Changes in Neurocognition and Mood in People Aging with HIV

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Disclosures

- Nothing to disclose

CASE

- Background: 69 year old male living with HIV (CD4 159, VL 24,651)
  - 2-week history of progressive somnolence, malaise, anorexia and weakness
  - 1 week of abdominal pain
  - 5 days of fevers & drenching night sweats

- Three months prior to admission
  - Fall with a 10min loss of consciousness
  - Developed progressively worsening headache post fall x 1month

CASE

Past Medical History:

- Hypertension
- Obstructive sleep apnea
- Stage 3 chronic kidney disease
- Cerebrovascular accident
- Gout
- Syphilis
- Depression

Family History:

- Aneurysm - mother deceased at age 45
- Coronary artery disease - father deceased at age 70

Meds:

- Dapsone
- Nifedipine
- Furosemide
- Metoprolol
- **(NOT on ART)**

Social History:

- Alcohol
- Consumption of runny eggs

CASE

PE: T 39.4, P 93, BP 118/57, RR 18, O2 sat 95% RA

Gen: somnolent but arousable

HEENT: oral thrush

Neuro: oriented to person, place, month (not year), mildly confused, impairment in following one-step commands

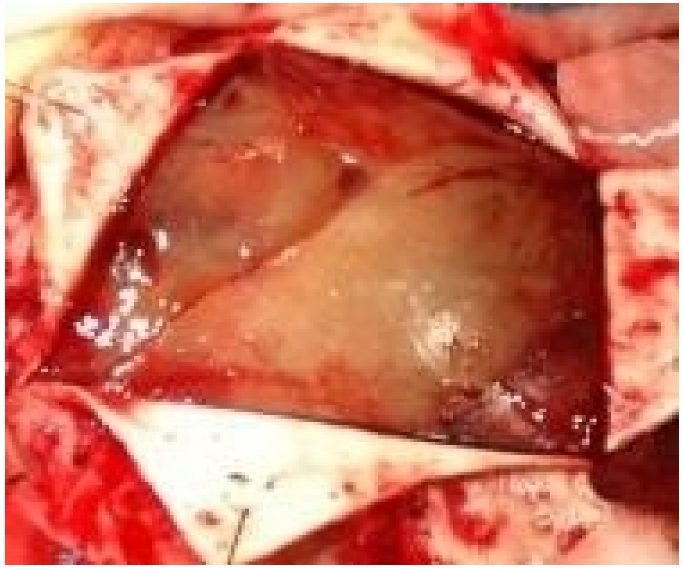
Head CT

- Hypodense fluid collection along the right frontotemporoparietal convexity
- 5mm right to left midline shift

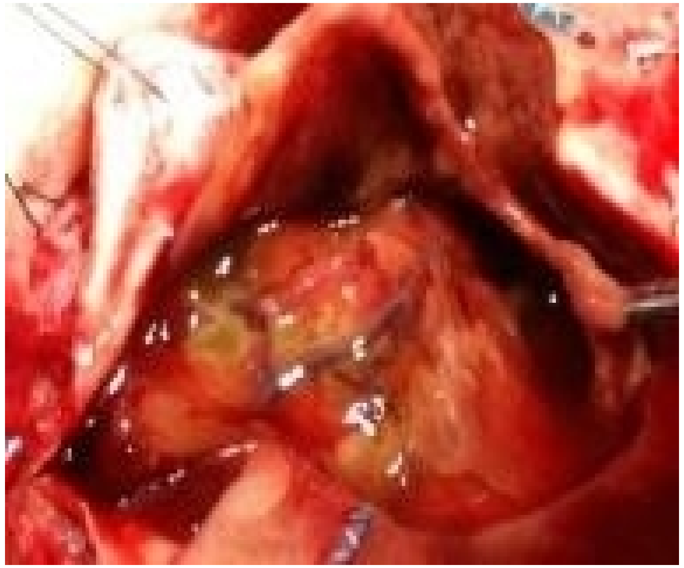
CSF: 43 WBC (43 monos), glucose 53, protein 62
CSF HSV/CMV/VZV/EBV/JC virus PCR negative; VDRL/crypto Ag negative
CSF mycobacterial/fungal cultures negative

CASE

Persistent fever, mental status deterioration, urinary incontinence ➔ TO OPERATING ROOM



Intraoperative subdural space prior to debridement



Intraoperative subdural space post debridement: residual fibrinous material adjacent to cortical structures

Right frontotemporoparietal subdural empyema with *Salmonella enteritidis*

- Blood cultures: *Salmonella enteritidis*
- Intraoperative cultures: *Salmonella enteritidis*

CASE

- 1 week post surgical debridement
  - Left sided ptosis, facial droop, dysarthria, hemiparesis
  - Acute right frontal/temporal/parietal cerebral infarcts (adjacent to subdural empyema)
    - MRA: left middle cerebral and left carotid artery atherosclerotic disease
    - Started on aspirin and atorvastatin
- Discharged to rehabilitation facility
- Rehospitalized 1 day later
  - Fever, left sided neglect, flaccid paralysis of left upper and left lower extremity
    - MRI: progression of infarcts
    - Mental status deterioration, seizures (EEG) -> initiation of antiepileptic medication
- Discharged to nursing facility at 7 weeks post initial presentation
  - Defervesced, residual cognitive deficits
  - Persistent left sided neglect/left facial droop; 4/5 LLE strength; 0/5 LUE strength
- Two years post event still resident at nursing facility
  - Improved speech; decreased neglect; persistent motor and cognitive deficits

CASE CONSIDERATIONS

- What was the role of HIV, age and cognition in this patient’s clinical course?

Global HIV Statistics

- 91.4 million people infected with HIV since the start of the epidemic
- 40.8 million people globally living with HIV (2024)
  - 1.3 million people newly infected
  - 31.6 million people accessing antiretroviral therapy
- Estimated 25% of people living with HIV globally aged 50 years and over

UNAIDS Fact Sheet https://www.unaids.org/en/resources/fact-sheet

Substantial Burden of Cognitive Impairment in HIV

- Estimated prevalence among persons with HIV: 20-90%
- Pooled prevalence in ART era: 42.6%
  - Adults 18+
  - Meta-analysis: January 1996 - May 2020
- Estimated 16 million adults globally with HIV have cognitive impairment

Wang et al. Neurology 2020; 95: e2610-21

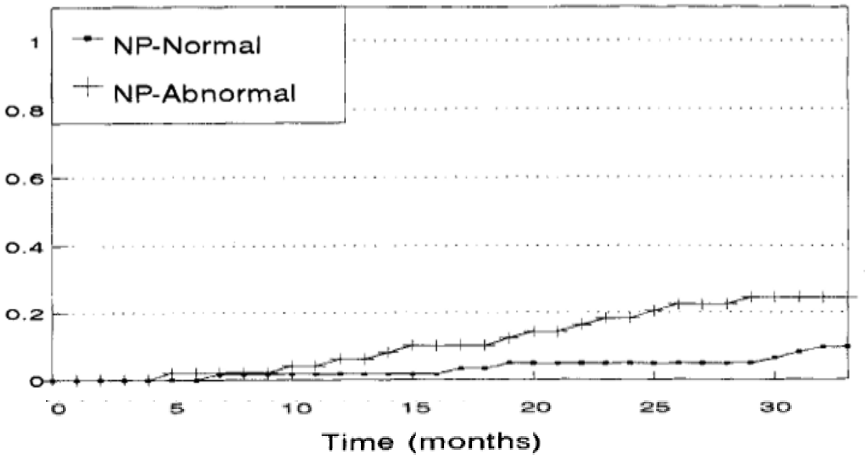
Cognitive Impairment Outcomes in HIV

- Mortality
- Hospitalization & ↑Health care utilization
- Challenges in navigation of medical care/medication intake
- ↓Quality of life
- Frailty
- Disability & Institutionalization

Cognitive Impairment Associated with ↑Mortality Risk in HIV

- Pre-ART era

Cumulative Probability of Death over 36-month period



- 111 Persons with HIV
    - Assessments through August 1991
- NP Abnormal: Score ≥2 SD below mean of neuropsychologic test
- **2.9-Fold ↑ mortality if cognitively impaired**

Mayeux R et al. Neurology 1993; 43: 176 - 182

- Post ART era
    - Northeast AIDS Dementia Study Cohort
    - 1998 - 2002
    - **HIV dementia: 6-Fold ↑ mortality**

Sevigny JJ et al. JAMA Neurology 2007; 64: 97-102

- Danish Nationwide Cohort Study
- 1997 – 2008
- **Median survival for persons with severe neurocognitive disorders (dementia) & HIV 4.3 years (compared with 9.7 years for persons with severe neurocognitive disorders without HIV)**

Lescure FX et al. Clin Infect Dis 2011; 52: 235-43

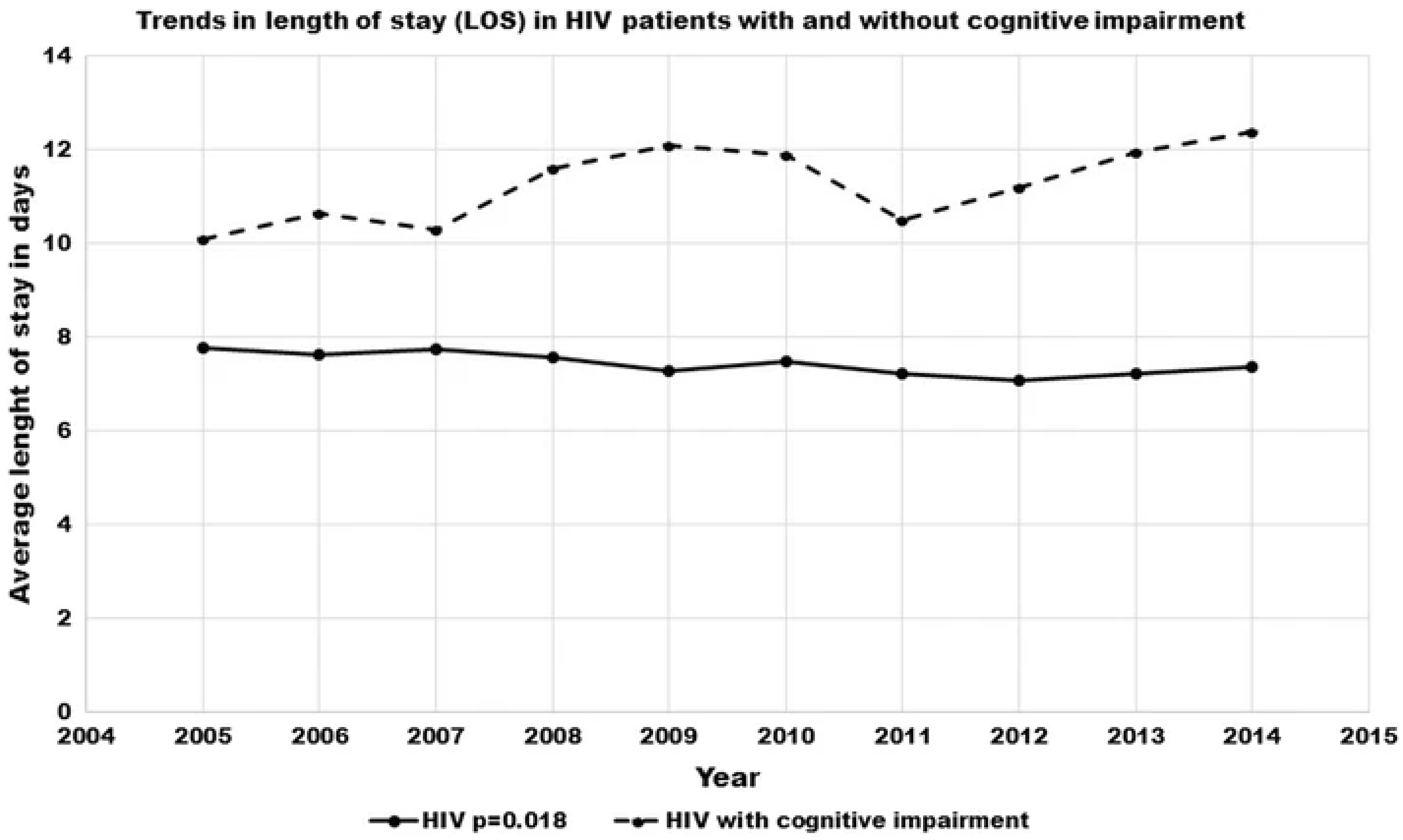
↓Cognitive Function and Physical Frailty Independently Associated with Increased Risk of Death

	Mortality Risk Adjusted HR (95% CI)
↓ Cognitive Function*	**1.44 (1.13, 1.85)**
Physical frailty**	**2.03 (1.18, 3.48)**

**Per unit decrease in z score (neuropsychological test battery)*
***Fried physical frailty phenotype*
AIDS Linked to the IntraVenous Experience (ALIVE) Cohort
(Persons with history of injection drug use with and without HIV)

Piggott DA et al. AIDS 2025; 39: 1214-23

Cognitive Impairment and Health Care Utilization: Increased Hospital Length of Stay



U.S. Nationwide Inpatient Sample – AHRQ HCUP Project
National Estimate of Hospital Inpatient Stays
Patel S et al. AIDS Behav 2018; 22: 3198-3208

Cognitive Impairment and Health Care Utilization: Institutionalization

Disposition	Cognitive Impairment (HAND)	No Cognitive Impairment (No HAND)
Facility	**45.5%**	**13.2%**
Home	**35.1%**	**67.6%**
Home health care	11.4%	9.4%
Died in hospital	5.3%	4.2%
Against medical advice	2.8%	5.5%

- ↑ Cost of hospital admission
- ↑ Mortality
- ↑ Institutionalization

U.S. Nationwide Inpatient Sample – AHRQ HCUP Project
National Estimate of Hospital Inpatient Stays
Patel S et al. AIDS Behav 2018; 22: 3198-3208

Defining Cognitive Impairment among Persons with HIV
Evolving Nomenclature

- 1991 American Academy of Neurology
  - HIV-associated dementia
  - Minor cognitive motor disorder

- 2007 Frascati Criteria
  - HIV-associated Neurocognitive Disorders (HAND)
  - NIMH/NINDS convened working group

- 2023 International HIV Cognition Working Group
  - HIV-associated Brain Injury vs. Other Causes of Brain Injury in HIV

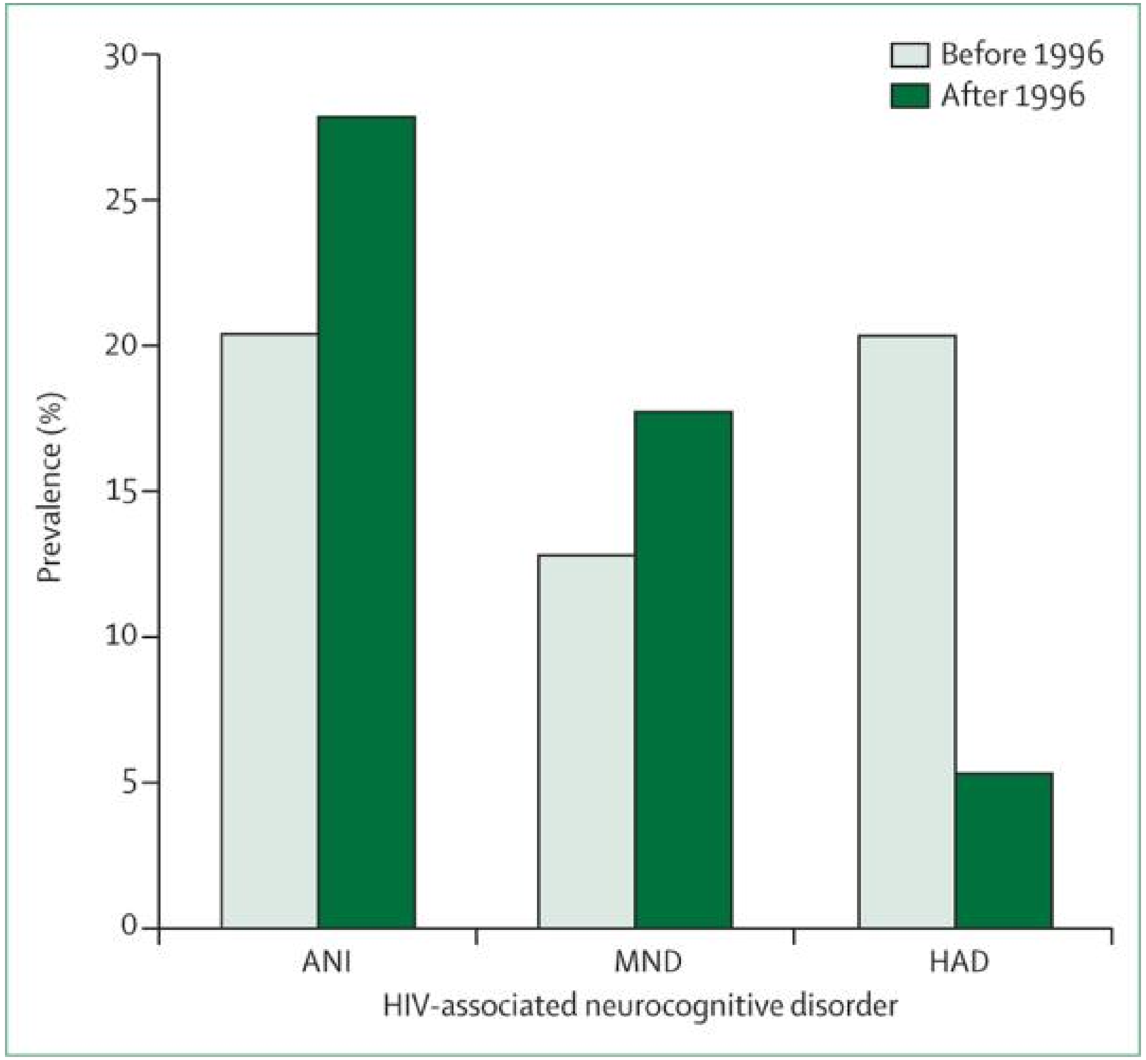
Defining Cognitive Impairment HIV-associated Neurocognitive Disorders (HAND)

Type	Characteristics
HIV-associated Asymptomatic neurocognitive impairment[†*]	Impairment in ≥ 2 neurocognitive domains • ≥1 SD below mean for age/education norms on neuropsychological tests Normal daily functioning
HIV-associated Mild neurocognitive disorder[†*]	Impairment in ≥ 2 neurocognitive domains • ≥1 SD below mean for age/education norms on neuropsychological tests Mild impairment in daily functioning (↓ mental acuity, inefficiency in work, home or social functioning)
HIV-associated dementia[π*]	Severe impairment in ≥ 2 neurocognitive domains • ≥2 SD below mean for demographic norms on neuropsychological tests Severe impairment in daily functioning
Neurocognitive domains	Verbal/language; attention/working memory; abstraction/executive function; memory (learning; recall); speed of information processing; sensory-perceptual; motor skills

[*] Any major depression in remission
[*] Diagnosis made ≥1 month after cessation of substance use
[*] No evidence of another preexisting cause
[†] Not meeting criteria for delirium or dementia
[π] Not meeting criteria for delirium

Antinori A et al. Neurology 2007; 69: 1789-99

Change in HAND Prevalence - before and after ART



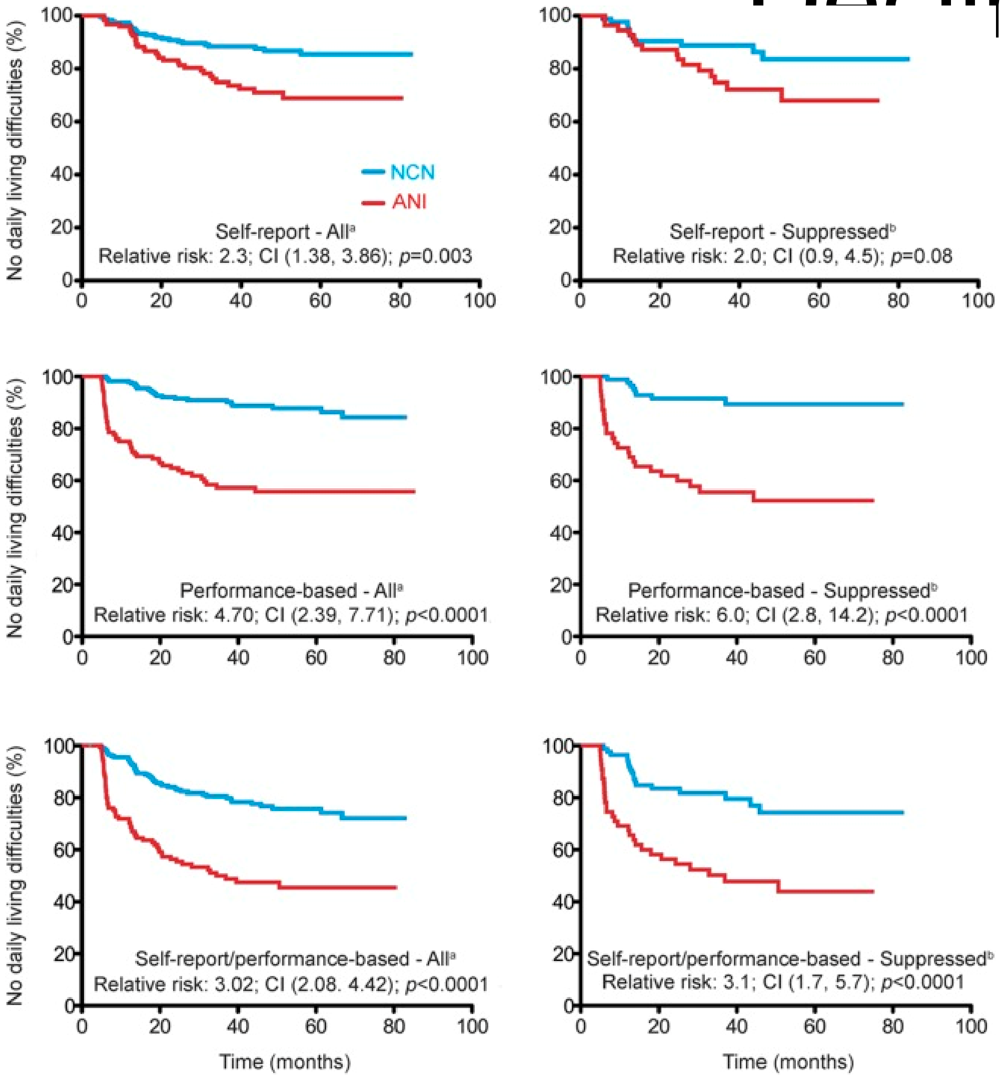
Nightingale S et al. Lancet Neurol 2014; 13: 1139-51

Estimated Global Prevalence of HAND Subgroups

- Pooled Prevalence in ART era:
  - Asymptomatic Neurocognitive Impairment: 23.5% (~9 million)
  - Mild Neurocognitive Disorder: 13.3% (~5 million)
  - HIV-associated dementia: 5% (~2 million)
    - 10-20% in pre-ART era

Wang et al. Neurology 2020; 95: e2610-21

Asymptomatic Neurocognitive Impairment Associated with Increased Risk for Symptomatic Decline



NCN – Neurocognitively normal
ANI – Asymptomatic neurocognitive impairment

- CHARTER cohort
- 2 to 6-fold ↑ risk of progression to symptomatic HAND for those with ANI

Grant I et al. Neurology 2014; 82: 2055-62

HAND Definition – Proposed Limitations

- Concern for overestimation – false positive rate
- Clinical relevance of asymptomatic neurocognitive impairment
- What does "HIV-associated" mean?
  - Are observed cognitive deficits truly attributable to direct HIV effects on the brain?
- Multifactorial contributors to cognitive impairment possible in single individual with HIV

Defining Cognitive Impairment
HAND -> Cognitive Impairment in HIV

- Direct HIV-associated brain injury (HABI)
- Other causes of brain injury
- Multifactorial

International HIV Cognition Working Group
Nightingale S et al. Nat Rev Neurol 2023; 19: 424-33

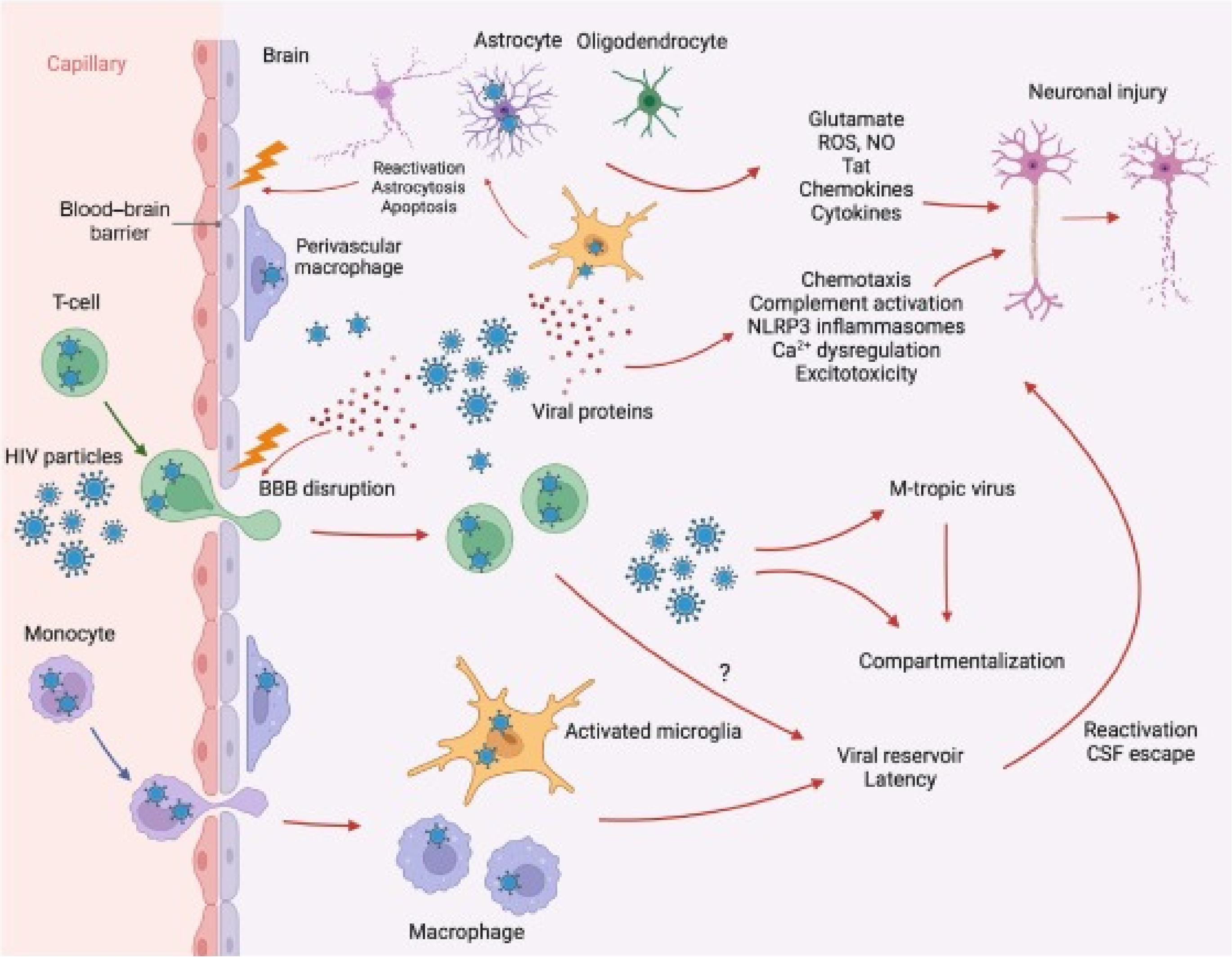
HIV-Associated Brain Injury

- Uncontrolled plasma viremia

- Legacy (without plasma viremia)
  - Pre-treatment damage
  - Robust association of cognitive impairment with CD4 nadir
  - Concern permanent/irreversible component

- Active (without plasma viremia)
  - Clinical and radiological progression of CNS damage

Pathophysiology of HIV-Associated Brain Injury



- Early CNS entry
- Release of neurotoxic HIV viral proteins
- HIV persistence
- Host immune/inflammatory response
  - Persistent immune activation
  - Chronic neuroinflammation
- Blood brain barrier disruption
- Neuronal injury
  - (Indirect – not direct HIV infection)

Moschopoulos CD et al. Trends in Molecular Medicine 2024; 30: 1076-89

Other Causes of Brain Injury in HIV

- CNS opportunistic infections/AIDS-defining conditions
  - Tuberculosis, Toxoplasma, Cryptococcus, JC virus/PML, Cytomegalovirus, Histoplasma, Salmonella
- Other infections
  - Syphilis, Hepatitis C
- CNS lymphoma
- ART neurotoxicity

Other Causes of Brain Injury in HIV

- Cerebrovascular disease
- Substance use disorders (alcohol, other drug use)
- Neurodegenerative/neurological disorders (Alzheimer’s, seizure disorders)
- Brain trauma
- Nutritional deficiencies (Vitamin B12, niacin deficiency)
- Developmental disorders

Other Causes of Brain Injury in HIV
HIV and Stroke

- Stroke incidence 40% higher in HIV than general population
  - Meta-analysis 1990-2019

- Contributing factors
  - CNS opportunistic infections
  - CNS neoplasm
  - Cardioembolic events
    - Bacterial endocarditis
    - HIV associated cardiomyopathy
    - Ischemic heart disease
  - HIV vasculopathy
    - Aneurysmal formation
    - Vasculitis
    - Accelerated atherosclerosis

Yang Y et al. Stroke 2023; 54: 2390

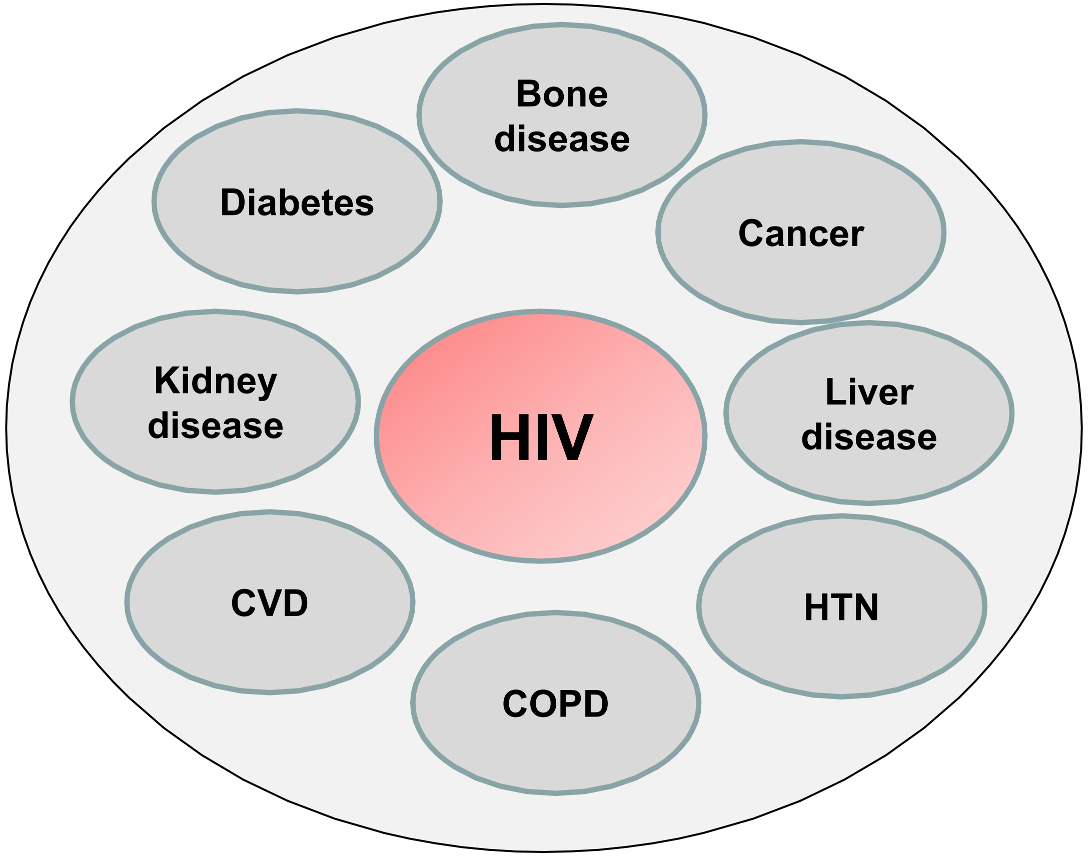
Psychiatric/Mood Disorders Associated with Impaired Cognitive Function in HIV

- Major depression (MDD)
  - ↑ Prevalence in HIV:
    - NIH All of Us Research Program - **MDD prevalence 43% in HIV** (↑**2.8-fold compared to persons without HIV)**
  - Biology: association with neuroinflammation
  - Screening (multiple): Patient Health Questionnaire (PHQ-2 -> PHQ-9), Geriatric Depression Scale, Center for Epidemiologic Studies Depression Scale, WHO (five) well-being index
  - Diagnosis: Structured clinical interviews for DSM-V diagnostic criteria
- Mania
  - Bipolar disorder
  - AIDS mania with advanced HIV - ↓prevalence in ART era
- Mood disorders linked to other comorbid conditions
- Substance-induced mood disorder
  - ↑ Prevalence of substance use in HIV (polysubstance use)
  - Biology: synergistic effects of HIV and substance use on brain injury

Matacotta JJ et al. HIV Med 2024; 25: 998 – 1004
Shiau S et al. Addict Behav 2017; 68: 39-44

Other Causes of Brain Injury in HIV
Aging Phenotypes/Geriatric Syndromes

<u>Multimorbidity</u>
Sum>Parts



Multimorbidity
↓

- Polypharmacy
  - Daily utilization of multiple classes of medication
- Polypharmacy increases risk of
  - Adverse drug reactions
  - Drug-drug interactions
  - Poor medication adherence

- Falls
- Multimorbidity
- Polypharmacy

↓

↑Cognitive Impairment/ Cognitive Disability

Social Contributors to Cognitive Impairment in HIV

- Direct and indirect effects
  - Achieving and sustaining virologic suppression -> HIV-associated Brain Injury
  - Predispose persons with HIV to other causes of brain injury

- Social contributing factors
  - Education/literacy
  - Income/employment
  - Housing
  - Food security
  - Access to healthcare
  - Psychosocial support
  - Social isolation

Clinical Presentation: HIV-Associated Dementia

- Cognitive deficits
  - ↓Attention, concentration, executive function, memory, processing speed
  - "Subcortical dementia" – absence of cortical signs such as aphasia/apraxia
- Mood and behavior changes
  - Irritability/apathy -> psychosis/mania
- Motor symptoms
  - Gait impairment, poor balance, tremors
- CD4<200
- Imaging
  - Cerebral atrophy
  - T2 white matter hyperintensities

Clinical Presentation: Other HIV-associated Brain Injury

- CNS Viral Escape Syndrome
  - Clinical/radiological progression of CNS injury with no plasma viremia
  - CSF HIV RNA+ with ↓/- Plasma HIV RNA
    - CSF VL > 50 & plasma HIV VL < 50 copies/mL OR
    - Both CSF and plasma HIV VL > 50 copies/mL, with CSF HIV VL > 0.5 log10 higher than plasma HIV VL
  - Exclusion of alternative etiologies

- Immune Reconstitution Inflammatory Syndrome
  - Weeks to months post ART
  - Immune reconstitution response to HIV reservoirs
  - Uncommon

Clinical Presentation: Symptoms of Cognitive Impairment

- Impaired language comprehension and expression
  - Difficulty understanding what others are saying, word finding difficulties
- Poor attention and concentration
  - Inability to focus, easily distractable, trouble following conversations/completing tasks
- Difficulty with planning, organization and problem solving
- Difficulty with decision making and judgment
- Memory loss - difficulty learning and recalling information
  - More forgetful of events, appointments, etc.
- Changes in mood and behavior
  - Irritability, restlessness, apathy, depressed mood
- Gait impairment
  - Slowed gait, impaired balance

- Changes noted by individual and/or by observers (family, friends, caregivers)

Diagnosis: Cognitive Impairment in HIV

- Cognitive symptoms
- Cognitive tests
- Neurological evaluations
- Clinical history for potential contributing factors
- Assessment of function/activities of daily living

- At least 2 of cognitive symptoms, cognitive tests and neurological evaluations for classification as cognitively impaired

International HIV cognition working group

Diagnosis/Evaluation: Clinical History Multifactorial Contributors

- HIV clinical factors (ART status, disease history/stage)
- Psychiatric/mood disorders
- Substance use
- Other comorbid conditions
  - Cerebrovascular disease
  - Neurodegenerative/neurological disorders
  - Brain trauma
  - Nutritional deficiencies
  - Developmental disorders

Diagnosis: Cognitive Tests

- Full neuropsychological test battery
  - "Gold standard"
  - Heterogenous instruments
  - Domains (2007 HAND guidelines)
    - Verbal/language
    - Attention/working memory
    - Abstraction/executive function
    - Memory
    - Speed of information processing
    - Sensory-perceptual
    - Motor skills
- Limitations
  - Clinical correlation
  - Influence of sociocultural factors on test performance/ interpretation
  - Time intensive
  - Clinical expertise

Diagnosis: Neurological Imaging & Laboratory Assessments

- Lumbar Puncture
  - CNS opportunistic infections
  - Other comorbid conditions
  - CSF viral escape syndrome

- MRI
  - New or progressive findings
  - Other comorbid conditions

Diagnosis: Cognitive Screening Tests

- Montreal Cognitive Assessment
  - 30-item instrument – paper & app versions – 10 minutes to administer
  - Attention, concentration, executive function, short term/working memory, visuospatial skills
  - 72-89% sensitivity; 22-67% specificity (MoCA≤26)

Fazeli PL et al. J Clin Exp Neuropsychol 2017; 39: 842-53; Joska JA et al. AIDS Behav 2016; 20
Janssen MAM et al. J Neurovirol 2015; 21: 383-90; Brouillette MJ et al. AIDS 2015; 29: 895-902
Milanini B et al. J Acquir Immune Defic Syndr 2014; 67: 67-70

- International HIV Dementia Scale
  - Interviewer administered – 5 minutes to administer
  - Timed finger tapping, timed alternating hand sequence, 4-word 2-minute delayed recall
  - Psychomotor speed, processing, short term memory
  - 36-91% sensitivity; 17-86% specificity (IHDS≤10)

Molinaro M et al. J Acquir Immune Defic Syndr 2020; 83: 278-83; Kellett-Wright J et al. AIDS Behav 2020; 25: 542-53;
Milanini B et al. AIDS 2018; 32: 2477-83; Monteiro de Almeida S et al. J Acquir Immune Defic Syndr 2017; 74: 332-8;
Joska JA et al. AIDS Behav 2016; 20: 1621-31; Sacktor NC et al. AIDS 2005; 19: 1367- 74

- Mini-Mental State Exam (MMSE)
  - 30-item instrument/Interviewer administered – 10 minutes to administer
  - Attention/concentration, language, memory, visuospatial skills
  - Ceiling effect (↓ detection mild cognitive impairment) & less sensitive for subcortical dysfunction
  - 24-46% sensitivity; 55-98% specificity

Skinner S et al. HIV Med 2009; 10: 246-52; Joska JA et al. AIDS Behav 2016; 20: 1621-31

Diagnosis: Emerging Technological Platforms for Neuropsychological Testing in HIV

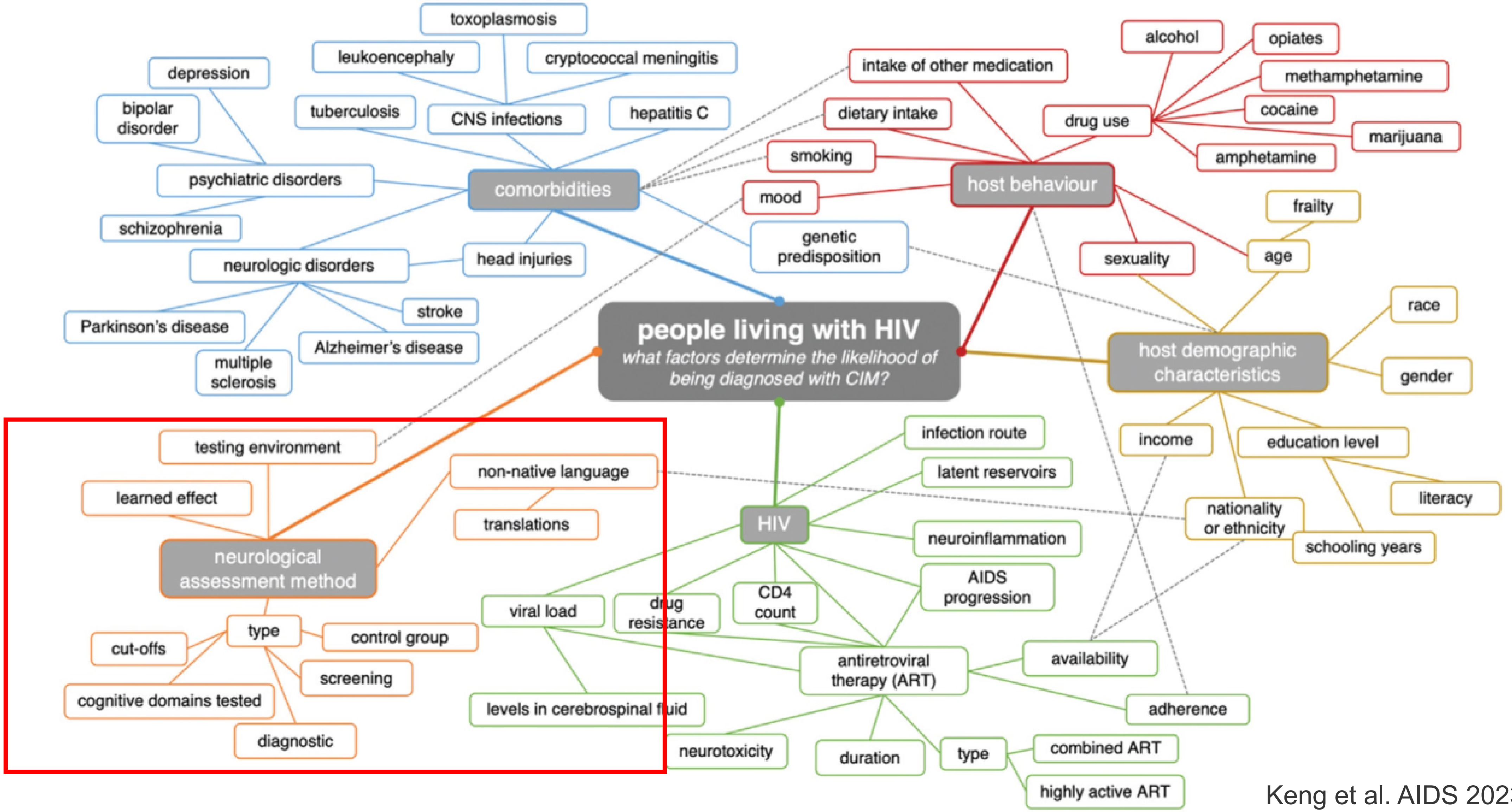
- Brain Baseline Assessment of Cognition and Everyday Function (BRACE)
  - Ipad-based screening tool - 12 minutes to administer
  - Psychomotor speed, set-shifting/mental flexibility, processing speed, visuospatial learning, memory
  - 4 neuropsych tests: trail making tests A&B, stroop-color test, visual-spatial learning test
  - 84% sensitivity, 94% specificity (gold standard NP test battery)

- Neuroscreen
  - Software application for Android smartphone - 25 minutes to administer
  - Assessment of 6 domains (10 tests)
  - 90% sensitivity, 63% specificity (gold standard NP test battery)

- Novel Computerized Cognitive Assessment Device (NCAD)
  - Video display and automated voice-overs - 20 minutes to administer
  - Processing speed, episodic memory, working memory, executive function
  - 67% sensitivity, 83% specificity (gold standard NP test battery)

Dantuluri ML et al. AIDS Care 2022; 35: 1619-2

Factors impacting Cognitive Impairment Diagnosis in HIV



Keng et al. AIDS 2023; 37: 61-70

Management: Antiretroviral Therapy

- Early ART
  - Preempt legacy damage
- CSF HIV genotype
  - CNS viral escape syndrome
- Specific regimens
  - Neuropsychiatric symptoms
  - CNS Penetration Effectiveness Score
    - Proposed CNS ART penetrance/potency
    - Studies to date not definitive

Ellis RJ et al. Clin Infect Dis 2014; 58: 1015
Caniglia EC et al. Neurology 2014; 83: 134-41

Management: Long acting injectables (LAI) IAS-USA Guidelines Updated Recommendation

- Injectable cabotegravir and rilpivirine (CAB-RPV) may be considered for people with viremia who meet the following criteria:
  - Unable to take oral ART consistently despite extensive efforts and clinical support
  - High risk of HIV disease progression (CD4 cell count <200/μL or history of AIDS-defining complications)
  - Virus susceptible to both CAB and RPV
- Supported by intensive follow-up and case management services
- No other treatment options are effective due to persistent inability to take oral ART
- If applicable, referral should be made for treatment of substance use disorder and/or mental illness
- No RCT – recommend refer to eligible clinical trials
  - ACceptability of long-acting ART in Cognitive ImpAirment (ACCIA) – exploratory study of acceptability and impact on health-related quality of life of LAI in people with HIV and cognitive impairment (UK)

Sax PE et al. JAMA 2024; 331: 1060-1

Management: Comorbid Conditions

- Psychiatric/mood disorders
- Substance use disorders
- CNS opportunistic infections
- Other neurological disorders
- Multimorbidity
- Polypharmacy

CASE: Intersection of HIV & Aging Phenotypes

- 69 year old male with HIV/AIDS with Salmonella empyema/bacteremia then complicated course with persistent cognitive and motor deficits 2 years post hospitalization

- Poorly controlled HIV/AIDS
  - Initially not on ART
  - HIV-associated brain injury
  - Invasive nontyphoidal CNS *Salmonella* infection
- Fall
  - Presumptive structural brain injury
  - Hematoma
- Substance use
  - Alcohol

- Multimorbidity
  - Cerebrovascular disease
  - Chronic kidney disease
  - Depression
  - Hypertension
  - Obstructive sleep apnea
- Polypharmacy
- Physical Frailty
- Disability
- Institutionalization

Summary: Management of Cognitive Impairment in HIV

- Patient or informant (relatives/caregiver) complaint of cognitive problems without or with optimally managed confounding conditions (psychiatric conditions, substance use, prior or current CNS OIs or neurologic disorders)
- 3 item physician assessment/questions to confirm (or other screening assessment)

  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 difficulties paying attention (e.g. to a conversation, book or movie)?

  For each question, answers could be: a) never, b) hardly ever, or c) yes, definitely. Persons with HIV are considered to have an "abnormal" result when answering "yes, definitely" on at least one question.

- Evaluate/treat depression, anxiety and sleep disorders
- Neurological exam, brain MRI with gadolinium, CSF assessment including HIV RNA, neuropsychological assessment
  - Consider neuropsychological assessment when cognitive symptoms present
    - Test for fluency, executive function, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills
    - Assessment of daily functioning

European AIDS Clinical Society Guidelines
https://eacs.sanfordguide.com/en/eacs-part2/eacs-cognition-mental-sleep-health-substance-use/neurocognitive-impairment

Summary: Management of Cognitive Impairment in HIV

- Causes other than HIV excluded and/or optimally managed -> HIV-associated brain injury (HABI)
    - Off ART -> start or restart ART
    - On ART and CSF viral escape -> optimize ART based on both CSF and plasma genotype testing
        - CSF viral escape:
            - CSF HIV viral load (VL) > 50 and plasma HIV VL < 50 copies/mL OR
            - Both CSF and plasma HIV VL > 50 copies/mL & CSF HIV VL > 0.5 log10 higher than plasma HIV VL
    - On ART with no CSF viral escape
        - Consider alternative causes of HIV associated brain injury
            - Legacy
            - ART toxicity
        - Reconsider causes other than HIV

- Clinical, MRI and CSF follow up examinations per clinical judgment

European AIDS Clinical Society Guidelines
https://eacs.sanfordguide.com/en/eacs-part2/eacs-cognition-mental-sleep-health-substance-use/neurocognitive-impairment

Management: Aging with HIV and Cognitive Impairment

- Prioritize and tailor interventions
  - Clinical feasibility
  - Informed patient preference
- Therapeutic choice
  - Optimize benefit
  - Minimize harm
  - Enhance quality of life
- Interdisciplinary care
- Frequent medication reconciliation
  - Reduce medication burden when possible
  - Stop inappropriate medications
- Support social engagement and broader psychosocial support

4Ms: Age-friendly health systems for older adults

- What Matters
  - Align care with each older adult's goals and health preferences
- Medication
  - If medication is necessary, use age-friendly medication that does not interfere with What Matters to the older adult
- Mentation
  - Prevent, identify and treat dementia, depression and delirium across settings of care
- Mobility
  - Ensure that older adults move safely every day in order to maintain function and do What Matters

Mate K et al. J Aging Health 2021; 33: 469-81
https://www.ihi.org/partner/initiatives/age-friendly-health-systems

Future Directions/Needs

- Clinical definition
  - Characterization of phenotypic subtypes/biotypes
    - Distinct patterns of cognitive impairment in HIV
    - Heterogeneity of neuropathologies underlying cognitive impairment in HIV (multifactorial in single individual)
- Diagnostic approach (measurement)
  - Defining clinically meaningful cognitive impairment
  - Distinction between true cognitive impairment and test performance
  - Screening Tools
    - Feasible, cost-effective, sensitive, specific
    - HIV associated brain injury vs. multifactorial (performance target)
- Adjunctive therapies for management beyond ART
  - Pharmacologic approaches
    - Elucidation of biology to inform therapeutic targets for prevention and treatment of cognitive impairment in HIV
  - Non-pharmacologic approaches
- Optimal integrated care models for holistic management
  - Care transitions and enhanced structural holistic psychosocial supports (HIV, mental health, substance use, other comorbidity, social supports)