# Increasing burden of noninfectious lung disease in persons living with HIV: a 7-year study using the French nationwide hospital administrative database

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ABSTRACT An overall reduction in the incidence of AIDS and a change in the spectrum of lung disease have been noticed in persons living with HIV (PLHIV). Our aim was to provide an epidemiological update regarding the prevalence of lung diseases in PLHIV hospitalised in France.

We analysed the prevalence of lung disease in PLHIV hospitalised in France from 2007 to 2013, from the French nationwide hospital medical information database, and assessed the association between HIV and incident noninfectious disease over 4 years of follow-up.

A total of 52 091 PLHIV were hospitalised in France between 2007 and 2013. Among PLHIV hospitalised with lung disease, noninfectious lung diseases increased significantly from 45.6% to 54.7% between 2007 and 2013, whereas the proportion of patients with at least one infectious lung disease decreased significantly. In 2010, 10 067 prevalent hospitalised PLHIV were compared with 8 244 682 hospitalised non-PLHIV. In 30–49-year-old patients, HIV infection was associated with chronic obstructive pulmonary disease (COPD), chronic respiratory failure, emphysema, lung fibrosis and pulmonary arterial hypertension (PAH) even after adjustment for smoking.

The emergence of noninfectious lung disease, in particular COPD, emphysema, lung fibrosis, PAH and chronic respiratory disease, in PLHIV would justify mass screening in this population.

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## Introduction

The lung is the organ most frequently affected by opportunistic infections in AIDS. Initially, opportunistic infections and cancer were the main lung diseases in persons living with HIV (PLHIV). The introduction of anti-*Pneumocystis* prophylaxis in 1989 and highly active antiretroviral therapy (HAART) in 1996 progressively reduced the incidence of opportunistic infections in the USA and Europe [1]. The increased risk of noninfectious respiratory diseases in PLHIV was demonstrated by Crothers *et al.* [2] in a retrospective study based on 33 420 cases in the USA, with the most common diseases being lung cancer, Hodgkin's lymphoma and pulmonary arterial hypertension (PAH). The increased risk of developing these specific diseases for PLHIV has been confirmed in other studies [3–6]. Since 2013, French recommendations have advocated rapid initiation of HAART in all PLHIV [7]. Reaching the immunological therapeutic goals is associated with an overall reduction in the incidence of AIDS and non-AIDS manifestations [8], and a change in the spectrum of lung disease [9]. Recent comparative studies reported an increased risk of chronic obstructive pulmonary disease (COPD) (OR 1.1–1.5) [2, 10] and emphysema [11–14] in PLHIV. To date, there are few and controversial data regarding asthma and pulmonary fibrosis [2, 15, 16].

The aim of this study was to provide an epidemiological update regarding the prevalence of lung diseases in PLHIV hospitalised in France from 2007 to 2013 and to assess the risk of noninfectious lung diseases. We used the medical and administrative data collected from the national administrative database for hospitalised patients (Programme de Médicalisation des Systèmes d'Information (PMSI)), which gathers exploitable epidemiological data on such patients. Data for HIV and respiratory comorbidities are clearly defined and coded in this database.

## Methods

### *The national administrative database*

Inspired by the US diagnosis-related group model, the hospital discharge abstract database (PMSI) contains individual, exhaustive and linkable but anonymous data on healthcare for the entire hospitalised population in France, and collects primary and associated diagnoses (secondary events and comorbidities). The data are encoded using the World Health Organization International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), and procedures performed during all hospital stays are encoded with the common classification system for medical procedures (Classification Commune des Actes Médicaux). The very good quality of the French hospital database has previously been evaluated, and we have published several epidemiological and health service-related research studies on hospitalised patients in France using PMSI data [17–19].

The use of the PMSI data for this study was approved by the National Commission for Data Protection (CNIL 1576793). As the database is de-identified, written consent was not required. This study conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh in 2000). The PMSI data were transmitted by the Technical Agency for Information on Hospital Care (ATIH 2015-111111-47-33).

### *Study design*

This study was based on the multicentre retrospective collection of national PMSI data. We collected the diagnosis justifying hospitalisation, main or associated diagnosis, coded according to ICD-10, from the medical data.

All patients ⩾18 years of age infected with HIV, coded as main or associated diagnosis (Z21, B20, B21, B22, B240, B241 and B249), and hospitalised >1 day at least once in France per year from 2007 to 2013 were included. We distinguished between two levels of HIV infection in hospitalised PLHIV: HIV infection in the AIDS stage (HIV-AIDS) coded in B20, B21, B22 and B241, and HIV infection in the non-AIDS stage (HIV-non-AIDS) coded in Z21, B240 and B249. Pregnant females were excluded from the analyses.

The first analysis included a description of annual prevalence rates (follow-up at 1 year after hospital discharge for HIV) of lung diseases coded as main or associated diagnosis (see the supplementary material) in PLHIV hospitalised between 2007 and 2013.

We carried out a second set of analyses to assess the association between HIV and incident noninfectious diseases in a follow-up of 4 years in an exposed *versus* nonexposed study model. 1) The first exposed population was called "incident PLHIV hospitalised in 2010", and defined as PLHIV hospitalised as main diagnosis in 2010 with no previous hospitalisation for HIV infection in 2007, 2008 or 2009 (coded as main or associated diagnosis). 2) The second exposed population was all hospitalised PLHIV in 2010, which we called "prevalent PLHIV hospitalised in 2010". 3) The nonexposed population included non-PLHIV hospitalised in 2010 which we called "general hospitalised population in 2010". Incident noninfectious diseases were defined from 2010 to 2014 with no previous noninfectious diseases in 2007, 2008 and 2009.

A third analysis was performed in the same exposed ("prevalent PLHIV hospitalised in 2010") *versus* nonexposed study model including only patients identified as smokers in main or associated diagnoses (F17, Z720 and T652) in 2009 and 2010.

### *Variables*

The age and sex of patients and the hospital location were collected from the administrative data. We included the following lung diseases from the medical data (coded as main or associated diagnosis, see the supplementary material): community-acquired pneumonia (excluding *Legionella* pneumonia, mycobacterial and mycosis infections), *Pneumocystis* pneumonia, lung tuberculosis, *Legionella* pneumonia, aspergillosis pneumonia, pleural empyema, lung abscess, cytomegalovirus pneumonia, pneumothorax, chronic respiratory failure, lung cancer, PAH, sleep apnoea, COPD, emphysema, asthma, pulmonary sarcoidosis, lung fibrosis, drug-induced pneumonia and pulmonary embolism.

Hepatitis C virus (HCV) and hepatitis B virus (HBV) were identified in main or associated diagnoses (B16, B170, B171, B180, B181 and B182). Obesity with a body mass index >30 $kg \cdot m^{-2}$ was identified in main or associated diagnoses (E66). Left heart dysfunction was identified in main or associated diagnoses (I501). Smoking was identified in main or associated diagnoses (F17, Z720 and T652) in 2009 and 2010.

### *Statistical analysis*

The qualitative variables were expressed as percentages. Percentage comparisons were made using the Chi-squared test or Fisher's exact test according to the conditions of application. The Cochran–Armitage test was used to study the evolution of trends over time for annual prevalence rates of lung diseases. To assess the association between HIV and incident noninfectious diseases, the Fine–Gray model was used to identify the effect of the group (HIV-AIDS, HIV-non-AIDS and nonexposed) on the different noninfectious diseases to be explained, stratified according to age (18–29, 30–49, 50–69 and ⩾70 years old). The survival model was chosen to take into account competing risk problems related to patients who die during follow-up. All hazard ratios were adjusted for sex, smoking, and HCV and HBV infections, and the 95% confidence intervals were calculated. Moreover, sleep apnoea hazard ratios were adjusted for obesity, and PAH hazard ratios were adjusted for COPD and left heart dysfunction.

SAS version 9.3 (SAS Institute, Cary, NC, USA) was used for data analysis. All assumptions were tested with an $\alpha$ risk of 0.05.

## Results

### *Annual prevalence rate of lung diseases in PLHIV hospitalised in France from 2007 to 2013*

A total of 52 091 PLHIV were hospitalised in France between 2007 and 2013. The annual number remained stable at ~10 500 hospitalisations per year (from 10 445 to 11 071). Of these, 26.0% were diagnosed with at least one lung disease and this proportion was constant over time (figure 1). Among hospitalised PLHIV

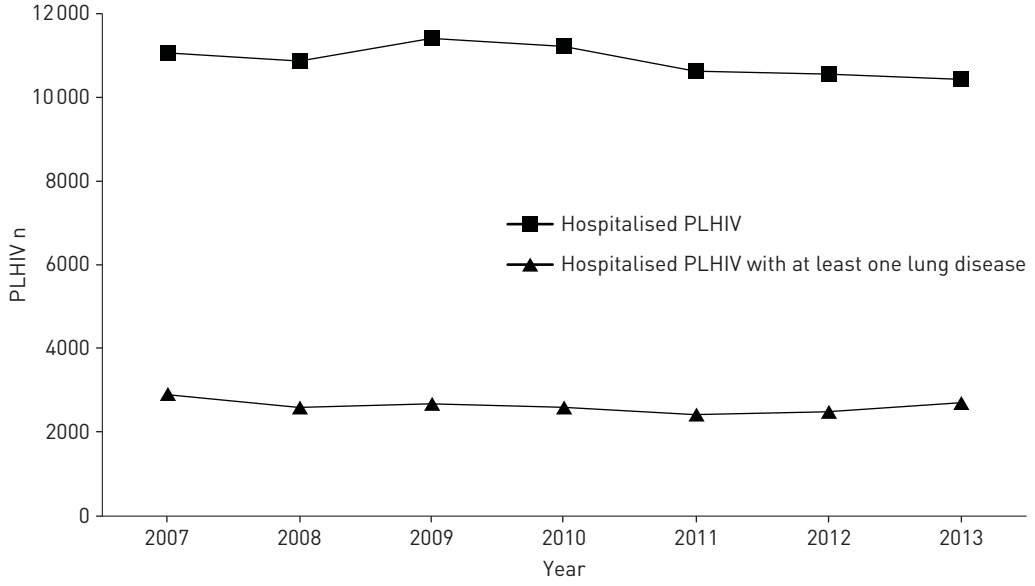


FIGURE 1 French annual prevalence rates from 2007 to 2013 of hospitalised persons living with HIV (PLHIV) and those with at least one lung disease.

with at least one lung disease, the proportion of those with at least one noninfectious lung disease increased significantly from 45.6% to 54.7% between 2007 and 2013 (p<0.01), whereas the proportion of those with at least one infectious lung disease decreased significantly from 67.9% to 61.8% (p<0.01) (table 1). The annual prevalence rates of lung disease in hospitalised PLHIV are summarised in table 1.

The infectious lung diseases diagnosed most commonly in hospitalised PLHIV were community-acquired pneumonia, *Pneumocystis* pneumonia and lung tuberculosis at, respectively, 12.02%, 3.39% and 1.99% in 2013. The annual prevalence rates of these three lung diseases decreased significantly from 2007 to 2013 (p⩽0.02). The annual prevalence rate of other infectious lung diseases was very low (table 1).

Among noninfectious lung diseases screened in 2013, the most frequently diagnosed were COPD (4.61% of hospitalised PLHIV), emphysema (1.57%), chronic respiratory failure (1.55%), lung cancer (1.48%), sleep apnoea (1.39%), asthma (1.33%), pulmonary embolism (1.30%), PAH (0.66%), pneumothorax (0.53%) and lung fibrosis (0.27%). The annual prevalence rates of COPD, emphysema, chronic respiratory failure, sleep apnoea, lung fibrosis, pulmonary embolism and lung cancer increased significantly between 2007 and 2013 (table 1).

### *Evaluation of the risk of incident noninfectious lung disease over 4 years in prevalent and incident PLHIV hospitalised in 2010 compared with that in the general hospitalised population in 2010*

In 2010, 10 067 (4328 HIV-AIDS and 5739 HIV-non-AIDS) prevalent hospitalised PLHIV were compared with 8 244 682 hospitalised non-PLHIV. The results of the univariate analysis for lung diseases, age, sex and HBV or HCV infection are shown in table 2. The survival curve of 2010 prevalent PLHIV with lung disease is shown in the supplementary material.

In the incident analysis over time (Fine–Gray model), after adjustment for sex, smoking and HBV or HCV infection, HIV infection without AIDS was associated with noninfectious lung disease taken as a whole in 18–49-year-old patients (HR 1.6 (95% CI 1.1–2.4) in 18–29-year-old patients and HR 1.2 (95% CI 1.1–1.4) in 30–49-year-old patients), but not in patients >49 years old (table 3). Hazard ratios

TABLE 1 Annual prevalence rates of lung diseases in hospitalised persons living with HIV (PLHIV) from 2007 to 2013

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | p-value[#] |
|---|---|---|---|---|---|---|---|---|
| **Hospitalised PLHIV** | 11 071 | 10 878 | 11 418 | 11 226 | 10 638 | 10 568 | 10 445 | |
| **With at least one lung disease** | 2884 (26.05) | 2580 (23.72) | 2666 (23.35) | 2585 (23.03) | 2409 (22.65) | 2477 (23.44) | 2688 (25.73) | |
| **With at least one infectious lung disease** | 1959 (17.69) | 1768 (16.25) | 1766 (15.47) | 1667 (14.85) | 1555 (14.62) | 1532 (14.50) | 1661 (15.90) | <0.01 |
| CAP | 1445 (13.05) | 1323 (12.16) | 1307 (11.45) | 1188 (10.58) | 1131 (10.63) | 1126 (10.65) | 1255 (12.02) | <0.01 |
| *Pneumocystis* pneumonia | 430 (3.88) | 392 (3.60) | 368 (3.22) | 364 (3.24) | 339 (3.19) | 338 (3.20) | 354 (3.39) | 0.02 |
| Lung tuberculosis | 327 (2.95) | 285 (2.62) | 289 (2.53) | 280 (2.49) | 226 (2.12) | 222 (2.10) | 208 (1.99) | <0.01 |
| Aspergillosis pneumonia | 27 (0.24) | 33 (0.30) | 28 (0.25) | 19 (0.17) | 26 (0.24) | 26 (0.25) | 24 (0.23) | 0.60 |
| Lung abscess | 23 (0.21) | 19 (0.17) | 15 (0.13) | 32 (0.29) | 19 (0.18) | 26 (0.25) | 19 (0.18) | 0.55 |
| *Legionella* pneumonia | 22 (0.20) | 20 (0.18) | 11 (0.10) | 20 (0.18) | 11 (0.10) | 12 (0.11) | 13 (0.12) | 0.08 |
| Pleural empyema | 19 (0.17) | 20 (0.18) | 24 (0.21) | 20 (0.18) | 21 (0.20) | 22 (0.21) | 15 (0.14) | 0.90 |
| CMV pneumonia | 16 (0.14) | 19 (0.17) | 19 (0.17) | 21 (0.19) | 25 (0.24) | 22 (0.21) | 24 (0.23) | 0.07 |
| **With at least one noninfectious lung disease** | 1316 (11.89) | 1187 (10.91) | 1285 (11.25) | 1299 (11.57) | 1228 (11.54) | 1319 (12.48) | 1471 (14.08) | <0.01 |
| COPD | 344 (3.11) | 331 (3.04) | 337 (2.95) | 330 (2.94) | 332 (3.12) | 413 (3.91) | 482 (4.61) | <0.01 |
| Asthma | 198 (1.79) | 130 (1.20) | 152 (1.33) | 130 (1.16) | 136 (1.28) | 146 (1.38) | 139 (1.33) | 0.11 |
| Chronic respiratory failure | 118 (1.07) | 116 (1.07) | 123 (1.08) | 117 (1.04) | 132 (1.24) | 135 (1.28) | 162 (1.55) | <0.01 |
| Lung cancer | 115 (1.04) | 110 (1.01) | 145 (1.27) | 146 (1.30) | 141 (1.33) | 125 (1.18) | 155 (1.48) | <0.01 |
| Pulmonary embolism | 106 (0.96) | 99 (0.91) | 97 (0.85) | 116 (1.03) | 112 (1.05) | 112 (1.06) | 136 (1.30) | <0.01 |
| Emphysema | 67 (0.61) | 59 (0.54) | 80 (0.70) | 101 (0.90) | 107 (1.01) | 126 (1.19) | 164 (1.57) | <0.01 |
| PAH | 66 (0.60) | 54 (0.50) | 54 (0.47) | 53 (0.47) | 60 (0.56) | 59 (0.56) | 69 (0.66) | 0.23 |
| Sleep apnoea | 53 (0.48) | 68 (0.63) | 55 (0.48) | 87 (0.77) | 85 (0.80) | 89 (0.84) | 145 (1.39) | <0.01 |
| Pneumothorax | 47 (0.42) | 57 (0.52) | 50 (0.44) | 50 (0.45) | 43 (0.40) | 52 (0.49) | 55 (0.53) | 0.47 |
| Lung fibrosis | 21 (0.19) | 8 (0.07) | 23 (0.20) | 14 (0.12) | 22 (0.21) | 24 (0.23) | 28 (0.27) | 0.01 |
| Pulmonary sarcoidosis | 17 (0.15) | 9 (0.08) | 9 (0.08) | 6 (0.05) | 16 (0.15) | 17 (0.16) | 18 (0.17) | 0.11 |
| Drug-induced pneumonia | 6 (0.05) | 1 (0.01) | 4 (0.04) | 4 (0.04) | 2 (0.02) | 2 (0.02) | 4 (0.04) | 0.63 |

Data are presented as n or n (%), unless otherwise stated. CAP: community-acquired pneumonia; CMV: cytomegalovirus; COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension. [#]: Cochran–Armitage trend tests were conducted on prevalence from 2007 to 2013, p<0.05 was considered statistically significant.

TABLE 2 Incidence rate of noninfectious lung diseases in 2010 in prevalent hospitalised HIV-AIDS, HIV-non-AIDS and the hospitalised population (univariate analysis)

| | HIV-AIDS | HIV-non-AIDS | General population | p-value[#] |
|---|---|---|---|---|
| **Patients hospitalised in 2010** | 4328 | 5739 | 8 244 682 | |
| **With at least one lung disease** | 1651 (38.2) | 1173 (20.4) | 1 129 121 (13.7) | <0.01 |
| **With at least one infectious lung disease** | 1401 (32.4) | 768 (13.4) | 531 820 (6.5) | <0.01 |
| **With at least one noninfectious lung disease** | 936 (21.6) | 823 (14.3) | 882 234 (10.7) | <0.01 |
| Asthma | 95 (2.2) | 140 (2.4) | 160 504 (1.9) | 0.01 |
| COPD | 291 (6.7) | 338 (5.9) | 344 585 (4.2) | <0.01 |
| Emphysema | 121 (2.8) | 140 (2.4) | 53 722 (0.6) | <0.01 |
| Chronic respiratory failure | 145 (3.4) | 150 (2.6) | 182 678 (2.2) | <0.01 |
| Lung fibrosis | 30 (0.7) | 13 (0.2) | 22 531 (0.3) | <0.01 |
| PAH | 40 (0.9) | 58 (1.0) | 50 001 (0.6) | <0.01 |
| Lung cancer | 114 (2.6) | 92 (1.6) | 103 180 (1.3) | <0.01 |
| Sleep apnoea | 57 (1.3) | 125 (2.2) | 241 142 (2.9) | <0.01 |
| **Age** | | | | |
| <30 years | 265 (6.1) | 283 (4.9) | 796 099 (9.7) | <0.01 |
| 30–49 years | 2506 (57.9) | 3089 (53.8) | 1 940 530 (23.5) | <0.01 |
| 50–69 years | 1380 (31.9) | 2082 (36.3) | 29 326 391 (35.6) | <0.01 |
| ⩾70 years | 177 (4.1) | 285 (5.0) | 2 575 414 (31.2) | <0.01 |
| **Male** | 3006 (69.5) | 3826 (66.7) | 3 911 997 (47.5) | <0.01 |
| **Smoking** | 736 (17.0) | 877 (15.3) | 436 930 (5.3) | <0.01 |
| **HBV or HCV infection** | 746 (17.2) | 1019 (17.8) | 31 019 (0.4) | <0.01 |
| **Obesity (BMI >30 kg·m$^{-2}$)** | 40 (0.9) | 187 (3.2) | 358 055 (4.3) | <0.01 |
| **Left heart dysfunction** | 36 (0.8) | 33 (0.6) | 201 338 (2.4) | <0.01 |

Data are presented as n or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension; HBV: hepatitis B virus; HCV: hepatitis C virus; BMI: body mass index. [#]: Chi-squared test comparing the three groups.

for noninfectious lung diseases varied according to lung disease and patient age (table 3) when comparing PLHIV without AIDS to the general population. In 30–49-year-olds, HIV infection without AIDS was a factor associated with COPD (HR 1.4 (95% CI 1.2–1.6)), chronic respiratory failure (HR 1.5 (95% CI 1.2–2.0)), emphysema (HR 2.6 (95% CI 2.0–3.4)) and PAH (HR 3.4 (95% CI 2.2–5.1)). In 50–69-year-olds, HIV infection without AIDS was associated with emphysema (HR 1.7 (95% CI 1.3–2.2)) and PAH (HR 1.8 (95% CI 1.2–2.7)). HIV infection without AIDS was not associated with lung cancer and asthma in patients ⩾18 years old. Finally, HIV infection without AIDS was a protective factor for sleep apnoea in 30–69-year-old patients (HR 0.6 (95% CI 0.4–0.8) in 30–49-year-old patients and HR 0.6 (95% CI 0.4–0.7) in 50–69-year-old patients).

TABLE 3 Incident analysis over time to identify the effect of persons living with HIV without AIDS on lung diseases, according to age group (after adjusting for sex, smoking and hepatitis B virus or hepatitis C virus infection)

| | Age group | | | |
|---|---|---|---|---|
| | 18–29 years | 30–49 years | 50–69 years | ⩾70 years |
| **At least one lung disease** | 2.6 (2.0–3.5) | 1.5 (1.4–1.7) | | |
| **At least one infectious lung disease** | 5.8 (4.1–8.1) | 2.7 (2.4–3.0) | 1.8 (1.6–2.0) | |
| **At least one noninfectious lung disease** | 1.6 (1.1–2.4) | 1.2 (1.1–1.4) | | |
| COPD | | 1.4 (1.2–1.6) | | |
| Emphysema | | 2.6 (2.0–3.4) | 1.7 (1.3–2.2) | |
| Chronic respiratory failure | | 1.5 (1.2–2.0) | | |
| Lung fibrosis | 11.3 (1.6–80.2) | | | |
| PAH[#] | | 3.4 (2.2–5.1) | 1.8 (1.2–2.7) | |
| Lung cancer | | | | |
| Sleep apnoea[¶] | | 0.6 (0.4–0.8) | 0.6 (0.4–0.7) | |

Data are presented as hazard ratio (95% CI); only statistically significant hazard ratios are reported. COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension. [#]: after adjusting for COPD and left heart dysfunction; [¶]: after adjusting for obesity.

TABLE 4 Incident analysis over time to identify the effect of persons living with HIV with AIDS on lung disease, according to age group (after adjusting for sex, smoking and hepatitis B virus or hepatitis C virus infection)

| | Age group | | | |
|---|---|---|---|---|
| | **18–29 years** | **30–49 years** | **50–69 years** | **⩾70 years** |
| **At least one lung disease** | 6.8 (5.5–8.4) | 3.5 (3.2–3.7) | 2.1 (1.9–2.4) | 2.0 (1.5–2.6) |
| **At least one infectious lung disease** | 18.1 (14.3–22.8) | 8.2 (7.5–8.9) | 4.5 (4.5–5.0) | 3.0 (2.2–3.9) |
| **At least one noninfectious lung disease** | 2.2 (1.5–3.1) | 2.2 (2.0–2.4) | 1.4 (1.2–1.6) | 1.5 (1.1–2.1) |
| COPD | | 1.8 (1.5–2.1) | | |
| Emphysema | | 3.0 (2.3–3.9) | 2.1 (1.5–2.8) | |
| Chronic respiratory failure | | 2.3 (1.8–3.0) | | |
| Lung fibrosis | | 4.7 (2.8–8.1) | | 4.6 (1.9–11.1) |
| PAH[#] | | 3.5 (2.3–5.3) | | |
| Lung cancer | 9.2 (1.8–47.8) | 2.8 (2.1–3.7) | 1.3 (1.0–1.7) | |
| Sleep apnoea[¶] | | 0.4 (0.3–0.5) | 0.3 (0.2–0.5) | |

Data are presented as hazard ratio (95% CI); only statistically significant hazard ratios are reported. COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension. [#]: after adjusting for COPD and left heart dysfunction; [¶]: after adjusting for obesity.

In the incident analysis over time (Fine–Gray model), after adjustment for sex, smoking and HBV or HCV infection, HIV infection with AIDS was associated with noninfectious lung disease taken as a whole in patients ⩾18 years old (HR 2.2 (95% CI 1.5–3.1) in 18–29-year-old patients, HR 2.2 (95% CI 2.0–2.4) in 30–49-year-old patients, HR 1.4 (95% CI 1.2–1.6) in 50–69-year-old patients and HR 1.5 (95% CI 1.1–2.1) in patients ⩾70 years old) (table 4). Hazard ratios for noninfectious lung diseases varied according to the disease and the age of the patient (table 4). In 30–49-year-old patients, HIV infection with AIDS was a factor associated with COPD (HR 1.8 (95% CI 1.5–2.1)), emphysema (HR 3.0 (95% CI 2.3–3.9)), chronic respiratory failure (HR 2.3 (95% CI 1.8–3.0)), lung fibrosis (HR 4.7 (95% CI 2.8–8.1)), PAH (HR 3.5 (95% CI 2.3–5.3)) and lung cancer (HR 2.8 (95% CI 2.1–3.7)). In 50–69-year-olds, HIV infection with AIDS was a factor associated only with emphysema (HR 2.1 (95% CI 1.5–2.8)) and lung cancer (HR 1.3 (95% CI 1.0–1.7)). In the oldest group, patients ⩾70 years old, HIV infection with AIDS was only associated with lung fibrosis (HR 4.6 (95% CI 1.9–11.1)). HIV infection with AIDS was not associated with asthma in patients ⩾18 years old. HIV infection with AIDS was a protective factor for sleep apnoea in 30–69-year-old patients (HR 0.4 (95% CI 0.3–0.5) in 30–49-year-old patients and HR 0.3 (95% CI 0.2–0.5) in 50–69-year-old patients).

Patient sex impacted hazard ratios for noninfectious lung diseases. These hazard ratios, detailed in the supplementary material, were also calculated in an incident analysis over time (Fine–Gray model), after adjustment for age, smoking and HBV or HCV infection.

The incidence rates of noninfectious lung diseases in incident PLHIV hospitalised in 2010 are summarised in table 5. The results of the incident analysis over time (Fine–Gray model), after adjustment for sex and HBV or HCV infection are detailed in the supplementary material.

### *Evaluation of the risk of incident noninfectious lung disease over 4 years in prevalent smoker PLHIV hospitalised in 2010 compared with the general hospitalised smoker population in 2010*

The results of the incident analysis over time (Fine–Gray model), after adjustment for sex and HBV or HCV infection, are detailed in the supplementary material. In 30–49-year-old smokers, HIV infection without AIDS was associated with emphysema and chronic respiratory failure. In 30–49-year-old smokers, HIV infection with AIDS was associated with emphysema, chronic respiratory failure, lung fibrosis, lung cancer and PAH.

## Discussion

This 7-year retrospective study is, to the best of our knowledge, the first to demonstrate the substantial rise in the number of cases of noninfectious lung disease in PLHIV hospitalised in France. We showed an increased risk of COPD, emphysema, PAH, chronic respiratory failure and lung fibrosis in PLHIV, particularly in 30–49-year-old patients. Our study showed that noninfectious lung diseases occur at a younger age in PLHIV than in the general hospitalised population.

Since the late 1990s, the use of combined antiretroviral therapies in Western countries has considerably reduced mortality in PLHIV, from 8.3 per 100 000 in 1994 to 1.2 per 100 000 in 2006 in France [20]. The

TABLE 5 Incidence rate of noninfectious lung diseases in 2010 in incident hospitalised HIV-AIDS, HIV-non-AIDS and the general population (univariate analysis)

| | HIV-AIDS | HIV-non-AIDS | General population | p-value[#] |
|---|---|---|---|---|
| **Patients hospitalised in 2010** | 592 | 251 | 8 244 682 | |
| **With at least one lung disease** | 318 (53.7) | 59 (23.5) | 1 129 121 (13.7) | <0.01 |
| **With at least one infectious lung disease** | 283 (47.8) | 38 (15.1) | 531 820 (6.5) | <0.01 |
| **With at least one noninfectious lung disease** | 125 (21.1) | 33 (13.1) | 882 234 (10.7) | <0.01 |
| Asthma | 4 (0.7) | 3 (1.2) | 160 504 (1.9) | 0.06 |
| COPD | 26 (4.4) | 10 (4.0) | 344 585 (4.2) | 0.96 |
| Emphysema | 15 (2.5) | 7 (2.8) | 53 722 (0.6) | <0.01 |
| Chronic respiratory failure | 11 (1.9) | 1 (0.4) | 182 678 (2.2) | 0.12 |
| Lung fibrosis | 4 (0.7) | 0 (0) | 22 531 (0.3) | 0.13 |
| PAH | 2 (0.3) | 2 (0.8) | 50 001 (0.6) | 0.65 |
| Lung cancer | 4 (0.7) | 2 (0.8) | 103 180 (1.2) | 0.38 |
| Sleep apnoea | 3 (0.5) | 6 (2.4) | 241 142 (2.9) | <0.01 |
| **Age** | | | | |
| <30 years | 53 (8.9) | 46 (18.3) | 796 099 (9.7) | <0.01 |
| 30–49 years | 352 (59.5) | 126 (50.2) | 1 940 530 (23.5) | <0.01 |
| 50–69 years | 167 (28.2) | 72 (28.7) | 29 326 391 (35.6) | <0.01 |
| ⩾70 years | 20 (3.4) | 7 (2.8) | 2 575 414 (31.2) | <0.01 |
| **Male** | 414 (69.9) | 180 (71.7) | 3 911 997 (47.5) | <0.01 |
| **Smoking** | 60 (10.0) | 26 (10.4) | 436 930 (5.3) | <0.01 |
| **HBV or HCV infection** | 62 (10.5) | 31 (12.4) | 31 019 (0.4) | <0.01 |

Data are presented as n or n (%). COPD: chronic obstructive pulmonary disease; PAH: pulmonary arterial hypertension; HBV: hepatitis B virus; HCV: hepatitis C virus. [#]: Chi-squared test comparing the three groups.

lung diseases seen today in patients treated with long-term antiretroviral drugs are different from those described at the beginning of the epidemic [9].

In our study, the annual prevalence rate of lung diseases in hospitalised PLHIV was stable at 26%, confirming the close relationship between HIV infection and respiratory diseases. Infection remained the primary cause of lung disease in hospitalised PLHIV. Nevertheless, our study highlighted the rise of noninfectious lung diseases, particularly sleep apnoea, COPD, emphysema and PAH.

In hospitalised PLHIV, the prevalence rates of COPD (3.1%), asthma (1.8%) and pulmonary fibrosis (0.2%) were slightly lower than those described by Crothers *et al.* [2] of 4.6%, 2.0% and 0.4%, respectively. A substantial number of patients with these diseases were probably not hospitalised and were thus not included in our study. Nevertheless, the prevalence rate of lung cancer in PLHIV in our study (1.0%) is higher than in the USA (0.1%) [21]. The fact that lung cancer is usually cared for in hospital may explain the higher proportion in our hospitalised population study. Moreover, it may also reflect the increase in prevalence rates of lung cancer in the general population over the last 20 years as a result of increased smoking, particularly among females [22]. The increased risk of lung cancer in PLHIV is well documented in the literature [3, 4] and confirmed by our results in PLHIV with AIDS.

Our data confirm the results of previous studies revealing an increased risk of PAH [6, 23, 24]. In our study, this risk was age-related and only significant in 30–69-year-old patients. Intravenous drug abuse, which is more frequent in young patients, is a risk factor for PAH [25]. This factor could not be taken into account in our study and may have increased hazard ratios in young PLHIV. Our data regarding the risk of COPD and emphysema in PLHIV confirm the results of previous studies [2, 10]. As in our study, the risk reported in these previous studies persists regardless of smoking and is increased in the youngest patients. The hypothesis of the early development of COPD and emphysema in PLHIV was thus discussed. In small series of patients, smoking, drug abuse, antiretroviral therapy, a high viral load (>200 000 copies·mL$^{-1}$) and a history of pneumonia (in particular *Pneumocystis*) were found to be additional risk factors for COPD [26–29] and emphysema [30–33]. Bronchial obstruction and emphysema are therefore linked to factors associated with poor control of HIV infection. However, two studies found an increased risk with antiretroviral therapy [26, 34]. Regarding lung fibrosis, data from the literature are rare in PLHIV [2, 12] and histological substrates are not described [12]. The risk of lung fibrosis also appears to be related to factors associated with poor control of HIV infection [12]. The emergence of these noninfectious lung diseases in young patients suggests premature lung ageing in PLHIV.

HIV induces lymphocyte senescence even in patients on antiretroviral drugs with an undetectable plasma viral load [35]. In the lungs, HIV infection associated with smoking and microorganisms of the respiratory microbiome will jointly induce alveolar macrophage activation [36]. Differences in the risk of noninfectious respiratory diseases (PAH, COPD, emphysema and chronic respiratory failure) observed between AIDS and non-AIDS patients in our study may support the role of a high HIV viral load and opportunistic microorganisms in the development of noninfectious lung diseases.

One limitation of this study is related to the impact of tobacco use in the emergence of noninfectious lung disease in hospitalised PLHIV. In France, the proportion of current smokers in PLHIV was estimated at 37.5% in 2011 [37]. However, in order to get around this bias, we adjusted all our multivariate analyses for smoking and we confirmed our results in a complementary analysis limited to smoker patients. The PMSI database may lead to an overestimation of some diseases in hospital discharge abstracts because hospital funding has been based on medical activity since 2008. However, this overestimation does not usually impact data collection for the pathologies included in this study. Coding quality is checked by medical information professionals in each hospital and by national health insurance to correct diagnoses. The use of the PMSI database may also have led to an underestimation of smoking and lung diseases, such as asthma, sleep apnoea and COPD, which can be managed in nonhospital settings. However, these two types of bias were identical in HIV and non-PLHIV, and therefore were unlikely to affect the calculated hazard ratios. Since our study population was an exclusively hospitalised population, our results cannot be generalised to all PLHIV, but only to hospitalised PLHIV.

Owing to the progression of noninfectious lung diseases in PLHIV, we believe that the prevention of these lung diseases needs to be improved by acting on well-identified and frequent risk factors in PLHIV, such as smoking and drug abuse. We believe that screening for lung diseases needs to be systematically proposed to PLHIV, as is already the case for cardiovascular and endocrine diseases. In order to prevent lung diseases that may lead to the irreversible development of respiratory failure, new recommendations should include mass screening for lung diseases. The modalities of this screening, which are yet to be established, would be proposed to all patients infected with HIV and in particular those who smoke. Even if the benefit of lung computed tomography screening seems to be limited in PLHIV for lung cancer screening [4, 38, 39], it should be evaluated in prospective studies for emphysema and lung fibrosis screening. For PAH, screening based on a pulmonary artery systolic pressure ultrasound could easily be done during screening for cardiovascular diseases [24]. For COPD and emphysema screening, respiratory functional exploration should be proposed in PLHIV, in particular those who smoke.

In conclusion, we demonstrated the rise of noninfectious lung disease in PLHIV from a nationwide hospital administrative database. The increase in COPD, emphysema, lung fibrosis, PAH and chronic respiratory failure in particular justify mass screening in PLHIV.

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