

## A new approach to cognitive impairment in people with HIV

Article (Accepted Version)

Nightingale, Sam, Cinque, Paola, Joska, John A, Price, Richard W, Underwood, Jonathan, Ances, Beau, Dravid, Ameet, Dreyer, Anna J, Gisslén, Magnus, Kwasa, Judith, Meyer, Ana-Claire, Mpongo, Nombeko, Nakasujja, Noeline, Pebody, Roger, Pozniak, Anton et al. (2022) A new approach to cognitive impairment in people with HIV. The Lancet HIV. ISSN 2352-3018

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/108173/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

### **Copyright and reuse:**

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

## COMMENT – THE LANCET HIV

### Authors:

Sam Nightingale PhD [1]\*

Beau Ances PhD [2]

Paola Cinque PhD [3]

Ameet Dravid MD [4]

Anna J Dreyer MA [1]

Magnus Gisslén PhD [5]

John A Joska PhD [1]

Judith Kwasa MMed [6]

Ana-Claire Meyer MD [7]

Nombeko Mpongo [8]

Noeline Nakasujja PhD [9]

Roger Pebody MA [10]

Anton Pozniac MD [11]

Richard W Price MD [12]

Christopher Sandford MA [13]

Deanna Saylor MD [14]

Kevin G F Thomas PhD [15]

Jonathan Underwood PhD [16]

Jaime H Vera PhD [17]

Alan Winston FRCP [18]

\*Corresponding author: Dr Sam Nightingale, HIV Mental Health Research Unit, Room 36, F floor, Neuroscience Institute, Groote Schuur Hospital, Observatory, 7925, Cape Town, South Africa. Tel: (+27) 064 773 8224. Email: sam.nightingale@uct.ac.za

### Affiliations:

[1] HIV Mental Health Research Unit, Division of Neuropsychiatry, Department of Psychiatry and Mental Health, Neuroscience Institute, University of Cape Town, South Africa

[2] Department of Neurology, Washington University School of Medicine, St Louis, Missouri, USA

[3] Unit of Infectious Diseases, San Raffaele Institute, Milan, Italy.

[4] Department of Medicine, Poona Hospital and Research Centre and Noble Hospital, Pune, Maharashtra, India.

- [5] Institute of Biomedicine, Department of Infectious Diseases, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden; Region Västra Götaland, Sahlgrenska University Hospital, Department of Infectious Diseases, Gothenburg, Sweden,
- [6] Department of Clinical Medicine and Therapeutics, Faculty of Health Science, University of Nairobi, Nairobi, Kenya
- [7] Department of Neurology, Johns Hopkins University, Baltimore, Maryland, USA
- [8] Desmond Tutu HIV Centre, Cape Town, South Africa.
- [9] Department of Psychiatry, College of Health Sciences, Makerere University, Kampala, Uganda.
- [10] NAM, London, UK
- [11] Department of HIV Medicine, Chelsea and Westminster Hospital NHS Foundation Trust, London, UK; Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK.
- [12] Department of Neurology, University of California San Francisco, San Francisco, California, USA
- [13] UK Community Advisory Board (UK-CAB), United Kingdom.
- [14] University Teaching Hospital, Lusaka, Zambia, Department of Neurology; Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
- [15] Applied Cognitive Science and Experimental Neuropsychology Team (ACSENT), Department of Psychology, University of Cape Town, Cape Town, South Africa
- [16] Division of Infection and Immunity, Cardiff University, United Kingdom
- [17] Department of Global Health and Infection, Brighton and Sussex Medical School, Falmer, Brighton, UK.
- [18] Department of Infectious Disease, Imperial College London, London, United Kingdom; HIV Clinical Trials, Winston Churchill Wing, St Mary's Hospital, London, United Kingdom

## **Working towards a new approach to cognitive impairment in people living with HIV**

The most frequently used criteria for cognitive impairment in people living with human immunodeficiency virus (PLWH) are the HIV-associated neurocognitive disorders (HAND) criteria, developed in 2007 by a working group formed by the United States National Institute of Mental Health (NIMH).<sup>1</sup> The HAND criteria (sometimes referred to as the *Frascati criteria*) were intended for use in research, but the terminology has become widely used to refer to clinical burden of cognitive impairment across diverse settings globally.<sup>2</sup>

Minimum criteria for HAND are met based on cognitive test performance compared to HIV-negative populations without the need for a clinical assessment. Several authors have expressed that this approach overestimates disease burden and HAND criteria are not appropriate for the modern era.<sup>3-8</sup> Criticism of HAND centres on three main points, as recently outlined by authors from our group.<sup>9</sup> Firstly, the statistical approach applied to cognitive data has the potential for a very high false positive rate: over 20% of cognitively normal HIV-negative control subjects can be defined as impaired based on the current approach.<sup>5,7</sup> Secondly, cognitive test performance is strongly influenced by complex educational, cultural and socioeconomic factors which can interact with HIV risk such that low cognitive test performance may not correspond to a pathological state. Thirdly, in the modern era of effective ART and an ageing population of PLWH, cognitive impairment in PLWH is frequently multifactorial, hence not synonymous with the direct effect of HIV on the brain and not best described as 'HIV-associated' in that sense.

HAND criteria were intended to harmonise methodology allowing comparisons across settings. However, it is suggested this approach relies too heavily on quantitative neuropsychology, i.e. the results of cognitive testing without clinical context, which does not transfer well to the clinical setting and is not appropriate for diverse populations of PLWH. HAND criteria typically classify 20–60% (and sometimes up to 90%) of PLWH with a cognitive impairment,<sup>2</sup> which does not seem to align with clinical observations that cognitive impairment in PLWH presents less frequently in the modern era, and then usually in the context of viral non-suppression, significant comorbidities or as a legacy of pre-treatment damage.<sup>10</sup> Lack of diagnostic precision hampers clinical trials for cognitive impairment and biomarker discovery. Importantly, overestimation of cognitive impairment risks creating fear among PLWH and worsening stigma and discrimination towards them.

Although multiple authors have outlined issues with the HAND approach since its inception over 15 years ago,<sup>3-8</sup> no alternative approach has been proposed. In response we established an International HIV-Cognition Consortium to develop new consensus criteria for cognitive impairment in PLWH. Our group is globally representative with almost half our members are based in low-to-middle-income countries, includes academics and clinicians across a range of disciplines (neurology, psychiatry, neuropsychology and HIV/infectious disease), and involves representatives from the community of PLWH.

Our group has been meeting since November 2021 to work towards a new approach, using the framework proposed in the recent HAND critique as a starting point.<sup>9</sup> This new approach is intended to better represent the changing profile of cognitive impairment in PLWH in diverse global settings and provide a clearer framework of classification for clinical management and research studies. Our specific aims are to produce criteria which: i) are applicable clinically as well as in research, ii) are appropriate for diverse populations of PLWH

globally, iii) can be applied in low- as well as high-resource settings, and iv) reduce the risk of fear, stigma and discrimination for PLWH.

To achieve these aims we feel changes are needed in a number of key areas. All causes of brain injury should be considered in PLWH experiencing cognitive issues. This is in contrast to HAND criteria which assumes cognitive impairment is caused by HIV, at least in part, unless a confounding condition is present.<sup>1</sup> This distinction is intended to better represent changes to the clinical burden of disease and facilitate the study of more representative samples in research. Brain injury caused directly by HIV (from a number of potential mechanisms) should be conceptually separated from other causes of brain injury which can occur in PLWH. This allows better clinical phenotyping and improved study of mechanisms underlying cognitive impairment. Brain injury caused directly by HIV should be divided into active and legacy, the latter representing inactive damage sustained prior to HIV disease control. This is important as treatment and prognosis differ substantially. HAND criteria do not make a distinction based on disease activity, which risks null findings in treatment trials by inclusion of participants with irreversible damage. We recommend a move away from a quantitative neuropsychological approach towards a reemphasis on clinical assessment, such that a label of cognitive impairment is not applied based on neuropsychological testing alone. This is intended to correlate more closely with clinical diagnosis and give more accurate prevalence figures for clinically apparent disease. We recommend that studies continuing to report rates of low neuropsychological performance without clinical assessment should also report the false classification rate of the test, i.e. the proportion of a cognitively normal population that would be classified as impaired based on the statistical methodology alone. The interpretation of a study reporting low neuropsychological performance in 30% of a population is different when the false classification rate is known to be 25% compared to 2.5%. At present the false classification rates are rarely acknowledged.

Our group is now working to develop specific recommendations and establish consensus on a roadmap to validation and implementation of this new approach. The initial outputs of our group will represent expert consensus rather than presenting new empirical data. Going forward our recommendations will require evaluation and field testing before being fully operational. It is hoped that this process will stimulate discussion and promote further study on methodology to help move the field forward in this area. We believe this is crucial so that PLWH in diverse global settings can understand their risk of cognitive impairment in the era of widespread effective ART coverage, be better informed of their prognosis, and know how to protect their brain health as they age.

## REFERENCES

1. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; **69**(18): 1789-99.
2. Wang Y, Liu M, Lu Q, et al. Global prevalence and burden of HIV-associated neurocognitive disorder: a meta-analysis. *Neurology* 2020.
3. Torti C, Foca E, Cesana BM, Lescure FX. Asymptomatic neurocognitive disorders in patients infected by HIV: fact or fiction? *BMC Med* 2011; **9**: 138.
4. Nightingale S, Winston A, Letendre S, et al. Controversies in HIV-associated neurocognitive disorders. *Lancet neurology* 2014; **13**(11): 1139-51.

5. Underwood J, De Francesco D, Leech R, et al. Medicalising normality? Using a simulated dataset to assess the performance of different diagnostic criteria of HIV-associated cognitive impairment. *PloS one* 2018; **13**(4): e0194760.
6. Meyer AC, Boscardin WJ, Kwasa JK, Price RW. Is it time to rethink how neuropsychological tests are used to diagnose mild forms of HIV-associated neurocognitive disorders? Impact of false-positive rates on prevalence and power. *Neuroepidemiology* 2013; **41**(3-4): 208-16.
7. Gisslen M, Price RW, Nilsson S. The definition of HIV-associated neurocognitive disorders: are we overestimating the real prevalence? *Bmc Infect Dis* 2011; **11**: 356.
8. Ciccarelli N. Considerations on nosology for HIV-associated neurocognitive disorders: it is time to update? *Infection* 2019.
9. Nightingale S, Dreyer AJ, Saylor D, Gisslen M, Winston A, Joska JA. Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2021; **73**(6): 1113-8.
10. Ferretti F, Mora-Peris B, Underwood J, Waldman A, Everitt A, Winston A. Cognitive Impairment in a Clinical Setting. *J Acquir Immune Defic Syndr* 2018; **77**(1): e10-e3.