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Causes of Death in HIV-Infected Individuals with Immunovirologic Success in a National Prospective Survey

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Abstract

This prospective multi-center observational survey describes causes of death and their trends from 2000 to 2010 among treated HIV-infected patients with immunovirologic success (PIVS) in France. In 90 clinical sites providing HIV care and treatment, representing a cohort of 82,000 patients in 2010, the underlying causes of death and characteristics of deceased patients were prospectively recorded in 2000, 2005, and 2010 by using a standardized form. We provide data on PIVS, define as patients with a CD4+ T cell value above 500/mm3 and a plasma HIV-1 RNA below 50 copies/ml at their last periodic checkup before death, compare them with immunovirologic uncontrolled patients, and describe trends in these data from 2000 onward. The main underlying causes of death of the 120 PIVS recorded in 2010 were: a non-AIDS/nonviral hepatitis-related malignancy (19%), suicide (12.5%), cardiovascular disease (11.5%), and liver disease (11%). Only three PIVS died of an AIDS-related event. Socioeconomic difficulty was identified in 41% of PIVS in 2010. This percentage had constantly grown since 2000 ($p < .001$). Median age at death also increased (40, 46, and 52 years in 2000, 2005, and 2010, respectively; $p < .001$). The distribution of the main causes of death of PIVS was statistically different from that of uncontrolled patients ($p < .001$). Although immunovirologic control is fundamental, a parallel multidisciplinary approach to care is essential to accurately detect and treat comorbidities, particularly cancer, psychiatric disorders, and cardiovascular disease. Psychosocial aspects must be considered.

Keywords: HIV, epidemiology, comorbidity, cause of death, cancer, suicide

Introduction

Highly active antiretroviral therapies (HAARTs) have transformed the epidemiology of HIV infection in industrialized countries.[1] The mortality rate of people living with HIV (PLHIV) who have a sustained undetectable viral load and a $CD4^+$ T cell count greater than $500/mm^3$ is currently approaching that of the general population.[2] However, early mortality still persists and seems to be related to disease duration, suboptimal treatment, moderate immunosuppression, and specific risk factors that are overrepresented in this population.[3] The causes of death in PLHIV have also changed considerably: Death from AIDS-related events is less frequent, whereas the proportion of non-AIDS-related solid cancers, Hodgkin's lymphoma, complications linked to coinfection with viral hepatitis, and cardiovascular events is growing.[4]

HIV infection is said to be controlled when immunovirologic success is achieved (i.e., when viral replication is stopped and $CD4^+$ T cell numbers are optimized). Only

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limited data are available regarding the causes of death in patients with immunovirologic success (PIVS), despite this sub-group representing the majority of treated patients in countries with general access to HAART. PIVS constitute an aging population where deaths from AIDS are rare, and where other comorbidities—such as cardiovascular disease, cancers, and co-infection with viral hepatitis—seemingly related to the chronicity of HIV infection and the aging process are becoming more common.[5–7] A better understanding of these comorbidities could help to optimize care for these patients in terms of monitoring and prevention and to improve their long-term prognosis. This study uses data collected during the ANRS EN20 ''Mortalité 2010'' study, which aimed at providing an overview of the causes of death in France in 2010 of HIV-infected patients.[8] We focused on the PIVS subgroup. Our results provide a snapshot of the causes of PIVS mortality in 2010 and their trends since 2000.

Materials and Methods

The Mortalité 2010 survey followed two similar studies: Mortalité 2000 and Mortalité 2005.[9,10] It examined characteristics of PLHIV who died during 2010 in 90 hospitals providing HIV care in metropolitan France and French overseas territories, comprising a cohort of 82,000 patients.

Throughout the calendar year 2010, each participating hospital had to report all deaths of PLHIV followed up by their establishment on a dedicated website. Investigating doctors at each hospital then completed an online standardized questionnaire. Duplicates were eliminated by cross-referencing sex, date of birth, and date of death. Two specialist physicians in HIV clinical research were responsible for checking the consistency of collected data and their validation. Causes of death were determined by using the guidelines of the International Classification of Diseases—10th revision by the Epidemiology Center for the Medical Causes of Death (CépiDc-Inserm), on the basis of questionnaire responses. The underlying cause of death was defined as the disease or injury that resulted in the disease process leading to death, according to an algorithm previously used in Mortalité 2000 and 2005. Deaths were classified according to nine major causes: AIDS, non-AIDS/nonviral hepatitis-related malignancies (NANH malignancies), cardiovascular disease, liver-related death, non-AIDS-related infection, suicide, other non-AIDS-related causes, unexplained sudden death, and unknown causes in the absence of information.

This study focused on deceased PIVS. We defined PIVS as patients with a $CD4^+$ T cell value above 500/mm^3 and a plasma HIV-1 RNA below 50 copies/ml at their last periodic checkup before death. This definition reflects current guidelines for HAART success in France. A descriptive analysis of this subgroup's characteristics was performed, and a comparison was made with the characteristics of two other groups defined as follows: patients not controlled immunologically (PNCI) with a $CD4^+$ T cell count below 500/mm^3 and with an HIV-1 RNA below 50 copies/ml, and immunovirologic-failure patients (IVFP) defined by a $CD4^+$ T cell value below 500/mm^3 and an HIV-1 RNA above 50 copies/ml.

A direct data comparison between the three Mortalité studies involving PIVS using the earlier definition was not feasible, because the reverse transcription polymerase chain reaction detection threshold used to assess patients' viral load in the 2010 study was higher, and because low numbers of patients died with a $CD4^+$ T cell above 500/mm^3 in previous studies. Accordingly, the following less restrictive definition of immunologic success (PIVS2) was used to enable a comparison: A $CD4^+$ T cell value above 350/mm^3 and HIV-1 RNA below 500 copies/ml at the last checkup before death.

A comparison between groups of categorical variables was performed by using the χ^2 test, the corrected χ^2 or Fisher's exact test, according to the application conditions. Continuous variables were compared by using the Student's *t*-test or the Wilcoxon test. Some analyses were stratified by age and sex. Statistical analyses were performed by using SAS® Version 9.1.3 Service Pack 2 software (SAS Institute, Inc., Cary, NC).

Results

General characteristics of PIVS

Of the 728 deaths recorded in Mortalité 2010, 120 were PIVS deaths, reported by 63 of the 90 participating sites. Men accounted for 79%, 34% of whom were men who had sex with men (MSM) and 32% of whom were intravenous (IV) drug users. In the female subgroup, 40% were IV drug users. A quarter of the deceased PIVS were foreign born (15% born in Africa). The median age at time of death was 51 years, and the median known HIV infection duration was 17 years. We found equal proportions of patients at AIDS stages A, B, and C, according to the CDC classification.[11] All patients were on antiretroviral therapy with a median treatment duration of 13 years. The median final $CD4^+$ T cell count before death was 644/mm^3, and the median time between the last CD4 checkup and death was 2.8 months (interquartile range:1.5–5). Death occurred at home and in hospital in 38% and 46% of cases, respectively. Forty-one percent of patients (36% men; 60% women) had socioeconomic problems (defined as the presence of any one of the following characteristics: no social security, unemployment, illegal residence status, or homelessness). Ongoing or former tobacco use was identified in 68% of cases with available data ($n = 112$), mainly among those less than 50 years and men. A history of IV drug or cocaine abuse was found in 37% of cases ($n = 115$), mainly among those less than 50 years and women. Excessive alcohol consumption (>30 g per day) was found in 19% of patients with available data ($n = 97$). A total of 41% of the deceased patients had a history of depression or pathological anxiety, with this proportion reaching 75% in women younger than 50 years. Among male patients, a history of schizophrenia or bi-polar disorder was identified in 8% of cases (reaching 13% in men older than 50 years). From a metabolic standpoint, 12% of patients had diabetes and 26% were dyslipidemic. High blood pressure was found in 22% of cases. Unsurprisingly, these three ailments were more frequent in patients older than 50 years. Coinfection with hepatitis B virus was identified in 15% of individuals. We found anti-hepatitis C virus antibodies in 35% of cases and active hepatitis C in 29%. Cirrhosis and hepatocarcinoma (HCC) were identified as primary causes of death in 18% and 7% of cases, respectively (Table 1).

Table 1. Characteristics of HIV-Infected Patients with Immunovirologic Success (PIVS, i.e., CD4 > 500/mm^3 and an HIV-1 RNA <50/ml) Who Died in 2010 According to Data from the Mortalité 2010 Study

	Women			*Men*			
	Age ≤50	*Age >50*	*All*	*Age ≤50*	*Age >50*	*All*	*All patients*
Characteristic	n = *16 (13.5%)*	n = *9 (7.5%)*	n = *25 (21%)*	n = *41 (34%)*	n = *54 (45%)*	n = *95 (79%)*	(n = *120)*
Median age at death (year) (interquartile range)	42 (38.3–47.1)	60 (57.2–66.6)	48 (40–57.2)	47 (43.5–47.9)	59 (53.6–69.9)	52 (46.7–61.9)	51 (46.4–60.1)
Born outside of France ($n = 116$) (%)	33	25	30	17	21	19	22
Born in Africa ($n = 116$) (%)	33	12.5	26	12	11.5	12	15
Median duration of known HIV infection (year) (interquartile range)	17 (10.9–20.3)	22 (14.7–23.6)	18 (10.9–21.7)	18 (12.5–22.8)	16 (12–20.9)	17 (12–21.5)	17 (12–21.7)
Mode of transmission (%)							
MSM	—	—	—	27	39	34	27
Heterosexual	37.5	44.5	40	12	31.5	23	27
IV drugs user	37.5	44.5	40	49	18.5	32	33
Transfusion	12.5	—	8	5	2	3	4
Unknown or Other CDC stage (%)	12.5	11	12	7	9	8	9
A	31	22	28	39	26	32	31
B	31	33.5	32	32	33	32.5	32.5
C	37.5	44.5	40	29	41	36	37
Median last CD4$^+$ (/mm^3) (interquartile range) before death	751 (563–862)	680 (560–799)	744 (560–834)	643 (590–800)	641 (589–722)	641 (589–743)	644 (580–800)
Median time between last CD4$^+$ and death ($n = 116$) (month) (interquartile range)	2.5 (1.7–3.6)	2.4 (0.7–4.1)	2.4 (1.6–4.1)	3.8 (1.5–6)	2.7 (1.7–4.7)	2.9 (1.5–5.6)	2.8 (1.5–5)
On HAART ($n = 119$) (%)	94	100	96	100	100	100	99
Median treatment duration ($n = 115$) (year) (interquartile range)	13 (7.7–14.5)	14 (10.2–14.3)	14 (9.1–14.4)	12 (7.9–14.5)	13 (9–15.1)	13 (8.5–14.7)	13 (8.5–14.6)
Place of death ($n = 115$) (%)							
Home	44	22	36	55	29	40	39
Hospital	50	67	56	32	56	46	48
Socioeconomic difficulty (%)	69	44	60	46	28	36	41
Tobacco use ($n = 112$) (%)	67	33	52	87	71	78	73
Alcohol abuse ($n = 97$) (%)	17	—	10.5	26	17	20.5	19
IV drug user ($n = 115$) (%)	40	44.5	42	51	26	37	38
Depression or pathological anxiety ($n = 119$) (%)	75	22	56	47.5	30	37	41
Schizophrenia or bipolar disorder (%)	—	—	—	2	13	8	7
Diabetes (%)	6	56	24	2	13	8	12
Arterial hypertension (%)	—	56	20	7	33	22	22
Dyslipidemia ($n = 118$) (%)	6	33	16	22.5	34	29	26
Coinfection (%)							
HBV	12.5	11	12	15	17	16	15
HCV	44	44	44	49	22	34	36
Cirrhosis (%)	31	11	24	19.5	15	17	18
HCC ($n = 118$) (%)	12.5	—	8	10	4	6	7

Percentages take into account all patients, including those for whom data are missing.

HAART, highly active antiretroviral therapy; HBV, Hepatitis B virus; HCC, hepatocarcinoma; HCV, Hepatitis C virus; MSM, men who had sex with men; PVIS, patients with immunovirologic success.

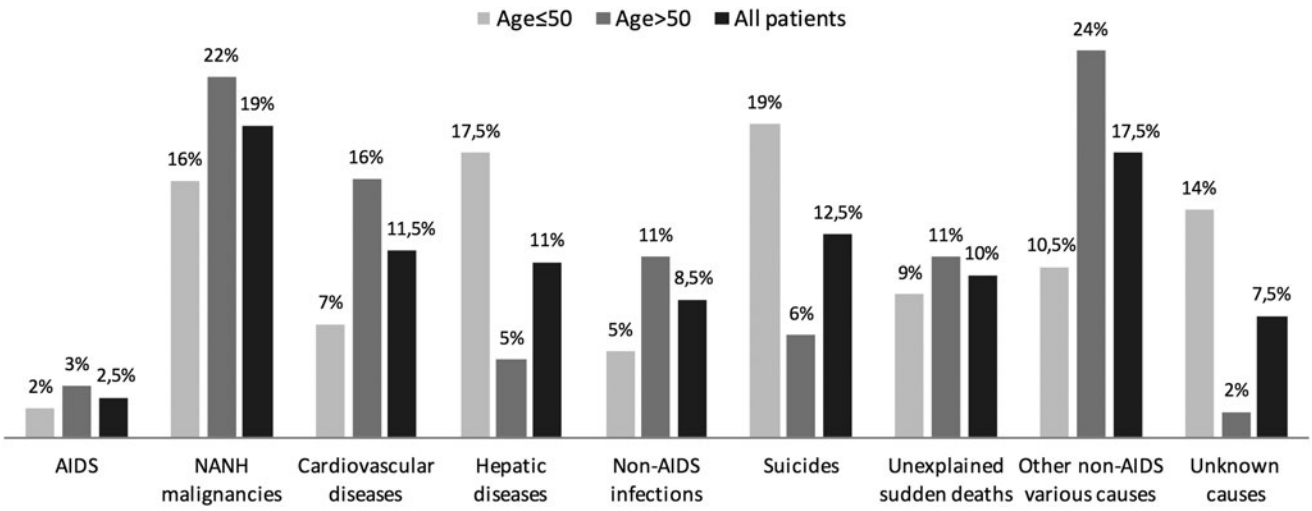

FIG. 1. Underlying cause of death in 2010 in France of HIV-infected patients with immunovirologic success ($N = 120$).

Causes of death in patients with immunovirologic success, and comparison with patients not controlled immunologically and immunovirologic-failure patients

Causes of death among PIVS in 2010 were as follows (Fig. 1): NANH malignancies, 19%; suicide, 12.5%; cardiovascular disease, 11.5%; liver-related death, 11%; unexplained sudden deaths, 10%; and non-AIDS-related infection, 8.5%. Only three patients (2.5%) died after an AIDS-related event. Among the 17.5% remaining deaths, we identified seven accidental deaths, three deaths from myelodysplasias, and two deaths from complicated diabetes. Unknown causes represented 7.5% of deaths.

The breakdown of the 23 NANH malignancies causing death in 2010 was as follows: 11 lung, 2 anal, 1 penile, 1 esophageal, 1 colorectal, 1 cholangiocarcinoma, 1 ovarian, 1 breast, 1 prostatic, 1 pancreatic, 1 Ewing's sarcoma, and 1 acute myeloblastic leukemia. Suicide was the second most common cause of death. In those younger than 50 years of age, suicide was the leading cause of death (17% men; 25% women). Among MSM, suicide accounted for 22% of deaths, and it was the joint-leading cause with cancer. In the suicide subgroup, a history of IV drug or cocaine abuse and socioeconomic problems was identified in 14% and 40% of cases, respectively. A history of depression or pathological anxiety was observed in 71% of cases, and bipolar disorder or schizophrenia was identified in 7%. Among the 13 deaths of hepatic origin (7 HCC and 8 decompensated cirrhosis), 11 had active chronic hepatitis C and 2 had chronic hepatitis B. Eleven of the 13 (85%) were IV drug abusers, and 5 (45.5%) had excessive alcohol consumption. Ten people died from non-AIDS-related infection: five pneumopathies, two gastrointestinal infections, one *Streptococcus pneumoniae* bacteremia, one aspergillosis, and one undocumented sepsis.

A significant difference was observed in the distribution of the main causes of death in comparisons of PIVS with PNCI and PIVS with IVFP ($p < .001$) (Fig. 2). That analysis excluded patients younger than 30 and older than 70 because of age stratification. AIDS-related deaths represented only 2.5% of PIVS. This increased to 13% and 45%, respectively, in the PNCI and the IVFP groups. NANH malignancies were overrepresented among PNCI, accounting for 32% of deaths. Suicide, which was the second leading cause of death among PIVS (12.5%), was much less present in the PNCI and IVFP groups (2% and 4%, respectively).

Trends of characteristics of deceased PIVS—less restrictive definition (PIVS2) and causes of death in 2000, 2005, and 2010

In 2010, 229 PIVS2 deaths were reported, representing 31.5% of the total number of deaths in our survey, compared with 81 (9%) in 2000 and 153 (15%) in 2005. Importantly, the median age at the time of death increased from 40 years in 2000, to 46 in 2005 and 52 in 2010 ($p < .0001$). Thirty-nine percent of PIVS2 in 2010 had socioeconomic problems (22% in 2000; 16% in 2005). The proportion of PIVS2 patients with cardiovascular risk factors increased over the three surveys: In 2010, 13% of deceased PIVS2 were diabetic (5% in 2000; 9% in 2005), 24.5% were hypertensive (10% in 2000; 11% in 2005), and 24% were dyslipidemic (22% in 2000; 11% in 2005) (Table 2).

With regard to the underlying causes of death, NANH malignancies represented 25% of deaths in 2010 (22% in 2000; 20% in 2005), cardiovascular disease represented 12% (17% in 2000; 16% in 2005), liver-related deaths represented 13% (16% in 2000; 13% in 2005), and AIDS represented 7% (10% in 2000; 12% in 2005).

Discussion and Conclusion

To our knowledge, this is the first representative study in a European country that focuses specifically on the causes of death of PLHIV with immunovirologic success by using such a strict threshold ($CD4^+$ T-cell count >500/mm^3 and HIV-1 RNA <50 copies/ml). This threshold reflects the current biological goal of antiretroviral therapy in France.[12]

The 120 PIVS deaths reported in 2010 represented 16% of all deaths registered during the Mortalité 2010 survey. Thanks to immunological control while on treatment, a very small number of deaths attributable to AIDS were observed. Recent data from controlled trials have shown that the mortality rate of PIVS on antiretroviral treatment is now almost equal to that of the general population in industrialized

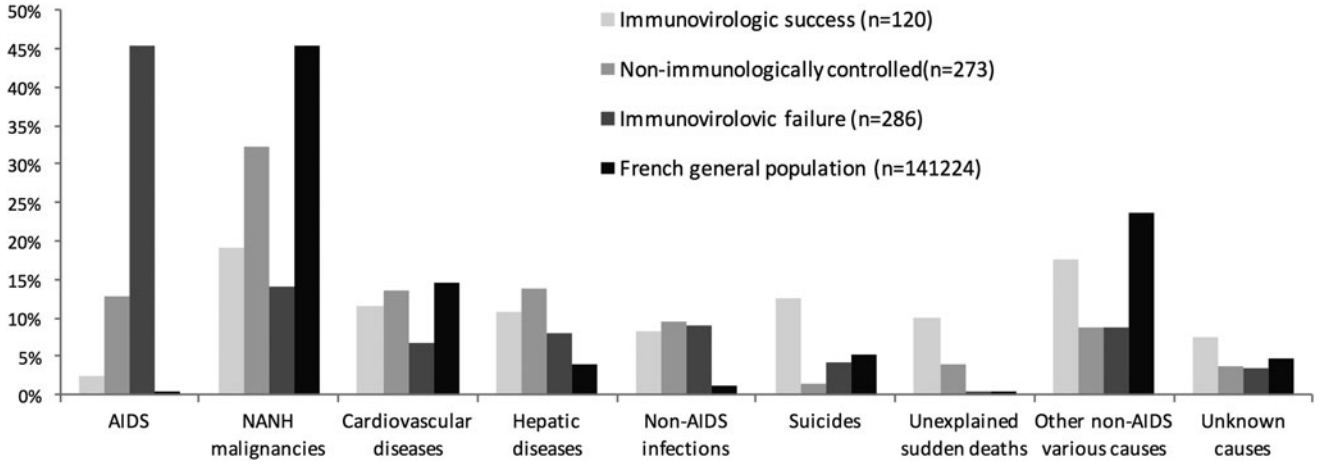

FIG. 2. Comparison of the underlying cause of death in 2010 of HIV-infected patients: those with immunovirologic success (CD4 > 500/mm^3 and an HIV-1 RNA <50 copies/ml), those nonimmunologically controlled (CD4 < 500/mm^3 and an HIV-1 RNA <50 copies/ml), and those with immunovirologic failure (CD4 < 500/mm^3 and HIV-1 RNA >50 copies/ml), according to data from the Mortalité 2010 survey. χ^2 test: $p < .001$. The causes of death of the French general population aged 30–70 years in 2010 were provided by CépiDc-Inserm, France.

countries.[2] Data from a study of a European cohort also revealed an absence of excess mortalities in the case of sustained immunovirologic control (CD4$^+$ T cell count >500/mm^3 and an undetectable HIV viral load for at least 6 months), when substance abusers were excluded.[13] It was also demonstrated that antiretroviral treatment reduced the occurrence of non-AIDS-related morbid events in patients with CD4$^+$ T cell count >350/mm^3.[14]

In our study, the median age at death was 51 years. A steady increase in the age at death since the 2000 survey was observed, reflecting the aging of the seropositive population, improved care of these individuals, and a massive scale-up of treatment access.

It is striking to see the large proportion of patients with socioeconomic problems (41%) and of substance abusers (37%), both of which are indicators of poor disease prognosis.

The main cause of death among PIVS was NANH malignancies (19%). This proportion also steadily increased from 2000 onward, perhaps because of the aging seropositive population and tobacco use, the latter being a comorbidity in at least 68% of our patients. Forty-six percent of fatal cancers were bronchopulmonary carcinomas. Papillomavirus-induced cancers represented 17% of all cancers (anus, penis, esophagus). Furthermore, we know that patients living with HIV have a higher incidence of HPV infection, especially of high-risk strains.[15] No deaths were attributable to cervical cancer, possibly due to improved screening of this population. Interestingly, there was a higher proportion of cancer-related deaths in virologically controlled patients who remained immunocompromized (PNCI). This highlights the importance of cellular immunity against neoplasms.[16] Recent results from a large European cohort showed that patients in immunovirological discordance were at greater risk of an

Table 2. Trends of Characteristics of Deceased HIV-Infected Patients with Immunovirologic Success (CD4 > 350/mm^3 HIV Viral Load <500 copies/ml), According to Data from the Mortalité 2000, Mortalité 2005, and Mortalité 2010 Surveys

Characteristic	*Mortalité 2000 (N = 81)*	*Mortalité 2005 (N = 153)*	*Mortalité 2010 (N = 229)*	p-*value 2000/2005/2010*	p-*value 2005/2010*
Median age at death (year) (interquartile range)	40 (36.8–47.9)	46 (41.8–55.2)	52 (46.5–59.5)	<.001	<.001
Male (%)	75	80	75	.5	.25
Social uncertainly (%)	22	16	39	<.001	<.001
Actual IV drug user (%)	10	4	33	<.001	<.001
Former IV drug user (%)	12	15	23	.054	.068
Median HAART duration (year) (interquartile range)	3.4 (2.4–5.3)	8.5 (6.4–10.9)	11.8 (7.6–14.4)	<.001	<.001
CD4 + ≥ 500/mm^3 (%)	53	57	58	.7	.8
Diabetes (%)	5	9	13	.1	.3
Arterial hypertension (%)	10	11	24.5	.002	.006
Dyslipidemia (%)	22	11	24	.03	.01
HBV coinfection (%)	10	8	13.5	.2	.08
HCV coinfection (%)	34.5	38	35	.8	.5

AIDS-unrelated event causing death.[17] The proportion of deaths from cancer in 2010 was lower than that in the French general population aged 30–70 years (40%) (Fig. 2). However, the age distribution at death was different, and, therefore, we cannot conclude that the risk of cancer was not higher among PIVS. It is possible that these events occurred earlier in our sub-population compared with the general population. It is most probable that in the coming years, the proportion of cancer deaths among HIV patients will exceed that of the general population.

Suicide was the second leading cause of death in this population (12.5%), and the leading cause (19%) in those aged 50 and younger, mainly women and MSM. In stark contrast, suicide only represented 3% of deaths among the general French population.[18] More specifically, suicide accounted for 5% of deaths in 2010 in the French population aged between 30 and 70 years old (Fig. 2). Unfortunately, data on antiretroviral therapy that may have contributed to suicide, such as efavirenz, were not collected in our study.[19] A statistical relationship between seropositive patients committing suicide and both socioeconomic difficulty and substance abuse was shown in one cohort study,[20] but was not found by us. However, we did find a significant proportion of individuals suffering from depression or pathological anxiety. A multidisciplinary approach including psychosocial actors could lead to improved prognosis for these patients.

Cardiovascular-related problems (11.5%) were the third leading cause of death in PIVS, a population overexposed to modifiable risk factors such as tobacco use and dyslipidemia. In the absence of data, we cannot make any conclusions on the impact of antiretroviral treatments such as abacavir, whose role in cardiovascular mortality is hotly debated.[21] Cardiovascular-related mortality was probably underestimated, as it is likely that a significant proportion of deaths from sudden unexplained death (10%) were of cardiovascular origin.[22]

Coinfection by viral hepatitis, mainly hepatitis C, remained a significant factor of poor prognosis. It played a major role in liver-related death (11% of all deaths in our study). The highest proportion of substance abuse was found in this group, a population often associated with socioeconomic problems, psychological disorders, lack of therapeutic compliance, and irregular follow-up, all of which are detrimental to survival.[23,24] By comparison, only 4% of deaths in 2010 among the French general population of the same age were from liver-related problems, and only 0.2% of these was directly related to viral hepatitis.

Non-AIDS-related infections accounted for a non-negligible proportion (8.5% of the PIVS) of deaths. Although these patients were not immunocompromized, this percentage is much higher than that in the general population where such infections accounted for 1.2% of deaths.

This study has several limitations. Our data were not exhaustive: Our sample of sites providing HIV treatment represented a cohort of 82,000 patients out of a total of 150,000 PLHIV in France in 2010.[25] We do not know how representative our results were of all PLHIV who died in France in 2010. However, the Mortalité 2000 survey conducted in a cohort of $\sim$64,000 patients provides us with a good indication, as it represented 55% of HIV-infected patients who died in France that year, according to a study estimating total HIV patient numbers by using the capture-recapture method.[26] Our prospective data collection did not include information on treatments, and, consequently, their impact on non-AIDS mortality cannot be assessed in our study. Unexplained and sudden deaths may be overrepresented, as the diagnostic reliability of recorded deaths occurring outside hospital (54% in our study) may be poorer than for deaths in hospitals. To compare the 2010 data with the previous surveys, we had to change to a less restrictive definition of immunovirologic success, which is no longer considered a positive outcome in many parts of the world. This affected the distribution of the causes of death, as highlighted by hepatic mortality exceeding cardiovascular mortality in PIVS2, and AIDS deaths in 2010 doubling (6.5% vs. 2.5%) compared with the PIVS definition.

Although immunovirologic control is fundamental, a parallel multidisciplinary approach—including prevention, screening strategies, and therapeutic management of comorbidities (mainly malignancies, viral hepatitis, psychological disorders, and cardiovascular diseases)—needs to be optimized to reduce mortality among these patients. Taking these into account, the social component is also essential, given the number of deceased patients in a state of socioeconomic difficulty. Physicians providing care to HIV-infected patients must be made aware about the benefits of such a multidisciplinary approach through appropriate training.

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Author Disclosure Statement

No competing financial interests exist.

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