

THE LANCET HIV

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Panel S1		
	HAND is correctly estimated ^{1,2}	HAND is over estimated ³⁻⁷
Statistics	<p>Globally, the majority of people living and aging with HIV have had AIDS which is a risk factor for cognitive impairment.</p> <p>Studies that have used standard neuropsychological testing across HICs and LMICs have demonstrated same prevalence of HAND², that is 20%-30% in virally suppressed individuals without historical AIDS, 40% in virally suppressed who had AIDS. This prevalence is generally 10% higher in people aged 50+ years old. HIV-associated dementia remains rare in treated HIV infection.</p> <p>In highly comorbid cohorts, the prevalence of HAND can reach up to 80%².</p> <p>People with clinically stable HIV and long-term viral suppression are not at risk of rapid cognitive decline. At most, 30% have vulnerabilities for cognitive decline including premature cognitive aging and sustained mild cognitive impairment⁸.</p>	<p>Most people living with HIV do not have clinically significant disease (i.e., they do not have dementia) and/or do not have active HIV disease.</p> <p>The current HAND criteria by clinical rating determine that at least 16% of people without HIV have cognitive impairment; use of stricter threshold is needed, and better methods exist to account for false positives⁶.</p> <p>It is not correct to state that 50% of people living with HIV have cognitive impairment and this statement leads to stigma.</p>
Mild HAND	<p>Mild Cognitive Impairment (MCI) is akin to the HIV-associated Asymptomatic Neurocognitive Impairment – (HIV-ANI) (34) in its degree of cognitive impairment and preserved functional status.</p> <p>Mild forms of cognitive impairment without major interference on everyday functioning (assuming that function is optimally assessed, ⁹⁻¹¹ that is HIV-ANI, ¹²) should not be neglected as there is cumulative evidence from MND and NeuroHIV research that such episodes of mild abnormal cognitive functioning are one of the strongest predictors of cognitive decline¹³ and dementia¹⁴. The relevance of mild forms of cognitive impairment in people living with HIV is also supported by a large body of neuroimaging research¹⁵.</p>	<p>HIV-associated brain injury (HABI)¹⁶ should be differentiated based on HIV RNA suppression and the activity of pathology to differentiate legacy and active HABI.</p> <p>Mild cognitive deficits diagnosed by the current HAND criteria do not represent clinically significant deficits and stigmatized people living with HIV who for the most part have healthy cognitive functioning especially if they low level of comorbidity.</p>
Comorbidity	<p>There is overwhelming evidence that age-related multimorbidity is a major risk factor for cognitive deterioration ¹⁷. Critically, there is good evidence that a large part of the multimorbidity burden in people living with HIV is driven by HIV and some ART ¹⁸. There is also good evidence that HIV itself as a whole or in part [pro-inflammatory and neurotoxic HIV protein¹⁹, and transcriptional HIV activity^{20,21} is still active.</p>	<p>Even when there is impairment, most of it is dissociated from HIV disease markers, but it is strongly explained by multimorbidity and legacy effects where chronological age has a lesser role.</p> <p>HIV-associated brain injury (HABI)¹⁶ should be considered as one cause of cognitive impairment alongside other potential causes of brain injury occurring in people living with HIV.</p>

Classification	Sensitivity and specificity are inversely related; hence some level of false positive diagnoses is expected. It is lower than claimed ⁶ when degree of cognitive impairment is integrated ² .	Cognitive symptoms should refer to any change in cognition that has been noticed by the individual or an observer, whether this change has an impact on daily functioning.
	HAND is correctly estimated ^{1,2}	HAND is over estimated ³⁻⁷
IADL	Functional assessment needs to be thoroughly evaluated to correctly attribute HIV-ANI versus HIV-MND including ART adherence ²² using validated tools.	The clinical investigation establishes the functional status
Diagnosis	HAND is a diagnosis of exclusion; hence the use of HIV ²² -associated ¹² . The diagnosis of exclusion is based on a cross-disciplinary neurology review including blood/CSF tests, neuroimaging, and a clinical neurology exam.	A research classification of cognitive impairment in people living with HIV should consider a combination of cognitive symptoms, low performance on cognitive testing, and abnormality on neurological investigations.
Evidence-based	The HAND criteria were originally developed against evidence-based of HIV-related brain injury ²³ . Neuroimaging studies have also demonstrated the clinical relevance of the HIV-ANI category included in low confounded cases ¹⁵ .	The HABI criteria lack evidence based and yet are currently recommended by the 2024 EACS guidelines. https://eacs.sanfordguide.com/prevention-non-infectious-comorbidities/neurocognitive-impairment
Already in agreement	An update is needed to account for more recent knowledge. Reintroduction of the clinical assessment as the central part of the criteria.	
Likely agreement	Present each relevant clinical investigations so that the neuropsychological assessment represents one of them and not the main one as it is currently provided in the 2007 criteria. Improve the assessment of the functional status using most recent research evidence and tools. Includes investigations that will assist in discriminating HIV-related and non-HIV-related brain injury. Improve the relevance of the criteria to LMICs	

Rourke and Cysique have started a project to update the HAND criteria in 2016-2018²⁴, principally to include the question of aging, to better integrate multimorbidity, to incorporate a chronic illness framework (requiring longitudinal criteria), and to improve the assessment of everyday function. However, this and other attempts^{9,25} have failed to reach consensus and eventually, efforts were disrupted by the COVID-19 pandemic. More recently, an effort supported by the NIH has focused on research biotyping²⁶. While this is a worthwhile research goal, it does not help resolve the disagreements amongst NeuroHIV researchers and does not respond to the urgent need for dedicated care for people living with HIV.

1. Selection of the group's articles in basic and clinical research^{2,8,9,21,27-37}, research that includes the patients' lived experience,^{1,31,38-54} and novel HIV and aging care models^{55,56}.

2. The successful cognitive aging framework

As in the general population, people living with HIV may also age successfully, including regarding their cognitive health⁵⁷⁻⁶⁰. We must however consider the fact that, at the global level, people living with HIV who are currently aging are, for the most part, survivors of the no-treatment and pre-ART eras. Most have been through intense periods of cumulative and collective grief and trauma (including 'survivorship guilt'), losing many friends and being told that they only had a few months or years to live. This is one reason why we are proposing, in the intervention section, that cognitive health in people living with HIV who are aging should systematically encompass mental health as offered in a holistic geriatric framework⁶¹. With this context in mind, these people living with HIV are not only aging successfully, but by token of their survivorship some are also "super agers" (being neurocognitively unimpaired and functionally independent⁶²). It would be important to acknowledge in the HIV community and among clinicians that while super aging *is not the norm*, expectations of "normal aging" are nevertheless realistic goals. Hence, when planning an appropriate health response it is important to remember that no one should be left behind and that the dignity of older people should be respected⁶³. The successful cognitive aging literature in people living with HIV has the advantage of linking well with the broader resiliency framework and tenants of promoting mental health per the 'recovery model' which is a less pathologizing model/approach to mental health and wellbeing than more traditional disease/deficits models⁶⁴. This research shows that factors that negatively impact successful aging include depression, cognitive functioning, low socioeconomic status⁵⁷ and loneliness⁵⁸. Positive psychosocial factors that could be useful in

intervening for promoting successful aging include emotional and social support, reducing social isolation, use of active coping strategies, hardiness and life stressor resilience, optimism, personal mastery, attitudes toward aging, resilience, and life satisfaction⁵⁹; while health factors include cognitive reserve⁶⁵, maintenance of cardiometabolic and mental health⁶², and lower frailty and multi-comorbidity⁶⁰.

Altogether, it is important to understand that most of the evidence, whether for successful, premature, accentuated, or accelerated aging, is still mainly derived from samples of people living with HIV in their mid-50s to early 60's. We need studies with participants closer to their 70s and older to develop an adequate and comprehensive healthcare response. Furthermore, we would like to emphasize that an appropriate healthcare response would encompass considerations of healthcare equity and access, in addition to minimum enforced standards⁶⁶. Finally, there is existing research from the lived experience showing that people living with HIV who are aging are greatly concerned with these questions^{54,67,68}, and need dedicated support^{50,69}.

3. HIV community and professional websites with information about cognitive health and HIV and aging

<https://www.natap.org/>

<https://www.harp-ps.org/>

[NAPWHA peer support links and their home page](#)

[OPP \(Queensland Positive People\) HAND information](#)

[OPP \(Queensland Positive People\) Home page](#)

[Positive Life NSW \(New South Wales\) Get Support includes Peer Support and a Home page](#)

[Living Positive Victoria Peer Support and other support programs](#)

[Positive Life SA \(South Australia\) resources including community support and Home page](#)

[ASHM Home page and Health Professional Resources](#)

<https://www.poz.com/tag/aging>

<https://www.iasociety.org/>

https://www.hivguidelines.org/guideline/hiv-aging/?mycollection=hiv-care#tab_3

<https://aahivm.org/>

4. More information about The NeuroHIV and Aging Advocacy Group

Our group meets bi-monthly on zoom. You can contact the corresponding author if you are interested in joining this group.

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