Neurocognitive Change Observed in the CHARTER HIV Cohort Could Be Due to Chance, and May Be a Cause as Well as a Consequence of Detectable Viremia

To the Editor—We read with interest the article by Heaton and colleagues describing 438 human immunodeficiency virus (HIV)-infected adults from the CNS HIV Anti-Retroviral Therapy Effects Research cohort followed up for a median of 35 months with neuropsychological assessments every 6 months [1]. Longitudinal data are critically important but scarce in this area. However, we have 2 major concerns relating to the interpretation of their results.

Patients were categorized at each follow-up visit, with change in neurocognitive function defined using reference data described elsewhere [2]. Those with a change in *z* score falling below the 5th percentile of a reference population were categorized as "declined," those scoring above the 95th percentile as "improved," and those with intermediate level of change as "stable." Over the entire follow-up period (4–7 visits), patients who were consistently stable were in the overall category of Stable; patients who were stable or improved on every visit were categorized as an Improver; patients who were stable or declined on every visit were categorized as a Decliner. Two patients who both declined and improved on different visits were excluded. Final dispositions of the remaining 436 were 22.7% Decliners, 16.5% Improvers, and 60.8% Stable.

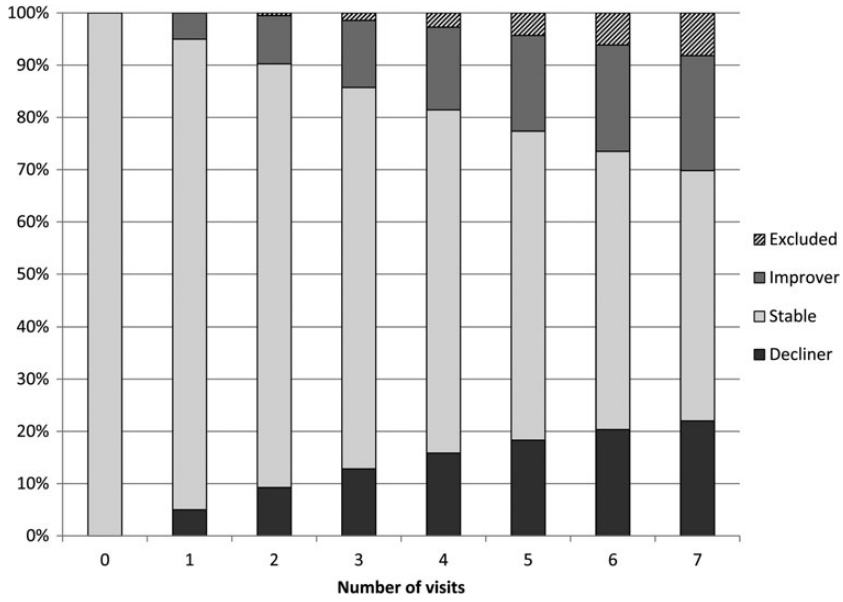

Figure 1. Expected cumulative risks of neurocognitive change due to chance alone, using methodology described in the CNS HIV Anti-Retroviral Therapy Effects Research cohort [1] and standard binomial probability equations.

The study did not contain HIV-infected control participants. However, we calculated the number who would be expected to improve or decline by chance alone. Assuming that all visits for any individual patient are independent, then at every visit each individual has 5% chance of declining and 5% chance of improving. Standard binomial probability predicts that after 2 visits, the cumulative risks of declining and improving are both 9.3%; after 3 visits, 12.8%; and so on to 6 visits when the cumulative probabilities of being a Decliner and being an Improver are both 21.7% of those not excluded (Figure 1), or 20.4% overall. We would conclude, therefore, that the results observed in this cohort for Decliners and Improvers are close to those expected by chance, and we question the editorial commentary [3] that the results are "nonnegligible." The only surprising finding is that just 2 patients (0.5%) were excluded on the basis of having both improvements and declines.

We also have concerns regarding paragraphs 3 and 4 of the discussion, in which the authors reflect on the observed association between neurocognitive decline, antiretroviral therapy (ART) status, and associated HIV biomarkers. By concluding that "being off ART uniquely increases risk for NC decline," they mistake association for causation. They do not acknowledge another, equally plausible explanation: that neurocognitive decline, or the factors that cause it, is responsible for poorer health outcomes, disengagement from care, and nonadherence to ART. An important clinical implication of this would be that patients with neurocognitive decline (or its risk factors) should be targeted to maintain good adherence to treatment.

In summary, although we welcome these longitudinal data, we are disappointed that misinterpretation may have been made in their reporting. With neurocognitive impairment high on the agenda for both clinicians and those living with HIV, the conclusion that "neurocognitive change is common in HIV infection" should have been tempered with some analysis of the frequency of change expected in the general population.

Notes

Author contributions. All authors contributed equally to this manuscript.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2015;60(9):1441–2

DOI: 10.1093/cid/civ043