Abnormal Lung Function in HIV-infected Adults: An Under-recognized Risk Factor for Early Mortality

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Advancements in the treatment of human immunodeficiency virus (HIV) infection have reduced acquired immunodeficiency syndrome (AIDS)-related mortality and extended life expectancy. As a consequence, in the aging HIV population, comorbid chronic diseases have become more prevalent (1), and noninfectious causes of mortality have increased (2, 3). Screening for, diagnosing, and managing chronic conditions are now recognized as critical components of providing longitudinal HIV care.

The prevalence of tobacco use among HIV-infected persons is more than double the prevalence in the general U.S. population (4). HIV infection is associated with increased incidence and prevalence of obstructive lung disease, independent of tobacco exposure, suggesting that the risk for chronic lung disease in the HIV population extends beyond tobacco exposure (5–7). In the HIV-uninfected chronic obstructive pulmonary disease (COPD) population, worse lung function, increased dyspnea, and reduced exercise capacity have been associated with increased mortality. The effect of these factors on mortality among persons with comorbid HIV and COPD is unknown.

In this month's issue of the *AnnalsATS*, Gingo and colleagues (pp. 192–199) determined the association between pulmonary function and all-cause mortality among HIV-infected adults by analyzing data from participants recruited from three studies into the Pittsburgh HIV lung cohort: the Pittsburgh AIDS Center for Treatment, Multicenter AIDS Cohort Study, and Women's Interagency HIV

Study (8). As part of enrollment, participants underwent pulmonary function testing and standardized noncontrast computerized tomography imaging, with a subset ($n = 228$, 58%) also completing echocardiograms. Deaths were ascertained via active surveillance and the National Death Registry matching in the Multicenter AIDS Cohort Study and Women's Interagency HIV Study, as well as medical record review in the Pittsburgh AIDS Center for Treatment.

The cohort of nearly 400 adults with HIV infection was notable for the inclusion of 32% females and 44% African-Americans with a relatively young age (median, 49 years), and well-controlled HIV infection (81% were receiving antiretroviral therapy, median CD4 count was 514 cells/ml, and 65% had an undetectable HIV RNA plasma level). Tobacco use was very common, with 74% being current or former smokers. Higher baseline plasma HIV RNA level, self-reported hepatitis C infection, and lung diffusing capacity (DL_{CO}) below 60% predicted were independently associated with all-cause mortality in multivariable Cox Proportional Hazards models. Airflow obstruction consistent with COPD (forced expiratory volume in 1 s/forced vital capacity [FEV_1/FVC] < 0.70) was also independently associated with all-cause mortality, even after adjusting for smoking status. Computerized tomography measures of emphysema and airways disease, and echocardiographic measures of pulmonary hypertension, were not associated with increased mortality.

This study raises important points and questions regarding chronic lung disease in HIV-infected persons. First, the newly demonstrated association between airflow obstruction, as well as moderately to severely decreased DL_{CO} , and increased all-cause mortality in persons living with HIV underscores the effect of chronic lung disease in this population. Whereas other comorbid conditions such as cardiovascular disease, liver disease, and non-AIDS cancers have been recognized for their clinical significance among persons living with HIV, chronic lung diseases have been relatively underemphasized, despite the fact that chronic lung diseases such as COPD are a leading cause of mortality worldwide. Further, COPD is prevalent among HIV-infected persons (7) and is significantly associated with frailty (9), impaired physical function (10), and risk for hospital admission among those living with HIV (11). Given that HIV-infected patients are at increased risk for the development of chronic comorbid disease and mortality relative to their HIV-uninfected counterparts (12), the association between pulmonary function abnormalities and mortality identifies a subpopulation at greater risk for death but that might also potentially benefit from interventions, including pharmacologic therapy and intensive smoking cessation efforts, that might improve patient outcomes.

Second, what are the particular disease processes that these markers of impaired pulmonary function reflect? Presumably, given the prevalence of smoking, the majority of individuals with spirometric

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airflow obstruction have COPD, yet whether this reflects the same pathophysiology of disease in the setting of concomitant HIV remains uncertain. Complicating the question, a decreased DL_{CO} is nonspecific. HIV infection has been shown to be an independent risk factor for reduced DL_{CO} , with markers of worsening HIV severity correlating with greater reductions in DL_{CO} (13). Studies have found this reduction in DL_{CO} among HIV-infected persons to represent early emphysema by chest computerized tomography imaging (14), yet emphysema did not correlate with increased mortality in the study by Gingo and colleagues (8). Reduced DL_{CO} in HIV-infected persons has also been associated with comorbid pulmonary hypertension (15); however, in this study, echocardiographic measures of pulmonary pressures were not elevated and also did not correlate with mortality. This may be explained by the relatively mild measures of emphysema (median global emphysema score of 0 in both those with and without airflow obstruction; percentage emphysema ≤ 950 of 3% and 1% in those with vs. without airflow obstruction, respectively) and pulmonary hypertension (median estimated pulmonary arterial systemic pressure of 40 mm Hg and 33 mm Hg in those with vs. without airflow obstruction) that were observed. A reduced DL_{CO} has been linked to increased immune activation, as well as systemic inflammation in HIV-infected persons, which are both associated with increased mortality in this population (16, 17), providing a potential mechanistic basis for the association of DL_{CO} with mortality, but leaving a clinical intervention to improve outcomes uncertain.

Third, because chronic lung diseases including COPD are underdiagnosed among persons living with HIV, as demonstrated by Gingo and others (8, 18), the true effect of pulmonary dysfunction on morbidity and mortality of HIV-infected

persons is likely underestimated. An intriguing finding in the study by Gingo and colleagues was that participants lacking a physician diagnosis of COPD but with airflow obstruction on study pulmonary function tests suffered a statistically significant 2.6-fold increase in the hazard ratio of all-cause mortality as compared with a referent group of those without COPD (8). The reasons for this finding are unclear, but suggest that a greater recognition of disease may be beneficial for patient outcomes. Further studies to understand how best to enhance the diagnosis of COPD in persons living with HIV are warranted.

Fourth, how should these chronic lung diseases in HIV-infected patients be treated? This study reminds us of the key questions still facing the broader COPD community. Beyond tobacco cessation, lung volume reduction surgery, and lung transplantation in appropriate populations, what COPD-specific therapy can be administered to reduce mortality? Even if mortality is not affected, what therapies are effective for the treatment of COPD in HIV-infected patients to reduce symptoms, decrease COPD-related morbidity, and improve health-related quality of life? No studies have assessed whether treatment of COPD should be tailored for those with HIV infection, or whether guidelines applied to the general population can be implemented in the HIV-infected population. Finally, is there a role for screening spirometry in those with HIV? Given the challenges of employing methods to identify a COPD diagnosis in the HIV-infected population that are considered standard of care in the general population (19), perhaps studies should be tailored to identify HIV-infected subpopulations in whom spirometric sensitivity and specificity to diagnose COPD are optimized and in whom case-finding can lead to the initiation of therapies that improve patient outcomes.

Several limitations to the work of Gingo and colleagues should be noted. Sociodemographic and clinical characteristics were obtained at baseline and may not represent cumulative or fluctuating exposures, such as ongoing tobacco use or cessation, relevant to mortality. Cardiovascular disease was not assessed beyond echocardiographic measures, and therefore the effect of cardiovascular disease on all-cause mortality cannot be comprehensively assessed in this population with prevalent tobacco use and independently elevated cardiovascular risk. The relatively small sample size (396 participants) and number of deaths ($n = 30$; 8%) limit the ability to fully understand modifiable factors contributing to the observed association, for example, with regard to the role of cardiovascular disease. Although the authors note that the relative effect of pulmonary function testing abnormalities on mortality in the studied HIV population was greater than has previously been observed in the general population, a limitation is the lack of a demographically similar HIV-uninfected population to allow a direct comparison.

In summary, Gingo and colleagues have newly demonstrated the increased risk for mortality among HIV-infected persons with airflow obstruction on spirometry as well as impaired DL_{CO} (8). Their findings align with our understanding that HIV is an independent risk factor for worse pulmonary outcomes, ranging from increased respiratory symptoms (20) to increased incident chronic lung disease (7) and to worse morbidity and mortality from chronic lung disease (3). Interventions to enhance recognition, improve treatment, and reduce morbidity and mortality from chronic lung diseases need to be investigated and readily and appropriately applied in this high-risk population. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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