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COMMENTARY

Persistence of cognitive impairment among well-treated older adults with HIV in low- to middle-income countries

Commentary on "Prevalence and 1-year incidence of HIV-associated neurocognitive disorder (HAND) in adults aged ≥ 50 years attending standard HIV clinical care in Kilimanjaro, Tanzania" by Flatt *et al.*

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Since the beginning of the epidemic, neurological complications of HIV have been observed including cognitive impairment commonly termed HIV-associated neurocognitive disorders or HAND. However, the profile of cognitive impairment has shifted with the advent of effective antiretroviral therapy (ART) in persons with HIV (PWH). Relatedly, the age demographic of PWH has changed with near-normalized life expectancy. Although estimates of HAND ranging from 12% to 56% (Robertson *et al.*, 2010) have remained relatively stable over time, HIV-associated dementia has become far less common while milder forms of cognitive impairment have increased. The aging demographic of PWH has led to new challenges and mounting concerns that chronic HIV infection in combination with aging, age-related comorbidities, and long-term ART treatment may increase vulnerability to cognitive impairment in PWH. This is true not only in high-income countries (HIC) but also in low- to middle-income countries (LMIC) such as sub-Saharan Africa (SSA) where increased ART coverage is resulting in a rapidly aging population of PWH. With 70% of the world's HIV-infected population living in SSA (UNAIDS, 2017), the question of the prevalence of cognitive impairment among the changing demographic of PWH becomes even more salient.

In this issue of *International Psychogeriatrics*, Flatt *et al.* (2021) present a longitudinal study that aimed to examine the prevalence and incidence of HAND among ART-treated, older adults with HIV obtaining long-term routine care from a HIV Care and Treatment Centre in Kilimanjaro, Tanzania. The novelty of the study lies in the application of the classification of cognitive impairment and its stability to this newly emerging population of older, well-treated PWH in LMIC. Region-specific estimates of cognitive impairment are important as estimates are not generalizable across regions, particularly HIC vs. LMIC, given differences in HIV clade, host responses and genetics, sociocultural factors such as barriers to healthcare services and environmental exposures and common comorbidities such as tuberculosis, malnutrition, and malaria. Efforts to determine the prevalence of cognitive impairment globally and regionally have yielded varying estimates, ranging from 12% to 56% (Robertson *et al.*, 2010), likely due to differences in sample demographics, patterns of ART use, and diagnostic criteria. Flatt et al. article cites the prevalence estimate of 28% for cognitive impairment among men with high rates of viral suppression from the USA-based Multicenter AIDS Cohort Study (MACS; Sacktor *et al.*, 2016). Other studies have reported higher global rates. Two meta-analyses on the global prevalence of cognitive impairment were conducted recently; Wang *et al.* (2020) reported a prevalence of 42.6% (95% CI: 39.7, 45.5) across 123 studies from 32 countries. A meta-analysis of studies examining the prevalence of cognitive impairment specifically in the sub-Saharan country of Ethiopia reported a prevalence of 39.15% (95% CI 29.36, 48.94) (Zenebe *et al.*, 2021).

In this Tanzania-based clinical sample of 253 older PWH (age 50 and older), Flatt et al. reported that 47% of PWH met criteria for HAND using standard Frascati criteria. Consistent with HIC, the majority of these cases (92%) demonstrated milder forms of HAND (i.e., asymptomatic neurocognitive

disorder and mild neurocognitive disorder). Among those cognitively normal at baseline, incident HAND was reported in 37.2%. Among those diagnosed with HAND at baseline, 17.6% no longer met HAND criteria 1 year later. The 47% prevalence of HAND in this study is substantially higher than the 28% estimate in the MACS and in the upper range of HAND estimates more globally. Thus, the main message of this study is straightforward: HAND is highly prevalent in this setting despite well-controlled infection. Study strengths included use of a neuropsychological test battery designed for low-literacy settings and of neuropsychological test norms from a local, age-, and education-matched sample of HIV-negative adults.

The reasons for the higher prevalence of cognitive impairment in this sample are unclear. The authors argue that it is likely due to demographic and HIV-specific differences including high rates of illiteracy, longer durations of untreated infection, and inclusion of PWH with common comorbidities such as stroke and hypertension albeit the prevalence of these factors was not provided. Another possible explanation has to do with the male to female ratio in the study. The majority of participants in this study were women (72%) which is the opposite of the predominantly male cohorts that are typically seen in the USA. The male to female ratio is an important factor given evidence that women with HIV may be more cognitively vulnerable than men with HIV (Rubin *et al.*, 2019; Dreyer *et al.*, 2022). Most studies reporting sex differences in cognitive function in PWH were conducted in the USA. However, two studies in Africa also reported that the frequency of cognitive impairment was higher in women versus men (Royal *et al.*, 2016; Kabuba *et al.*, 2016) suggesting that this sex disparity is not region specific. Some of the biopsychosocial drivers that have been postulated to contribute to this sex disparity include sex/gender differences in cognitive reserve, psychiatric comorbidities (mental health and substance use disorders), and biological factors (e.g. inflammation, hormonal, genetic). Female-specific factors may be particularly relevant to this older cohort given that many of the women are likely to be peri- or postmenopausal given the age range of the sample (50–79, median age = 57) and the menopause is known to lead to cognitive change.

Another important consideration is the high prevalence of comorbid conditions (e.g. cardiovascular disease, major depression, substance use diagnoses, co-infections, etc.) among PWH that can compromise central nervous system integrity and potentially contribute to cognitive impairment. According to Frascati criteria, clinical judgment is required to determine the degree to which non-HIV-related comorbidities contribute to cognitive performance with a severe comorbidity classification precluding a HAND diagnosis. The authors acknowledge this issue and all participants were carefully screened for DSM-IV-defined psychiatric diagnoses when sufficient clinical information was available. However, individuals with DSM-IV-defined psychiatric comorbidities (i.e. depression) were included in the study population to increase generalizability of the cohort. Consequently, in the present cohort it remains unknown as to the degree to which mental health disorders contributed to cognitive impairment. Mental health risk factors and disorders such as depression, anxiety, post-traumatic stress disorder, and perceived stress are strongly associated with cognitive function in PWH, particularly in women with HIV (Rubin *et al.*, 2019). In addition to mental health factors, it is unclear the degree to which cardiovascular and metabolic conditions were assessed and their contribution to the high prevalence of HAND.

A novel aspect of this study was the assessment of the stability of HAND diagnosis over a 1-year period. They found that, among the 83 PWH who were cognitively normal at baseline and had follow-up data, 35 (37%) met HAND criteria at 1 year. Conversely, among the 91 PWH with HAND at baseline and assessed at follow-up, 16 (17.6%) were deemed cognitively normal at follow-up. The authors refer to the rate of non-HAND to HAND converters as "incident HAND"; however, we believe this is more appropriately termed "stability of HAND" as newly incident cases cannot be determined without a neuropsychological assessment prior to seroconversion. As cognitive deficits are known to fluctuate in PWH – as demonstrated by the instability in HAND diagnosis across 1 year in the current study – it is possible that HAND was present previously in these "incident" cases. The authors comment that the rate of instability in HAND diagnosis is greater than that seen in neurodegenerative dementias; however, perhaps a more equivalent comparison is with the precursor conditions to neurodegenerative dementias, mild cognitive impairment (MCI). Similarly, MCI diagnosis shows incidence rates of 51–77 per 1,000 person-years (Luck *et al.*, 2010) and reversion rates from 18% to 24% (Thomas *et al.*, 2019) among older adults, with community-based studies reporting more reversion than clinically based samples. The instability surrounding mild cognitive deficit disorders is not surprising given that the diagnosis is typically based on a one-time assessment in which cognitive performance can be easily influenced by mood symptoms, daily rhythms, environmental stressors, fatigue, and other state-dependent factors.

The findings from Flatt *et al.* are a much-needed first step in a large-scale endeavor to improve our

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understanding of cognitive impairment among older, well-treated PWH in LMIC. There are a number of follow-up analyses that could be undertaken within this data set that would be informative. The comprehensive neuropsychological test battery could be leveraged to determine whether certain cognitive domains are driving the prevalence of cognitive impairment. The panel of demographic, clinical, and biological variables could also be leveraged to examine predictors of cognitive impairment as well as domain-specific cognitive impairment. Understanding the phenotype of cognitive impairment and the risk factors is critical for developing effective pharmacological or non-pharmacological risk reduction or treatment/management strategies. Although age 50 and older was an inclusion criteria, the age span of the sample (50–79 years) could be utilized to examine a dose effect of age on the likelihood of cognitive impairment. Related to age, the sample has a large range in duration of infection (range 0.7–23.9 years), which suggests that there are PWH who have been living for many with the virus in combination with older, newly-infected PWH. The question arises whether the prevalence of cognitive impairment and profiles is similar or different in these two groups of PWH. There is some evidence to suggest that certain measures of HIV disease severity are more advanced (e.g. CD4 count) in those who acquired HIV over age 50 versus those who acquired HIV at a younger age when matched on duration of HIV (McMillan *et al.*, 2020). It is unknown whether this difference extends to cognitive impairment.

The take away message from Flatt *et al.* (2021) is that, despite effective ART, cognitive impairment persists mostly in mild versions, in resource-limited settings. The high prevalence of cognitive impairment (44%) in this Tanzania-based cohort of older PWH was comparable to other meta-analyses although in the higher range and considerably higher than rates reported in the US-based MACS. The clear consistent theme across the broader literature is that cognitive impairment remains an issue among older PWH in the ART era. A prior study reported that, among older PWH, 34% showed cognitive impairment on a global cognitive screen (Bourgeois *et al.*, 2020). Consistent with the previously discussed sex disparity, they found that a higher likelihood of cognitive impairment was associated with female sex as well as the other sociodemographic characteristics including nonwhite race, high school or less educational attainment, annual income below $10,000, and heterosexuality. Despite the mass of evidence regarding cognitive impairment in HIV, Woods *et al.* (2020) reported that PWH possesses moderately low general dementia knowledge, and, thus, may not engage in primary prevention, monitoring, or their own cognitive change or general healthcare. These results suggest that, in addition to the need for more research to better our understanding of cognitive impairment in PWH, there is also a need for healthcare providers to PWH to provide educational materials regarding cognitive health and promote evidence-supported, lifestyle prevention strategies (e.g. physical activity).

There is still much to be done to characterize cognitive impairment and its risk/protective factors in this population; however, simply identifying the burden of cognitive impairment may help to instigate policy change leading to more efforts to education PWH on cognitive health, to detect cognitive impairment in PWH and develop interventions to prevent further decline or to reduce risk in PWH without cognitive impairment. For instance, routine screening for cognitive impairment in PWH may be recommended. Furthermore, the persistence of cognitive impairment in the ART era signals the importance of bolstering research efforts into the effects of chronic HIV infection, low-grade inflammation, and long-term ART use on the brain to help us understand the biological pathways of cognitive impairment. Such insights can assist in developing effective treatment strategies and risk reduction protocols and to target these protocols to the most at-risk.

Conflict of interest

None.

Description of authors' roles

The authors, Erin E. Sundermann and Leah H. Rubin, equally contributed to the manuscript, revised, read, and approved the submitted version.

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