HIV, Aging, and the Brain: A Practical Approach



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

IAS–USA

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 November 10, 2025)

Slide 2

2

Learning Objectives

After attending this presentation, learners will be able to:

- Describe how HIV affects the aging brain, including the role of persistent immune activation and structural brain changes in people with HIV on suppressive antiretroviral therapy
- Identify modifiable clinical and lifestyle risk factors that contribute to cognitive decline among older adults with HIV
- Apply a practical, evidence-based approach to evaluating cognitive symptoms in older adults with well-controlled HIV, including when to use screening tools, laboratory tests, and specialty referrals

Slide 3

3

A Clinical Case



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

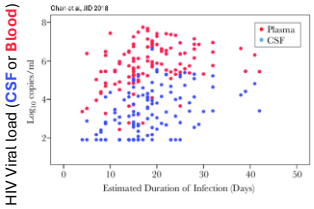
Is his problem due to HIV?
To "accelerated aging?"

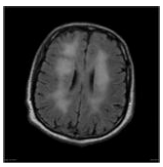
[illegible]

controlled HIV?

7

HIV enters the CNS within days of infection…



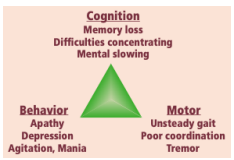


…without treatment, can lead to brain injury

8

HIV Dementia: Very rare in individuals on ART!

AIDS Dementia Complex
HIV Encephalopathy



Chan and Valcour 2022

Before ART, HIV dementia was the defining presentation of AIDS for 5% of patients

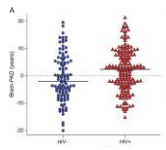
Typically presents as late-stage disease, with low CD4, but can present earlier during HIV infection.

Microglial activation; loss of neurons/brain volume

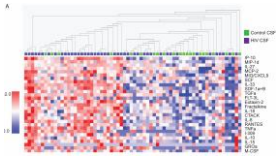


9

Brain Impacts of HIV Persist Despite ART



- "Brain Predicted Age" is higher in people with HIV[1]
- Higher Brain Predicted Age associates with worse cognition[1]



- Abnormally elevated inflammatory proteins in spinal fluid of PWH despite decades of ART[2]

1. Cole et al, Neurology, 2017 (COBRA study)

2. Farhadian et al JCI Insight 2022, PMID: 35801589

10

We do not know the true estimate of clinically significant cognitive impairment in PWH on suppressive ART

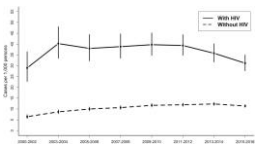
- Current estimates largely based on HAND criteria, which was designed for **RESEARCH** and not clinical assessment
- HAND estimates include asymptomatic cognitive impairment, which may not be clinically significant
- The HAND criteria typically classify 20–60% (and sometimes up to 90%) of people living with HIV as cognitively impaired. **This figure does not align with clinical observations**



11

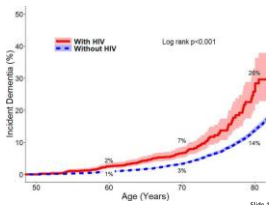
PWH on ART have Increased Risk for **Age-Associated Dementias**

Prevalence of Dementia over time and by HIV status



Lam et al, AIDS 2021
Lam et al, AIDS 2022
(Kaiser study)

Incident Dementia by Age and HIV status



12

(Modifiable) Risk Factors for Cognitive Complications in PWH

HIV related risk factors

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

Comorbid Conditions

- **Substance use disorder**
- Multimorbidity
- **Polypharmacy**
- **Vascular disease, hypertension, elevated LDL**
- **Hearing Loss**
- **Depression**
- **Social Isolation**
- **Sleep apnea**

Bhaskaran, 2008
Heaton, 2010
Heaton, 2011
Ellis, 2011
Wright, 2015

Slide 13

13

Should we screen ASYMPTOMATIC older adults with HIV for cognitive and mental health disorders?

Slide 14

14

Audience Response Question 1

What is the current IAS–USA ARV Guidelines Panel position on screening asymptomatic older adults with HIV for cognitive or mental health disorders?

A. Routine screening is recommended for all adults over 50 years with HIV
B. Screening is not recommended due to lack of evidence of benefit
C. The IAS–USA ARV Guidelines Panel does not make a specific recommendation for or against screening
D. Screening should only be done if CD4 nadir <200

Gandhi RT, Landovitz RJ, Sax PE, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2024 recommendations of the International Antiviral Society–USA Panel. *JAMA*. 2025; 333(7):609-628. doi:10.1001/jama.2024.24543.

Slide 16

16

	Mental Health Screening		Cognitive Screening	
European AIDS Clinical Society (EACS)	Consider screening at each routine HIV clinic visit	(1)Have you often felt depressed, sad or without hope in the last few months? (2) Have you lost interest in activities that you usually enjoy? -- Over the last 2 weeks, how often have you been bothered by the following problems?" (1)Feeling nervous, anxious or on edge (2) Not being able to stop or control worrying	Only in those with symptoms	(1) Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)? (2) Do you feel that you are slower when reasoning, planning activities, or solving problems? (3) Do you have major difficulties paying attention (e.g. to a conversation, book or film)?
U.S. Department of Health and Human Services (DHHS)	"Screening for depression and management of mental health issues are critical aspects of HIV primary care"		"Screening for neurocognitive impairment is important, though optimal primary care-based screening methods remain unclear"	

IAS-USA ARV Guidelines Panel does not make specific recommendations for or against screening for mental health and cognitive disorders

Slide 17

17

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

Slide 18

18

Clinical Assessment

History and Physical
- Cognitive, Motor, Behavioral symptoms
- Time course
- Neurological exam: Gait, motor
- Orthostatic vital signs

HIV History
- Duration on/off ART
- Brain opportunistic infections
- CD4/CD8 (current)
- Nadir CD4
- Current Efavirenz use



Medication Inventory

Sleep

Mental Health

Substance Use

Short Cognitive Assessment
- MOCA
- iCOPE
- others

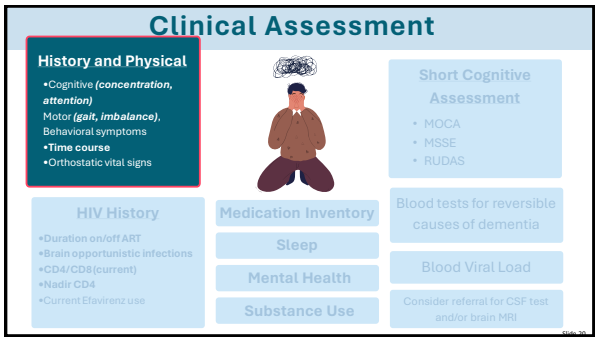
Blood tests for reversible causes of dementia

Blood Viral Load

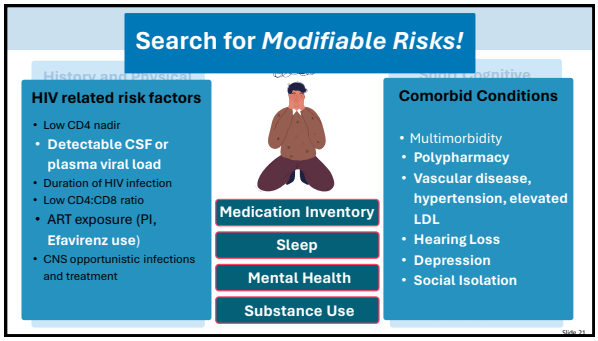
Consider referral for CSF test and/or brain MRI

Slide 19

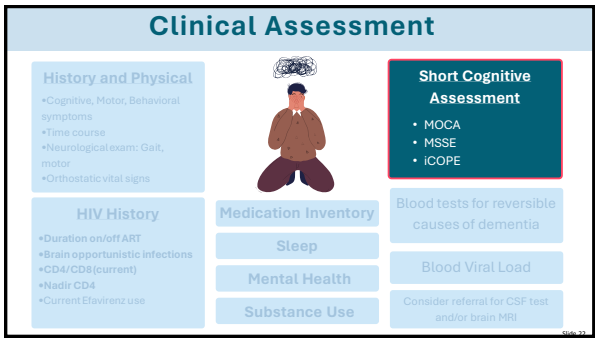
19


Clinical Assessment
History and Physical
•Cognitive (concentration, attention)
Motor (gait, imbalance),
Behavioral symptoms
•Time course
•Orthostatic vital signs
Short Cognitive Assessment
• MOCA
• MSSE
• RUDAS
HIV History
•Duration on/off ART
•Brain opportunistic infections
•CD4/CD8 (current)
•Nadir CD4
•Current Efavirenz use
Medication Inventory
Sleep
Mental Health
Substance Use
Blood tests for reversible causes of dementia
Blood Viral Load
Consider referral for CSF test and/or brain MRI

20


Search for Modifiable Risks!
HIV related risk factors
• Low CD4 nadir
• Detectable CSF or plasma viral load
• Duration of HIV infection
• Low CD4:CD8 ratio
• ART exposure (PI, Efavirenz use)
• CNS opportunistic infections and treatment
Medication Inventory
Sleep
Mental Health
Substance Use
Comorbid Conditions
• Multimorbidity
• Polypharmacy
• Vascular disease, hypertension, elevated LDL
• Hearing Loss
• Depression
• Social Isolation

21


Clinical Assessment
History and Physical
•Cognitive, Motor, Behavioral symptoms
•Time course
•Neurological exam: Gait, motor
•Orthostatic vital signs
Short Cognitive Assessment
• MOCA
• MSSE
• iCOPE
HIV History
•Duration on/off ART
•Brain opportunistic infections
•CD4/CD8 (current)
•Nadir CD4
•Current Efavirenz use
Medication Inventory
Sleep
Mental Health
Substance Use
Blood tests for reversible causes of dementia
Blood Viral Load
Consider referral for CSF test and/or brain MRI

22

When should I refer my patient to a neurologist? When should I consider brain MRI and/or LP?

- Symptoms are **acute/subacute** (weeks to months)
- Symptoms are **rapidly progressive**
- Family history or other clinical concern for **neurodegenerative disease** (e.g., AD, PD, Lewy Body)
- Non-memory predominant syndromes
- Subacute confusion, inattention, or fluctuating cognition

If screening and basic labs are normal and symptoms are stable, a period of observation with primary care management may be reasonable.

Slide 23

23

Audience Response Question 2

Which of the following best describes the relationship between polypharmacy and cognitive health in people with HIV (PWH)?

A. Polypharmacy has minimal relevance to cognitive symptoms in PWH
B. Polypharmacy may contribute to cognitive symptoms and frailty, partly through drug-drug interactions
C. Polypharmacy mainly affects adherence, not cognition
D. Polypharmacy improves CNS penetration of ART and thus brain outcomes

Slide 25

25

Polypharmacy in People with HIV

- Higher rates of comorbidities in PWH compared to uninfected → polypharmacy
- Potential for drug drug interactions, leading to neurological symptoms
- Polypharmacy associates with frailty, recurrent falls, slow gait, and other geriatric syndromes



Slide 26

26

Perform medicines reviews at each visit[1]
Questions to consider when reviewing a prescription

- Is there an indication for the medicine?
- Is this medicine appropriate for older persons with HIV?
- Is the dose correct (e.g. adjusted for the renal function)?
- Is there a significant drug-drug interaction?
- Is there a significant drug-disease interaction (e.g. delirium)?
- Is the duration of treatment acceptable?
- Is there any missing medicine?
- Is the person able to manage his/her own medicines or does he/she need assistance?

Check for DDI with HIV drugs: www.hiv-druginteractions.org
Check for inappropriate drugs use: Beers[1] and STOPP/START[1] criteria

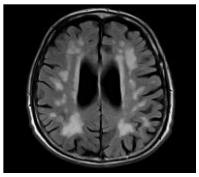
EACS 2024

Slide 27

27

HIV and Cerebral Small Vessel Disease

- HIV, hyperlipidemia, and HTN are independent risks for CSVD
- CSVD associates with poor cognitive performance in PWH

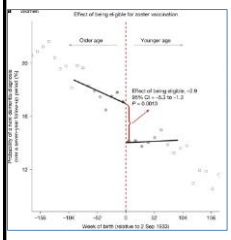


White Matter Hyperintensities (MRI, FLAIR)

Mukerji et al CID 2016
Wright et al, Neurology 2010
Slide 28 Becker et al, Neurology 2009

28

Zoster Vaccination & Dentistry Risk



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

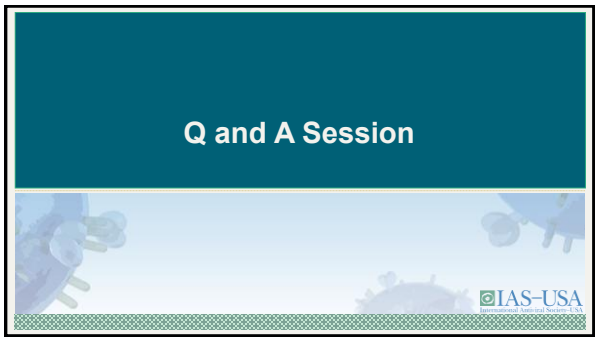
Australia (JAMA 2025) – Zostavax: **↔1.8 percentage point absolute reduction in dementia over** 7.4 years.

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

Eyting et al

Eyting M et al. "A natural experiment on the effect of herpes zoster vaccination on dementia." Nature. 2025.
Pomirchy M et al. "Herpes Zoster Vaccination and Dementia Occurrence." JAMA. 2025.
Taquet M et al. "The recombinant shingles vaccine is associated with lower risk of dementia." Nat Med. 2024.

29



36