

# Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000

Philippe Morlat<sup>a,b</sup>, Caroline Roussillon<sup>a,c</sup>, Sandrine Henard<sup>d</sup>,  
Dominique Salmon<sup>e,f</sup>, Fabrice Bonnet<sup>a,b</sup>, Patrice Cacoub<sup>g,h</sup>,  
Aurore Georget<sup>a,c</sup>, Albertine Aouba<sup>i</sup>, Eric Rosenthal<sup>j,k</sup>, Thierry May<sup>d</sup>,  
Marie Chauveau<sup>l</sup>, Bilghissa Diallo<sup>m,n</sup>, Dominique Costagliola<sup>o,p</sup>,  
Geneviève Chene<sup>a,c,q</sup>, for the ANRS EN20 Mortalité 2010 Study Group

**Objective:** The Mortalité 2010 survey aimed at describing the causes of death among HIV-infected patients in France in 2010 and their evolution since 2000.

**Design and methods:** A national sample of clinical sites, providing HIV care and treatment, notified and documented deaths using a standardized questionnaire.

**Results:** The 90 participating wards notified 728 deaths. Median age at death was 50 years (interquartile range 45–58) and 75% were men. The main underlying causes of death were AIDS-related (25% in 2010 vs. 36% in 2005 and 47% in 2000), non-AIDS non-viral hepatitis-related malignancy (22 vs. 17 and 11%), liver-related (11 vs. 15 and 13%), cardiovascular diseases (10 vs. 8 and 7%) and non-AIDS-related infections (9 vs. 4 and 7%). Malignancies (AIDS and non-AIDS-related) accounted for a third of all causes of death. AIDS accounted for 33% of all causes of death among patients mono-infected with HIV vs. only 13% among those co-infected with hepatitis B virus or hepatitis C virus.

**Conclusion:** In 2010, 25% of the causes of death among HIV-infected patients remained AIDS-related. Improved screening and earlier HIV treatment should lead to a smaller proportion of deaths due to AIDS. The majority of patients died of various causes, whereas their HIV infection was well controlled under treatment. Improving case management of HIV-infected patients should include a multidisciplinary approach (prevention, screening, treatment), especially in oncology. Smoking cessation should be a priority goal.

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<sup>a</sup>INSERM, ISPED, Centre INSERM U897-Epidémiologie-Biostatistiques, <sup>b</sup>Service de Médecine Interne et Maladies Infectieuses, Hôpital Saint-André, CHU de Bordeaux, <sup>c</sup>University Bordeaux, ISPED, Centre INSERM U897-Epidémiologie-Biostatistiques, Bordeaux, <sup>d</sup>Service de Maladies Infectieuses, Hôpital Brabois, Vandoeuvre-Les-Nancy, <sup>e</sup>Unité de Pathologie Infectieuse, Pôle Médecine, Hôpital Cochin, AP-HP, <sup>f</sup>Université Paris Descartes, <sup>g</sup>Department of Internal Medicine and Immunology, AP-HP Hôpital La Pitié-Salpêtrière, <sup>h</sup>Département Hospitalo-universitaire I2B, UPMC Univ Paris 06, UMR 7211, Paris, <sup>i</sup>INSERM-CépiDC, Le Kremlin-Bicêtre, <sup>j</sup>Service de Médecine Interne, Hôpital de l'Archet, <sup>k</sup>Université de Nice-Sophia Antipolis, Nice, <sup>l</sup>Service des Maladies Infectieuses et Tropicales, Hôpital Purpan, Toulouse, <sup>m</sup>Service des Maladies Infectieuses et Tropicales, Hôpitaux Universitaires Paris Nord Val de Seine, <sup>n</sup>Université Paris 7, <sup>o</sup>INSERM, UMR-S 1136, <sup>p</sup>Sorbonne Universités, UPMC Univ Paris 06, UMR\_S 1136, Paris, and <sup>q</sup>CHU de Bordeaux, Pole de Santé Publique, Bordeaux, France.

Correspondence to Professor Philippe Morlat, Médecine Interne et Maladies infectieuses, Hôpital Saint-André, 1, rue Jean Burguet, 33075 Bordeaux cedex, France.

E-mail: philippe.morlat@chu-bordeaux.fr

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## Introduction

Recent studies have shown that life expectancy of treated HIV-infected adults with controlled infection and high CD4<sup>+</sup> T-cell count has dramatically increased in the HAART era and can be estimated as being close to the general population of the same age and sex [1,2]. Nevertheless, HIV-infected patients still experience early mortality associated, in particular, with late HIV diagnosis, cardiovascular risk factors, comorbidities, or injection drug use. Better characterization of the causes of deaths and of the population of those who die in the most recent years would help to better prioritize prevention interventions and case management. Recently, cohorts and collaborative cohorts have started to standardize the recording and coding of a large number of causes of death in the context of HIV infection across Europe [3–6]. These cohort studies allowed calculating mortality rates among HIV-infected patients, but did not detail the causes of deaths and the characteristics of the patients who died in the very recent years, as they reported mainly cumulative data over a period of several years. Mortalité 2010 is a nation-wide survey, which aimed at describing the distribution of underlying causes of deaths among adults infected with HIV in France in 2010, at studying the characteristics of patients who died, and to describe the evolution of these causes of death over a 10-year period.

## Methods

The Mortalité 2010 survey follows two similar surveys (Mortalité 2000 and Mortalité 2005), which, respectively, included data from 185 and 341 hospital wards providing care and treatment to HIV-infected patients in France [7,8]. These wards were involved in the case management of an estimated 64 000 and 78 000 patients, respectively. In 2000, a study based on the capture–recapture method estimated that deaths in the Mortalité 2000 survey accounted for around 55% of deaths among people infected with HIV in France [9].

In order to optimize logistics, the 2010 survey was conducted only in the centres reporting at least five deaths during one of the previous surveys. Thus, 90 centres participated in the survey, representing approximately 82 000 HIV-infected patients at follow-up (from registries of participating sites collecting data on HIV-infected patients). Each participating centre had to report all deaths among HIV-infected patients that occurred in 2010 in their hospital, or among patients followed up in their department, but who died in another institution or at home. After an initial simplified quarterly report of deaths, HIV specialists in charge of the patients completed an online standardized questionnaire (<http://etudes.isped.u-bordeaux2.fr/M2010/TELECHARGEMENTS/>

CRF\_Mortalite2010\_v20.pdf). Duplicates were identified by cross-checking observations for sex, dates of birth, and death. Coherence of data collected was validated by two physicians specialized in HIV clinical research.

The Epidemiology Centre on Medical Causes of Death (INSERM, CépiDc) determined the underlying cause of each death according to the rules of the International Classification of Diseases – 10th revision [10], based on the questionnaire data. The underlying cause of death was defined as the disease or injury, which initiated the train of morbid events leading directly to death. In order to allow comparisons between the three Mortalité surveys, we used the same algorithm for determining the underlying cause of death in 2010 than in 2000 and 2005, rather than the more recent Coding Causes of Death in HIV (CoDe) [3]. Our algorithm is nevertheless adapted to the specificities of HIV infection [7] and allows categorization of deaths as follows: AIDS-related causes (1993 Centers for disease Control clinical classification), deaths related to non-AIDS-defining and non-viral hepatitis (NaNH)-related malignancies, hepatic diseases, cardiovascular diseases, non-AIDS-defining infections and suicide. When the only information about the circumstances of a death was its brutal occurrence, it was defined as ‘unexplained sudden death’. When no information at all was available, the cause of death was considered as ‘unknown’.

When a drug was considered responsible for the occurrence of death, the algorithm recommended to mention this death not as iatrogenic, but to consider the disease that led to the drug administration as the cause of death.

Patients were considered as co-infected with hepatitis C virus (HCV) when HCV antibody and/or HCV plasma RNA were notified. They were considered as co-infected with hepatitis B virus (HBV) when hepatitis B surface antigen and/or HBV plasma DNA were notified.

Crude mortality in 2010 was estimated as the number of deaths in 2010 divided by the total number of patients seen at least once during the year in the participating centres.

Comparisons of categorical variables between groups were performed using the chi-squared test or chi-square corrected, or Fisher’s exact test, as appropriate. Group comparisons of quantitative variables were performed with Student’s *t* tests (comparison of means) or the Wilcoxon test (comparison of distributions) according to the distribution of the variable of interest. The distribution of underlying causes of death was compared between 2000, 2005 and 2010 using a multinomial logistic model adjusting for sex and age [11]. All analyses were performed using the 9.1.3 service pack 2 version of

SAS software (SAS Institute Inc., Cary, North Carolina, USA).

In order to study characteristics associated with death among HIV-infected patients, we compared (chi-square test or Student's *t* test) the main characteristics of the patients reported in the Mortalité 2010 survey with those of patients registered in 2010 in the 'Agence nationale de recherches sur le sida et les hépatites virales' (ANRS) CO4 French Hospital Database on HIV (FHDH) ([http://www.ccde.fr/main.php?setlg=en&main\\_file=f1-1309272043-794.html](http://www.ccde.fr/main.php?setlg=en&main_file=f1-1309272043-794.html)) and alive at the end of that year [12].

## Results

### General characteristics

The total number of deaths reported in 2010 by the 90 centres was 728 (836 for the same centres in 2005 and 783 in 2000). Two centres declared no death. Main epidemiological, biological and therapeutic data are given in Table 1.

Crude mortality was 0.9%.

### Underlying cause of death

The main underlying causes of death were the following (Fig. 1): AIDS (25%), NaNH-related malignancies (22%), hepatic diseases (11%), cardiovascular diseases (10%), non-AIDS-defining infections (9%) and suicide (5%). The distribution of these underlying causes of death differed significantly between 2000, 2005 and 2010 ( $P < 10^{-4}$ ), even after adjustment for age and sex.

In 2010, following the specific process mentioned in the Methods section, 220 AIDS-defining illnesses were diagnosed in 182 patients who died of AIDS causes (Fig. 2). The most frequent were non-Hodgkin's lymphoma (NHL) (24% of AIDS causes), *Pneumocystis jirovecii* pneumonia (13%) and progressive multifocal leukoencephalopathy (10%). Median time between AIDS-defining illness diagnosis and death was 2.6 months.

The 165 NaNH malignancies responsible for the deaths of 161 patients were mainly bronchopulmonary malignancies (38% of causes of NaNH malignancies), gastrointestinal malignancies (14%), ear-nose-throat malignancies (10%), anal malignancies (9%) and urogenital malignancies (9%). Ninety-five percent of patients who died due to bronchopulmonary malignancies were past or current smokers.

Among the 77 hepatic deaths, 32 were due to hepatocarcinoma, 37 due to cirrhosis, five due to non-viral cirrhosis, two due to HCV (no further information) and one due to nodular regenerative hyperplasia. In total,

65% of deaths due to chronic liver disease occurred in patients co-infected with HCV, 19% with HBV, and 6% with HBV and HCV infections.

Taking into account all malignancies as causes of death (71 AIDS-defining malignancies, 165 NaNH malignancies and 32 hepatocarcinoma), 268 malignancies were deemed responsible for the death of 250 patients, that is, 34% of all deceased patients.

The 73 cardiovascular causes of death were mainly ischemic heart disease (40%), stroke (26%) and heart failure (11%).

Half of the 68 deaths related to non-AIDS-defining infections were broncho-pulmonary infections ( $n = 35$ ).

The unexplained sudden deaths accounted for 3.6% of causes of death.

Seventy-four patients died of 'various' causes: 18 injuries, 12 neurological causes, eight haematological causes, eight bronchopulmonary causes (including seven chronic obstructive bronchopneumopathies), eight endocrinal and metabolic causes, six renal causes, six related to active drug use, five digestive causes and three iatrogenic causes (bone marrow aplasia under cotrimoxazole prophylaxis, gastrointestinal bleeding with NSAIDs and anticoagulants, and unspecified iatrogenic toxicodermia).

Unknown causes accounted for 4% of all causes of death.

Twenty-nine percent of the cases of deaths reported in our study occurred outside hospitals. Compared to patients dying inside hospitals, patients dying outside the hospitals died less often of AIDS events (14 vs. 31%), NaNH malignancies (13 vs. 26%), non-AIDS-defining infections (3 vs. 12%), and more often of suicide (14 vs. 0.8%), unexplained sudden deaths (11 vs. 0.4%) and unknown deaths (11 vs. 1%).

### Characteristics according to cause of death

Patients who died from an AIDS cause had been diagnosed with HIV less than 6 months previously in 26% of cases (vs. 4% of patients who died of non-AIDS causes). Their infection was less frequently controlled than patients who died of non-AIDS causes: median CD4<sup>+</sup> T-cell count was 66/ $\mu$ l (vs. 307/ $\mu$ l;  $P < 10^{-4}$ ), 23% had CD4<sup>+</sup> T-cell count above 200/ $\mu$ l (vs. 66%;  $P < 10^{-4}$ ) and 21% had plasma HIV RNA below 50 copies/ml (vs. 67%;  $P < 10^{-4}$ ).

### Characteristics by age at time of death

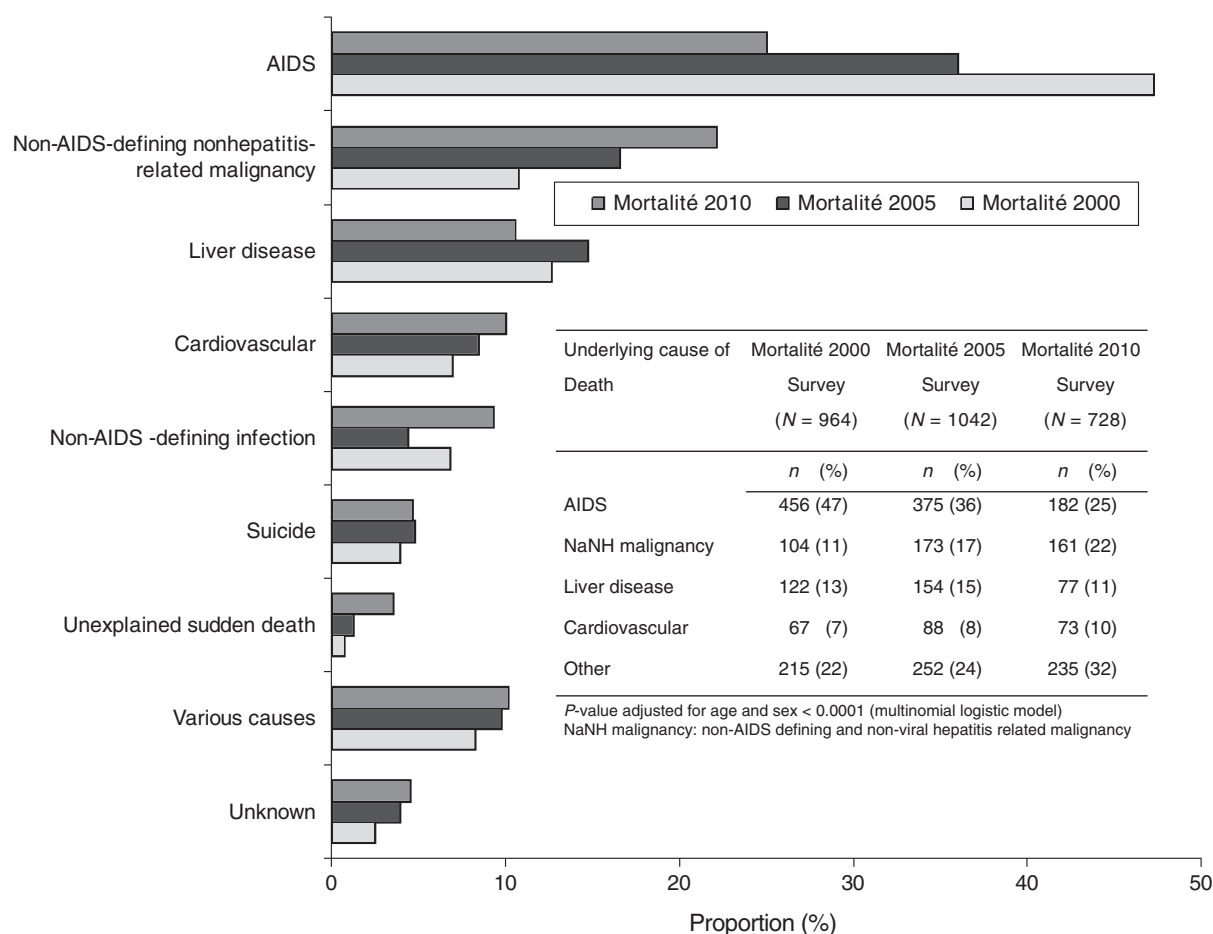
AIDS was the leading cause of death in those patients dying before 50 years, but NaNH malignancies were the leading causes of death in those dying after 50 years (Table 2).

Table 1. Characteristics of HIV-infected adults dying in 2010 according to the underlying causes of death, Mortalité 2010 survey, France.

| N (%)   | All causes<br>728 (100) | AIDS<br>182 (25) | NaNH<br>malignancy<br>161 (22) | Liver<br>disease<br>77 (11) | Cardiovascular<br>73 (10) | Non-AIDS-defining<br>infection<br>68 (9) | Suicide<br>34 (5) | Various<br>causes<br>74 (10) | Unexplained<br>sudden death<br>26 (4) | Unknown<br>33 (4) |
|---|-------------------------|------------------|--------------------------------|-----------------------------|---------------------------|--|-------------------|------------------------------|---------------------------------------|-------------------|
| Male sex (%)  | 75                      | 74               | 80                             | 78                          | 80                        | 65                                       | 74                | 80                           | 73                                    | 64                |
| Median age<br>(years)   | 50                      | 49               | 53                             | 48                          | 52                        | 51                                       | 47                | 53                           | 53                                    | 48                |
| (Interquartile<br>range)  | (45–58)                 | (43–56)          | (47–60)                        | (44–53)                     | (47–60)                   | (47–58)                                  | (43–50)           | (47–63)                      | (45–59)                               | (42–51)           |
| Non-native from<br>France   | 27                      | 32               | 20                             | 22                          | 23                        | 34                                       | 9                 | 35                           | 27                                    | 44                |
| Median known<br>duration of<br>HIV infection<br>(n = 723)         | 14.5                    | 7.2              | 15.8                           | 19.6                        | 16.8                      | 14.8                                     | 15.8              | 13.2                         | 18.7                                  | 15.0              |
| (years)   |                         |                  |                                |                             |                           |  |                   |                              |                                       |                   |
| (Interquartile<br>range)  | (6.8–21.2)              | (0.4–15.2)       | (10.3–21.7)                    | (13.3–22.4)                 | (11.3–23.1)               | (6.4–20.6)                               | (6.1–20.7)        | (7.0–20.6)                   | (10.6–22.2)                           | (10.0–21.2)       |
| HIV infection<br>diagnosed<br>within<br>6 months<br>(n = 723) (%) | 9                       | 26               | 4                              | 1                           | 1                         | 6  | 9                 | 8                            | 0                                     | 0                 |
| HIV transmission<br>group   |                         |                  |                                |                             |                           |  |                   |                              |                                       |                   |
| (n = 726) (%)   |                         |                  |                                |                             |                           |  |                   |                              |                                       |                   |
| Heterosexual  | 37                      | 42               | 40                             | 14                          | 30                        | 43                                       | 27                | 46                           | 27                                    | 42                |
| Homo-bisexual   | 24                      | 32               | 23                             | 16                          | 26                        | 15                                       | 38                | 24                           | 23                                    | 9                 |
| Injecting drug<br>user  | 26                      | 10               | 25                             | 60                          | 34                        | 25                                       | 24                | 20                           | 42                                    | 24                |
| Blood product<br>recipient  | 3                       | 2                | 3                              | 6                           | 1                         | 1  | 3                 | 4                            | 4                                     | 0                 |
| Other/<br>undetermined  | 10                      | 14               | 9                              | 4                           | 8                         | 16                                       | 9                 | 5                            | 4                                     | 24                |
| AIDS stage<br>(n = 716) (%)                                       | 60                      | 100              | 47                             | 36                          | 53                        | 64                                       | 41                | 36                           | 31                                    | 67                |
| Median CD4 <sup>+</sup><br>T-cell count<br>(n = 714) (μl)         | 243                     | 66               | 288                            | 280                         | 307                       | 191                                      | 504               | 307                          | 520                                   | 336               |
| (interquartile<br>range)  | (91–451)                | (19–182)         | (176–451)                      | (148–477)                   | (167–487)                 | (83–384)                                 | (301–649)         | (136–572)                    | (400–688)                             | (97–590)          |

|   |    |    |    |    |    |    |    |    |    |    |
|---|----|----|----|----|----|----|----|----|----|----|
| HIV RNA <50 copies/ml (n = 682) (%)             | 56 | 21 | 69 | 68 | 72 | 55 | 58 | 64 | 89 | 60 |
| No prior antiretroviral treatment (n = 727) (%) | 9  | 18 | 4  | 3  | 6  | 15 | 6  | 10 | 8  | 3  |
| HCV antibodies (n = 726) (%)                    | 30 | 14 | 27 | 73 | 36 | 30 | 35 | 22 | 46 | 22 |
| Hepatitis B surface antigen (n = 724) (%)       | 13 | 7  | 14 | 27 | 16 | 10 | 9  | 12 | 4  | 9  |
| Dyslipidaemia with medical care (n = 705) (%)   | 14 | 5  | 16 | 11 | 30 | 9  | 15 | 18 | 15 | 16 |
| Diabetes (n = 721) (%)                          | 10 | 7  | 9  | 14 | 11 | 13 | 12 | 11 | 19 | 3  |
| Arterial hypertension (n = 721) (%)             | 17 | 12 | 11 | 12 | 39 | 15 | 21 | 30 | 12 | 9  |
| Depression or generalized anxiety (n = 709) (%) | 33 | 24 | 25 | 33 | 44 | 32 | 66 | 32 | 46 | 45 |
| Excessive alcohol consumption (n = 610) (%)     | 25 | 19 | 20 | 41 | 32 | 20 | 15 | 32 | 45 | 24 |
| Smoking (n = 667) (%)                           | 71 | 58 | 80 | 85 | 75 | 65 | 60 | 65 | 76 | 75 |

HCV, hepatitis C virus; NaNH malignancy, non-AIDS-defining and non-viral hepatitis-related malignancy. Dyslipidaemia with medical care: dyslipidaemia leading to specific care (stop or modification of antiretroviral therapy, hypolipidaemic drugs, dietetic treatment). Depression: history of depression leading to specific care (drug therapy or psychotherapy treatment). Excessive alcohol consumption: more than 50 g/day. Smoking: current or past consumption. Unexplained sudden death: the only information about the circumstances of a death is its brutal occurrence. Unknown: no information at all is available about the circumstances of death. Various causes: a cause of death is available but does not fall under other specified categories.



**Fig. 1. Distribution of the underlying cause of death among HIV adults, French national 2000 ( $n = 964$ ), 2005 ( $n = 1042$ ) and 2010 ( $n = 728$ ) surveys, France.**

The decrease in the proportion of deaths due to AIDS and the increasing proportion of deaths due to NaNH malignancies between 2000 and 2010 were observed in all age groups. An increase in the proportion of cardiovascular deaths was only observed in patients between 40 and 59 years.

### Characteristics according to time since HIV diagnosis

Sixty-eight patients (9%) died within 6 months after the diagnosis of HIV infection. Compared to patients with an HIV diagnosis known for more than 6 months, they were more likely ( $P < 10^{-4}$ ) to have died of an AIDS complication (69 vs. 21%), to be born overseas (50 vs. 28%), to have been infected through heterosexual intercourse (50 vs. 35%) and to be less often co-infected with HCV (15 vs. 42%). In median, the last CD4<sup>+</sup> T-cell count was 62/ $\mu$ l (vs. 268/ $\mu$ l) and plasma HIV RNA was below 50 copies/ml in only 4% of them (vs. 58%).

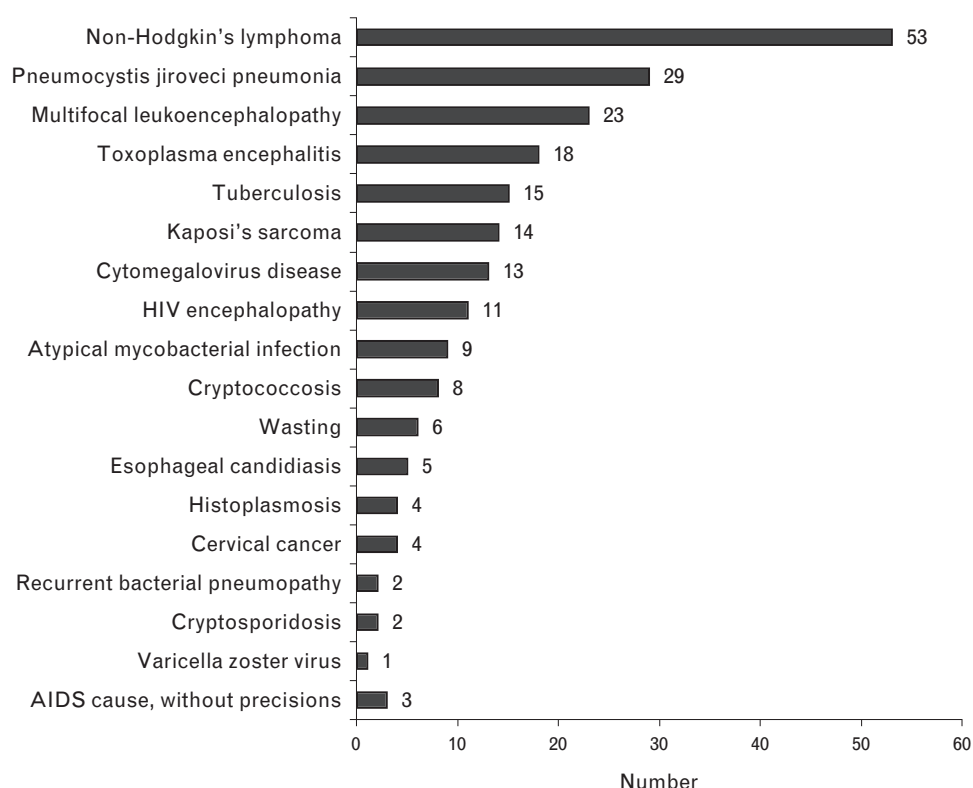
### Characteristics according to hepatitis B virus/hepatitis C virus co-infection status

The distribution of the main causes of death differed between patients co-infected with HIV and HBV or

HCV, vs. those not co-infected ( $P < 10^{-4}$ ): the main causes of death in co-infected patients ( $n = 290$ ) were hepatic diseases (24%), NaNH malignancies (21%), AIDS (13%), cardiovascular diseases (12%) and non-AIDS-defining infections (9%). Twenty-seven percent of patients co-infected with HBV and 47% of those co-infected with HCV had not received treatment for their hepatitis. Among patients not co-infected, the distribution of causes of death was: AIDS (33%), NaNH malignancies (23%), non-AIDS-defining infections (9%), and cardiovascular diseases (9%); hepatic diseases accounted for 1% of causes of death.

### Comparison with ANRS CO4 FHDH data

Characteristics reported in 2010 of 49 366 patients followed as part of the ANRS CO4 FHDH cohort, who were not deceased in 2010, were compared to data reported among the patients who died in 2010 in our Mortalité 2010 survey; proportion of women was higher in the CO4 FHDH cohort as compared to the Mortalité 2010 survey (33 vs. 25%), patients were younger (46 vs. 50 years), less often infected by intravenous drug injection (11 vs. 26%), less likely to have reached the AIDS stage (24 vs. 61%), less frequent carriers of hepatitis B surface



**Fig. 2. Distribution of AIDS-defining diseases ( $n = 220$ ) among HIV-infected adults dying of an AIDS-related cause of death ( $n = 182$ ), French national 2010 survey, France.**

antigen (8 vs. 13%) or HCV antibodies (15 vs. 30%), less often smokers (42 vs. 71%) and had better immuno-virological control (median last CD4<sup>+</sup> T-cell count: 532 vs. 243/ $\mu$ l; last HIV RNA <50 copies/ml: 66 vs. 56%) ( $P < 10^{-4}$  for all comparisons). They were similarly exposed to antiretroviral therapy (92 vs. 91%;  $P = 0.104$ ).

## Discussion

### Distribution of the causes of death

The 90 centres participating in the Mortalité 2010 survey reported 728 deaths. The main underlying causes of death were AIDS (25 vs. 36% in 2005 and 47% in 2000), NaNH malignancy (22 vs. 17% in 2005 and 11% in 2000), hepatic (11%), cardiovascular diseases (10%) and non-AIDS-defining infection (9%).

Data in the literature regarding the distribution of causes of death among HIV-infected patients followed up in industrialized countries compile pluri-annual data and were collected within, most of the time, small populations in the most recent years [4–6,13]. All studies report a progressive decrease in the proportion of deaths due to AIDS and an increase in the NaNH malignancies. Data from the D:A:D cohort ('Data Collection on Adverse events of Anti-HIV Drug', a prospective multi-cohort

study initially implemented to study adverse events of antiretroviral drugs and recently expanded to emergent morbidity in HIV-infected persons) regarding the causes of 548 deaths that occurred between 2009 and 2011 (International AIDS conference 2012, abstract THAB0304) are very similar to ours: AIDS (22%), NaNH malignancies (20%), hepatic (9%) and cardiovascular diseases (10%).

### Underlying causes of death

In 2010, AIDS represented only a quarter of the causes of death in HIV-infected patients deceased in France. This nevertheless remains a high proportion in a country with universal access to care. Among patients not co-infected with viral hepatitis B or C, AIDS still represented a third of all deaths. A recent diagnosis of HIV infection, a lower frequency of antiretroviral treatment and a lower immuno-virological control observed in patients who died of AIDS indicate that improved screening and earlier treatment prescription should lead to a smaller proportion of deaths due to AIDS.

The high incidence of comorbidities (chronic viral hepatitis, diabetes, hyperlipidaemia, hypertension, depression) and addictions (tobacco, alcohol, drugs) plays an important role in the occurrence of non-AIDS death cases. Cumulative exposure to these factors has indeed been more important in recent years because of the

Table 2. Underlying causes of death in HIV-infected adults according to age [distribution in 2000 (*n* = 917<sup>a</sup> among 964), 2005 (*n* = 1012<sup>a</sup> among 1042) and 2010 (*n* = 728); Mortalité 2000, 2005 and 2010 surveys, France].

| Age (years)                               | 18–29                    |                          |                          | 30–39                     |                           |                          | 40–49                     |                           |                           | 50–59                     |                           |                           | 60 or older              |                           |                           |
|---|--------------------------|--------------------------|--------------------------|---------------------------|---------------------------|--------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|--------------------------|---------------------------|---------------------------|
|   | 2000<br>( <i>n</i> = 42) | 2005<br>( <i>n</i> = 25) | 2010<br>( <i>n</i> = 13) | 2000<br>( <i>n</i> = 366) | 2005<br>( <i>n</i> = 209) | 2010<br>( <i>n</i> = 78) | 2000<br>( <i>n</i> = 293) | 2005<br>( <i>n</i> = 443) | 2010<br>( <i>n</i> = 263) | 2000<br>( <i>n</i> = 123) | 2005<br>( <i>n</i> = 193) | 2010<br>( <i>n</i> = 232) | 2000<br>( <i>n</i> = 93) | 2005<br>( <i>n</i> = 142) | 2010<br>( <i>n</i> = 142) |
| Underlying cause of death [ <i>n</i> (%)] |                          |                          |                          |                           |                           |                          |                           |                           |                           |                           |                           |                           |                          |                           |                           |
| Aids                                      | 28 (67)                  | 17 (68)                  | 6 (46)                   | 170 (46)                  | 106 (49)                  | 27 (35)                  | 142 (48)                  | 142 (31)                  | 69 (26)                   | 57 (46)                   | 67 (34)                   | 47 (20)                   | 40 (43)                  | 41 (28)                   | 33 (23)                   |
| NaNH malignancy                           | 1 (2)                    | 3 (12)                   | 1 (8)                    | 26 (7)                    | 14 (7)                    | 14 (18)                  | 39 (13)                   | 75 (17)                   | 46 (18)                   | 18 (15)                   | 46 (23)                   | 63 (27)                   | 14 (15)                  | 35 (24)                   | 37 (26)                   |
| Cardiovascular disease                    | 2 (5)                    | 1 (4)                    | –                        | 21 (6)                    | 8 (4)                     | 3 (3)                    | 16 (6)                    | 33 (7)                    | 23 (9)                    | 12 (10)                   | 21 (11)                   | 30 (13)                   | 14 (15)                  | 25 (17)                   | 17 (12)                   |
| Liver disease                             | –                        | –                        | –                        | 58 (16)                   | 25 (12)                   | 7 (9)                    | 40 (14)                   | 90 (20)                   | 43 (16)                   | 15 (12)                   | 26 (13)                   | 22 (10)                   | 5 (5)                    | 12 (8)                    | 5 (4)                     |
| Other                                     | 11 (26)                  | 4 (16)                   | 6 (46)                   | 91 (25)                   | 61 (28)                   | 27 (35)                  | 56 (19)                   | 115 (25)                  | 82 (31)                   | 21 (17)                   | 37 (19)                   | 70 (30)                   | 20 (22)                  | 33 (23)                   | 50 (35)                   |

NaNH malignancy, non-AIDS-defining and nonviral hepatitis-related malignancy.

<sup>a</sup>Available data.

gradual increase in life expectancy of patients related to a better management of HIV infection [14]. Smoking seems to be associated with occurrence of death since more than 70% of HIV infected-patients who died in our study were smokers whereas only 42% among patients living with HIV at the end of 2010 and followed in the ANRS CO4 FHDH cohort.

The proportion of deaths due to NaNH malignancies doubled between 2000 and 2010 (from 11 to 22%), and these have become the leading cause of death in HIV-infected patients over 50 years. Taking into account the AIDS-defining malignancies and hepatocellular carcinoma, all malignancies represent the leading cause of mortality in patients with HIV in 2010; despite a significant difference between median age at death in our study and in the general population (50 vs. 81 years, respectively), the percentage of malignancy-related deaths was quite similar in the two populations (33 vs. 30%, respectively) [15–17].

The proportion of deaths from cardiovascular causes increased moderately (10% in 2010 vs. 7 and 8% in 2000 and 2005). Aging of the HIV-infected population, more exposed to traditional cardiovascular risk factors than the general population, may contribute to this trend. The role of HIV infection through chronic inflammation could be a contributing factor of cardiovascular death, independent of other risk factors [18].

In our study, 13 and 30% of deceased people were co-infected by hepatitis B and C, respectively. These proportions are much higher than those observed in non-deceased HIV-infected patients followed in France in 2010 (8 and 15%, respectively) and suggest the poor prognosis associated with co-infection with hepatitis virus [19,20]. Liver diseases remain the leading cause of death (24%) in co-infected individuals [21]. The decrease of the proportion of deaths related to liver damage between 2005 and 2010 (from 15 to 11%) probably reflects a better management of HIV and of hepatitis B and C, which are responsible for 92% of liver-related deaths in this study [22,23]. The number of liver-related deaths may decline further with better access to hepatitis C treatment for HIV-infected patients, early detection of hepatocellular carcinoma (16% of liver-related causes of death in 2000 and 42% in 2010) and the dissemination of awareness and prevention messages on the risks associated with excessive alcohol consumption. It should be underlined that liver-related diseases are the leading cause of death in co-infected patients, whereas AIDS in this population only represents 13% of causes of death.

Among the non-AIDS-defining infections, bronchopulmonary infections predominate and probably also represent a significant proportion of deaths reported as undocumented sepsis. Improved prevention measures (pneumococcal vaccine, influenza vaccine, smoking



cessation) should contribute to their decline. In all, 105 bronchopulmonary-related deaths were observed (62 bronchopulmonary malignancies, 35 infections and eight other causes) accounting for 14% of all causes of death.

The proportion of deaths by suicide (5%) in the Mortalité 2010 survey is higher than in the general population (2%) and suggests the need for increased vigilance regarding the mental health of these patients (one-third of deceased patients presented with depression or generalized anxiety disorder).

We noted an increase over time in the frequency of unexplained sudden deaths (from 0.7% in 2000 to 3.6% in 2010), which follows the same trend as that observed for deaths from cardiovascular causes, known to represent the majority of these sudden deaths [24].

The importance of HIV-related immunosuppression in the occurrence of non-AIDS-related deaths is likely since median CD4<sup>+</sup> T-cell count is around 300/ $\mu$ l in these circumstances (Table 1), whereas it is more than 500/ $\mu$ l in patients not deceased and of the ANRS CO4 FHDH cohort.

A significant proportion of 'various causes' of deaths was observed in our survey (10% in 2010): this is probably related to the chronicity of infection that allows lethal diseases to occur in HIV-infected patients.

### Mortality

In our study, we estimated the mortality in 2010 as being 0.9%, vs. 1.3% in 2005 and 1.5% in 2000. Our results are in accordance with cohort studies which reported a reduced mortality in HIV-infected patients [4–6,25]. Moreover, some recent analyses showed equal life spans in HIV-infected and non-infected adults in the HAART era [1,2]. This is especially true for patients with more than 500/ $\mu$ l CD4<sup>+</sup> T-cell count and treated by antiretroviral therapy for several years. The median age at death observed in our study (50 years) reflect the median age of HIV-infected patients who died prematurely in 2010 mainly due to poor prognostic factors.

Regarding the specific mortality by cause, since the survival has increased over time leading to an increasing prevalence of HIV infection and an increasing number of patients in follow-up, we can confirm decreasing trends when the proportion of deaths from specific causes among the overall number of deaths is stable (liver diseases) or decreasing (AIDS) over time. When the proportion of deaths from specific causes is increasing over time (i.e. malignancies, cardiovascular diseases), survival analysis would be better suited to conclude about the increasing trend. Of note, only very few large cohorts or collaborations of cohorts are organized to document causes of death at the level achieved in the Mortalité studies [26].

### Limitations

Patients in care in the centres participating in the 2010 survey (82 000) represented 74% of the entire HIV-infected population estimated to be in care in France in 2010 (111 500) and 55% of all HIV-infected patients living in France (149 900, including those who ignore their diagnosis) ([http://www.sante.gouv.fr/IMG/pdf/Rapport\\_Morlat\\_2013\\_Mise\\_en\\_ligne.pdf](http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf)).

The possibility that the centres providing routine HIV care are less confronted with non-AIDS end-of-life clinical situations and that they are less likely to report these types of causes of death should not be excluded, but this has been limited by the incentive provided to investigators to report the deaths of patients who died within a structure other than their own service, whether or not they were or had been part of active follow-up.

As in other studies [12], we acknowledge that there are some limitations in ascertaining causes of deaths given the absence of autopsy among patients registered in the study and given the high proportion of deaths occurring outside hospitals. Although unexplained and sudden deaths could be over-represented due to a high number of deaths occurring outside hospital (29%), we believe that the process of documentation and classification performed in the Mortalité studies (expertise from two previous similar studies, detailed standardized questionnaire, coherence of data validated by two experienced physicians and role of the national reference Centre on Medical Causes of deaths) gives an accurate estimation of the causes of deaths observed among HIV-infected patients followed in France.

Moreover, our study was better designed to estimate the distribution of the causes of deaths of HIV-infected patients in care rather than outside HIV care. Nevertheless, the distribution of causes of deaths among deceased patients whose HIV infection has been diagnosed less than 6 months before death (AIDS events represented in our study 69% of the deaths in this population) may provide a fair approximation for the distribution of causes of death among patients outside HIV care. This is in accordance with the increased rate of AIDS/deaths associated with late presentation in care of HIV-positive persons [27].

In total, in 2010, AIDS represented only a quarter of the causes of death in HIV-infected patients, and most of the patients died from a range of causes, whereas HIV infection was controlled with treatment. Screening for HIV infection can be further improved and for patients whose infection is known, a multidisciplinary approach is essential, especially for prevention, screening, early diagnosis and treatment of malignancies and cardiovascular diseases [16,17,28]. As it could favourably influence a lot of potentially lethal diseases, we emphasize that

smoking cessation should be a primary goal in HIV-infected patients [5,6].

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The authors from the study group ANRS EN20 Mortalité 2010 study group in collaboration with Mortavic are listed below (<http://links.lww.com/QAD/A488>)

### Investigator sites

Aix-En-Provence: A.P. Blanc, T. Allègre, M. Marquiant; Angers: E. Pichard, J.M. Chennebault; Antibes: D. Quinsat; Argenteuil: L. Sutton, P. Genet, J. Gerbe; Avignon: G. Lepeu, G. Pichancourt; Basse-Terre: B. Giffo, F. Boulard; Bayonne: F. Bonnal, C. D'Ivernois; Besançon: B. Hoen, P. Humbert; N. Magy-Bertrand, G. Helder, C. Bourdeaux; Bobigny: O. Bouchaud, P. Honoré; Bondy: V. Jeantils, L. Tegna, M. Coupard; Bordeaux: M. Dupon, L. Lacaze-Buzy; P. Mercié; P. Morlat, S. Caldato; J.M. Ragnaud; Boulogne: E. Rouveix, E. Reimann; Caen: R. Verdon, P. Feret; Cayenne: F. Djossou; Clamart: F. Boué, I. Kansau, H. Schoen; Clermont-Ferrand: J. Beytout, C. Jacomet, L. Cormerais; Colmar: G. Blaison, M. Mohseni, Z.A. Pachart; Colombes: I. Mahe, E. Mortier, F. Zeng; Compiègne: D. Merrien, J.C. Seghezzi; Corbeil-Essonnes: A. Devidas, P. Chevojon, I. Turpault; Créteil: Y. Lévy, S. Dominguez, C. Dumont; Dijon: P. Chavanet, A. Faivre, C. Braconnier; Fort-De-France: A. Cabié, G. Hurtrel; Fréjus: R. Armero, P. Del Giudice; Garches: C. Perronne, P. De Truchis, D. Le Du, H. Berthé; Grenoble: C. Brambilla, P. Leclercq, S. Dusfresne, M.C. Gailland; Kourou: P. Simon; La Roche-Sur-Yon: P. Perré, I. Suaud; La Rochelle: E. Brottier-Mancini; Lagny-Sur-Marne: E. Froguel, S. Tassi; Le Grand-Lucé: F. Thibous; Le

Kremlin-Bicêtre: J. Delfraissy, C. Goujard, K. Bourdic; Limoges: P. Weinbreck, C. Genet; Lyon: J.L. Touraine, F. Jeanblanc; F. Zoulim, L. Cotte, J. Koffi, C. Brochier, V. Thoirain; D. Peyramond, S. Degroodt; Mantes-La-Jolie: F. Granier, C. Billy, J.L. Ecobichon; Marseille: P. Brouqui, J. Moreau; I. Poizot-Martin, O. Faucher Zaegel, A. Ivanova; A. Stein, I. Ravau; Metz: B. Christian, A. Armand; Montpellier: J. Reynes, J.M. Jaquet, C. Tramoni; Nancy: T. May, S. Hénard; Nantes: F. Raffi, H. Hue; Nevers: H. Djerad, C. Sautereau; Nice: P. Dellamonica, N. Oran, S. Sausse; J.G. Fuzibet, E. Rosenthal, S. Bréaud; Nîmes: A. Sotto, R. Doncesco; Paris: J. Blacher, J.P. Viard, A. Maignan; J.F. Bergmann, J.D. Magnier; J. Cadranet, A. Lavole; P.M. Girard, N. Valin; L. Guillevin, D. Salmon-Ceron, V. Le Baut, M.P. Pietri; C. Katlama, A. Chermak, P. Bourse; O. Lortholary, C. Duvivier, M. Shoai, F. Touam; J.M. Molina, D. Ponscarne; E. Oksenhendler, L. Gérard; G. Pialoux, L. Slama, P. Thibaut; D. Séréni, C. Lascoux-Combe; L. Weiss, M.L. Lucas; P. Yéni, B. Diallo; Perpignan: H. Aumaître, M. Malet; Pointe-A-Pitre: G. Beaucaire, I. Lamaury; Poissy: C. Veyssier, B.H. Masson, J.L. Ecobichon; Poitiers: P. Roblot, G. Le Moal, D. Plainchamp; Pontoise: O. Danne, L. Blum, M. Deschaud; Reims: R. Jaussaud, C. Rouger, I. Kmiec; Rennes: C. Michelet, G. Cotten, M. Ratajczak; Rouen: F. Caron, I. Gueit; Saint-Denis: M.A. Khuong, B. Taverne; Saint-Germain-En-Laye: I. Welker, B. Montoya; Saint-Etienne: F. Lucht, M. Detoc; Saint-Laurent du Maroni: J.L. Daigre, V. Vanticke; Saint-Martin: S. Paucod, C. Clavel, S. Stegmann-Plancharde, V. Walter; Saint-Nazaire: S. Hily, C. Michau; Saint-Pierre De La Réunion: P. Poubeau; Sète: B. Kitschke; Saint-Denis De La Réunion: C. Gaud, C. Sautron; Strasbourg: D. Rey, C. Cheneau, P. Fischer; Suresnes: O. Bletry, D. Zucman, D. Bornarel, C. Majerholc; Toulon: A. Lafeuillade, V. Lambry, G. Philip; Toulouse: B. Marchou, M. Chauveau, F. Balsarin; Tourcoing: Y. Yazdanpanah, T. Huleux; Tours: L. Bernard, V. Laplantine; Villejuif: D. Vittecoq, E. Teicher, C. Bolliot.

Steering committee: A. Aouba, F. Bonnet, P. Cacoub, G. Chêne, D. Costagliola, F. Lert, T. May, P. Morlat, E. Rosenthal, C. Roussillon, D. Salmon and C. Semaille.

Coordinating investigators: G. Chêne and P. Morlat.

Clinical trials unit/INSERM U897, Bordeaux School of Public Health (ISPED), University Bordeaux Segalen: F. Couturier, G. Chêne, A. Georget, L. Hardel, C. Roussillon, N. Tabbal and A. Taïeb.

Clinical research physician: C. Béjan and S. Hénard.

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## Conflicts of interest

P.M. has received honoraria from Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme and ViiV Healthcare. F.B. has received honoraria from Bristol-Myers Squibb, Gilead, Janssen Cilag and ViiV Healthcare. E.R. has received honoraria from Amgen, Bristol-Myers Squibb, Gilead, Janssen Cilag, Merck Sharp and Dohme and Roche. T.M. has received honoraria from Janssen Cilag and ViiV Healthcare. D.C. has received honoraria from Abbott, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Janssen, Merck Sharp and Dohme and Roche. For the remaining authors none were declared.

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