
Article:
Collini, P. orcid.org/0000-0001-6696-6826 (2021) Lung function declines more rapidly in treated HIV-positive people than in HIV-negative people. The Lancet Healthy Longevity, 2 (4). e183-e184. ISSN 2666-7568

https://doi.org/10.1016/s2666-7568(21)00059-3

Lung function declines more rapidly in treated HIV-positive people than in HIV-negative people

See Articles page e202

As ever greater numbers of people living with HIV now have access to antiretroviral therapy and achieve sustained viral suppression,[1] the focus of HIV care turns toward optimising long-term outcomes of age-associated non-communicable comorbidities that are common in people living with HIV, including obstructive pulmonary disease.[2] Cohort and cross-sectional studies demonstrate higher prevalence of respiratory symptoms, diagnoses (eg, COPD or emphysema), abnormal lung imaging (eg, emphysema), and impairments on spirometry and diffusion capacity measurements in people living with HIV.[3] Though increased smoking among people living with HIV is a contributor,[4] associations between HIV and impairments in pulmonary function are independent of smoking. Legacy effects of uncontrolled HIV infection before initiation of antiretroviral therapy (eg, bacterial pneumonia, tuberculosis, *Pneumocystis jirovecii* pneumonia, immunosuppression, and viral replication), and ongoing chronic inflammation despite viral suppression are also implicated.[5] As the prevalence of pulmonary morbidity is increased in older people living with HIV, an epidemic of chronic lung disease in people living with HIV could emerge as cohorts age.

However, cross-sectional studies have limitations and prospective longitudinal studies with appropriate HIV-negative controls that also control for confounding risk behaviours (eg, smoking) are needed to discern the relative contribution of HIV infection and risk behaviour to ongoing lung damage and to predict the trajectory of these lung diseases with ageing.

In *The Lancet Healthy Longevity*, Sebastiaan Verboeket and colleagues[6] report results from the prospective AGE_hIV cohort study. Over a median follow-up of 6 years, the investigators regularly measured pre-bronchodilator spirometry in 500 virally suppressed people living with HIV and, crucially, compared them with a demographically and lifestyle-matched control group of 481 HIV-negative individuals recruited from a sexual health service in the Netherlands.

Forced expiratory volume in 1 s (FEV_1) declined over time in all participants, and declines in FEV_1 and the ratio of FEV_1 to forced vital capacity (FVC) were steeper for current smokers than non-smokers, for both HIV-positive and HIV-negative participants. However, although both smoking and non-smoking HIV-negative control participants showed relatively little change in FVC and a rate of FEV_1 decline similar to that seen in healthy population studies,[7] smoking and non-smoking HIV-positive participants had significantly steeper declines in FEV_1 and FVC. These associations with HIV remained when analyses were restricted to the quintile with the highest declines. Notably, however, FEV_1/FVC ratio decline was not greater in HIV-positive participants, a pattern that suggests declines related to HIV infection are phenotypically distinct from declines related to smoking and that will require more sophisticated measures of pulmonary function to dissect the contribution of small airways and parenchymal damage.[8,9]

The association of faster FEV_1 and FVC decline with HIV remained statistically significant in both current smokers and non-smokers (ie, former smokers or those who never smoked]), but when analyses were restricted to only those participants who had never smoked, this trend was no longer statistically significant. Importantly, the HIV-positive group included more current or former smokers, with greater smoking pack-years, compared with the HIV-negative group. However, the absolute differences in smoking prevalence between the HIV-positive and HIV-negative groups were small, and the effect of smoking pack-years on the association between HIV status and declines in FEV_1 and FVC was not significant in sensitivity analyses. Importantly, neither nadir CD4 count, previous *P jirovecii* pneumonia, nor previous pulmonary tuberculosis were associated with faster FEV_1 or FVC decline in HIV-positive participants, suggesting that ongoing effects of HIV-related pulmonary damage, rather than HIV-associated legacy effects, underlie these declines.

The team also sought to measure markers of HIV-associated inflammation. Elevated baseline and time-updated concentrations of high-sensitivity C-reactive protein were associated with faster FEV_1 and FVC decline in the HIV-positive group but not in the HIV-negative group. Again, this association was not statistically

significant in participants who never smoked, and it is therefore not possible to rule out the possibility that the observed association between high-sensitivity C-reactive protein and lung function decline was driven by smoking. HIV-specific associations between lung function change and other inflammatory markers were less consistent. Nevertheless, these issues do not exclude an important role of chronic inflammation but rather, as the investigators suggest, point to the need for measurements directly from the lung compartment. This has been achieved in cross-sectional studies, most recently with the demonstration that airway basal stem (progenitor) cells isolated from virally suppressed HIV-positive but not HIV-negative non-smokers spontaneously release inflammatory mediators.[10]

Thus, the study demonstrated that HIV is associated with faster lung function decline independent of smoking or legacy effects from before initiation of antiretroviral therapy, and further supports a role of chronic immune activation in this association. The phenotypic difference between declines in HIV-related pulmonary function and declines related to smoking provide further support that the evidenced effects on pulmonary health were driven largely by HIV status. The key message, then, is that as the trajectory of lung function decline is steeper in people living with HIV as they age, a larger proportion of people living with HIV than might be expected will cross the threshold of symptomatic disease. The implications are that health services for people living with HIV will need to be prepared to diagnose and manage patients with symptomatic airways disease and to learn to predict and intervene for those who are at risk.

Several questions still need addressing. First, there were few non-white and female participants in the study, and these individuals also completed fewer follow-up visits. Do women and those of non-white ethnicity also have accelerated lung function decline? Given that COPD is more common in people living with HIV compared with HIV-negative people in every WHO region, do the study findings generalise to low-income and middle income countries?[11] Second, as the study did not correlate symptoms with lung function, the extent and timing of the clinical effect of this decline remains uncertain. Third, as cost-effective strategies for early detection and treatment of COPD are challenging,[12] what profile of risk factors, biomarkers, and lung function and imaging tests should be employed? Finally, does a phenotypically distinct pattern of disease driven by chronic inflammation require novel interventions and will current treatment approaches for obstructive airways diseases be effective in people living with HIV? We now have the evidence that lung function declines more rapidly in HIV-positive people. What then, other than support for smoking cessation, needs to be done?

I declare no competing interests.

Paul Collini
p.collini@sheffield.ac.uk

Department of Infection, Immunity and Cardiovascular Diseases (IICD), University of Sheffield, Sheffieldv S10 2RX, UK

1 UNAIDS. Fact sheet—World Aids Day 2020. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (accessed March 10, 2021).
2 Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGE$_h$IV cohort study. *Clin Infect Dis* 2014; **59:** 1787–97.
3 Collini P, Morris A. Maintaining lung health with longstanding HIV. *Curr Opin Infect Dis* 2016; **29:** 31–38.
4 Johnston PI, Wright SW, Orr M, et al. Worldwide relative smoking prevalence among people living with and without HIV: a systematic review and meta-analysis. *AIDS* 2021; published online Jan 18. DOI:10.1097/QAD.0000000000002815.
5 Singhvi D, Bon J, Morris A. Obstructive lung disease in HIV—phenotypes and pathogenesis. *Curr HIV/AIDS Rep* 2019; **16:** 359–69.
6 Verboeket SO, Boyd A, Wit FW, et al. Changes in lung function among treated HIV-positive and HIV-negative individuals: analysis of AGE$_h$IV prospective cohort study. *Lancet Healthy Longev* 2021; **2:** 202–11.
7 Thomas ET, Guppy M, Straus SE, Bell KJL, Glasziou P. Rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies. *BMJ Open* 2019; **9:** e028150.
8 Ronit A, Mathiesen IH, Gelpi M, et al. Small airway dysfunction in well-treated never-smoking HIV-infected individuals. *Eur Respir J* 2017; **49:** 1602186.
9 Wang Z, Bier EA, Swaminathan A, et al. Diverse cardiopulmonary diseases are associated with distinct xenon magnetic resonance imaging signatures. *Eur Respir J* 2019; **54:** 1900831.
10 Chung NPY, Khan KMF, Kaner RJ, O'Beirne SL, Crystal RG. HIV induces airway basal progenitor cells to adopt an inflammatory phenotype. *Sci Rep* 2021; **11:** 3988.
11 Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. *Lancet Glob Health* 2018; **6:** e193–202.
12 UK NSC recommendation on adult screening for Chronic Obstructive Pulmonary Disease (COPD). Public Health England, 2018. https://legacyscreening.phe.org.uk/policydb_download.php?doc=844 (accessed March 10. 2021).