Should Longitudinal Multisite Studies Become the New Standard for Investigating Neurocognitive Functions in HIV Infection?

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(See the Major Article by Heaton et al on pages 473–80.)

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In this issue of Clinical Infectious Diseases, Heaton et al present the longitudinal neuropsychological results of the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study [1]. The study included a large sample (436 human immunodeficiency virus [HIV]-infected adults across several US sites) followed over a period of almost 3 years; long-term follow-up is increasingly relevant because chronically HIV-infected persons are living longer. The assessments took place every 6 months and included a comprehensive neurobehavioral assessment (standard neuropsychological testing assessing 7 cognitive domains and premorbid abilities as well as standard psychiatric assessments). This study represents the unique achievement of a tremendous collaborative effort. The study is observational and nationally representative because it includes HIV-infected adults who have various levels of comorbid complications that are common in the HIV population.

The importance of the study is 3-fold. First, to define clinically meaningful neurocognitive change, the study used a statistical methodology (ie, standard regression-based change scores) that is widely acknowledged as one of the most robust and clinically relevant among neuropsychologists [2]. This method provides an easily interpretable global standard z score (mean, 0 [standard deviation, 1]) representing global neurocognitive change. Using this method, the magnitude of declining cognition was found to be global z score change = 0.50, which represents a medium effect size. This is a benchmark that can be used to compute a priori power in future studies. This value could appear trivial, but in fact it is not certain how much neurocognitive decline can be expected in chronically HIV-infected persons unless this type of study is conducted.

Second, the method classifies significant change as decline (22.7%) and improvement (16.5%) vs stable. These are nonnegligible numbers and they can also serve as a reference for incidence rates for future studies. Because of the paucity of well-conducted longitudinal neuropsychological studies in neuro-HIV research, these incidence rates are rarely available. Importantly, in the current study, global neurocognitive change and incidence rates were corrected for practice effect and regression toward the mean as well as baseline performance. This again could appear to be a trivial matter, but without such corrections, predictions of neurocognitive change based on repeated neuropsychological testing are imprecise or even erroneous [3].

Third, the authors then combined this method with longitudinal statistical analyses, which account for attrition and progress to yield an optimal fit rather than a significant P value. I have used this type of modeling in a smaller study [4] and have advocated its use. The model not only gives a clear picture of who is experiencing neurocognitive change, it also pinpoints the combination of factors that lead to this change. Knowing that subjects show neurocognitive impairment at one time in their life is simply not sufficient. We need to have a robust understanding of the trajectory of their brain health so that when we marry these neurocognitive data with other types of data (neuromedical, laboratory as in this study; but also neuroimaging data), the combined data yield a powerful model of brain change that has clinical relevance.
Using the data results, I highlight here the findings’ clinical implications, some confirmatory results, and novel findings:

1. In this sample, HIV-associated neurocognitive disorder (HAND) persists over the long term in most subjects. We know this because HAND prevalence was estimated at baseline. It is very important to know the baseline level of impairment in longitudinal studies, as this will have an impact on the level of global neurocognitive change that can be expected. When this baseline impairment level is unknown, the clinical relevance of stability or change remains unclear [5]. The study (Figure 1) [1] shows very clearly that there is baseline cognitive impairment in some patients (46%), and because the majority remain stable, it means that many remain stably impaired. This emphasizes the need for long-term neurological monitoring in chronically HIV-infected persons and the unique role that neuropsychological testing has to play. It also highlights a major limitation of any cross-sectional study in this field because almost 40% of HIV-infected individuals show significant neurocognitive change. This means that any cross-sectional neurocognitive association with any biomarkers may be either transient or inaccurate. I therefore believe that longitudinal studies should become a new standard in HIV-infected persons, who are now living almost as long as the general population. But because these are resource intensive, collaborations are required.

2. Some patients experience neurocognitive decline for a complex set of reasons, and this can be robustly linked to how such decline was defined (see Table 3 [1], which provides relative risk for each factor in the final multivariable model). This finding again emphasizes that neuropsychological evaluation should remain one of the key clinical assessments in this population, particularly in those with comorbidity.

3. Currently we are not certain what the long-term trajectory of the stably impaired will be. However, one unique finding that the study clearly demonstrated is that the level of comorbidity is a strong detrimental factor for brain health over time (decline happens in 38.5%, vs 24.6% for those with “contributing” and 18.3% for those with “incidental” comorbidities). But without even longer-term study, it is unclear if those comorbidities are a “speeding up” factor or a “mediating” factor in decline. On the flip side, the study confirms that relatively low differences in education and premorbid abilities protect against neurocognitive decline.

4. The study presents a complex multifactorial model of longitudinal HIV brain damage and resilience for HIV-infected adults in the United States. One interpretation of the CHARTER study might suggest that all change is driven by presence or absence of comorbidities (eg, depression, substance use). But a more complex interpretation is possible, namely, that neurocognitive decline is based on a combination of complex sociomedical determinants that may affect optimal HIV treatment and long-term brain health because HIV has been detectable and immune functions do not recover to their full potential. Although neurocognitive improvement is also marked by a complex set of factors, it uniquely includes surrogates of better social functioning and health (premorbid IQ and education), which in the United States overlap with racial/ethnicity background. Individuals with better premorbid social functioning and health are likely to manage their HIV disease more optimally, leading to greater brain resilience due to briefer periods of viral detection and greater immune recovery.

The study’s focus on the United States means that some of the findings may not be generalizable to an international population where antiretroviral adherence rate is higher or, on the contrary, where antiretroviral accessibility is reduced and more patients have AIDS. International multisite studies are needed because they will bring their own unique set of information on HIV and the brain and how it relates to their specific demographics, HIV history, and comorbidities. Eventually, the interpretation I presented above could be tested using data sharing and structural equation modeling, which requires a very large sample size. This will only be possible with another significant collaborative effort.

Notes

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