Interactive Symposium-02

Monday, February 23, 2026

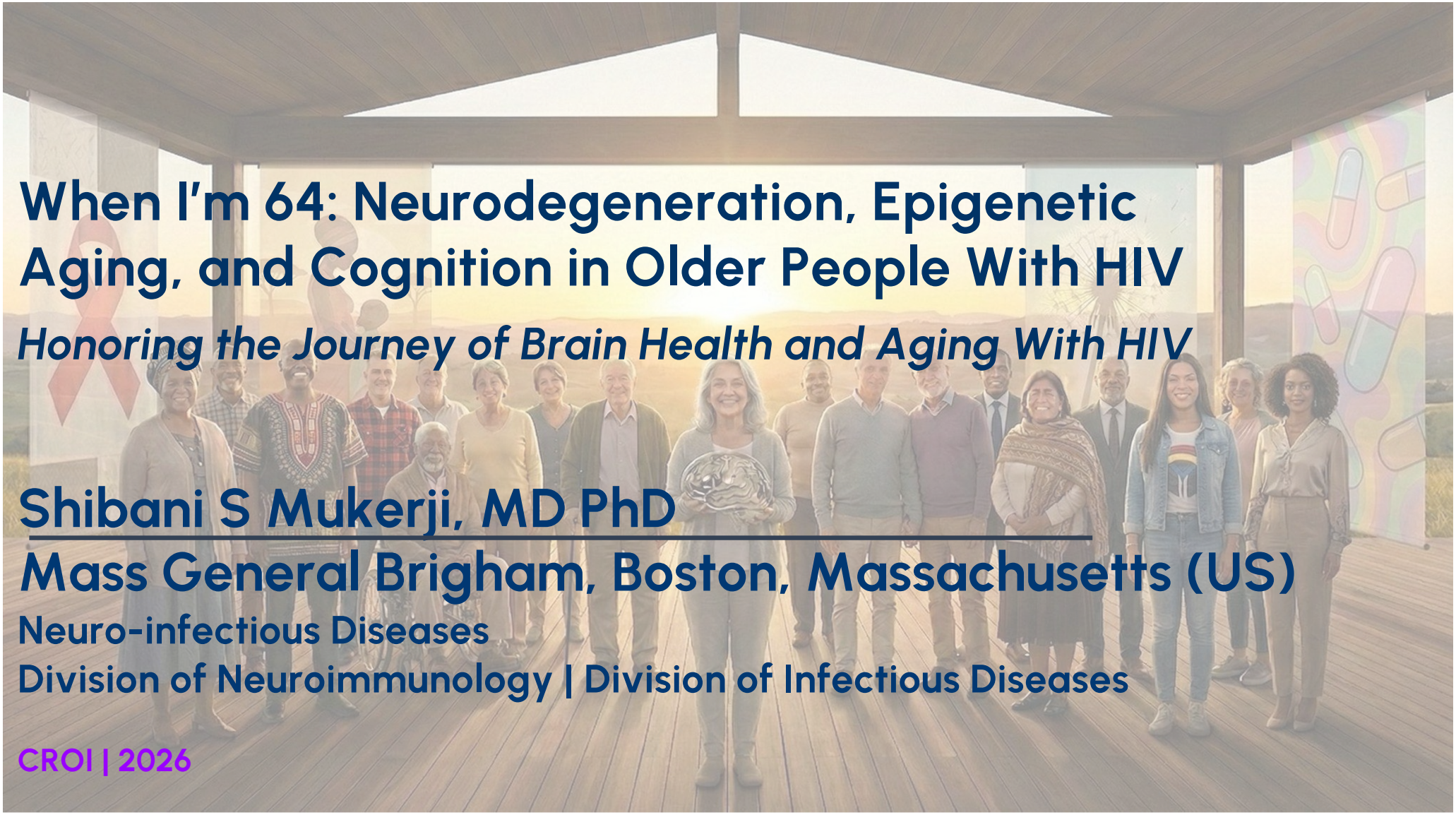
20 - Cognitive Aging in HIV: Clinical Assessment and Management

Shibani S. Mukerji

Massachusetts General Hospital, Boston, MA, USA

Financial Relationships:

Dr Mukerji reported Self: Stock/stock options with Gilead Sciences, Inc.



When I'm 64: Neurodegeneration, Epigenetic Aging, and Cognition in Older People With HIV

Honoring the Journey of Brain Health and Aging With HIV

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Neuro-infectious Diseases

Division of Neuroimmunology | Division of Infectious Diseases

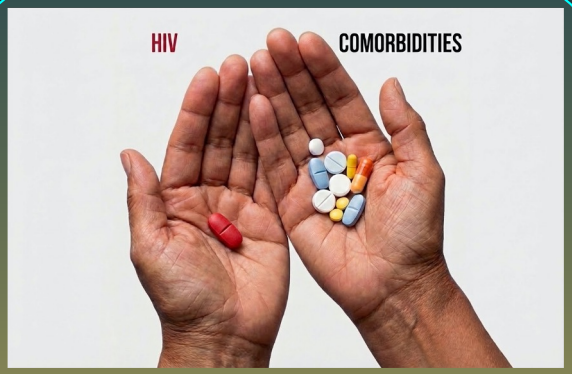
CROI | 2026

Caring for Overlapping Generations of Survivors

Meeting the needs for all persons with HIV

Longest Term Survivor

(lived in an era without therapy)



Long-Term Survivors

(>10 years of living with HIV)

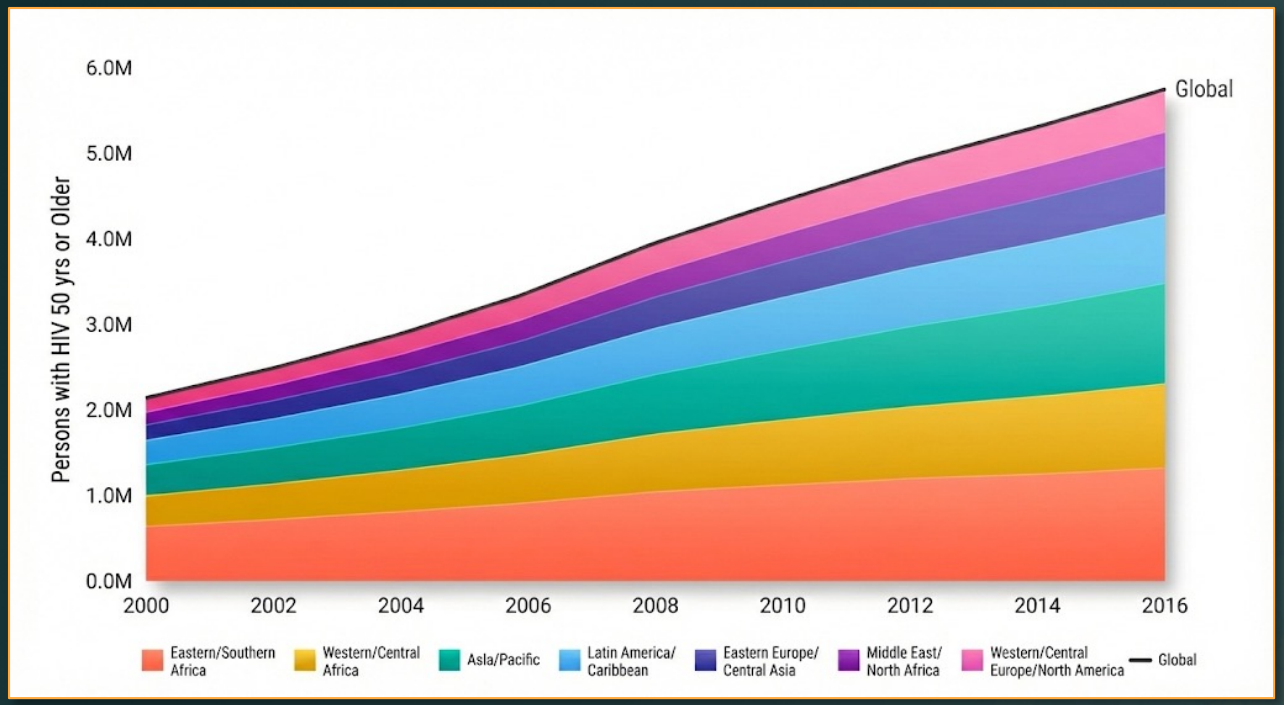
Lifetime Survivors

(perinatally acquired HIV)

The aging HIV population is heterogeneous.
Chronological age-based approaches risk missing individual variation, misallocating resources, and overlooking what people may need

The Scale of HIV Longevity Will Warrant a New Approach

Persons with HIV aged 50 or older increased 2.7× globally (2000–2016)



Waiting for symptoms or signs of dementia cannot serve a population that has tripled.
Brain health care will need to be proactive, systematic, and global, preserving as much neurologic function for as long as possible.

Autenrieth et al. 2020. doi:10.1371/journal.pone.0207005

When I'm 64: Will You Still Need Me, Will You Still...?

Interactive Symposium 02: Making Brain Health Care Work for Persons with HIV

1. Building Brain Health Beyond Treating Disease
   (With a Little Help from My Friends)
2. Delivering Brain Health Where People Receive HIV Care
   (Come Together)
3. Ideas To Implement Brain Research Into HIV Care
   (Revolution)

Brain Health - An Active, Lifelong Conversation

Reactive treatment to proactive optimization across neurologic domains

*A **continuous** state of attaining and maintaining **optimal neurologic function** that supports **physical, mental, and social well-being** throughout life - WHO*

Movement | **Senses** | **Touch & Balance** | **Cognition** | **Emotional**

https://www.nia.nih.gov/health/brain-health/what-brain-health; World Health Organization. (2022). https://www.who.int/publications/i/item/9789240054561

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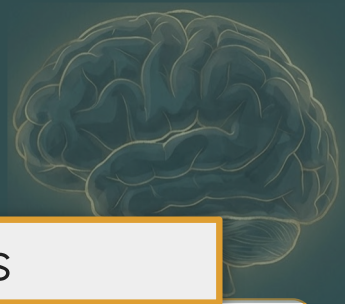
Isabella, 64 y.o. woman

Memory Concerns



Cognitive Symptoms

Misplacing **keys and forgetting names, for the last 1-2 years**
She eventually finds the keys and remembers names later

HIV History

- Diagnosed 1993 (31 years with HIV)
- Nadir CD4 <200, current CD4+ T-cell 373 cells/mm^3
- Virally suppressed >25 years on first-line antiretroviral therapy

Health Risk Factors

Diabetes • Hypertension • Hyperlipidemia * Coronary artery disease
• Chronic pain • Depression • Insomnia

Social Determinants

Economic: Limited fixed income
Social: Estranged from two children, former HIV community advocate

Environmental: Stopped public transit after harassment, no age-appropriate community spaces

If HIV goals are met, how can providers, persons with HIV, and the community optimize neurological function, focusing on what matters most?

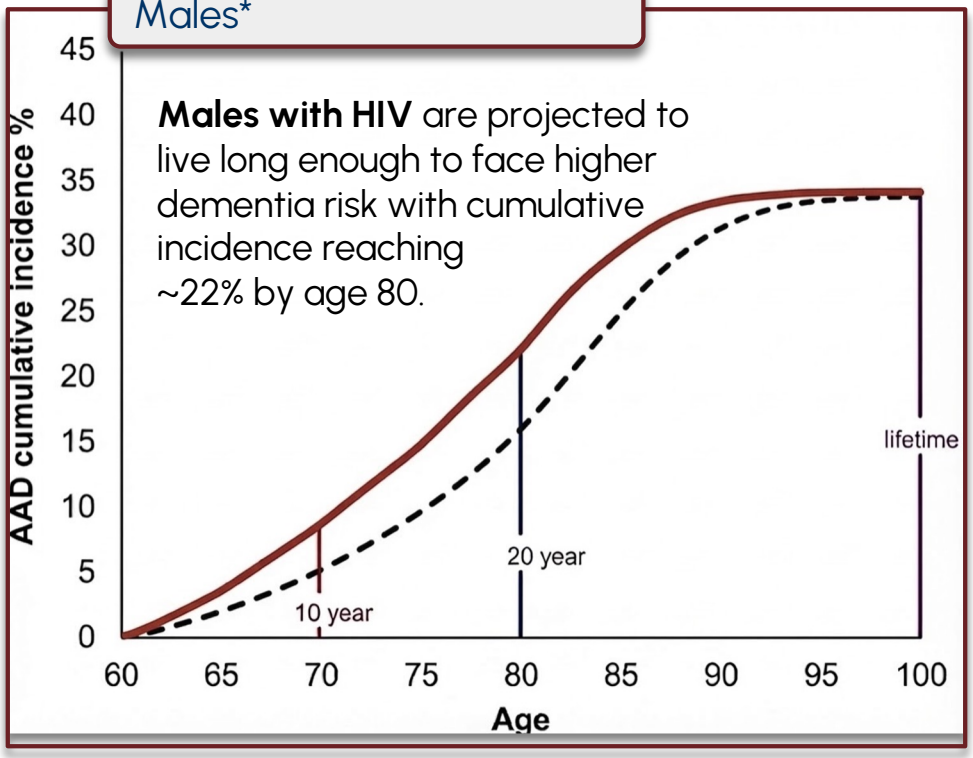
- Stroke Risk and Small Vessel Disease
- Sleep, Pain and Depression with Social Isolation
- Financial, Independence, Care

The Lancet. Neurology. 2024. GBD 2021 Stroke Collaborators.

Brain Health Trajectories Are Not Uniform

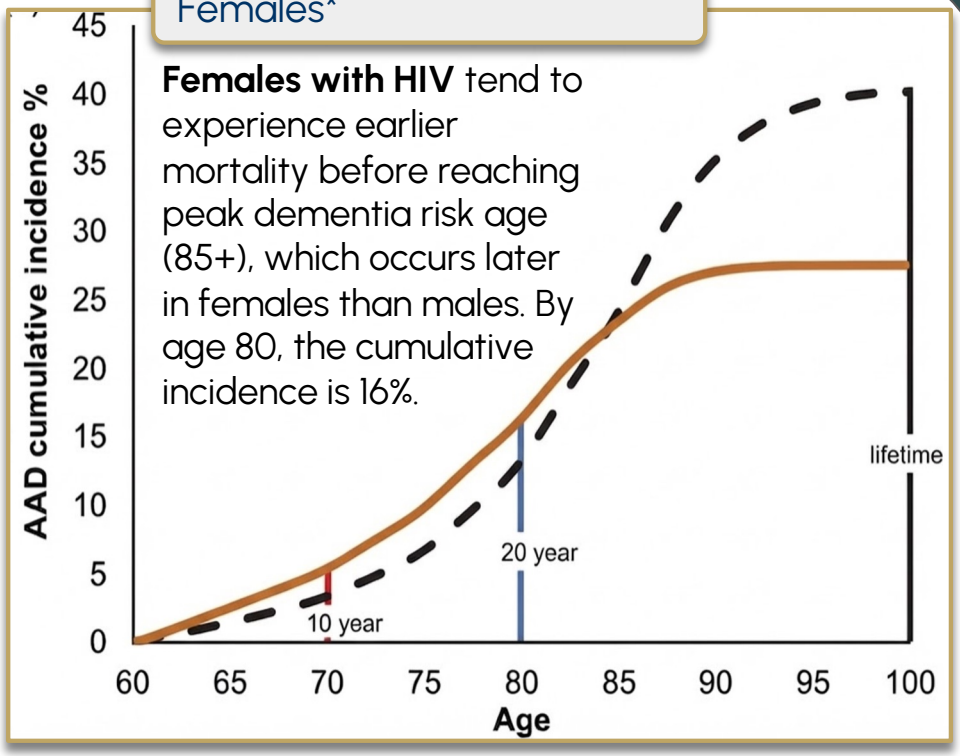
Life expectancy shapes dementia risk and care priorities

Males*



Males with HIV are projected to live long enough to face higher dementia risk with cumulative incidence reaching ~22% by age 80.

Females*



Females with HIV tend to experience earlier mortality before reaching peak dementia risk age (85+), which occurs later in females than males. By age 80, the cumulative incidence is 16%.

PWH

Population

*sex at birth

Hyle et. al AIDS 2022

Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

Pre-clinic | **Symptom Assessment** | **Viral load, T-Cell and ART History** | **Medications & Substance Use** | **Mental Health and Sleep** | **Exam**

- **Some persons hesitate** but want their physician to discuss brain health.
- **Some physicians hesitate** after receiving denials from patients/families, lack of effective tools, difficult to diagnose, other pressing concerns, perceptions of limited treatment *

*A recent survey primary care physicians on views on the underdiagnosis of Alzheimer's Disease, their familiarity with screening methods and using blood-based biomarkers, which are gaining attention and are commercially available in certain regions of the world (Neurology Clinical Practice 2026).

Sabbagh MN, Alzheimers Dement. 2022; Borson S, BMC Prim Care. 2023 BOLD Public Health Center of Excellence on Early Detection of Dementia. (2024) ; Gerontology Society Toolkit for Brain Health https://www.kaerbrain.org/;

Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

Pre-clinic | **Symptom Assessment** | **Viral load, T-Cell and ART History** | **Medications & Substance Use** | **Mental Health and Sleep** | **Exam**

- Harder to learn new things (recipe, new transit route)
- Misplacing items and unable to think back and retrace steps
- Trouble recognizing people they know
- Unexplained coordination or balance challenges, including falls
- Probing for the time course (weeks, months, years)

https://training.alz.org; MemoryHIV.org;

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Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

- HIV-1 viral load, CD4+ T-cell, and nadir
- Time to ART initiation, Time since HIV diagnosis
- Concerns regarding skipped doses or prolonged periods (>12 weeks) with viral loads >200 copies/mL.
- History of Drug Resistance Mutations

- Brain or spinal cord infection or disorders of the muscles and nerves related to HIV.

Alagaratnam J et al. J Virus Erad 2024; Joseph J et all. J Virus Erad 2016; Kincer LP et al, J Clin Ivest 2024

Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

Does benefit of a med (e.g., anticholinergics, gabapentinoids, benzodiazepine) outweigh risks.

1. Deprescribing trial with reminders succeeded without increased harm.
2. R2D2 trial is testing the causal association between deprescribing anticholinergics and cognition

Certain substances have linear or J-shaped dose-response relationships with cognitive impairment stroke, and hospitalization risk.

Justice, Lancet Healthy Longev 2021; Doctor J, HIV Med 2023l; Cooley, AIDS 2021; Kosana, Clin Infect Dis 2024; Campbell, Trials 2024; Lauffenburger, JAMA 2026. clinicaltrials.org (accessed January 2026); Beers Criteria

Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

Emergence or exacerbation of mood disturbances (e.g., depression, apathy), anxiety, personality shifts, or social withdrawal **is a guideline-recommended indicator in cognitive disorders.**

New sleep disturbances, including nightmares, acting out during sleep, breathing issues (such as sleep apnea), or excessive daytime fatigue, can also serve as a clinical biomarker.

*** Use Scales recommended by Guidelines, if unavailable there are scales available in culture appropriate questionaires**

Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

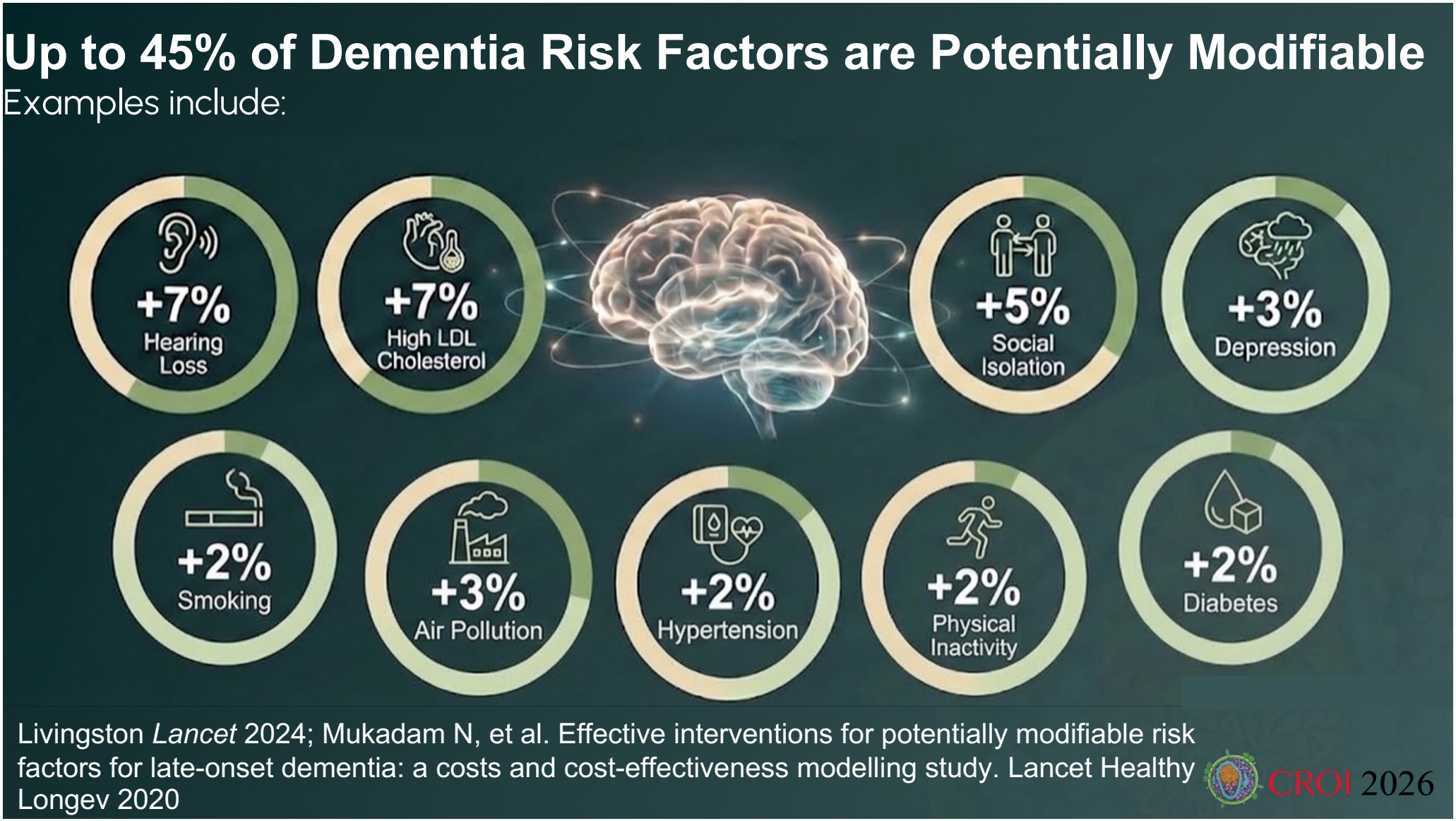
- **Validated Bedside Cognitive Assessment***
- **Neurologic exam** for signs of visual or hearing deficits, tremor, weakness and signs of orthostasis, abnormal movements, timed walking assessment.

*Montreal Cognitive Assessment (MoCA); RUDAS

Valcour CROI (I KEEP FORGETTING: HIV, AGING, AND COGNITIVE DISORDERS) 2019

Up to 45% of Dementia Risk Factors are Potentially Modifiable

Examples include:



Livingston *Lancet* 2024; Mukadam N, et al. Effective interventions for potentially modifiable risk factors for late-onset dementia: a costs and cost-effectiveness modelling study. Lancet Healthy Longev 2020

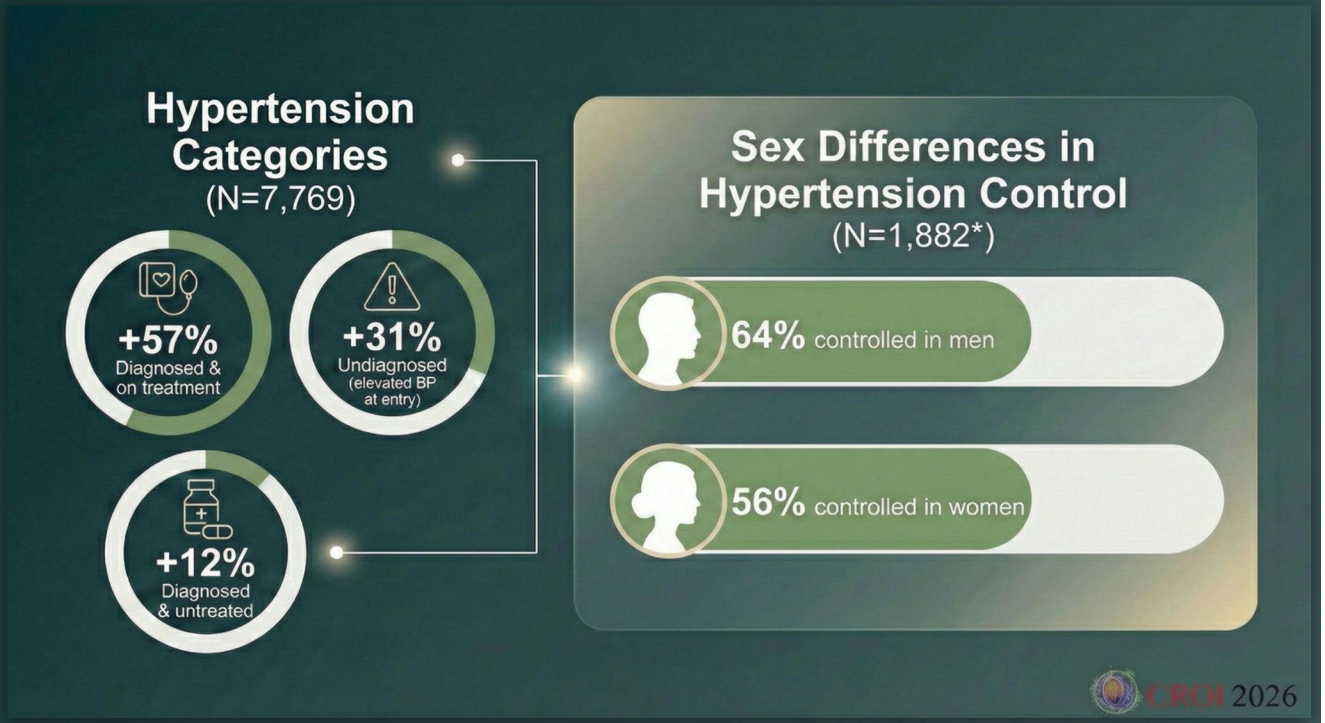
Delivering Brain Health Where People Receive HIV Care

A workflow for primary care

Poster:

A5332/87: High Baseline Prevalence and Suboptimal Control of Hypertension in the REPRIEVE Trial

A5332/84: Incident Hypertension in REPRIEVE;
A5332/88: Characterization of Heterogeneous Statin Benefit in REPRIEVE to Inform Prevention;
A5332/86: Pitavastatin Effects on Lipids in Relation to MACE



Hypertension was more common in women 39% vs. 34%

*Among people diagnosed with hypertension

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Optimizing Today's Brain Health Care – A Tiered Framework

Proactive holistic care and selective escalation when needed

Longitudinal Proactive Brain Health: Having a brain health toolkit, understanding priorities, explaining rationale, targeting brain health risk factors early. When available or needed, B12, Thyroid, Glucose Monitoring and Syphilis.

Blood pressure: 145/90, LDL-C 120, Wakes up 3 hours after sleeping with racing thoughts and nerve pain, MOCA 24/30 (errors in attention, cube drawing, and subtraction, not memory recall). She feels tired and in pain but no specific area is weak. She struggles walking 25m.

Tier 2: Lumbar Puncture or Imaging if:

- Rapid decline (< 6 months)
- Focal neurologic findings
- Diagnostic uncertainty after basic workup.

Tier 3 Referral if:

- Neurology: unexplained worsening
- Neuropsychologist: diagnostic uncertainty, cognitive strengths/weaknesses, longitudinal assessment

European AIDS Clinical Society; British HIV Medical Association; Australasian HIV Management Guide; South African HIV Clinicians Guide

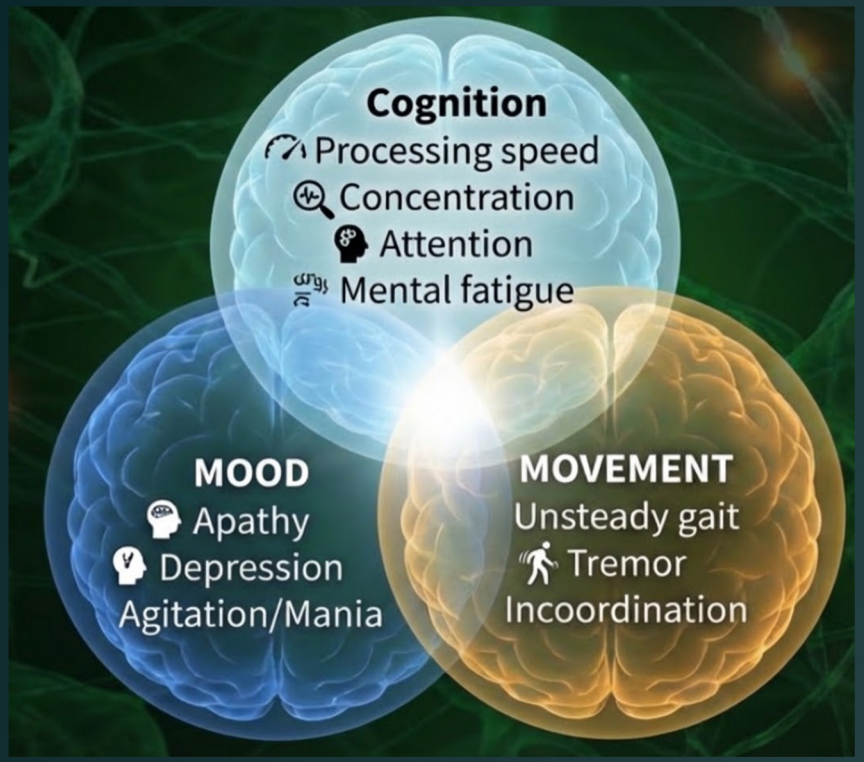
Ideas To Implement Brain Research Into HIV Care

....A Few Early Moves

The Treatable Traits Approach

Moving from single labels to specific, actionable interventions for trials

Optimize continual care with access to ART



Vascular Traits

- **Traits:** Hypertension, diabetes, hyperlipidemia
- **Outcomes**: Stroke, subcortical vascular impairment, falls.
- **Actions:** BP control (<130/80), statin, antiplatelet if indicated, diabetes optimization, and smoking cessation

Insomnia

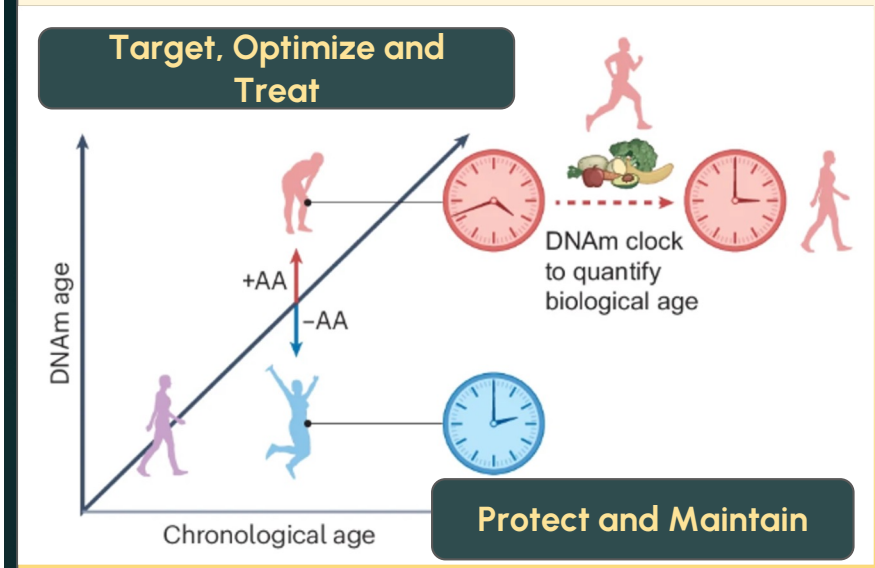
- **Traits:** Poor sleep quality disrupting activities daily living
- **Outcomes:** Untreated sleep apnea, CNS sedating medications, worsening depression
- **Actions:** Sleep study, CPAP, sleep behavioral therapy

Social Isolation

- **Traits:** Loss of community, estrangement, environmental barriers
- **Outcomes:** Depression, future dementia
- **Actions:** Multimodal Intensive Therapy: Group visits, memory café, hearing aids

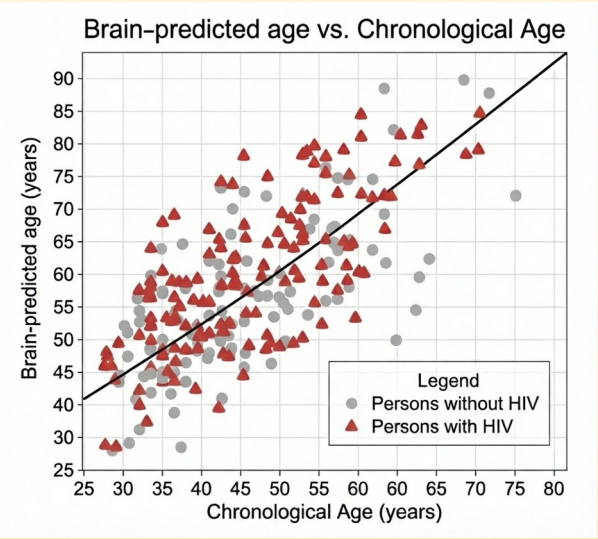
Translating Biological Age Biomarkers to Brain Health Practice

Can AI-derived biological age predict decline and serve as proximate endpoints in trials?



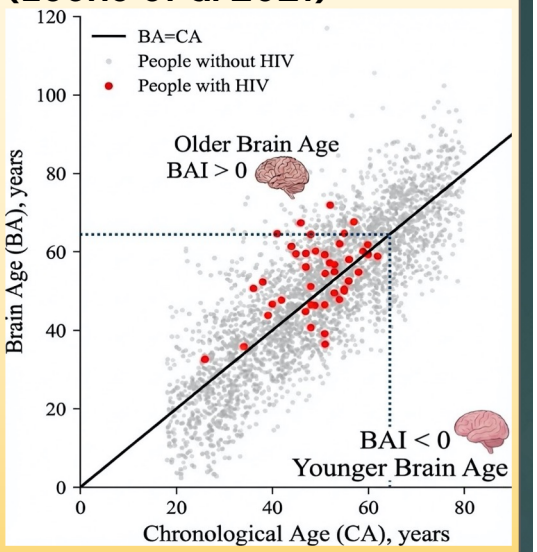
Blood Biological Age - Epigenetics

(Cole et al 2017)



Brain Age – MRI

(Leone et al 2021)



Brain Age - EEG

1. **Make models interpretable** (understand what drives predictions, not just black-box outputs)
2. **Validate as proximate biomarkers** (show they predict clinical endpoints in longitudinal cohorts)
3. **Demonstrate clinical utility** (prove interventions that improve biomarkers also improve outcomes)

Implementation Research Strategies: Evidence to Practice

Ensuring lifespan gains from ART are matched by brain health in the last decades

Study: Proactive Care Model Implementation

Question:
Does shifting from reactive to proactive brain health care improve patient, clinical and economic outcomes?

NIMH Neuro Working Group

Study: Innovative Trial Designs for Brain Health

Question:
Can novel trial designs provide real-time, clinically meaningful benefit?

NIMH Neuro Working Group

Study: Evidence-Based Brain Health Messaging

Question:
How do we implement trusted, evidence-based brain health resources that serve diverse communities globally?

Cysique et al *Lancet Healthy Aging* 2024 (NeuroHIV and Aging Advocacy Group)

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Key Takeaways

1. We Can Prevent Nearly Half of Dementia, But Only If We Act Intentionally on Multiple Modifiable Risk Factors.

2. HIV Primary Care Can Deliver Effective Brain Health Care at Scale Without Delays in Waiting for Specialists.

3. We Can Strengthen Brainspan By Studying How Bundled Viral Suppression And Comprehensive Brain Health Support Improve Outcomes In Clinical Trials, Real World Care and Community Trust.

It's OK To Stand Up And Sing...In Fact Your Doctor May Prescribe It

When I get older, losing my hair
Many years from now,
Will you still be sending me a valentine,
birthday greetings, bottle of wine?

If I'd been out till quarter to three,
Would you lock the door?
Will you still need me, will you still feed me,
When I'm sixty four? Ooh

You'll be older too.
Ah, and if you say the word,
I could stay with you.

I could be handy mending a fuse
When your lights have gone.
You can knit a sweater by the fireside,
Sunday mornings, go for a ride.

Doing the garden, digging the weeds,
Who could ask for more?
Will you still need me, will you still feed me,
When I'm sixty four?

I welcome your feedback on brain health implementation after the session, if not discussed during the moderated session. I can **stay in person** until 6:15pm.

My thanks to Bridgette Picou, Elena Beideck, and David Moore for their review of these slides.