Université de Poitiers
Faculté de Médecine et Pharmacie

Année 2024

THESE
POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(décret du 25 novembre 2016)

présentée et soutenue publiquement
le 12 avril 2024 à Poitiers
par Madame Elise Puel

Évolution de l'incidence de l'hypertension artérielle pulmonaire (HTAP) associée à l'infection par le VIH au cours des 15 dernières années : données du registre français de l'hypertension pulmonaire.

COMPOSITION DU JURY

Président : Monsieur le Professeur Jean-Claude MEURICE

Membres :
- Monsieur le Docteur Etienne-Marie JUTANT
- Monsieur le Docteur Gwenaël LE MOAL
- Monsieur le Professeur Olivier SITBON
- Mme la Docteure Magali CROQUETTE

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TABLE DES MATIERES

INTRODUCTION

L'hypertension artérielle pulmonaire (HTAP) est une complication rare mais grave de l'infection par le virus de l'immunodéficience humaine (VIH). Elle appartient au groupe 1 de la classification clinique de l'hypertension pulmonaire [1] et on sait actuellement qu'elle représente entre 3 et 7 % de tous les cas d'HTAP [2-4]. L'étiologie est complexe, multifactorielle et n'est pas encore complètement élucidée, mais on connaît le rôle important de l'inflammation chronique notamment en lien avec certaines protéines de surface du VIH comme Negative Regulatory Factor (NEF), Trans-Activator of Transcription (TAT) et gp120 [5-7]. Cette inflammation chronique provoque, par une cascade de réactions cytokiniques, un remodelage vasculaire aboutissant in fine au développement d'une HTAP.

Le rôle de cofacteurs déclenchant le développement de l'HTAP dans cette population est également reconnu, comme la prise de substances toxiques (amphétamines, cocaïne, opioïdes, drogues intraveineuses) [8-10], ou les comorbidités hépatiques [11-13]. Des facteurs liés au VIH sont également suspectés de favoriser le développement de l'HTAP, tels qu'une charge virale détectable (> 500 copies/ml) et un taux de CD4 inférieur à 200 cellules/µL [14-18].

Depuis l'avènement de la thérapie antirétrovirale dans les années 1990, l'espérance de vie des patients VIH a considérablement augmenté [19], et l'incidence des maladies pulmonaires et cardiovasculaires chroniques non infectieuses dans cette population s'est accrue [20,21]. Cependant, la prévalence de l'HTAP chez les patients VIH (HTAP-VIH) et la sévérité de l'HTAP au moment du diagnostic semble décroître depuis la dernière décennie.

Cette étude descriptive, rétrospective, multicentrique, menée à partir du registre national Français de l'hypertension pulmonaire, avait pour objectif principal de décrire l'évolution de l'incidence de l'HTAP-VIH sur la période 2007-2022 parallèlement à l'évolution de l'épidémiologie de l'HTAP et du VIH en France. L'objectif secondaire était de décrire l'évolution des caractéristiques des patients au diagnostic d'HTAP-VIH sur la période 2007-2022, en particulier avant et après 2015, ainsi que la réponse au traitement, la survie et les facteurs pronostiques.

ARTICLE ORIGINAL

Trends in the incidence of pulmonary arterial hypertension (PAH) associated with HIV infection over the past 15 years: data from the French pulmonary hypertension registry.

Authors : Elise Puel[1,2], Gwenaël Le Moal[1,3], Magali Croquette[1,4], Vanessa Bironneau[1,2,5], Jean-Claude Meurice[1,2,5], Élisa Larrieu[1,6], Xavier Jaïs[7,8,9], Athénaïs Boucly[7,8,9], Marc Humbert[7,8,9], David Montani[7,8,9], Laurent Savale[7,8,9], Olivier Sitbon[7,8,9]*, Etienne-Marie Jutant[1,2,5]*

* co last authors

Authors affiliations:

[1] Université de Poitiers, Poitiers, France CHU de Poitiers

[2] Service de Pneumologie, CHU de Poitiers, Poitiers, France

[3] Service de maladies infectieuses, CHU de Poitiers, Poitiers, France

[4] Service de Médecine vasculaire, CHU de Poitiers, Poitiers, France

[5]INSERM CIC 1402, Axe Is-ALIVE, Poitiers, France

[6] Service de cardiologie, CHU de Poitiers, Poitiers, France

[7]Université Paris-Saclay, Faculté de Médecine, Le Kremlin-Bicêtre, France

[8]INSERM UMR_S 999 « Hypertension pulmonaire : Physiopathologie et Nouvelles Thérapies », Le Kremlin-Bicêtre, France

[9]AP-HP, Service de Pneumologie et Soins Intensifs Respiratoires, Centre coordonnateur du CRMR PulmoTension, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

ABSTRACT

Rationale: Pulmonary arterial hypertension (PAH) is a rare but severe complication of HIV infection. In France, it seems to be a decline in the incidence and severity at diagnosis of PAH in HIV patients since 2007, but no study has reported on the evolution of the epidemiology and characteristics of PAH associated with HIV (PAH-HIV) over the last decade.

Objectives: Describe the evolution of PAH incidence in the HIV population (PAH-HIV) since 2007, in parallel with the evolution of HIV and PAH epidemiology in France and describe the evolution of patient characteristics at diagnosis of PAH-HIV over the period 2007-2022, as well as the response to treatment, survival and prognostic factors.

Methods: We conducted an observational, restrospective study based on the French pulmonary hypertension (PH) registry. We reported the evolution of incidence of PAH-VIH between 2007 an 2022 as well as clinical, functional and hemodynamic characteristics. Annual incidence, response to PAH approved drugs and overall survival of patients with PAH-HIV have been analysed.

Results: Between 2007 and 2022, 251 PAH-HIV patients were registered in the French PH registry. The incidence of PAH-HIV has decreased since 2007 (23 new cases in 2007 *vs.* 7 in 2022, HIV representing 6,1% of all PAH cases in 2007 *vs.* 1.7% in 2022), while the incidence of PAH and HIV has remained stable. The phenotype of PAH-HIV patients has evolved at diagnosis as patients diagnosed since 2015 were older, more frequently smokers, with a higher BMI, and had less hepatic comorbidities. Hemodynamics appeared to be similar in patients diagnosed before and after 2015 as well as survival. We observed a significant hemodynamic response in the 77% patients who were reassessed.

Conclusion: Incidence of PAH-HIV has been declining since 2007, while the incidence of PAH and HIV has remained stable. Phenotype of PAH-HIV patients has changed. Earlier introduction of antiretroviral treatment regardless of CD4 count since 2015 could explain the lower incidence of PAH-HIV, but does not seem to have major impact on the hemodynamic severity and survival.

Key words: pulmonary hypertension, pulmonary arterial hypertension, HIV, epidemiology, prognostic, inflammation

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare but severe complication of human immunodeficiency virus (HIV) infection. It belongs to group 1 of the clinical classification of pulmonary hypertension (PH) [1] and it is currently known to account for between 3% and 7% of all PAH cases [2–4].

The etiology is complex, multifactorial and not completely elucidated, with an important role of chronic inflammation, notably via the HIV proteins Negative Regulatory Factor (NEF), Trans-Activator of Transcription (TAT) and gp120. This chronic inflammation, through cascades of cytokine reactions, provoke a chronic inflammatory state involved in the alteration of pulmonary artery endothelium and smooth muscle cells, and participate in chronic pulmonary arterial remodeling through mechanisms of proliferation, cell migration and vasoconstriction [5–7].

The role of cofactors triggering the development of PAH in this population is also acknowledged, such as the intake of toxic substances (amphetamines, cocaine, opioids, intravenous drugs cut or not with certain foreign bodies) [8–10], or hepatic comorbidities [11–13]. HIV-related factors are also suspected of favoring the development of PAH, such as detectable viral load (> 500 copies/ml) and CD4 counts below 200 cells/µL [14–18].

Since the advent of antiretroviral therapy (ART) in the 1990s, the life expectancy of HIV patients has increased considerably [19], and there has been an increase in the incidence of chronic non-infectious pulmonary and cardiovascular diseases in this population [20,21]. However, the prevalence of PAH associated with HIV (PAH-HIV) remained stable after the introduction of ART: it was estimated at 0.5% before ART use [22] and 0.46% in a previous study based on the French PH registry in 2008 [23]. This makes the impact of the introduction of ART on the incidence of PAH-HIV a highly controversial subject. The question also arises about the impact of these therapies on the prevalence and severity of PAH-HIV, especially since 2015, corresponding to the publication of the INSIGHT START study. This study demonstrated the clear advantages of initiating antiretroviral therapy in HIV-positive adults with a CD4+ count of more than 500 cells/µL compared to initiating therapy after the CD4+

count had declined to 350 cells/µL. It led to the recommendation to begin treating HIV infection from diagnosis, regardless of CD4 count [16, 20, 21, 24–30]. A decline in the incidence of PAH-HIV, and a decrease in the severity of PAH at diagnosis have been empirically suspected during the last decade, especially since 2015, but no study has recently reported the evolution of the epidemiology and characteristics of PAH-HIV.

Our primary objective was to describe the evolution of the incidence of PAH-HIV over the period 2007-2022 in France in parallel with the evolution of PAH and HIV epidemiology in France. The secondary objective was to describe the evolution of patient characteristics at diagnosis of PAH-HIV over the period 2007-2022, especially before and after 2015, as well as the response to treatment, survival and prognostic factors.

METHODS

Patient selection

We performed a population-based study using clinical, functional, and hemodynamic data of every patient registered as PAH-HIV in the French PH registry from 2007 to 2022. The French PH registry is the registry of the French PH Network, which includes since 2007 all patients with PH from the French PH national referral center (Department of Respiratory and Intensive Care Medicine, Hôpital Bicêtre, Le Kremlin-Bicêtre, France) and 25 associated centers across France. The French PH registry is conducted in accordance with French bioethics laws (French Commission Nationale de l'Informatique et des Libertés), approval number 842063 on the 24th of may, 2003. All patients provided informed consent. The diagnosis of PH was established by right heart catheterization (RHC) according to the former definition from the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines on PH (2015) [31]. This project was examined and approved by the members of the scientific committee of the French PH registry on April 29, 2022.

Data on PAH-HIV incidence, PAH and HIV incidence between 2007 and 2022

The incidence of PAH-HIV and of PAH over the period 2007-2022 in France was reported thanks to the French PH registry which is supposed to exhaustively report every case of precapillary PH in France. The incidence was defined as new cases of PAH-HIV and of PAH per

year during this period. Data on HIV incidence were obtained from the 'Santé Publique France' website [32], relying on mandatory declarations.

Clinical, functional, biologic and hemodynamic characteristics at diagnosis

We reviewed clinical data (age, medical history, treatments and physical examination), dyspnea assessed by modified New York Heart Association (NYHA) functional class, 6-minute walk distance (6MWD), pulmonary functional tests (PFTs), including diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DLCO) and arterial blood gases. For subjects with a NYHA functional class IV unable to perform the 6MWD, the distance was imputed as zero meters. Brain natriuretic peptide (BNP) was considered as increased when it was over 50 ng/L and N-terminal prohormone of BNP (NT-proBNP) when it was over 300 ng/L. We also reviewed hemodynamic measurements measured by RHC including mean pulmonary artery pressure (mPAP), pulmonary artery wedge pressure (PAWP) and right atrial pressure (RAP). Cardiac output (CO) was measured by the standard thermodilution technique, and the cardiac index (CI) was calculated as the CO divided by body surface area. Pulmonary vascular resistance (PVR) was calculated as [(mPAP-PAWP)/CO]). Precapillary PH was defined as mPAP ≥ 25 mmHg and PAWP ≤ 15 mmHg and combined precapillary and postcapillary PH was defined as mPAP ≥ 25 mmHg, PAWP > 15 mmHg and PVR > 3 WU based on the former definition from the ESC/ERS guidelines on PH, (2015) [31]. Furthermore, we reviewed medical history related to HIV disease from the PH registry, including the date of HIV diagnosis, and at the diagnosis of PAH-HIV: HIV stage, CD4 count, and viral load as well as data about HIV treatments. At times, we reached out to infectious diseases centers in France to supplement the data from the French PH registry, which were occasionally incomplete.

High-resolution computed tomography of the chest

We retrieved reports of the initial high-resolution computed tomography scans of the chest, interpreted by radiologists from each center. We recorded parenchymal abnormalities (including emphysema, ground glass opacities) and mediastinal abnormalities such as mediastinal lymph node enlargement.

Follow-up and clinical outcomes

Medical therapies approved for PAH, including prostacyclin derivatives, endothelin receptor antagonists (ERA) and phosphodiesterase type-5 inhibitors (PDE5i), were administered to patients according to the clinical judgment and discretion of individual treating physicians. Clinical, functional, and hemodynamic follow-up data at the second evaluation and at last reassessment as well as time to death or lung transplantation were collected and entered into the French PH registry.

Statistical analysis

The analyses were carried out using GraphPad Prism 8 (GraphPad Software Inc., La Jolla California USA). We reported continuous variables as mean (SD), and categorical variables as number and frequency (percentage of group). Comparisons between continuous variables in patients diagnosed before and after 2015 were performed using the Student's t-test and comparisons between categorical variables were conducted using the Chi-squared test and Fisher's exact test, as appropriate. Comparisons between continuous variables before and after treatment were performed using the paired Student's t-test for quantitative variables, the Wilcoxon matched-pair signed rank test for ordinal variables and the McNemar's test for qualitative binary data. Time to death or transplantation was analyzed by the Kaplan-Meier method and the survival without transplantation were compared using the logrank test. Differences were considered significant when p was less than 0.05.

RESULTS

Incidence of PAH-HIV compared with incidence of PAH and HIV during the 2007-2022 period

The incidence of PAH-HIV has been falling since 2007, with 23 new cases in 2007 compared with 7 in 2022, registered in the French PH registry **(Figure 1.A)**. HIV represented 6,1% of all PAH cases in 2007, compared with 1.7% in 2022 **(Figure 1.B)**. In parallel, PAH incidence has remained stable during this period with 378 new cases in 2007 compared with 409 registered in the French PH registry in 2022 **(Figure 1.A)**. HIV incidence has also remained stable overall in France during the same period with 6500 new cases in 2007 and 5738 in 2022, except a 25% drop in incidence between 2019 and 2020, attributed to delayed screening and reduced comprehensiveness of mandatory reporting amidst the context of the SARS-CoV-2 pandemic **(Figure 1.A)**.

Clinical, functional, biological and hemodynamic characteristics at diagnosis

Between 2007 and 2022, 251 PAH-HIV patients were registered in the French PH registry. The mean age of the population at diagnosis was 49 $\pm$ 9 years, with a predominance of males (female/male ratio 0.74) **(Table 1)**. Most patients were current or former smokers (74%), 57% had hepatic comorbidities (hepatitis C virus (HCV), hepatitis B virus (HBV), cirrhosis, or portal hypertension), 15% had taken interferon-alpha for HCV, and 33% were declared intravenous drug users. The mean time between the diagnosis of HIV and the identification of PAH was 17 $\pm$ 9 years but 10 patients were diagnosed with HIV at the same time as PAH. ART was introduced on average 5 $\pm$ 6 years after HIV diagnosis. On average, 18 months elapsed between the first reported symptoms of PAH and the first assessment. At the diagnosis of PAH-HIV, mean CD4 was 399 cells/mm3 and viral load was detectable in 35% of patients. Regarding ART treatment at PAH diagnosis, we had information for 153 patients. Among them, 65 were treated by protease inhibitors, 49 by integrase inhibitors, 109 by nucleoside reverse transcriptase inhibitors, and 40 by non-nucleoside reverse transcriptase inhibitors **(Table 1)**. Concerning the characteristics of PAH at diagnosis, patients had mild to severe functional impairment at diagnosis, with 142 (57%) patients in NYHA functional class III or IV and a mean 6MWD of 404 $\pm$ 116m. PFTs showed normal or mild abnormalities in lung volume

measurements in most patients with mean forced vital capacity (FVC) of 86 ± 24% of predicted, and mean forced expiratory volume during the first second (FEV1) 75 ± 23% of predicted. Diffusing capacity was decreased in most patients with a mean DLCO of 48 ± 17% of predicted. Most patients had mild hypoxemia. BNP or NT-proBNP were increased in 74% of patients. One hundred and twelve patients performed high resolution computed tomography (HRCT) of chest, and the most frequent abnormality was emphysema, present in more than one third of patients. Right heart catheterization showed pre-capillary PH in 237 patients (94%) and combined pre- and post-capillary PH in 14 patients (6%) with a mean mPAP of 44 ± 11 mmHg, a CI of 2.8 ± 0.9 L/min/m² and PVR of 7.9 ± 4.0 WU **(Table 1)**. None of the patients exhibited isolated post-capillary PH.

Evolution of Clinical, functional, biological and haemodynamic characteristics before and after 2015

The clinical characteristics of patients at diagnosis changed between the 2007-2015 and 2015-2022 periods, with a higher age at diagnosis after 2015, a higher body mass index (BMI) and a higher proportion of smokers or ex-smokers **(Table 1)**. Conversely, there were fewer intravenous drug users after 2015 than before and fewer patients with hepatic comorbidities **(Table 1 and Figure 3)**. Functional characteristics were comparable between the two periods (6MWD, FVC, FEV1, DLCO, PaO2 in room air), as was the number of patients with increased NT pro BNP. Concerning hemodynamic severity during the 2 periods, mPAP was lower after 2015 (mPAP 42 ± 8 mmHg vs. 45 ± 12, p=0.047), as was the CI (2.7 ± 0.7 L/min/m2 vs. 2.9 ± 1 L/min/m2, p=0.028), resulting in no statistical difference in PVR between the 2 periods (PVR 7.4 ± 3.2 vs. 8.2 ± 4.3 WU, p=0.15) **(Table 1 and Figure 4)**.

Evolution of the characteristics of HIV infection at PAH diagnosis before and after 2015

The number of patients with a positive viral load at PAH diagnosis appeared comparable between the two periods, affecting around 1/3 of patients **(Table 1)**. The levels of CD4 count were also similar at PAH diagnosis between the two periods. However, HIV seemed more advanced in the pre-2015 period: the last known stage was stage A for only 28% of patients before 2015, compared to 51% in the post-2015 period. More patients were treated with

protease inhibitors at the time of PAH diagnosis before 2015 than after (52% vs 26%, p=0.002), while conversely, more patients have been treated with integrase inhibitors since 2015 (54% vs 19%, p=0.0001). The number of patients treated with nucleoside and non-nucleoside reverse transcriptase inhibitors was comparable over the two periods (71% and 26% respectively, p=0.71 et p=0.13) **(Table 1)**.

Treatments and response to approved drugs for pulmonary arterial hypertension

After PAH-HIV diagnosis, approved drugs for PAH were initiated in 154 patients in monotherapy (ERA or PDE5i), in 39 patients as dual therapy (ERA and PDE5i), and as triple therapy (ERA, PDE5i and prostacyclin derivative) in 2 patients **(Table 2)**. Among the 195 patients who received treatment, 153 were reassessed with a RHC after the initiation of PAH-approved drugs, with a mean delay of 10 $\pm$ 15 months. Of the 42 patients who were not reassessed, 16 died within a year of diagnosis and the others were lost to follow-up. Among patients who were reassessed, a significant improvement in dyspnea, in biologic tests (increased BNP/NTproBNP) and hemodynamic parameters (CO, CI, PVR) was observed after initiation of PAH specific therapy. However, there was no difference in 6-minute walk distance **(Table 2)**. One hundred and eleven patients had a last assessment with RHC, with a mean delay of 58 $\pm$ 41 months, and hemodynamic improvement appeared to be stable in hemodynamic parameters. Dual therapy with ERA and PDE5i was started in 3 more patients (36 in total) in this population.

Treatments and evolution of PAH in patients treated with ART only

Thirty patients were treated with ART only at the time of PAH-HIV diagnosis, with no specific PAH treatment, and had an hemodynamic reassessment. These patients were less smokers, less intravenous drug users, had higher 6MWD, and had less severe hemodynamic impairment at diagnosis with mPAP 40 $\pm$ 11mmHg and PVR 5.8 $\pm$ 4.5 WU **(Table 3)**. A significant improvement in NYHA score and in mPAP was observed but not in 6MWD nor in PVR. Approved drugs for PAH were finally initiated in 9 patients (30%) in monotherapy (ERA or PDE5i), and in 3 patients (10%) as dual therapy (ERA and PDE5i) after the second evaluation.

Long-term outcomes

One hundred and eleven patients died during the follow-up, with a mean delay of 49 ± 48 months after PAH-HIV diagnosis and a median survival of 12,5 years. Four patients were transplanted, among whom 1 finally died 2 days after TP and the 3 others were still alive at the time of analysis, respectively 6, 7, and 8 years after their transplantation. Survival without transplantation at 1, 3, 5 and 10 years was 87%, 76%, 68% and 56% respectively **(Figure 2.A)**. The cause of death was known in 59 patients and included 14 due to right heart failure (24%). There was no significant difference in survival without transplantation when the diagnosis of PAH-HIV was made before and after 2015 (survival at 1, 3 and 5 years was 85%, 77% and 67% before 2015, and 88%, 77% and 67% after 2015, p=0.8) **(Figure 2.B)**. Nine patients over 46 died due to right heart failure (20%) before 2015, and 5 patients over 13 (38%) after 2015.

DISCUSSION

Pulmonary arterial hypertension is a rare but severe complication of HIV infection, generally appearing several years after the onset of HIV infection. In this study, we described the evolution of the incidence of PAH-HIV in the French PH registry between 2007 and 2022 as well as the evolution of the phenotype over the same period. We observed a decrease in the incidence of PAH-HIV since 2007, while the total incidence of PAH and the incidence of HIV remained relatively stable during the same period. PAH at diagnosis remained severe and there was a significative functional and hemodynamical improvement after initiation of PAH therapy. The phenotype of PAH-HIV has evolved over the period from 2007 to 2022, with older patients, with a higher BMI and more often smokers or ex-smokers, but with fewer liver comorbidities and less toxic intake.

Here, we demonstrated a decrease of the incidence of PAH-HIV in the last 15 years in France. Several hypotheses could explain the reduced incidence of PAH in this population. First, HIV patients are being treated earlier in the history of the disease in 2022 than in 2007. Indeed, until 2009/2010, patients were only treated when CD4 counts were <200 cells/µL. Then studies validated the introduction of treatment for CD4 counts between 200 and 350 cells/µL [33] then as soon as CD4<500 cells/µL [34–36] and since the INSIGHT START study published in 2015 [30], patients are treated from diagnosis and regardless of their CD4 count. This may have contributed to better control of viral load and therefore a reduction in the chronic inflammation, which could influence the pulmonary vascular remodeling involved in PAH-HIV. Then, studies have already shown the adverse effect of illicit drugs (such as stimulants and opioids) on pulmonary endothelium, which could explain the higher prevalence of PAH in HIV-positive drug-using patients [9, 16]. The observed decrease in intravenous drug use may contribute to the lower incidence of PAH in HIV-positive individuals. Finally, a lower percentage of patients with hepatic comorbidities and improved control of co-morbidities, such as HCV viral infections, may also contribute to prevent the development of PAH. Notably, HCV is currently more widely treated, as recommended by the 2016 EASL (European Association for the Study of the Liver) guidelines, where all patients, regardless of hepatic fibrosis stage, should be treated [37]. Advancements in therapeutics, with the advent of direct-acting antivirals from 2014, have also enabled the discontinuation of PAH-inducing

drugs like alpha interferons [38], which were officially ruled out in the EASL (European Association for the Study of the Liver) recommendations of 2021.

Regarding the evolution of hemodynamic severity over the 2007-2022 period, there was no significant difference in PVR before and after 2015. However, mPAP was significantly lower after 2015 than before, but cardiac output was also lower which result in similar PVR. This could be related to a lower proportion of hepatic comorbidities/cirrhosis since 2015, resulting in less cardiac hyperoutput. Indeed, since 2015, the number of patients with hepatic comorbidities, primarily viral hepatitis, has decreased. Moreover, the phenotype of patients has evolved: patients diagnosed with PAH-HIV after 2015 tended to be older, have a higher BMI, and were more likely to be smokers or ex-smokers. This trend is also observed in other types of PAH, such as idiopathic PAH, where a new 'lung phenotype' has been described [39] and characterizes patients with features reminiscent of Group 3 PAH, older and with more smoking habits.

In the whole population, we observed a clinical and hemodynamical response to PAH treatment. It was in accordance with other previously published studies investigating the effect of specific PAH therapies combined or not with ART in the PAH-HIV population [14, 25, 40, 41]. A significant improvement in dyspnea and mPAP was also observed after initiation of PAH specific therapy in patients treated with ART only, but not in the CO. The predominant effect of treatment on mPAP and not on cardiac output might suggest an effect of ART on pulmonary vascular remodeling, thanks to an anti-inflammatory effect. A potentially direct beneficial effect of protease inhibitors on experimental vascular remodeling has been suggested on PAH induced by monocrotaline on rats [24], via inhibition of Akt phosphorylation. However, most studies since then have reported a potentially deleterious effect of long-term ART on pulmonary endothelial function and vascular remodelling, especially protease inhibitors [29]. Likewise, long term treatment with ART could increase production of endothelial cell adhesion factors such as Vascular Cell Adhesion Molecule 1 (VCAM-1), InterCellular Adhesion Molecule (ICAM-1), and E-selectin, leading to chronic vascular inflammation, and decreased endothelium-dependent vasorelaxation via inhibition of the Nitric Oxide (NO) synthase system, increased oxidative stress, leading to endothelial proliferation, endothelial dysfunction and thus potentially contributing to exacerbate

underlying HIV-related PAH [16, 20, 21, 42, 43]. In particular, protease inhibitors (PIs) are thought to induce endothelial dysfunction via a lipoatrophy-induced reduction in leptin levels, which induces an increase in Nox1 expression. This elevation in Nox1 expression leads to elevated vascular CCR5 levels, promotes vascular inflammation, reduces NO bioavailability, and consequently, leads to impaired endothelium-dysfunction [29]. However, in these same studies, it was suggested that patients undergoing ART had a reduced risk of PAH. This implies that the risk of HIV-related PAH can be reduced by decreasing chronic inflammation thanks to ART, and that any potential negative effects of ART-induced cardiovascular toxicity may not outweigh the benefits of viral suppression. Furthermore, PIs have been less prescribed since the advent of integrase inhibitors in the 2010s, which have fewer adverse effects and drug interactions. However, it is only since the 2021 recommendations from the European AIDS Clinical Society (EACS) that PIs are considered as a second-line option [44]. It is likely, though, that due to drug interactions with ERAs and PDE5i, affecting the digestive tolerance of these medications, this drug class has been less prescribed in PAH-HIV patients.

The prognosis remained poor, as 111 of the 251 patients died during follow-up, on average 49 $\pm$ 48 months after PAH-HIV diagnosis, with a 5-year survival rate of 68%. This is in line with another cohort published in 2010 [25], which reported a 5-year survival rate of 63%, but lower than in a recent study based on the Spanish PH Register, reporting a 5-year survival rate of 74% [3]. Transplantation appears to be a possible option for patients with severe PAH-HIV as 4 patients were transplanted amongst whom 3 were still alive at the time of analysis.

This study had some limitations. Out of the 195 patients treated with specific PAH therapy, only 153 underwent re-evaluation through right heart catheterization. Among the 42 patients who were not reassessed, 16 died within a year of diagnosis and the others were lost to follow-up. This may have induced a bias in the analysis of response to treatment, as data from reassessment of patients who died, and potentially responded less well to treatment, were not available and therefore not analyzed. Second, some data were missing for some patients, especially about functional tests or about HIV history. Finally, the period of inclusion included the COVID-19 pandemics period and we can't exclude that the pandemics has also contributed to the decline in diagnosis and incidence of PAH-HIV. However, the incidence of both PAH and

HIV has remained stable during this period, implying that physicians continued to diagnose these diseases during this period.

CONCLUSION

In conclusion, the incidence of PAH-HIV in the French network has decreased during the period 2007-2022, while the incidence of PAH and HIV has remained stable. The phenotype of incident PAH-HIV patients has evolved, but these changes do not seem to impact the hemodynamic severity at diagnosis and survival. Research is still needed to better understand the pathophysiology of PAH in HIV and the impact of HIV treatments on PAH itself.

ANNEXES

Table 1. Characteristics of patients with PAH-HIV at the time of PAH diagnosis.

	n	All population (251)	2007-2014 (162)	2015-2022 (89)	p-value
Demographic data					
Age, y (SD)	251	49 (9)	47 (8)	53 (11)	**0.0001**
Gender, F/H (ratio)	251	108/143 (0.74)	74/88 (0.84)	34/55 (0.62)	0.29
BMI, kg/m2 (SD)	251	22.4 (4.6)	21.7 (4.4)	23.5 (4.8)	**0.005**
Smoker or ex-smoker, n (%)	251	186 (74)	128 (79)	87 (98)	**0.0001**
Intravenous drug user, n (%)	251	82 (33)	62 (38)	20 (22)	**0.01**
Hepatic comorbidities, n (%)	251	143 (57)	101 (62)	42 (47)	**0.024**
Interferon intake, n (%)	251	38 (15)	26 (16)	12 (13)	0.71
Characteristics of HIV infection at PAH diagnosis					
Time HIV diagnosis-PAH diagnosis, y (SD)	173	17 (9)	15 (8)	19 (10)	**0.012**
CD4 at diagnosis of PAH, cells/mm3 (SD)	129	399 (246)	389 (229)	417 (273)	0.52
Detectable viral load at PAH diagnosis, n (%)	129	45 (35)	26 (34)	19 (37)	0.85
Treatments by ART					
Time HIV diagnosis – ART therapy, y (SD)	147	5 (6)	6 (7)	4 (6)	0.11
Treatment by protease inhibitors, n (%)	153	65 (43)	50 (52)	15 (26)	**0.002**
Treatment by integrase inhibitors, n (%)	153	49 (32)	18 (19)	31 (54)	**0.0001**
Treatment by NRTIs, n (%)	153	109 (71)	67 (70)	42 (74)	0.71
Treatment by NNRTIs, n (%)	153	40 (26)	21 (22)	19 (33)	0.13
Functional parameters					
NYHA functional class, n (%) **I-II** **III-IV**	251	 109 (43) 142 (57)	 66 (41) 96 (59)	 43 (48) 46 (52)	0.29
6MWD, m (SD)	184	404 (116)	405 (111)	401 (128)	0.8
FEV1, % of predicted (SD)	186	75 (23)	77 (23)	71 (23)	0.09
FVC, % of predicted (SD)	184	86 (24)	87 (22)	85 (28)	0.58
FEV1/CV < 70%, n (%)	181	26 (14)	13 (12)	13 (18)	0.28
TLC < 80% of predicted, n (%)	168	30 (18)	12 (12)	18 (28)	**0.01**
DLCO, % of predicted (SD)	101	48 (17)	47 (16)	48 (17)	0.69
PaO2 on room air, mmHg (SD)	153	70 (15)	71 (13)	67 (18)	0.052
PaCO2 on room air, mmHg (SD)	152	34 (7)	34 (8)	35 (7)	0.76
Hemodynamics					
mPAP, mmHg (SD)	251	44 (11)	45 (12)	42 (8)	**0.047**
PAWP, mmHg (SD)	233	8.9 (4.2)	8.8 (4.4)	9 (3.7)	0.6
CO, L/min (SD)	242	4.9 (1.6)	5 (1.7)	4.7 (1.1)	0.07
CI, L/min/m2 (SD)	232	2.8 (0.9)	2.9 (1.0)	2.7 (0.7)	**0.028**
PVR, WU (SD)	229	7.9 (4.0)	8.2 (4.3)	7.4 (3.2)	0.15
Biologic tests					
Increased NT-pro BNP, n (%)	201	148 (74)	84 (72)	64 (76)	0.52
Radiological characteristics on HRCT					
Enlarged mediastinal lymph node, n (%)	112	17 (15)	11 (18)	6 (11)	0.31
Emphysema, n (%)	112	42 (38)	23 (39)	19 (36)	0.85
Ground glass opacities, n (%)	112	13 (12)	7 (12)	6 (11)	1
Specific treatments for PAH after initial assessment					
Monotherapy, n (%)	251	153 (61)	110 (68)	43 (48)	**0.003**
Dual therapy, n (%)	251	39 (15)	11 (7)	28 (31)	**0.0001**
Tritherapy, n (%)	251	2 (1)	1 (0.6)	1 (1.1)	1
Antiretroviral therapy alone, n (%)	251	44 (17)	30 (19)	14 (16)	0.61

Values are expressed as the mean (SD) or as number and frequency. The p-values refer to a comparison between 2007-2014 and 2015-2022 periods. 6MWD: 6-minute walk test; ART: antiretroviral therapy; BMI: body mass index; BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; DLCO: diffusing capacity for carbon monoxide corrected for hemoglobin level; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HIV: human immunodeficiency virus; HRCT: high-resolution computed tomography; mPAP: mean pulmonary artery pressure; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAH-HIV: PAH associated with HIV; *PaO2: partial pressure of oxygen in arterial blood; PaCO2: partial pressure of carbon dioxide in arterial blood; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; TLC: total lung capacity.*

Table 2. Characteristics of patients with PAH-HIV at the time of PAH diagnosis, at the time of second evaluation after initiation of PAH approved drugs (mean delay 10 ± 15 months) and at the last reassessment (mean delay 58 ± 41 months) for patients treated by PAH therapy and who had a reevaluation.

	n	Baseline (n=153)	Second evaluation (n=153)	p-value		Last evaluation (n=133)
Demographic data						
Age, years diagnostic		48 (10)	-			-
Gender, F/M (ratio)		76/77 (1)	-			-
BMI, kg/m2		22.8 (4.7)	-			-
Smoker or ex-smoker, n (%)		112 (74.6)	-			-
Intravenous drug users, n (%)		55 (39.6)	-			-
1st symptoms-1st assessment, m		18.9 (36.5)	-			-
Functional parameters						
NYHA functional class, n (%) **I-II** **III-IV**	153	 73 (47.7) 80 (52.3)	 112 (73) 41 (27)	**0.001**		 100 (75) 33 (25)
Six-minute walk distance, m	106	418 (120)	428 (135)	0.30		426 (142)
PaO2 on room air, mmHg	47	69 (17)	68 (18)	0.77		66 (21)
Biologic tests						
Increased BNP/NTproBNP, %	87	64 (74)	36 (41)	**0.001**		43 (38)
Hemodynamics						
mPAP, mmHg	152	44.9 (10.8)	37.4 (9.7)	**0.0001**		35.4 (12.3)
CO, L/min	146	4.7 (1.5)	6.0 (1.7)	**0.0001**		5.8 (1.8)
CI, L/min/m^2	109	2.7 (0.8)	3.4 (0.9)	**0.0001**		3.2 (0.8)
PVR, WU	133	8.6 (4.1)	5.5 (5.7)	**0.0001**		4.8 (2.9)
PAH-approved drugs						
ERA monotherapy, n (%)		-	89 (58)	-		72 (54.1)
PDE5i monotherapy, n (%)		-	29 (19)	-		23 (17.3)
ERA + PDE5i, n (%)		-	33 (21.7)	-		36 (27.1)
ERA + PDE5i + Prostacyclin derivative, n (%)		-	2 (1.3)	-		2 (1.5)

Values are expressed as the mean (SD) or as number and frequency. The p-values refer to a comparison between baseline and the second evaluation. BMI: body mass index; BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; ERA: endothelin receptor antagonist; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAH-HIV: PAH associated with HIV*; PaO2: partial pressure of oxygen in arterial blood; PDE5i: phosphodiesterase 5 inhibitors; PVR: pulmonary vascular resistance.*

Table 3. Characteristics of patients with PAH-VIH at the time of diagnosis, at the time of second evaluation after initiation of PAH approved drugs (mean delay 17 ± 14 months) and at the last reassessment (mean delay 57 ± 45 months) for patients treated by antiretrovirals only (without any PAH therapy) and who had a reevaluation (n=30).

	n	Baseline (n=30)	Second evaluation (n=30)	p-value	n		Last evaluation
Demographic data							
Age, years diagnostic	30	49 (8)	-				-
Gender, F/M (ratio)	30	12/18 (0.7)	-				-
BMI, kg/m2 (SD)	30	23 (5)	-				-
Smoker or ex-smoker, n (%)	30	18 (64)	-				-
Intravenous drug users, n (%)	30	7 (23)	-				-
1st symptoms-1st assessment, m (SD)	30	17 (14)	-				-
Functional parameters							
NYHA functional class, n (%) **I-II** **III-IV**	30	 14 (47) 16 (53)	 23 (77) 7 (23)	**0.01**	24		 21 (88) 3 (22)
Six-minute walk distance, m	20	447 (72)	465 (80)	0.22	21		459 (95)
PaO2 on room air, mmHg (SD)	4	65 (11)	76 (20)	0.09	9		79 (17)
Biologic tests							
Increased BNP/NTproBNP, n (%)	16	8 (50)	7 (44)	0.99	17		6 (35)
Hemodynamics							
mPAP, mmHg (SD)	30	40 (11)	34 (12)	**0.02**	14		31.4 (8.2)
CO, L/min (SD)	29	5.7 (2.1)	5.7 (1.6)	0.97	13		5.1 (1.1)
CI, L/min/m²(SD)	22	3.1 (1.0)	3.1 (0.9)	0.91	12		2.8 (0.6)
PVR, WU (SD)	27	5.8 (4.5)	5.1 (3.5)	0.45	13		4.0 (1.5)
PAH-approved drugs							
ERA monotherapy, n (%)		-	-	-			3 (10)
PDE5i monotherapy, n (%)		-	-	-			6 (20)
ERA + PDE5i, n (%)		-	-	-			3 (10)
ERA + PDE5i + Prostacyclin derivative, n (%)		-	-	-			0

Values are expressed as the mean (SD) or as number and frequency. The p-values refer to a comparison between baseline and the second evaluation. BMI: body mass index; BNP: brain natriuretic peptide; CI: cardiac index; CO: cardiac output; ERA: endothelin receptor antagonist; mPAP: mean pulmonary artery pressure; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; NYHA: New York Heart Association; PAH: pulmonary arterial hypertension; PAH-HIV: PAH associated with HIV; *PaO2: partial pressure of oxygen in arterial blood; PDE5i: phosphodiesterase 5 inhibitors; PVR: pulmonary vascular resistance.*

Figure 1. Evolution of the epidemiology of PAH-HIV, PAH and of HIV in France between 2007 and 2022.

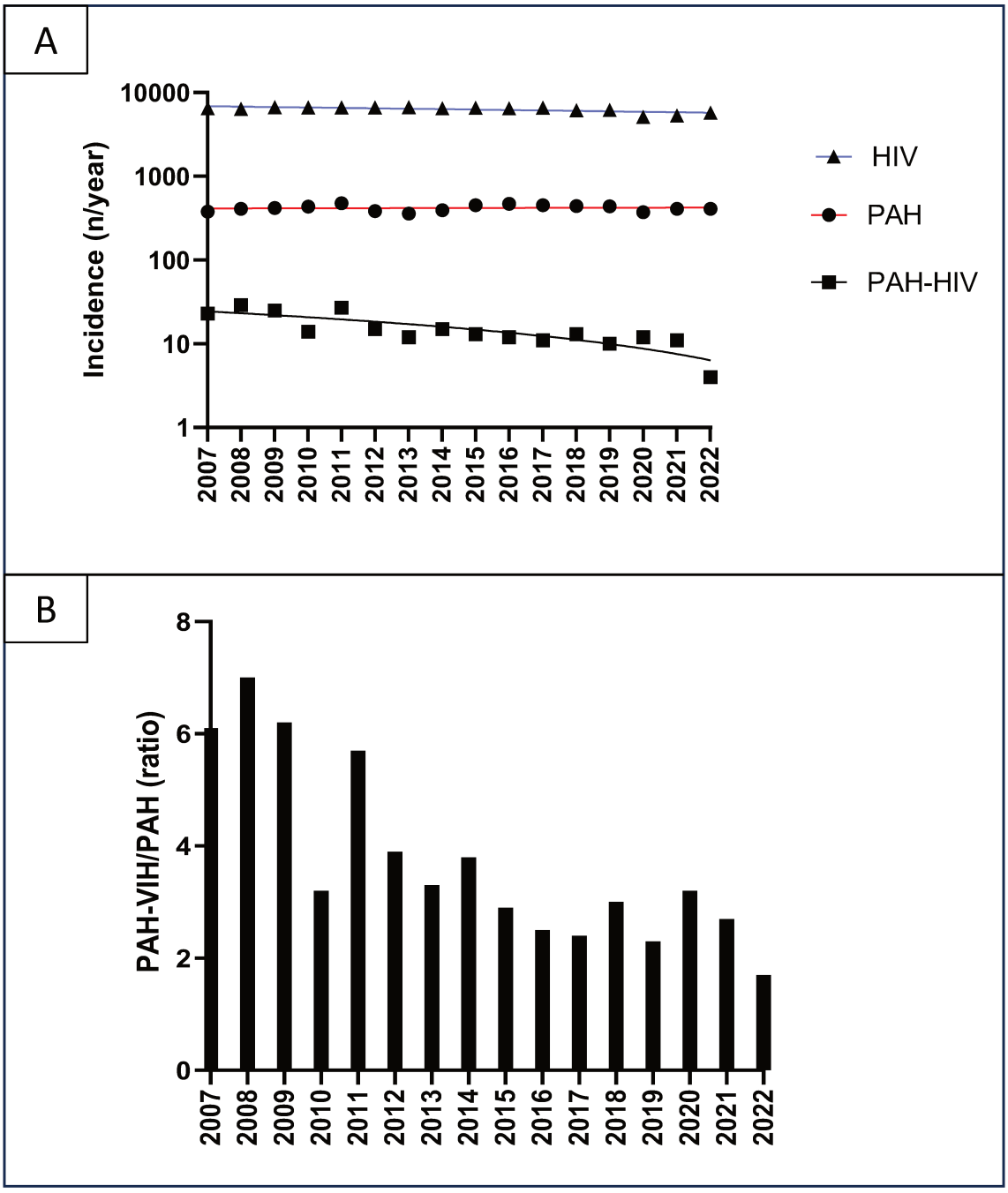


Figure 1.A: Incidence of PAH-HIV in the French registry from 2007 to 2022 (n), incidence of all-causes PAH in the French PH registry from 2007 to 2022 (n), incidence of HIV in France from 2007 to 2022. For HIV incidence, data are collected from mandatory reporting registred from 'Santé publique France'. Figure 1.B: Ratio of PAH-HIV/PAH in the French PH registry from 2007 to 2022 (%). HIV: human immunodeficiency virus ; PAH: pulmonary arterial hypertension; PAH-HIV: PAH associated with HIV.

<u>Figure 2.</u> Survival without transplantation of patients with PAH-HIV in the whole population diagnosed between 2007 and 2022 and in patients diagnosed in the 2007-2014 and 2015-2022 periods.

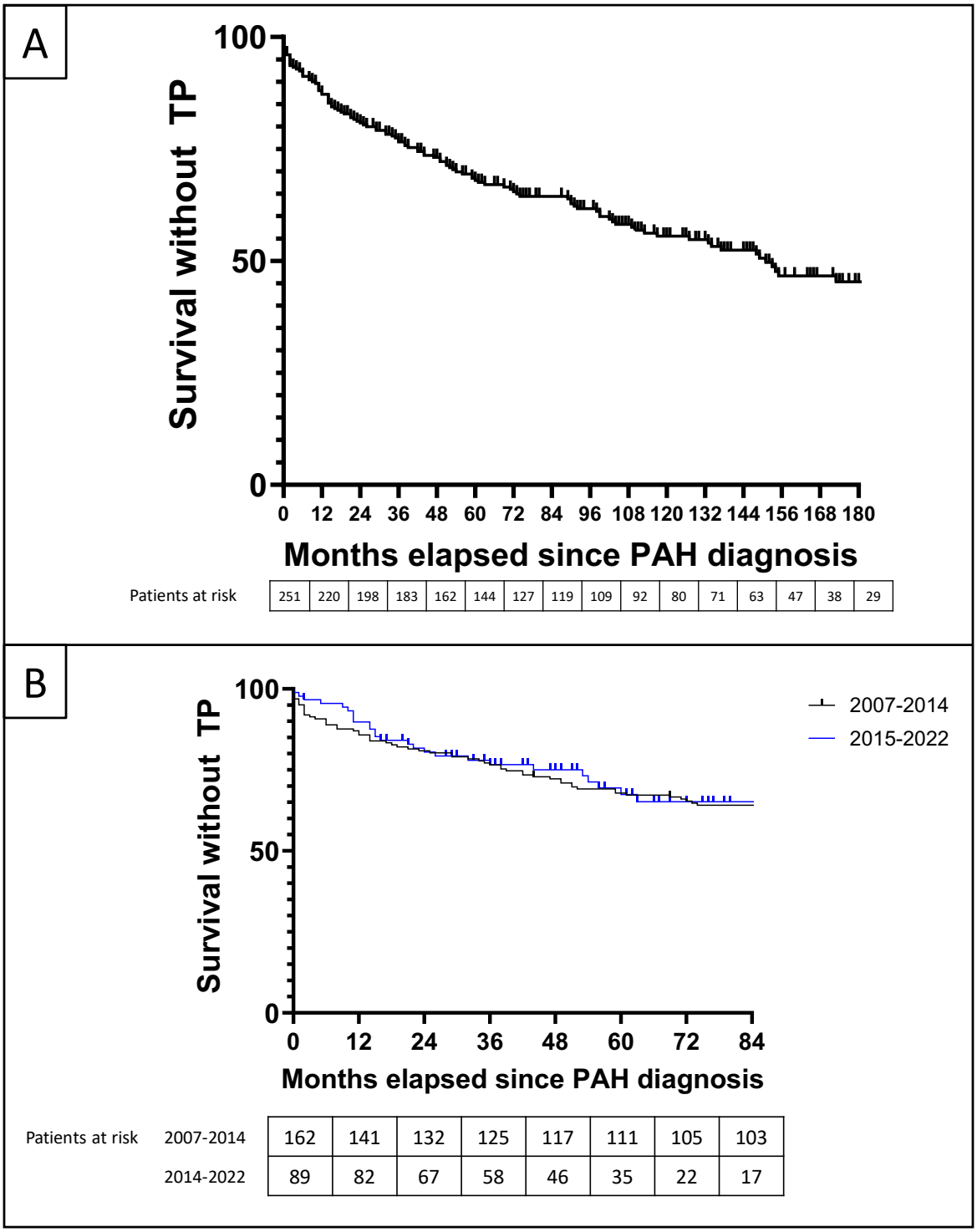
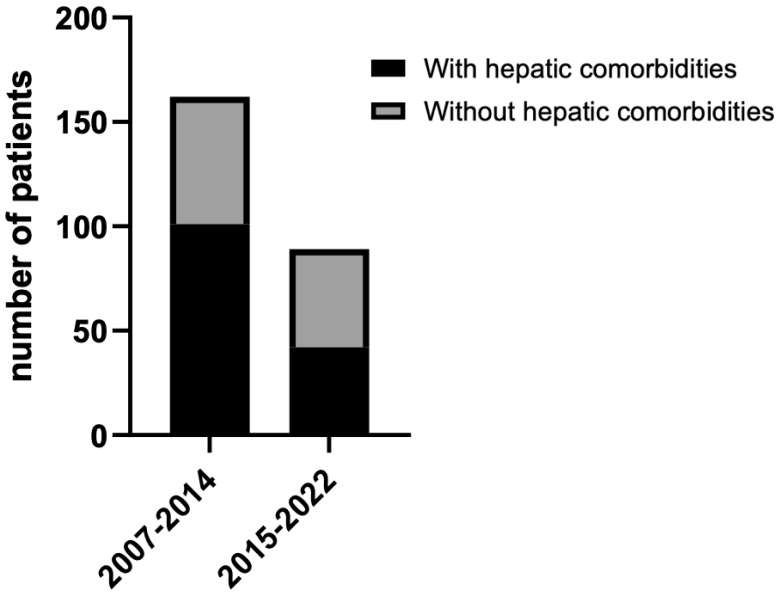


Figure 2.A: Overall transplant-free survival at 1, 3, and 5 years was 87%, 76%, and 68% respectively. Figure 2.B: Transplant-free survival, before and after 2015, p=0.8. PAH: pulmonary arterial hypertension; TP: transplantation.

<u>Figure 3.</u> Proportion of patients with hepatic comorbidities among patients with PAH-HIV before and after 2015, p=0.024.



<u>Figure 4.</u> Hemodynamic characteristics according to the period of PAH diagnosis.

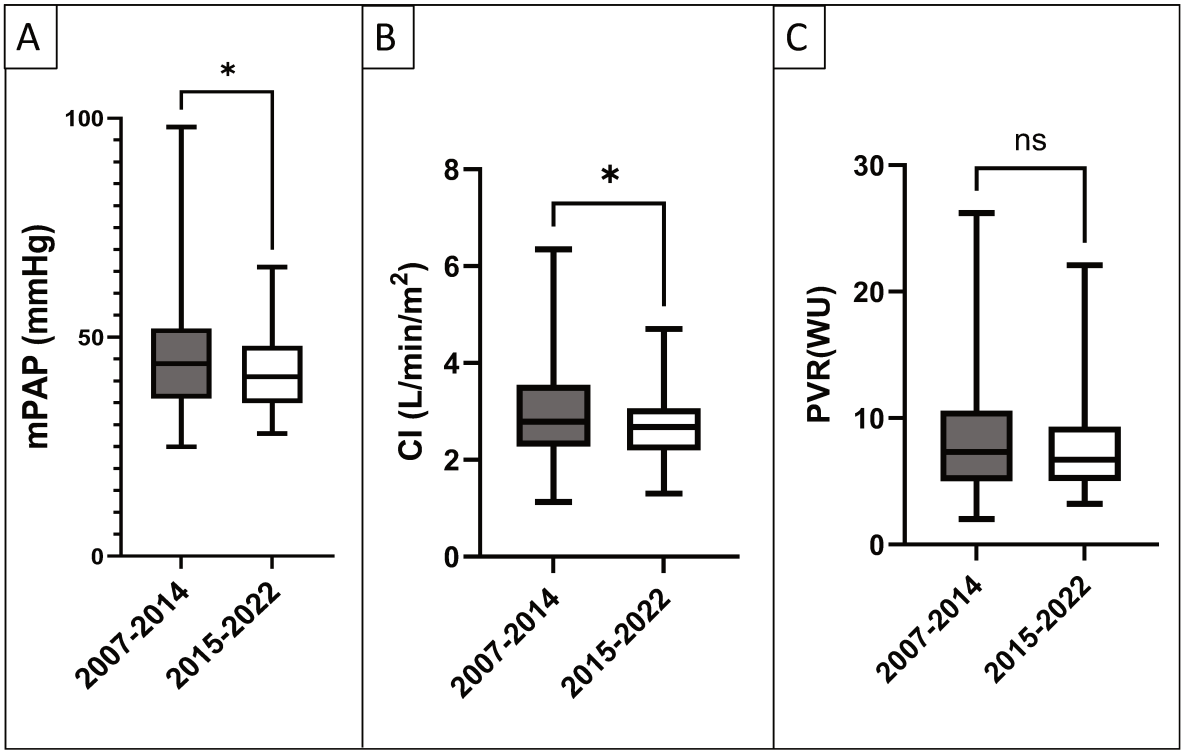


Figure 4. Hemodynamic characteristics by time period. Figure 4.A: mPAP (mmHg), p=0.047. Figure 4.B :CI (L/min/m^2), p=0.028. Figure 4.B: PVR (WU). CI: cardiac index; mPAP: mean pulmonary artery pressure; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance.

CONCLUSION

En conclusion, l'incidence de l'HTAP-VIH a diminué au cours de la période 2007-2022 en France, alors que l'incidence de l'HTAP et du VIH est restée stable. Le phénotype des patients atteints d'HTAP-VIH a évolué, les patients diagnostiqués depuis 2015 étant plus âgés, moins consommateurs de drogues intraveineuses, avec moins de comorbidités hépatiques, recevant une intervention plus précoce pour le VIH mais moins d'inhibiteurs de protéase. Cependant, ces changements ne semblent pas avoir eu d'impact sur la gravité hémodynamique au moment du diagnostic et sur la survie. Des recherches restent nécessaires pour mieux comprendre la physiopathologie de l'HTAP chez les personnes atteintes du VIH et l'impact des traitements contre le VIH sur l'HTAP elle-même.

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RESUME

Contexte : L'hypertension artérielle pulmonaire (HTAP) est une complication rare mais sévère de l'infection par le VIH. En France, il semble y avoir une diminution de l'incidence et de la sévérité au diagnostic de l'HTAP chez les patients VIH depuis 2007, mais aucune étude n'a rapporté l'évolution de l'épidémiologie et des caractéristiques de l'HTAP associée au VIH au cours de la dernière décennie.

Objectifs : Décrire l'évolution de l'incidence de l'HTAP dans la population VIH (HTAP-VIH) depuis 2007, en parallèle avec l'évolution de l'épidémiologie du VIH et de l'HTAP en France et décrire l'évolution des caractéristiques des patients au diagnostic de l'HTAP-VIH sur la période 2007-2022, ainsi que la réponse au traitement, la survie et les facteurs pronostiques.

Méthodes : Nous avons mené une étude observationnelle et rétrospective à partir du registre français de l'hypertension pulmonaire (HTP). Nous avons rapporté l'évolution de l'incidence de l'HTAP-VIH entre 2007 et 2022 ainsi que les caractéristiques cliniques, fonctionnelles et hémodynamiques. La réponse aux médicaments approuvés pour l'HTAP et la survie globale des patients atteints d'HTAP-VIH ont été également analysées.

Résultats : Entre 2007 et 2022, 251 patients atteints d'HTAP-VIH ont été enregistrés dans le registre français de l'HTP. L'incidence de l'HTAP-VIH a diminué depuis 2007 (23 nouveaux cas en 2007 contre 7 en 2022, le VIH représentant 6,1% de l'ensemble des cas d'HTAP en 2007 contre 1,7% en 2022), alors que l'incidence de l'HTAP et du VIH est restée stable. Le phénotype des patients atteints d'HTAP-VIH a évolué au moment du diagnostic, les patients diagnostiqués depuis 2015 étant plus âgés, plus souvent fumeurs, avec un IMC plus élevé, et présentant moins de comorbidités hépatiques. L'hémodynamique semble être similaire chez les patients diagnostiqués avant et après 2015, de même que la survie.

Conclusion : L'incidence de l'HTAP-VIH a diminué depuis 2007, tandis que l'incidence de l'HTAP et du VIH est restée stable. Le phénotype des patients atteints d'HTAP-VIH a évolué. L'introduction plus précoce du traitement antirétroviral indépendamment du taux de CD4 depuis 2015 pourrait expliquer la baisse de l'incidence de l'HTAP-VIH, mais ne semble pas avoir d'impact majeur sur la sévérité hémodynamique et la survie.

Mots clés : hypertension pulmonaire, hypertension artérielle pulmonaire, VIH, épidémiologie, pronostic, inflammation

UNIVERSITE DE POITIERS

Faculté de Médecine et de Pharmacie

SERMENT

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En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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RESUME

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