Mass General Brigham

HIV Psychiatry Update 2025

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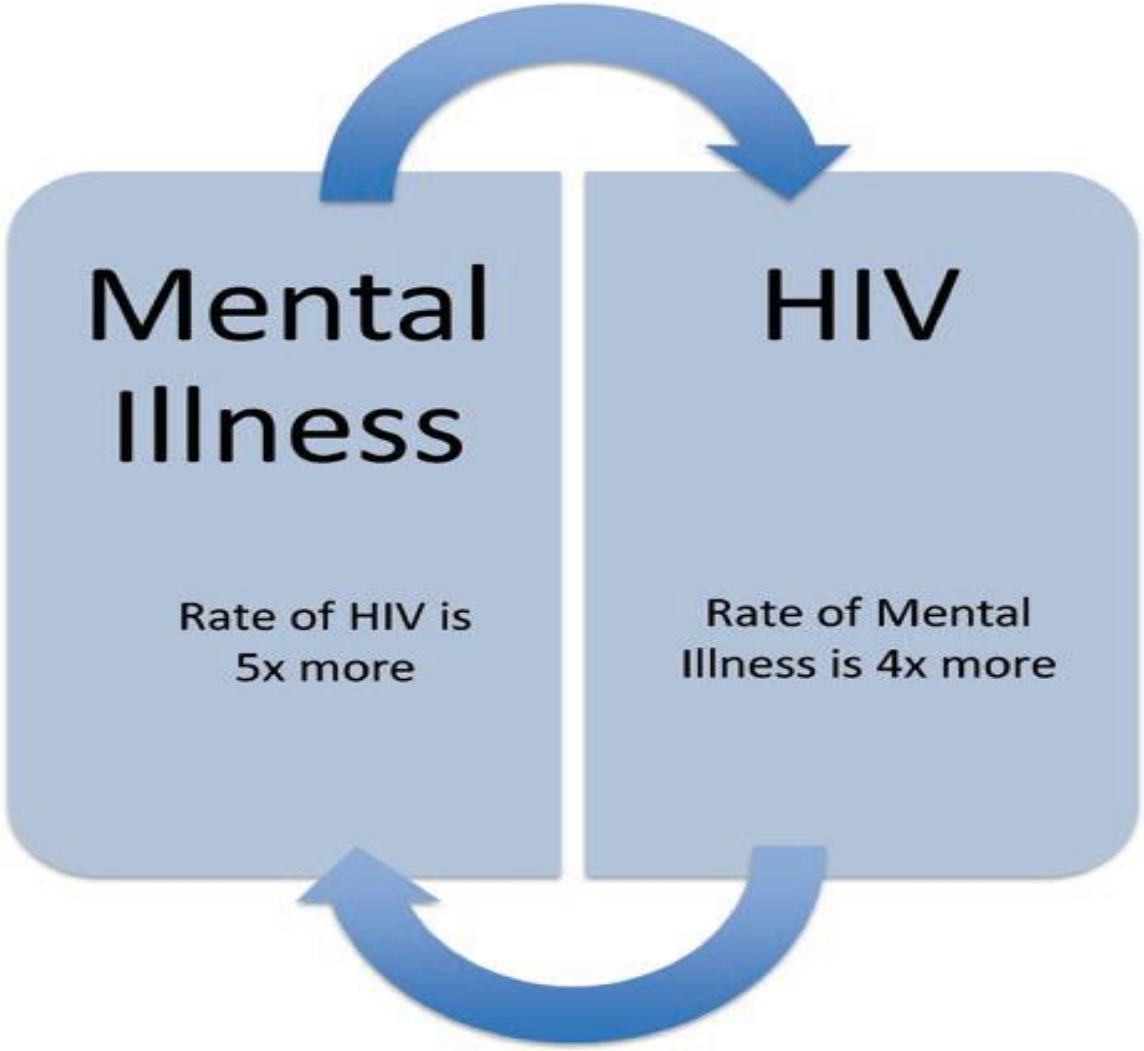
Agenda

- HIV Epidemiology
- HIV Prevention
- HIV-associated Neurocognitive Disorders HAND
- Psychiatric co-morbidity

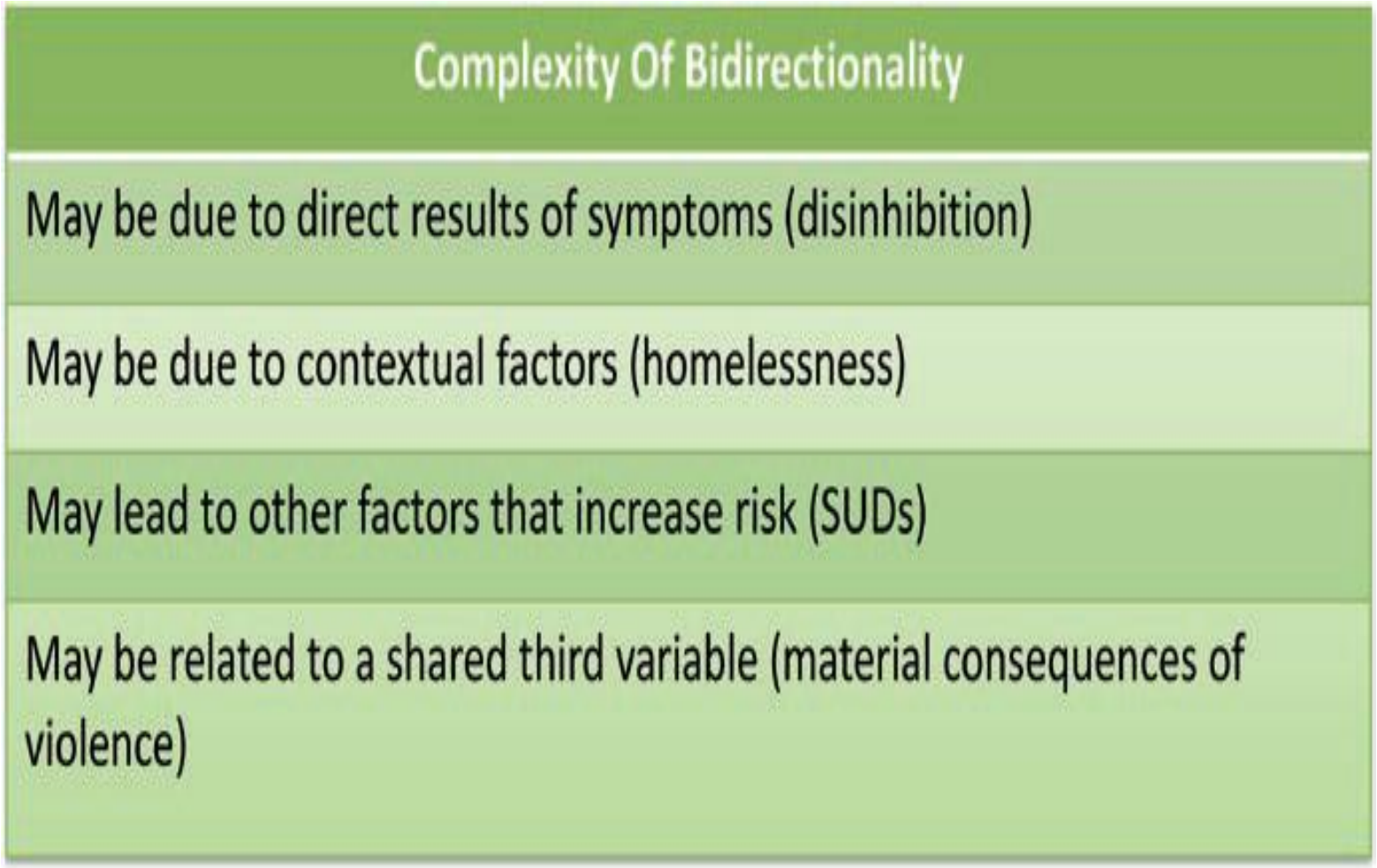
HIV Epidemiology

Bidirectional relationship between mental illness and HIV



Bourgeois, JA, Cohen MA, Makurumidze G. *HIV Psychiatry – A Practical Guide for Clinicians*. pp 7-8. Springer Nature Switzerland AG 2022.

Factors contributing to complex relationship



Bourgeois, JA, Cohen MA, Makurumidze G. *HIV Psychiatry – A Practical Guide for Clinicians*. pp 7-8. Springer Nature Switzerland AG 2022.

Increase morbidity and mortality and nonadherence

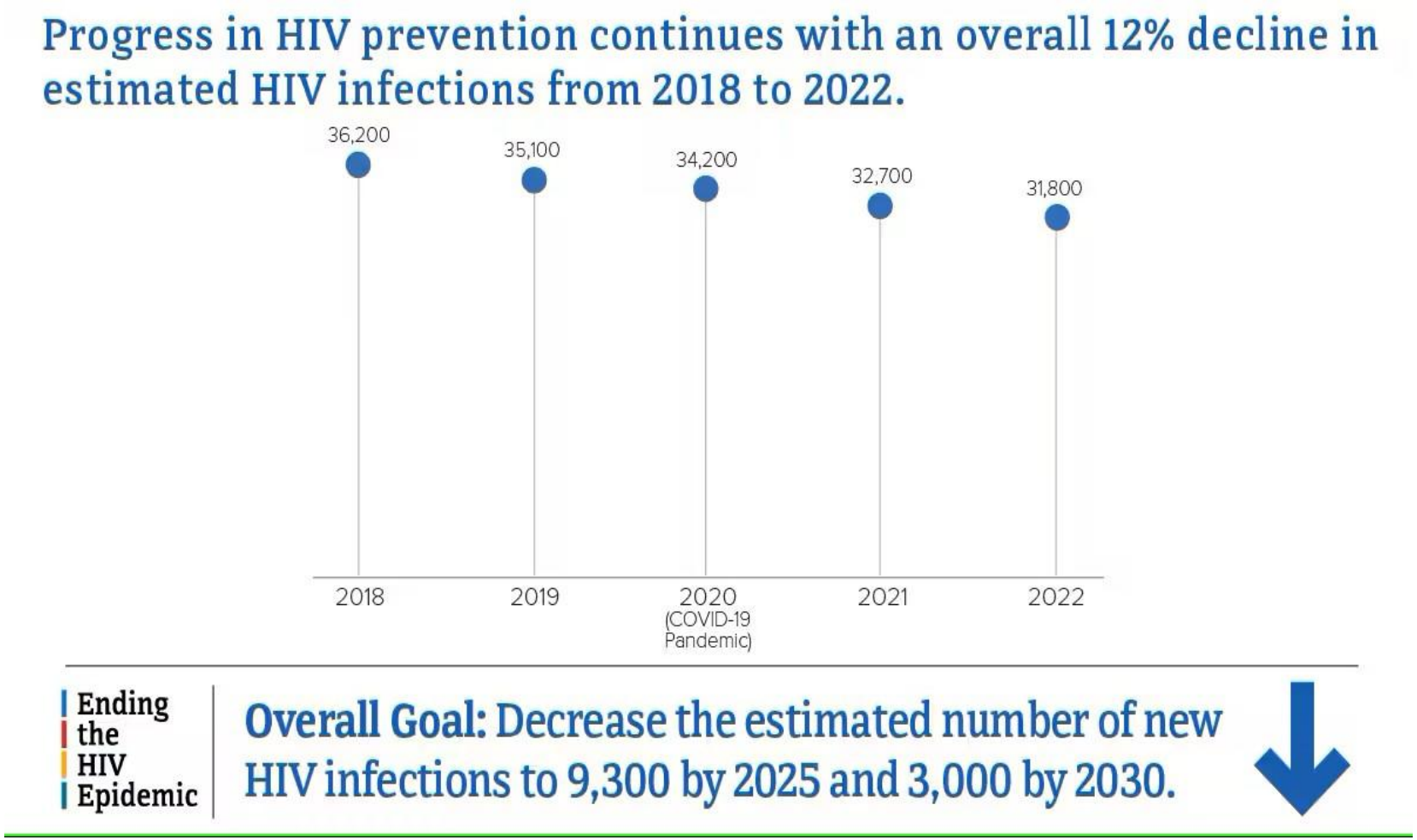
Psychiatric Disorders - Vectors of HIV + Barriers to Adherence	
PTSD	Impairs self-care, partner choice, trust in clinicians, adherence
Depressive Disorders	Decrease in self-care & self-worth impairs adherence
Anxiety Disorders	Concerns about HIV stigma may impair adherence
Neurocognitive Disorders	Impairs risk reduction, executive functioning, adherence
Addictive Disorders	Direct transmission & non-adherence
Psychotic Disorders	Impairs self-care & adherence
Bipolar Disorders	Hypersexuality & non-adherence

Bourgeois, JA, Cohen MA, Makurumidze G. *HIV Psychiatry – A Practical Guide for Clinicians*. pp 7-8. Springer Nature Switzerland AG 2022.

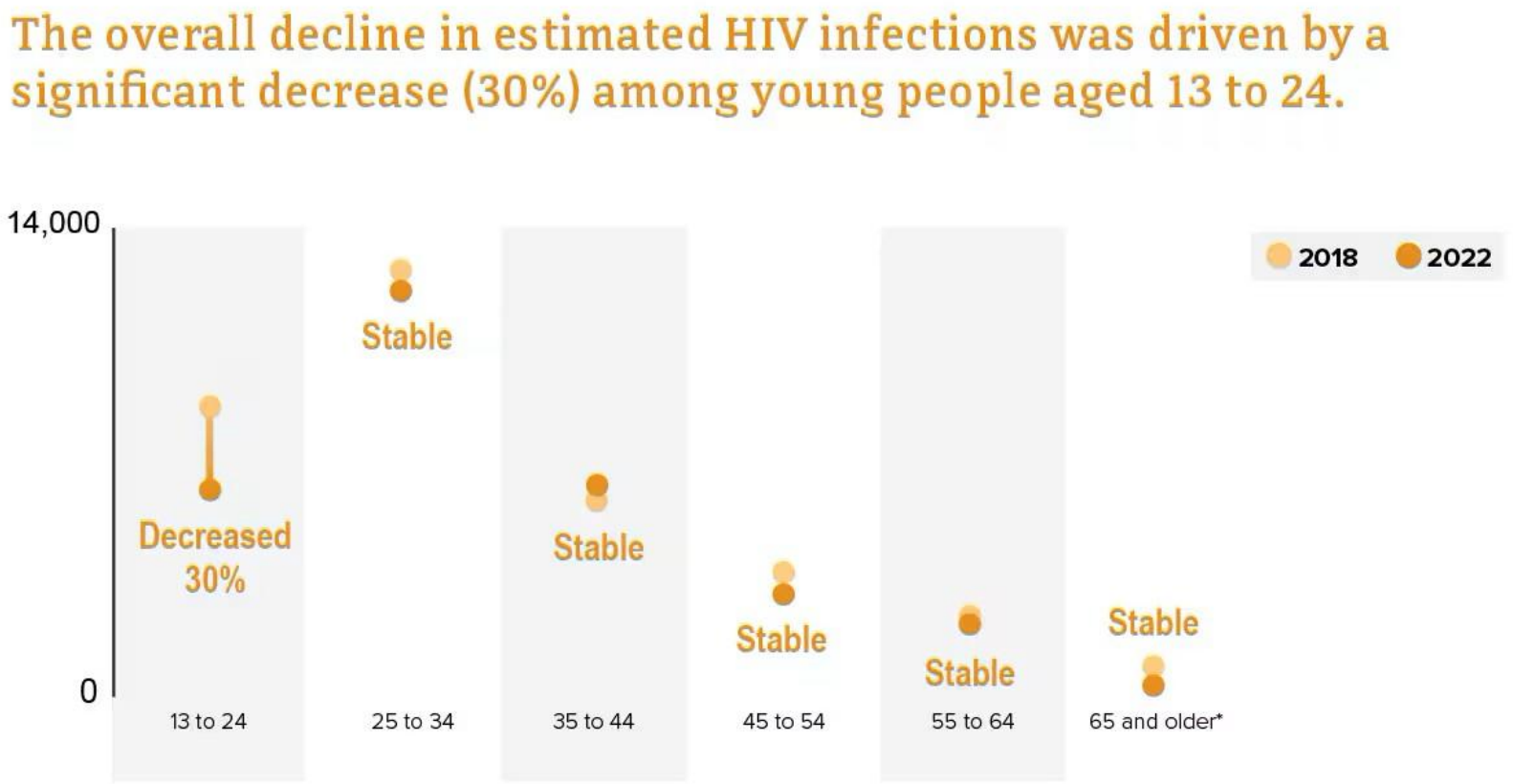
Estimated HIV Incidence in the United States, 2018–2022

Centers for Disease Control and Prevention. Estimated HIV incidence and prevalence in the United States, 2018–2022. *HIV Surveillance Supplemental Report*, 2024; 29 (No.1).

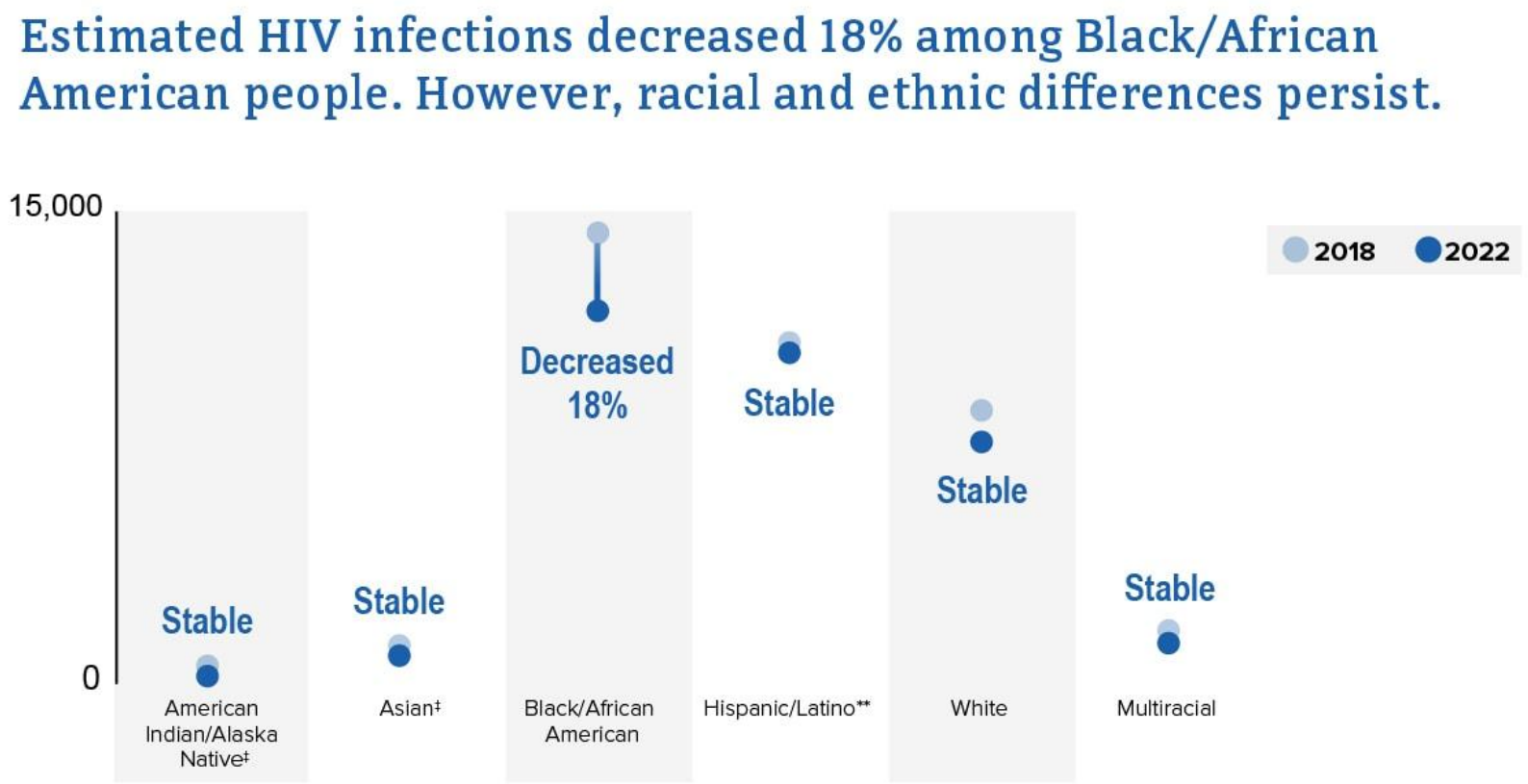
Estimated HIV infections in the United States over time, 2018–2022*



Estimated HIV infections by age, 2018–2022



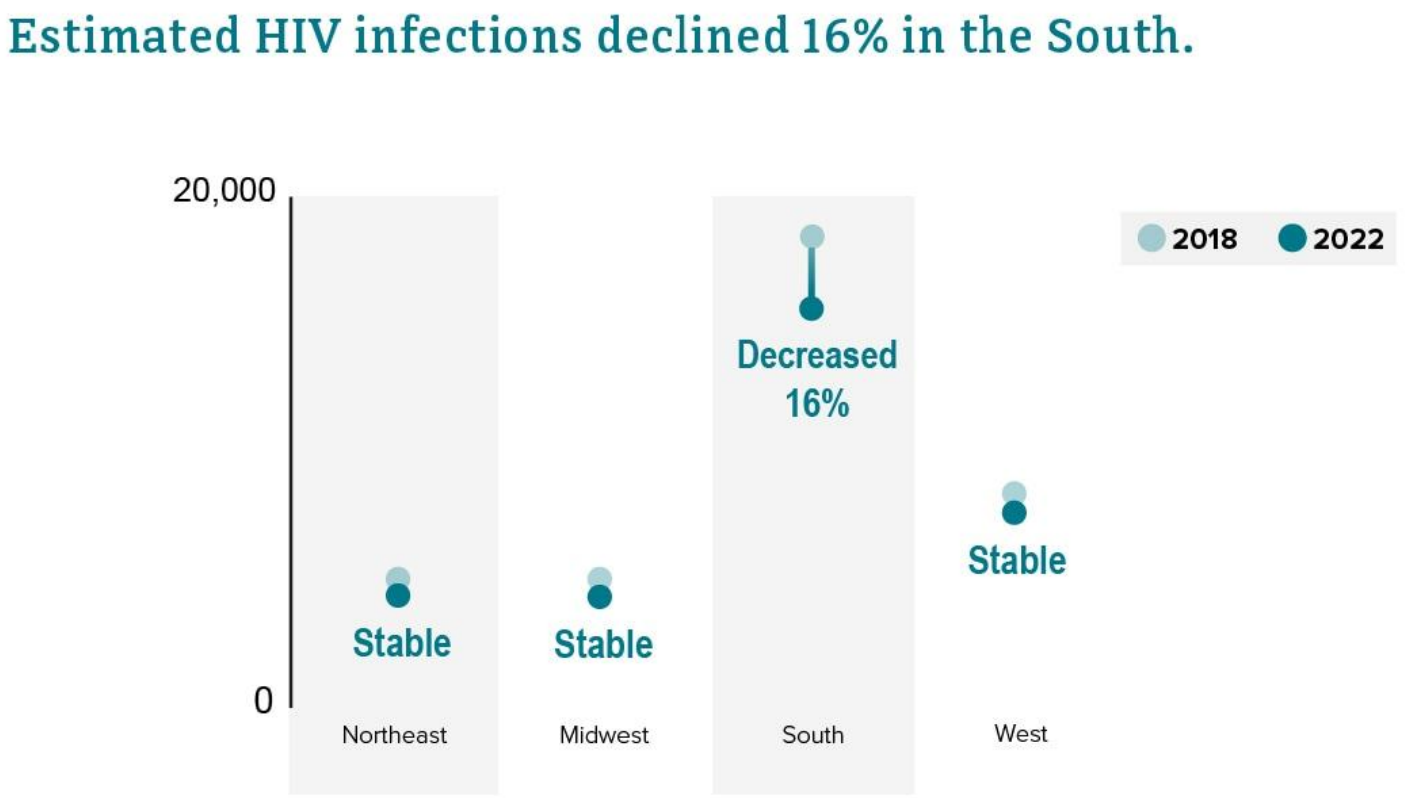
Estimated HIV infections by race and ethnicity, 2018–2022



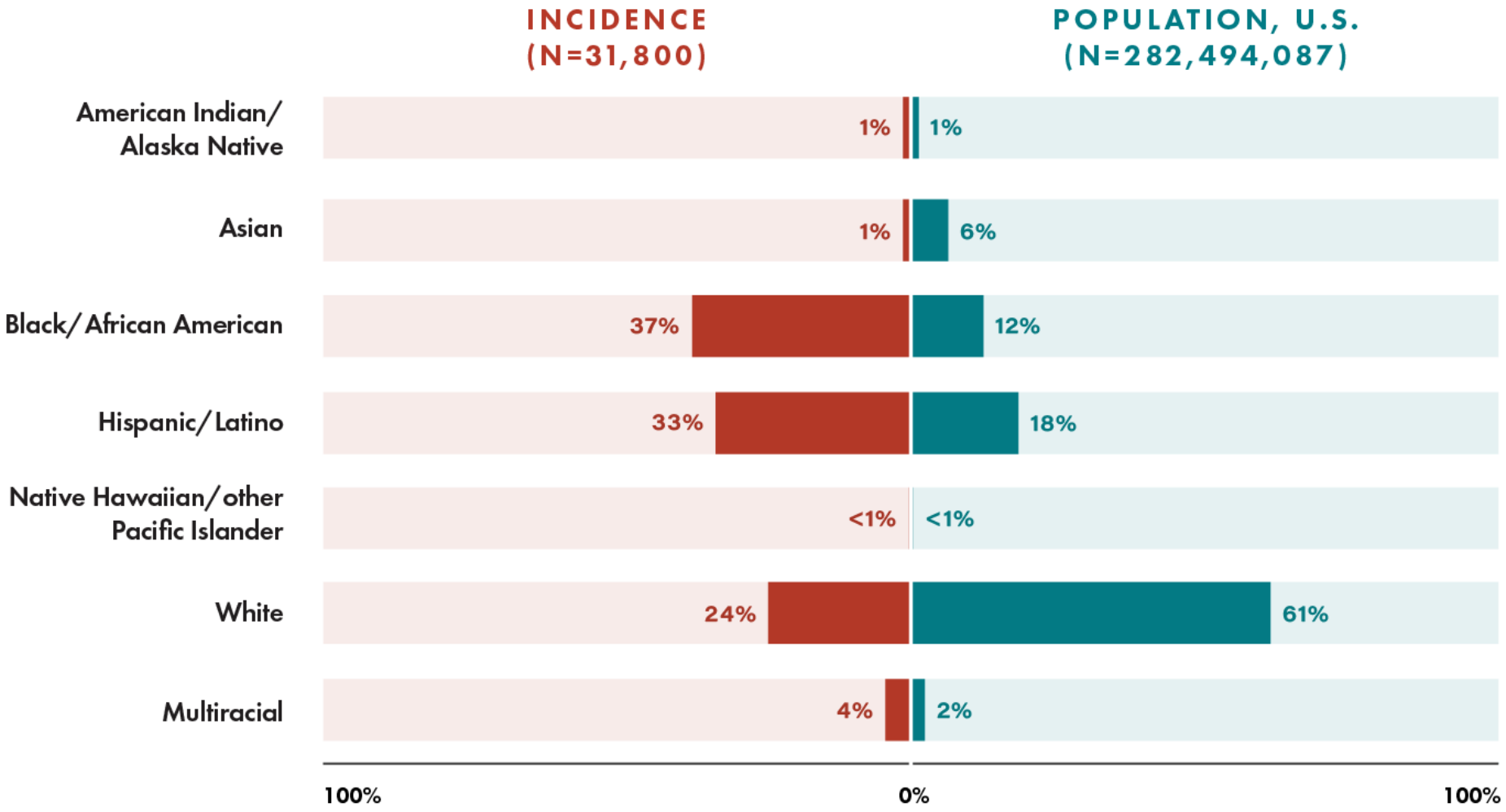
Estimated HIV infections among gay and bisexual men by race and ethnicity, 2018–2022

In recent years, estimated HIV infections decreased 10% overall among gay and bisexual men, with considerable declines among Black/African American gay and bisexual men (16%) and White gay and bisexual men (20%).

Estimated HIV infections by region, 2018–2022



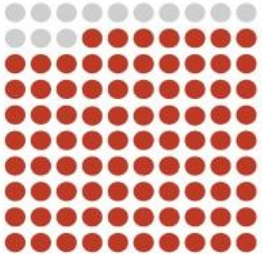
Estimated HIV incidence and population among persons aged ≥ 13 years, by race/ethnicity, 2018–2022—United States



Knowledge of HIV status in the United States, 2022

In 2022, an estimated **1.2 million people** had HIV.

For every 100 people with HIV



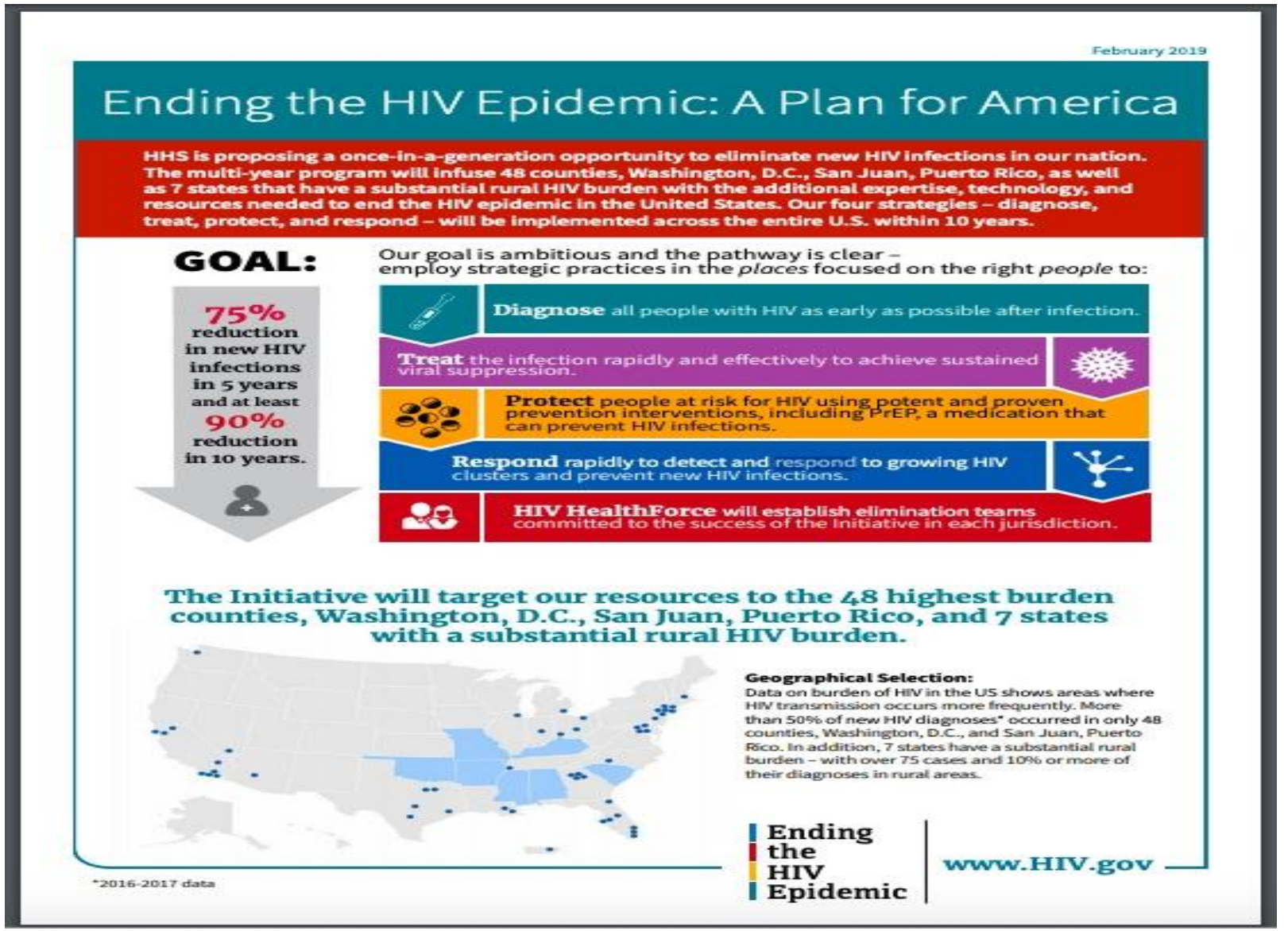
87 knew their HIV status.

Ending the HIV Epidemic

Overall Goal: Increase the estimated percentage of people with HIV who have received an HIV diagnosis to at least 95% by 2025 and remain at 95% by 2030.

HIV Prevention

Ending HIV in the US



Biomedical Interventions

Antiviral therapy

- **PrEP – Pre-exposure prophylaxis**
- **PEP - Post-exposure prophylaxis**
- **“Test and Treat” - Treatment as prevention**

Behavioral: individual and societal (structural)

- **E.g. condom use, needle exchange, sexual habits**

Diagnosis and treatment of STIs (e.g. HSV to prevent HIV)

Prevention of mother-to-child transmission of HIV

Voluntary male circumcision

Contraception to prevent unplanned pregnancy among women with HIV

Blood safety

Injection safety

Topical microbicides

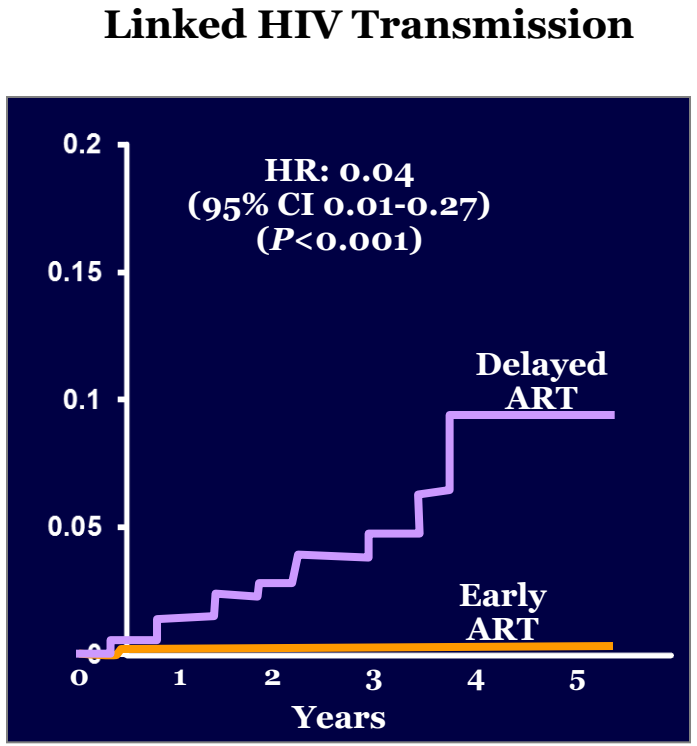
Vaccines and other immune modulatory therapy

HPTN 052: Treatment as Prevention

Randomized study of early vs delayed ART in 1763 serodifferent couples

Early ART led to a 96% reduction of linked HIV transmissions

Study stopped early



The most important HIV study in the last decade?

Cohen MS, et al. *N Engl J Med*. 2011;365:493-505.

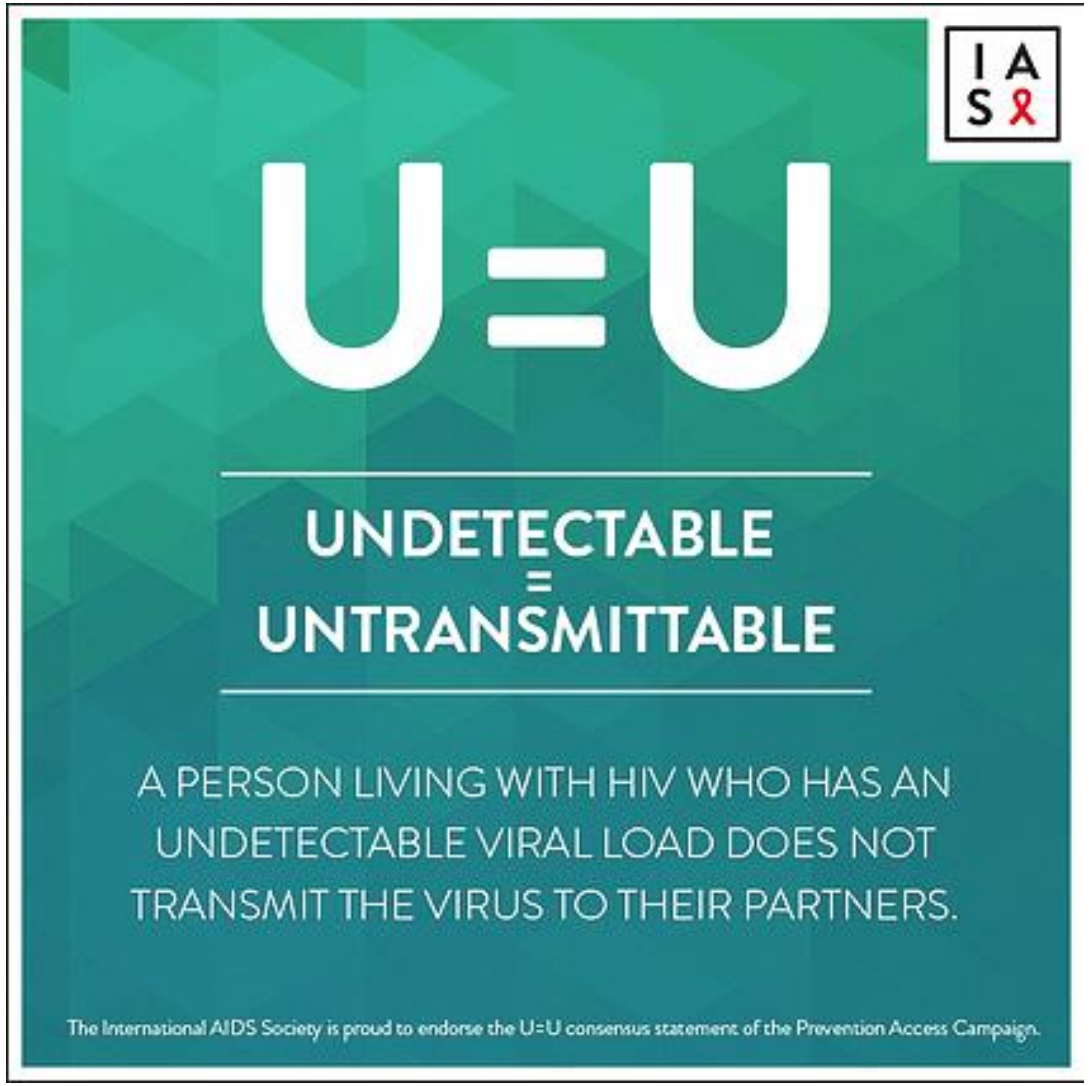
The PARTNER1 Study

Original Investigation

Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy

JAMA. 2016;316(2):171-181. doi:10.1001/jama.2016.5148

- 1,200 serodiscordant couples (62% man/woman, 38% man/man) in 14 European countries
- HIV positive partner on ART, virologically suppressed (VL <assay)
- Followed for a median of 1.3 years of condomless sex
  - median 37 condomless sex acts/year
  - **58,000 condomless sex acts**
- **ZERO documented cases of within couple HIV transmission**
  - 11 seroconversions; none which were phylogenetically linked
  - **U=U** Undetectable equals Untransmittable



Based on PARTNER 1 and PARTNER 2 studies:

Result: zero linked HIV transmissions after having sex 77,000 times without condoms

Has greatly reduced stigma among patients living with HIV.

Pre-Exposure Prophylaxis

PrEP

What is the evidence that PrEP works?

Randomized controlled trials
Real world studies

Populations studied

- Men who have sex with men
- Injection drug use
- Heterosexual women and men
- Transgender women

Interventions

- Oral Truvada or emtricitabine plus tenofovir disoproxil, daily oral
- Oral Descovy or emtricitabine plus tenofovir alafenamide, daily oral
- Cabotegravir LAI every 2 months
- Lenacapavir LAI every 6 months

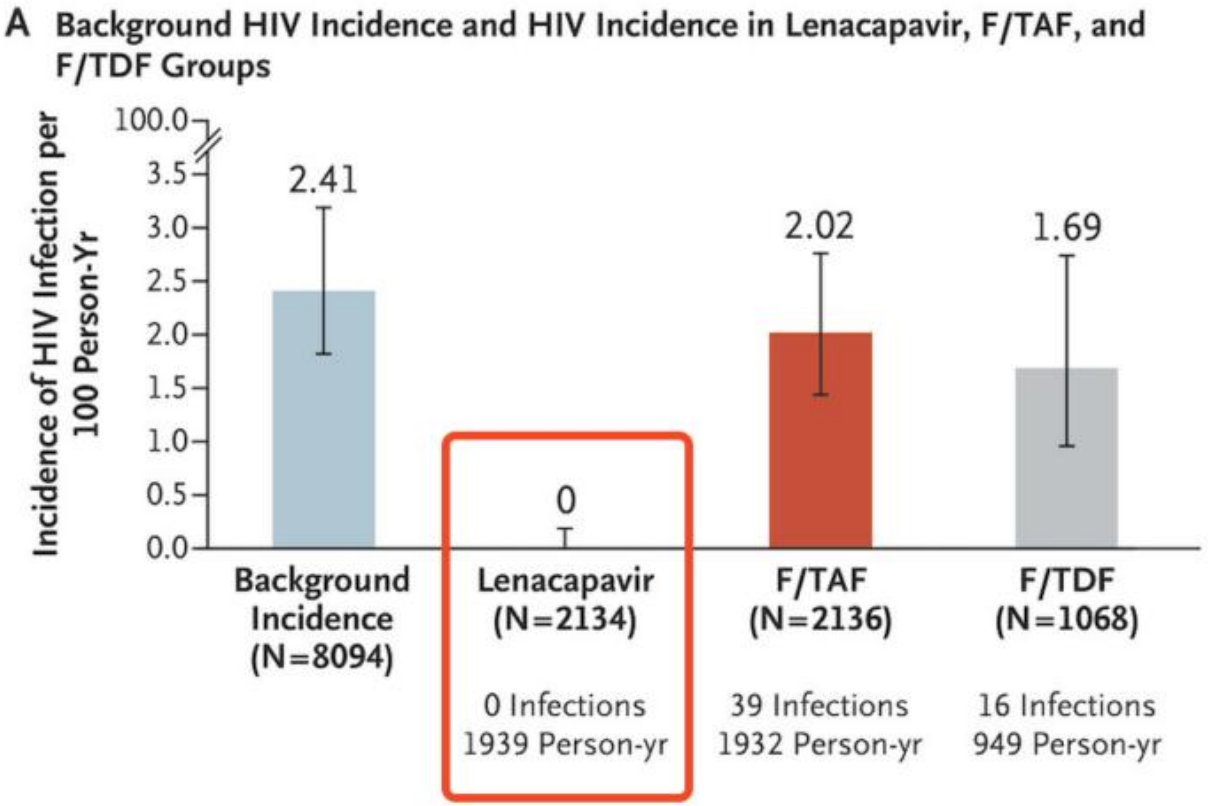
Lenacapavir is a moderate inhibitor of cytochrome P450 3A and should be used with caution with medications metabolized via that pathway. Clinically significant interactions with hormonal contraceptives or gender-affirming hormone therapy are not anticipated

Landovitz JAMA. Published online June 27, 2025. doi:10.100.1/jama.2025.11410

Lenacapavir PrEP Trial Brings Down the House at the International AIDS Conference

Beginning of End of HIV Epidemic?

NEJM Journal Watch HIV and ID Observations has published a new blog post:
By Paul Sax | July 25, 2024 12:05 pm



HIV-associated Neurocognitive Disorder

HAND

Clinical case

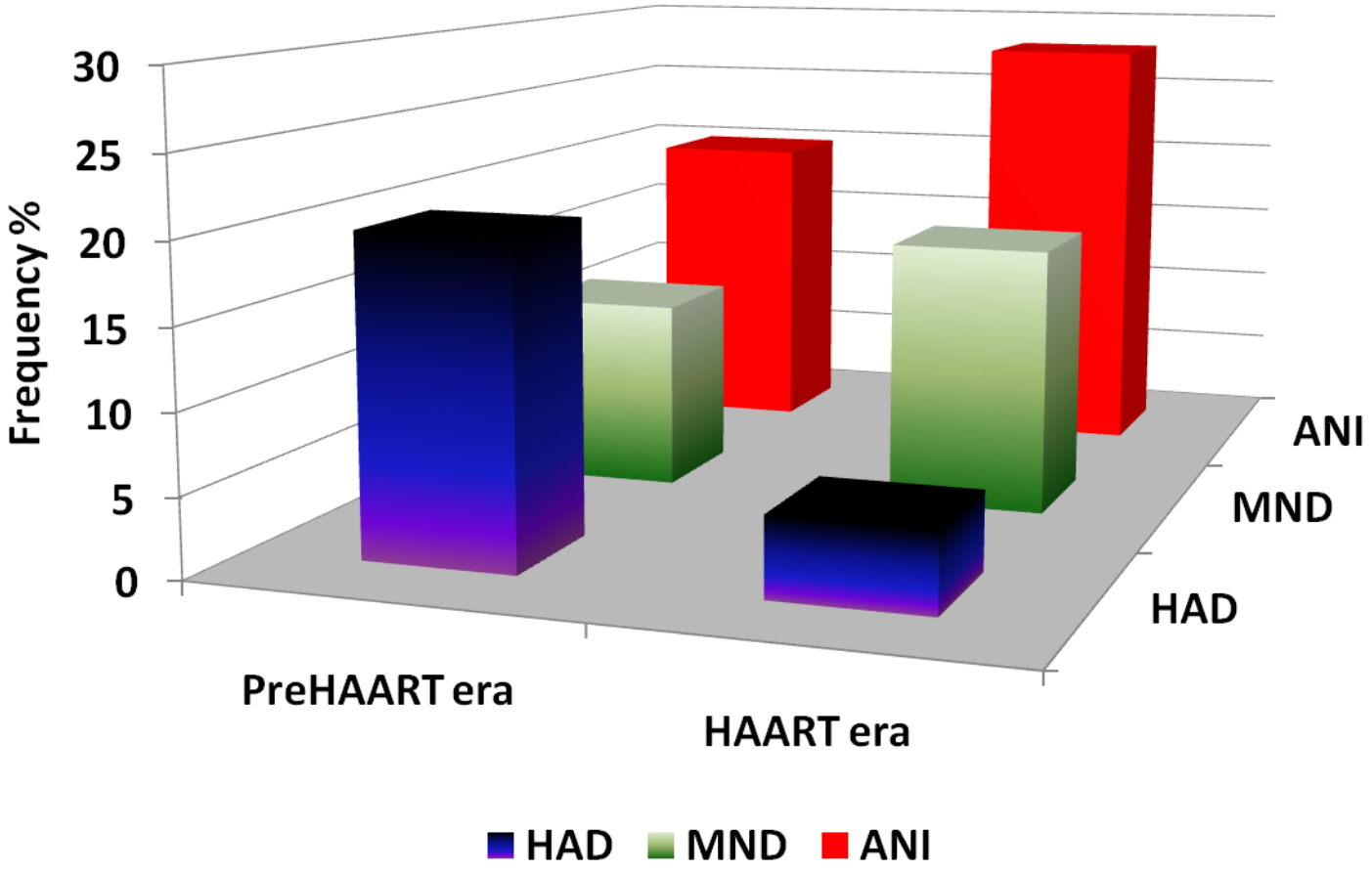
J is a 60-year-old man who presents with worsening forgetfulness over the past several months.

- **CC**: “walking into a room and forgetting reason for going there.”
- **HPI**: J reports forgetting appointments, important birthdays, and misplacing personal belongings in the house. He is more easily distracted than usual and sometimes must read a newspaper article several times.
- Sometimes when driving, places do not seem as familiar as they used to.
- J is not able to calculate simple math problems mentally as well as he used to. He has difficulty balancing his checkbook and difficulty completing tasks once started.
- He denies getting lost, or forgetting to lock doors, or to turn off stove top or oven.

J was diagnosed with HIV 6 years prior in setting of a diagnosis of non-Hodgkins Lymphoma. He was treated with chemotherapy and intrathecal methotrexate and is in sustained remission. At time of HIV diagnosis, Cd4 cell count was 65 and viral load was 450,000 copies per ml. He is currently asymptomatic with Cd4 533 and undetectable viral load. HIV medications include dolutegravir and lamivudine, Dovato. He experienced a major depressive episode at time of HIV and NHL diagnoses. He had good response to citalopram. He was also successfully treated for hepatitis C.

- What are the possible causes of his forgetfulness?
- What are your next steps?

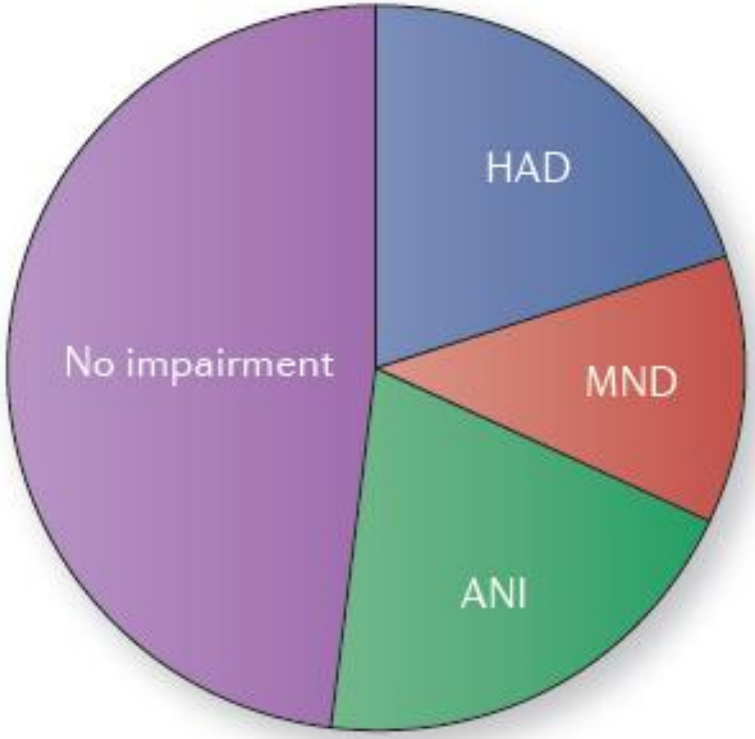
Changing prevalence of HAND



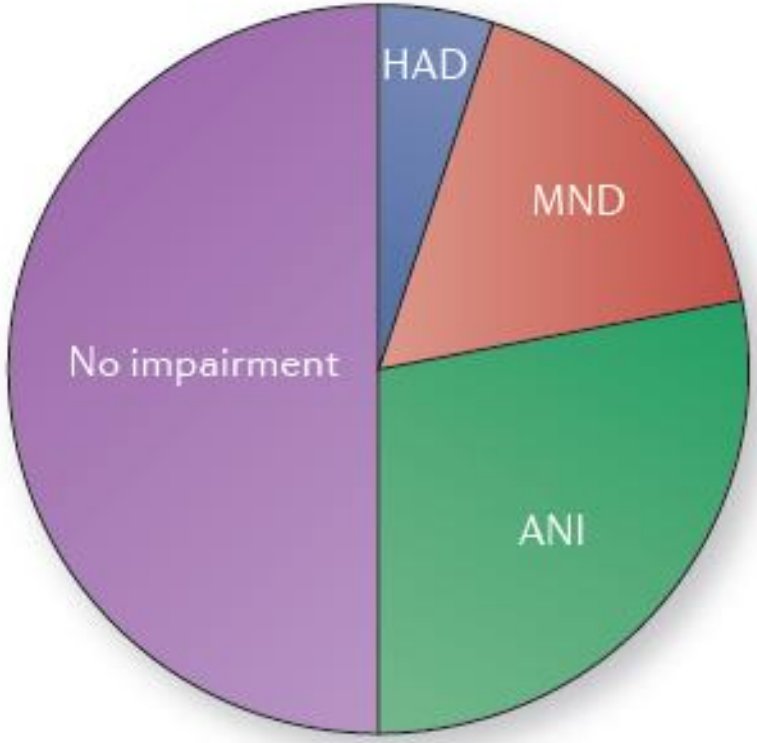
Modified from Heaton R., et al: HIV-associated neurocognitive disorders (HAND) persist in the era of potent antiretroviral therapy: The CHARTER Study; and Heaton R., *J Int Neuropsychol Soc.* May 1995;1(3):231-251)).

HAND Prevalence

Pre ART



Post ART



ANI = Asymptomatic neurocognitive impairment
MND = Minor neurocognitive disorder
HAD = HIV-associated dementia

Grant et al, Neurology, 2014

HAND Classification

Pre ART

1-2 SD below mean for 2 NC domains (of 7 tested) PLUS:

- **Minor Cognitive Motor Disorder – MCMD**
  Mild to moderate effect on functioning

- **HIV-associated Dementia - HAD**
  Marked effect on functioning

Post ART - Frascati criteria 2005

1 SD below mean for 2 NC domains (of 7 tested) PLUS:

- **Asymptomatic Neurocognitive Impairment – ANI**
  No effect on functioning

2 SD below mean for 2 NC domains (of 7 tested) PLUS

- **Mild Neurocognitive Disorder - MND**
  Mild to Moderate effect on functioning

- **HIV-associated Dementia – HAD**
  Marked effect on functioning

Antinori et al, Neurology, 2007

HAND Natural History 1

- In more advanced HIV disease, then NC impairment confers additional risk of mortality, compared to those without NC impairment.
- Comparing no NC impairment and asymptomatic impairment - relative risk of progression was **three-fold** even with full viral suppression at baseline in each group. Suggests progression occurs in persons with optimal HIV treatment.
- Higher IQ score and not having depression predicted cognitive stability or improvement

Banerjee et al, AIDS, Behav, 2019; Power et al, J AIDS Hum Retro, 1995; Heaton et al, CID, 2015; Cysique et al, Neurology, 2006; Ances et al, Top Antivir Med, 2019; Moulignier et al, Curr Top Behav Neurosci, 2020; Nasi et al, Clin Exp, Immuno, 2017; Grant et al, Neurology, 2014.

HAND Natural History 2

- **History of MDD, methamphetamine use, greater comorbidity, being off ART** predicted cognitive decline.

- Other studies have shown conflicting results related to diversity of sample cohorts. Characteristics consistently associated with a worse prognosis are **low nadir CD4 cell count, history of depression and having had an AIDS-defining illness.**

- Other psychosocial and biological factors also influence prognosis in HAND, especially in **aging** persons. **Cardiovascular disease and metabolic syndrome** that may be HIV-related or not, can also contribute to the development and progression of HAND, even in virologically suppressed persons.

- Recall that J in the clinical example had a nadir cd4 of 65 and he presented with non-Hodgkins Lymphoma, an AIDS-defining condition. He had a history of successfully treated hepatitis C and depression. These features raise our suspicion for HAND.

Banerjee et al, AIDS, Behav, 2019; Power et al, J AIDS Hum Retro, 1995; Heaton et al, CID, 2015; Cysique et al, Neurology, 2006; Ances et al, Top Antivir Med, 2019; Moulignier et al, Curr Top Behav Neurosci, 2020; Nasi et al, Clin Exp, Immuno, 2017; Grant et al, Neurology, 2014.

HAND Risk factors

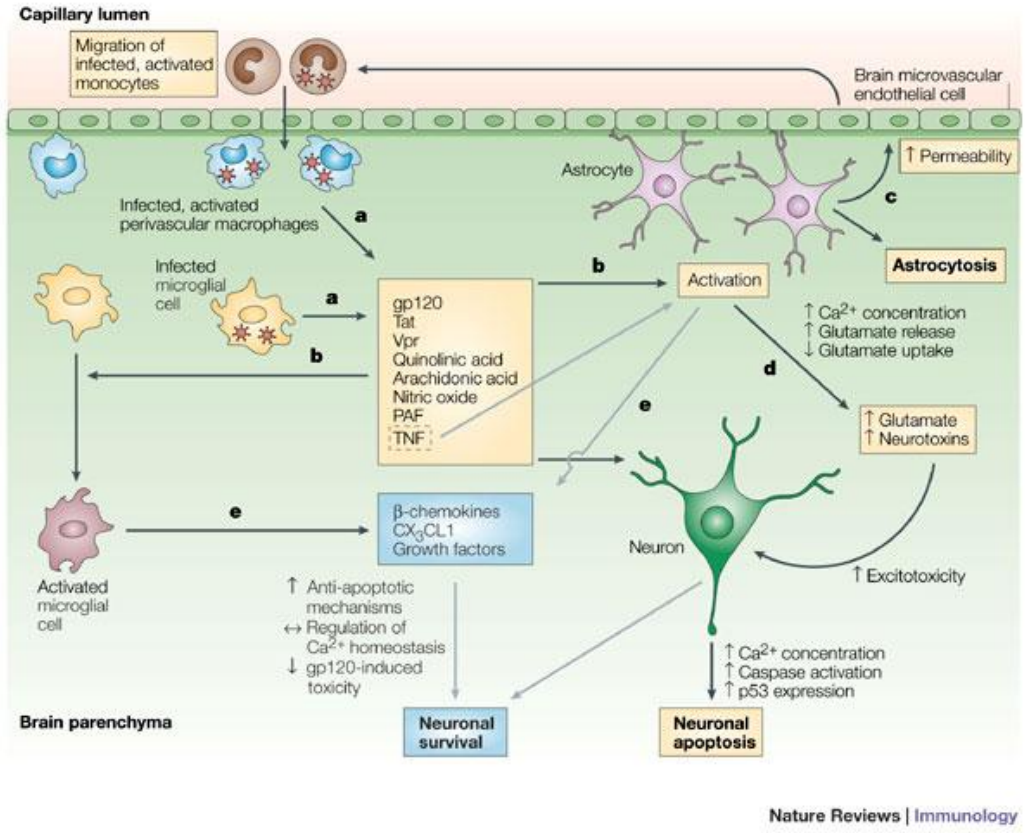
- Low CD4 nadir
- History of AIDS-defining illness
- Advanced age
- Hepatitis C Comorbidity
- Substance abuse, particularly amphetamines, methamphetamine
- Cerebrovascular risk factors (diabetes mellitus, hypertension, hypercholesterolemia)
- Psychiatric disorders (major depression, bipolar disorder, anxiety disorders)
- Sleep disorders

Banerjee et al, AIDS, Behav, 2019; Power et al, J AIDS Hum Retro, 1995; Heaton et al, CID, 2015; Cysique et al, Neurology, 2006; Ances et al, Top Antivir Med, 2019; Moulignier et al, Curr Top Behav Neurosci, 2020; Nasi et al, Clin Exp, Immuno, 2017; Grant et al, Neurology, 2014.

HAND Pathogenesis: why neurocognitive decline despite virological suppression?

- Ongoing neuroinflammation
- Inadequate penetration of antiretrovirals into the CNS
- Neurotoxicity of antiretroviral drugs
- Aging of the HIV population
- Premature aging associated with HIV

Mechanisms of neurodegeneration and neuroprotection



HAND Pathogenesis

Other possible mechanisms involve

- The existence of a reservoir of HIV sequestered in macrophages and microglia, and that is able to evade antiretroviral therapy
    - The idea that the CNS may act as a reservoir for HIV is supported by the phenomenon of viral escape. This refers to the appearance of HIV in the cerebrospinal fluid despite peripheral viral suppression, and which may occur in up to 25% of people with HIV.
- A self-perpetuating neuroinflammatory cross-talk among microglia and astrocytes that was initiated by the original HIV infection.

Inadequate ARV CNS penetration
CNS Penetrating Index - CPE

- Antiretroviral drugs differ in their ability to cross the blood-brain barrier.
  - based on known properties of the drugs and measurement of peripheral and CSF concentrations.
- Differences translated into a scoring system, called the CNS Penetration Effectiveness Ranking System, or CPE score, that ranks each antiretroviral according to its penetration into the CNS.
  - 4 represents the best penetration and a stronger association with a lower CSF viral load.
  - A regimen's total score is obtained by adding the scores of each individual drug.
- Studies that have attempted to correlate CPE scores and neurocognitive outcomes are mixed.
- **Clinical application:** In practice, there is general agreement that CPE should be considered in selecting initial antiretroviral therapy in someone with neurocognitive symptoms/depression and low nadir CD4. There is not strong evidence for using CPE to select therapy in antiretroviral naïve person without neurocognitive impairment/depression with the goal of preventing HAND.

Lanman et al, J Newuroimmune Pharmacol, 2019; Lipsky et al, Lancet, 1993; Abers et al, CNS Drugs, 2014; Shah et al, Nerotoc Res, 2016; Ekins et al, AIDS, 2017; Lynch et al, Am Fam Physician, 2007.

CPE Ranks 2010 Letendre et al. CROI 2010

	4	3	2	1
NRTIs	AZT*	ABC* Emtricitabine	ddi, 3TC d4T	Tenofovir Zalcitabine
NNRTIs	Nevirapine*	Delavirdine Efavirenz**	Etravirine*	
PIs	Indinavir-r	Darunavir Fosampre Lopinavir/* Indinavir/r	Atazanv* ATV/r* FPV	Nelfinavir Ritonavir Tipranavir Saquinavir
Entry		Maraviroc		Enfuvirtide
Integrase		Raltegravir*		r=ritonavir booster

Antiretroviral neurotoxicity

CLASS	Medication	Side Effects
NRTIs	Zidovudine	Anxiety, irritability, mania, psychosis
	Emtricitabine	Insomnia, irritability, depression, and mood lability
	Abacavir	Depression, mania and psychosis
NNRTIs	Efavirez**	Insomnia, nightmares, irritability, mania, depression, psychosis, suicidal ideation
	Nevirapine	Vivid dreams, psychosis, mood changes
	Rilpivirine*	Vivid dreams, irritability, mania, depression, psychosis
PIs	Ritonavir	Fatigue, dizziness
	Saquinavir	Fatigue, psychosis, suicidal ideation
ISTIs	Raltegravir	Insomnia, nightmares, depression, mania, psychosis, dizziness
	Elvitegravir	Suicidal ideation
	Dolutegravir	Sleep disturbance, dizziness, headache

HAND Premature aging 1

- Chronic inflammation as a result of HIV's effect on immune system interacts either additively or synergistically with inflammation resulting from the effect of age on the immune system.
- Interaction leads to premature aging and changes to the brain that are common to both persons with HIV and non-HIV older persons, including cognitive changes.
    - For example, the definition of mild and major vascular cognitive impairment (VCI) overlap with criteria for asymptomatic neurocognitive impairment (ANI) and HIV-associated dementia (HAD), respectively, and share multiple common radiographic and pathologic features.

HAND Premature aging 2

- There has been a similar interest in the relationship between HAND and Alzheimer's Disease since both may be associated with chronic neuroinflammation.
  - We know that HIV and HAND are associated with abnormal amyloid metabolism and that Tat may inhibit enzymes that play a role in amyloid beta degradation.
  - However, studies using PET technology were able to distinguish between amyloid deposition seen in both cognitively impaired and unimpaired persons with HIV and non-HIV persons with Alzheimer's disease.
    - This finding suggests that HIV-related immune dysfunction is not associated with amyloid abnormalities seen in Alzheimers's disease.
    - Other studies compared CSF Alzheimer's biomarkers in persons with HIV and non-HIV persons with Alzheimer's. These studies did not find overlap in CSF biomarkers, including tau and beta amyloid, which also suggests different mechanisms underlying HAND and Alzheimer's.

Trunfio et al, Viruses, 2022

Clinical Presentation

- Gradual, subtle changes in memory and functioning, sometimes noticed by others before noticed by patients
- Other signs that should raise suspicion for HAND include depression and apathy, which may either co-exist with HAND or occur as a secondary sign or symptom.
- Patients may also manifest motor slowing and poor motor coordination and not being able to multi-task and perform more complex sequencing tasks. For example, patients may have difficulty fastening small buttons or difficulty registering for and accessing certain websites.
- In the case of J, it would be easy to dismiss his complaints of forgetfulness and longer time it takes to balance his checkbook, especially since these symptoms did not significantly limit his functioning or cause distress. Although J was not depressed, anxiety was a prominent feature of his presentation.
- Systematic cognitive assessments can be the most effective means of identifying problems early and monitoring for progression.

Neurocognitive domains

Neurocognitive domains underlying the Frascati criteria

- Attention and information processing
- Abstraction and executive functioning
- Language
- Complex perceptual motor skills, e.g. fastening buttons
- Memory including learning and recall
- Simple motor skills or sensory perceptual abilities

- Multi-tasking
- Judgment
- Impulse control

- Formal neuropsychological testing is gold standard for assessing cognition and diagnosing HAND. However, it is time-consuming, expensive, and not always available to patients.

HAND Screening tools

3 simple questions that can be used in persons with cognitive complaints and undetectable viral loads, developed by Simioni and colleagues (Simioni et al, AIDS, 2010)

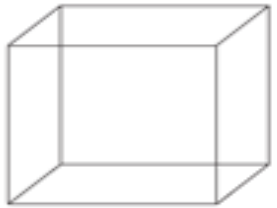
Never/hardly ever/yes, definitely

1) Do you experience frequent memory loss (e.g. do you experience the occurrence of special events, even more recent ones, appointments, birthdays, etc)?
2) Do you feel that you are slower when reasoning, planning activities, or solving problems?
3) Do you have difficulty paying attention (e.g. to a conversation, a book, or a movie)?

- HIV patients with complaints were 15 times more likely than non-complaining patients to be diagnosed with MND or HAD.
- The European AIDS Clinical Society (EACS) recommends using the Simioni questions to screen at time of diagnosis and periodically after initiating treatment depending on patients' symptoms. If a patient answers "definitely yes" to any question, then it's advised to first rule out depression and then refer for neuropsychological testing.
- J answered "definitely yes" to all 3 questions suggesting that further testing was indicated
- Medical Outcomes Study HIV (MOS-HIV). Validated 35-item questionnaire, assesses pain, physical functioning, quality of life, and social and cognitive functioning in 5 minutes Questions based on ability to perform activities of daily living, ADLs, using the telephone, managing medications and finances. By definition, they are normal in ANI. However, asking questions about advanced activities of daily living (AADL) may suggest the presence of ANI. For example, there may be subtle changes in work performance or ability to participate in previously routine leisure activities such as playing card games.

HIV Dementia Scale

- HIV Dementia Scale developed early in the epidemic when prevalence of dementia was 20% and annual incidence was 7%.
- The instrument consists of 4 timed tests and one recall test, but it requires training in measuring anti-saccadic eye movements which many psychiatrists do not have.
- A cut-off score of <10/16 suggests dementia with a sensitivity of 80% and specificity of 91%. These are relevant for the detection of dementia and not for milder impairment.
- In the setting where most persons are virologically suppressed, the sensitivity remains high at 96% but the specificity drops to 54%.

Maximum score	*Score*	*Subtests*
—	—	**Memory: registration** 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	( )	**Attention** Antisaccadic eye movements: 20 commands. _____ errors of 20 trials. [≤ three errors = 4; four errors = 3; five errors = 2; six errors = 1; > six errors = 0] *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.*
6	( )	**Psychomotor speed** 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	( )	**Memory: recall** 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	( )	**Construction** Copy the cube below; record time: _____ seconds. [< 25 seconds = 2; 25 to 35 seconds = 1; > 35 seconds = 0] 
Total score	__/16*	

NOTE: *This scale requires training to administer and may not be preferable for use in a clinical setting. The Modified HIV Dementia Scale[11] 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.*

International HIV Dementia Scale IHDS

NC domain	Task	Scoring	Notes
Memory-registration	four words to recall (**dog, hat, bean, red**)	1 point per correct word	Advantages: • absence of anti-saccadic movts • tested in non-English speaking populations • trans-cultural validity Disadvantages • developed when HIV dementia was more prevalent • sensitivity and specificity for milder HAND poor. When IDS combined with either Simioni questions or Tail making A test, its performance improved.
Motor speed	**Tap the first two fingers of the non-dominant hand as widely and as quickly as possible.**	≥ 15 taps = **4 points** 11-14 taps = **3** 7-10 taps = **2** 3-6 taps = **1** 0-2 taps = **0** **Timed 5 seconds**	Limited data to guide longitudinal screening, or frequency of screening, or to tell us much about the biasing effect of repeat testing or practice effect. However, there is a consensus that a sensitivity and specificity of 70% are needed for effective screening.
Psychomotor speed **Executive functioning** execution of a learned motor program, inhibitory control, attentional flexibility, working memory, and motor planning	**Fist-** **palm down-** **hand perpendicular** **Luria test or sequence**	≥ 4 sequences **= 4 points** 3 sequences = **3** 2 sequences = **2** 1 sequence = **1** unable = 0 points **Timed 10 seconds**	Score of ≤10/12 should be evaluated further for possible dementia.

The International HIV Dementia Scale (IHDS) was developed by Dr. Ned C. Sacktor, Professor of Neurology, Johns Hopkins Medicine.

Montreal Cognitive Assessment MoCA

- MoCA was not developed for use in HIV populations
- Validated for use in older adults to detect milder neurocognitive impairment
- Adds Trails B, copying a diagram and clock draw which broadens its applicability to ANI and MND
- When tested in persons with HIV it yielded a sensitivity of 72% and specificity of 67% using a cut-off score of <25. Thus, although sensitive enough to identify mild deficits, it will also yield false positives.
- Some researchers proposed using neurocognitive testing “lite” as an acceptable screen. It employs the Hopkins Verbal Learning Test and the Wechsler Adult Intelligence Scale III, or, Trail making test A and B used in combination with letter fluency (number of words beginning with the letter “F” that can be named in 60 seconds).

Clinical case 1

J is a 67-year-old man who presents with worsening forgetfulness over the past several months.

- He describes walking upstairs and forgetting reason for going there.
- He also reports forgetting appointments, important birthdays, and misplacing personal belongings in the house. He describes being more distractible than usual and sometimes has to reread parts of a book he just read.
- Sometimes when driving, places do not seem as familiar as they used to.
- J is not able to calculate simple math problems in his head as well as he used to. He has difficulty balancing his checkbook and difficulty completing tasks once started.
- He denies getting lost, or forgetting to lock doors, or to turn off stove or oven.

J was diagnosed with HIV 6 years prior to presentation in setting of a diagnosis of non-Hodgkins Lymphoma, treated with chemotherapy and intrathecal methotrexate. Cd4 cell count 65 and viral load was 450,000 copies/ml. He is currently asymptomatic with Cd4 580 and viral load 21. Medications include dolutegravir (CPE?) and lamivudine (CPE=2), Dovato. He was also successfully treated for hepatitis C and experienced a major depressive episode when diagnosed with NHL and HIV, which was treated with citalopram with benefit

- MoCA 22/30:
  - 3 points clock
  - 1 point copy cube
  - 2 points delayed recall
  - 2 points subtraction
- IHDS 9/12
  - missed 2 words and lost 1 point for psychomotor speed

Clinical case 2

Brain MRI w/ and w/o contrast: Generalized parenchymal volume loss without a regional pattern suggestive of a specific neurodegenerative diagnosis.

Neuropsychological testing

- Impairments: memory, processing speed, executive function, sustained attention, visuospatial processing, and naming.
- Significant slowness across all timed measures.
- Problems on tasks of abstract reasoning, working memory, and set-shifting. Although, J did not endorse elevated anxiety on a questionnaire, he displayed significant anxiety throughout the evaluation
- Given his level of global impairments, reported functional decline, and increased anxiety symptoms since 2017, J meets criteria for **Major Neurocognitive Disorder with behavioral disturbance (anxiety).**
- The etiology of his cognitive limitations is not clear. AD is in the differential as his clinical course (slow, progressive decline, **MRI significant for volume loss**) and the pattern of findings (accelerated forgetting, problems with executive functions, reduced performance on tasks of naming) is consistent with AD.
- It may also be the case that his cognitive problems are exacerbated by anxiety.
- **HIV-associated Neurocognitive Disorder (HAND) is less likely as J's viral load has been undetectable for years.**

Clinical case 3

NM PET CT Scan Brain Amyloid

Diffusely Positive Scan: Scan with pronounced Beta-amyloid deposition.

NOTE: A positive amyloid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with Alzheimer's disease, but may also be present in patients with other types of neurologic conditions, as well as older people with normal cognition. Amyloid PET scans are adjuncts to other diagnostic evaluations, and a positive scan does not establish a diagnosis of Alzheimer's disease or other cognitive disorder.

10/22/24

HIV Clinic note

Discussion regarding possibility of CSF escape/HIV-associated dementia however there are two alternate diagnoses (amyloid-related dementia and vascular dementia) that seem more likely in this case. Can discuss utility of LP with CSF HIV 1 PCR at upcoming visit.

Neuroimaging

Magnetic resonance imaging, magnetic resonance spectroscopy, diffusion tensor imaging and functional MRI correlate with HAND severity

Evidence does not support use of any of these modalities as a replacement for neuropsychological testing

Neuroimaging can be used to support the diagnosis of HAND and help differentiate it from other causes of neurocognitive impairment.

In younger healthy persons with HIV, MRI may show cerebral atrophy and periventricular white matter changes in excess of normative values, even in the absence of cognitive impairment.

In older persons, imaging sometimes useful in differentiating HAND from vascular and Alzheimer's dementia. In early AD, there may be cortical atrophy affecting the entorhinal cortex and hippocampus, while in milder HAND there may be subcortical atrophy affecting the cerebellum and basal ganglia.

In J's case, MRI shows generalized volume loss with no regional pattern suggestive of a specific neurodegenerative diagnosis. Currently being evaluated by cognitive neurology and neurology infectious disease

Blood and CSF markers

- Apolipoprotein E (Apo-E), a genetic risk factor for Alzheimer's Disease, and CSF neurofilament light (NF-L): neither is used in differentiating HAND from other dementias and cognitive disorders since they can be present in several neurodegenerative disorders.

- Detectable viral replication in the CSF may occur in the setting of peripheral suppression and should be considered in patients with new onset neurological symptoms or acceleration of cognitive decline.

- **In J's case,** Neurology may recommend CSF HIV RNA determination

Viral escape 1

In 4 BWH cases patients had plasma HIV RNA < 1000, but CSF HIV RNA > plasma HIV RNA → all diagnosed w HAND

1 case:

- long-standing HIV infection on TDF/FTC/FPV
- plasma CD4 = 624
- plasma HIV RNA = 569
- multiple neurologic complaints (hyperesthesia, hypersensitivity to odors and sounds, temp fluctuations
- CSF HIV RNA = 30,623
- CSF + plasma = 41L, 210W, 215Y, 184V, 98G
- Changed to RAL/ETV/DRV/r → plasma/CSF VLs decreased, symptoms improved

Viral escape 2

- Documented cases of plasma/CSF HIV RNA discordance
- 11 patients with plasma HIV RNA < 50 presenting with neurologic symptoms with detectable CSF HIV RNA > 200
- Resistance mutations identified in the CSF HIV of some, optimization of ART lead to clinical improvement in all patients

Canestri et al, CID, 2010

HAND Role of medications

- Advantages of antiretroviral therapies with better CNS penetration are unclear.
- Evidence does not support higher CPE regimens to prevent HAND.
- In patients who are not already on antiretroviral therapy, and now have HAND, it is worth considering CPE in selecting a regimen. This is not true for patients with HAND who have already achieved full suppression in plasma.
- Starting antiretroviral therapy as close to HIV diagnosis as possible is probably the single most effective strategy for preventing HAND.
- Managing other comorbidities and risk factors relevant to HAND are also important.

Do cognitive enhancers have a role?

Cognitive enhancers such as cholinesterase inhibitors and memantine have not shown promise in small clinical trials to date in improving cognitive functioning in patients with HAND. Therefore, they cannot be recommended for use in HAND to improve functioning.

Hirsch et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

What can we do?

- Manage psychiatric comorbidities such as depression and treat as indicated.
- Monitor for polypharmacy and address when appropriate.
- Assist patients to optimize functioning in terms of IADLs and AADLs since persons with HIV often experience faster declines in motor functioning.
- Attend to priorities in setting treatment goals.
- Mitigate risk factors for accelerated aging. This may involve preventing and managing risk factors for atherosclerosis such as hypertension, diabetes, and obesity.
- Follow J and monitor for progression. Consider CSF evaluation for viral escape and change HIV medication regimen if appropriate.

Delirium

Delirium

- Broad overlap between People with HIV and non-HIV patients regarding diagnosis and prevention of delirium in people with HIV.

- Notable differences are the vulnerability conferred by previously unidentified HAND and risk associated with antiretroviral medications and other neurotoxic substances and drug withdrawal states.

Delirium treatment

- Same basic principles of treating delirium in non-HIV patients.
- Physical restraints and antipsychotic medications should be used when other means of insuring safety of patients and staff have not been effective.
- Patients with more advanced immune dysfunction are going to be more sensitive to the motor side effects of antipsychotic medications.

Delirium treatment

- Research is limited on the use of antipsychotic medications in people with HIV and delirium.
- 1996, placebo controlled, double-blind trial, compared haloperidol, chlorpromazine, and lorazepam.
  - Lorazepam discontinued due to cognitive impairment.
  - Antipsychotic arms showed decrease in delirium scores compared to placebo. Low doses of antipsychotic medications were used to avoid extrapyramidal side effects.

- Lowest possible doses recommended, especially with poorly controlled HIV.
- Hyperactive delirium, sedating agents like olanzapine and quetiapine can be used. If intravenous administration is required, then haloperidol can be useful.
- Ziprasidone and olanzapine can be given intramuscularly if intravenous access is lost.

- As with non-HIV patients, caution is warranted regarding anticholinergic and cardiac, QTc prolonging effects of some of these medications. There is not sufficient data on the use of dexmedetomidine in patients with HIV to comment on its use in this population.

Psychiatric co-morbidity

Depressive disorders

Clinical case

O is a 60-year-old female with longstanding, now stable, HIV disease, on Genvoya (elvitegravir, cobicistat, tenofovir alafenamide, emtricitabine) admitted for management of heart failure.

- CC: frustrated with being rehospitalized so soon after her previous inpatient admission for pulmonary edema.
- Psychiatry consulted after O expressed feelings of hopelessness and reluctance to take her HIV and cardiac medications.
- Past psychiatric history: recurrent major depressive disorder managed in outpatient setting by supportive psychotherapy alone. Past treatment with nortriptyline with good response. Past treatment with methadone for OUD, now in sustained remission.
- **DSM Diagnosis:**
  - Major depressive episode emerging from the stress of worsening medical problems
  - Opioid and cocaine use disorder in stable remission.
- Recommend antidepressant medication
  - How does cardiac disease influence recommendation?
  - How does Genvoya influence your recommendation?

Ferrari et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Depression

- Discrete major depressive episodes are not as common as depressive symptoms co-occurring with, or arising from other conditions(pts will sometimes view these other conditions as the primary problem)
- Other conditions comprise
  - Stigma
  - Shame
  - Traumatic events, either acute (assault) or complex (developmental), healthcare system
  - HIV-related medical illness
  - Antiretroviral drugs
  - Neurocognitive disorders
  - Non-HIV-related medical illness
  - Housing, finances, immigration
  - Family- or relationship-related
  - Insomnia
- Substance-related (syndemics, chemsex)

Depression

- Most common neuropsychiatric disorder in people with HIV
- One of the most common reasons for psychiatric consultation from our medical colleagues
- Occurs at all stages of HIV disease though its prevalence is highest in people with advanced HIV.
- Often undiagnosed, and when identified, is undertreated.
- Common consult questions related to neuropsychiatric side effects of antiretroviral medications and drug-drug interactions with antidepressant medications.
- Strong evidence that depression is associated with poor adherence to HIV medications, poorer quality of life and worse medical outcomes.
- When depressive symptoms are effectively addressed, there is a corresponding improvement in morbidity and mortality.

Prevalence

- There are very few large population-based studies available to give us better estimates of the prevalence of depression in HIV
- Prevalence rates vary among studies likely due to different methodologies used and selection of subjects.
- Most studies have found a 2- to 4-fold greater prevalence compared to people without HIV.
- Best recent estimate comes from a systematic review and meta-analysis by Rezaei and colleagues which found an overall prevalence of 31% across 118 studies.

Rezaei, BMJ Support Palliat Care, 2019

Risk Factors

- Female sex
- Pre-existing and family history of depression
- Psychosocial factors with a known association with depression in people without HIV
  - Trauma
  - Exposure to violence
  - Financial instability, insecure housing, immigration problems, all of which more commonly found in people with HIV.
- Neurobiological changes linked to HIV may help account for high rates of depression.
  - **Neuroinflammation**
  - **Reduction in trophic factors**
  - **Alterations in dopamine and other neurotransmitters.**

Diagnosis

- Similar to identification in other medical conditions.

- Some differences
  - hypogonadism more common in PWH, consider in patients with sexual dysfunction.
  - CNS opportunistic conditions, toxoplasmosis and lymphoma, uncommon yet consider in advanced illness.
  - HIV medications can cause depressive symptoms: efavirenz, rilpivirine and integrase inhibitors
  - HIV CNS involvement – overlapping symptoms: apathy, weight loss, fatigue, psychomotor and motor slowing.
  - Reaction to life stressors that are more common in HIV such as homelessness and stigma.

- In practice, difficult to differentiate among these causes. Consider assessing for the affective-cognitive dimensions of depression to improve diagnostic accuracy. Signs and symptoms such as pessimism, hopelessness, social withdrawal, and lack of reactivity
- Endicott criteria that have been proposed for use in cancer, may be helpful.

- No instruments developed for screening for depression in HIV. May use **Hospital Anxiety and Depression Scale,** designed for use in medically ill patients, advantage of not including the somatic symptoms of depression and relies mostly on anhedonia.

Endicott, Cancer, 1984

Etiology

- Far from understanding the etiology of depression in people without HIV.
- Same neuroinflammatory and neuroendocrine pathways thought to underly the generation of depression have been studied in relation to the effect of HIV on the CNS.
- Research suggests HIV renders people vulnerable to depressive disorders through its direct and indirect effect on the brain and this effect is mediated by immune dysfunction.

Antiretroviral neurotoxicity

Hirsch et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

CLASS	Medication	Side Effects
NRTIs	Zidovudine	**Anxiety, irritability**, mania, psychosis
	Emtricitabine	**Insomnia, irritability, depression, and mood lability**
	Abacavir	**Depression**, mania and psychosis
NNRTIs	Efavirez**	**Insomnia, nightmares, irritability,** mania**, depression,** psychosis**, suicidal ideation**
	Nevirapine	Vivid dreams, psychosis, **mood changes**
	Rilpivirine*	Vivid dreams**, irritability,** mania**, depression**, psychosis
PIs	Ritonavir	Fatigue, dizziness
	Saquinavir	Fatigue, psychosis, **suicidal ideation**
ISTIs	Raltegravir	**Insomnia, nightmares, depression,** mania, psychosis, dizziness
	Elvitegravir	**Suicidal ideation**
	Dolutegravir	Sleep disturbance, dizziness, headache

The CDC recommends screening for depression and suicidality in patients on an **Efavirenz-containing regimen,** which once was a first-line treatment for HIV and no longer is due to its neuropsychiatric side effect profile. Dolutegravir and other integrase strand transfer inhibitors may also cause depression and suicidality.

Pharmacotherapy 1

- Similar to people without HIV, yet with important additional considerations.
  - Drug-drug interactions and risk of non-adherence may be greater by virtue of polypharmacy.
  - PWH with depression have higher mortality rates and if you treat depression, adherence to HIV medications improve.
  - Indirect public health benefit of improving community viral suppression which in turn reduces HIV transmission rates.

- Meta-analyses and randomized controlled trials demonstrate antidepressant medications are effective in treating depression in HIV and none is more effective than others.
  - Choice based on other factors such as tolerability, side effects and drug-drug interactions.
  - SSRIs and SNRIs well tolerated , first-line agents, though sexual side effects are common and sometimes interfere with adherence.
  - Bupropion well tolerated and can be useful in patients with HIV related fatigue and depression due to its activating properties, regardless of HIV clinical stage. Early concern about seizure risk, due to CNS HIV, not as significant

Pharmacotherapy 2

Published consensus statement: Survey of HIV psychiatrists						
Citalopram and escitalopram emerged as preferred first-line option						
Switch			**Augmentation**			
Preferred	**2nd line**	**3rd line**	**Preferred**	**2nd line**	**3rd line**	
SNRIs; also consider bupropion another SSRI	mirtazapine	Fluvoxamine, amitriptyline and MAOIs	second non-SSRI antidepressant medication	Lithium, psychostimulants, 2nd generation antipsychotics, and thyroid hormone replacement	Buspirone	

HIV as well as HIV medications can also be associated with QTc prolongation, especially ritonavir, lopinavir, efavirenz and atazanavir.

Freudenreich et al, Psychosomatics, 2020

Drug-Drug interactions

Pharmacokinetic, involve the CYP450 system	
HIV medications either inhibit or induce the metabolism of antidepressant and other psychiatric medications.	
Metabolic inhibition, which occurs almost immediately, with **CYP 3A4, 2D6 and 1A2** **Ritonavir and cobicistat** are the two most commonly used HIV medications that are inhibitors.	
Ritonavir	• was once used as a component of antiretroviral regimens, now is almost exclusively used to boost the effect of other HIV medications by inhibiting their metabolism.
Cobicistat	• on the other hand, has no antiviral activity and like ritonavir, is used to boost other HIV medications.
Induction with 3A4, 2D6 and 1A2 can take up to 7-10 days to achieve effect. **Carbamazepine**, best example of pan inducer.	
All protease inhibitors, and Bictegravir (integrase inhibitor)	• rely on **CYP 3A4** for their metabolism and risk dropping below therapeutic levels if used with carbamazepine.
Efavirenz, and nevirapine (NNRTIs) are potent **3A4 inducers**.	• Due to this effect, **methadone**, may need higher than usual doses if efavirenz used. • Patients who discontinue taking efavirenz, may experience toxic levels of methadone.

Smith et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Psychotherapy and other therapies

- Large meta-analyses have demonstrated that **cognitive-behavioral therapy** has improved depressive and anxiety symptoms in people with HIV.
- Similarly, group psychotherapy has been shown to be an effective treatment for depression in HIV.
- Evidence for interpersonal therapy, including teletherapy, and psychoeducation and supportive psychotherapy.

Other therapies

- There is not sufficient research into the use of **ECT, TMS, and ketamine and esketamine** in depression in people with HIV to recommend best practices. However, there are **case reports of the successful use of ECT** for treatment of depression.

Clinical case

O is a 60-year-old female with longstanding, now stable, HIV disease, on Genvoya (elvitegravir, cobicistat, tenofovir alafenamide, emtricitabine), admitted for management of heart failure.

- Psychiatry consulted after O expressed feelings of hopelessness and reluctance to take her HIV and cardiac medications.
- She carries a diagnosis of recurrent major depressive disorder managed in outpatient setting by supportive psychotherapy alone.
- Past medication history: successful treatment with nortriptyline. Good response to methadone for OUD
- Evaluation significant for frustration with rehospitalization so soon after her previous inpatient admission for pulmonary edema.
- DSM Diagnosis:
  - Major depressive episode emerging from the stress of worsening medical problems
  - Opioid and cocaine use disorder in stable remission.
- Recommend antidepressant medication
  - How does cardiac disease influence recommendation?
  - How does Genvoya influence your recommendation

Clinical case

O is a 60-year-old female with longstanding, now stable, HIV disease, on Genvoya (elvitegravir, cobicistat, tenofovir alafenamide, emtricitabine), admitted for management of heart failure.

Despite consensus among HIV psychiatrists for citalopram and escitalopram, you avoid because of possible QTc prolongation in the setting of cardiac disease and electrolyte abnormalities. Avoid nortriptyline since cobicistat may boost blood levels and result in toxicity. You recommend sertraline which has few drug-drug interactions and documented use in people with HIV.

Other choices you would have considered?

- Avoid fluoxetine due to its CYP 2D6 and 2C19 inhibition of antiarrhythmics.
- Fluvoxamine's potent inhibition of CYP 1A2 and 2C19 and paroxetine's CYP inhibition of 2D6 and 2B6, which antiarrhythmics utilize, make these less desirable choices.
- Mirtazapine less potential for interactions with HIV medications though you may want to avoid due to its side effect profile.
- No data on vortioxetine and interactions with HIV medications.

Bipolar disorder

Bipolar disorder

Bipolar disorder is overrepresented in people with People with HIV

- National Epidemiologic Survey on Alcohol and Related Disorders, 12-month prevalence rate: 10.8% among PWH, compared to 3.7% among people without HIV.

- NIMH Multisite Acute HIV Infection Study: lifetime history of depressive or bipolar disorder, 53% of PWH

- Brazilian study found prevalence of bipolar I disorder was 5.6% in PWH, nearly 6 times higher than in the general US population.

- People with HIV and bipolar disorder are more likely to engage in condomless sex, less likely to adhere to HIV medication therapy and more likely to have a co-occurring substance use disorder.

De Sousa, AIDS Care, 2013

Diagnosis

- **Consider AIDS mania in PWH presenting with new onset mania**
  - Clinically indistinguishable from primary mania, though some reports suggest that it is more likely to manifest with irritability.
  - Less to be associated with a personal or family history of bipolar disorder
  - More likely to present with cognitive impairment.
  - Longitudinal cohort studies suggest that AIDS mania is more likely to emerge during the progression from HIV to AIDS.
- As with depression, consider mania due to CNS opportunistic conditions or non-HIV related medical conditions such Cushing's syndrome and may be substance-induced.
- Early in the epidemic, zidovudine was associated with mania.

Lyketsos, Am J Psychiatry, 1993

Pharmacotherapy

Studies designed to guide best practice for drug treatment of bipolar disorder in HIV are scarce.	
General considerations:	
Lithium	• Can be an effective mood stabilizer that should be used with caution due to its narrow therapeutic window. • Trough levels should be checked frequently during dose escalation, especially in patients with advanced disease who are at higher risk of toxicity. • HIV nephropathy, if present, may affect lithium levels. • Lithium use in secondary mania may be more likely to cause delirium and dehydration.
Valproate	• May be more likely to cause hepatotoxicity, pancreatitis and hyperammonemia in the setting of HIV. **Recommended by Consensus Survey** Freudenreich et al, Psychosomatics, 2020
Atypical antipsychotics	• Atypical antipsychotics may more quickly address manic symptoms than mood stabilizers do, though also more likely to be associated with extrapyramidal and anticholinergic side effects, compared to non-HIV persons.
Quetiapine	• Quetiapine recommended for secondary mania by **Consensus Survey** Freudenreich et al, Psychosomatics, 2020

Douaihy et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Drug-drug interactions

Lithium	• **Lithium is the least likely mood stabilizer to pose problems with drug interactions and antiretroviral medications.** • **Is Lithium neuroprotective? A randomized controlled trial of lithium in HAND did not show benefit to cognitive functioning.** • **A recent randomized, placebo-controlled trial of lithium and tenofovir combination did not show evidence for increased renal toxicity.**
Valproate	• Valproate may inhibit drugs that depend on uridine glucuronosyltansferase, such as zidovudine and lamotrigine, and may raise their blood levels. • Valproate acid may increase risk of hepatotoxicity when taken with HIV medications that are CYP inducers, such as efavirenz and nevirapine.
Carbamazepine Oxcarbazepine, Phenobarbital, Phenytoin	• Should be used with caution with protease inhibitors, non-nucleoside reverse transcriptase inhibitors, and integrase inhibitors due to their CYP-inducing effects and consequent increased risk of HIV treatment failure.

Psychosis

Antiretroviral neurotoxicity

CLASS	Medication	Side Effects
NRTIs	Zidovudine	Anxiety, irritability, mania, **psychosis**
	Emtricitabine	Insomnia, irritability, depression, and mood lability
	Abacavir	Depression, mania and **psychosis**
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	Nevirapine	Vivid dreams, **psychosis**, mood changes
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PIs	Ritonavir	Fatigue, dizziness
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ISTIs	Raltegravir	Insomnia, nightmares, depression, mania, **psychosis**, dizziness
	Elvitegravir	Suicidal ideation
	Dolutegravir	Sleep disturbance, dizziness, headache

Hirsch et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Pharmacotherapy 1

- No randomized controlled trials evaluating antipsychotic use in people with HIV and primary or secondary psychotic disorders.
- Several open label studies and case reports support the use of risperidone, ziprasidone and clozapine for AIDS-related psychosis.
- Consensus Survey recommended quetiapine, risperidone, aripiprazole for primary psychosis
- Consensus Survey recommended quetiapine, risperidone for psychosis secondary to HIV
- Atypical antipsychotics preferred since first generation antipsychotic medications carry higher risk for extrapyramidal side effects and neuroleptic malignant syndrome. No evidence supporting one antipsychotic medication over others in PWH and a primary psychotic disorder.

Freudenreich et al, Psychosomatics, 2020
Smith et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Pharmacotherapy 2

Metabolic syndrome

- People with HIV taking antiretroviral medications, especially protease inhibitors and nucleoside reverse transcriptase inhibitors are at greater risk for metabolic syndrome and lipodystrophy.
- Combination of HIV medications and second generation antipsychotics associated with higher mean BMI, blood pressure, and triglycerides as well as increased rates of developing diabetes.
- Recommended that caution be used when prescribing clozapine, quetiapine and olanzapine and to a lesser degree, risperidone.
- When metabolic syndrome is a concern, consider aripiprazole, ziprasidone or lurasidone, possibly with metformin.

Pharmacotherapy 3

QT prolongation	
HIV can also be associated with QTc prolongation	
Antiretrovirals Ritonavir Lopinavir Efavirenz Atazanavir	HIV medications that can also especially be associated with QTc prolongation
Antipsychotics Ziprasidone Haloperidol	Should be avoided
Antipsychotics Aripiprazole Brexpiprazole Cariprazine Lurasidone	Have been associated with the least QTc prolongation

Drug-drug interactions

Nucleoside reverse transcriptase inhibitors (NRTIs) integrase inhibitors (ISTIs)	Less likely to lead to clinically significant drug-drug interactions with psychiatric medications.
Elvitegravir (ISTI), used with CYP inhibitor boosters, **cobicistat (Genvoya)**	• May elevate levels of **quetiapine** while other integrase inhibitors do not have such interactions. • Therefore**, quetiapine** dose adjustment may be necessary.
CYP 3A4 inhibitors and pan inhibitors	• **May raise blood levels of** • Aripiprazole • Brexpiprazole • Clozapine • Lurasidone • Quetiapine • Risperidone
CYP inhibitors or inducers	• **Ziprasidone** may be the least affected by CYP inhibitors or inducers.

Smith et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Trauma-related disorders

Trauma-related disorders

Consider the difference between complex PTSD, or exposure to prolonged trauma from which there was no escape such as ongoing childhood abuse and DSM PTSD caused by a single traumatic event.

- **HIV Costs and Service Utilization Study:**
  - 20.5% of women
  - 11.5% of men who have sex with men
  - 7.5% of men who did not report sex with men were exposed to violence since their HIV diagnosis.
  - For many respondents, violence was related to their HIV diagnosis.
- People with HIV also report higher rates of childhood sexual abuse, and prior sexual trauma as adults.
- A recent meta-analysis found that persons with HIV have a PTSD prevalence of 28%, greatly exceeding the rate in the general population.
- These and other studies suggest that complex trauma and PTSD may be risk factors for HIV acquisition.
- Increased frequency or types of trauma may be associated with risk behaviors such as younger age at first sexual experience, more frequent condomless sex, sex work and multiple sexual partners, drug and alcohol use.

Zierler et al, Am J Publ Hlth, 2000

Types of trauma experienced by people with HIV

PWH are at higher risk for trauma and being traumatized. Trauma overrepresented in marginalized groups, homelessness and belonging to the LGBTQ community.

- **Sexual assault -** shared risk factors with HIV and psychological sequelae of assault increases downstream risk of HIV exposure. People with HIV are at higher risk for sexual assault. Know about non-occupational post-exposure prophylaxis.
- **Intimate partner violence -** similar to sexual assault, **the relationship between HIV and IPV is bidirectional**. The abusive power dynamics seen with IPV may contribute to forced sex without the use of barrier protection
- **Military trauma -** PTSD related to combat may predispose veterans to HIV risk behaviors
- **Migration trauma -** Trauma experienced before or during immigration and post-immigration experiences such as homelessness and financial instability may be associated with trauma and attendant HIV risk.
- **Intergenerational trauma -** The concept of intergenerational trauma may be useful for persons with HIV whose trauma histories are embedded in a larger context of family or intergenerational traumatic stressors.

Trauma, treatment adherence and medical outcomes

- One of the most damaging aspects of trauma is its effect on adherence.

- Studies suggest that avoidance, dissociation and problems coping mediate this relationship.

- Some of the most tragic deaths experienced in our practice have involved a link between trauma and HIV medication non-adherence. One patient developed an intense aversion to HIV medications, after learning that she acquired HIV from her husband who was aware yet didn't disclose his HIV status to her and did not use barrier protection.
- She eventually progressed to AIDS and survived only because her HIV medical team went to heroic lengths to engage her in treatment.

- This case illustrates findings from studies linking trauma to lower CD4 cell counts, higher viral loads, and higher likelihood of progression to AIDS.

- Biological mechanisms proposed to explain the connections. The sympathetic activation and autonomic arousal associated with acute arousal have been shown to be associated with increased rates of viral replication.

Bradley et al, HIV Psychiatry: A Practical Guide for Clinicians, ed: Bourgeois, Cohen, Makurumidze, 2022

Summary

- HIV has a disproportionate effect on marginalized subpopulations
- U = U Undetectable equals untransmittable
- PrEP is available as oral or long-acting injectable formulation
- CNS may act as reservoir for HIV
- Milder forms of HAND predominate
- Asymptomatic HAND significant for being at increased risk of progression
- HIV medications can cause depressive symptoms: efavirenz, rilpivirine and integrase inhibitors
- Ritonavir and cobicistat are potent CYP inhibitors that may interact with psychiatric medications
- Efavirenz is a CYP inducer that may reduce levels of methadone
- Consider AIDS mania in new onset mania in PWH
- PWH are more sensitive to motor and metabolic side effects of antipsychotic medications
- Awareness of relationship of trauma and HIV


Mass General Brigham