

# Updated mortality and causes of death in 2020–2021 in people with HIV: a multicenter study in France

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**Objective:** The aim of this study was to assess updated mortality and causes of death in people with HIV (PWH) in France.

**Design and methods:** We analyzed all deaths in PWH followed up between January 1, 2020, and December 31, 2021, in 11 hospitals in the Paris region. We described the characteristics and causes of death among deceased PWH, and evaluated the incidence of mortality and associated risk factors using a multivariate logistic regression.

**Results:** Of the 12 942 patients followed in 2020–2021, 202 deaths occurred. Mean annual incidence of death [95% confidence interval (95% CI)] was 7.8 per 1000 PWH (6.3–9.5). Forty-seven patients (23%) died from non-AIDS nonviral hepatitis (NANH)-related malignancies, 38 (19%) from non-AIDS infections (including 21 cases of COVID-19), 20 (10%) from AIDS, 19 (9%) from cardiovascular diseases (CVD), 17 (8.4%) from other causes, six (3%) from liver diseases, and five (2.5%) from suicides/violent deaths. The cause of death was unknown in 50 (24.7%) patients. Risks factors for death were age [adjusted odds ratio (aOR) 1.93; 1.66–2.25 by additional decade], AIDS history (2.23; 1.61–3.09), low CD4<sup>+</sup> cell count (1.95; 1.36–2.78 for 200–500 cells/ $\mu$ l and 5.76; 3.65–9.08 for  $\leq$ 200 versus  $>$  500 cells/ $\mu$ l), and viral load more than 50 copies/ml (2.03; 1.33–3.08), both at last visit.

**Conclusion:** NANH malignancies remained in 2020–2021 the first cause of death. COVID-19 accounted for more than half of the mortality related to non-AIDS infections over the period. Aging, AIDS history, and a poorer viro-immunological control were associated with death.

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## Introduction

Antiretroviral therapy (ART) has considerably reduced mortality among people with HIV (PWH) [1]. PWH now have a longer life expectancy [2], approaching that of the general population [3,4]. By 2030, almost 20% of PWH in France will be aged 70 years or over [5]. This demographic shift has led to a change in death causes [6], with an increase in non-AIDS-related mortality rates [7,8] due to age-related comorbidities [9]. The Paris region has the highest HIV prevalence in mainland France [10]. We aimed to provide up-to-date information on mortality rates, causes of death, and associated factors, and compare these findings with our previous study [11].

## Materials and methods

As previously described [11], we used Nadis (Advanced Biological Laboratories, L-2550 Luxembourg, Luxembourg), an electronic medical record system, to gather data on PWH (type 1 or 2), hepatitis B (HBV), or hepatitis C (HCV) receiving care in French public hospitals [12,13]. The cohort is registered on Clinical-Trial.gov (NCT02898987), and all participants provided informed consent. The study was conducted in compliance with the principles of the Declaration of Helsinki, the Public Health Code, and the European Union General Data Protection Regulation.

We enrolled all PWH, aged 18 years or more, who attended at least one visit as an inpatient or outpatient between January 1, 2020, and December 31, 2021, at one of the 11 participating hospitals in the North and East regions of Paris belonging to the COREVIH Ile-de-France East Cohort. Enrollment date was the date of first visit to a participating hospital during the study period, while the date of analysis was either the last visit before death during the study period or December 31, 2021. All PWH who died were consecutively registered in the database and promptly notified for a retrospective analysis of medical chart. We assessed:

- (1) Incidence of death, measured by crude mortality: the number of deaths divided by the number of PWH who were seen at least once during the study period.
- (2) Causes of death were determined using the same algorithm as our previous study [11], which was adjusted to account for the specificities of HIV infection [14]. This algorithm is used in all French mortality surveys, including the most recent one, 'Mortalité 2010' [15], facilitating the comparison between the two surveys.

- (3) Risk factors for death were evaluated by comparing participants' characteristics [sex, age, country of birth, HIV transmission group, AIDS status, time since HIV diagnosis, co-infections, and treatment-related information (duration of ART)] and biological data [CD4<sup>+</sup> T-cell count and plasma viral load (pVL) at baseline and last visit, presence of HBV (positive hepatitis B surface antigen) and/or HCV (positive HCV antibody)] between PWH who died and those who were still alive.
- (4) Risk factors for death were assessed through a multivariate logistic regression, including age in additional decades with the reference group being 18–27 years, gender, country of birth, HIV transmission group, time since HIV diagnosis in additional decades with the first decade as the reference, AIDS status, the latest CD4<sup>+</sup> T-cell count, the latest pVL, and presence of HBV and/or HCV co-infections.
- (5) We compared death rates, patient characteristics, and causes of death between individuals who died in 2020–2021 and those who died during our previous study conducted from 2011 to 2015. Univariate tests were used to compare data from the two studies.

We compared the incidence of deaths between surveys using the test of equal proportion, categorical variables using Fisher's exact test and quantitative variables using Wilcoxon rank sum tests. All tests were two-sided at the significance level of 0.05. We performed analyses using the R statistical package, version 4.1.1 (R Foundation, Vienna, Austria).

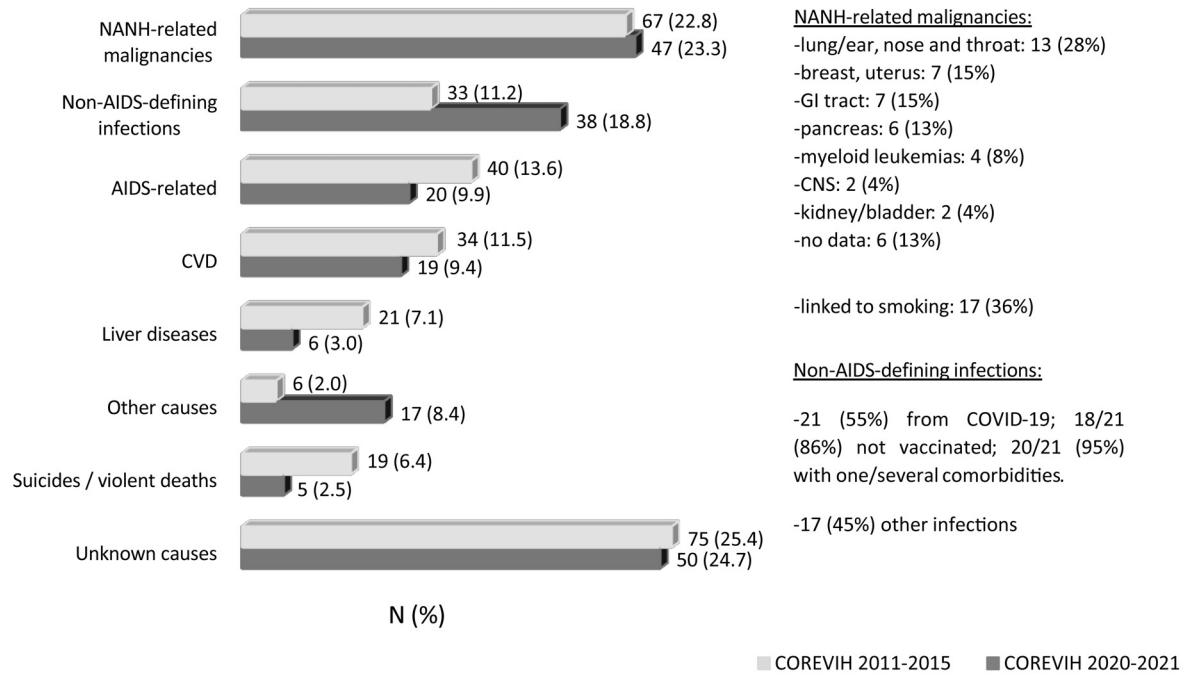
## Results

### General characteristics

The characteristics of the 12 942 PWH included in the study are described in Table 1. Over the 2-year period, 202 deaths occurred (96 in 2020 and 106 in 2021). The mean annual incidence of death [95% confidence interval (CI)] was 7.8 (6.3–9.5) per 1000 PWH.

### Causes of death

The main causes were non-AIDS-defining nonviral hepatitis (NANH)-related malignancies and non-AIDS-defining infections (Fig. 1). Of the 21 PWH who died from COVID-19, 20 (95%) had one or more several comorbidities, and 18 (86%) were not vaccinated. No significant differences were observed in the characteristics of patients who died from COVID-19 compared with those with HIV (PWH) who died from other causes, aside from the presence of comorbidities (data not presented).



**Fig. 1.** Distribution of the causes of death among adult people with HIV in the 2011–2015 study (light) and in the 2020–2021 study (dark). CNS, central nervous system; CVD, cardiovascular diseases; GI tract, gastrointestinal tract; NANH malignancies, non-AIDS-defining nonviral hepatitis-related malignancies.

The proportion of deaths from liver-related diseases was low (3%). Only 4% and 17% of the deceased patients had HBV or HCV-coinfection, respectively.

### Risk factors for death

We assessed risk factors (Table 1, Supplemental Digital Content 1, <http://links.lww.com/QAD/C926>) and (Fig. 2). The PWH who died were significantly older, diagnosed with HIV for a longer time, and more frequently with AIDS status. At enrollment and the last visit, they had lower CD4<sup>+</sup> T-cell counts and higher pVL. The deceased PWH were more commonly born in France, had a higher prevalence of intravenous drug use (IVDU) and HCV co-infection, and were less likely MSM or born in sub-Saharan Africa. The PWH born in sub-Saharan Africa were significantly younger, median age  $\pm$  IQR 48 years (41–56) than those who were not, median age  $\pm$  IQR 53 years (42–60),  $P < 10^{-4}$ . PWH born in sub-Saharan Africa had a significantly ( $P < 10^{-4}$ ) shorter median duration of HIV diagnosis (13 years, IQR 7–19) compared with those who were not (16 years, IQR 7–26).

### Comparison to the previous survey

The mean annual incidence (95% CI) was significantly higher than the incidence in 2011–2015 (4.1 (3.2–5.4) per 1000 PWH),  $P$  value less than  $10^{-4}$ . The characteristics of PWH in the 2011–2015 and 2020–2021 cohorts were comparable, except for the age and the time from diagnosis (data not shown). PWH followed in 2020–2021 were slightly older: 50 (41–59) years versus

47 (38–54) years previously. They had a longer diagnosis of HIV infection: 14 (7–22) years versus 11 (5–18) years previously. More PWH presented with a complete immuno-virological control than previously: last CD4<sup>+</sup> T-cell more than 500 cells/ $\mu$ l 68 versus 60% previously, and last pVL 50 copies/ml or less 90% versus 81% previously. Of the 12 942 PWH, 7548 (58.3%) were part of the 2011–2015 survey. Among the 202 reported deaths, 141 (69.8%) occurred in PWH who were already being followed during the 2011–2015 study. They accounted for the highest annual mortality incidence. PWH who died in 2020–2021 were older than those included in the 2011–2015 survey [61 (55–70) versus 52 years (47–60)], had a longer diagnosis of HIV infection, had more frequently an immunological control of HIV infection, and were less frequently HBV or HCV co-infected (Table 2, Supplemental Digital Content 2, <http://links.lww.com/QAD/C927>). Excluding PWH who died in 2020–2021 from COVID-19, the mean annual incidence (95% CI) was slightly lower: 7.0 (5.7–8.6) per 1000 PWH, remaining significantly higher than the mean annual incidence in 2011–2015.

## Discussion

### Mortality

The incidence in our cohort approached the incidence (9 per 1000 PWH) in the 2010 French survey [15] and those reported from other high-income countries, such as the

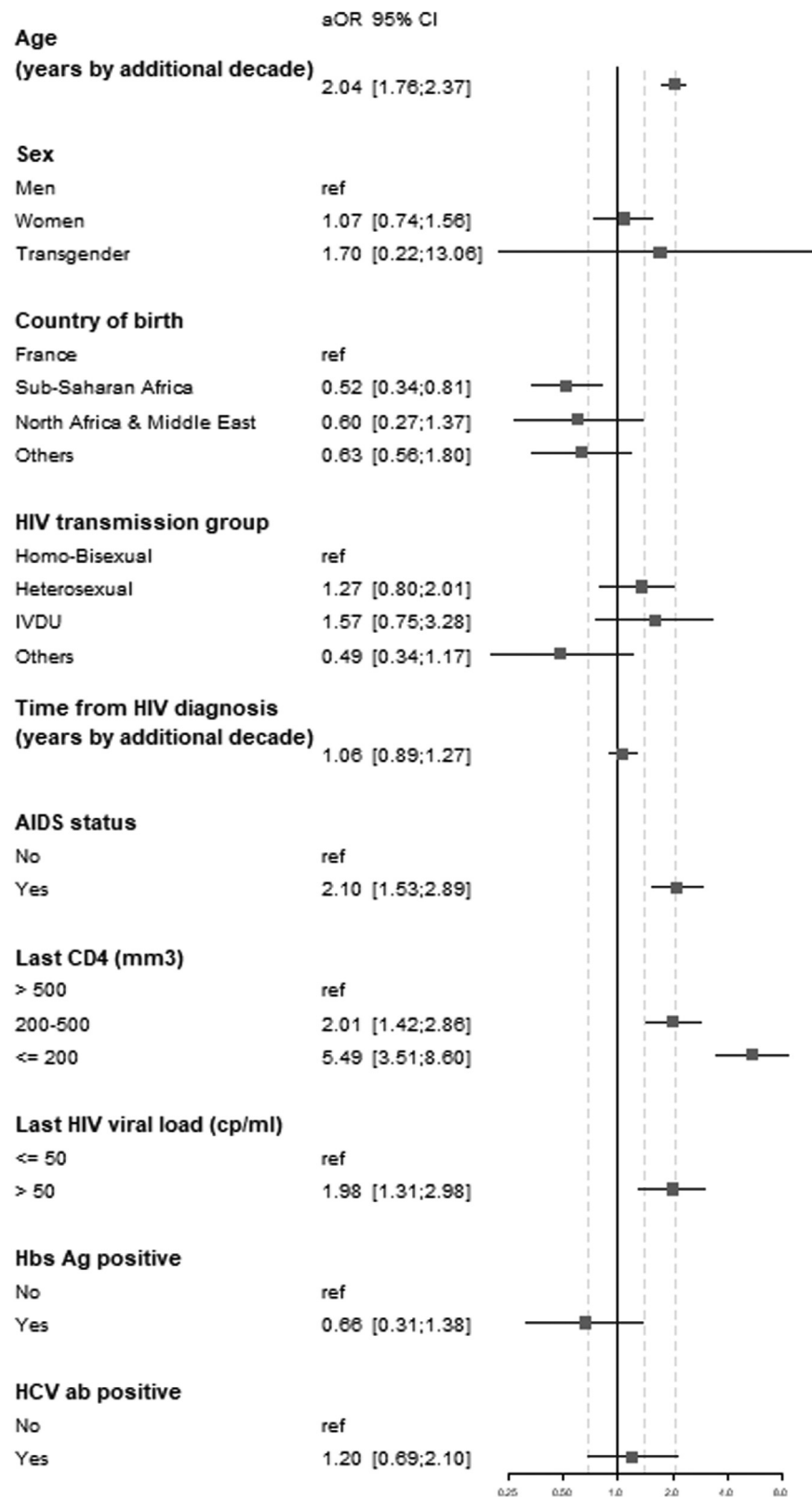


Fig. 2. Risk factors (by logistic regression) for death in the Northeast Paris area 2020–2021 study. HBs Ag, hepatitis B virus surface antigen; HCV ab, hepatitis C virus antibodies; IVDU, intravenous drug user.

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Canadian-UK Cohort (7.7 per 1000 person years) [16]. First, the aging of our cohort contributes to expected mortality. Although the rate of non-AIDS-defining malignancies, which is the leading cause of death, remained constant, there was an increase in the rate of non-AIDS-related infections, primarily driven by COVID-19, during the second survey, resulting in unexpected mortality.

### Causes of death

Aging has been confirmed at the national level: in 2018, in France, there was an estimated 160 000 PWH, of whom 55% were aged at least 50 years, 22% at least 60 years, and 8% at least 70 years [5]. Age is associated with chronic conditions such as NANH-related malignancies, cardiovascular, renal, liver, bone, and neurological diseases [5]. Nevertheless, in our survey, PWH were slightly older compared with the previous 2011–2015 survey, indicating a continuous renewal of the cohort with younger PWH between the two periods.

NANH-related malignancies emerged as the leading cause of death, accounting for nearly one-quarter of all deaths, and were frequently associated with smoking and aging [17]. Hernández-Ramírez *et al.* [18] found an increased risk of lung cancer in PWH compared with the general population in the USA. A systematic review found increased mortality (hazard ratio of almost 4) from lung cancer in PWH [19]. The patients who died from NANH-related malignancies lived with HIV for more than two decades, a significantly longer time than the patients who died from other causes. They died despite the HIV infection being controlled in more than 90% of them. Our results confirm the differential impact of ART on all-causes, AIDS-related, and non-AIDS related mortality rates, with 65%, 81%, and 45% respective decreases from the pre-ART to late-ART eras in the Atlanta Cohort [20]. Non-AIDS-related infections were the second cause (one-fifth of deaths). Among PWH who died from non-AIDS-related infections, approximately 50% of the deaths were attributed to COVID-19. The majority of these individuals had a plasma viral load (pVL) below 50 copies/ml and CD4<sup>+</sup> T-cell counts above 200 cells/ $\mu$ l. COVID-19 was the third cause of death in France in 2020, following malignancies and cardiovascular diseases (CVDs), with an estimated 69 000 deaths. [21]. In USA [22], from January 01, 2020, to May 8, 2021, after adjusting for all covariates, PWH had a higher risk of COVID-19 death (hazard ratio 1.3) than people without HIV. In the UK, two studies have reported an elevated mortality risk among PWH, with hazard ratios of 1.7 [23] and 2.6, respectively. Similar to our study, the majority of PWH who died in these studies had comorbidities [24]. In France, the number of deaths due to COVID-19 was greater than the excess number of all-causes deaths estimated by the National Institute of Statistics and Economic Studies (INSEE) (47 000) because non-COVID-mortality decreased, suggesting a competition

between COVID-19 and the other main causes of death [21]. We observed a similar pattern in our survey with 95% of patients who died from COVID-19 having one or several comorbidities (CVD and/or malignancies in one-third of patients each), explaining the lack of difference between the characteristics of PWH who died from COVID-19 and PWH who died from other causes. Lung cancer has already been found associated with a higher risk (hazard ratio 4.00) of COVID-19-related mortality [25]. Among PWH in a Spanish cohort, being at least 75 years old (hazard ratio 5.2), having chronic respiratory diseases (hazard ratio 1.8), and chronic metabolic diseases (hazard ratio 2.6) were identified as factors associated with a higher risk of severe outcomes related to COVID-19. [26]. AIDS-related mortality represented 10% of the total deaths, which confirms a consistent decline in France since the year 2000. Previous surveys conducted in 2000 [14], 2005 [27], and 2010 [15] reported proportions of AIDS-related mortality at 47%, 36%, and 25%, respectively, indicating a significant reduction over time. Liver-related mortality accounted for only 3% of deaths, possibly due to the availability of direct antiviral agents in France since 2014.

### Risk factors for death

The patients who died, compared with patients alive at the end of the study period, had a significantly poorer control of HIV infection (assessed by CD4<sup>+</sup> T-cells and pVL, both at the last visit). Multivariate analysis of risk factors found the effect of age, AIDS status, low CD4<sup>+</sup> T-cell count, and pVL more than 50 copies/ml (both at the last visit); being born in sub-Saharan Africa was associated with a lower risk of death. They were significantly younger and had a significantly shorter time of HIV diagnosis than those who were not born in sub-Saharan Africa, but these variables were included in the multivariate logistic regression model. The results about the country of birth were therefore adjusted on these variables. The lower risk was perhaps related to less tobacco use (only hypothesized due to several missing data) or more healthy food, even if other biases not taken into account cannot be ruled out.

### Comparison to the previous survey

The mortality almost doubled in the 2020–2021 survey compared with the 2011–2015 period. The patients who died were almost 10 years older and lived with HIV for a significantly longer time than those who died during the 2011–2015 period. The proportion of deaths due to NANH-related malignancies was stable but non-AIDS-related infections (mainly COVID-19) almost doubled between the two periods. AIDS-related and liver-related mortalities decreased, possibly due to ART and anti-HCV treatments.

### Strengths

Our cohort accounts for 10% of PWH in care in France. PWH are often originating from sub-Saharan Africa,

which could have an impact on the results. Describing the same cohort during two periods allowed us to mitigate this impact.

### Limitations

One possible hypothesis to explain the higher incidence of death is the improved comprehensiveness in collecting data on deaths. This hypothesis seems unlikely, as the proportion of deaths from unknown causes was identical to our previous survey. The tobacco use could not be properly assessed due to missing data. The patients with unknown cause of death were more frequently IVDU and HCV co-infected. We cannot completely rule out an underestimation of liver-related diseases.

In 2020–2021, the incidence of death almost doubled compared with 2011–2015. NANH-related malignancies represented one death from four, non-AIDS-related infections (mainly COVID-19) one death from five. In aging PWH, preventive interventions addressing lifestyle risk factors such as smoking cessation, repeated vaccines against COVID-19, and other respiratory pathogens are crucial, as well as the improvement in the early diagnosis and treatment of HIV infection.

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Pierre Sellier conceived the study and wrote the manuscript; Guylaine Alexandre-Castor, Gwenn Hamet, and Alexandre Brun extracted the data and performed the statistical analyses; Olivier Bouchaud, Pierre Leroy, Sylvain Diamantis, Amélie Chabrol, Moïse Machado, Marie-Anne Bouldouyre, Diane Ponscarne included the patients from their respective centers; Nathalie De Castro, and Jean-Michel Molina corrected the manuscript; and Isabelle Turpault and Willy Rozenbaum allowed the use of COREVIH Ile-de-France East Nadis cohort. Geoffroy Liegeon corrected the grammar and turns of phrase.

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Meaux, France et Centre Hospitalier du Sud Seine-et-Marne, Fontainebleau, France participated in this study.

### Conflicts of interest

There are no conflicts of interest.

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