

# Changes in Cancer Mortality among HIV-Infected Patients: The Mortalité 2005 Survey

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(See the editorial commentary by d'Arminio Monforte on pages 640–1)

**Background.** The goal of the current study was to describe the distribution and characteristics of malignancy-related deaths among human immunodeficiency virus (HIV)-infected patients with use of data obtained from a national survey conducted in France in 2005 and to compare with results obtained from a similar survey conducted in 2000.

**Method.** The underlying cause of death was documented using a standardized questionnaire fulfilled in French hospital wards and networks that were involved in the treatment of HIV-infected patients.

**Results.** Among the 1042 deaths reported in 2005 (964 were reported in 2000), 344 were cancer related (34%), which represented a significant increase from 2000 (29% of deaths were cancer related) ( $P = .02$ ); 134 of the cancer-related deaths were AIDS related and 210 were not AIDS related. Among the cancer-related causes of death, the proportion of hepatitis-related cancers (6% in 2000 vs. 11% in 2005) and non-AIDS/hepatitis-related cancers (38% in 2000 vs 50% in 2005) significantly increased from 2000 to 2005 ( $P = .03$  and  $P = .01$ , respectively), compared with the proportion of cancer that was AIDS related and adjusting for age and sex. Among cases involving AIDS, the proportion of non-Hodgkin lymphoma-associated deaths did not change statistically significantly between 2000 and 2005 (11% and 10% of deaths, respectively).

**Conclusions.** In this study, an increasing proportion of lethal non-AIDS-related cancers was demonstrated from 2000 to 2005; meanwhile, the proportion of lethal AIDS-related cancers remained stable among HIV-infected patients. Thus, cancer prophylaxis, early diagnosis, and improved management should be included in the routine long-term follow-up of HIV-infected patients.

HIV-infected patients are at an increased risk of non-Hodgkin lymphoma (NHL), Kaposi sarcoma, and cervical cancer, all of which were considered to be AIDS-related events in the 1993 revised classification system for HIV infection [1]. This increased risk seems to be partly related to oncogenic virus coinfections (i.e., Epstein-Barr virus, human herpes virus 8, human papil-

lomavirus, and hepatitis B virus [HBV] infection) and to cellular immunodepression, as demonstrated by the use of immunosuppressive drugs, particularly during transplantation [2, 3]. The widespread use of combination antiretroviral therapies (cART) in industrialized countries since the middle of the 1990s has been associated with a dramatic decrease in the incidence of both mortality and AIDS-related events. However, the incidences of NHL and cervical cancer decreased in a lower proportion than did other opportunistic infections [4, 5]. Prolonged life expectancy was associated with a diversification of morbidity and causes of death to include cardiovascular events, hepatic complications, bacterial infections and non-AIDS-related cancers [6–12]. In a national survey conducted in France in 2000, we demonstrated that 12% of deaths were attributable

Received 3 July 2008; accepted 3 October 2008; electronically published 28 January 2009.

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**Clinical Infectious Diseases** 2009;48:633–9

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1058-4838/2009/4805-0019\$15.00

DOI: 10.1086/596766

non-AIDS-related cancers and that all cancers (i.e., AIDS-related and non-AIDS-related malignancies) accounted for 29% of the deaths [13]. The monitoring of epidemiologic trends would permit the defining of priorities with regard to prevention, early detection, and treatment of AIDS-related and non-AIDS-related malignancies. The objectives of the present study were to describe the distribution and characteristics of malignancy-related deaths among HIV-infected patients in France in 2005 and to assess changes that occurred from the study in 2000.

## PATIENTS AND METHODS

**Data collection.** All hospital wards and networks in France that were known to be involved in the treatment of HIV-infected patients were contacted, including wards that participated in the Mortalité 2000 survey. Apart from contacting a greater number of physicians than in 2000, the study design was similar to that of the previous survey [7].

Physicians were asked to prospectively report and document deaths and provide an abstract of the cause of death for HIV-infected adults (aged  $\geq 18$  years) every 3 months in 2005. Each death was then documented using a standardized questionnaire that included all contributing causes of death, diseases present at time of death, and a global assessment of the underlying cause of death. One physician, who was a part of the coordinating team, oversaw the harmonization of data collection. Double reports were identified by matching the dates of birth and death. Hepatitis C virus (HCV) infection was defined as the presence of HCV antibodies or HCV RNA in serum; excessive alcohol consumption was defined as a daily alcohol intake greater than 50 grams and/or 5 glasses; and poor socioeconomic condition was defined as health insurance, no employment, no accommodation, income below 535€ per month, and/or an illegal immigration status.

**Determination of the underlying cause of death.** Information contained in the questionnaire was used to determine the underlying cause of death according to the rules of the International Classification of Diseases, 10th revision. The underlying cause of death was defined as the disease or injury that initiated the sequence of morbid events that led to death [14]. The algorithm of determination was adapted to the specific concerns of HIV infection [7] and allowed the categorization of deaths as follows: AIDS-related causes were categorized according to the 1993 clinical classification [1]; deaths related to HCV/HBV infection, including hepatocarcinoma; cancers and other causes not related to AIDS or HCV/HBV infection; and adverse effects of antiretroviral treatment. Adverse effects of antiretroviral treatment was considered to be the underlying cause of death only when this was the explicit conclusion of the physician. Cancers were classified as AIDS related when

active pathology at the time of death included one AIDS-defining cancer, according to the classification of the Centers for Disease Control and Prevention for HIV infection as revised in 1993 (i.e., high grade NHL [including Burkitt and immunoblastic lymphoma], primary brain lymphoma, Kaposi sarcoma, and cervical cancer) [1]. Other cancers were classified as either hepatitis-related hepatocarcinoma or non-AIDS/hepatitis-related cancer.

**Statistical analysis.** The distribution of malignancy-related causes of death was compared between 2000 and 2005 with use of the  $\chi^2$  and Kruskal-Wallis tests. To compare the distribution of causes of cancer-related deaths between 2000 and 2005, we performed a multinomial logistic model adjusted for sex and age. Statistical analyses were performed using SAS software, version 9.0 (SAS Institute).

## RESULTS

A total of 1042 deaths were reported in 2005 (964 were reported in 2000) among  $\sim 78,000$  HIV-infected patients observed (i.e., patients with at least 1 contact with participating physicians during 2005) at the 340 wards participating in the survey. Documentation was available for 1013 decedents (97%); 76% were men, the median age was 46 years (median age in 2000, 41 years), the known duration of HIV infection was 12 years (duration in 2000, 8 years), 87% had received an antiretroviral treatment (86% in 2000), 47% had a plasma HIV-RNA level  $< 500$  copies/mL (33% in 2000), the median CD4 lymphocyte count was 161 cells/mm<sup>3</sup> (median count in 2000, 94 cells/mm<sup>3</sup>), 55% of patients had a CD4 cell count  $< 200$  cells/mm<sup>3</sup> (68% in 2000), and 12% of patients had a CD4 cell count  $> 500$  cells/mm<sup>3</sup> (9% in 2000).

**Underlying causes of death.** In the Mortalité 2005 survey, the most frequent underlying cause of death was an AIDS-defining illness in 375 cases (36% in 2005 vs. 47% in 2000), followed by non-AIDS/hepatitis-related cancer ( $n = 173$ ; 17% vs. 11%), liver-related cause ( $n = 154$ ; 15% vs. 13%), cardiovascular disease ( $n = 88$ ; 8% vs. 7%), suicide ( $n = 50$ ; 5% vs. 4%), and other infections ( $n = 46$ ; 4% vs. 7%).

Among the 1013 cases with information provided, 344 malignancy-related causes of death (34% of deaths) were recorded; they were distributed as NHL ( $n = 103$ ; 10% of the causes of death), Kaposi sarcoma ( $n = 25$ ; 2%), hepatitis-related hepatocarcinoma ( $n = 37$ ; 4%) and non-AIDS/hepatitis-related cancers ( $n = 173$ ; 17%) (table 1). The proportion of deaths attributable to malignancies increased statistically significantly, compared with that in 2000 when malignancies accounted for 29% of the causes of death ( $P = .02$ ) (table 2). Adjusted for age and sex, the proportion of deaths attributable to hepatocarcinoma or non-AIDS/hepatitis-related cancer increased statistically significantly from 2000 to 2005, with a greater diver-

**Table 1. Patients' characteristics, by underlying cause of death, the Mortalité 2005 survey.**

Characteristic	Cause of death			
	Non-Hodgkin lymphoma <sup>a</sup> (n = 84)	Hepatitis-related hepatocarcinoma (n = 37)	Non-AIDS/hepatitis-related cancer (n = 173)	Not cancer (n = 676)
Male sex	81	81	80	74
Age, median years (IQR)	48 (41–55)	49 (45–56)	49 (45–58)	45 (40–53)
Duration of HIV infection, median years (IQR)	9.6 (0.9–15.0)	15.4 (10.5–17.9)	11.7 (6.6–16.1)	11.9 (5.6–17.0)
AIDS	100	43	48	62
CD4 count, median cells/mm <sup>3</sup> (IQR)	76 (20–239)	231 (116–367)	205 (75–360)	172 (41–361)
CD4 count >500 cells/mm <sup>3</sup>	7	11	11	14
Previous antiretroviral treatment	88	95	90	86
Duration of antiretroviral treatment, median years (IQR)	7.8 (0.8–11.0)	9.7 (6.3–12.1)	8.2 (5.3–10.9)	8.2 (4.2–10.9)
HIV-RNA level <500 copies/mL	48	69	61	43
Intravenous drug user	15	62	23	33
Hepatitis C virus infection	15	78	29	42
Hepatitis B virus infection	8	23	9	13
Poor socioeconomic conditions	25	16	22	34
Excessive alcohol use	13	38	26	33
Tobacco use	39	56	63	58

**NOTE.** Data are percentage of patients, unless otherwise indicated. IQR, interquartile range.

<sup>a</sup> Excluding primary brain lymphoma.

sification of cancer types. The proportion of AIDS-defining cancers remained stable during the same period.

Patients whose deaths were attributable to non-AIDS/hepatitis-related cancer were older (median age, 49 years), were known to be infected with HIV for a median of 11.9 years, had moderate immunosuppression (median CD4 count, 205 cells/mm<sup>3</sup>; median CD4 count among this group of patients in 2000 was 218 cells/mm<sup>3</sup>), and 61% had a plasma HIV-RNA level <500 copies/mL (table 1).

Respiratory cancer occurred the most frequently among cases of lethal non-AIDS/hepatitis-related cancers (*n* = 65; including 53 cases of lung cancer and 12 cases of nose and throat cancer). The proportion of deaths attributable to respiratory cancer was stable between 2000 and 2005 (5% and 6%, respectively). Patients whose death was attributable to respiratory cancer were older in 2005 (median age, 50 years) than in 2000 (median age, 46 years) and were moderately immunosuppressed at the time of death in 2005 (median CD4 count, 163 cells/mm<sup>3</sup>; median CD4 count among this group of patients in 2000 was 262 cells/mm<sup>3</sup>). Ninety-one percent of patients with death attributable to respiratory cancer had previously been treated with antiretrovirals, and 63% had plasma HIV-RNA levels <500 copies/mL. Ninety percent of these patients were smokers, and 34% had excessive alcohol consumption.

A significant increase in the proportion of lethal digestive cancer was observed from 2000 to 2005, especially pancreatic cancer. Pancreatic cancer was the cause of 10 deaths in 2005

versus 3 deaths in 2000, whereas the rate of anal cancer remained stable. The rate of lethal hemopathies, including Hodgkin lymphoma, remained similar between 2000 and 2005. Deaths of 7 patients were attributed to breast cancer in 2005, compared with none in 2000, and 10 patient deaths were attributable to skin cancer (4 melanoma and 6 non-melanoma cancers), compared with 2 patient deaths in 2000.

Hepatocarcinoma was mainly associated with hepatitis C virus coinfection in 2005, whereas hepatocarcinoma etiology was better balanced between HBV and HCV coinfection in 2000. Patients who died of hepatocarcinoma had a median age of 49 years and were known to be infected with HIV for a median of 15 years. Ninety-five percent of these patients had previously been treated with antiretrovirals, 69% had HIV-RNA levels <500 copies/mL at time of death, and these patients had moderate immunosuppression (median CD4 count, 231 cells/mm<sup>3</sup>; median CD4 count among this group of patients in 2000 was 157 cells/mm<sup>3</sup>). Thirty-eight percent of patients had excessive alcohol consumption.

Among AIDS-related events, the proportion of NHL-associated deaths (*n* = 103; 16 cases of primary brain NHL) was not different between 2000 and 2005 (11% and 10%, respectively), with CD4 cell counts of similar magnitude (median CD4 count, 86 cells/mm<sup>3</sup> in 2000 vs. 76 cells/mm<sup>3</sup> in 2005, for patients with systemic NHL). However, 32% of the patients who died of NHL had CD4 cell counts >200 cells/mm<sup>3</sup> at time of death. The proportion of deaths attributable to Kaposi sar-

**Table 2. Cancer-related causes of death, the Mortalité 2000 and the Mortalité 2005 surveys.**

Cancer cause or location	No (%) of deaths		P
	Mortalité 2000 (n = 924)	Mortalité 2005 (n = 1013)	
<b>Cancer related overall</b>			
All	269 (29)	344 (34)	.02
AIDS related	149/269 (55)	134/344 (39)	
Hepatitis related	17/269 (6)	37/344 (11)	.03 <sup>a</sup>
Non-AIDS/hepatitis related	103/269 (38)	173/344 (50)	.01 <sup>a</sup>
<b>AIDS related</b>			
All	149 (16)	134 (13)	
Non-Hodgkin lymphoma	105 (11)	103 (10)	
Kaposi sarcoma	40 (4)	25 (3)	
Cervical cancer	4 (0.4)	6 (0.6)	
<b>Hepatitis related</b>			
All	17 (2)	37 (4)	
Hepatitis C virus	8 (0.9)	28 (3)	
Hepatitis B virus	7 (0.8)	6 (0.6)	
Hepatitis B and C virus	2 (0.2)	3 (0.3)	
<b>Non-AIDS/hepatitis related</b>			
All	103 (11)	173 (17)	
<b>Respiratory</b>			
All	50 (5)	65 (6)	
Lung	44 (5)	53 (5)	
Nose and throat	6 (0.6)	12 (1)	
<b>Digestive</b>			
Pancreas	3 (0.3)	11 (1)	
Anal	6 (0.6)	11 (1)	
Skin	2 (0.2)	10 (1)	
Hodgkin lymphoma	12 (1)	9 (0.9)	
Other hemopathies	5 (0.5)	8 (0.8)	
Breast	3 (0.3)	7 (0.7)	
CNS	4 (0.4)	6 (0.6)	
Others <sup>b</sup>	12 (1)	33 (3)	

**NOTE.** The Mortalité 2005 survey included 924 documented deaths (964 reported), and the Mortalité 2005 survey included 1013 documented deaths (1042 reported).

<sup>a</sup> Comparisons are adjusted for age and sex

<sup>b</sup> In the Mortalité 2000 survey, others included unknown origin (n = 4), prostate (n = 3), uterus (n = 1), hepatocarcinoma (n = 1), intrahepatic bile duct (n = 1), connective and soft tissue (n = 1), penis (n = 1), and bladder (n = 1). In the Mortalité 2005 survey, others included unknown origin (n = 15); hepatocarcinoma (n = 4); ovary (n = 2); prostate (n = 2); uterus (n = 2); penis (n = 2); bladder (n = 2); head, face, and neck (n = 1); kidney (n = 1); intrahepatic bile duct (n = 1); and mandible (n = 1).

coma and cervical cancer remained similar between the 2000 and 2005 surveys.

## DISCUSSION

In this large national prospective survey specifically designed to assess the primary causes of death among HIV-infected patients, we demonstrated that malignancies accounted for more than one-third of the causes of death in this population of

patients. We also demonstrated that the proportion of deaths attributable to malignancies increased statistically significantly since 2000.

The proportion of non-AIDS-related cancers also significantly increased from 2000 to 2005, although these patient populations had similar CD4 cell counts (median CD4 count, 218 cells/mm<sup>3</sup> in 2000 vs. 205 cells/mm<sup>3</sup> in 2005). These results are consistent with those of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, which demonstrated that immunosuppression, as reflected by the latest CD4 count, was strongly associated with the risk of death attributable to non-AIDS-defining malignancies; patients whose death was attributable to these malignancies in the D:A:D study had a median CD4 cell count of 211 cells/mm<sup>3</sup> at time of death [15]. The risk of non-AIDS-related cancer is greater among HIV-infected patients than in the general population [16, 17]. The increasing proportion of deaths attributable to non-AIDS-defining malignancies may be related first to the aging of this subpopulation (median age, 46 years in 2000 vs. 49 years in 2005), but it is also probably related to poor control of risk factors (e.g., tobacco use among patients with respiratory cancer and human papillomavirus infection among patients with anal cancer). The increasing proportion of respiratory malignancies emphasizes the need for a better implementation of active smoking cessation programs. In addition, the increased proportion of lethal digestive cancers (especially pancreatic cancer) and breast cancer (7 patients in 2005 vs. none in 2000) observed in this study should be emphasized.

The role of cART is still a matter of debate. Burgi et al. [18] demonstrated that cART appeared to be beneficial in protecting against the development of malignant disease, whereas conflicting results have been reported in the D:A:D study, especially with regard to Hodgkin lymphoma [15]. This issue should be specifically addressed in future studies to provide evidence-based recommendations for cART treatment in HIV-infected patients. The beneficial role of cART, in terms of cancer prevention, might be delayed for non-AIDS-defining causes of death, especially cancers. Because of this, after several years of cART, the mortality rate in a subgroup of HIV-infected persons with CD4 counts >500 cells/mm<sup>3</sup> was demonstrated to reach a similar level to that of the general population [19]. From 2000 to 2005, the proportion of hepatitis-related hepatocarcinoma significantly increased, which confirming data reported in other series [20]. However, the proportion of HBV-related hepatocarcinoma remained stable, whereas a 3-fold increase was observed for HCV-related hepatocarcinoma. The widespread use of antiretroviral treatments (e.g., emtricitabine and tenofovir) that are effective against HBV might explain this discordant change over time. We also noticed an increased proportion of HCV-related hepatocarcinoma in the older population that was described in 2005, despite a better control

of HIV infection (median CD4 count, 231 cells/mm<sup>3</sup> in 2005 vs. 157 cells/mm<sup>3</sup> in 2000), suggesting that the control of HCV infection is insufficient among HIV-infected patients.

Despite the widespread use of cART and the improved management of long-term antiretroviral treatments, the proportion of AIDS-defining cancer, particularly NHL, did not decrease over time. NHL remained the most frequently observed AIDS-defining event leading to death. The incidence of NHL has decreased dramatically since the introduction of cART but to a lesser degree than the other opportunistic infections, and the incidence has remained stable since 1996 [21]. Moreover, the response rate and the survival rate remain poor (~75%), particularly among patients with CD4 counts <100 cells/mm<sup>3</sup>, a history of previous opportunistic infections, and poor general status [22]. Because the risk of NHL clearly decreases with increases in CD4 count, the best way to prevent NHL could be to reach or maintain a high CD4 count [23]. However, other factors independent of immunosuppression (i.e., HIV and Epstein-Barr virus replication) may also have an impact on the risk of NHL [21–24].

In conclusion, this study demonstrated a stable proportion of AIDS-related cancer that led to death between 2000 and 2005. However, an increasing proportion of patients with death attributable to non-AIDS-related cancer was observed among HIV-infected patients; these cancers included lung cancer, nose and throat cancer, digestive and pancreas cancer, skin cancer, breast cancer, and anal cancer. Cancer prevention, screening, early diagnosis, and improved management and surveillance should be included in routine long-term follow-up of HIV-infected patients and could have some immediate impact on mortality. Moreover, because the median CD4 cell level was <250 cells/mm<sup>3</sup> in this population of HIV-infected patients, the therapeutic goal should be to maintain or to reach as high a CD4 count as possible, in addition to other usual prevention policy that is systematically implemented in this population, to prevent cancer-related deaths.

#### **MORTALITÉ 2005 GROUP (AGENCE NATIONALE DE RECHERCHES SUR LE SIDA ET LES HÉPATITES VIRALES [ANRS] EN19), IN COLLABORATION WITH MORTAVIC GROUP**

Information available at: [http://etudes.isped.u-bordeaux2.fr/M2005/TELECHARGTS/M2005\\_GroupeEtude.pdf](http://etudes.isped.u-bordeaux2.fr/M2005/TELECHARGTS/M2005_GroupeEtude.pdf).

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**Financial support.** ANRS, through a grant from the Scientific Sector-based Group number 5.

**Other support.** Collège des Universitaires de Maladies infectieuses et Tropicales (CMIT), Société Française de Lutte contre le Sida (SFLS), Société Nationale Française de Médecine Interne (SNFMI), Société de Pathologie Infectieuse de Langue Française (SPILF), Association des Epidémiologistes de Langue Française (ADELF), Groupe d'Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l'hépatite (GERMIVIC), Fédération des Pôles de Références et Réseaux Hépatites (FPRRH), Association Française Etude du Foie (AFEF), Société de Réanimation de langue Française (SRLF), and Société de Pneumologie de Langue Française (SPLF).

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## Acknowledgments

**Financial support.** ANRS, through a grant from the Scientific Sector-based Group number 5.

**Potential conflicts of interest.** All authors: no conflicts.

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