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EDITORIAL COMMENTARY

Thinking About Getting Older With Human Immunodeficiency Virus

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The development of combination antiretroviral therapy (cART) offers an extended life to people living with human immunodeficiency virus (HIV), fulfilling many of the dreams of therapeutic enthusiasts. That HIV, a stealthy but relentlessly lethal viral infection, can almost always be suppressed by a generally well-tolerated, single pill a day regimen is truly a spectacular scientific success. A cloud causing ongoing concern in this otherwise sunny story centers on the concern that the quality of this extended life might be inferior or even downright miserable for some people living with HIV, because of developing dementia. Living a life that becomes a burden to the patient or to caregivers would be a tragic twist to this saga.

In this issue, Makinson and colleagues have provided a well-crafted analysis of the current status of aging people living with HIV (PLHIV) who have survived to have chronic, well-controlled HIV infections on current cART. The analysis provides hope, while raising realistic concerns that must be addressed in future studies. The manuscript reports the outcome of neurologic performance studies performed on 200 sequentially selected, HIV virally controlled PLHIV, compared with a matched (age, education, gender) community population of 1000. The study confirms that these PLHIV had worse neurocognitive performance than did controls. The primary analysis used the Frascati definition of impairment of at least 1 standard deviation (SD) in 2 domains, which, even when adjusted for confounders, gave an odds ratio of 1.5 (confidence interval 1.04–2.16) for neurocognitive impairment. More conservative methods, including increasing the SD to 1.5 to define impairment, or a more conservative multivariate normative comparison analysis, all supported the presence of HIV-associated impairments. The report has many strengths, including the use of the large, matched control group from a community study that provided contemporaneous norms; focusing the study on virally controlled patients without other seriously confounding illnesses; and sequentially selecting clinic patients to fill an age-balanced cohort representing ages 55–70 years. Confounders included in the adjusted analysis were cardiovascular disease, hypertension, diabetes, smoking, alcohol use, physical activity, depressive symptoms, and living alone. The fact that HIV remained associated with cognitive dysfunction in this older group is important.

Recognition that HIV in itself creates a more disabled population with special needs is a call to design care systems to meet the increased needs that this disability brings. This is particularly true given the more isolated living status reflected in the demographics of this population, where more than a third live alone. This isolation not only threatens support systems, but challenges the optimal ways for physicians to recognize, measure, and follow the real impacts of cognitive disabilities. In the setting of Alzheimer disease, an optimal means of understanding the true impact of advancing cognitive loss is through the clinical dementia rating (CDR) scale. This relies on an informant: generally someone living with the patient. Partners are sensitive to changes in behavior in everyday life and, with structured interviews, can alert and quantify changes remarkably well. With HIV patients often lacking such an observer, advancing disability may go unreported, and needed support will be delayed. This disadvantage is compounded due to the characteristics of the frontal predominant damage often seen in HIV brains, which may make patients less aware of their own deficits. Proactive care systems will be needed to identify and seek to ameliorate this impairment.

Having established that HIV populations experience more impairments for their age than controls, a very critical issue is whether the decline is accelerating. Aging comes with a predictable degree of progressive declines in performance on tests, and there is no expectation that HIV will be protective. However, if the

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persistent viral infection, drugs required to control it, or associated injuries accelerate the decline, aging would become exponentially difficult for HIV patients. Investigators have raised this specter in recent years, and caused considerable alarm for PLHIV. In this careful study examining a span of 15 years of aging, up to age 70, evidence was not found to suggest an acceleration of change by age. However, the authors were appropriately cautious not to claim that this is a reliable observation, noting that this study was underpowered to demonstrate such an association. Superficially, it would seem that this large a study would detect meaningful age-related changes. However, survival bias and the changing historical patterns of the epidemic make a cross-sectional analysis of these populations particularly treacherous. More severely impaired patients may have died at earlier ages, leaving increasingly mildly affected patients represented in older cohorts. Therapy has changed rapidly through the years, and survivors with different durations of infection will likely have had very different therapeutic histories. Classes of antiretroviral drugs keep changing, as has timing of the initiation of therapy. The fact that the duration of infection is not tightly linked to age further complicates the analysis. These factors will require longitudinal comparisons to ascertain that HIV and its therapies are not accelerating the development of impairment during controlled infections. Longitudinal observations currently are not uniformly coherent with regard to the progression of disability. Shorter, well-matched studies, such as those reported by Cole et al [1], have not found acceleration. Imaging analyses similarly did not find accelerating atrophy in the brains of PLHIV who were receiving effective therapy [2].

The elephant in the room related to serious, age-related cognitive decline is Alzheimer disease (AD). While the prevalence of AD in the general population rises above age 70, it is logical that, if there were an acceleration of AD related to HIV, it should be emerging in this population as PLHIV approach age 70. That was not seen. While the clinical onset of AD is in older patients, biomarkers of AD are present in the brains of patients at least 15-20 years before the onset of dementia. The pattern of markers associated with AD has not been identified in PLHIV as a group, making it unlikely that AD is prematurely expressed in PLHIV [3]. Further, there are actually only a very few case reports of documented AD in any HIV patients [4]. These observations should lend hope that the doomsday scenarios around AD in HIV patients are unfounded. Fortunately, tools to predict cognitive impairments with AD are improving rapidly [5, 6]. Amyloid and tau positron emission tomography imaging allow noninvasive measures of the key markers associated with AD. More encouraging is the prospect of a serum amyloid measurement sensitive enough to screen for preclinical AD [7]. As more cases of AD in HIV patients are seen in coming years, a careful analysis of the characteristic evolution of AD markers in the setting of HIV-Associated Neurocognitive Disorder (HAND) will be required. However, there is good reason to expect that the biomarker-based, positive identification of AD will be possible. Furthermore, the typical clinical course of AD is recognizable. AD is reliably progressive once it causes disability, whereas in a substantial majority of HAND patients, progression was not evident over some years of longitudinal follow-up [8]. While it will be important to further characterize the interaction of HAND and AD as our population enters the ages in which AD is prevalent, it seems likely that the differentiation will not be too difficult. What remains to be accomplished is the discovery of a disease-modifying therapy that could be provided early in the course so that the tragic disability of AD is averted.

Finding a marked increase in neurocognitive impairments in aging PLHIV is a sobering task, and calls health-care providers to prepare additional support and therapy for the associated disability that this population suffers. However, there are also reassuring signs in this report. The majority of disabilities identified were asymptomatic or caused only a minor disability. Only 1 patient in 200 had dementia. Further, the mix of these problems did not worsen with successively older cohorts, up to age 70. While the study of survivors is, by nature, a selected population, this older population of PLHIV might be predicted to have maximal deficits. They reflect long-abandoned care patterns, as a majority experienced periods of advanced disease with a median CD4 nadir below 200, and suffered acquired immunodeficiency syndrome–defining complications. In future aging populations, PLHIV who are now receiving more virologically potent therapies with fewer side effects, starting treatment immediately on a diagnosis of HIV, and in general starting treatment long before the immune system has collapsed, could see fewer impairments.

However, it is the responsibility of physicians to continue to advocate for our patients, and this report emphasizes significant and ongoing disabilities that we have yet to reverse and which are associated with HIV. Our HIV clinics will need to expand services to protect and support these patients appropriately. Meanwhile, prospective studies will be required to understand the details of interactions with HIV, its treatment, and associated conditions as patients enter the later years of their lives.

Note

Potential conflicts of interest. D. B. C. has received personal fees from Biogen, Millennium/Takeda, Genzyme (Sanofi), Pfizer, Amgen, Genentech, GlaxoSmithKline, Merck/Serono, Inhibikase, Dr Reddy's Laboratories, Shire Pharmaceuticals, Hoffmann LaRoche, Atara, Wave Life Sciences, and Mitsubishi Tanabe, outside the submitted work. The author has 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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