

# Aging and HIV-Related Cognitive Loss

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**A**LTHOUGH ANTIRETROVIRAL THERAPY HAS HAD A MAJOR effect on improving the survival of individuals with human immunodeficiency virus (HIV), cognitive disorders related to HIV remain an important burden of disease and disability worldwide. Among the more than 30 million adults living with HIV worldwide, a substantial proportion is estimated to have some form of HIV-associated neurocognitive disorders encompassing HIV dementia, mild neurocognitive impairment, and asymptomatic neurocognitive impairment.<sup>1</sup> Conservative estimates from better resourced countries suggest that the number of individuals of all ages living with HIV-related cognitive disorders will increase 5- to 10- fold by 2030.<sup>2</sup> Although data from Africa are sparse, 30% of the HIV-infected population in 1 Ugandan outpatient clinic experienced some form of HIV-associated cognitive loss.<sup>3</sup>

Several factors may contribute to HIV-related cognitive disorders. HIV is a neuroinvasive virus. Many antiretroviral therapy drugs have minimal penetrance through the blood-brain barrier and several of the newer drugs have even less penetrance into the central nervous system than older medications.<sup>4</sup> Beyond the risks of coinfections that can contribute to cognitive loss, such as cryptococcal meningitis or neurological manifestations of tertiary syphilis, delays in HIV diagnosis and treatment of some individuals who eventually take antiretroviral therapy may lead to irreversible brain damage. To date, there are no effective treatments for HIV-related cognitive decline beyond antiretroviral therapy. Nonetheless, clinicians often do not consider long-term cognitive outcomes when selecting antiretroviral therapy, particularly for patients who are middle-aged or elderly.

Complicating HIV-related neurocognitive disorders is older age, which is the major risk factor for multiple forms of cognitive decline. People with HIV are aging, including those in low- and middle-income countries where the life expectancy is steadily approaching that experienced in high-income countries. More than 3 million people with HIV infection in sub-Saharan Africa are older than 50 years, the World Health Organization (WHO) definition for elderly, comprising more than 14% of the sub-Saharan population living with HIV.<sup>5</sup> In the United States, more than 30% of the HIV-infected popula-

tion is older than 50 years.<sup>6</sup> It is uncertain whether HIV-related cognitive disorders predispose individuals to other forms of neurodegenerative disease or stroke. Older age is also associated with higher rates of Alzheimer disease, vascular dementia, and Parkinson disease-related dementia, as well as other factors such as depression, isolation, and certain nutritional deficiencies that can be associated with cognitive deficits. Untreated comorbidities that are more common with age, such as hypertension and diabetes, as well as medication toxicities and polypharmacy, may exacerbate cognitive deficits in individuals with HIV.

Older individuals with HIV and cognitive loss face societal challenges in at least 4 areas. First, the stigma of HIV infection remains despite important public health efforts. Second, research on aging in HIV has received limited funding, attention, and media coverage. Third, cognitive disorders are prone to misunderstanding by clinicians and can be difficult to diagnose. Screening methods are mostly inadequate unless severe disease is present. The perception of cognitive decline as normal aging, instead of the disease that it is, may conceal an important and emerging disease within the more familiar HIV epidemic. Fourth, older individuals in many parts of the world may have lost their children to the HIV epidemic and lack the social support network they need to cope with aging.

Reduced recognition of HIV-related cognitive disorders may be due to a lack of well-described and characterized disease names. Since the HIV epidemic began, the HIV-related cognitive disorders have ranged in classification from HIV encephalopathy to AIDS dementia complex and other terms. Treatment with antiretroviral therapy reduces the rate of HIV dementia and can reverse cognitive deficits, but for unclear reasons, milder forms of cognitive impairment are more difficult to treat and increase with age.<sup>7</sup> HIV-associated neurocognitive disorders remain common in antiretroviral therapy-treated HIV-positive patients, even among those with longstanding suppression of HIV viremia.<sup>8</sup> The more recent addition of diagnostic terms for mild neurocognitive impairment and asymptomatic neurocognitive impairment is im-

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portant. These terms recognize that individuals with HIV may experience higher-order cognitive deficits but lack the impediment to activities of daily living and severity that traditionally characterize dementia. A large proportion of individuals with milder forms of HIV-associated neurocognitive disorders may be asymptomatic.<sup>1,7</sup> However, some patients may experience deficits in work-related tasks and complex cognitive abilities, making mild neurocognitive deficits in HIV a contributing cause of disability and a barrier to antiretroviral therapy adherence and good health.

Several strategies are needed to address the issues related to aging and HIV-related cognitive decline. In the least resourced settings, strategies to deal with cognitive impairment in HIV may require more than the training of local clinicians. It will be necessary to develop community-based strategies that shift the tasks of screening for cognitive loss; testing for reversible causes of dementia; and safety precautions for those with cognitive deficits from physicians to nurses, medical assistants, and community support groups. Guidelines on the diagnosis of neurocognitive disorders and the best use of antiretroviral therapy are needed, including regimens to prevent and reduce HIV-associated neurocognitive disorders. To date, the WHO has not offered guidance about screening for neurocognitive disorders in HIV infection or antiretroviral therapy–related prevention and management of neurocognitive disorders. This likely derives from the need for prospective trials on the cognitive benefits of specific antiretroviral therapy regimens in low-income settings, particularly among older individuals. In better resourced areas, biomarker development for HIV-associated cognitive disorders and consensus about the best antiretroviral therapy regimen to use when many drugs are available could lead to improved patient outcomes.

Despite competing priorities in the care of HIV-infected individuals in many settings, there are reasons and means to effectively focus on neurocognitive disorders. Home-based testing that is a targeted intervention for identifying HIV-infected individuals before they become ill represents an important step in engaging at-risk individuals while they are still healthy. Earlier access to antiretroviral therapy can reduce the risk of cognitive disorders and neurological immune reconstitution inflammatory syndrome.<sup>9</sup> Among cognitively impaired patients, even in the poorest of settings, community-based care involving family members, neighbors, or patient-selected individuals to provide the psychosocial aspects of treatment support plays an important role in maintaining medication adherence, treatment retention, and preventing death. In turn, some patients receiving antiretroviral therapy will regain some cognitive abilities, allowing more full participation in the community. Locally relevant interventions aimed at promoting rehabilitation can mimic rehabilitation services found in wealthier settings.

The increasing number of people with HIV experiencing cognitive deficits will also lead to social and economic consequences for countries at all income levels. Developed coun-

tries already report that dementia is among the highest financial costs to society for brain disorders. Younger patients experiencing cognitive loss have direct health care costs, but also costs associated with their lack of employment and costs to caregivers. The only effective treatment for cognitive disorders in this population, early access to antiretroviral therapy, is a minimal cost compared with allowing patients to become ill.<sup>10</sup> As difficult decisions are made about prioritizing patient groups for resource allocation, the treatment of aging patients with HIV infection may also be recognized as a means to strengthening health systems. The necessary development of neurocognitive programs has relevance beyond HIV and may include survivors of stroke, traumatic brain injury, and other common causes of neurocognitive deficits.

Diseases and epidemics are not static. The era of focusing exclusively on preventing opportunistic infections and simply averting additional harm to the nervous system during HIV treatment should end. Research funding for HIV and HIV-related disorders can foster scientific discovery and lead to advancements well beyond those specific to a single virus. An improved understanding of cognitive function in individuals with HIV infection would promote a better understanding of the epidemic of cognitive decline and provide an opportunity for scientific and community discussion on interventions that can be offered in a culturally relevant manner.

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## REFERENCES

1. Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. *Clin Infect Dis*. 2011;53(8):836-842.
2. Cysique LA, Bain MP, Brew BJ, Murray JM. The burden of HIV-associated neurocognitive impairment in Australia and its estimates for the future. *Sex Health*. 2011; 8(4):541-550.
3. Wong MH, Robertson K, Nakasujja N, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology*. 2007;68(5):350-355.
4. Smurzynski M, Wu K, Letendre S, et al. Effects of central nervous system antiretroviral penetration on cognitive functioning in the ALLRT cohort. *AIDS*. 2011; 25(3):357-365.
5. Negin J, Cumming RG. HIV infection in older adults in sub-Saharan Africa: extrapolating prevalence from existing data. *Bull World Health Organ*. 2010;88 (11):847-853.
6. Centers for Disease Control and Prevention. Diagnoses of HIV infection and AIDS in the US and dependent areas, 2009. HIV Surveillance Report, vol 21. <http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/>. Accessed February 28, 2012.
7. Heaton RK, Franklin DR, Ellis RJ, et al; CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011; 17(1):3-16.
8. Simioni S, Cavassini M, Annoni JM, et al. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*. 2010;24(9):1243-1250.
9. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*. 2007;21(14):1915-21.
10. Walensky RP, Wolf LL, Wood R, et al. When to start antiretroviral therapy in resource-limited settings. *Ann Intern Med*. 2009;151(3):157-66.

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