Changes in lung function among treated HIV-positive and HIV-negative individuals: analysis of the prospective AGEhIV cohort study

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Summary
Background The AGEhIV cohort study is a prospective cohort study evaluating the occurrence of age-related comorbidities in people living with and without HIV. We previously reported a lower forced vital capacity (FVC) in HIV-positive compared with HIV-negative participants in those without heavy smoking exposure at time of enrolment in the AGEhIV cohort study. In this study we evaluate longitudinal changes in spirometry indices in the same AGEhIV cohort accounting for smoking behaviour and other risk factors.

Methods We obtained pre-bronchodilator spirometry measurements in AGEhIV cohort participants during biennial visits over a median of 5·9 years (IQR 5·7–6·0). Adjusted declines in forced expiratory volume in 1 s (FEV1), FVC, and FEV1/FVC ratio were modelled using linear mixed-effects models and compared by HIV status and smoking status. To evaluate whether changes in spirometry measurements could be driven by increased levels of chronic inflammation, we assessed associations between rates of FEV1, and FVC decline and CD4 and CD8 T-cell counts, and plasma concentrations of C-reactive protein (CRP), interleukin 6, soluble CD14, soluble CD163, and intestinal fatty-acid-binding protein in separate models. The study is registered at ClinicalTrials.gov, NCT01466582.

Findings 500 HIV-positive and 481 HIV-negative participants were included with spirometry data from Oct 29, 2010, to Aug 14, 2018. HIV-positive participants were virally suppressed (<40 copies per mL) during 1627 (95%) study visits, and 159 (32%) HIV-positive and 183 (38%) HIV-negative participants had never smoked. Adjusted declines in FEV1 were 10·0 mL per year faster in HIV-positive non-smokers (95% CI 4·2 to 15·7, p=0·00066) compared with HIV-negative non-smokers, and 11·1 mL per year faster in HIV-positive smokers (95% CI 0·7 to 21·4, p=0·036) compared with HIV-negative smokers. In comparison, smoking was associated with a 16·4 mL per year steeper decline in FEV1, among HIV-positive participants (95% CI 8·0 to 24·7, p=0·00012), and 15·3 mL per year steeper decline among HIV-negative participants (95% CI 6·7–24·0, p=0·00052) compared with not smoking. Adjusted yearly declines in FEV1 and FVC, but not FEV1/FVC, were significantly greater in HIV-positive than HIV-negative participants overall (additional decline in HIV-positive participants, FEV1 10·5 mL per year [95% CI 4·7 to 16·3], p=0·00040; FVC 11·5 mL per year [2·8 to 20·3], p=0·0096; FEV1/FVC 0·07% per year [−0·05 to 0·19], p=0·26). With a similar observation for never-smokers (FEV1 6·0 mL per year [−1·8 to 13·7], p=0·13; FVC 9·1 mL per year [−3·0 to 21·1], p=0·14; FEV1/FVC ratio 0·00% per year [−0·18 to −0·18], p=0·97). Higher CRP concentrations during follow-up were associated with accelerated declines in FEV1, and FVC among HIV-positive participants but not among HIV-negative participants.

Interpretation Treated HIV infection was associated with faster declines in both FEV1, and FVC, but not in the FEV1/FVC ratio. These changes were independent of smoking and might have been driven by ongoing interstitial or small airway damage, potentially related to increased inflammation.

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Introduction Chronic obstructive pulmonary disease is more frequently diagnosed among people living with HIV compared with the general population, independent of risk behaviours such as tobacco smoking.12 HIV infection appears to have distinct consequences for pulmonary health, including in people living with HIV who have suppressed viraemia using combination antiretroviral therapy (cART).3 These changes have been most evidently characterised by a lower pulmonary diffusion capacity in people living with HIV.13 Studies evaluating airway obstruction or emphysema have been less consistent in showing differences between people living with HIV on cART and uninfected controls.4–7 Disentangling the ongoing effects of suppressed HIV infection on pulmonary health from those effects related to previously untreated HIV infection and historical risk behaviours remains challenging, mainly because most
Research in context

Evidence before this study

We searched PubMed on Oct 1, 2020, with the terms “spirometry”, “respiratory function tests”, “pulmonary function test”, “chronic obstructive pulmonary disease”, “COPD”, “obstructive lung disease”, “restrictive pulmonary disease”, or “pulmonary fibrosis”, and “HIV Infections” or “HIV” (both free text and MeSH terms). We restricted our search to publications from 2006 onwards, corresponding to the year at which a higher prevalence of obstructive lung disease was first described in people living with HIV despite the use of antiretroviral therapy. We also searched conference abstracts of major HIV conferences to include more recent findings. Although there have been numerous cross-sectional analyses evaluating the pulmonary health of people with treated HIV, studies reporting longitudinal measurements while including HIV-negative controls are scarce. Only one adequately powered study has assessed longitudinal follow-up with spirometry measurements during suppressed HIV infection, while including an HIV-negative comparison group. This cohort (the AIDS Linked to the Intravenous Experience [ALIVE] study) included people who inject drugs, most of whom smoked during follow-up, potentially obscuring HIV-specific changes in spirometry indices. In that study, accelerated declines in forced expiratory volume in 1 s (FEV1) were reported in HIV-positive participants with a viral load greater than 75 000 copies per mL, and in HIV-positive participants younger than 50 years with a suppressed viral load, compared with HIV-negative controls.

Added value of this study

To our knowledge, this is the first study to report long-term longitudinal spirometry measurements in people living with HIV on antiretroviral therapy compared with HIV-negative individuals, while including a sufficient number of never-smokers and former-smokers to appropriately evaluate any smoking-independent effects. We show that HIV infection, independent of smoking, is associated with accelerated declines in spirometry indices despite adequate viral suppression (<40 copies per mL) and that these changes (ie, declines in both FEV1 and FVC, but not the FEV1/FVC ratio) are phenotypically different from those associated with smoking (ie, declines in FEV1 and FEV1/FVC ratio, but to a lesser extent FVC). Although the precise cause of these HIV-associated changes cannot be established in the context of our study, several markers of chronic systemic inflammation were associated with accelerated declines in spirometry indices among HIV-positive participants only.

Implications of all the available evidence

Clinicians should be aware that HIV can have an independent effect on pulmonary function, which also arises in the context of adequate viral suppression. These effects might not be evident with typical cutoffs for obstructive lung disease (ie, FEV1/FVC ratio below 70% or below the lower limit of normal). In both clinical practice and future research, pulmonary diagnostic modalities in addition to spirometry should be used to identify the causes of HIV-associated respiratory impairments presenting in people living with HIV on antiretroviral therapy.

Studies evaluating such differences have been cross-sectional in design. In a previous cross-sectional analysis of baseline data from the AGE,IV cohort, we showed that HIV-positive participants reporting less than 25 pack-years of cumulative smoking had a lower forced vital capacity (FVC) but a similar forced expiratory volume in 1 s (FEV1) compared with HIV-negative participants with similar smoking exposure. This finding resulted in a seemingly lower prevalence of obstructive lung disease (FEV1/FVC ratio <70%) in the HIV-positive participants with little smoking exposure. Moreover, we evaluated whether such changes in spirometry indices could be driven by increased levels of chronic inflammation, which can accelerate functional decline of other organ systems in ageing people living with HIV on cART.

Methods

Study design and participants

The AGE,IV Cohort Study is an ongoing prospective cohort study of 1148 participants evaluating the occurrence of age-related comorbidities in HIV-1-infected and HIV-negative participants. HIV-positive participants were...
recruited from the HIV outpatient clinic of the Amsterdam University Medical Centers, location AMC, Amsterdam, Netherlands. HIV-negative participants were recruited from the sexual health clinic and the Amsterdam Cohorts Studies at the Amsterdam Public Health Clinic. Recruiting the control group from a sexual health clinic allowed for a comparable group with respect to sexual orientation, geographical region, and sociodemographic background. The inclusion criteria were age 45 years or older and, for controls, a documented HIV-negative antibody test at enrolment. Study enrolment was open between Oct 29, 2010, and Oct 9, 2012. Once every 2 years (ie, biennially), participants underwent a standardised screening programme to diagnose age-related comorbidities, details of which are included in appendix p 1. Detailed information on current and past HIV characteristics were obtained from the Dutch HIV Monitoring Foundation. Written informed consent was obtained from all participants and the study was approved by the ethical review board of the Academic Medical Center, University of Amsterdam.

Procedures
Information on demographics and risk behaviours was prospectively collected via questionnaires, including a detailed record of ongoing and past smoking behaviour. At each study visit, a spirometry measurement without bronchodilatation was obtained by trained nurses according to European Respiratory Society/American Thoracic Society (ERS/ATS) criteria using a SpiroUSB spirometer (Carefusion; Hoechberg, Germany). A maximum of six forced expiratory efforts were performed. Three or more efforts meeting the ERS/ATS criteria were needed to determine FEV₁ and FVC. If fewer than three efforts met ERS/ATS criteria, the highest FEV₁ and FVC were selected from the qualifying values. If no ERS/ATS-qualifying effort was recorded, the spirometry measurement was excluded. All participants with more than one successful spirometry measurement at enrolment. Study enrolment was open between Oct 29, 2010, and Oct 9, 2012. Once every 2 years (ie, biennially), participants underwent a standardised screening programme to diagnose age-related comorbidities, details of which are included in appendix p 1. Detailed information on current and past HIV characteristics were obtained from the Dutch HIV Monitoring Foundation. Written informed consent was obtained from all participants and the study was approved by the ethical review board of the Academic Medical Center, University of Amsterdam.

Statistical analysis
Baseline was defined as the first visit with a successful spirometry measurement and follow-up continued until the fourth scheduled study visit, loss to follow-up, or death. HIV-negative participants who seroconverted during follow-up (n=5) continued follow-up in the HIV-positive group. Baseline characteristics of included versus excluded participants and of HIV-positive versus HIV-negative included participants were compared with Wilcoxon rank-sum, Pearson’s χ², or Student’s t tests as appropriate.

We modelled mean yearly changes in FEV₁, FVC, and FEV₁/FVC ratio over study follow-up using mixed-effect linear regression. We included a random intercept to account for baseline variability between participants. The following covariates were included in the multivariable models: baseline age; sex at birth; ethnicity (based on region of origin); (time-updated during follow-up) weight; (time-updated) height; baseline number of pack-years smoking (ie, number of years smoking multiplied by packs of 20 cigarettes smoked daily); baseline number of years since cessation of smoking (for former smokers); the interaction between baseline pack-years and years since smoking cessation; (time-updated) daily marijuana use; former injecting drug use; and (time-updated) bronchodilator use during the 24 h before spirometry measurements. These covariates were selected a priori on the basis of findings from the baseline analysis of AGEhIV cohort spirometry data or known associations with variation in spirometry indices. Moreover, the variables of HIV status, time-updated recent (during past month) smoking behaviour (ie, smoking [current-smoking] vs non-smoking [former-smoking or never-smoking]), and follow-up time were included, as well as all two-way and three-way interactions of these three variables. Differences in the yearly decline in spirometry indices between HIV-positive and HIV-negative groups were assessed, while stratifying by time-updated smoking status. This test was done with the contrast command in Stata. From this model, we also calculated mean yearly changes in spirometry indices by HIV and smoking status using the lincom command. To evaluate whether previous severe immunodeficiency or AIDS-related conditions might influence differences observed between HIV-positive participants and controls, we assessed whether nadir CD4 count, previous Pneumocystis jirovecii pneumonia, or pulmonary tuberculosis were associated with rates of decline in FEV₁ and FVC in HIV-positive participants. In sensitivity analyses, we restricted the analysis to (1) high-quality spirometry measurements (ie, ≥3 ERS/ATS-qualifying efforts), (2) measurements from HIV-positive participants for which HIV viral load was undetectable (<40 copies per mL) and all measurements from HIV-negative participants, and (3) never-smokers. We also did a sensitivity analysis to account for covariate imbalances.
Table 1: Baseline demographic, behavioural, and clinical characteristics of included participants

| Demographics | HIV-positive (n=500) | HIV-negative (n=481) | p value |
|--------------|----------------------|----------------------|---------|
|              | N | n (%) or median (IQR) | N | n (%) or median (IQR) |
| Sex assigned at birth | 500 | 447 (89%) | 481 | 411 (85%) | 0.062 |
| Male | – | – | 411 (85%) | – | – |
| Female | – | 53 (11%) | 70 (15%) | – | – |
| Age | 500 | 53.2 (48.3–59.6) | 481 | 52.5 (48.4–58.7) | 0.21 |
| Ethnic descent | 500 | 445 (89%) | 454 (94%) | 0.0025 |
| White | – | – | 454 (94%) | – | – |
| Black | – | 46 (9%) | 35 (7%) | – | – |
| Asian | – | 9 (2%) | 9 (2%) | – | – |
| MSM | 477 | 371 (78%) | 474 | 344 (73%) | 0.063 |
| BMI (kg/m²) | 500 | 24.2 (22.5–26.7) | 481 | 24.5 (22.9–27.0) | 0.027 |
| Risk behaviours | | | | |
| Smoking status | 474 | 470 | – | – | 0.017 |
| Never | – | 159 (34%) | 183 (39%) | – | – |
| Former | – | 164 (35%) | 176 (37%) | – | – |
| Current | – | 151 (32%) | 111 (24%) | – | – |
| Pack-years smoking (former or current smokers only) | 308 | 22 (8–37) | 284 | 14 (4–28) | <0.0001 |
| Marijuana use | 466 | 466 | – | – | 0.29 |
| No or less than weekly use | – | 412 (88%) | 426 (91%) | – | – |
| Weekly use | – | 29 (6%) | 23 (5%) | – | – |
| Daily use | – | 25 (5%) | 17 (4%) | – | – |
| Previous intravenous drug use | 464 | 468 | – | – | 0.014 |
| Hepatitis C RNA positive | 500 | 480 | – | – | 0.069 |
| HIV-related characteristics | | | | |
| Years since HIV diagnosis | 498 | 12 (7–17) | – | – | – |
| Last HIV-1 viral load measurement <40 copies per mL | 497 | 456 (91%) | – | – | – |
| Last CD4 count (cells per μL) | 496 | 570 (450–760) | – | – | – |
| Nadir CD4 count (cells per μL) | 500 | 180 (80–260) | – | – | – |
| Previous CDC stage 3 AIDS-defining illness† | 500 | 146 (29%) | – | – | – |
| Previous Pneumocystis jirovecii pneumonia | 500 | 48 (10%) | – | – | – |
| Previous pulmonary tuberculosis | 500 | 8 (2%) | – | – | – |
| Baseline spirometry indices | | | | |
| Absolute FEV₁ (mean L, SD) | 500 | 3.37 (0.77) | 481 | 3.51 (0.80) | 0.0068* |
| FEV₁ (mean % predicted†, SD) | 500 | 91.4% (25.0) | 481 | 91.6% (14.7) | 0.017* |
| FEV₁ (Z score less than –1.64)¶ | 500 | 70 (14%) | 481 | 48 (10%) | 0.053 |
| Absolute FVC (mean L, SD) | 500 | 4.56 (1.00) | 481 | 4.72 (1.01) | 0.012* |
| FVC (mean % predicted†, SD) | 500 | 96.5% (14.8) | 481 | 94.8% (13.3) | 0.034* |
| FVC (Z score less than –1.64)¶ | 500 | 32 (6%) | 481 | 25 (5%) | 0.42 |
| FEV₁/FVC ratio (mean, SD) | 500 | 74.5% (14.8) | 481 | 74.3% (7.7) | 0.82* |
| FEV₁/FVC ratio <70% | 500 | 117 (23%) | 481 | 110 (23%) | 0.84 |
| FEV₁/FVC ratio (Z score less than –1.64)¶ | 500 | 78 (16%) | 481 | 63 (13%) | 0.26 |
| Baseline inflammatory marker concentrations | | | | |
| High-sensitivity C-reactive protein (mg/L) | 491 | 1.5 (0.7–3.1) | 479 | 1.0 (0.6–2.0) | <0.0001 |
| Interleukin 6 (pg/mL) | 499 | 1.5 (1.0–2.8) | 480 | 1.9 (1.2–3.1) | 0.0001 |
| Soluble CD14 (ng/mL) | 499 | 1565 (1310–1975) | 480 | 1358 (1081–1734) | <0.0001 |
| Soluble CD163 (ng/mL) | 499 | 284 (206–417) | 478 | 249 (182–343) | <0.0001 |
| Intestinal fatty-acid-binding protein (ng/mL) | 499 | 2.2 (1.5–3.7) | 480 | 1.1 (0.7–1.6) | <0.0001 |

N represents number of individuals with available data. Data are n (%) median (IQR) unless otherwise noted. Wilcoxon rank-sum and Pearson’s χ² tests were used for statistical comparisons, unless stated otherwise. MSM=men who have sex with men. BMI=body-mass index. FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity.

*Student’s t test. †Based on Global Lung Initiative reference calculations (ie, predicted based on age, sex, ethnicity and height).‡

Table 1: Baseline demographic, behavioural, and clinical characteristics of included participants
between HIV-positive participants and HIV-negative controls at baseline by estimating pulmonary function declines using linear mixed effects models weighted by the inverse probability of belonging to the HIV-positive participant group (appendix p 4). Furthermore, we explored the influence of all other covariates included in the multivariable model (eg, age, sex, pack-years smoking) on the main associations between HIV status and change in FEV$_1$ and FVC (appendix pp 6–7), and whether HIV status was associated with a more rapid (ie, highest quintile) decline in FEV$_1$ and FVC (appendix p 8).

We evaluated the association between individual markers of inflammation and the rates of both FEV$_1$ and FVC decline. All marker concentrations were natural log-transformed and were considered time-fixed (for markers measured at baseline only) or time-updated (for markers measured at baseline and during follow-up). We used mixed-effects linear regression while including the same covariates as in the primary analysis and a random intercept to account for participant variability at baseline. We included an interaction term between continuous inflammatory marker concentrations and follow-up time, from which we could test whether changes in spirometry indices were faster or slower with increases in marker concentrations. These analyses were stratified by HIV status. Sensitivity analyses were restricted to participants who had never smoked. Statistical significance was defined as p less than 0·05.

Figure 1: Adjusted predicted mean yearly declines in FEV$_1$, FVC, and FEV$_1$/FVC ratio from baseline by HIV status and smoking behaviour during follow-up
(A) Full cohort analysis. (B) Subgroup analysis in never-smoking participants only. Figure shows the mean predicted yearly declines in spirometry indices provided in the appendix (p 3). FEV$_1$=forced expiratory volume in 1 s. FVC=forced vital capacity. *Smoking or non-smoking during the month before spirometry measurements (ie, time-updated smoking behaviour).

Statistical analyses were done with Stata software (version 12.0). The study is registered at ClinicalTrials.gov, NCT01466582.

Role of the funding source
None of the study funders had a role in the design or conduct of the study, the analysis and interpretation of the results, the writing of the report, or the decision to publish.

Results
We included 1700 spirometry measurements from 500 HIV-positive participants in the analysis, of which 1264 (74·4%) had at least three ERS/ATS-qualifying efforts, and 1732 spirometry measurements from 481 HIV-negative participants, of which 1396 (80·6%) had at least three qualifying efforts. Included data in the study were collected between Oct 29, 2010, and Aug 14, 2018. 99 (17%) HIV-positive and 68 (12%) HIV-negative participants were excluded for having one or no spirometry measurements. Excluded participants were more likely to be HIV-positive, female, younger, and of black ethnicity than included participants (appendix p 2). At baseline, spirometry results from excluded participants with a single qualifying spirometry measurement (141 [84%] of excluded participants) did not seem to differ from those of participants included in the analysis (appendix p 2).

Among individuals included in our analysis, HIV-positive participants were more likely to be of black ethnicity, had a slightly lower body-mass index, were
Table 2: HIV-related predictors of FEV1 and FVC decline over time among HIV-positive participants

| Predictor | FEV1 (mL) | p value | FVC (mL) | p value |
|-----------|------------|---------|----------|---------|
| CD4 nadir count, cells per μL | | | | |
| <50 | 0.7 (-10.0 to 11.4) | 0.90 | -3.8 (-19.9 to 12.2) | 0.64 |
| 50 to <200 | -0.7 (-9.4 to 8.0) | 0.87 | -3.0 (-16.1 to 10.1) | 0.66 |
| 200 to <500 | Reference | Reference | Reference | Reference |
| ≥500 | 11.3 (-8.9 to 31.6) | 0.27 | -3.9 (-34.2 to 26.4) | 0.80 |
| Previous PCP (versus no previous PCP) | | | | |
| Previous pulmonary tuberculosis diagnosis (versus no previous pulmonary tuberculosis) | -1.9 (-31.8 to 28.0) | 0.90 | -15.5 (-60.2 to 29.2) | 0.50 |

Estimates were derived from an interaction term of the indicated variables with time in a mixed-effects model, including only HIV-positive participants while adjusting for the same covariates as reported in the main adjusted models. FEV1=forced expiratory volume in 1 s; FVC=forced vital capacity; PCP=Pneumocystis jirovecii pneumonia.

more likely to be smokers and had more pack-years of smoking compared with HIV-negative participants (table 1). Most HIV-positive participants were virally suppressed (<40 copies per mL) and had high CD4 counts at baseline, but had low nadir CD4 counts (table 1). Median follow-up was 6.0 years (IQR 4.0–6.1) in HIV-positive and 6.0 years (5.8–6.0) in HIV-negative participants. 129 (26%) HIV-positive and 71 (15%) HIV-negative participants were censored before the fourth follow-up visit due to poor spirometry measurement quality (16 (3%) HIV-positive and 19 (4%) HIV-negative), discontinuation of study participation (32 (6%) and seven (1%), loss to follow-up (71 (14%) and 41 (9%)), or death (ten (2%) and four (1%)). During follow-up, HIV-positive participants were virally suppressed (<40 copies per mL) at 1627 (95.5%) of spirometry measurements. 159 (32%) HIV-positive and 183 (38%) HIV-negative participants had never smoked. Smoking during the month before spirometry was reported at 522 (31%) measurements in HIV-positive participants and 392 (23%) measurements in HIV-negative participants. Recent inhaler use was reported at 56 (3.3%) measurements in HIV-positive participants and 66 (3.8%) measurements in HIV-negative participants.

Baseline spirometry measurements of the AGEhIV cohort have previously been reported in detail.4 In the current selection of participants, baseline mean FEV1 was 3.37 L for HIV-positive participants versus 3.51 L for HIV-negative participants (p=0.0068), and mean FVC was 4.56 L versus 4.72 L (p=0.034), respectively. 78 (16%) HIV-positive and 63 (13%) HIV-negative participants had an FEV1/FVC ratio below the lower limit of normal cutoff values (Z score less than –1.64; p=0.07). FEV1 declined more steeply among HIV-negative participants (95% CI 7.8–20.3, p=0.0096), but not in the FEV1/FVC ratio (95% CI 4.7 to 16.3, p=0.00040), FVC (11.5 mL/year [2.8 to 20.3, p=0.0096], but not in the FEV1/FVC ratio (0.07%/year [−0.05 to 0.19], p=0.26). FEV1 declined 10.0 mL per year faster in HIV-positive non-smokers (95% CI 4.2–15.7, p=0.00066) compared with HIV-negative non-smokers, and 11.1 mL per year faster in HIV-positive smokers (95% CI 0.7–21.4, p=0.036) compared with HIV-negative smokers. In comparison, smoking was associated with a 16.4 mL per year steeper decline in FEV1 among HIV-positive participants (95% CI 8.0–24.7, p=0.00012), and 15.3 mL per year steeper decline among HIV-negative participants (95% CI 6.7–24.0, p=0.00052) compared with not smoking.

FVC declined significantly faster at 15.4 mL per year (95% CI 6.8–24.0, p=0.00046) in non-smoking HIV-positive versus non-smoking HIV-negative participants, and non-significantly faster at 7.7 mL per year (95% CI 2.7–12.3, p=0.033) in HIV-positive smokers versus HIV-negative smokers. There were no significant differences between smokers and non-smokers in FVC decline (HIV-positive p=0.26, HIV-negative p=0.93).

Decline in the FEV1/FVC ratio did not differ between HIV-positive versus HIV-negative participants: 0.01% per year (95% CI –0.14 to 0.11, p=0.81) among non-smoking and 0.13% per year (–0.35 to 0.59, p=0.26) among smoking participants. However, smoking was associated with a 0.51% per year steeper decline in FEV1/FVC ratio in HIV-positive participants (95% CI 0.33–0.68, p=0.0001) and a 0.40% per year steeper decline in HIV-negative participants (0.21–0.58, p=0.0001).

Nadir CD4 count, previous P jirovecii pneumonia, or pulmonary tuberculosis were not associated with faster FEV1 or FVC decline in HIV-positive participants (table 2). Sensitivity analyses showed that when restricting analyses to high-quality spirometry measurements (n=2707), the FEV1/FVC ratio declined significantly faster among HIV-positive versus HIV-negative participants overall (0.17% per year, p=0.014) but not within the smoking or non-smoking subgroups. Results from the main analysis did not change when restricting analyses to only virally-suppressed HIV-positive participants (and
When restricting analyses to never-smokers, the declines in FEV1 and FVC were faster in HIV-positive, compared with HIV-negative, participants, but the difference did not reach statistical significance (additional decline in HIV-positive individuals 6·0 mL per year, 95% CI −1·8 to 13·7, p=0·13 for FEV1; 9·1 mL per year, 95% CI −3·0 to 21·8, p=0·14 for FVC; figure 1, appendix p 3).

Results from the inverse probability-weighted model were similar to results from the main analysis (overall additional decline in HIV-positive participants: FEV1 11·9 mL per year [p=0·0014], FVC 12·7 mL per year [p=0·010], and FEV1/FVC ratio 0·07% per year [p=0·34]; appendix p 4). Further analyses on appendix pp 6–7 show that any imbalances in other covariates (eg, age, sex, and pack-years of smoking) between HIV-positive and HIV-negative participants were unlikely to have changed the associations between HIV-status and declines in FEV1 and FVC. Positive HIV status was also independently associated with a higher probability of rapid FEV1 and FVC decline (highest quintile of change, appendix p 8).

Figure 2 shows the associations between concentrations of inflammatory markers and declines in FEV1 and FVC. Higher baseline and time-updated high-sensitivity CRP concentrations were associated with significantly steeper declines in FEV1 (baseline p=0·036, time-updated p=0·0029) and FVC (p=0·044 and p=0·0012) among HIV-positive participants, but not among HIV-negative participants (FEV1 p=0·63 and p=0·97, FVC p=0·56 and p=0·15, respectively). In contrast, in both HIV-positive and HIV-negative participants higher concentrations of IL-6 at baseline were associated with less steep declines in FEV1 (HIV-positive p=0·025, HIV-negative p=0·10) and FVC (HIV-positive p=0·036, HIV-negative p=0·039). Higher concentrations of baseline soluble CD14 were associated with a steeper decline in FVC in HIV-positive participants (p=0·0018), while higher baseline concentrations of soluble CD163 and lower baseline concentrations of I-FABP were associated with a steeper decline in FVC in HIV-negative participants (p=0·0015 and p=0·0077, respectively). Analyses limited to participants who never smoked are shown in the appendix (p 9). Among never-smoking HIV-positive participants, high-sensitivity CRP concentrations at baseline and during follow-up and IL-6 and soluble
CD14 concentrations at baseline were not statistically associated with differences in the rates of FEV₁ or FVC decline.

Discussion
During 6 years of follow-up we found an accelerated decline in FEV₁ and FVC, but not in the FEV₁/FVC ratio, in predominantly virally-suppressed HIV-positive AGE, IV cohort participants compared with HIV-negative controls, independent of smoking. HIV status was also independently associated with a higher probability of rapid decline in FEV₁ and FVC. Tobacco smoking during follow-up was associated with accelerated FEV₁ and FEV₁/FVC decline, but not an accelerated decline in FVC. These results suggest that declines in spirometry-measured HIV-related pulmonary function are phenotypically different from declines related to smoking and could continue even during suppressive antiretroviral therapy.

Simultaneous declines in FEV₁ and FVC might indicate development of isolated interstitial restrictive pulmonary disease or restrictive pulmonary disease combined with obstructive disease. Both pathophysiological processes have been associated with HIV in previous studies. In a cross-sectional analysis of baseline data from the Danish COCOMO cohort, HIV-positive participants had lower FEV₁ and FVC, but slightly higher FEV₁/FVC ratios. In that cohort, CT imaging did not indicate more frequent emphysema, but did show more interstitial pulmonary abnormalities among HIV-positive participants. In a subgroup of never-smoking participants, small airway dysfunction was also identified to be more frequent among HIV-positive participants with use of a lung clearance index (ie, multiple breath nitrogen washout) compared with HIV-negative participants. Several studies have reported higher lung densities on CT imaging in people living with HIV versus controls, suggesting interstitial pulmonary pathology. However, CT imaging studies evaluating never-smokers or adolescents with HIV have shown that both airway disease in general as well as small airway disease specifically were more frequently observed in HIV-positive participants compared with controls. Importantly, these studies have been cross-sectional in design and reflect not only recent and ongoing HIV-related damage, but also historical tissue damage. This historical damage includes insults from previous HIV-associated pulmonary infections, lengthy exposure to HIV viraemia, and the cumulative exposures to inhaled toxic substances, such as those from smoking. Since spirometry can definitively distinguish pulmonary pathology only in the medium-sized and large airways, the exact aetiology of accelerated declines in both FEV₁ and FVC in our virally-suppressed HIV-positive participants remains unclear. Differences between historical and ongoing damage could also explain the contrast between our current findings and findings from our baseline analysis (ie, lower FVC in our baseline analysis but similar FEV₁ in HIV-positive vs HIV-negative participants without heavy smoking experience). The characteristics of historical cumulative damage might be phenotypically different from current ongoing HIV-related pulmonary damage during cART. Given that neither lower nadir CD4 count nor previous *P jiroveci* pneumonia or pulmonary tuberculosis was associated with faster declines in FEV₁ or FVC during follow-up, our findings instead suggest that ongoing pulmonary damage underlies these declines.

We explored whether the faster FEV₁ and FVC declines in our participants were associated with higher concentrations of several inflammatory markers. Higher concentrations of high-sensitivity CRP were strongly associated with faster declines in both FEV₁ and FVC among HIV-positive participants, but there was no association among HIV-positive never-smokers. Smoking has been associated with increased CRP, which could partly have driven the association between higher CRP concentrations and faster FEV₁ and FVC declines in our participants. Moreover, people living with HIV remain more prone to bacterial pneumonias compared with the general population even when they are virally suppressed, especially among smokers. Repeated insults from infections might result in both increased CRP and faster declines in spirometry indices. Although IL-6 and CRP are on similar inflammatory pathways, we found no association between IL-6 concentrations and declines in FEV₁ and FVC. IL-6 and CRP are more strongly correlated in cases of high levels of inflammation. Perhaps CRP, specifically during low-level inflammation, might be more linked to accelerated decline in lung function compared with IL-6. Higher concentrations of the monocyte activation marker soluble CD14, but not soluble CD163, were associated with a faster FVC decline among HIV-positive participants. Monocyte activation in people living with HIV is suggested to be chronically elevated via increased microbial translocation from the gut, leading to a state of chronic systemic inflammation and end-organ damage. As such, soluble CD14 has been associated with more frequent emphysema as detected by CT imaging, and soluble CD163 has been associated with a lower FEV₁/FVC ratio and lower diffusion capacity in people living with HIV. In our study, I-FABP, a marker of intestinal permeability, was not associated with faster declines in pulmonary function among HIV-positive participants. This finding suggests that monocyte activation could be driven by other processes, including pulmonary tissue damage itself or exposure to infections. Importantly, these inflammatory markers were measured in plasma, which might poorly correlate with marker concentrations in the lung compartment. Furthermore, indications for pathophysiological processes in the lungs of people with HIV on antiretroviral therapy other than chronic inflammation have recently been reported; Chelvanambi and colleagues have shown the presence
of HIV-Nef protein in bronchoalveolar fluid in people living with HIV with suppressed viraemia and its link to surface expression of proapoptotic endothelial-monocyte-activating polypeptide II, which is implicated in the progression of pulmonary emphysema. This finding could indicate that local pulmonary tissue damage by HIV itself can still occur even when HIV is undetectable in plasma.

The extent to which HIV-positive participants in our study had functional impairments related to the measured accelerated decline in pulmonary function remains unclear, since pulmonary symptoms and related functional decline were not assessed. However, since the effect size of HIV status on the additional decline in FEV1 was two-thirds of that of smoking, suppressed HIV infection might become associated with clinically relevant functional impairments, especially over the longer term. We believe our results are illustrative of the independent effects of HIV infection and as such are generalisable to all people living with HIV. However, pulmonary function might differ in populations of people living with HIV with different risk profiles for lung disease (eg, differing smoking rates or history of pulmonary co-infections like tuberculosis). Few women and people of non-white ethnicity were included in the AGE,IV cohort and in this analysis. Generalisability of our results could thus be poor among these specific groups of people living with HIV. HIV-positive participants were more frequently excluded from the analysis due to missing data and had less follow-up time compared with HIV-negative participants. Since HIV-positive participants are at increased risk of developing comorbidities, a health-related differential rate of drop-out might have resulted in an underestimated effect of HIV infection on lung function. Further limitations of our analysis were the lack of a post-bronchodilator measurement, little data on marijuana or e-cigarette use, and potential self-reporting bias of risk behaviours.

In conclusion, despite adequate antiretroviral treatment, HIV infection is associated with a faster decline in pulmonary function as measured by spirometry, independent of tobacco smoking. Future studies are needed to evaluate the aetiology and clinical consequences of these changes. Since the FEV1/FVC ratio appears mostly unaffected by HIV status and the underlying cause of these HIV-specific pulmonary changes cannot be identified by spirometry alone, clinicians should be aware of the limitations of using spirometry as a single diagnostic tool for pulmonary disease in people living with HIV on cART. Both diffusion capacity testing and CT imaging would prove particularly valuable in identifying interstitial pulmonary disease, aiding in distinguishing interstitial disease from the presence of small airway disease. In the absence of specific treatments for the long-term pulmonary sequelae of HIV infection, smoking cessation should remain the mainstay of improving pulmonary health in people living with HIV.

Contributors
All authors contributed to the conceptualisation and design of the study. SOV and EV curated data and contributed to data collection and coordination of the study. SOV and AB designed the methodology of the study and did the formal analysis. PR obtained funding and supervised the conduct of the study. SOV provided the original draft of the manuscript including figures. All authors contributed to reviewing and editing the manuscript to its final form. SOV, EV, and AB had access to, and verified, the underlying data.

Declaration of interests
FWW has served on scientific advisory boards for ViIV Healthcare and Gilead sciences. MFsvdL has received independent scientific grant support from Sanofi Pasteur, MSD Janssen Infectious Diseases and Vaccines, and Merck; has served on the advisory board of GlaxoSmithKline; and has received non-financial support from Stichting Pathologie Onderzoek en Ontwikkeling. MvdV through his institution has received independent scientific grant support and consultancy fees from AbbVie, Gilead Sciences, Johnson & Johnson, MSD, and ViIV Healthcare, for which honoraria were all paid to his institution. MBD has participated in advisory consulting or received research support from the following companies outside of this work: AstraZeneca, Boehringer-Ingelheim, Enterprise Therapeutics, GlaxoSmithKline, Midmark, Parion, Teva, and Theravance Biopharma/Mylan; he has received grant support from the National Institutes of Health and the US Department of Defense outside of this work. GDK was supported by a Fulbright Global Scholar award (US Department of State) and by the National Institute of Allergy and Infectious Diseases (grant number K24-AI118591). PR through his institution has received independent scientific grant support from Gilead Sciences, ViIV Healthcare, Merck, and Janssen Pharmaceuticals, and has served on scientific advisory boards for Gilead Sciences, ViIV Healthcare, Merck, and Teva pharmaceutical industries, for which his institution has received remuneration. SOV, AB, EV, NK, and RPvS declare no competing interests.

Data sharing
Data sharing has been restricted by the Ethical Review Board of the Amsterdam University Medical Centers because the data underlying this study contains very sensitive and potentially identifying information. Requests for data sharing can be made on a case-by-case basis following submission of a concept sheet as per instructions on the project website. Once submitted the proposed research or analysis will undergo review for evaluation of the scientific value, relevance to the study, design and feasibility, statistical power, and overlap with existing projects. If the proposed analysis is for verification or replication, data will then be made available. If the proposed research is for novel science, upon completion of the review, feedback will be provided to the proposers. In some circumstances, a revision of the concept may be requested. If the concept is approved for implementation, a writing group will be established consisting of the proposers (up to three people that were centrally involved in the development of the concept) and members of the AGE,IV Cohort Study group (or other appointed cohort representatives). All persons involved in the process of reviewing these research concepts are bound by confidentiality.

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