HIV-Associated Pulmonary Disease: Is There a Link to Lung Aging?

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Growing older with HIV: the accelerated presentation of comorbidities
In the era of successful viral suppression with antiretroviral therapy (ART), persons infected with human immunodeficiency virus (HIV) face fewer direct complications of immunosuppression and opportunistic infections, and much of the HIV-infected population is now living past the age of 50. With the “graying” of HIV, patients are encountering chronic comorbid conditions, including cardiovascular disease, neurologic dysfunction, renal disease, malignancy, and chronic pulmonary disease. While in part due to routine aging as the HIV-infected population becomes older, these disease states occur at higher prevalence and in younger ages than in the general population. This finding has prompted the recognition of chronic disease states occur at higher prevalence and in younger ages than in the general population. This finding has prompted the recognition of chronic HIV infection, at least for some infected patients, as a model of “accelerated aging.”

Noninfectious pulmonary dysfunction among persons with HIV
Chronic obstructive pulmonary disease (COPD), typically an age-related disease associated with cellular senescence, seems to be a disease that presents prematurely and at higher frequency among HIV-infected persons. In fact, premature emphysema (in persons as young as age 30) had been noted among HIV-infected persons since the late 1990s. Current ART-era cohorts have also shown that persons with HIV, including those who are virally suppressed, have higher prevalence and incidence of COPD than the general population, and that HIV is an independent risk factor for COPD. At the University of Pittsburgh, in conjunction with the Pittsburgh AIDS Center for Treatment, we have studied a cohort of participants with mean age in their 40s, and have found a high prevalence of irreversible airflow obstruction (21 percent), and an even more striking frequency of diffusing capacity impairment (64 percent). These findings are consistent with results from other research cohorts. While these pulmonary function testing abnormalities are most prevalent among former and current smokers, they are also present among lifetime nonsmokers, supporting the independent contribution of HIV to lung dysfunction.

Potential mechanisms of HIV-associated pulmonary dysfunction: immune activation and senescence
During acute and chronic HIV infection, T-cells demonstrate elements of immune cell aging, with features of both senescence and persistent activation. Either HIV or its co-infections (including cytomegalovirus or hepatitis C) elicit repeated cycles of immune system activation and T-cell proliferation. Due to repeated triggering and clonal expansion, immune cells reach a replicative limit. This replicative senescence is associated with changes in T-cell phenotype and function. Senescent T-cells are dysfunctional; while less able to clear infections, they continue to provoke upregulation of the inflammatory response, with increases in peripheral inflammatory cytokines (including IL-6 and CRP, among others). The lung may thus sustain collateral damage, either from circulating inflammatory cytokines or from more direct insults, when activated and senescent T-cells are recruited through the pulmonary circulation. Because of its vulnerability to airborne exposures such as tobacco smoke, environmental toxins, and microbes (via infection or colonization), the lung and its circulation are at heightened risk to sustain damage from senescent and activated circulating immune cells. Immune-mediated inflammatory pulmonary cell damage and resultant accelerated alveolar epithelial cell senescence may contribute to HIV COPD.

Ongoing research and clinical considerations
In the HIV Lung Research Center at the University of Pittsburgh, we are actively investigating the potential contributions of accelerated aging to HIV-associated COPD. Determining potential risk factors for the aged immune and lung phenotypes in HIV is very important, because some of these factors (including ART regimens, cigarette smoke, and inhaled drug exposure, viral co-infection, and microbial colonization) may be modifiable in the future.

At the present time, what we do know is that persons with HIV are at higher risk for development of both airflow obstruction and diffusing capacity impairment, and that they develop pulmonary abnormalities at a younger age than clinicians might typically expect. HIV-infected persons with pulmonary abnormalities are frequently symptomatic with cough, wheeze, or breathlessness. Despite symptoms, pulmonary function testing is underused in this population, likely because COPD and other chronic pulmonary diseases have only recently come to the attention of those who provide front-line HIV care. As in the general population, persons with HIV with pulmonary symptoms benefit from a complete evaluation, including timely pulmonary function testing in those with signs and symptoms of COPD. Considering “chronic” diseases such as COPD in comparably young patients with HIV is the first step toward appropriate diagnosis and management.

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