Neurocognition and the Aging Brain

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Financial Relationships With Ineligible Companies

Dr Valcour has no financial relationships with ineligible companies to disclose. (Updated 06/16/21)

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Key Points

- Cognition impairment remains common in older people living with HIV
  - Estimate that about one-third will have impairment, of which only about half will be symptomatic
- Causes of cognitive impairment is sometimes multi-factoral
  - Research shows that chronic inflammation links to axonal integrity measures on brain imaging and cognitive performance
  - Common co-morbidities include cerebrovascular disease and medication effects
- Co-occurrence of age-associated neurodegenerative disorders, such as Alzheimer's disease are a major challenge in geriatric neuroHIV
- Recommendations for screening across published guidelines are inconsistent

Aging and HIV: Issues of Screening, and Management in Individuals as They Age – June 2021
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HIV-related cognitive impairment

Epidemiology, Clinical Presentation and Likely Causes

Frequency Estimates of Cognitive Impairment among PLWH

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, 100% on cART and suppressed for years)
- Europe (2018)[4]: 35% (89% on cART)
- Zimbabwe (2020)[5]: 50% (all on cART, viral suppression not reported)

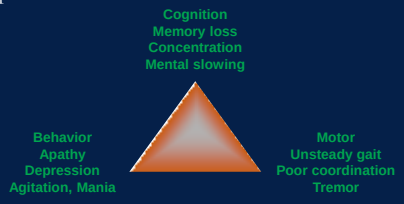
- Challenge for clinical settings: Many studies continue to publish rates of cognitive impairment that include individuals not optimally treated, making it difficult to understand clinical relevance
- CHARTER, for example, possibly representative at the time, but under-treated

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. Haddow et al. AIDS Behav 2018; 5. Nyamayaro et al BMC 2020

Commonly Reported Symptoms among PLWH who are Cognitively Impaired

- Memory problems (usually due to attentional deficits rather than memory)
- Trouble multi-tasking
- Attention challenges (re-reading, not hearing a partner, improvement with cues, reminders and lists)
- Slowed responses (not being able to keep up with banter in conversations, difficulty learning new music or dances)
- Fluctuation – good days and bad days

Clinical presentation



Clinical Features – Cognitive Profile

- Often attentional deficits are noted and can explain memory gaps
  - Poor performance on the first time words are read and asked to be repeated
  - Inefficient learning of tests
- Slowed information processing
  - Timed tasks take more time to do
- Higher cognitive thinking and working memory
  - More challenge with more complex tasks on a cognitive battery, particularly those that test a person's ability to hold one item in memory while doing another
- Multiple cognitive domains are often involved
- Typically mild to moderate deficits with fluctuating rather than progressive course

Clinical Features – Other Findings

- Imaging – can be normal or show a number of HIV-related findings
  - Common findings in older PLWH include global atrophy that may be more central and white matter changes on FLAIR imaging
- Lab tests
  - Can exist at any CD4 count, but more likely with lower CD4 count and with a past nadir <200 cells
  - Occurs commonly despite plasma and CSF viral suppression
- Neurological exam
  - Frequent errors on multi-tasking activities such as the Luria Sequence
  - Mild motor slowing can be seen

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

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

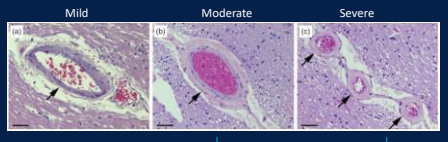
Further linked to cognitive impairment

- 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

Small Vessel Ischemic Disease in HIV

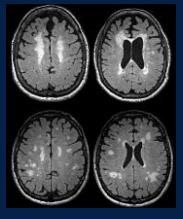


- Autopsy series in the US between 1999 to 2011

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]
- 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[3]

1. Seider J Neurovirology 2015; 2.Watsobn et al J Neurovirology 2017; 3. Wu et al AIDS 2018

Other potential contributors

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

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



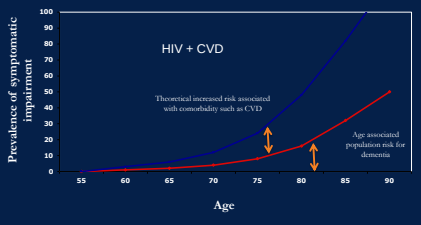
The Lancet Commission:

Potentially modifiable risk factors

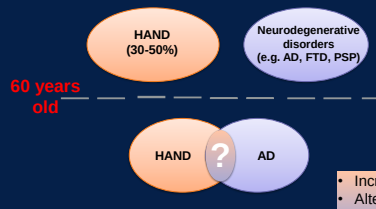
- Up to 35% of dementia risk is potentially modifiable
  - Hearing loss
  - Hypertension
  - Obesity
  - Smoking
  - Depression
  - Physical inactivity
  - Social isolation
  - Diabetes

Livingston et al, The Lancet, December 2017

Increased risk of symptomatic dementia associated with co-morbidity



Overlap between HAND and AD



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

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Screening for Cognitive Impairment in Older HIV-infected Patients

Screening Considerations (as applied to HAND)

Adapted from the US Prevention Service Task Force (UPPSTF)

- Does screening in primary care settings affect clinical outcomes? not known
- What is the prevalence of undiagnosed cognitive impairment in the primary care setting? moderate
- Does a reliable and valid screening test exist to detect cognitive impairment in older HIV patients? moderate
- Do pharmacological or non-pharmacological interventions, including care-giver interventions improve outcomes? probably
- What are the adverse effects of screening for cognitive impairment? some
- What are the costs/cost-effectiveness of screening for cognitive impairment? not known
- What are the side effects of any proposed treatment? Small

We must also consider screening for age-related dementias

Screening for HIV-related Impairment

Published Guidelines and Recommendations

- "Routine assessments of cognitive function every other year using a validated instrument is recommended for people with HIV who are older than 60 years (evidence rating: BIII)[1]
- "Cognitive health of older individuals with HIV should be monitored closely"…"For persons with progressively worsening symptoms of HAND, referral to a neurologist for evaluation and management or a neuropsychologist for formal neurocognitive testing may be warranted (evidence rating BIII)[2]
- "People with HIV also are at higher risk for…neurocognitive disorders" (recommendation on screening not discussed)[3]

- 1. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults JAMA 2020; 2. HIV and the Older Person guidelines at clincalinfo.hiv.gov (accessed June 2021); 3. Primary Care Guidance for Persons with HIV, Infectious Disease Society of America;

Screening for HIV-related Impairment

Published Guidelines and Recommendations

- No clear language on screening guidance, but infer that "PLWH themself or their relatives complaining of, or care giver noting cognitive problems – without obvious confounding conditions"[1]
  - The following questions may be used to guide doctor 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 major difficulties paying attention (e.g., to a conversation, book or film)?

1. Primary Care Guidance for Persons with HIV, European AIDS Clinical Society (https://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html Accessed June 2020

Screening for HIV-related Impairment

The Mind Exchange Working Group

- "It is appropriate to assess neurocognitive functioning in all patients with HIV…there is limited rationale for screening only symptomatic patients…or only those with recognized risk factors"
- "good practice suggests that a patient's neurocognitive profile should be assessed early (within 6 months of diagnosis)"
- Screening "should occur every 6-12 months in higher risk patients or every 12-24 months in lower-risk patients"
- Their published table lists available tests to include HDS, IHDS, total recall on list learning, grooved pegboard test, executive interview

Assessment, diagnosis and treatment of HAND: A consensus report of the Mind Exchange Program. CID 2013

Screening for HIV-related Impairment

2016 Underwood & Winston Review [1]

- "screening for cognitive impairment in both HIV-positive and HIV-negative populations is a controversial topic"
- "Most HIV treatment guidelines do not make any specific [screening] recommendations…of the ones that do, there is considerable variation in guidance reflecting the uncertainties in the literature"
- "In general, screening for cognitive impairment is not recommended in HIV-positive populations without symptomatology and diagnosis of HIV-associated cognitive impairment should be made only after a comprehensive assessment and exclusion of other potential causes"

1. Guidelines for the Evaluation and Management of Cognitive Disorders in HIV-Positive Individuals, HIV/AIDS Reports 2016

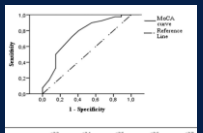
Screening for HIV-related Impairment

2011 Review of the Literature, Valcour et. al.

- "Only general recommendations can be made"
- MMSE is not likely to be useful to screen for HIV-related impairment or that related to vascular disease given the content of the test
- HIV Dementia Scale (HDS) has limited utility since it will detect only the most severe dementia that occurs in <5% of HIV-related impairment and is likely more apparent without screening (more recent data confirm its lack of utility – AIDS 2018)
- Montreal Cognitive Assessment (MoCA) is appealing as it taps cognitive domains impaired by HIV, vascular disease and Alzheimer's disease

Screening for Cognitive Impairment in HIV CID 2011 (Valcour et al.)

The MoCA to screen for cognitive impairment in HIV over age 60



	≤23	≤24	≤25	≤26	≤27
Sensitivity	0.90	0.80	0.72	0.50	0.38
Specificity	0.44	0.59	0.67	0.85	0.89
PPV*	0.75	0.67	0.62	0.53	0.77
NPV*	0.71	0.74	0.76	0.83	0.46

*Positive Predictive Value
*Negative Predictive Value

JAIDS 2014

- N=67; mean age 64 (60-84); 94% white; mean education of 16.3 years
- 100% on cART, 79% undetectable
- 60% cognitively normal; 12% with asymptomatic neurocognitive impairment (ANI); 28% with Mild Neurocognitive Disorder (MND); none with dementia
- Conclusions
  - At cut point of 25, AUC was 0.75
  - mall sample that may not represent most clinics but reasonable performance characteristics
  - Caveat – MoCA is no longer free

Digital Technologies

Validity of Digital Assessments in Screening for HIV-Related Cognitive Impairment: A systematic review (manuscript under review)

- NeuroScreen – 10 brief digitalized tasks created to mimic paper and pencil test used in HIV research; ~ 30 minutes to administer
  - 3 small studies show good performance characteristics and utility in a middle-income country
  - Good construct validity to paper an pencil tests.
- Cogstate – commercial test used form HIV and non-HIV cognitive impairment screening
  - 1 small sample showed good performance characteristics
- Brain Health Assessment on TabCat
  - Currently used for non-HIV setting and could be adapted for HIV
  - Uses regression-based norms which is a big plus and is free

Screening for Impairment in HIV-uninfected Populations
US

- "the evidence in insufficient to balance the benefits and harms of screening for cognitive impairment in older adults[1] (others note that USPSTF recommends screening when cognitive impairment is suspected)
- "In patients with suspected dementia, the Mini-Cog, the General Practitioner Assessment of Cognition or the Ascertain Dementia 8-item Informant Questionnaire should be used to determine the need for evaluation"[2]
- "Annual cognitive health assessment for patients 65 years and older"[3]

Mini-Cog = 3 word registration and recall plus clock drawing
General Practitioner Assessment of Cognition = combination of objective (recall address, recent events, clock drawing) and 6-item subjective reporting
Ascertain Dementia = 8 items subjective reporting

1. Preventative Service Task Force (USPSTF); 2. Evaluation of Suspected Dementia, American Family Physician 2018 ; 3. American Academy of Neurology 2019

My Conclusions

- Controversy exists around screening for cognitive impairment in both HIV-infected and uninfected populations
- More research is needed on its utility aligned with the USPSTF guidelines
  - Does it impact outcomes, is it cost effective, does it increase harm and unnecessary costs
- Screening is different from doing a work-up for people presenting with symptoms, where there is less controversy
- MMSE and HDS/iHDS have little utility for screening in today's environment of treated HIV and mild/moderate cognitive deficits
- MoCA is reasonable, although limited data show moderate performance deficits
  - Would be useful for HAND, AD and vascular cognitive impairment among others

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Thank you

Question-and-Answer Session

