

# HIV and the neuropsychology of everyday life

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*Neurology*® 2014;82:2046–2047

Early in the history of the HIV epidemic, investigators noted that carriers of HIV who were asymptomatic had poorer cognitive performance than matched HIV– controls. These HIV+ patients in early cohorts, mostly men who had sex with men, were medically asymptomatic but still showed performance deficits in verbal memory, executive function, and language. An early report concluded, “The constellation of subjective and objective neuropsychological and neurologic findings suggests the possibility of a definable syndrome associated with HIV infection in asymptomatic individuals.”<sup>1</sup>

Availability of combination antiretroviral therapy (CART) has reduced the incidence of HIV dementia, but mild neurocognitive disorders remain common in people with HIV. In the large CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study reported here, 47% had some form of neurocognitive impairment, with the vast majority falling into the range of asymptomatic neurocognitive impairment (ANI).<sup>2</sup>

The functional import of this level of cognitive deficit has been difficult to establish. Early studies found that mild cognitive deficits in asymptomatic patients were associated with increased risk of incident work disability and poorer medication management,<sup>3,4</sup> but the studies were suboptimal because they compared HIV+ and HIV– participants. The early studies were also unable to track linked transitions in cognitive and functional status using an appropriately wide range of self-reported and performance-based assessments of occupational skills.

The design of CHARTER allows this definitive study and the answer is now clear.<sup>5</sup> In models that adjusted for education, estimated verbal IQ, indicators of HIV progression, CNS medication penetration, and comorbid status, people with ANI at baseline, that is, mild cognitive impairment without functional limitations, were more likely to reach disability endpoints than HIV+ people with unimpaired cognition. Just over 50% of people with ANI declined in function, compared to 21.7% of neurocognitively normal (NCN) patients. In time-dependent analyses examining cognitive change, the risk of meeting disability endpoints among people with ANI was more than

3-fold higher than transitions in the NCN group, and thus the greater risk of disability in this group was likely related to worsening cognitive status. Because people with ANI had greater immunosuppression (lower CD4 nadir and greater likelihood of AIDS diagnosis), Grant et al.<sup>5</sup> conclude that ANI is HIV-driven and not benign. ANI was a risk factor for incident disability even when analyses were restricted to people who at baseline were virally suppressed.

Establishing the clinical import of subtle cognitive impairment can be challenging. Self-reports have their weaknesses (because of denial, loss of insight, or alteration of behavior to avoid challenges), while performance-based measures often lack ecologic validity (because participants are asked to perform tasks that are not typical behaviors). CHARTER got around this problem by developing a series of self-report, performance, and combined outcomes. In the absence of norms for the disability outcomes, the research team developed a criterion-based measure for the self-report measure (difficulty with 3 or more daily tasks) and a statistical criterion for the performance measure (scores for medication management and vocational skills at least 1 SD below the sample mean, or one test 2 SDs below the mean). The risk of poorer functional outcome associated with ANI was mostly consistent across the outcomes.

One missing component of this approach is information on the stability of disability. Grant et al.<sup>5</sup> do not report whether such disability persisted or perhaps remitted on subsequent assessments. This may also be important for assessing the risk of disability in ANI. On the other hand, time to first follow-up with disability may also be clinically important as an outcome in its own right.

Also notable in this research are differences in the risk of disability by sex. Women were nearly 3 times more likely to reach the disability endpoint than men. This difference provides strong support for reports of greater vulnerability to HIV-associated neurocognitive impairment among women.<sup>6,7</sup> Risk factors for poor neurocognitive performance, such as lower education, were more prevalent among women and indicate the importance of identifying potentially sex-

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specific biomarkers of neurocognitive decline and interactions with substance use disorders.<sup>8,9</sup> For example, women may be more vulnerable to addiction,<sup>10</sup> which in turn may increase risk of HIV neurocognitive impairment.

Grant et al. suggest that HIV+ people with ANI would benefit from more intensive monitoring since their risk of developing clinically relevant disability was 3 times higher than that of the cognitively normal HIV+ group. This seems clear. But findings from CHARTER also suggest that risk of disability due to neurocognitive impairment may be a feature of HIV generally. Over 21% of the NCN group also reached the disability endpoint. This is notable given that the mean age of the normal group was 43, nearly all had completed high school, and verbal IQ was in the normal range. Participants were followed for about 4 years (347 people completed 2,749 semiannual visits), a relatively short interval. Could it be that development of cognitive impairment and associated disability is a feature of HIV infection more generally, despite ART, viral suppression, and medical care? That is, with longer follow-up will most CHARTER participants who were initially diagnosed as cognitively normal also develop neurocognitive impairment and disability in their 40s and 50s? These results suggest that they may. Less clear is how well these results will apply to other HIV+ populations, such as populations with lower likelihood of substance use disorders or who never met criteria for AIDS.

#### AUTHOR CONTRIBUTIONS

S. Albert: drafting/revising the manuscript, analysis or interpretation of data. E. Martin: drafting/revising the manuscript.

#### STUDY FUNDING

No targeted funding reported.

#### DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to [Neurology.org](http://Neurology.org) for full disclosures.

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*Neurology* 2014;82:2046-2047 Published Online before print May 9, 2014

DOI 10.1212/WNL.0000000000000506

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