Lessons to be learned from the largest study of cognition in American women with HIV disease

Lucette A. Cysique, PhD
James T. Becker, PhD

Correspondence to
Dr. Cysique:
lcysique@unsw.edu.au

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In this issue of *Neurology*®, the Women's Interagency HIV Study (WIHS)[1] authors present findings whose scope and importance represent a landmark in the study of women with HIV disease. These data are of international relevance given that women now represent the majority of HIV-infected individuals worldwide. However, because of the complex socioeconomic and health burden of this cohort, the core study results concerning the state of neurocognitive health in HIV-infected women and their uninfected at-risk counterparts are not easily grasped.

The current study represents a unique snapshot of American urban-dwelling women, both with (HIV+, n = 1,019) and without (HIV−, n = 502) HIV disease. The data clearly demonstrate the complex interplay between HIV status (or risk for infection) and particular demographic factors, in addition to socioeconomic and health factors. Aged on average in their mid-40s, the majority of the cohort is African American non-Hispanic (>60%), Hispanic (~20%), and Caucasian (~12%). Almost half (45%) have an annual income of less than $12,000/year (meaning that many of these women live in poverty). One quarter of the study participants report clinically significant depressive symptoms, and some are currently drug and alcohol users (5%–25%). Childhood trauma (31%) and domestic violence (66%) were previously reported as common in the WIHS.[2]

The accumulation of detrimental psychiatric and socioeconomic factors in an HIV+ population (similar to what is seen in low to middle income countries) is a challenge for any neuropsychological study because those factors can confound normal neuropsychological performance above and beyond any specific disease effect. For this reason, the authors used the HIV− women, who were socially and demographically similar to the HIV+ women, as the reference for developing study-specific *t* scores. The authors found that the overall effect of HIV status was small (demographically adjusted Cohen $\delta < 0.20$ [table 3]), yet significant because of the large sample size. In relative terms, the effect of reading achievement, age, years of education, and racial/ethnicity category had a much larger explanatory value with respect to neuropsychological performance. However, HIV disease was a substantial factor for poorer neuropsychological performance in women with low education, low CD4+ T-cell count, detectable plasma viral load, and AIDS, all of which are well-established risk factors for HIV-associated neurocognitive disorder (HAND) in both men and women, and even in men who are at the opposite end of the social spectrum.[3–6] Also similarly to male cohorts, poorer neuropsychological performance was not driven by motor dysfunction as in the pre–combined antiretroviral therapy (cART) era,[7,8] but rather by higher cognitive functions such verbal learning and memory.

The majority of the infected women did not have compromised immune functions at the time of testing (87% had CD4+ T-cell counts >200), but 47% had HIV RNA detectable in plasma, and 37% had suboptimal cART adherence. Those latter 2 factors represent an important risk for brain dysfunction in other, mostly male, cohorts.[4,6] So why was there such a small HIV effect overall? One possible explanation is that clinically significant HIV-related brain damage has not occurred for the majority of the cohort despite detectable viral RNA. If so, any observed neuropsychological impairment would be driven by psychiatric and socioeconomic factors that occur equally in the HIV-infected and uninfected women. Another possible explanation is that women are less prone to HIV-related brain damage than men, in spite of apparently similar risk for HAND compared to men. Additional research would be needed to address this question, but would certainly involve the analyses of functional brain organization between the sexes. Finally, the development of the demographic *t* scores did not take into account complex interaction effects in their corrections (e.g., education × race/ethnicity or education × drug use) and in some respect the performance of the HIV+ group may have been overcorrected compared to that of the HIV− group. This possibility would need to be explored in a dedicated study.

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From UNSW Australia (L.A.C.); Neuroscience Research Australia (L.A.C.); St. Vincent's Hospital & St. Vincent's Centre for Applied Medical Research (L.A.C.), Sydney, Australia; and the Departments of Psychiatry, Neurology, and Psychology (J.T.B.), University of Pittsburgh, PA.

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A more complex picture emerges when education quality (indexed by reading level) and cognitive reserve were taken into account. Indeed, lower cognitive reserve and reading level mediated HIV-related neuropsychological dysfunctions. So, while at first glance the results might seem to say that the HIV effect is small in HIV+ women (an implicit comparison to men, although no men were compared directly), a better appreciation of the results, as noted by the authors, would suggest that the risk of HIV-related cognitive deficits may be substantially increased over the long term because of complex interactions between lifetime psychiatric and socioeconomic confounds. Both of these classes of moderator variables are associated with cognitive reserve and risk for HAND, as well as risk for other cognitive/behavioral syndromes associated with neurologic disorders.[5]

The longitudinal follow-up of this cohort will therefore be hugely important. The results of this study show that the complex socioeconomic and health factors that are otherwise known to be associated with economic and social inequalities cannot be ignored if we are to understand the effect of chronic illness on the brain. These factors are not mere confounds; they act as mediators and moderators of the disease before and after infection (and treatment). This observation resonates with one of the central messages of the 2014 AIDS conference that "the social determinants of the epidemic still need to be addressed,"[9] and are likely critical for understanding brain health.

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