Mortality and comorbidities in a Nationwide cohort of HIV-infected adults: comparison to a matched non-HIV adults’ cohort, France, 2006–18

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Introduction

The human immunodeficiency virus (HIV) continues to be a significant global health concern, causing a substantial burden of illness and death.1 Presently, there are >36 million individuals worldwide living with HIV/AIDS, and there has been a decline in overall HIV-related mortality.1 To combat the pandemic, the Joint United Nations Program on HIV/AIDS (UNAIDS) introduced the Fast-Track strategy, aiming to reduce HIV-related deaths to less than five hundred thousand by 2020, representing a 75% decrease from the mortality observed in 2010. Additionally, the goal is to achieve a 90% reduction in HIV-related deaths for each country from the mortality observed in 2010. Additionally, the goal is to achieve a 90% reduction in HIV-related deaths for each country from the mortality observed in 2010. Furthermore, the Fast-Track strategy, aiming to reduce HIV-related deaths to less than five hundred thousand by 2020, representing a 75% decrease from the mortality observed in 2010. Additionally, the goal is to achieve a 90% reduction in HIV-related deaths for each country from the mortality observed in 2010. Moreover, the Fast-Track strategy, aiming to reduce HIV-related deaths to less than five hundred thousand by 2020, representing a 75% decrease from the mortality observed in 2010. Additionally, the goal is to achieve a 90% reduction in HIV-related deaths for each country from the mortality observed in 2010. With the introduction of antiretroviral therapy (ART), HIV has become a manageable chronic disease, with the life expectancy of HIV-infected individuals on ART approaching that of the general population.4 However, despite improved access to ART, only a few countries have experienced a significant reduction in HIV mortality since 2000. Additionally, the average number of years that individuals aged 20 can expect to live remains approximately two-thirds of that in the general population.4

It is worth noting that certain cohorts of people living with HIV (PLWHIV) under proper care have demonstrated a considerable decrease in mortality, but they may not be entirely representative.5–7 Furthermore, PLWHIV experience higher mortality rates compared with the general non-HIV population, both due to AIDS-related causes and non-AIDS-related causes of death.5–10 PLWHIV are also more susceptible to various comorbidities, such as cardiovascular diseases, chronic viral hepatitis and cancers.10 These comorbidities may be linked to other associated risk factors, side effects of ART or the disease itself.

Methods

Data from the French National Insurance

The study utilized data from the French National Insurance Databases, known as the ‘Système National des Données de Santé’ (SNDS). This comprehensive database records healthcare expenditure reimbursements for all individuals covered by French health insurance, encompassing over 65 million inhabitants. The universal
health insurance system covers all residents born in France, whether French or foreign, as well as legal immigrants.

The database contains individual-level information on all reimbursed medication treatments provided outside of hospitals, and it includes data on various socio-demographic factors such as date of birth, gender, and whether the person is covered by the Complementary Universal Health Insurance (CMU-c). The CMU-c offers free healthcare access to individuals with low annual income. Since not all medical expenses are fully reimbursed, individuals in France typically opt for complementary insurance to cover the remaining costs. However, those with low income receive an equivalent of this complementary insurance, the CMU-c, free of charge.

Additionally, the State Medical Aid (AME) system provides free healthcare access to foreigners in an irregular situation, subject to residency and resource conditions. The data in this database are fully linked and available from as early as 2008, offering valuable insights into healthcare consumption patterns in France.

Patient data were irreversibly anonymized using a double anonymizing algorithm. The study was assessed by the Expert Committee for Research, Studies and Evaluations in the Field of Health of the French Ministry of Higher Education, Research and Innovation.

**Study population**

This study is a retrospective analysis of PLWHIV identified in the French SNDS database between 2006 and 2018, with a follow-up to 2019. PLWHIV have been matched to a non-HIV population (ratio 1:1) with the same age and gender.

COCOVIH study draws upon anonymized records from the SNDS. PLWHIV were identified based on ICD-10 HIV diagnoses, HIV-specific laboratory tests and/or prescription for ART specific to HIV. Adults patients living with HIV were included between 2006 and 2018 based on an ICD-10 diagnosis of HIV mentioned as a reason for long-term care (so-called ‘ALD 7, affection longue durée n°7’) or reason for hospitalization (the codes selected were: B20, B21, B22, B23, B24, F024 and Z21), or an HIV-specific laboratory test (genotypic drug resistance test, or genotypic human leucocyte antigen (HLA) *B5701 test), or at least three prescriptions for HIV-specific ART in 1 year over the period 2006–18. Excluded were recipients of ART without corresponding HIV diagnosis, notably HIV-negative individuals on pre-exposure prophylaxis (with emtricitabine/tenofovir dual therapy) and HIV-negative patients treated for hepatitis B with tenofovir monotherapy.

An age and gender-matched control group (1:1) with no criteria for HIV infection was also included between 2006 and 2018. Each control was identified on the same date as the PLWHIV and followed up from this date (figure 1).

PLWHIV were selected with an algorithm described in Supplementary file S1. The criteria to identify HIV patients using this algorithm were a full healthcare coverage for HIV, HIV-related hospitalization (ICD-10 codes: B20, B21, B22, B23, B24, F02.4, Z20.6, Z21), ART reimbursement, HIV-related biology test (i.e., genotypic resistance testing to antiretrovirals by sequencing the reverse transcriptase gene and the viral protease gene, or genotypic resistance testing to antiretroviral drugs by sequencing the envelope gene). Patients with only ART reimbursement of ATC J05AR03 were excluded from the analyses after 1 January 2016 (figure 1).

**Data extraction**

Data were extracted for each included participant for age, gender, date of death (if deceased) and any eligibility for ALD 7 status. Healthcare resources were extracted, such as hospitalizations, consultations, medical procedures and tests, and medications. The comorbidities were identified based on either chronic disease identified in hospital discharge summaries, ALD status or long-term medication prescription for vascular prevention or other disorders. Associated diseases were documented based on ICD-10 codes in hospital discharge summaries.

**Statistical analyses**

Mean, standard deviation, median, minimum and maximum were used to describe quantitative variables, and percentages were used for qualitative variables. Bivariate analyses were conducted using χ²-tests to assess qualitative variables with Yates continuity correction or Fisher’s exact test for sample sizes <5. For quantitative variables, a Student’s t-test or analysis of variance was performed.

For the survival analyses, an index date was defined as the first date of identification of the HIV infection or 1 January 2006, for patients with full healthcare coverage for HIV before 2006. Overall survival of patients was defined as the time from the index date until death or 31 December 2018. Survival was analyzed with Kaplan–Meier curves. A multivariate Cox model analysis was performed to explore the impact of comorbidities on overall mortality. A univariate Cox model was conducted to estimate the hazard ratio (HR) of PLWHIV compared with the control group.

The first series of 11 Cox models were run with two covariates: (i) the membership of subjects to the PLWHIV group or the control groups and (ii) each of the 11 comorbidities. The HR comparing the PLWHIV group to the control groups adjusted for each of the 11 comorbidities can then be compared with the HR of the univariate analysis. The difference between these two HRs represents the attributable risk of comorbidity on the over-mortality of HIV disease.

A second series of 11 Cox models were run, and comorbidities were additionally introduced one by one in a specific order: The first comorbidity introduced was the one that led to the highest decrease in the HR while adjusting for the first comorbidity. The second comorbidity introduced was the one that led to the highest decrease in the HR while adjusting for the first and second comorbidities. The remaining comorbidities were included in a specific order.
introduced in the same manner based on the decreased magnitude of the HR while adjusting for the previous comorbidities.

All statistical analyses were performed using SAS© software Version 9.4 (Cary, USA).

Results

We included 173,712 PLWHIV (66.5% men) and 173,712 non-HIV participants (66.5% men) matched for age and gender (Table 1). The mean age of the two populations was 41.8 (SD: 11.4) years old. PLWHIV were more frequently covered by the CMU-c additional public health insurance for low-income people and the AME additional public health insurance for illegal immigrants and mainly resided in the region of the capital of France (Table 1). Repartition of PLWHIV is shown in Supplementary file S2.

PLWHIV presented a higher proportion of comorbidities compared with non-HIV participants, including cardiovascular diseases, history of stroke (2.4% vs. 1.0%, P < 0.001), hypertension, viral hepatitis, history of infectious disease and cancer, as well as a higher rate of diabetes (Table 1).

During the 13 years of follow-up (2006–2018), 20,018 PLWHIV deaths were observed compared with 6,262 deaths among the non-HIV participants (11.52% vs. 3.60%, P < 0.001) (Figure 2). At 3 years of follow-up, the survival rate of PLWHIV was 96.5% [95% confidence interval (CI) 96.4–96.5] compared with 98.2% (95% CI 98.1–98.3) at 5 years of follow-up, it was 94.5% (95% CI 94.5–94.6) compared with 98.2% (95% CI 98.1–98.3) and at 10 years of follow-up, it was 89.6% (95% CI 89.4–89.7) compared with 95.4% (95% CI 95.2–95.5) (Table 2). The over-mortality of PLWHIV was expressed by univariable HR = 2.135 (2.072–2.199), which remained significant after adjustment for region, CMU-c and AME, with multivariable HR = 2.182 (2.118–2.248) (Table 2).

After adjustment for infectious diseases, the HR decreased from 2.135 to 1.587 (1.538–1.638), P < 0.0001. After adjustment for hepatitis C, the HR decreased from 2.135 to 1.791 (1.736–1.847). The adjustment for other comorbidities led to smaller decreases in the HR (Table 2).

The cumulative adjustments for comorbidities resulted in a significant decrease in the HR for infectious diseases [HR = 1.587 (1.538–1.638)], hepatitis C (in addition to infectious diseases) [HR = 1.393 (1.349–1.439)] and psychiatric disorders [HR = 1.354 (1.310–1.398)]. However, additional comorbidities led to much lighter decreases in the HR (1.341 for ischemic cardiopathies, 1.334 for hepatitis B), and the HR remained stable for the remaining comorbidities.

When considering stratification by gender, the over-mortality of PLWHIV was higher for women, after adjustment for region, CMU-c and AME, HR = 2.966 (2.767–3.180), than for men, HR = 1.961 (1.898–2.027) (Supplementary file S2). In both genders, infectious diseases and hepatitis C were mainly associated with mortality (Supplementary file S2). The over-mortality of PLWHIV was also higher in young people compared with older individuals (Supplementary file S2).

Discussion

The introduction of new therapies like ART has led to a significant decrease in mortality rates among PLWHIV with high CD4 levels on HAART, aligning with rates seen in the general population. However, our study demonstrated that the overall mortality rate of PLWHIV remained higher than age and gender-matched non-HIV individuals (11.52% vs. 3.60%, P < 0.001). This outcome is consistent with previous research. For instance, a Korean study found that the mortality of PLWHIV was five to six times higher than the general population, while in Spain, the mortality rate was 7.4 (95% CI 6.0–9.0) times higher for the same age group and gender during the period of 2014–18. Another study in France showed higher mortality rates in PLWHIV across all age groups compared with the general population.

The main cause of mortality among PLWHIV was AIDS-related, accounting for over 50% of overall deaths in England, Korea and Columbia. In contrast, other countries showed a decrease in HIV-related deaths, such as Spain showing 64% of the overall mortality for the period 1999–2003 and 35% for the period 2014–18, and also in Japan but depending on territories and specific populations in the USA.
In Spain, excess mortality among PLWHIV was primarily associated with drug addiction and liver disease, which may be linked to a history of drug use in this population. Nevertheless, our study also found other causes of mortality among PLWHIV, such as infectious diseases, psychiatric disorders and cardiovascular diseases. High-risk behavioral attitudes and activities, including injected drug use, were associated with mortality in PLWHIV. Injected drug use posed a risk for addiction, overdose and co-infections like hepatitis C and B. Additionally, it was linked to suicide, injuries, tobacco smoking and heavy alcohol consumption.

PLWHIV exhibited a higher consumption of tobacco smoking, alcohol, and recreational drugs than the general population, contributing to excess mortality from infectious diseases. Psychiatric disorders were significant contributors to mortality, with suicide being a major cause of death among PLWHIV. A recent meta-analysis showed that suicide ideation prevalence was 22.4% in PLWHIV, and the risk of successful suicide 100-fold than in the general population. The stigma associated with chronic therapy like HAART might impact personal relationships and mental health.

Furthermore, PLWHIV were at high risk of cardiovascular diseases and risk factors such as hypertension. HIV infection itself was identified as an independent risk factor for cardiovascular disease, with ART use potentially leading to metabolic abnormalities that increase cardiovascular risk. Several studies have shown that HIV infection is an independent risk factor for cardiovascular disease, including stroke, myocardial infarction and heart failure.

The possible mechanism underlining this relationship could be the HIV tropism in cardiac myocytes and inflammatory responses triggered by HIV. ART chronic use could be associated with metabolic abnormalities leading to cardiovascular risk in PLWHIV. As explained above, PLWHIV showed a high prevalence of tobacco smoking, hypertension and dyslipidemia.

Moreover, by the improvement of life expectancy of PLWHIV, the reduction of infectious diseases and changes in life behaviors, cardiovascular disease naturally increases as a cause of mortality as observed in the general population.

Our study revealed that the overall mortality rate was higher among women with HIV compared with men (HR = 2.966 (2.767–3.180) vs. HR = 1.961 (1.898–2.027)). This finding is consistent with prior research. Women exhibited a higher excess mortality in relative terms because, in the general population, women have lower mortality rates than men. This could be explained by the fact that women tend to take fewer risks and take better care of their health. However, this may not hold true for HIV-infected women, as they face higher levels of disadvantage in terms of healthcare access and quality. Moreover, women may experience more adverse effects related to ART, including hepatotoxicity, which could lead to mortality-related liver disease. Moreover, women also have a higher incidence of AIDS-related bacterial infections compared with men.
with black women in the USA accounting for a significant portion of new infections among women. 37

Mortality showed a significant association with HIV status, with an inverse age relationship. Mortality rates were higher among PLWHIV in younger age groups (18–30 years) compared with older stages. As our study matched the population for the same age groups, it indicates the importance of the impact of HIV infection on mortality at a young age. This finding could be related to the higher rates of suicide and psychiatric disorders observed among young PLWHIV. 38

Furthermore, since 2003, the number of HIV-related deaths has declined by 64% in overall age groups and by 74% among children aged 0–9 years, but the decline was only 10% among adolescents. 39

Several determinants could explain this observation, including restrictive laws on the age of consent for self-care, poor adherence to ART, and behavioral risks related to age, social, and economic status, which may limit adolescents’ access to information and healthcare services. 40

Limitations

The main strengths of this study are the utilization of the SNDS database, which covers the entire HIV French population, and the comparison of this population with a matched controlled non-HIV population of the same age and gender. In France, causes of death were recorded through INSEE certificates and supported by multiple administrative sources, ensuring the accuracy and validity of death-related information. The long follow-up period spanning over 13 years allowed for the assessment of long-term survival. However, this study also has some limitations. We may have underestimated the prevalence of hypertension, diabetes and dyslipidemia because these conditions were identified only through hospital records for hospitalization and prescriptions. As a result, cases of these conditions treated outside the hospital or not requiring ART prescriptions may have been missed in our analysis.

Conclusion

Although screening HIV tests, ART and general medications are free and reimbursed in France, the mortality among PLWHIV is higher than in a matched non-HIV population of the same age and gender. Thus, health policies should prioritize early HIV diagnosis, treatment and healthcare. Even though the life expectancy of PLWHIV has globally increased, prevention policies and care management should focus on addressing the specific causes of death. Gender-specific policies should be highlighted, as we observed a higher impact of HIV mortality in women. Special attention should be given to the treatment of the younger population to prevent early deaths. Moreover, efforts should be directed toward preventing avoidable infectious diseases through systematic and widespread vaccination, along with early treatment following guidelines. Mental health and cardiovascular prevention should be particularly investigated to prevent and reduce mortality among people living with HIV.

Supplementary data

Supplementary data are available at EURPUB online.

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Author contributions


Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Institutional Review Board Statement: Not applicable

Informed Consent Statement: A non-opposed consent was obtained for all participants. Patient data were irreversibly anonymized using a double anonymizing algorithm. The study was assessed by the Expert Committee for Research, Studies and Evaluations in the Field of Health (CEREES) of the French Ministry of higher Education, Research and Innovation.

Key points

- Mortality among PLWHIV is higher than in a matched non-HIV population.
- Health policies should prioritize early HIV diagnosis, treatment, and healthcare.
- Special attention should be given to the treatment of the younger population.

References


