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Neurocognitive Disorders in People Living with HIV

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Financial Relationships With Commercial Entities

Dr Valcour has served as a consultant to Merck & Co, Inc and ViiV Healthcare.

He also serves on faculty for IAS-USA where he provides CME presentations around HIV

(Updated 11/2020)

Learning Objectives

After attending this presentation, learners will be able to:

- Recognize signs and symptoms of cognitive problems in aging people living with HIV infection
- Describe the challenges in diagnosing Alzheimer's disease in aging people living with HIV infection
- Describe the inflammatory phenotype of cognitive issues in the setting of HIV infection

Key Points

- Impaired cognition remains an important challenge in the era of cART
  - Effects 1/3-/12 of patients despite successful plasma viral suppression
- Etiology is complex
  - Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy for many
  - Comorbidity is common
  - Cerebrovascular disease is a common comorbidity in older age
- Co-occurrence of Alzheimer's disease and other age-associated neurodegeneration is a reality
  - Distinguishing AD from HAND is one of the greatest clinical challenge in geriatric neuroHIV

Estimates of cognitive impairment

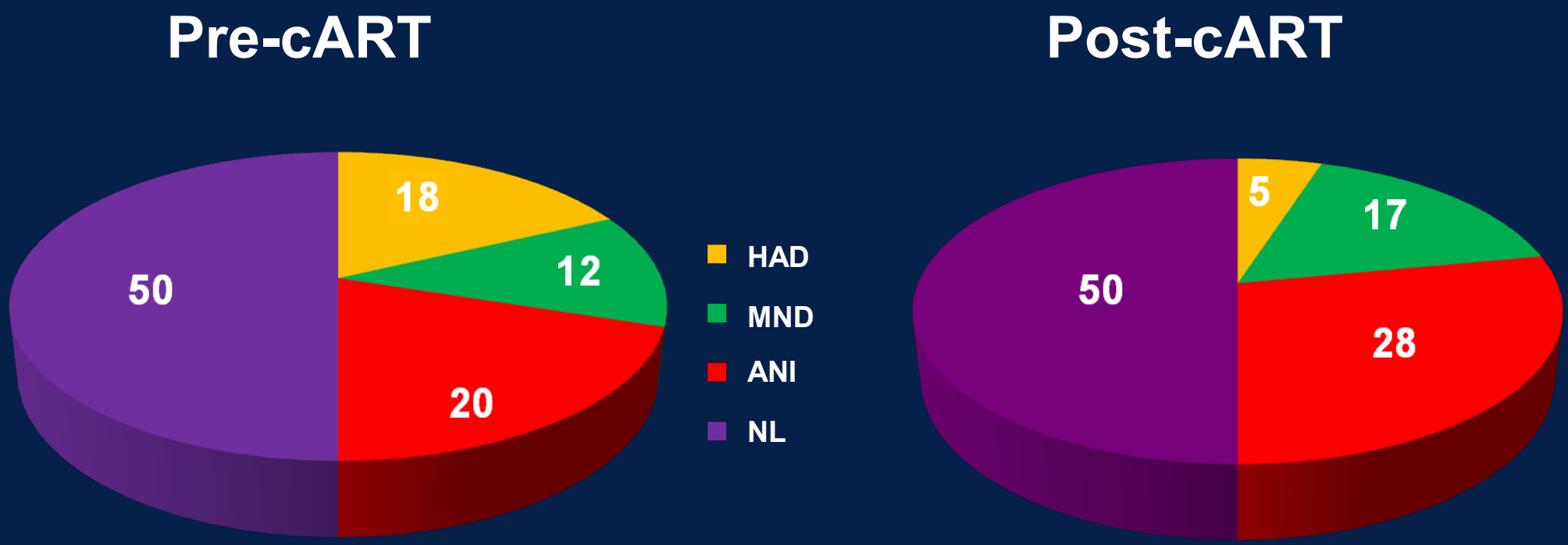
Despite suppression of plasma HIV RNA

- Switzerland (2010)[1]: 69% (aviremic for median of 48 months)
- Botswana (2010)[2]: 38% (98% on cART)
- Thailand (2010)[3]: 38% (2NN Cohort)
- US Military cohort (early treatment)[4]: 19%

- Concern: Many studies continue to publish rates of cognitive impairment that include individuals not optimally treated
- CHARTER, for example, possibly representative at the time, but under-treated

1. Simioni S, et al. AIDS 2010;
2. Lawler K, et al. J Int AIDS Soc 2010; 3. Pumpradit W, et al. J Neurovirol 2010; 4. Crum-Cianflone Neurology 2013

Prevalence of HIV-associated Neurocognitive Disorder (HAND)

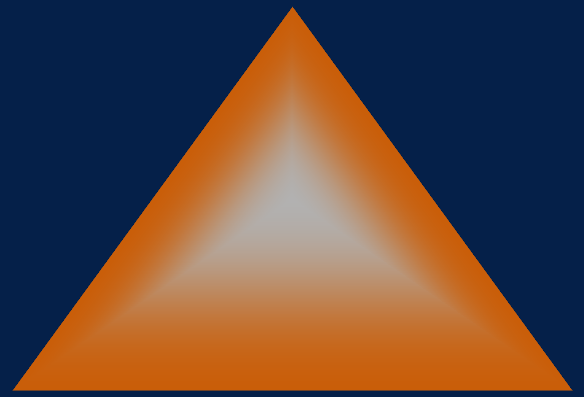


* Caveat: Post-cART rate is from a prevalence-type study and includes people without viral suppression - ? Truly representative of today's clinics

Modified from Nat Rev Neurosci 2007

Clinical presentation

Cognition
Memory loss
Concentration
Mental slowing



Behavior
Apathy
Depression
Agitation, Mania

Motor
Unsteady gait
Poor coordination
Tremor

Clinical Features – Cognitive Profile

- Multiple cognitive domains can be involved, including memory
- Common to see attentional deficits
  - Re-reading, use of lists
- Information processing may be impaired
  - Keeping up with banter
- Course does not tend to be progressive in the setting of cART but may fluctuate

Progressive atrophy in older HIV+

Despite persistent suppression of plasma HIV RNA

- Seen largely in subcortical regions, including asymptomatic suppressed participants[1]
- Seen in cerebellum, caudate, frontal lobe, total cortical gray matter, brainstem, and pallidum[2]
- Two contrasting studies among younger individuals compared to demographically matched controls and a study where individuals with substantial cerebrovascular disease were excluded[3,4]

1. Nir et al, J Neurovirologgy 2019; 2. Clifford & Samboju et al JAIDS 2017; 3. Samford et al JAMA Neurology2017; 4. Cole et al CID 2018

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The Role of Inflammation Despite Viral Suppression

Numerous studies demonstrate correlations to chronic inflammation

Among individuals optimally treated with plasma viral suppression

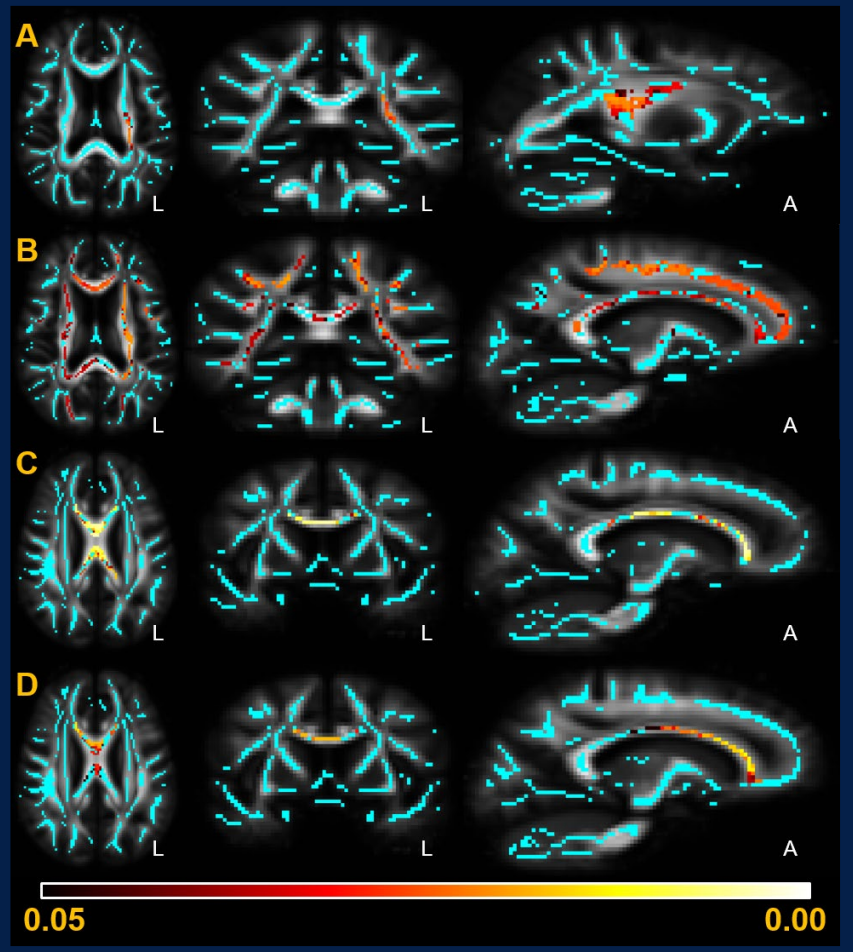
- *In vivo* brain imaging using ligands (PET)
  - TPSO binding (microglial activation) increased in HIV compared to controls and inversely associated with cognitive performance[1,2]
- Plasma markers and Immunological markers
  - sCD163 and global performance[3]
  - $CD^{14}CD^{16}CD^{163}$ and $CD^{14}CD^{38}$ (% CD14) and progressive worsening of memory performance[4]
- Additionally:
  - Chronic inflammation persists even when ARV started during acute HIV[5] $_{S}$CD163 links to brain pathology at autopsy[6]

1. Rubin et al AIDS 2018; 2. Vera et al Neurology 2016; 3. Imp et al JID 2017; 4. Fabbiani M JAIDS 2017;
5. Sereti et al CID 2017; 6. Bryant et al AIDS 2017

Imaging studies show damaged integrity linked to inflammation

Further linked to cognitive impairment

- MCP-1 and neopterin broadly linked to abnormal brain integrity by diffusion tensor imaging (DTI)
- These DTI abnormalities link to worse cognitive performance



1. Chang et al, JAIDS 2019

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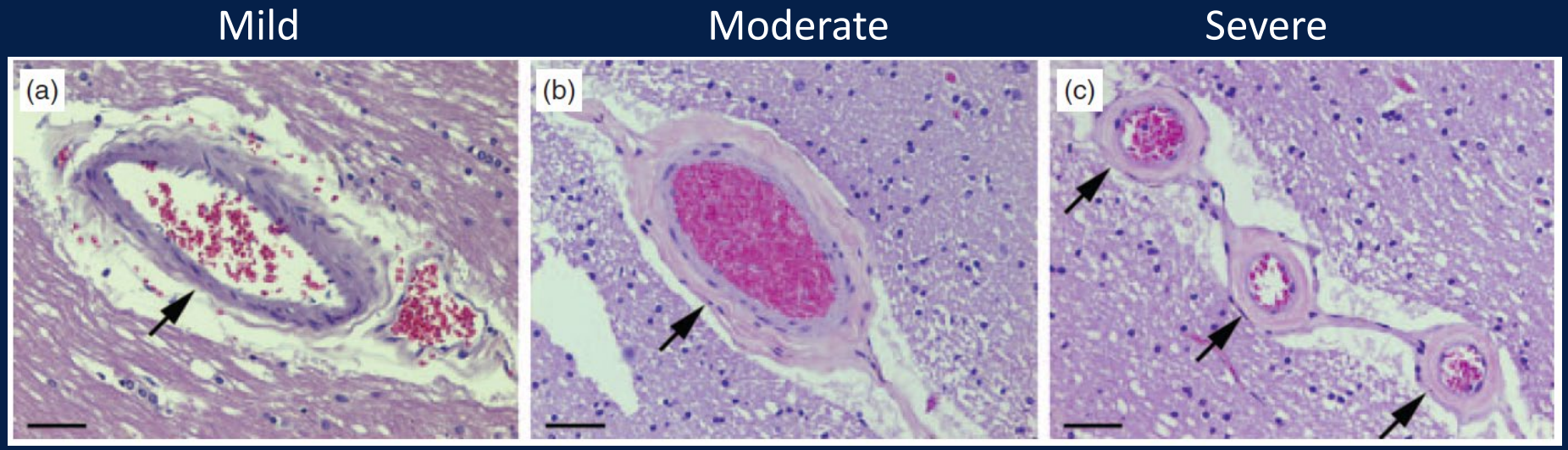
The Role of Cerebrovascular Disease

Small Vessel Ischemic Disease in HIV

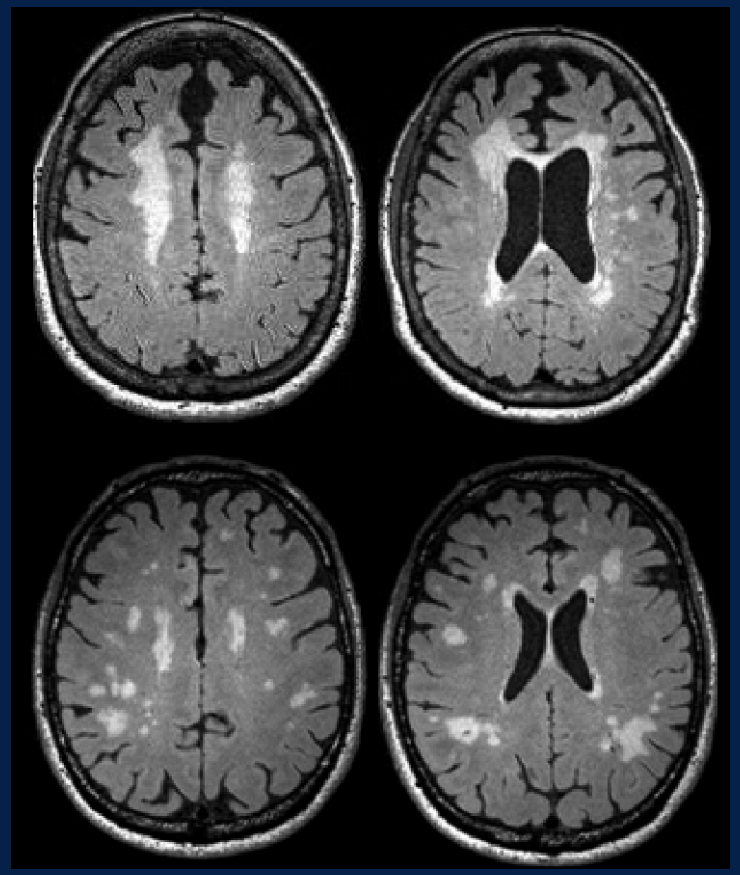


- Autopsy series in the US between 1999 to 2011

50 % of cases

Soontornniyomkij et al AIDS 2014

White matter lesion burden in aging with HIV



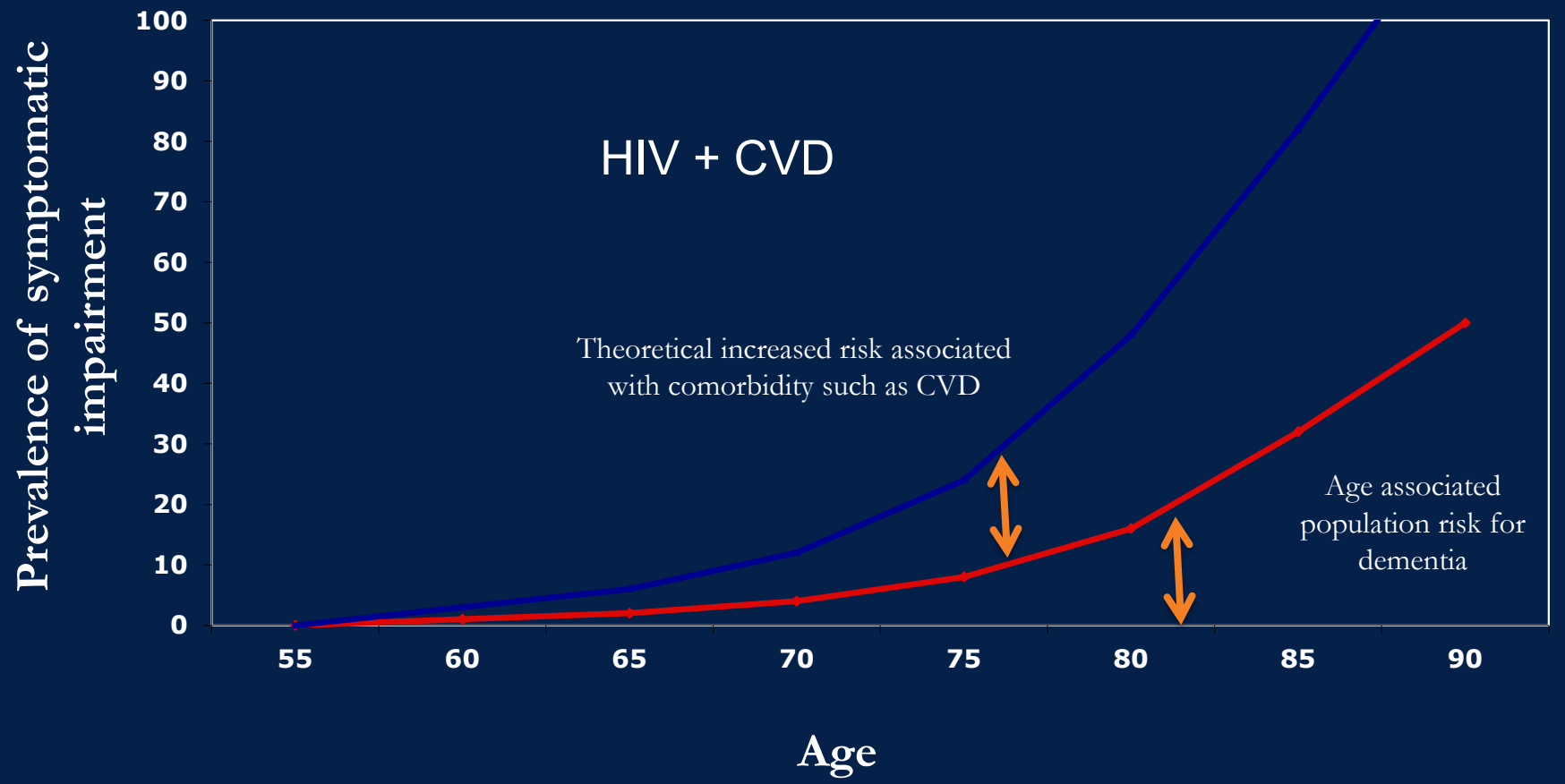
- Two patterns seen
- (1) Periventricular confluent lesions that are often described in small vessel ischemic disease (top)
- Discrete lesions (bottom)

Studies demonstrating contribution of cerebrovascular disease to cognition in HIV

- White matter hyperintensities link to abnormalities on diffusion tensor imaging and are accelerated in HIV[1] as well as to cognitive performance (age > 60)[2]
- Some contrasting studies exist (no added burden due to HIV in age >50)[3]
- May be particularly important for HIV over age 60 years
  - In HIV, the burden of white matter hyperintensities was predicted by age > 60 vs. < 60 years[4]

1. Seider J Neurovirology 2015; 2.Watsobn et al J Neurovirology 2017; 3. Haddow et al AIDS Res Hum Retrovir 2018; 4 Wu et al AIDS 2018

Increased risk of symptomatic dementia associated with co-morbidity



Other potential contributors

- Co-morbidities – infectious and non-infectious
- Psychiatric illness
- Medication effects
- Recreational drug use
- Others…

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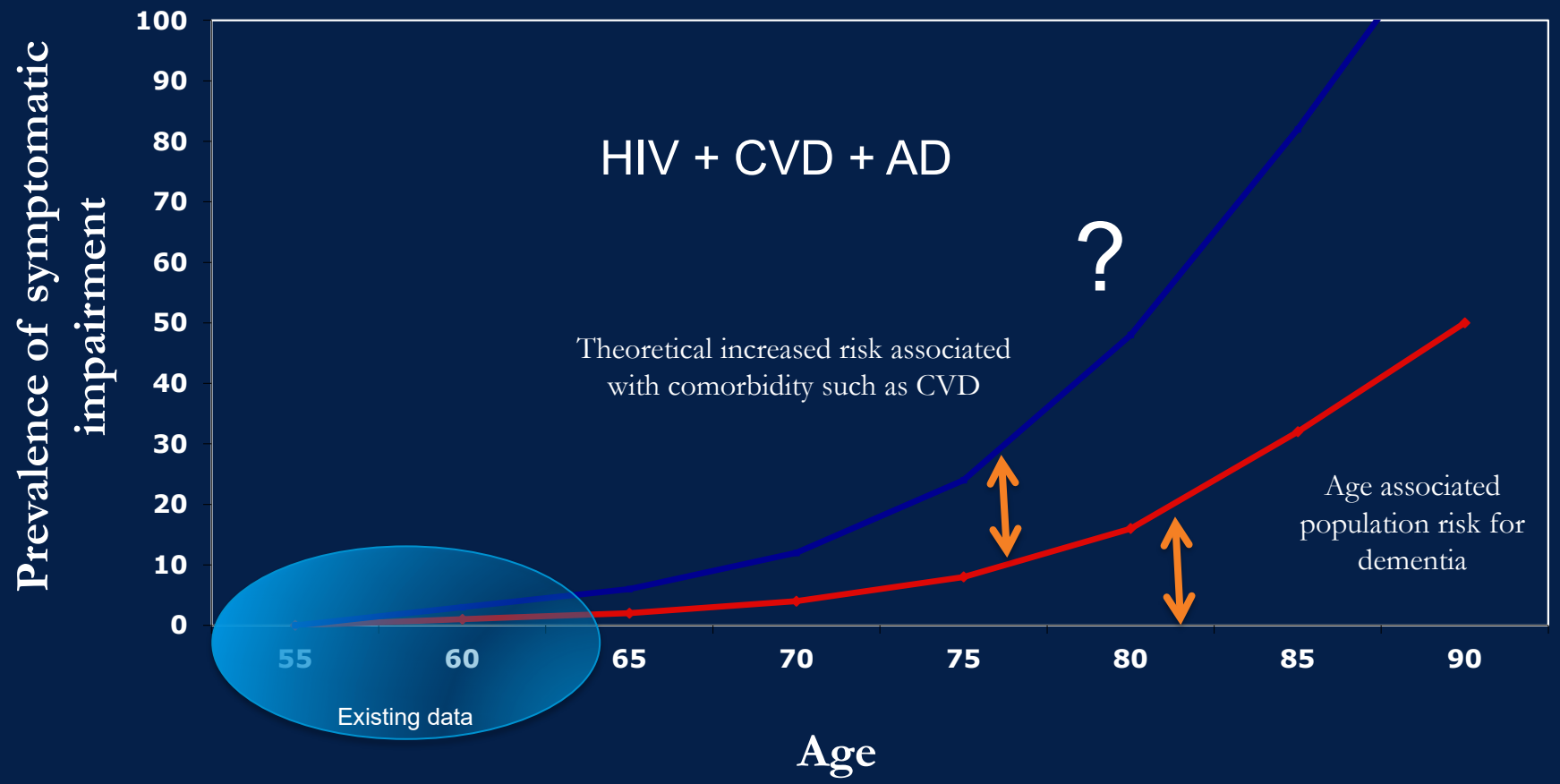
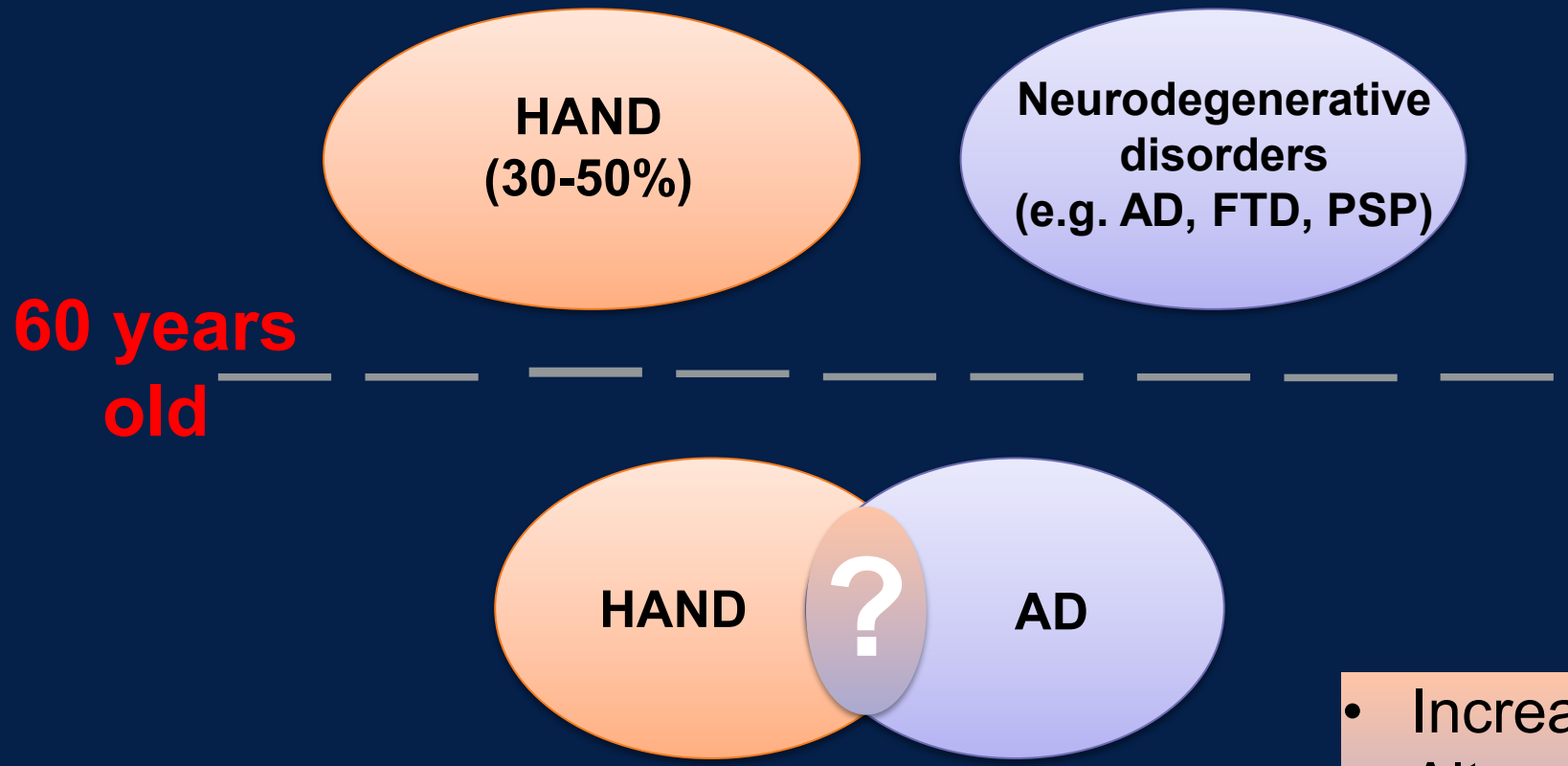
Distinguishing Alzheimer's disease from HIV-related cognitive impairment

Increased risk of symptomatic dementia associated with co-morbidity



Overlap between HAND and AD



- Increased risk?
- Altered phenotype?
- Accelerated course?

Why bother figuring out if it is HIV or AD?

- Sense of futility with each disease
  - Few effective pharmacological adjunctive treatments
- Planning for care
  - Clinical course vastly different between the two
- Clarity of diagnosis and optimal care
  - Currently, individuals living with HIV are at high risk for delayed diagnosis of Alzheimer's disease and other age-associated neurodegenerative disorders.

Course of AD in People Living with HIV

- Whether the course, features or timing of onset differ in HIV is unknown
- Pathology data worrisome that the course could be effected since multiple protein have been reported to accumulate in brain tissue with HIV. These are also seen in neurodegenerative disorders
  - Amyloid – multiple lines of evidence for soluble amyloid and diffuse plaques (rather than neuritic plaques of Alzheimer's disease (Reviewed in: Pulliam J Neuropharm 2009; Mackeiwitcz JNV 2018)
  - TDP-43 seen in fronto-temporal dementia (Ellis Nature Reviews 2008)
  - Alpha-synuclein seen in Lewy Body Dementia (Khanlou JNV 2008)

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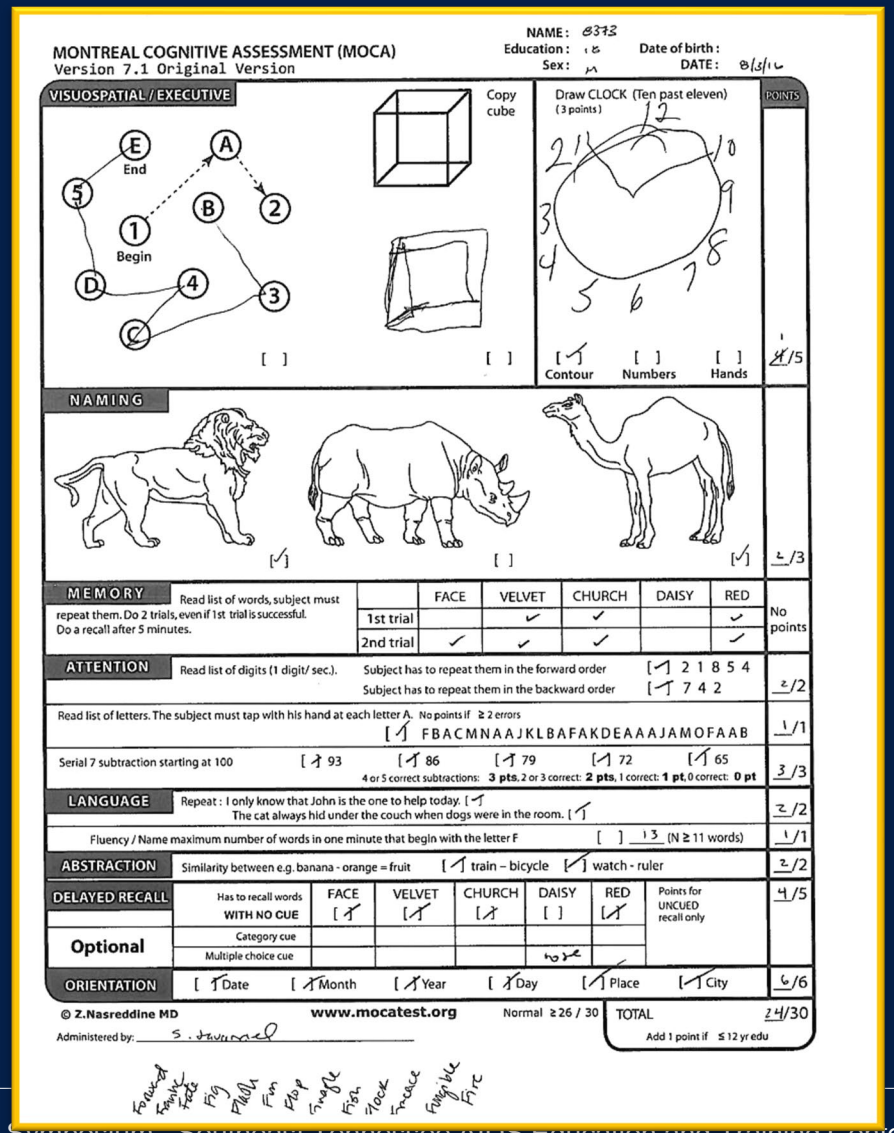
A Case Report

Case Report

- 75 year-old right-handed man with 16 years of education
- Sought evaluation due to memory changes and because a brother died of Alzheimer's disease at age 79 with symptoms "just like his"
- Subtle, insidious decline in memory started 5-10 years ago; no functional problem currently
- Medical history: Hyperlipidemia, hypertension, osteoarthritis, gout, and CAD with past MI. mild managed depression
- HIV history:
  - Diagnosed with HIV in the mid 1980s; nadir CD4 > 200 cells, no opportunistic infections
  - On integrase-based regimen for years, current, CD4 = 850 cells; UD plasma HIV RNA

Case Report - MoCA



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME: 8373
Education: 12
Sex: M
Date of birth:
DATE: 8/3/16

VISUOSPATIAL / EXECUTIVE — POINTS

Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [✓] Contour [ ] Numbers [ ] Hands — 4/5

NAMING — 2/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial		✓	✓		✓
2nd trial	✓	✓	✓		✓

No points

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [✓] 2 1 8 5 4. Subject has to repeat them in the backward order [✓] 7 4 2 — 2/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [✓] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — 1/1

Serial 7 subtraction starting at 100 [✓] 93 [✓] 86 [✓] 79 [✓] 72 [✓] 65 — 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt — 3/3

LANGUAGE — Repeat: I only know that John is the one to help today. [✓] The cat always hid under the couch when dogs were in the room. [✓] — 2/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] 13 (N ≥ 11 words) — 1/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [✓] train – bicycle [✓] watch - ruler — 2/2

DELAYED RECALL — Points for UNCUED recall only — 4/5

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED
		[✓]	[✓]	[✓]	[ ]	[✓]
Optional	Category cue				nose	
	Multiple choice cue					

ORIENTATION — [✓] Date [✓] Month [✓] Year [✓] Day [✓] Place [✓] City — 6/6

© Z.Nasreddine MD — www.mocatest.org — Normal ≥ 26 / 30 — TOTAL 24/30 — Add 1 point if ≤ 12 yr edu

Administered by: S. Townsend

forward family feet fig pillow fun play triangle fish flock increase family life fire

Marked dysfunction in executive performance and/or visual processing

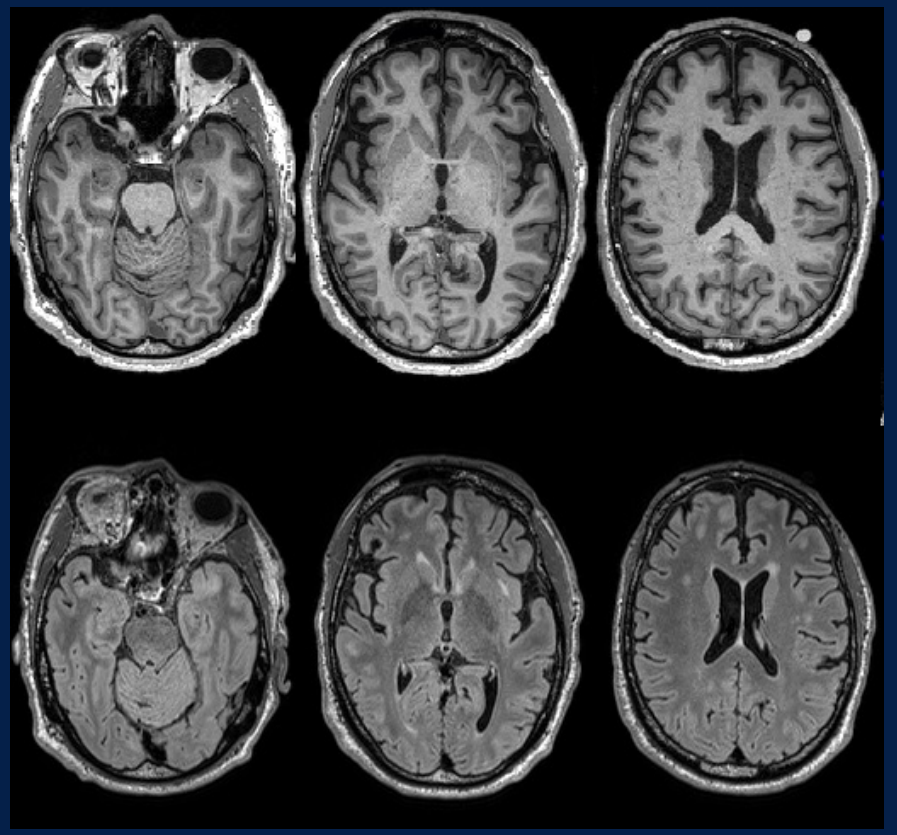
Unexpected error in confrontational naming

Inefficient learning/registration, achieving only 4 of 5

Retention of learned material supportive of proper encoding

Case Report – Clinical Assessment

- Neurological exam:
  - Slow motor serial sequencing (Luria)
  - Lower extremity neuropathy – longstanding
- MRI - normal



Neuropsychological testing – mixed picture

Frascati Domain		Score	Normal (> -1 SD)	Mild/moderate (-1≤ x > -2 SD)	Severe (≤ -2 SD)
Memory	CVLT-II trial 5	10	0.0		
	CVLT-II Immediate Recall	10	1.0		
	CVLT-II Delayed Recall	7	0.0		
	Benson Figure recall	9		**-1.57**	
Language	**Boston Naming Test (15 item)**	12			**-2.88**
	Category fluency (animals)	12			**-2.3**
	Lexical fluency (D words)	20	0.82		
	WRAT-4	68	X		
	Sentence Comprehension	4	-0.5		
Attention/ Working Memory	CVLT-II trial 1	8	2.0		
	Digits forward	6	-0.64		
	Digits backward	5	0.0		
	STROOP Interference	46	-0.56		
	1-back	25		**-1.06**	
	2-back	65	0.17		
Executive	**Trails B**	149”		**-1.31**	
	Design Fluency	8	-0.97		
	Flanker				
	Modified Trails				
	Abstraction/similarities				
Psychomotor speed	Trails A	24”	0.73		
	STROOP color naming	83	-0.62		
Motor	Grooved Pegboard (Dominant hand)	88”	-0.06		
	Grooved Pegboard (non-Dominant hand)	137”		**-1.77**	
	Finger Tapping (Dominant hand)	35.4		**-1.00**	
	Finger Tapping (non-Dominant hand)	34.4		**-1.35**	
Visuo-spatial	Benson Figure copy	16	0.45		
	VOSP	8	-0.83		
	CATS Face Matching	10			**-2.83**

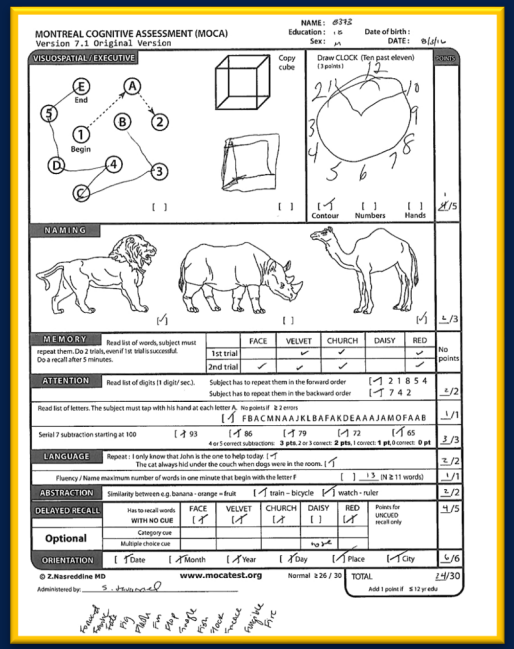
Visual memory impairment
Language impairment

Manual dexterity and speed decreased, often seen in HIV

Case Report - Next Steps?

- Modification of ARVs for greater CNS penetration?
  - No evidence to support this approach for a 10-year course
  - Most people are undetectable – thus CSF HIV RNA seldom linked to impairment
- Initiation of cholinesterase inhibitors for Alzheimer's disease?
  - Would be empiric and possibly wrong
- Watch and wait
  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
  - Reasonable, but would you want this for yourself?
- CSF assessment for neurodegenerative biomarkers or referral to a specialist?

Neuropsychological Testing


MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

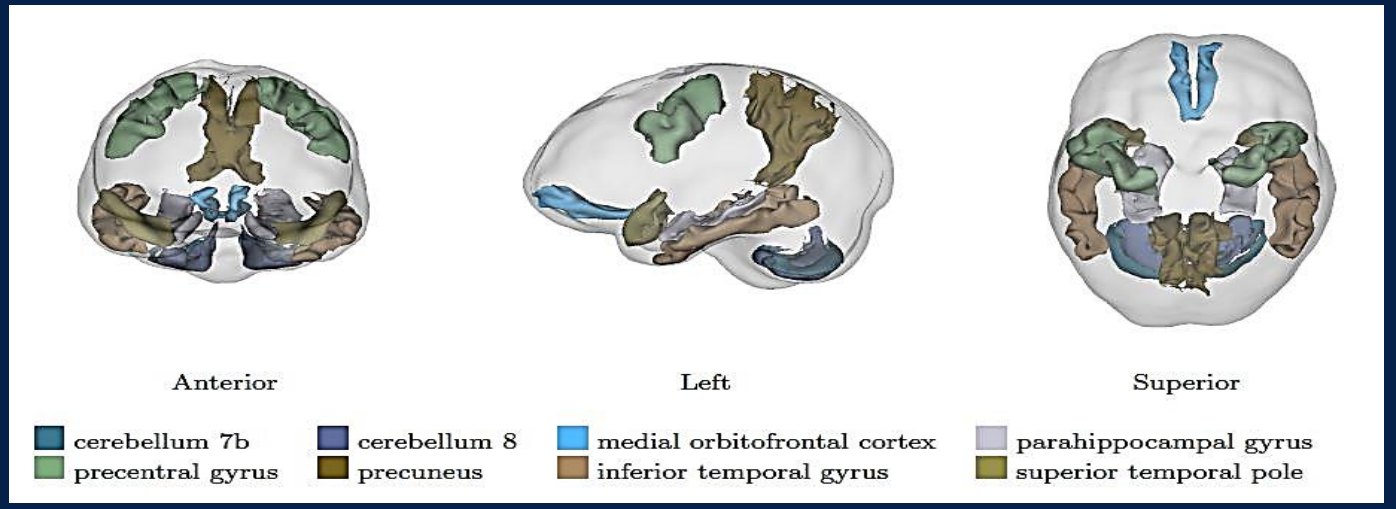
- Considerable overlap between HAND and Alzheimer's disease[1, 2]
- Cannot rely on cortical vs. sub-cortical pattern
  - Memory is one of many domains that can be perturbed in HAND[3]
  - Encoding vs. retrieval of information may help distinguish
  - Error-prone/impulsive in HAND confounds recognition memory

MoCA: errors due to impulsivity and executive planning (trails, cube, clock), flat learning curve with OK memory, phonemic fluency not great

1. Rubin et al J Neurovirol 2019; 2. Milaninin et al; Current HIV/AIDS Rpts 32017; 3. Woods et al Neuropsychology Reviews 2009

Structural Brain Imaging

- Machine learning approach to differentiate 15 HAND vs. 80 Mild Cognitive Impairment due to Alzhiemer's disease
- Eight regions show promise to differentiate HAND from MCI (machine learning was >90% accurate)

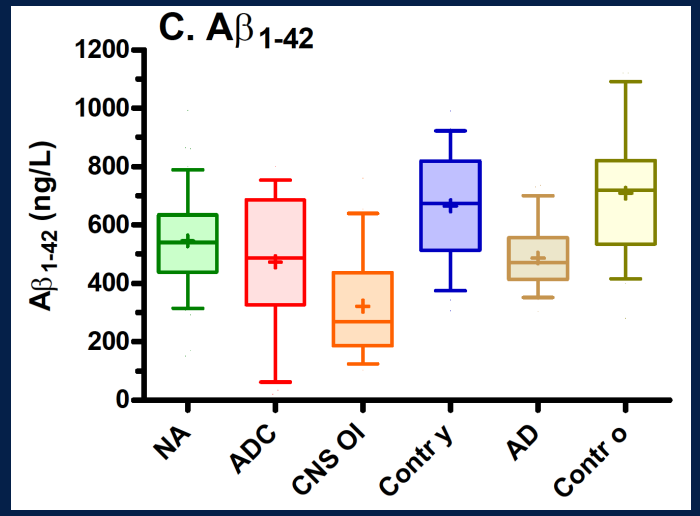


Zhang et al, Haman Brain Mapping 2016

CSF Alzheimer's disease biomarkers

No perfect for differentiating HAND from AD

- Patients with HIV dementia have abnormalizes in amyloid-beta, total-tau, and phosphorylated-tau similar to AD[1,2,3,4]



Gisslen et al BMC Neurology 2009;

- Personal experience suggest about 1/3 will have some abnormality in amyloid-beta or tau
- Having abnormalities in both is not frequent, thus could be helpful to differentiate AD from HAND

1. Brew Neurology 2005; 2. Gisslen et al BMC Neurology 2009; Clifford et al, Neurology 2009; 4. Krut et al J Neurolo 2012

Case Report - Next Steps?

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  - Natural longitudinal course is likely to distinguish the two over 3 years
  - Could implement broad recommendations without diagnostic clarity
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- CSF assessment for neurodegenerative biomarkers or referral to a specialist?

Summary Points

- Impaired cognition remains an important and frequent challenge in the era of cART
- Cognitive impairment affects one-third to one-half of patients despite successful plasma viral suppression
- Chronic inflammation underpins this continued mild/moderate fluctuating encephalopathy
- Cerebrovascular disease is a common comorbidity among older people living with HIV and it contributes to the cognitive burden

Summary Points

- Due to advancing age of people living with HIV, the likelihood for Alzheimer's disease (AD) will increase
- Distinguishing AD from HAND is an urgent issue with few data to define a clinical approach
- Patterns of neuropsychological testing deficits overlap between the two diseases
- Alzheimer's disease biomarkers including PET imaging and brain imaging are not likely to be enough, used individually. CSF AD biomarkers may add clarity

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What can we do now?

To screen or not screen

- Controversy exists

- Screening tools are not great
  - International HIV Dementia Scale is not useful – WOULD NOT USE
  - Mini-Mental State Exam (MMSE) does not target HIV-related changes (more designed for AD) – WOULD NOT USE
  - Montreal Cognitive Assessment test (MoCA) has some association
  - Computer or tablet-based measures may hold promise, particularly for longitudinal patterns

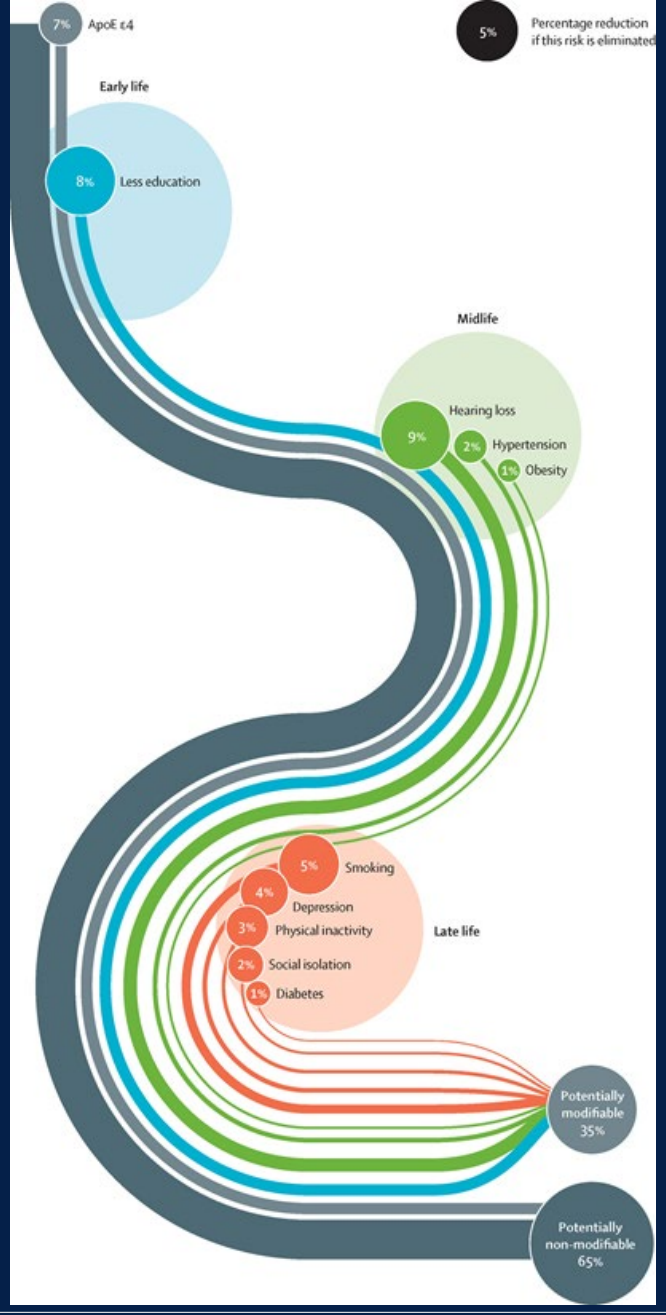
Treatment recommendations

1. Adherence to antiretroviral medications with persistent plasma viral suppression
2. Referral to a specialist if Alzheimer's disease or other age-associated neurodegenerative disorders is considered
3. Consideration for CSF escape (rare), particularly in more rapid and progressive presentations
4. Minimize polypharmacy and address medications that can impact cognition

   Beers criteria available online

Treatment recommendations

- Compensatory measures
  - Given an underlying attentional and speed component, many patients respond to Use of lists, reminders, alerts
  - Limiting multitasking
- Disclosing to friends when possible
  - Re: challenges keeping up with conversation/banter
- Reassurance on likely trajectory
- Empowerment with knowledge that symptoms are due to HIV and occur in others



The Lancet Commission:

Potentially modifiable risk factors

- Up to 35% of dementia risk is potentially modifiable
  - Hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes

Livingston et al, The Lancet, December 2017

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Thank you