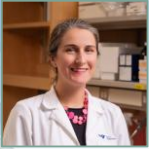


It's Not (Just) the Virus: Cognitive Aging in People With HIV



Shelli Farhadian, MD, PhD
 Associate Professor of Medicine
 Division of Infectious Diseases
 Yale School of Medicine
 New Haven, CT



1

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years

Dr Farhadian reported no relevant financial relationships with
 ineligible companies. (Updated September 18, 2026)

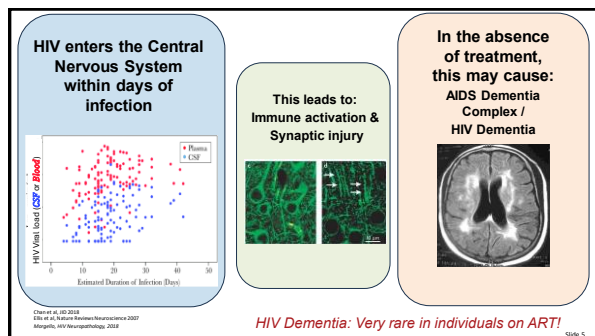
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Learning Objectives

After attending this presentation, learners will be able to:

- Explain why clinically significant cognitive impairment persists in people with HIV in the antiretroviral era
- Apply a practical, modifiable risk-focused approach to older adults with HIV and cognitive complaints
- Describe current and emerging strategies to protect brain health in people with HIV

3



5

NOW: A more common case

58-year-old man with long-standing HIV presents with several years of memory problems.

Slide 6

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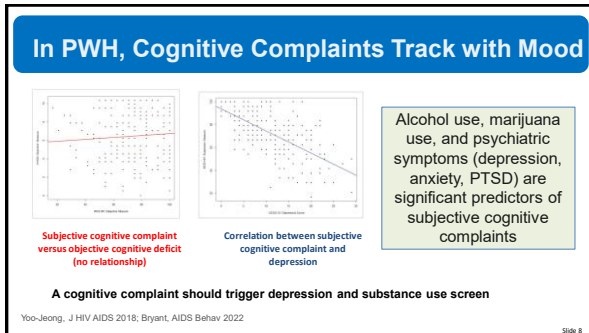
Audience Response Question #1

True or false: In people with HIV, the severity of cognitive complaints closely reflects performance on objective cognitive testing.

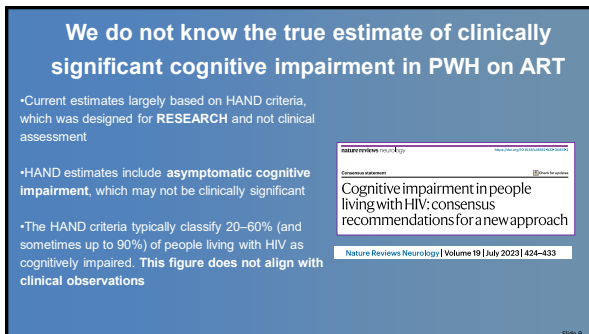
A. True
B. False

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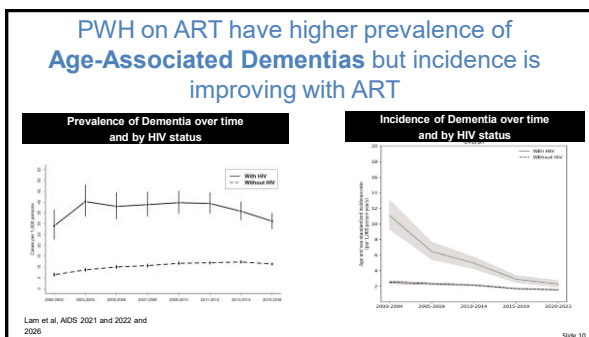
7



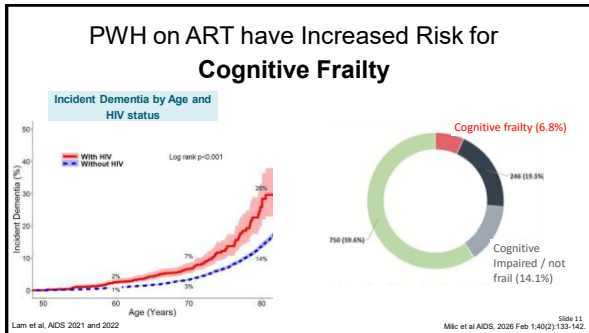
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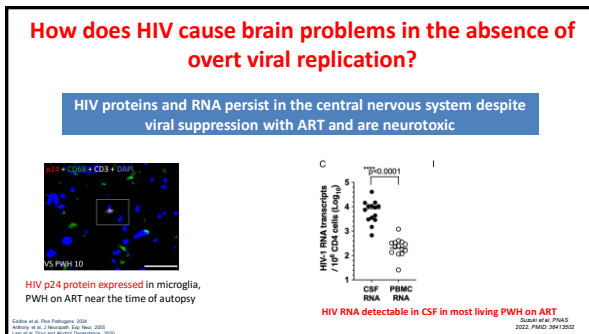
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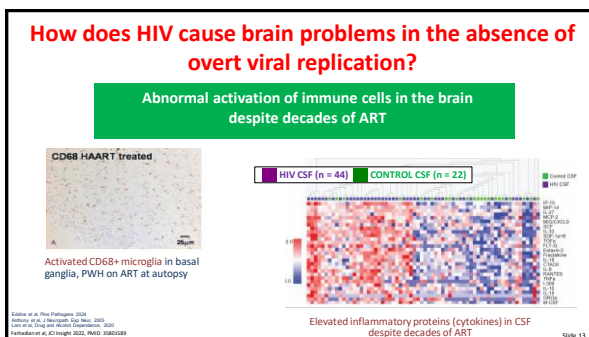
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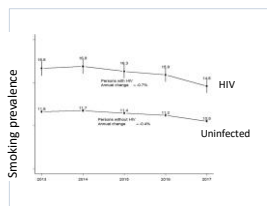
12



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How does HIV cause brain problems in the absence of overt viral replication?

High rates of multimorbidity, substance use disorder, smoking, vascular disease....



Esteban et al. The Lancet 2018; 391: 1000-1008. doi:10.1016/S0140-6736(18)30000-0

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How should we clinically approach the older adult with HIV and cognitive complaints?



15

Nearly half of dementia cases worldwide may be preventable

45%

- 7% High LDL
- 7% Hearing Loss
- 2% Smoking
- 5% Social Isolation

THE LANCET

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Audience Response Question #2

This 58-year-old has hypertension, high cholesterol, and a slow gait. Which approach is most likely to protect his long-term cognition?

- A. Intensify or switch to a more CNS-penetrating ART regimen
- B. Aggressively treat his vascular risk factors — blood pressure and lipids
- C. Recommend computerized brain-training games to build cognitive reserve
- D. Reassure him — an undetectable viral load means his brain is protected

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Search for MODIFIABLE Risks!

HIV related risk factors

- Low CD4 nadir
- Detectable CSF or plasma viral load
- Duration of HIV infection
- Duration of UNTREATED HIV infection
- Low CD4-CD8 ratio
- ART exposure (PI, Efavirenz use)
- CNS opportunistic infections and treatment



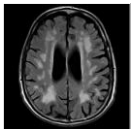
Comorbid Conditions

- Vascular disease
- Hypertension
- High LDL
- Hearing Loss
- Depression
- Social Isolation

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Vascular Risk Factors and Cognition: CSVD



White-matter hyperintensities (MRI, FLAIR)
A feature of both CSVD and HIV

Macgregor et al. Silent cerebral small-vessel disease twice as prevalent in middle-aged well-controlled cART-treated HIV-infected than HIV-uninfected individuals. Clin Infect Dis.

Cerebral small vessel disease (CSVD)

A chronic microvascular disorder of intracranial arterioles, venules, and capillaries — causes cognitive, psychiatric, and physical disability, ~20% of all strokes, and raises future dementia risk.

- **HIV, hypertension, hyperlipidemia, and advanced age** are independent risk factors for CSVD
- **~2× as prevalent** in middle-aged ART-treated PWH
- **In PWH, hypertension** is the strongest independent correlate of CSVD
- **CSVD (white-matter hyperintensities)** associates with worse cognitive performance in PWH

Why it matters : White Matter Hyperintensities are visible on routine MRI and the drivers are modifiable!

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Polypharmacy increases Cognitive Burden, independent of multimorbidity



Anticholinergic burden interacts with age and AIDS history to amplify frailty in people with HIV

Longitudinal effects of polypharmacy on cognitive function in people with HIV

Irene Korpetski¹, Ralu M. Ciorgheanu², Scott L. Litwin³, Donald R. Handelsky⁴, Qing Ma⁵, Leah H. Rubin^{6,7,8} and Tamas Szabo^{9,10}

Prevalence and risk factors of cognitive frailty in people with HIV

Irene Korpetski¹, Stefano Cella², Luca Lazzarini³, Maria Cocchi⁴, Roberto Marini⁵, Stefano Riccardi⁶, Laura Sighinolfi⁷, Michele Raggi⁸, Vera Todres⁹, Maddalena Albertini¹⁰, Anna Calzavara¹¹, Martina Albertini¹², Gianluca Caporali¹³, Giuseppe Martelli¹⁴, Chiara Mussi¹⁵, Cristina Stancu¹⁶, Andrea Calzavara¹⁷ and Giovanni Guaraldi¹⁸

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Audience Response Question #3

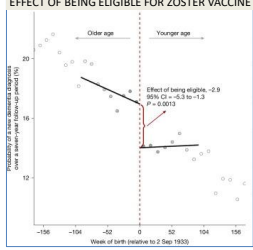
Recent large studies suggest the recombinant zoster (shingles) vaccine is associated with:

- A. Higher stroke risk
- B. Lower dementia risk
- C. No change in cognition
- D. Worse glycemic control

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Zoster Vaccination Lowers Dementia Risk !!!

EFFECT OF BEING ELIGIBLE FOR ZOSTER VACCINE



Wales (Nature 2025) – Zostavax (live attenuated): About ****20% relative reduction**** in dementia among vaccine-eligible adults. Effect was strongest in women.

Australia (JAMA 2025) – Zostavax: ****1.8 percentage point absolute reduction** in dementia over 7.4 years.

US/UK (Nat Med 2024) – Shingrix vs. Zostavax: Shingrix recipients had 17% more dementia-free survival time.

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Potential Brain Health Effects of GLP-1 Receptor Agonists

Roy et al, *Neurotherapeutics* 2025
Xie et al, *Nature Med* 2025, PMID: 39833406

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RECENT TRIALS TO IMPROVE BRAIN HEALTH IN PWH

Semaglutide (GLP-1 receptor agonist)	Phase 2b randomized, double-blind, placebo-controlled, PWH with overweight/central adiposity, 24 wk	20/25	108 (SAR m)	Positive signal.	Alabi et al, <i>Clin Infect Dis</i> 2025
Tesamorelin (GHRH analog)	Randomized, open-label vs standard of care, PWH with abdominal obesity, 6 mo	20/25	73 (largest study, stopped at early)	No cognitive benefit	Ellis et al, <i>J Infect Dis</i> 2023;277(S) 1250
Pitavastatin (REPRIEVE / ACTG A5332)	Phase 3 randomized, double-blind, placebo-controlled (primary endpoint = major CV events); neurocognitive/brain ancillary analysis	20/25	7,769	CV benefit; ~35% reduction in major CV events. Cognition not worse with statin.	Grimmson et al, <i>19 Eng J Med</i> 2023;386(B) 687 Erlundson et al, <i>ACS</i> 2023 Nov 1;38(13)

Visuospatial Performance

Delayed Recall

Alabi et al, *Clin Infect Dis* 2025, PMID: 41089140
[Download Infectious Diseases](#)

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WHAT'S IN THE PIPELINE?

	Design	Status	Brain Health Outcome
Menopausal HRT (ACTG A5424)	Phase 4	Enrolling	Sleep, mental health, cognitive testing
Fostemsavir (prevents binding of spg120 to CD4 receptor) (University of Montreal)	Randomized, open label Phase 2	Enrolling	Secondary outcome: Brief Cognitive Ability measure
Baricitinib (JAK 1/2 inhibitor) (Emory)	Phase 2, randomized placebo-controlled	Enrolling	CSF research, cognitive testing, depressive symptoms, brain MRI
Transcutaneous Vagus Nerve Stimulator plus probiotics (stimulate the autonomic nervous system, reduce inflammation) (University of Miami)		Enrolling	Cognitive improvement
Pregnenolone (neuroactive steroid lower in PWH with depression) (Harvard/MGH SMOOTH Trial)	Phase 2 randomized Double-Blind Placebo-Controlled Trial	Enrolling	Depression
LM11A-31 – (p75 neurotrophin receptor ligand, mimics nerve growth factor) (University North Carolina)		Planning	Cognition
Pranipexole (increases dopamine transmission)	Open label pranipexole versus escitalopram	Paused	Depression and Mild Neurocognitive Disorder
Tesamorelin + exercise (MGH and CU Anschutz)	Phase 2 randomized placebo-controlled	Enrolling	Primary endpoint physical function

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Suggested Readings

Lam, J. O., Fan, D., Pothamsetty, N., Samiezade-Yazd, Z., Hu, H., Lopez, E., Lee, C., Lea, A. N., Hou, C. E., Towner, W. J., Horberg, M. A., & Silverberg, M. J. (2025). Dementia incidence and prevalence in older adults with HIV: a 23-year retrospective cohort study. *AIDS*, 40(4), 486–495. <https://doi.org/10.1097/QAD.0000000000004421>

Filippidis P, Farhadian SF. Smoldering in the sanctuary: HIV-associated brain injury in the ART era. *J Clin Invest*. 2026 May 1;136(9):e204831. doi: 10.1172/JCI204831. PMID: 42065243; PMCID: PMC13132375.

Nightingale, S., Ances, B., Cinque, P. *et al*. Cognitive impairment in people living with HIV: consensus recommendations for a new approach. *Nat Rev Neurol* 19, 424–433 (2023). <https://doi.org/10.1038/s41582-023-00813-2>

Atieh O, Daher J, Abboud M, Wu Q, Sattar A, Baissary J, Koberssy Z, Labbato D, Eckard AR, McCormsey GA. Effects of Semaglutide on Cognitive Function in People With HIV: A Randomized, Controlled Trial. *Clin Infect Dis*. 2026 May 20;82(5):753–761. doi: 10.1093/cid/ciaf577. PMID: 41098140; PMCID: PMC13189676.

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Q and A Session

IAS-USA
International AIDS Society - United States of America

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