Published in final edited form as:

HIV Clin Trials. 2012 ; 13(5): 296–300. doi:10.1310/hct1305-296.

Comments to Garvey et al: “Low Rates of Neurocognitive Impairment Are Observed in Neuro-Asymptomatic HIV-Infected Subjects on Effective Antiretroviral Therapy”

Ignacio Perez-Valero, MD,

Unidad de VIH, Servicio de Medicina Interna – Hospital U. La Paz, Madrid, Spain

Luccette Cysique, PhD,

The University of New South Wales, Sydney, Australia

Scott Letendre, MD, and

HIV Neurobehavioral Research Center, University of California San Diego, San Diego, California

Robert Heaton, PhD

HIV Neurobehavioral Research Center, University of California San Diego, San Diego, California

TO THE EDITORS

We would like to respectfully comment on the manuscript published by Garvey et al in *HIV Clinical Trials* [2011;12(6):333–338] entitled, “Low rates of neurocognitive impairment are observed in neuro-asymptomatic HIV-infected subjects on effective antiretroviral therapy.”

1. The findings are unexpected in light of other results reported by these authors [“High rates of asymptomatic neurocognitive impairment (ANI) in HIV-1 infected subjects receiving stable combination anti-retroviral therapy with undetectable plasma HIV RNA”] at the 5th International AIDS Society Conference in 2009 (Abstract MOPEB027). This earlier report indicated a 31% rate of ANI; it was based on a sample of 45 individuals from the same clinic population; and it used the same methods of the current report.
2. In the current report, the authors stated, “Data describing neurocognitive function in HIV-infected subjects receiving effective cART are lacking.” This statement does not correctly represent the extensive work reported by several international groups in the past decade. There are several major publications from multiple continents showing high frequencies of neurocognitive deficits with a prevalence of 20% to 40% in HIV-infected individuals receiving suppressive HAART (21% in Robertson et al,¹ 21% in Sevigny et al,² 29% in Heaton et al,³ 36% in Cysique et al⁴). Although all of those publications included nonsuppressed HIV-infected subjects, the authors provided the prevalence of cognitive impairment in subjects

who had suppressed viral loads. All these studies used medium to large neuropsychological test batteries that were corrected for age as well as for education and followed Antinori et al criteria for the diagnosis of HIV-associated neurocognitive disorders (HAND).

3. The lack of correction for education in the current study of well-educated participants (14 years) is likely to have led to an underestimation of the rate of cognitive impairment, especially when using the brief screening method employed here. This should have been taken into account in the discussion and led to a more cautious interpretation of the overall rate of impairment. Higher level of education is well known to be associated with better performance on cognitive tests.⁵ Moreover, HIV-suppressed individuals and long-term survivors of the HIV epidemic are overrepresented by white men who have high levels of education and high premorbid cognitive abilities. In a cohort with these characteristics, failure to correct for education could substantially affect accurate classification of HAND, particularly when using a screening method alone.
4. The authors used a computerized screening of cognitive functions to diagnose presence or absence of neurocognitive impairment, employing a new tool called CogState. They justify the use of this screen based on a single study performed in another country.⁶ Although the authors likely used the same set of tasks and normative standards as in the CogState study published by Cysique et al in 2006, they do not provide this information. The current analysis does not appear to include the same specific outcome variables as in the original study (in the original study, the specific variables and variable weightings were selected on exploratory grounds to optimize within-study separation of impaired and unimpaired HIV+ participants). These participants' "gold standard" classifications were based on a comprehensive battery of traditional neuropsychological tests. The CogState variable selection and weighting in the Cysique et al 2006 study have not been validated with an independent sample. Therefore a direct comparison between this new study and the initial Cog-State study is not possible.
5. Based on the evidence published today, Cog-State may be useful for HAND screening, provided that appropriate, demographically corrected normative standards are also used. This does not equate to the recommended use of the CogState screen for a final HAND diagnosis.⁷ In this framework, Cysique et al have recommended the use of CogState to prioritize patients for a comprehensive neurological examination including a standard neuropsychological assessment. Because of this, the sole use of CogState to estimate HAND prevalence should be viewed with caution unless normative standards from an appropriate reference population are applied to the same CogState measures.

6. We agree that, in “higher income health care settings, individuals receiving suppressive HAART are one of the most clinically relevant groups for studying cognitive impairment.” Unfortunately, clinical populations include patients who are less than ideal, either because they are not on suppressive HAART, because they have other neurological, behavioral, or psychiatric comorbidities, or for other reasons. When interpreted in this context, the authors’ claim that their findings reflect the “true” prevalence of HAND is misleading, first, because their results can not applied to the HIV-infected individuals who are unsuccessfully treated and, second, as the authors commented in their discussion, because those groups in the current time of the epidemic are overly represented by long-term survivors, mostly men and persons of Caucasian ancestry. In other words, other types of individuals ought to be included to be representative of the overall HIV epidemic. Sweeping conclusions such as those made by the authors should be based on populations that include women (mostly excluded here), persons with non-Caucasian ancestry, and even nonadherent HIV-infected subjects who are still commonly seen in many clinical settings (45% in a meta-analysis published by Mills et al⁸), many of whom are cognitively impaired.⁹ Also, HIV-infected individuals living with systemic medical comorbidities including psychiatric comorbidities should be included, particularly in light of the aging of the HIV population. Although the authors suggested that the cognitive evaluation of these types of subjects “may overestimate the *true* prevalence in the cART era,” the limited methods of this analysis more likely underestimate the prevalence of HAND in HIV clinical populations.

In this regard, the stated conclusion that “in neuro-asymptomatic HIV-infected adults on stable cART, rates of neurocognitive impairment are low” is in fact misleading and has serious implications for public policies across many nations. It was produced without correction for education in a highly educated, male, and mostly Caucasian sample. It was presented without local HIV-negative controls with similar demographic characteristics and by using a selection and weighting of CogState variables that have never been validated in an independent sample.

References

1. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007; 21:1915–21. [PubMed: 17721099]
2. Seigney JJ, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. *Neurology*. 2004; 63:2084–2090. [PubMed: 15596754]
3. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010; 75:2087–2096. [PubMed: 21135382]
4. Cysique LA, Brew BJ. Prevalence of non-confounded HIV-associated neurocognitive impairment in the context of plasma HIV RNA suppression. *J Neurovirol*. 2011; 17:176–183. [PubMed: 21416169]

5. Heaton, R. Demographic influences and use of demographically corrected norms in neuropsychological assessment. In: Grant, I.; Adams, KM., editors. *Neuropsychological Assessment of Neuropsychiatric and Neuronal Disorders*. 3rd. New York: Oxford University Press; 2009. p. 127-155.
6. Cysique LA, Maruff P, Darby D, Brew BJ. The assessment of cognitive function in advanced HIV-1 infection and AIDS dementia complex using a new computerised cognitive test battery. *Arch Clin Neuropsychol*. 2006; 21:185–194. [PubMed: 16343841]
7. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69:1789–1799. [PubMed: 17914061]
8. Mills EJ, Nachega JB, Buchan I, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. *JAMA*. 2006; 296:679–690. [PubMed: 16896111]
9. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV+ adults. Effects of cognitive dysfunction and regimen complexity. *Neurology*. 2002; 59:1944–1950. [PubMed: 12499488]