Infectious disease

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Reply to 'Cognitive criteria in HIV: greater consensus is needed'

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We thank Cysique and colleagues for their considered response to our Consensus Statement (Nightingale, S. et al. Cognitive impairment in people living with HIV: consensus recommendations for a new approach. *Nat. Rev. Neurol.* **19**, 424–433; 2023)[1], and welcome discussion and debate on this important subject (Cysique, L. A. et al. Cognitive criteria in HIV: greater consensus is needed. *Nat. Rev. Neurol.* https://doi.org/10.1038/s41582-024-00927-1; 2024)[2].

First and foremost, we would like to reiterate that our approach does not seek to undermine the lived experience of people living with HIV who have, or are at risk of, cognitive impairment. Rather we feel these individuals would be best served by criteria that accurately delineate the underlying mechanisms and provide clear prognostic information.

Existing criteria for HIV-associated neurocognitive disorder (HAND)[3] can lead to ambiguity. Cysique and colleagues state that HAND is caused by HIV, but is also multifactorial[2]. Our approach seeks to address this ambiguity by conceptually separating 'HIV-associated brain injury (HABI)', caused directly by HIV, from 'cognitive impairment in people living with HIV', which can have several causes including HABI[1]. We believe this delineation is vital in an era in which effective HIV treatment is widespread and mixed pathology is common. The authors interpretation of our approach as a strict dichotomy between HIV-related and other causes[2] does not align with our position; indeed, we seek to emphasize the complexity of overlapping mechanisms[1].

Cysique and colleagues point out that distinguishing active from legacy HABI might be difficult, and that the two could coexist[2]. Although potentially true in some cases, failure to distinguish individuals with an active process caused by HIV from those with static damage or comorbidities might be the reason that clinical trials for cognitive impairment continue to be negative[4,5]. Furthermore, we agree that a reliance on viral suppression could miss pathology and for this reason proposed that treatment studies target a subgroup with active HABI despite viral suppression in blood and cerebrospinal fluid[1]. Studies of this group are crucial in a world in which viral suppression is increasingly the norm, while acknowledging that cognitive impairment from other causes is no less debilitating.

The advanced neuroimaging techniques mentioned by Cysique and colleagues[2] are undoubtably useful and we agree that their use in classifying brain injury in people living with HIV should be further explored. However, these techniques are not universally available and are not required for the diagnosis of clinically apparent disease; as such, we argue that they should not form an essential component of criteria designed to be applicable across diverse global settings.

Cysique and colleagues[2] raise concern that a wealth of historic data could be lost if existing criteria for HAND[3] are abandoned. We would like to reassure the authors that our category of 'low cognitive performance' is aligned with HAND, enabling direct comparisons going forward. Our proposed changes pertain mainly to the labels applied, distinguishing research classifications from clinical disease burden and separating the underlying mechanisms. Through clinically meaningful definitions with destigmatized terminology, we aim to improve care for people living with HIV.

We look forward to engaging further with the field to gain broader consensus on this important topic and are grateful for Cysique and colleagues' contribution towards that discussion.

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Competing interests

The authors declare no competing interests.