VIEWPOINT

Comorbidities in Persons With HIV
The Lingering Challenge

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The United States recently announced an initiative for ending the HIV epidemic in the United States.[1] The initiative is a joint effort of agencies across the US Department of Health and Human Services that is designed to decrease HIV transmissions in the United States by 75% over 5 years and by 90% over the next 10 years. This initiative represents the first time a coordinated effort of resources, programs, and infrastructure will focus on geographic areas and demographic groups with the highest rates of new HIV diagnoses in the United States.[1] If successful, this effort would substantially decrease HIV transmission in the United States, thus ending the epidemic as an epidemiological phenomenon and could serve as a model for implementation of similar plans on a global scale.

Even if this aspirational goal is achieved and HIV transmissions no longer occur in epidemic proportions in the United States, it still would not be possible to declare an end to HIV. There will still be at least 1 million people in the United States living with HIV, and it will be important to attend to their special medical needs even though they may have suppression of the virus to below detectable levels. Persons with HIV have a disproportionate risk of various comorbidities, such as cardiovascular disease, chronic kidney disease, osteopenia, osteoporosis, hepatic disease, and cancer, among others (**Table**),[2] as well as a significant burden of neurocognitive disorders.[3] In addition, they may develop some conditions at younger ages than persons without HIV. Unless a cure is developed for HIV, which would entail eradication of the replication-competent reservoir, persons with HIV will contend with this heightened risk of HIV-associated comorbidities for many decades because a person diagnosed with HIV today who is receiving potentially life-long antiretroviral therapy (ART) has a near-normal life expectancy.

To effectively solve the global health crisis HIV represents, the comorbidities among persons currently living with HIV must be addressed simultaneously with collective efforts to end the epidemic of new HIV transmissions. In this regard, successfully addressing the comorbidities will require new research advances. Paramount among these will be elucidation of the etiologies and pathogenesis of the conditions, which are variously driven by factors such as chronic immune activation, antiretroviral drug toxic effects, co-infections, and health care disparities.

Chronic immune activation, well described in HIV infection, is likely a common factor in the pathogenesis of multiple HIV-associated comorbidities. This immune activation is not completely abrogated with ART, and persons with HIV who are treated with ART and have undetectable viral loads experience persistent, slight elevations of certain proinflammatory and procoagulation biomarkers that are associated with poor outcomes including increased mortality.[4] Increasing the understanding of the complex mechanisms behind the immune activation and dysfunction seen in chronic HIV disease could potentially lead to new therapies that could help improve the clinical management of many HIV-associated comorbidities.

Persons with HIV, including individuals receiving ART, show an increased risk of ischemic heart disease and other serious cardiovascular conditions.[4] Although this risk has been associated with immune activation, numerous other factors are likely involved, including the effects of some antiretroviral drugs and the overrepresentation of certain established cardiovascular disease risk factors, such as tobacco use, in persons with HIV. It is critical to elucidate these mechanisms and develop and implement treatments that mitigate this risk. In this regard, a large ongoing clinical study (Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults [REPRIEVE]; NCT02344290) is investigating whether statin administration can reduce the incidence of major cardiovascular events in persons with HIV.

Kidney disease, neurocognitive disorders, and certain cancers remain continual challenges in the ART era, although the burden of specific conditions has shifted compared with the era prior to treatment with ART. In the United States, the prevalence of HIV-associated kidney diseases, such as HIV-associated nephropathy and thrombotic microangiopathy, which are associated with high viral loads and low CD4 T-cell counts, has decreased. In contrast, in persons with HIV who are effectively treated with ART, kidney disease associated with diabetes, hypertension, nephrotoxic medication effects, and aging is becoming more prominent.[5] Analogous to kidney disease, the distribution of HIV-associated neurocognitive disorders has shifted in the United States in the era of ART. Although the prevalence of HIV-associated dementia has decreased with effective anti-HIV therapy, mild neurocognitive disorder and asymptomatic neurocognitive impairment often persist despite viral suppression. The pathogenic mechanisms underlying HIV-associated neurocognitive disorders that persist despite undetectable plasma HIV levels remains unclear and continued research in this area is critical.[3] With regard to cancer, there is an increased incidence of certain cancers in persons with HIV, including several non–AIDS-defining cancers.[2]

Although ART prolongs life and prevents AIDS-defining complications, decreased bone mineral density is an HIV-associated comorbidity that is notable in that ART seems to be paradoxically associated with worsened outcomes. The Strategic Timing of Antiretroviral Treatment (START) study, which compared immediate

Table. Comparative Prevalence of Selected Comorbidities Among People With HIV Treated With Antiretroviral Therapy and Matched Controls Without HIV in the United States, 2003-2013[a]

	Commercial Insurance, No. (%)		Medicaid, No. (%)	
	HIV Cases (n = 20 519)	Controls (n = 46 763)	HIV Cases (n = 16 020)	Controls (n = 36 791)
Cardiovascular events	1375 (6.7)	1871 (4.0)	1666 (10.4)	2796 (7.6)
Kidney impairment	1806 (8.8)	1309 (2.8)	2435 (15.2)	2171 (5.9)
Fracture or osteoporosis	1559 (7.6)	2993 (6.4)	2083 (13.0)	3679 (10.0)
Liver disease	1272 (6.2)	1122 (2.4)	1810 (11.3)	1656 (4.5)
Cancer	1642 (8.0)	1917 (4.1)	1570 (9.8)	1545 (4.2)

[a] Adapted from Gallant et al.[2]

with deferred ART, found that the overall benefits of immediately starting ART were clear; however, greater bone mineral density loss was seen among patients in the immediate ART group compared with the deferred ART group.[6] Although the effects of certain antiretroviral drugs are not the only cause of decreased bone mineral density in persons with HIV, it is important to optimize treatment strategies and further understand the mechanisms of this condition, which is associated with increased risk of fractures that can decrease the quality and duration of life.

Hepatic diseases that affect persons with HIV have heterogeneous etiologies, including neoplasm, co-infection with viral hepatitis, toxic effects related to medications or alcohol, and nonalcoholic fatty liver disease. In individuals with chronic hepatitis C virus infection, co-infection with HIV, even in the context of ART, is associated with accelerated progression of liver disease.[7] Treatment of hepatitis C virus with direct-acting antiviral medications and the resulting undetectable hepatitis C virus levels has been a transformative medical advance, and is safe and effective in persons with HIV co-infection. However, these direct-acting antiviral medications must be made more widely accessible to persons with HIV and hepatitis C virus co-infection, and development of preventive innovations, such as a hepatitis C virus vaccine, must continue to be aggressively pursued.

HIV-associated comorbidities substantially add to health care use and direct treatment costs. Increased use of health care resources and associated higher direct medical costs are due to a greater proportion of inpatient admissions, complicated and expensive treatment regimens, and specialty outpatient services. In addition, persons with HIV and chronic kidney disease and persons with HIV and cardiovascular disease had significantly higher health care costs compared with those individuals with HIV without a comorbidity. Direct health care costs for persons with HIV and either cardiovascular disease or chronic kidney disease are between $1400 to $5000 greater per patient per month and for those with HIV and fracture or osteoporosis are $300 greater per patient per month compared with persons with HIV without these comorbidities. Furthermore, persons with HIV and both chronic kidney disease and cardiovascular disease had higher health care costs compared with those individuals with a single HIV-associated comorbidity.[8] Thus, increased health care costs and health care use resulting from HIV-associated comorbidities have a significant influence on both the individual and the United States health care system overall.

Since the early years of the HIV epidemic, much has been accomplished, mainly due to the advent of ART. Persons with HIV who are effectively treated with ART have a near-normal life expectancy, and with effective sustained viral suppression, do not transmit HIV to a sexual partner. However, much remains to be done in the identification, mitigation, and treatment of HIV-associated comorbidities that continue to be a challenge even in the era of ART. Additional research on the underlying pathogenesis of these conditions, randomized clinical trials to assess treatments, and a reduction in health care disparities must be prioritized moving forward. HIV-associated comorbidities also represent a significant economic challenge that must be addressed. In summary, while collectively working to end the HIV epidemic as an epidemiological phenomenon, it is imperative to concomitantly advance efforts to address HIV-associated comorbidities and thereby improve the lives of persons already living with HIV.

ARTICLE INFORMATION

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Additional Information: Dr Lerner is a clinical associate and Dr Eisinger is special assistant for scientific projects in the office of the director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health. Dr Fauci is the director of the NIAID.

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