

Bearing the Burden of Non-AIDS Comorbidities: This Is What Women Aging With Human Immunodeficiency Virus Look Like

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Non-AIDS comorbidities are leading causes of death in people living with human immunodeficiency virus (HIV), particularly among individuals on chronic antiretroviral therapy (ART) [1]. Human immunodeficiency virus infection accelerates the development of age-related comorbidities, with research showing that the presence of 2 or more conditions, such as diabetes mellitus, hypertension, cardiovascular disease, kidney disease, and bone fractures, may occur about a decade earlier in persons living with HIV compared with individuals without HIV [2]. A disproportionate burden of non-AIDS comorbidities has been described among women living with HIV compared with their male counterparts [3]. In this issue of *Clinical Infectious Diseases*, Collins et al [4] report on the prevalence and burden of non-AIDS comorbidities among participants of the Women's Interagency HIV Study (WIHS), a well-characterized cohort of women with and without HIV infection from 11

cities across the United States. Among 2309 women living with HIV and 923 women without HIV, the investigators found that women living with HIV had an overall higher number of non-AIDS comorbidities (3.6 vs 3.0) and a higher prevalence of psychiatric illnesses, non-AIDS cancer, dyslipidemia, and kidney, liver, and bone disease. These findings have significant implications when designing and prioritizing targeted interventions to prevent and control comorbidity burden in populations with HIV, as women account for about one-quarter of adults with HIV in the United States [5], and represent about half of people living with HIV globally [6]. Furthermore, because women have been traditionally underrepresented in HIV-related research [7], these results from the WIHS cohort underscore the need for continued efforts to ensure adequate representation of women and minority populations in translational and clinical HIV research. It is important to highlight that 65% of women included in the study by Collins et al were black and 20% were Hispanic, a breakdown comparable to the distribution of race and ethnicity among new HIV diagnoses in the United States [5].

Notably, the comparator group in this study included women without HIV at risk of HIV acquisition, with a high prevalence of risk factors for developing age-related comorbidities. Thus, the

observed difference in non-AIDS comorbidity burden may be even larger if women living with HIV were compared with a more generalizable population of women without HIV. Furthermore, because the majority of comorbidities were primarily defined by self-report, the authors acknowledge that the true rates of comorbidities may have been underestimated. Indeed, the real burden of multi-morbidity among women living with HIV may be even greater. To further our understanding on the occurrence and predisposing factors of comorbidity burden in women living with HIV, future longitudinal studies should include more objective criteria to define non-AIDS comorbidities and be able to tease out between prevalent versus incident comorbidities over time.

An inherent problem of cohort-based research is the cost and complexity of obtaining objective tests to confirm comorbidities. Typically, a subset undergo testing for various problems like cardiovascular or bone disease with computed tomographic angiography or dual-energy X-ray absorptiometry. It is usually cost-prohibitive to conduct these and other investigations on more than 3000 study participants like those enrolled in the WIHS cohort. This creates the paradox of trying to determine the extent and burden of disease with the cost, complexity, and risk of trying to ascertain the truth in as many participants as possible.

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To their credit, the authors readily acknowledge that many of the non-AIDS comorbidities identified in this analysis were done by self-report.

Collins et al [4] also showed that non-AIDS comorbidities among women living with or at risk for HIV infection were associated with risk factors of comorbidity burden that are well established in the general population and the broader population with HIV, including older age, lower income, higher body mass index, and reported tobacco or crack/cocaine use. These results highlight the need for interventions that target modifiable risk factors among women living with HIV using culturally sensitive approaches, including intensification of primary prevention programs, smoking cessation, and substance-abuse disorder treatment services. Interestingly, recent use of abacavir was the only HIV-related factor associated with increased non-AIDS comorbidity burden in this study. However, this finding should be interpreted with caution, as the study design did not allow for an in-depth analysis of specific ART regimens and their contribution on non-AIDS comorbidities. In addition, as noted by the authors, abacavir use may have been favored over tenofovir disoproxil fumarate among women living with HIV who were at risk or had known renal or bone disease [8, 9]. Longitudinal studies that collect detailed data on ART adherence and regimen changes over time would be needed to explore this finding further.

Recent studies indicate that several factors may contribute to the observed sex-related differences in HIV infection and outcomes, including biological features such as hormonal, immunologic, genetic, and epigenetic factors, as well as sociobehavioral determinants [10]. For instance, compared with men, women exhibit lower levels of HIV viremia during the early stages of HIV infection [11]. Furthermore, women on chronic ART appear to have less cell-associated HIV RNA, and lower plasma

HIV presence by single-copy assay [12], perhaps related to the role of estrogen receptor in maintaining virus latency [13]. Enhanced interferon- α production of plasmacytoid dendritic cells from women results from estrogen receptor signaling and X-chromosome complement [14]. T cells have higher expression of inflammatory and cytotoxic pathways upon re-stimulation, with estrogen likely playing a role in overexpressing related immune genes [15]. After initiation of ART, restricted declines in C-reactive protein have been reported in women compared with men living with HIV [16]. Additional studies are needed to improve our understanding of key drivers of sex-specific differences in non-AIDS comorbidities in people living with HIV.

Overall, there is increasing evidence that women living with HIV have a high burden of non-AIDS comorbidities. Additional research is needed to decipher the biological mechanisms, and environmental and sociobehavioral determinants of the increased occurrence of non-AIDS comorbidities in women living with HIV. The data presented by Collins et al provide a compelling rationale for implementing and testing interventions aimed at attenuating the effects of known risk factors of comorbidity burden among women living with HIV. These data should motivate various agencies and organizations to dedicate additional funding to allow researchers to continue to unravel these mysteries with the aim of helping to alleviate suffering for those afflicted by a chronic disease without a cure.

Note

Potential conflicts of interest. C. J. F. reports grants from Gilead Sciences Inc, grants from ViiV Healthcare, grants from Janssen, grants from Amgen, grants from Merck, grants from Cytodyn, and personal fees from Clinical Care Options, outside the submitted work. M. A. H. reports no potential conflicts. Both authors have 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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