



What It Means to Age With HIV Infection Years Gained Are Not Comorbidity Free

Lauren F. Collins, MD; Wendy S. Armstrong, MD

Once fatal, HIV infection has become a chronic condition for individuals with access to care and treatment. Combination antiretroviral therapy (ART) has proved to be not only life saving but life extending for persons with HIV infection. According to the Centers for Disease Control and Prevention,¹ nearly half of the population with an HIV infection diagnosis in the US are now at least 50 years of age.¹ Instead of AIDS-associated illnesses, in most parts of the country, morbidity and mortality among individuals with HIV infection are now largely attributed to age-related non-AIDS comorbidities, such as cardiovascular, kidney, liver, and bone disease as well as cancer and neurocognitive impairment.² Marcus et al³ report on overall and comorbidity-free life expectancy among insured adults with and without HIV infection at Kaiser Permanente locations from 2000 to 2016. Of importance, among 39 000 individuals with HIV infection and 387 785 HIV-uninfected matched controls, the investigators found that the difference in life expectancy by HIV status decreased from 22 years (2000-2003) to 9 years (2014-2016) but was not eliminated. Even among individuals with HIV infection who initiated ART at CD4 cell counts of 500/ μ L or greater, a 7-year difference persisted. Furthermore, the difference in comorbidity-free life expectancy did not improve over time, and age-related comorbidities occurred 16 years earlier among individuals with HIV infection than among HIV-uninfected individuals (2014-2016). This marked difference in comorbidity onset, attenuated to 9.5 years in association with early ART initiation, has far-reaching implications for HIV care models and research priorities. Together, these findings underscore the evolving need for data-driven clinical guidance on care optimization in the contemporary age of chronic HIV infection. This guidance will require an improved understanding of risk factors and pathophysiologic factors associated with comorbidity burden among individuals with HIV infection, innovative and HIV-specific tools for early comorbidity detection and prevention, and implementation science for interdisciplinary management of multimorbidity among increasing economic effects.

Despite treatment advances, these data suggest that life expectancy for individuals with HIV infection still falls short of that for their HIV-uninfected peers and that years gained in association with ART do not come without cost. For the individual aging with HIV infection, greater longevity may be accompanied by early comorbidity onset, which may in turn explain the attenuated but persistent differences in life expectancy. In addition to a potentially higher likelihood of feeling unwell compared with individuals without comorbidities, there may be a need for a greater number of medications, clinic appointments, and hospitalizations. For the clinician, managing multimorbidity in a prematurely aging population calls for the evaluation of frailty and other geriatric syndromes during routine visits and intensified care coordination. For the health care system, the increasing comorbidity burden among individuals with HIV infection is associated with higher resource utilization and direct medical costs (ie, \$300-\$5000 more per patient-month for individuals with HIV infection who have comorbidities than for those who do not).²

To mitigate comorbidity risk and progression, novel strategies for comorbidity screening and prevention that are specifically tailored to individuals with HIV infection are needed, as emphasized by Marcus et al.³ First, the premature onset of age-associated comorbidities in individuals with HIV infection (beginning at approximately 36 years of age) suggests that age-anchored clinical guidance offered by national prevention task forces and individual medical societies for the general adult

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population may be inappropriate for individuals with HIV infection. Second, routine health screening tools developed in the general population, such as for cardiovascular disease and bone fracture risk, underperform among individuals with HIV infection and thus fail to identify many with elevated comorbidity risk who could potentially benefit from risk-modification interventions. Third, it is crucial to consider both HIV-specific factors (ie, CD4 cell count, HIV load) and non-HIV-specific factors (ie, race/ethnicity, income, body mass index, smoking status, and hypertension) associated with comorbidity burden in individuals with HIV infection. Recent data suggest that non-HIV-specific risk factors, including sociodemographic characteristics, may have a stronger association with comorbidity development among individuals with HIV infection than factors that are specific to HIV infection and that interventions addressing social determinants of health and modifiable lifestyle factors should be prioritized for integration into sustainable care models for aging individuals with HIV infection.^{4,5}

The study cohort comprised members of Kaiser Permanente in northern and southern California and the mid-Atlantic states, and therefore, results may not be generalizable to those who are demographically dissimilar, uninsured, or underinsured. These data in an insured, predominantly white population with health care access likely represent a best-case scenario and show what can be achieved for all individuals with HIV infection. The observed differences in overall and comorbidity-free life expectancy are almost certainly underestimated for individuals with HIV infection who have reduced access to care and unfavorable social determinants of health, an important subset of individuals who have poorer HIV-related and overall health outcomes.¹ In the southern US, for example, complex interrelated personal and public health challenges, such as structural racism, stigma, housing instability, food insecurity, coexisting mental health and substance use disorders, and insufficient health care infrastructure, compound to obstruct ART-mediated advances in longevity among individuals with HIV infection.⁶

Socioeconomic differences are not the only important measures that affect the generalizability of these data. Although females represent more than 50% of people with HIV infection globally, they are historically underrepresented in HIV research. The cohort evaluated in this analysis was predominantly male (87.7%), which the authors readily acknowledge as a limitation. The authors³ found that, by HIV status, women compared with men had a larger difference in overall life expectancy but a smaller difference in comorbidity-free years. These findings are contrary to emerging data from large cohorts of individuals with HIV infection examining multimorbidity, including the Women's Interagency HIV Study, suggesting that women with HIV infection have a higher non-AIDS comorbidity burden than men.^{5,7} Further investigation is needed to better define the role of biologic and sociobehavioral factors differing by sex that are likely associated with comorbidity development and life expectancy among individuals with HIV infection. Given that the average life expectancy in the general US population is significantly longer for women than men, future studies should be sex or gender balanced to power sex-stratified analyses more robustly.

Although the composite of the 6 non-AIDS comorbidities did not substantially differ between adults infected and uninfected with HIV, the difference narrowed over time more substantially for certain comorbidities (ie, diabetes, cancer, and cardiovascular disease) than for others (ie, chronic lung, kidney, or liver disease).³ Non-AIDS comorbidities for individuals with HIV infection appear to occur in patterns, possibly owing to risk factors and/or pathophysiologic features.⁵ Chronic immune activation is a hallmark of HIV infection (even in the context of virologic suppression) and has been implicated as a common denominator in the pathogenesis of several HIV-associated comorbidities.² Further study is warranted to explore whether comorbidities among individuals with HIV infection occur in nonrandom clusters triggered by shared mechanisms downstream from HIV-mediated immunomodulation, such as metabolic dysfunction, or procoagulation and vasculopathy.

Individuals with HIV infection are living longer and early HIV infection diagnosis and treatment affords life expectancies near but not equivalent to those of their HIV-uninfected counterparts. However, the years gained in association with ART are not cost free, and individuals with HIV infection may be prematurely aging by starting to develop non-AIDS comorbidities 16 years earlier

than their HIV-uninfected peers. Consequences are considerable, including but not limited to decreased life expectancy among individuals with HIV infection, evolving complexity for HIV care models to integrate multimorbidity management, and increased health care expenditures. Additional research is needed to elucidate the effects of sex and access to care on overall and comorbidity-free life expectancy among individuals with HIV infection. The data presented provide persuasive rationale for agencies and organizations to dedicate significant resources to the development and implementation of novel HIV-specific tools for addressing sociodemographic disparity, modifiable lifestyle factors, and comorbidity screening and prevention to improve overall and comorbidity-free outcomes for individuals with HIV infection.

ARTICLE INFORMATION

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Correction: This article was corrected on July 15, 2020, to fix a typographical error.

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Corresponding Author: Wendy S. Armstrong, MD, Division of Infectious Diseases, Emory University School of Medicine, 341 Ponce De Leon Ave NE, Atlanta, GA 30308 (wsarmst@emory.edu).

Author Affiliations: Division of Infectious Diseases, Emory University School of Medicine, Atlanta, Georgia; Infectious Disease Program, Grady Healthcare System, Atlanta, Georgia.

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