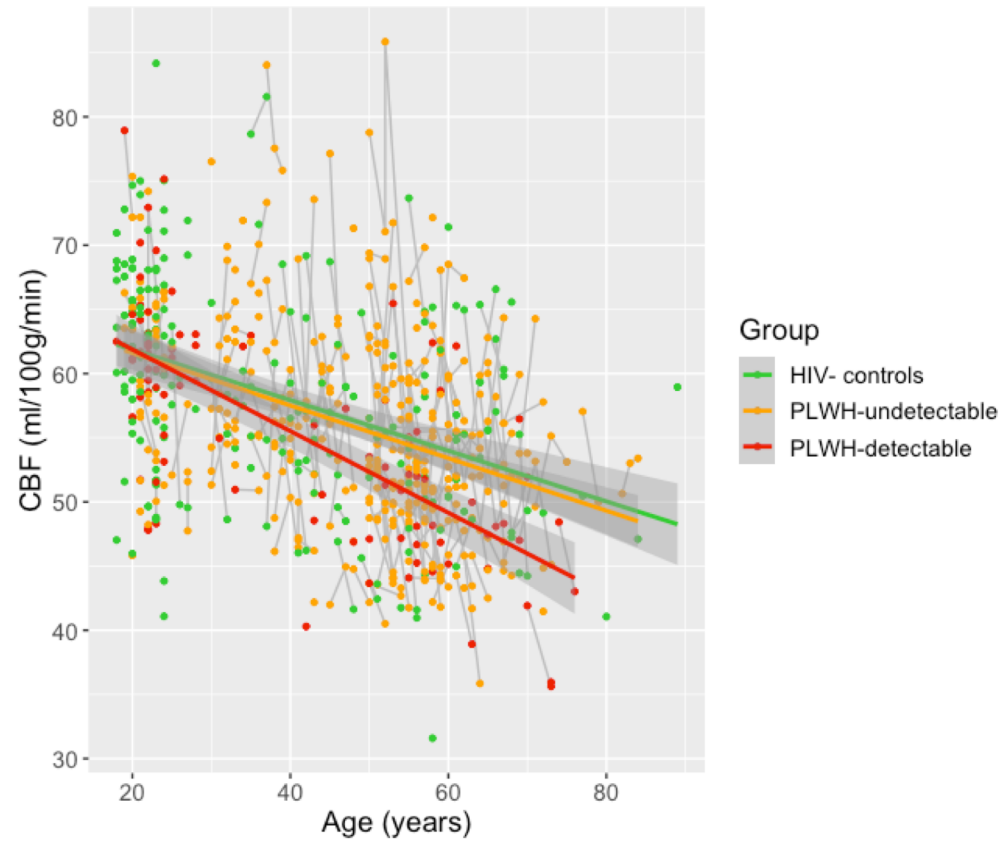


# HIV and Aging Independently Reduce Structural Neuroimaging Measures



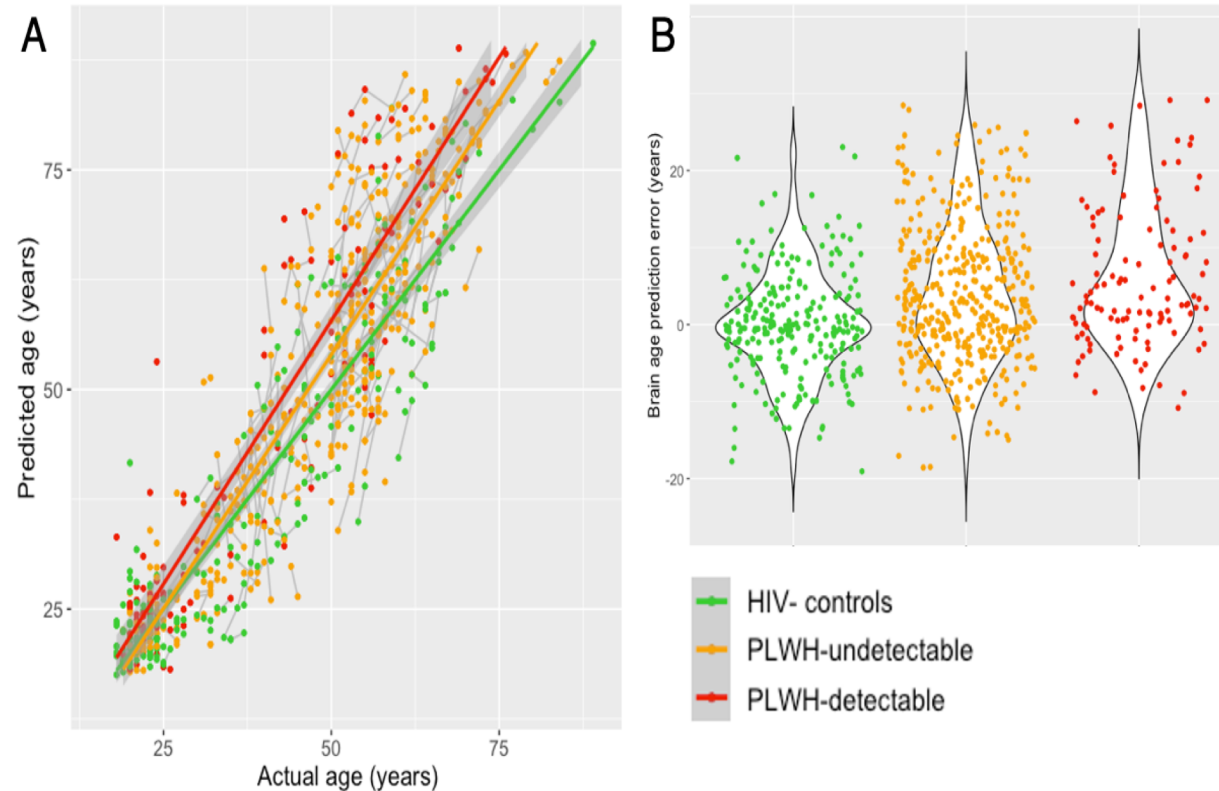
- Includes both detectable and undetectable PLWH

# Accelerated Aging, As Measured by CBF, Occurs in PLWH With Detectable Viral Load



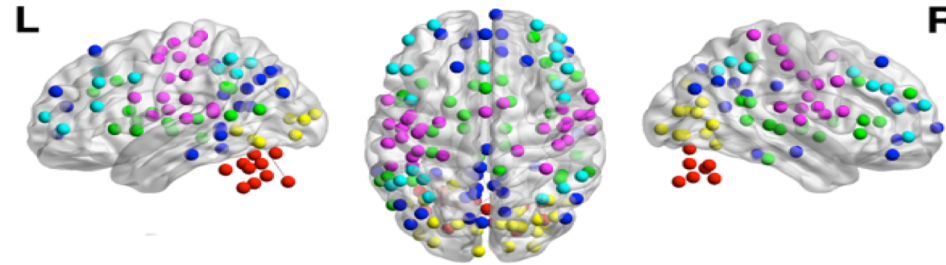


# Brain Predicted Age is Elevated in PLWH Compared to HIV- Controls

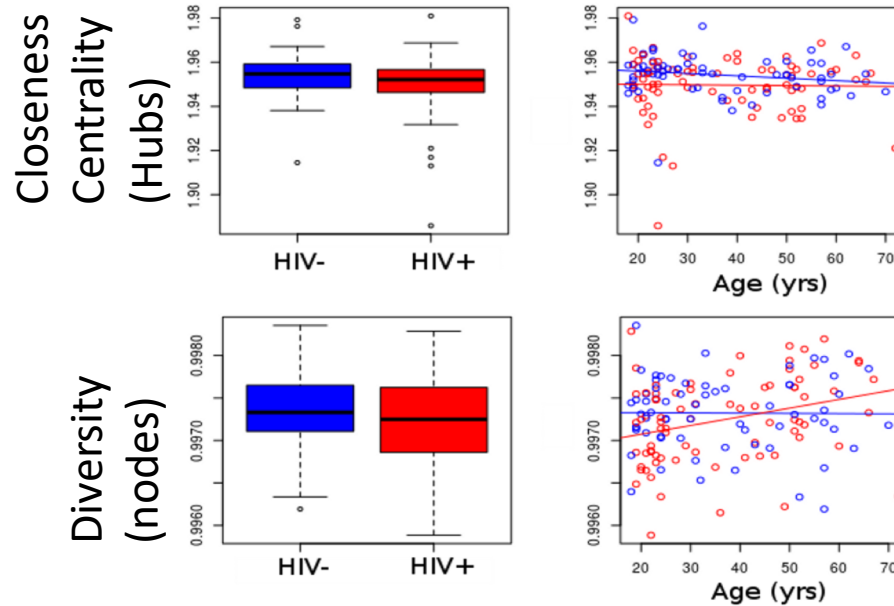


- Greatest BAG seen in older detectable PLWH

# HIV Primarily Affects Hubs While Aging Affects Distal Nodes



## GLOBAL



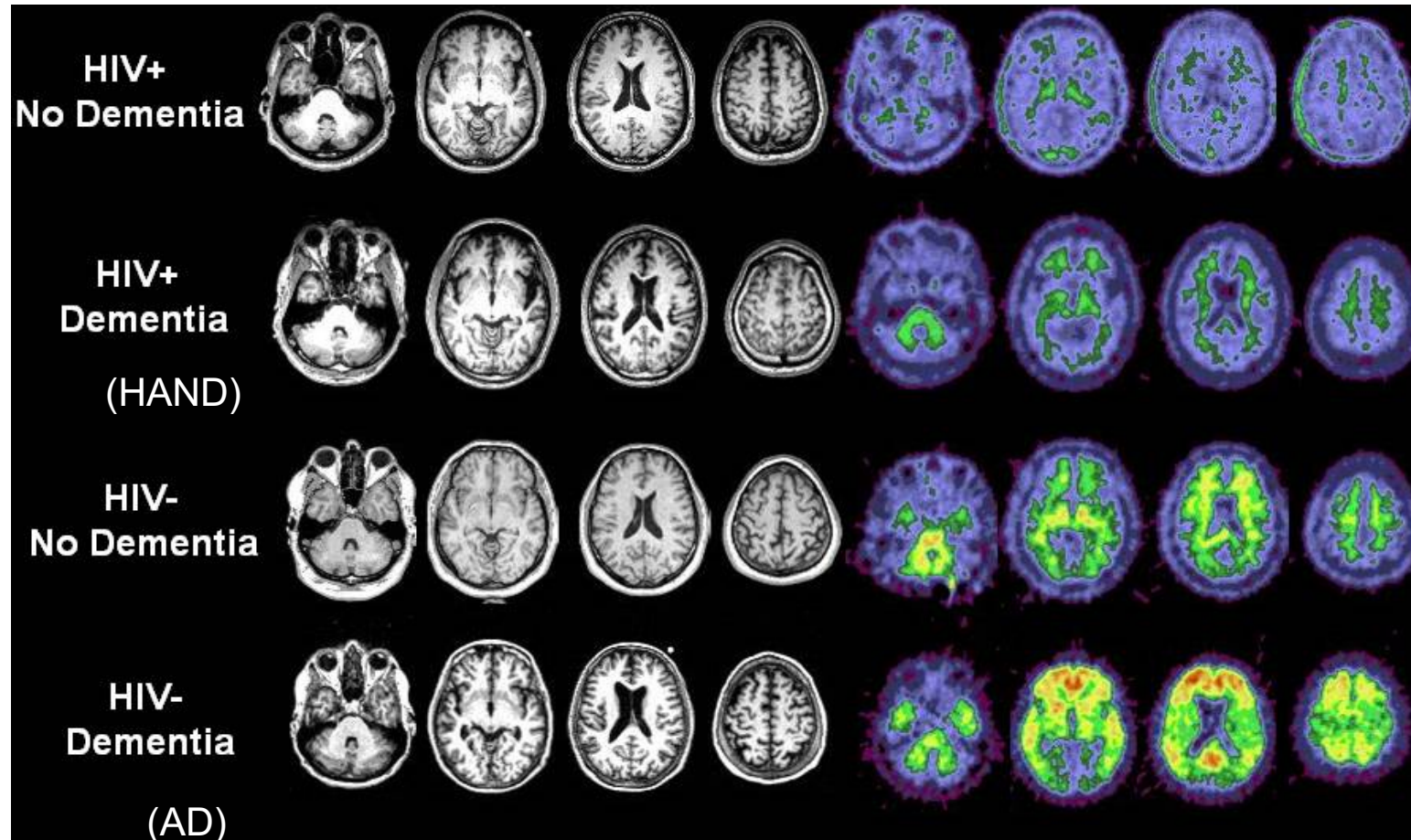
## NETWORK

Closeness centrality		HIV	Age	HIV:Age
DMN	p-value	<b>0.005587</b>	0.226942	0.440119
	beta	<b>-0.001408</b>	-0.000034	-0.000174
PAR	p-value	<b>0.032704</b>	0.255023	0.626612
	beta	<b>-0.003703</b>	-0.000070	-0.000130
CER	p-value	0.286310	0.167802	<i>0.0936636<sup>†</sup></i>
	beta	-0.022115	-0.000036	<i>0.000484</i>
CINGO	p-value	0.454033	0.382788	0.626612
	beta	-0.008279	-0.000025	0.000144
OCC	p-value	0.552404	0.255023	0.952956
	beta	-0.002890	-0.000175	0.000014
SMN	p-value	0.552404	0.255023	0.440119
	beta	-0.011797	-0.000275	0.000273

Eigenvector Centrality		HIV	Age	HIV:Age
DMN	p-value	0.754266	0.968081	0.808622
	beta	-0.007735	-0.000102	0.000187
PAR	p-value	0.754266	0.802798	0.808622
	beta	-0.009027	-0.000055	0.000217
CER	p-value	0.716851	0.802798	0.808622
	beta	0.002883	-0.000013	-0.000150
CINGO	p-value	0.448733	0.889757	0.808622
	beta	-0.005049	-0.000052	0.000043
OCC	p-value	0.273378	0.802798	0.808622
	beta	-0.006721	0.000047	0.000042
SMN	p-value	0.273378	0.802798	0.808622
	beta	-0.002816	0.000136	-0.000044

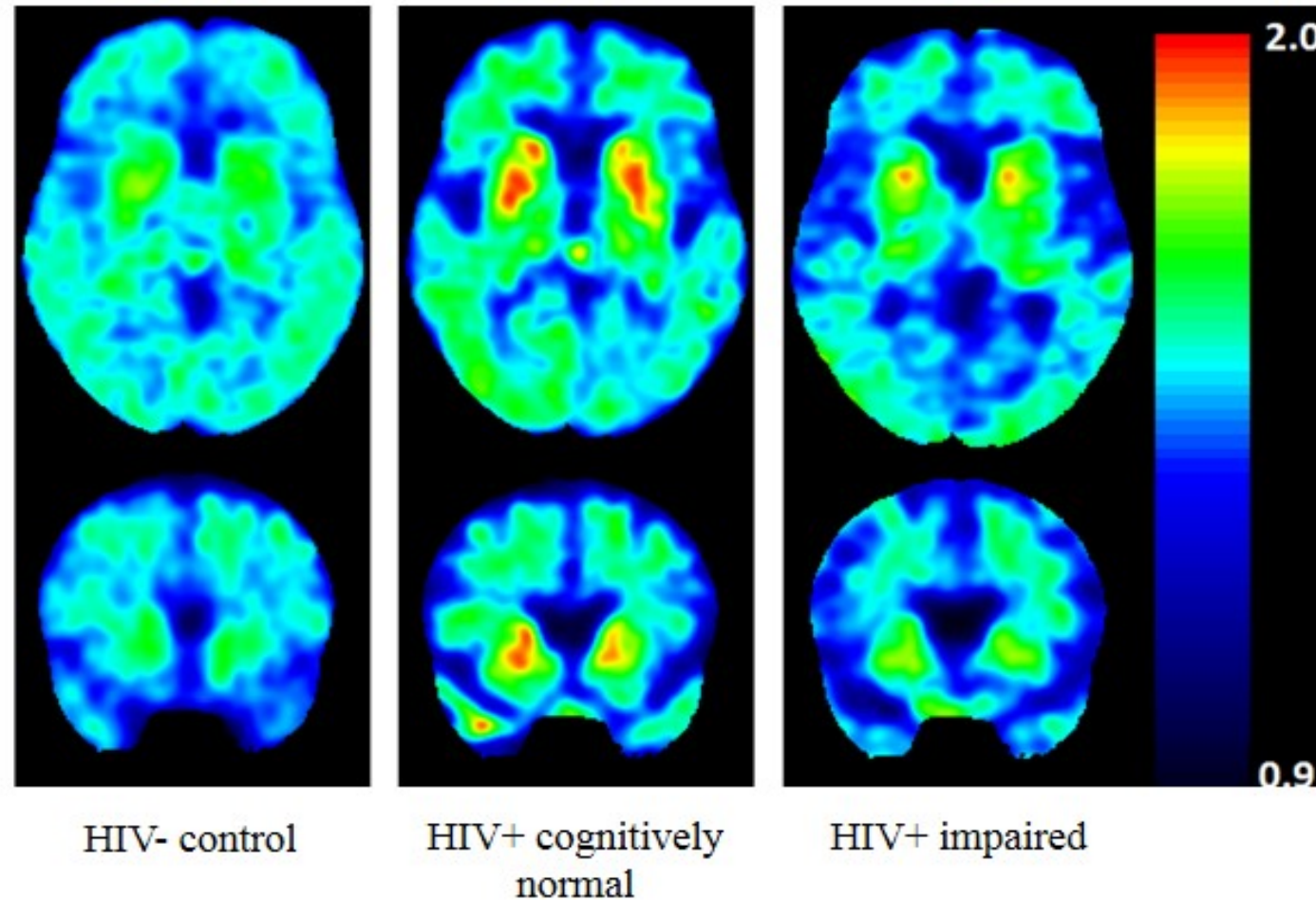
Diversity		HIV	Age	HIV:Age
DMN	p-value	0.845908	<b>0.000035</b>	0.291414
	beta	<b>0.000309</b>	<b>0.000014</b>	0.000009
PAR	p-value	0.773990	<i>0.05266136<sup>†</sup></i>	0.883927
	beta	0.000028	<i>0.000006</i>	0.000001
CER	p-value	0.491484	0.263394	<i>0.08233318<sup>†</sup></i>
	beta	-0.000884	-0.000015	<i>0.000018</i>
CINGO	p-value	0.573612	<i>0.05266136<sup>†</sup></i>	<i>0.08233318<sup>†</sup></i>
	beta	-0.000436	<i>-0.000010</i>	<i>0.000010</i>
OCC	p-value	0.491484	0.263394	<i>0.08233318<sup>†</sup></i>
	beta	-0.000535	-0.000005	<i>0.000021</i>
SMN	p-value	0.845908	0.332862	0.187336
	beta	-0.000473	-0.000010	0.000012

# Amyloid PET Distinguishes HAND from AD in PLWH



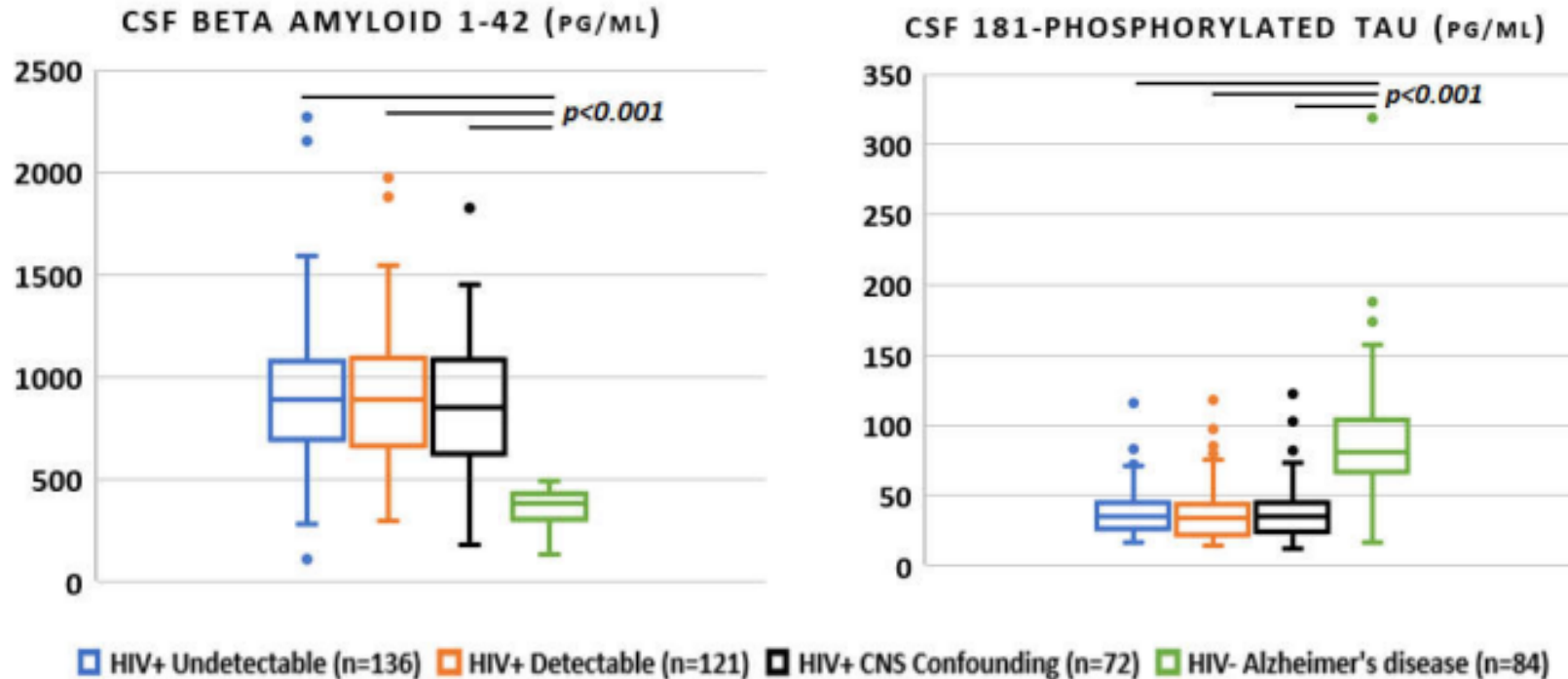
Ances et al. *Neurology*, 2010;  
Ances et al, *Arch of Neurol.*, 2012  
Ortega and Ances, *Journal of Neuroimmune Pharm*, 2014

# Tau PET Is Not Elevated In HAND





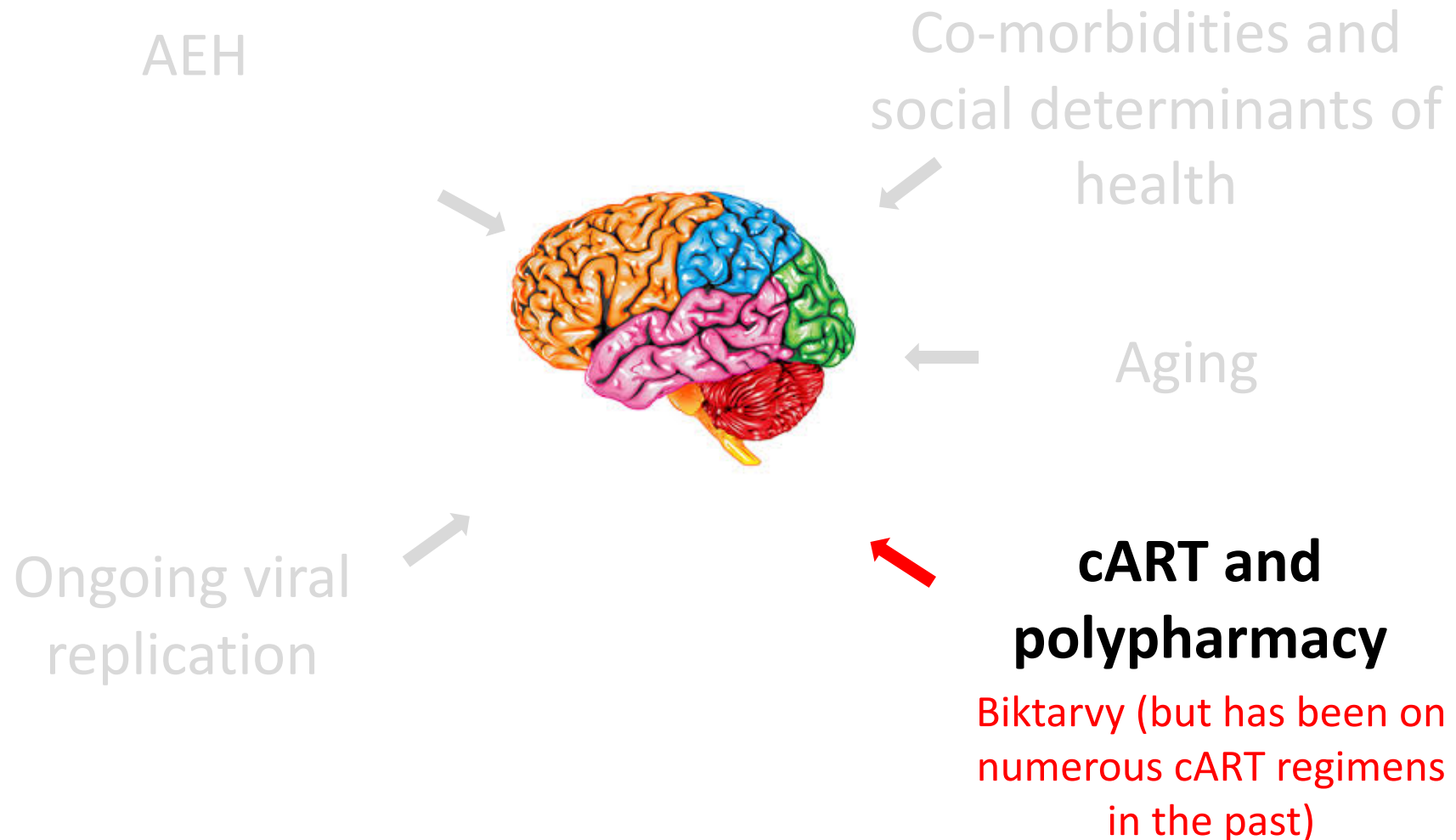
# CSF Amyloid and Tau Are Not Affected in PLWH Compared to AD



Trunfio et al., *Viruses*, 2022

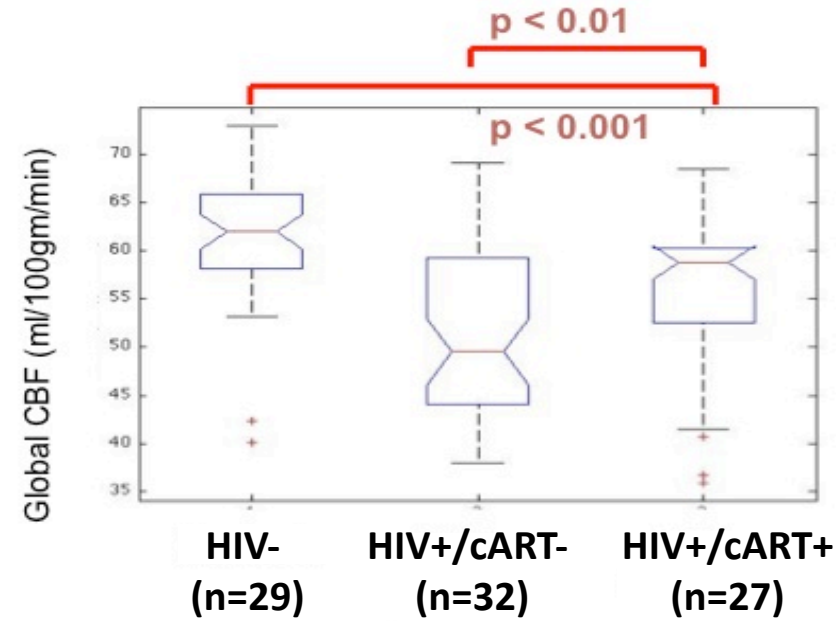
- Similar results are also seen for plasma markers for AD

# Mechanisms of CNS Injury In Our PLWH Living in Saint Louis in 2022

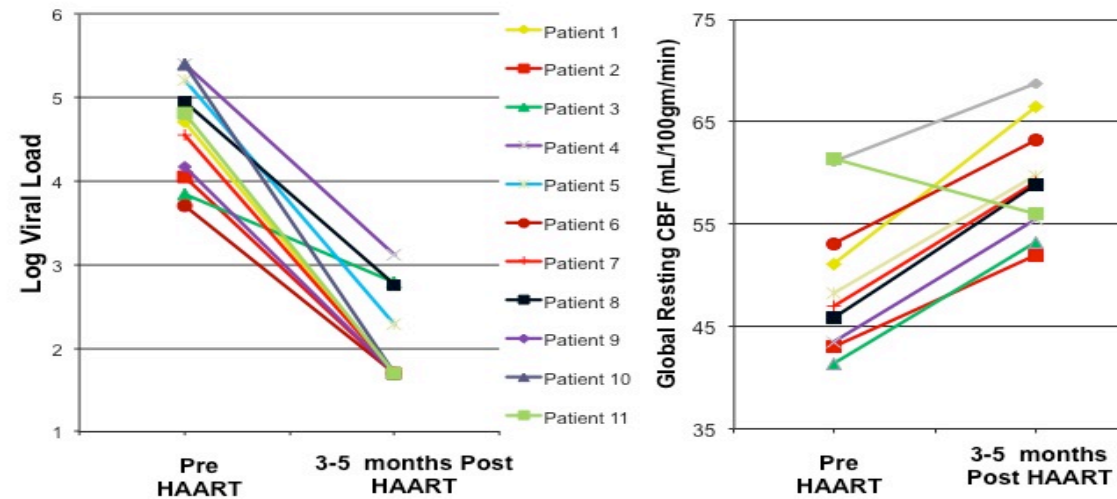


# cART Improves Resting CBF

*Cross-sectional*



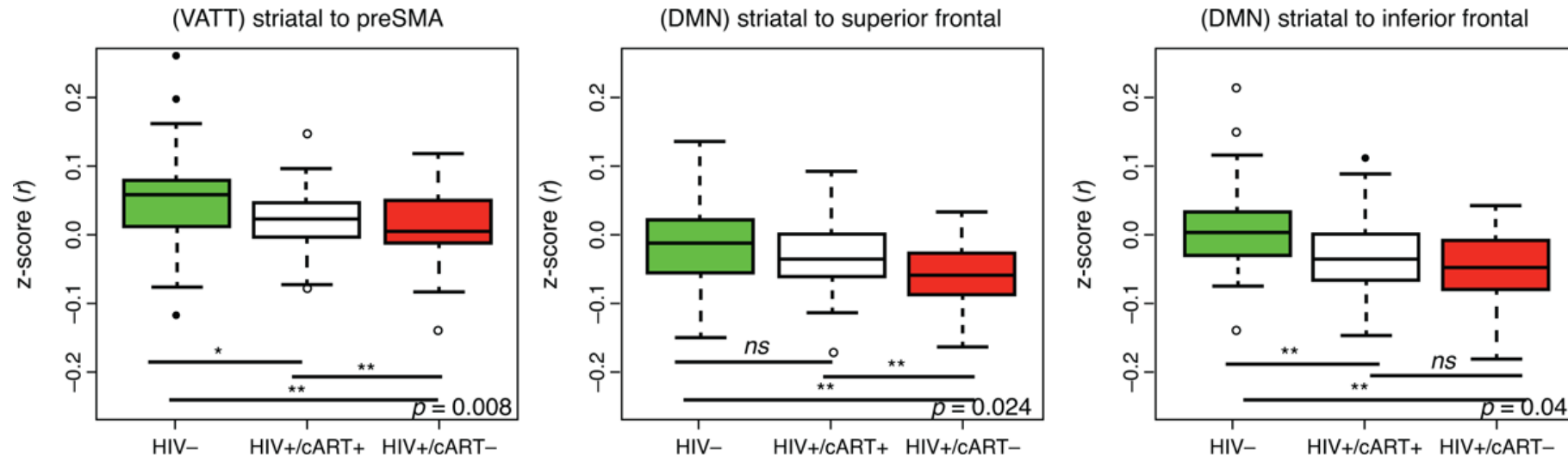
*Longitudinal*



Thomas et al.,  
*CROI*, 2012

- Neuroimaging measures can be dynamic and can be normalized with cART

# Response To cART Varies Throughout The Brain

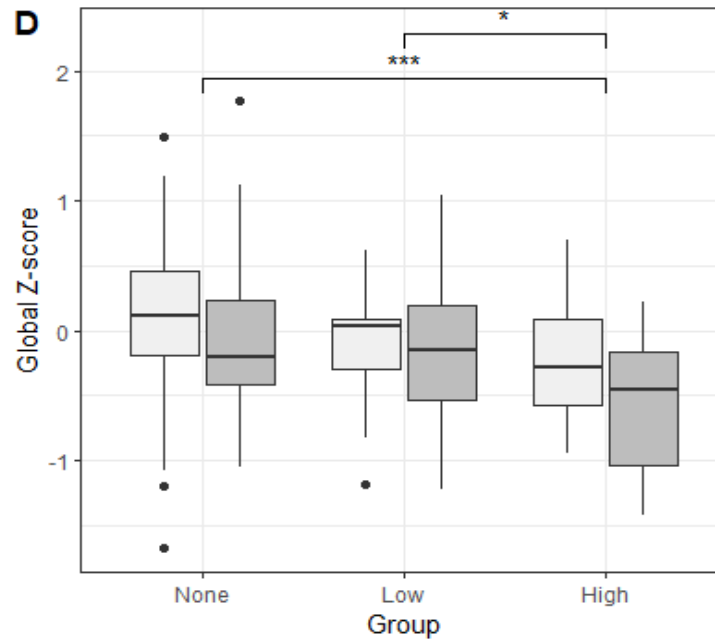


- Observed differences may lead to heterogeneity seen in PLWH

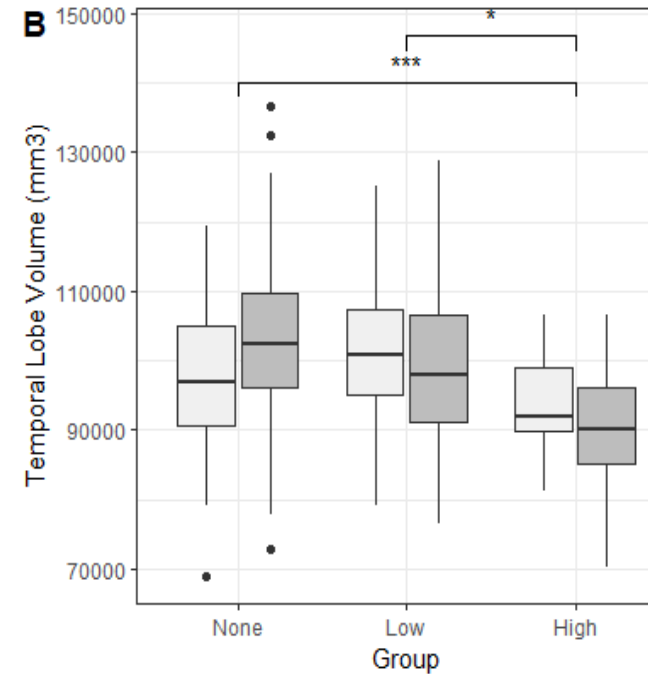


# Anti-Cholinergic Medications Are Associated with Worse Cognition and Reduced Brain Volume

Neuropsychological Performance



Brain Volume



Cooley et al., *AIDS*, 2020

- Anti-cholinergics are used to treat COPD (Ipratropium), Parkinson's disease (Benztropine), incontinence (Oxybutynin), and anti-emetic (Scopolamine).
- Drugs classified by anticholinergic cognitive burden (ACB) scale

# Section Summary

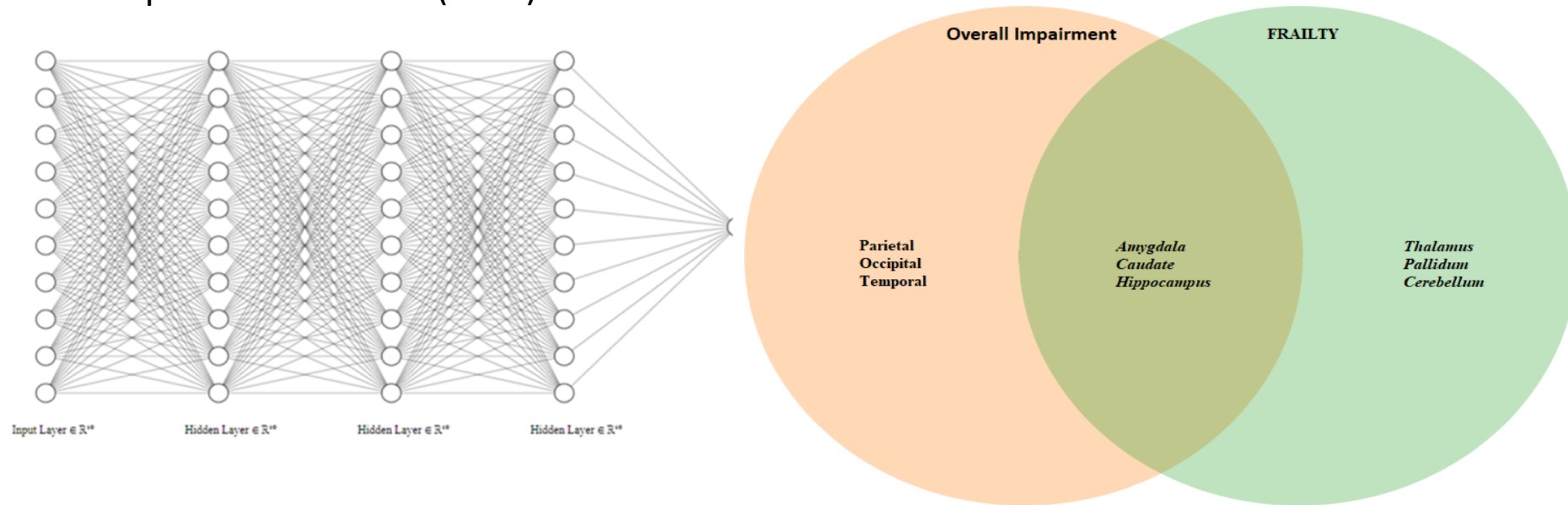
- A multi-hit process may occur for HAND
- 1<sup>st</sup> hit- social determinants of health may affect brain function
- 2<sup>nd</sup> hit- soon after seroconversion changes occur within the brain. Continued virological failure affects the brain. Starting cART that fully suppresses HIV early in disease is critically important.
- 3<sup>rd</sup> hit- Comorbidities (including drug use/abuse, cardiovascular, frailty, etc.) also affect brain health. Comorbidities are more common in older PLWH.
- 4<sup>th</sup> hit- An interaction can occur between HIV and aging at older ages. Brain predicted age is elevated in PLWH such that chronological  $\neq$  biological age.
- As PLWH get older, need to consider AD. Biomarkers can distinguish AD from HAND.
- Medication management needs to be considered in PLWH. Providers should work to reduce polypharmacy.

# The Next Steps



# Machine Learning Can Separate Cognitive Impairment From Frailty in PLWH

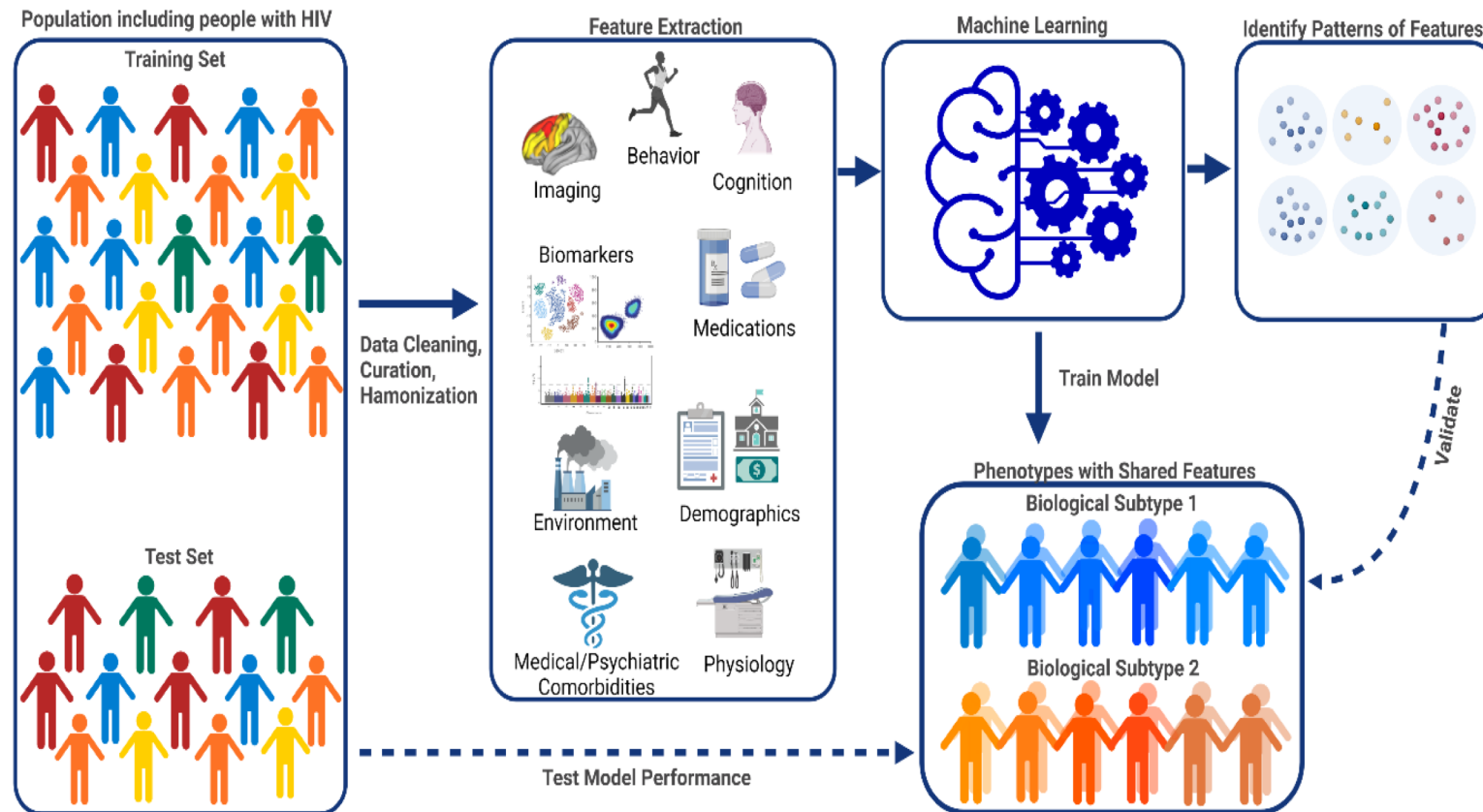
Deep neural network (DNN) model



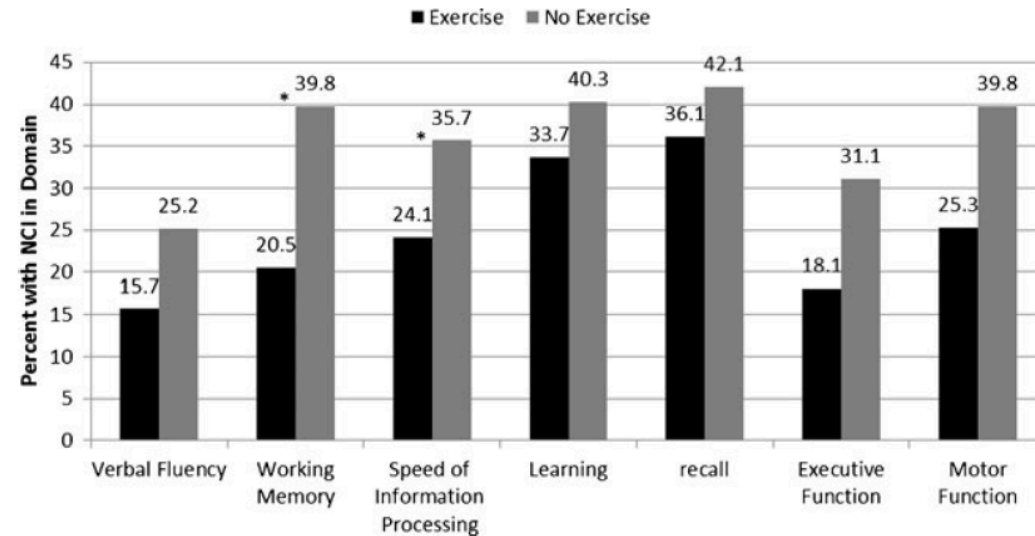
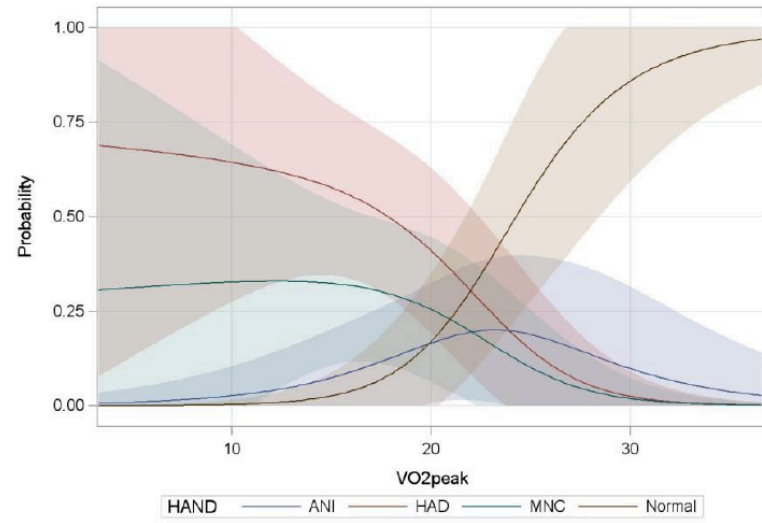
125 PLWH (virologically controlled) and 63 HIV- controls

- DNNs distinguished PLWH and HIV- controls with 90% accuracy
- Within PLWH DNN models classified individuals as having cognitive impairment with 82%-86% accuracy and frailty with 75% accuracy.

# Machine Learning Can Identify Biotypes or Fingerprints in PLWH



# Aerobic Fitness & Exercise are Associated with Better Cognitive Performance in PLWH



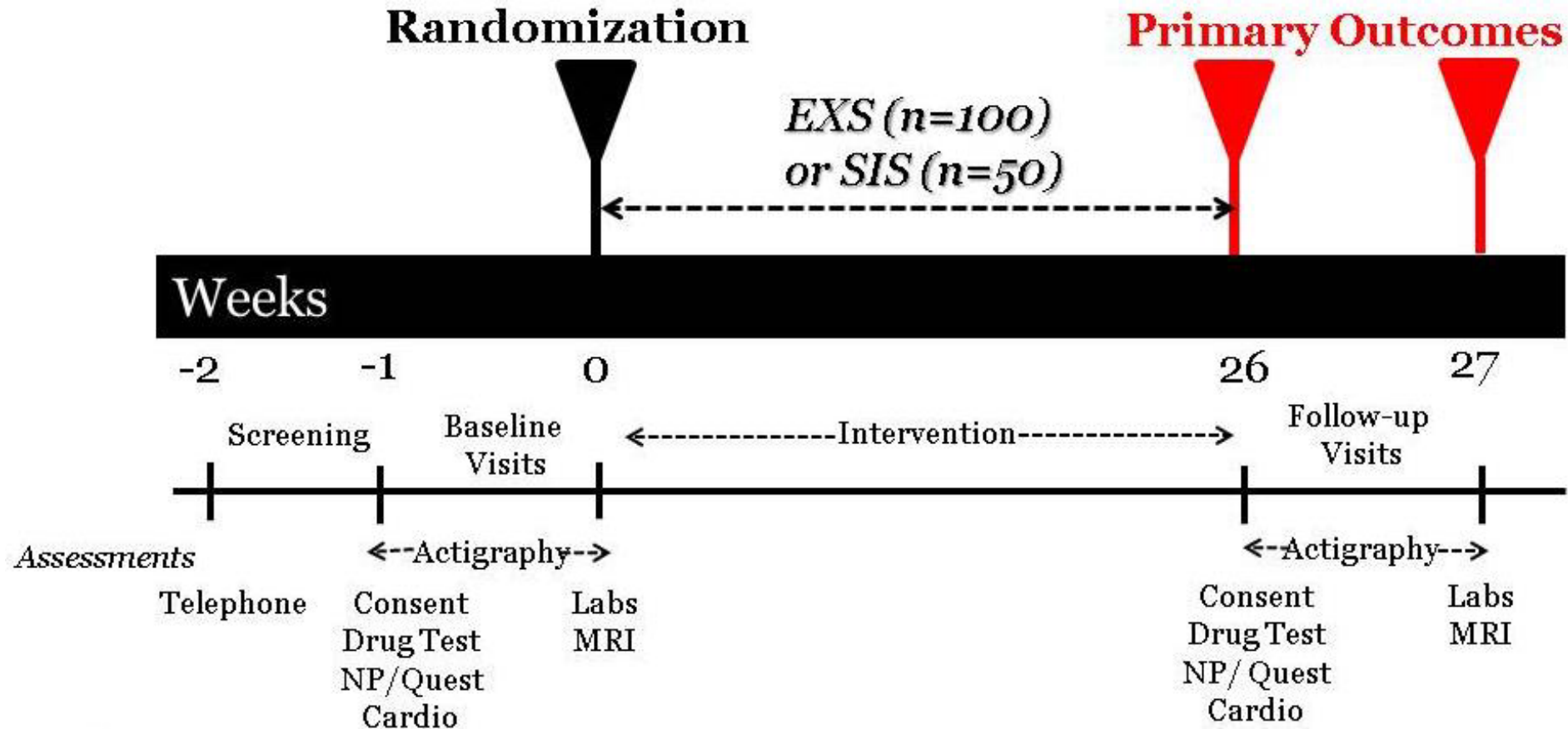
- Assessed 37 ( $\geq 50$  years old) PLWH on cART had VO<sub>2</sub> measurements using a treadmill
- Higher peak VO<sub>2</sub> (oxygen consumption) was associated with better verbal and visual memory, visual perception, and language and less risk of HAND
- 335 PLWH who provided self-reported activity over 72 hours
- PLWH who exercised had lower odds of global neurocognitive impairment as well as cognitive impairment within multiple domains

Mapstone et al, *Aging and Disease*, 2013

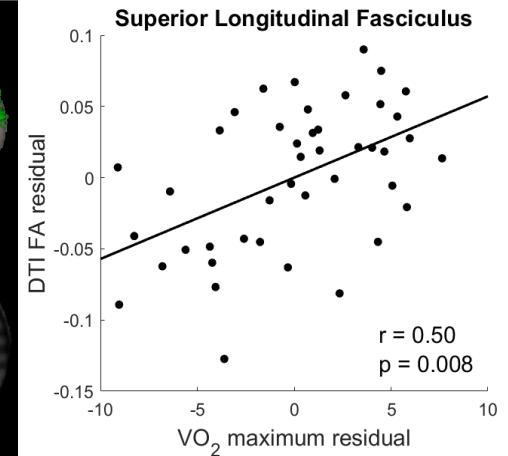
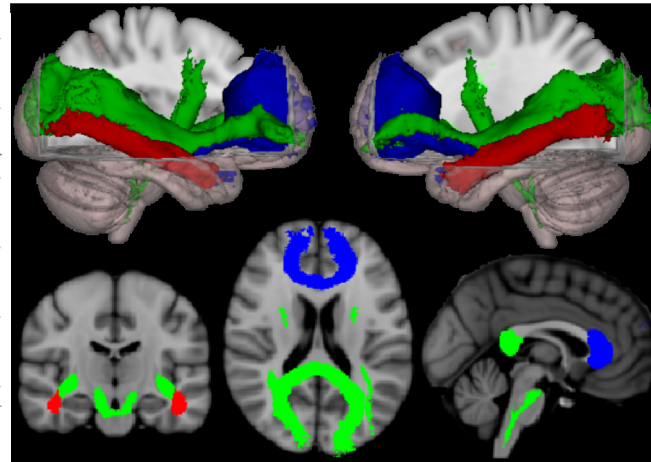
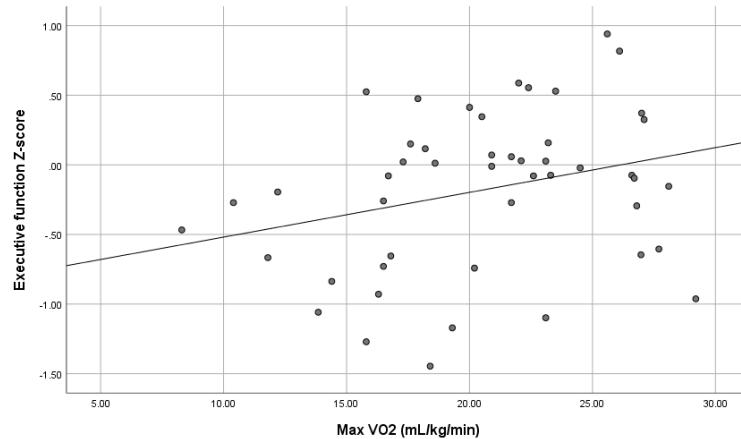
Dufour et al, *J Neurovirol* 2013

- A need existed for a clinical trial to assess exercise vs stretching on brain measures in PLWH*

# HIV Exercise Compared to Stretching (HECS) in Older PLWH



# An Active Lifestyle Was Associated With Better Cognition and Brain Imaging Measures in PLWH



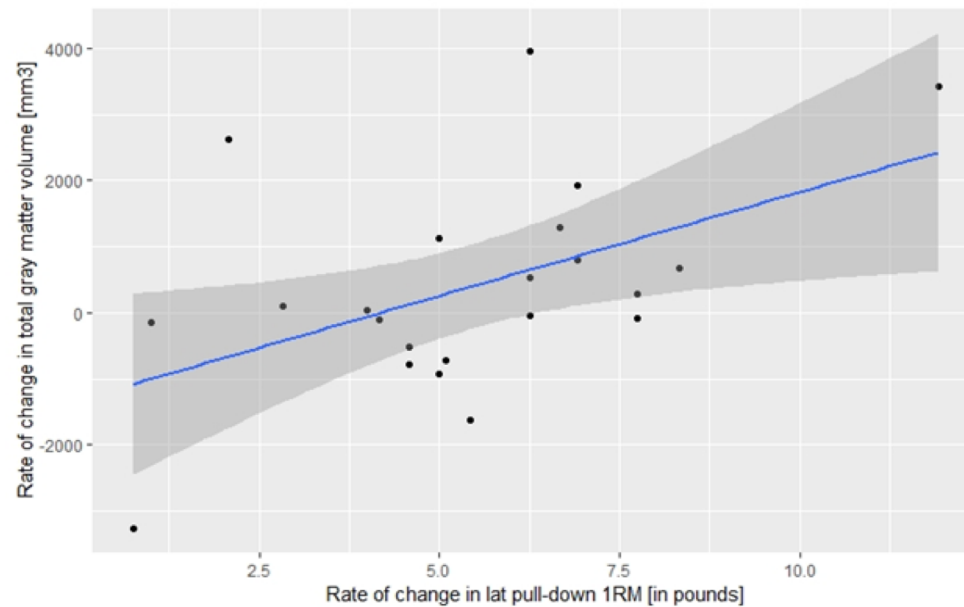
Killgore et al., *JAIDS*, 2021

- Higher baseline VO<sub>2</sub> max was associated with better cognitive performance (executive function) and more fibers within multiple white matter tracts
- Higher white matter fiber density in multiple tracts was associated with better visual and motor processing.

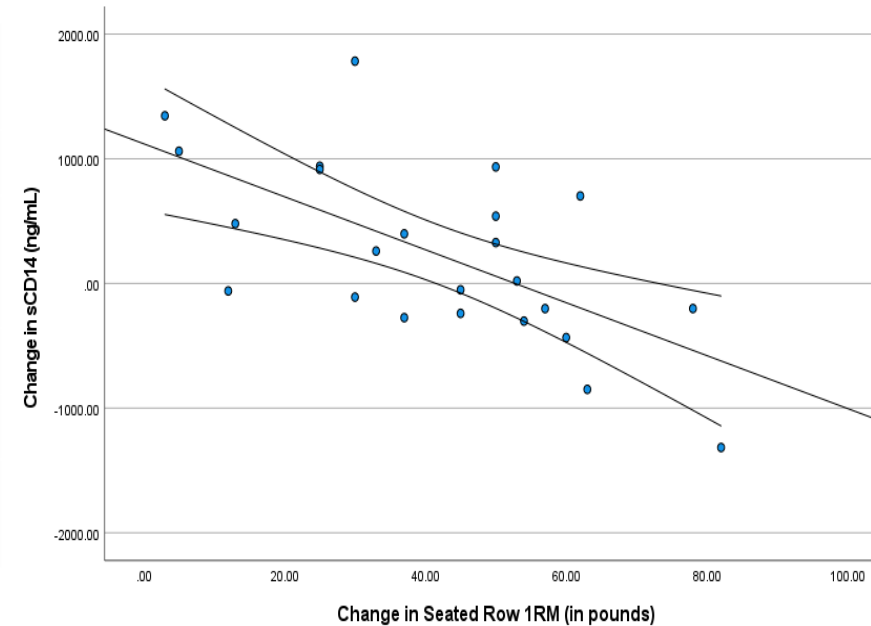


# Greater Change in 1 Repetition Max was Associated with Changes in Brain Volume and Inflammation

Brain Volume



Inflammation



Cooley et al, *in preparation*

- EXS participants had improvements in one rep maximum on multiple exercises

# **Section Summary: What Is Needed to Advance Field Forward**

- Establish ageing cohorts of PLWH and well-matched controls to account for differences in lifestyles and sociodemographic factors.
- Large longitudinal studies with multiple biomarkers are needed to accurately identify biological ageing for different clinical endpoints (mortality or serious non-AIDS events). These studies can help identify heterogeneity seen in PLWH.
- Implement machine learning algorithms to identify an optimal set of biomarkers that could be used in routine clinical practice.
- Develop mechanisms for disseminating optimal screening tests and assessment to HIV care providers around the world.
- Currently there is a push for earlier diagnosis and treatment for HIV but there needs to be adjunctive therapies for improving cognition in PLWH- including cognitive behavioral therapy.
- A prescription for physical activity could be included within comprehensive medical management.

# Overall Conclusions

- A multi-hit mechanism may lead to observed changes in brain function. Changes can occur due to social determinants of health, seroconversion, legacy effects, polypharmacy, and comorbidities.
- Biomarkers (especially neuroimaging) can identify brain dysfunction in PLWH and should be included in future diagnostic criteria.
- HIV and aging affect the brain with the greatest biological changes seen in older PLWH who have detectable VL.
- Large longitudinal studies of PLWH (especially older PLWH) with integrative biomarkers are needed to understand heterogeneity
- Adjunctive therapies (e.g. exercise) should be considered for improving cognition in PLWH.

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*In this lab,*  
**WE BELIEVE**



SCIENCE  
is real



LOVE  
is love



BLACK LIVES  
matter



FEMINISM  
is for everyone



MICROBES  
are cool



IMMIGRANTS  
are welcome

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Contact us if interested in participating in studies

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