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Fostering cognitive and mental health in aging people with HIV

while prioritizing the community

and lived experience perspectives

Overview of Neurocognitive health in aging people with HIV: Current and future treatments for brain health

I acknowledge the Traditional Owners of the land on which we meet today,
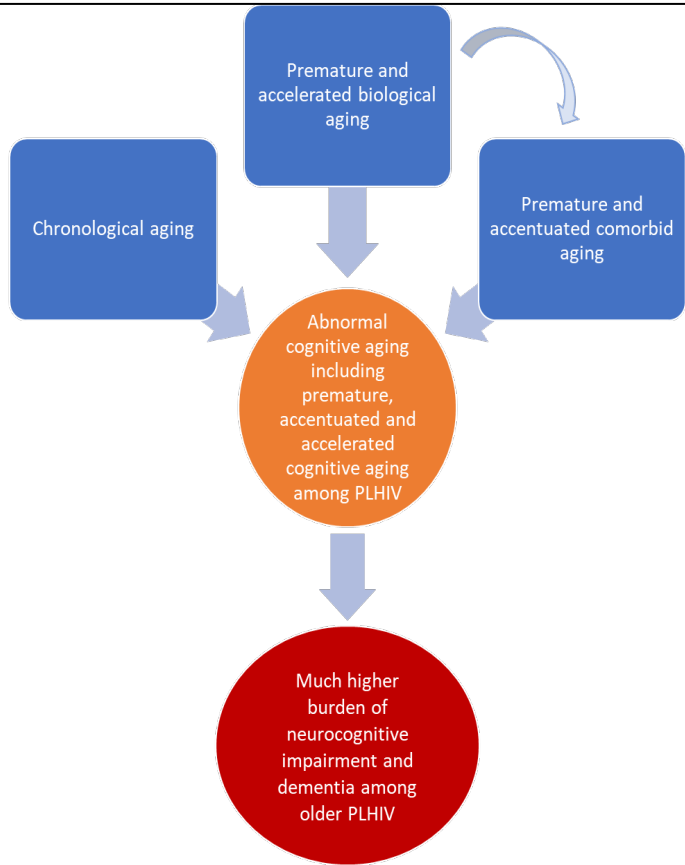
The Yuggera and Turrbul people and pay my respects to Elders past and present.

Overview

- The problem:
    - Epidemiology evidence
    - Neuropathology evidence

- The cause(s)

- The solution:
    - Now
    - (Near) Future

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The Problem

Premature and accelerated biological aging

Chronological aging

Premature and accentuated comorbid aging

Abnormal cognitive aging including premature, accentuated and accelerated cognitive aging among PLHIV

Much higher burden of neurocognitive impairment and dementia among older PLHIV

(a)

prevalence by country (%)

≥ 60
50 - 60
40 - 50
30 - 40
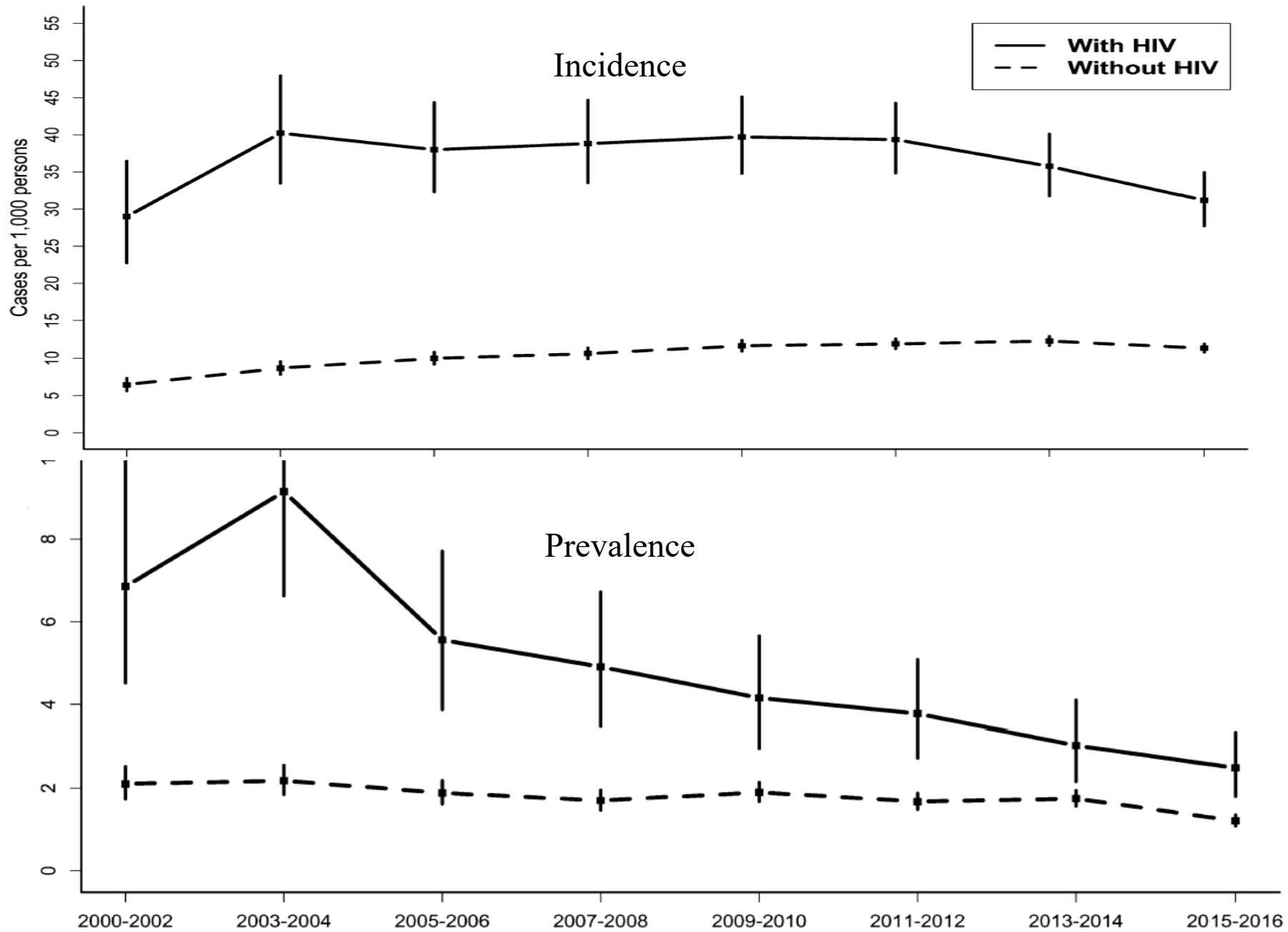< 30
no studies

Cognitive decline:

Aging:
 premature,
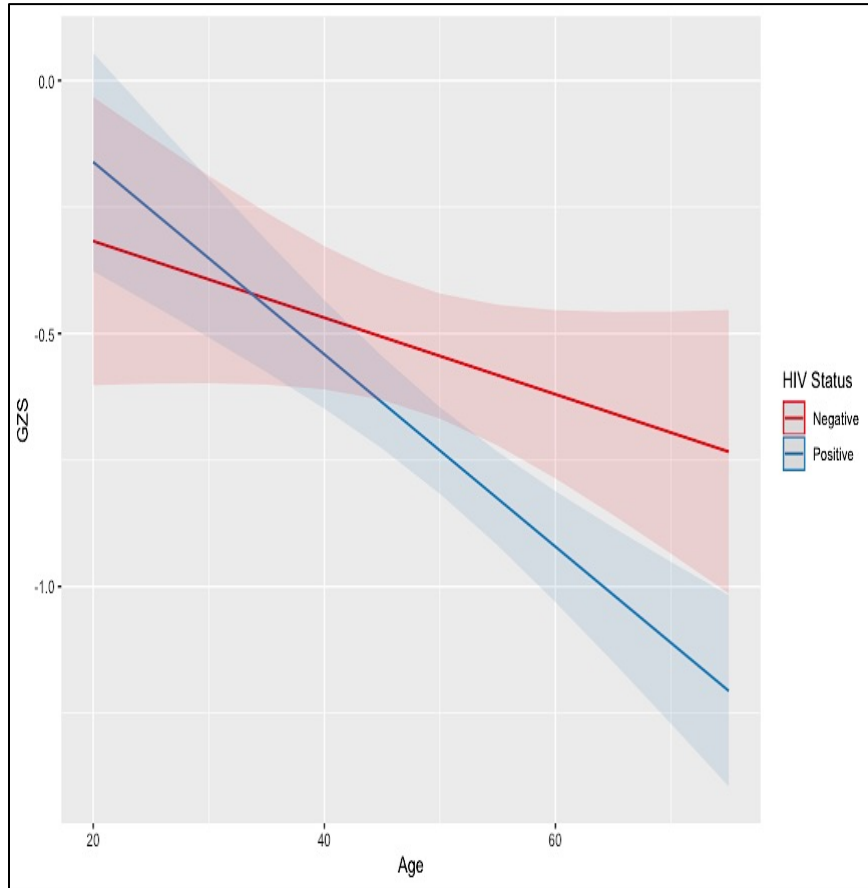accelerated and accentuated

Aging associated comorbidities
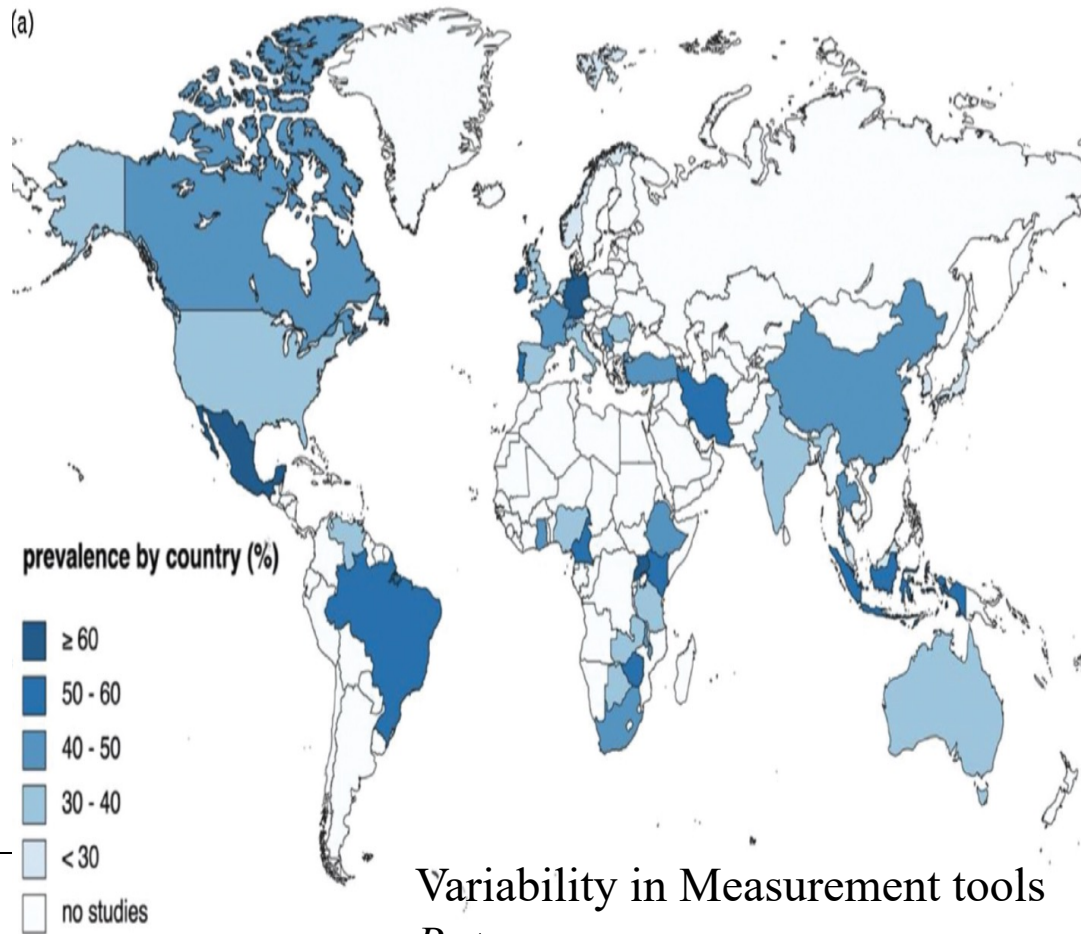
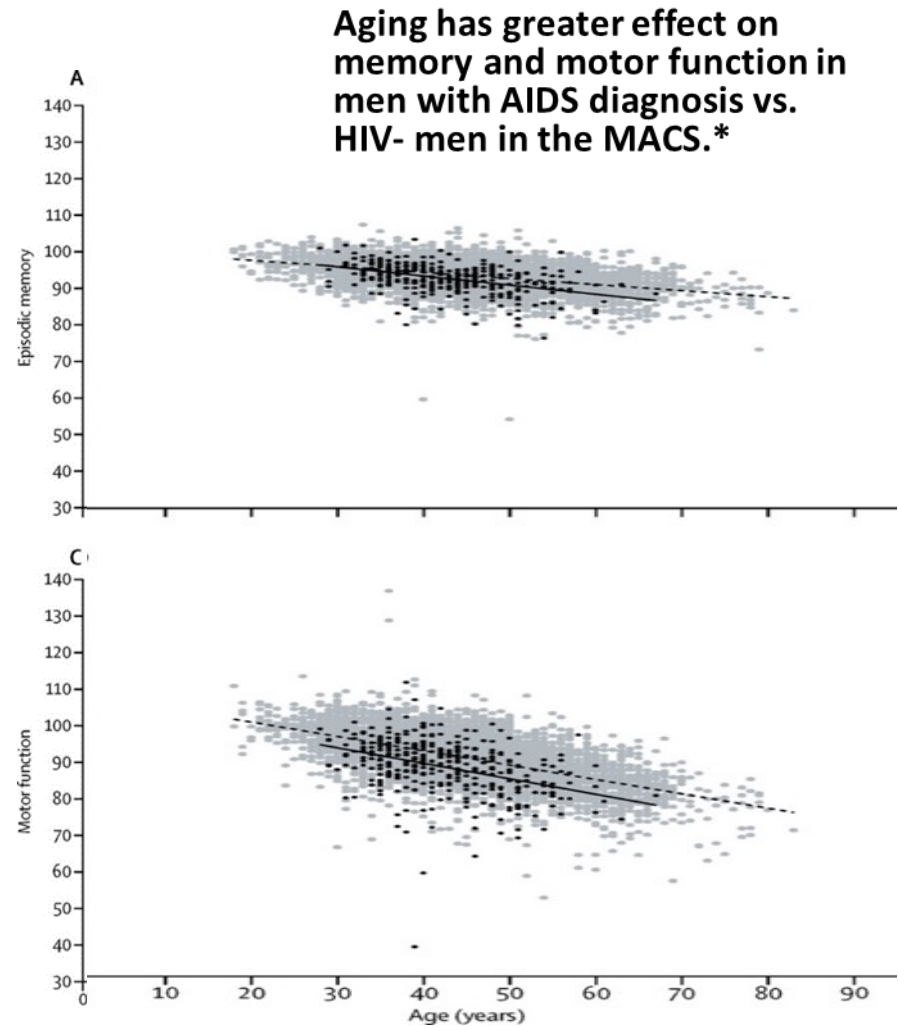Variability in Measurement tools
But
Variability in health equity

Keng et al AIDS 2023

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Incidence
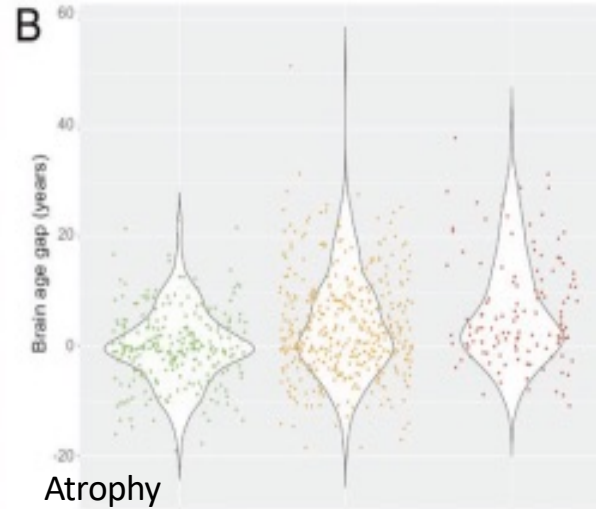
Prevalence

Legend: With HIV (solid line), Without HIV (dashed line)

Y-axis (top): Cases per 1,000 persons

X-axis: 2000-2002, 2003-2004, 2005-2006, 2007-2008, 2009-2010, 2011-2012, 2013-2014, 2015-2016

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Lam et al AIDS 2022

HIV and Premature Cognitive Aging

Aung et al HIV Med 2020

Aging has greater effect on memory and motor function in men with AIDS diagnosis vs. HIV- men in the MACS.*

Goodkin et al., *Lancet HIV,* 2017

A

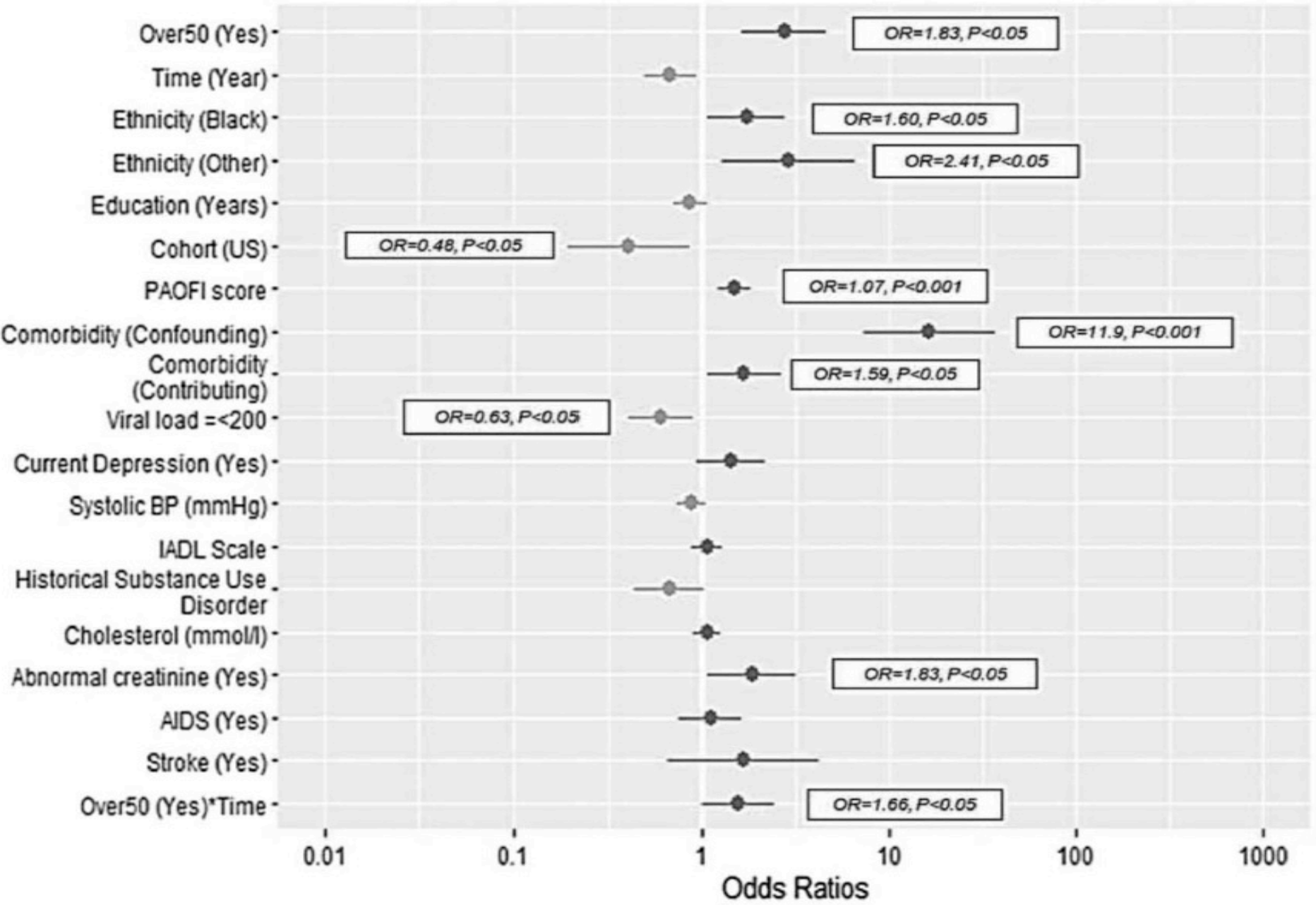**MRI abnormalities indicate premature brain aging and correlate with neuropsychologcal performance**

Atrophy
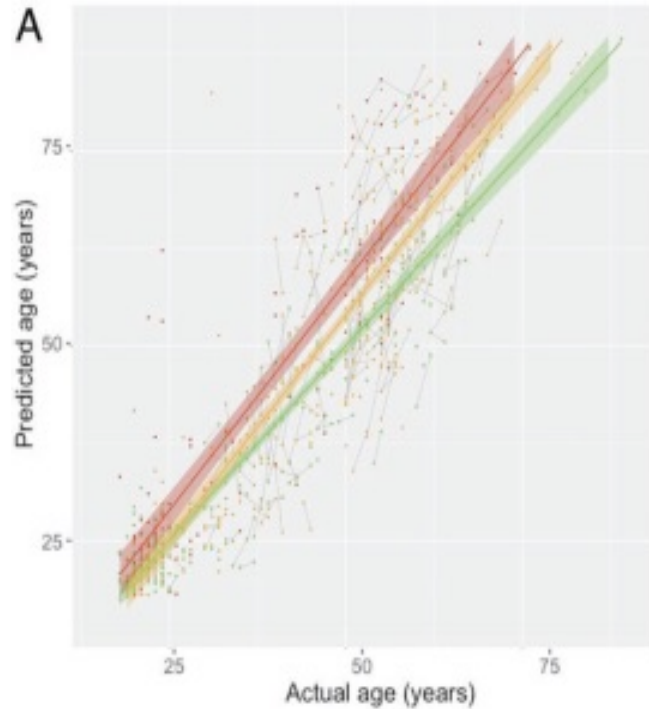
Cerebral blood flow

Group
HIV- controls
PWH with UVL
PWH with DVL

Petersen et al CID 2021

The Cause(s)

Forest plot of odds ratios. Variables (top to bottom): Over50 (Yes) OR=1.83, P<0.05; Time (Year); Ethnicity (Black) OR=1.60, P<0.05; Ethnicity (Other) OR=2.41, P<0.05; Education (Years); Cohort (US) OR=0.48, P<0.05; PAOFI score OR=1.07, P<0.001; Comorbidity (Confounding) OR=11.9, P<0.001; Comorbidity (Contributing) OR=1.59, P<0.05; Viral load =<200 OR=0.63, P<0.05; Current Depression (Yes); Systolic BP (mmHg); IADL Scale; Historical Substance Use Disorder; Cholesterol (mmol/l); Abnormal creatinine (Yes) OR=1.83, P<0.05; AIDS (Yes); Stroke (Yes); Over50 (Yes)*Time OR=1.66, P<0.05.

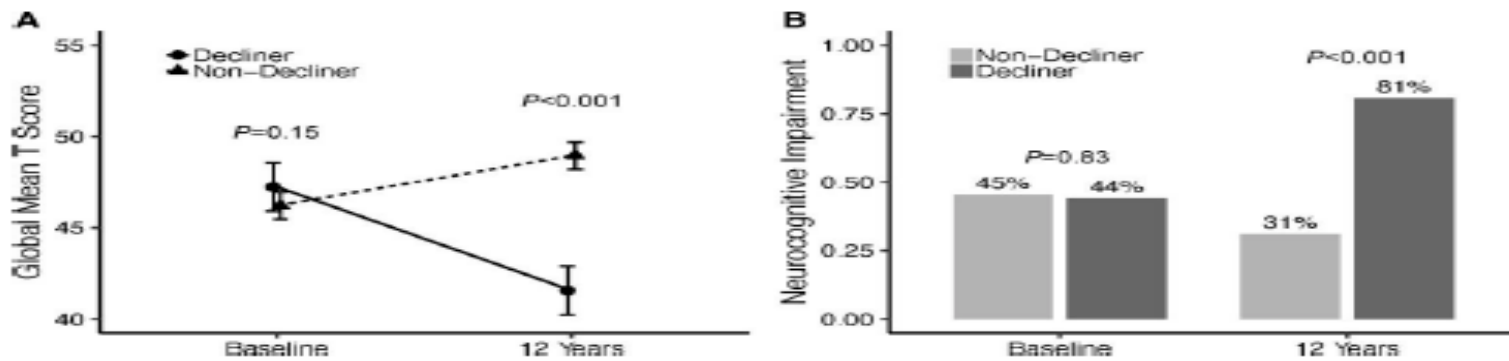Brew July 23, 2023

Aung et al 2022

Figure 1 Change by decliner status. (A) Global T-score by decliner status at baseline and 12 years (values are mean and 95% confidence interval). (B) ...al neurocognitive impairment by decliner status at baseline and 12 years (values are observed proportions).

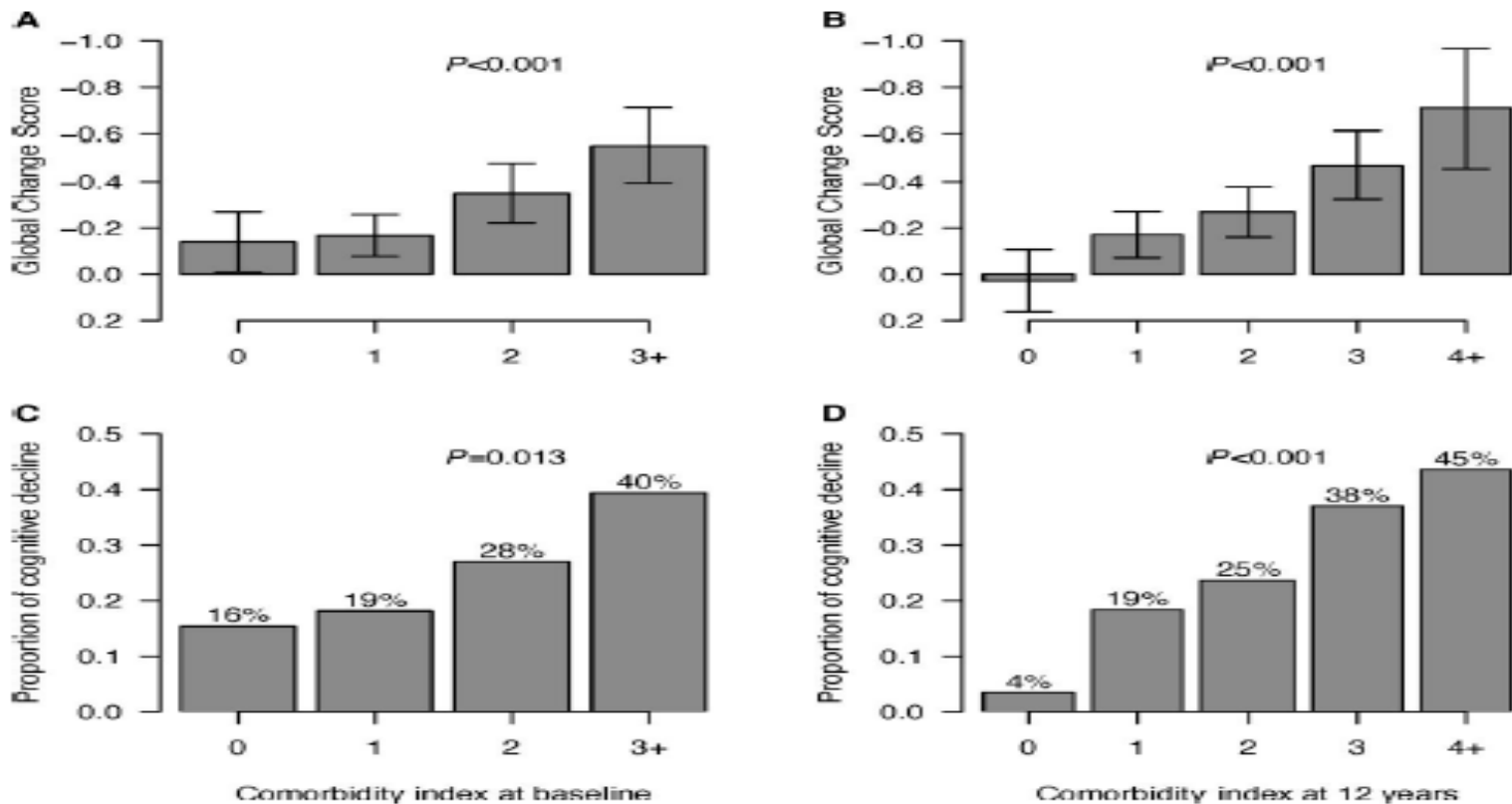...re 2 GCS and decliner status by comorbidity indices at baseline and at 12 Years. (A) GCS by number of comorbidities at baseline. (B) GCS by number ...morbidities at 12 years. (C) Proportion of decliners by number of comorbidities at baseline. (D) Proportion of decliners by number of comorbidities ... years. Values in A and B are mean and 95% confidence intervals. In C and D, values are proportions.

Heaton et al Brain 2023
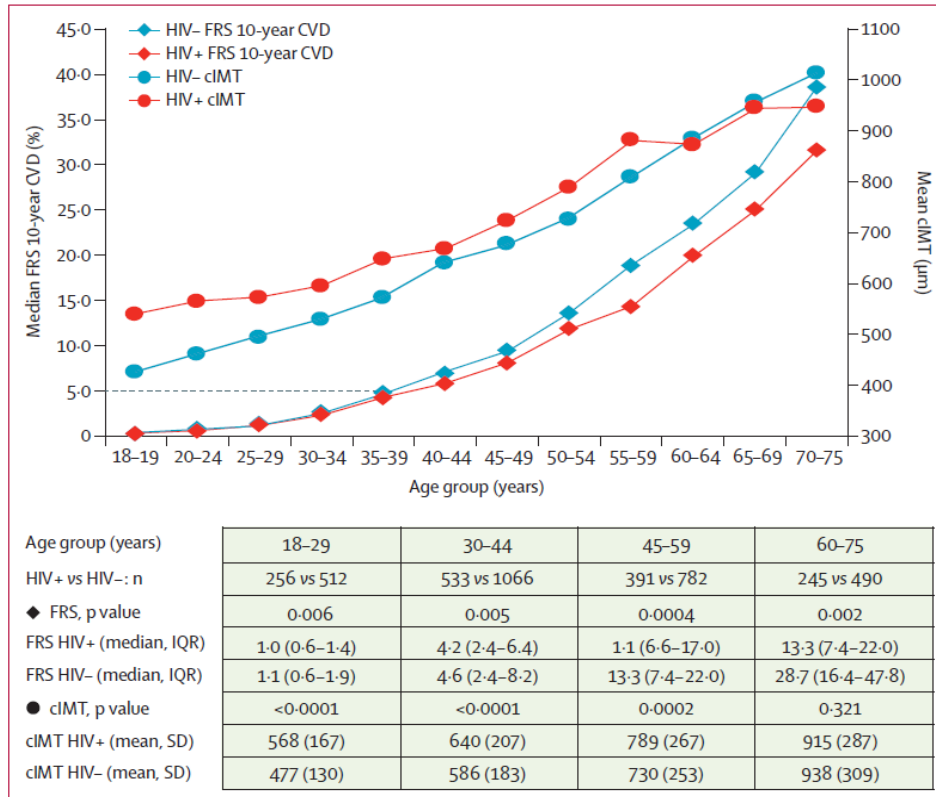
Accelerated Cerebrovascular Disease in HIV

Figure 2: Mean cIMT estimates (SD) and median FRS (IQR) across age groups in HIV-positive and HIV-negative participants

p values compare the FRS and cIMT values between HIV-positive and HIV-negative participants across four age groups (18–29 years, 30–44 years, 45–59 years, and 60–75 years) using t test and Wilcoxon rank-sum test when appropriate. FRS=Framingham risk score. cIMT=carotid intima-media thickness. HIV+=HIV positive. HIV-=HIV negative. CVD= cardiovascular disease.
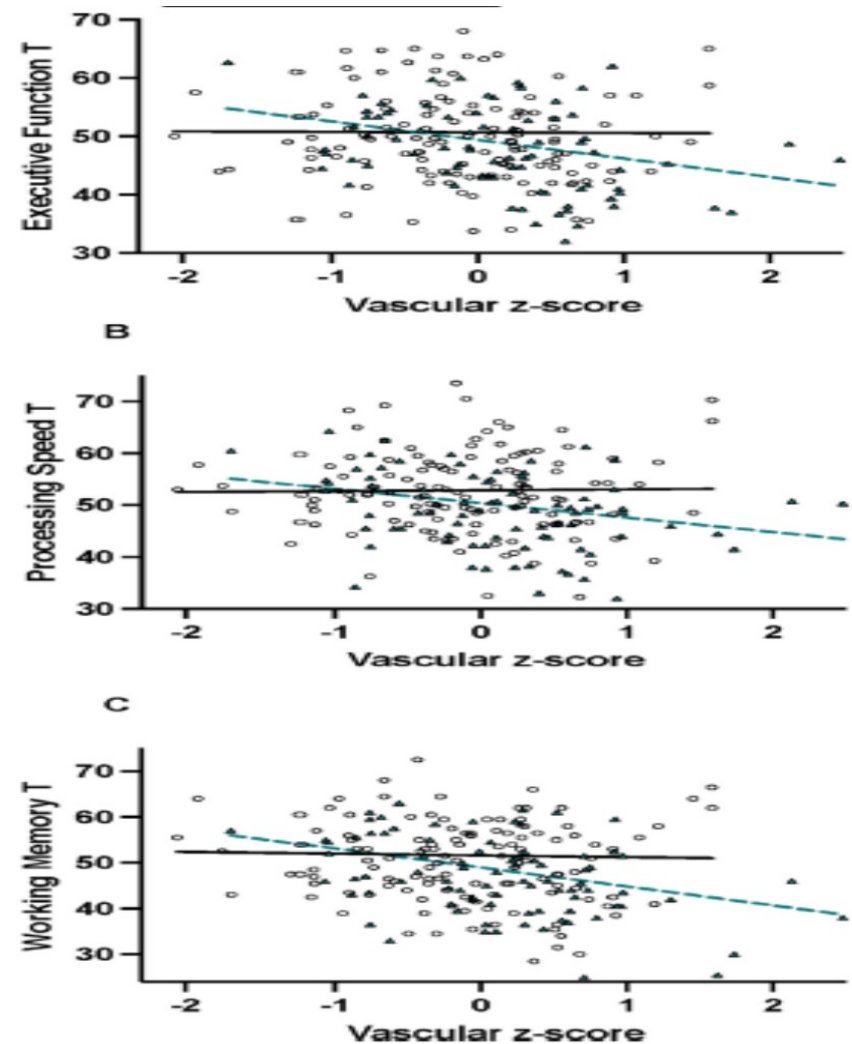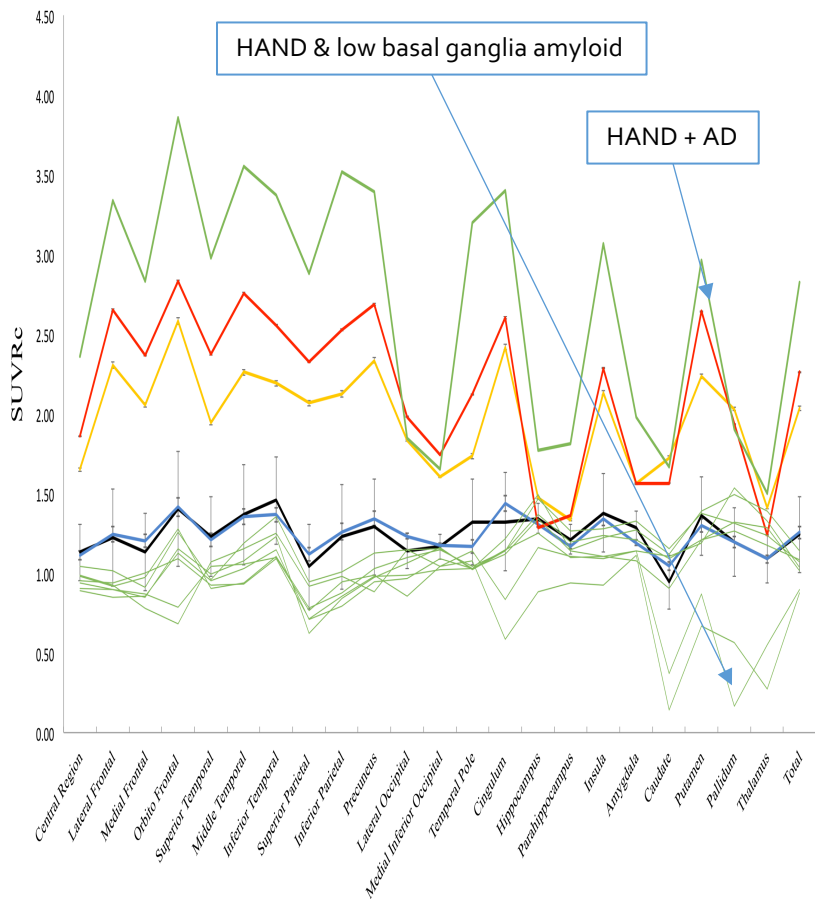
Lin et al Lancet HIV 2019

Saloner et al Brain Behav Imm 2022

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Amyloid deposition in HIV

Amyloid Burden
in chronic HAND
compared to the
general
population

HAND & low basal ganglia amyloid
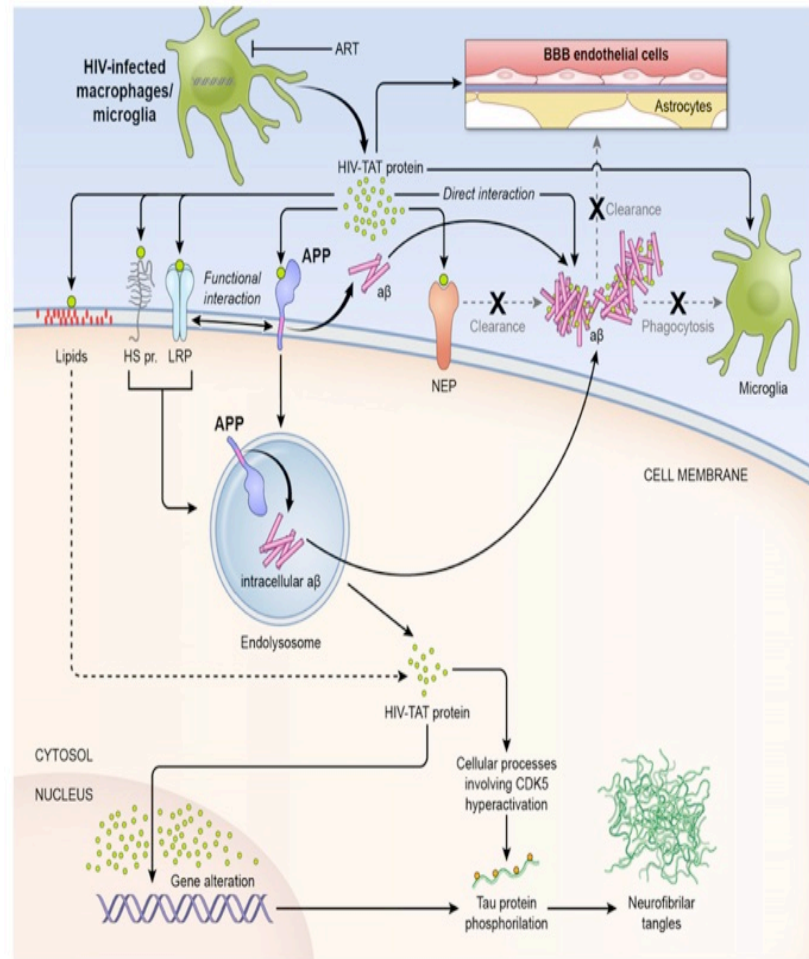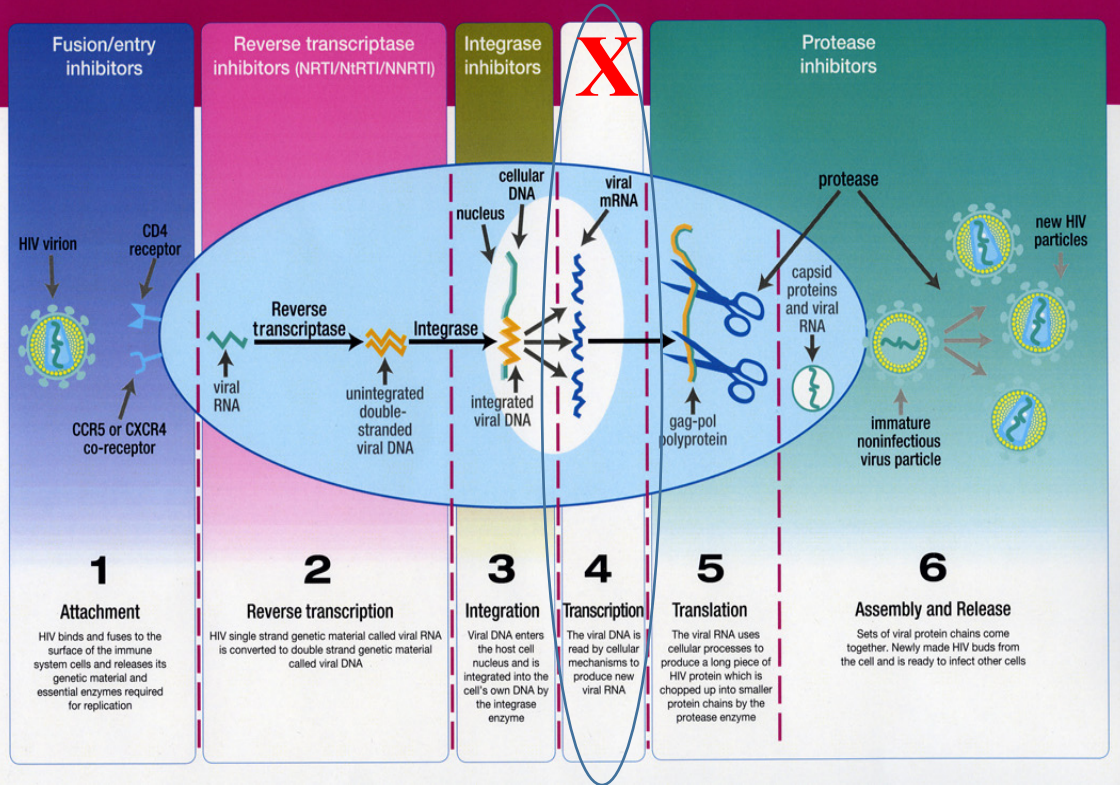
HAND + AD

Howdle et al Neurol Neuroimm Neuroinflamm 2020


Figure 3. Model of interaction of Tat with Aβ and Tau.

Hategan et al J Nvirol 2019

HIV replication cycle with sites of drug action

Fusion/entry inhibitors

Reverse transcriptase inhibitors (NRTI/NtRTI/NNRTI)

Integrase inhibitors

X

Protease inhibitors

HIV virion

CD4 receptor

CCR5 or CXCR4 co-receptor

cellular DNA

nucleus

viral mRNA

Reverse transcriptase

Integrase

viral RNA

unintegrated double-stranded viral DNA

integrated viral DNA

gag-pol polyprotein

protease

capsid proteins and viral RNA

new HIV particles

immature noninfectious virus particle

1

Attachment

HIV binds and fuses to the surface of the immune system cells and releases its genetic material and essential enzymes required for replication

2

Reverse transcription

HIV single strand genetic material called viral RNA is converted to double strand genetic material called viral DNA

3

Integration

Viral DNA enters the host cell nucleus and is integrated into the cell's own DNA by the integrase enzyme

4

Transcription

The viral DNA is read by cellular mechanisms to produce new viral RNA

5

Translation

The viral RNA uses cellular processes to produce a long piece of HIV protein which is chopped up into smaller protein chains by the protease enzyme

6

Assembly and Release

Sets of viral protein chains come together. Newly made HIV buds from the cell and is ready to infect other cells
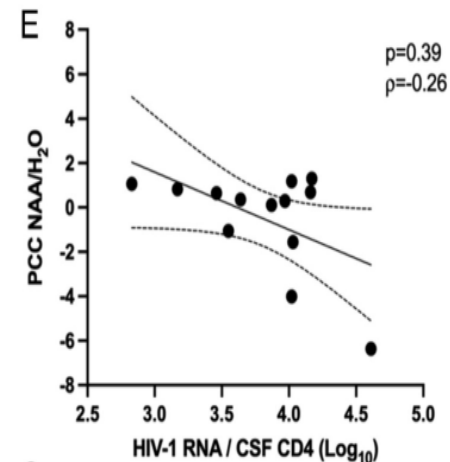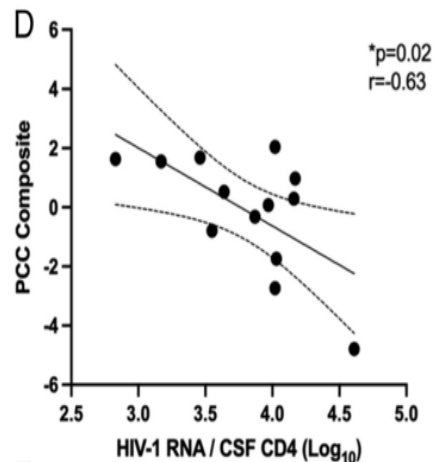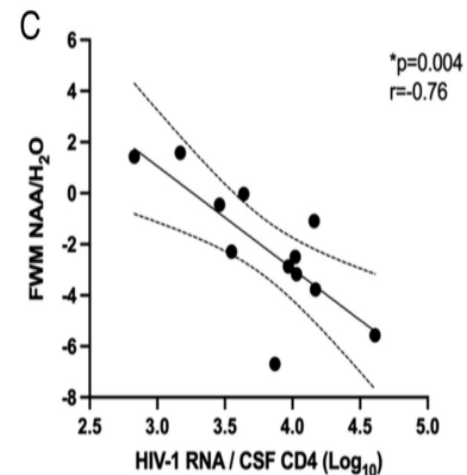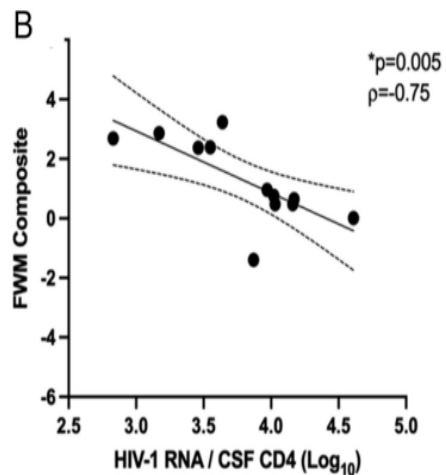
HIV DNA and RNA detectable in cerebrospinal fluid cells during long-term suppressive ART and relation to brain injury

Median ART duration = 8.6 years

Suzuki et al PNAS 2022
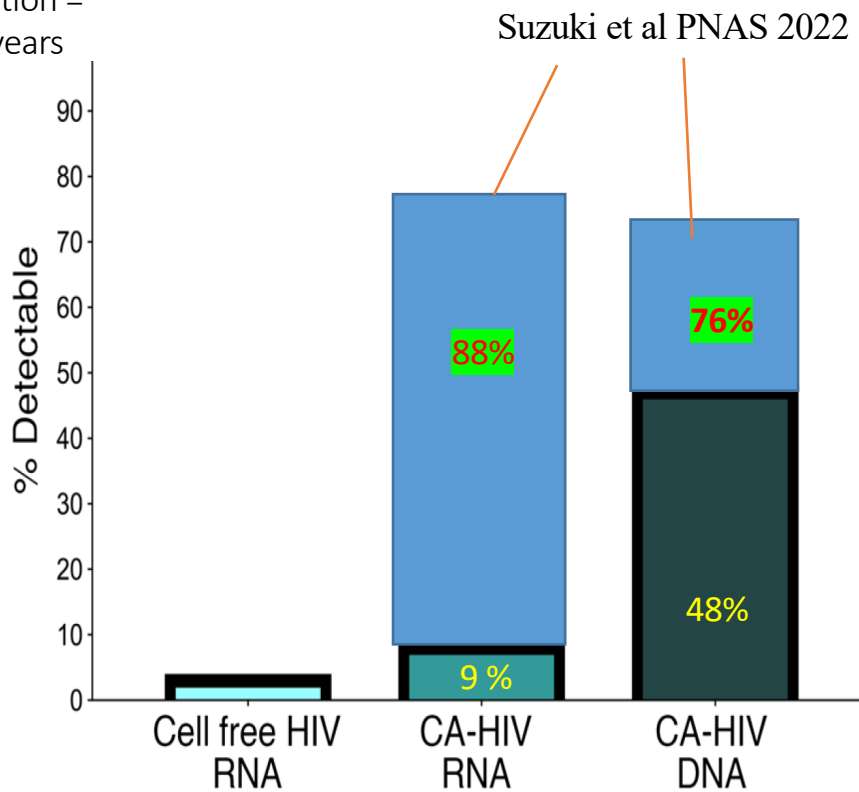
Spudich et al JCI 2019

Suzuki et al PNAS 2022

The Solution: Now

How?

Principles: <u>Prevention/early detection</u> and optimal treatment

- **(Treat to viral suppression)**

- **Screen for comorbidities (incl depression) regularly**

- **Screen for HAND regularly:**

  – **Remember to avoid "Don't ask don't tell"……**

  – **Corroborate (Two ask strategy)**

  – **Tools: MoCA etc**

Framework:

- **Multidisciplinary incl geriatrics**

- **Aim for STR and reduce polypharmacy**

- *Provide support and engagement*

- *RCTs to prove efficacy and health economic benefit for embedded funded care*

Table 4 Recommendations for Future Research

Recommendations for Future Research Derived from Included Studies

- Include a control group (Bitas et al., 2019)
- Include participants of diverse ages in evaluations (e.g., 'the oldest-old') (Bitas et al., 2019) to help determine who would benefit from services the most (Greene et al., 2020), include comprehensive geriatric assessments (Bitas et al., 2019; Levett et al., 2020)
- Use Delphi approaches to gain consensus on how issues of ageing should best be addressed in the context of HIV (Cresswell et al., 2017)
- Identify strategies for ensuring funding within the context of model spread and sustainability, including differences that exist in single-payer systems compared to multi-payer systems (Davis et al., 2022; Schmalzle et al., 2022)
- Include more patient-reported outcomes, including self-reports of health (Greene et al., 2018; 2020) and the perspectives of surrogate decision-makers (Schmalzle et al., 2022)
- Explore implementation differences in urban and rural settings (Greene et al., 2020)
- Conduct analyses of symptom relief, such as, depressive symptom relief over longer-term follow-up (e.g., 4-month and 8-month follow-up) (Heckman et al., 2010; 2017)
- Include outcomes related to mobidity and mortality in studies (Ruiz et al., 2010)
- Explore opportunities to foster collaboration with local governments, insurers, and foundations to co-develop and test novel programs (Seigler et al., 2018)

Kokorelias et al BMC Geriat 2023

Silver Clinic: protocol for a feasibility randomised controlled trial of comprehensive geriatric assessment for people living with HIV and frailty

Natalie St Clair-Sullivan ,[1,2] Katherine Bristowe,[3] Zoe Adler,[4] Stephen Bremner,[1] Richard Harding ,[3] Thomas Levett,[1] Matthew Maddocks,[2] Gary Pargeter,[5] Jonathan Roberts,[4] Deokhee Yi ,[6] Jaime Vera[1]

BMJ Open 2023

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The Solution: (Near) Future

What?

- **Novel HIV drugs (transcription inhibitors):**
  - Interact with eradication strategies that use" block and lock" approach

- **Integrate "wearable" data into clinical management**

- **Formalised multidisciplinary clinics with strong geriatric input**

Conclusions

- **Cognitive impairment in people aging and living with HIV cannot be ignored**

- **There are opportunities for better care and management:**
  - **Implementation of interventions for known risk factors**
  - **Structured care through multidisciplinary clinics with geriatrics**

- **There are two potential "catalysts" to facilitate advances:**
  - Improvement in Alzheimer management → "spill over" to HIV
  - Progress in block and lock HIV treatment strategies → "spill over"

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