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Title: Changes in cancer mortality among HIV-infected patients: The ANRS Mortalité 2005 survey.

Running head: Cancer mortality in HIV-infected patients

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Abstract

Background: The current study aimed at describing the distribution and characteristics of malignancy-related deaths in human immunodeficiency virus- (HIV) infected patients using data obtained from a national survey conducted in France in 2005 and at comparing them to those obtained from a similar survey in 2000.

Method: The underlying cause of death was documented using a standardized questionnaire fulfilled in French hospital wards and networks involved in the management of HIV infection.

Results: Among the 1,042 deaths recorded in 2005 (versus 964 in 2000), 344 were cancer-related (34%) with a significant increase from 2000 (29%) (p =0.02); these deaths were distributed as 134 acquired immunodeficiency syndrome- (AIDS) related and 210 non-AIDS-related cancer deaths. Among cancer-related causes of death, proportion of hepatitis-related cancers (6% in 2000 vs 11% in 2005) and non AIDS/non hepatitis-related cancers (38% in 2000 vs 50% in 2005) significantly increased between 2000 and 2005 (p=0.03 and p=0.01 respectively), as compared to AIDS-related cancer and adjusted on age and gender.

Among AIDS events, the proportion of non-Hodgkin lymphoma- (NHL) associated deaths was not statistically significantly different between 2000 and 2005 (11 and 10%, respectively).

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

Human immunodeficiency virus- (HIV) infected patients are at increased risk of non-Hodgkin lymphoma (NHL), Kaposi sarcoma and cervical cancer, considered as acquired immunodeficiency syndrome (AIDS) events in the 1993 revised classification system for HIV infection [1]. This increased risk seems to be partly related to oncogenic virus coinfections (Epstein-Barr Virus, Human Herpes Virus 8, Human Papillomavirus, Hepatitis B virus [HBV]) as well as to cellular immunodepression as demonstrated during the use of immunosuppressive drugs, particularly in transplantation field [2, 3]. The widespread use of combination antiretroviral therapies (cART) in industrialized countries since the mid 90s was associated with a dramatic decrease in both mortality and AIDS events incidences. However, the incidences of NHL and cervical cancer decreased in a lower proportion than the other opportunistic infections [4, 5]. Prolonged life expectancy was associated with a diversification of morbidity and causes of death such as cardiovascular events, hepatic complications, bacterial infections and non-AIDS cancers [6-12]. In a previous national survey conducted in France in 2000, we showed that non-AIDS cancers accounted for 12% of deaths and all cancers (ie, AIDS- and non-AIDS-related malignancies) for 29% of the deaths [13]. Monitoring epidemiologic trends would permit to define priorities in terms of prevention, early detection and management of AIDS and non-AIDS malignancies. The objectives of the present study were to describe the distribution and characteristics of malignancy-related deaths in HIV-infected patients in France in 2005 as well as at assessing changes from 2000.
Patients and Methods

Data collection

All hospital wards and networks known to be involved in the management of HIV infection in France were contacted, including wards participating in the "Mortalité 2000" survey. Apart from a greater number of contacted 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 with an abstract of the cause of death for HIV-infected adults (18 years or older), every three months in 2005. Each death case was then documented using a standardized questionnaire, including all contributing causes of death, diseases present at time of death and a global assessment of the underlying cause of death. One physician was especially dedicated to the survey in the coordinating team, and oversaw harmonization of data collection. Double reports were identified by cross-match of the dates of birth and death. Hepatitis C virus (HCV) infection was defined as the presence of serum HCV-antibodies or HCV-ribonucleic acid (RNA), excessive alcohol consumption as a daily alcohol intake higher than 50 grams and/or five glasses, and poor socio economic conditions as no health insurance, no employment, no accommodation, income below 535 € per month and/or immigrant in illegal situation.

Determination of the underlying cause of death

Information contained in the questionnaire was used to determine the underlying cause of death according to the International Classification of Diseases -10th revision (ICD-10) rules: the underlying cause of death was defined as the disease or injury, that initiated the sequence of morbid events leading to death [14]. The algorithm of determination was adapted to specific concerns in HIV infection [7] and allowed categorization of deaths as follow: AIDS-related causes according to the 1993 clinical classification [1], deaths related to infection with HCV and/or hepatitis B virus (HBV) including hepatocarcinoma, cancers and
other causes neither related to AIDS nor to HCV/HBV, and adverse effects of antiretroviral
treatment. The latter was considered as 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 time of death included one AIDS-defining cancer according to the classification
of the Centers for Disease Control and Prevention (CDC) for HIV infection as revised in 1993
[1]: high grade NHL including Burkitt and immunoblastic lymphoma, primary brain
lymphoma, Kaposi sarcoma and cervical cancer. Other cancers were classified as either
hepatitis-related hepatocarcinoma or non-AIDS-/non-hepatitis-related cancer.

Statistical analysis
The distribution of malignancy-related causes of death was compared between 2000 and 2005
using the chi-square 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 gender and age. Statistical analyses were performed using Statistical Analysis
System software (SAS, version 9.0).

Results
A total of 1,042 deaths were reported in 2005 (versus 964 in 2000), among around
78,000 HIV-infected patients followed (at least one contact in 2004) at the 340 wards
participating in the survey. Documentation was available for 1,013 decedents (97%): 76%
were men, the median age was 46 years (versus 41 years in 2000), the known duration of HIV
infection was 12 years (versus 8 years), 87% had received an antiretroviral treatment (versus
86%), 47% had less than 500 copies/mL of plasma HIV-RNA (versus 33%), and the median
CD4 lymphocytes count was 161/mm$^3$ (versus 94/mm$^3$) with 55% of patients (versus 68%)
having a CD4 cell count below 200/mm$^3$ and 12% (versus 9%) above 500/mm$^3$.

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% versus 47% in 2000) followed by non-AIDS-/non-hepatitis-related cancer (n = 173; 17% versus 11%), liver-related cause (n = 154; 15% versus 13%) cardiovascular disease (n = 88; 8% versus 7%), suicide (n = 50; 5% versus 4%), and other infections (n = 46; 4% versus 7%).

Overall, 344 malignancy-related causes of death representing 34% of deaths were recorded and distributed as NHL (N=84, 10% of the causes of death), Kaposi sarcoma (N=25, 3%), hepatitis-related hepatocarcinoma (N=37, 4%) and non-AIDS/non-hepatitis cancers (N=173, 17%) (Table 1). This proportion statistically significantly increased since 2000 where malignancies accounted for 29% of the causes of death (p=0.02) (Table 2). Adjusted on age and gender, the proportion of deaths attributed to hepatocarcinoma or to non-AIDS/non-hepatitis cancers statistically significantly increased from 2000 to 2005, with a greater diversification of cancer types. The proportion of AIDS-defining cancers remained stable during the same period.

Patients who died from non-AIDS/non-hepatitis related cancers were older than others (49 years in median), known to be HIV-infected for11.9 years in median, moderately immunosuppressed (median count: 205 CD4/mm³ in 2005, 218 CD4/mm³ in 2000), and 61% had less than 500 copies/mL of plasma HIV-RNA (table 1).

Respiratory cancers were the most frequent among lethal non-AIDS/non-hepatitis-related cancers (n = 65 including 53 lung cancers and 12 nose and throat cancers). Their proportion was stable between 2000 and 2005 (5 and 6%, respectively). Patients who died from respiratory cancers were older in median in 2005 (50 years) than in 2000 (46 years) and moderately immunosuppressed at time of death (median: 163 CD4/mm³) in 2005 but more than in 2000 (median: 262 CD4/mm³). Ninety-one percent of them had been previously
treated with antiretrovirals and 63% had less than 500 copies/mL of plasma HIV-RNA. Ninety percent of patients were smokers and 34% had excessive alcohol consumption. A great increase in the proportion of lethal digestive cancers was observed from 2000 to 2005, especially pancreatic cancer responsible for 10 cases of death in 2005 versus three cases in 2000, whereas the proportion of anal cancers remained stable. The rate of lethal hemopathies, including Hodgkin’s lymphoma, remained similar between 2000 and 2005. Seven patients died from breast cancer in 2005 but none in 2000, and 10 patients died from skin cancer (four melanoma and six non-melanoma) versus two patients in 2000. Hepatocarcinoma was mainly associated with hepatitis C coinfection in 2005 whereas aetiology was better balanced between hepatitis B and hepatitis C in 2000. Patients who died from hepatocarcinoma were 49 years-old in median and known to be HIV-infected for 15 years in median. Ninety-five percent of them had been previously treated with antiretrovirals, 69% had less than 500 copies/mL of HIV-RNA at time of death with a moderate immunosuppression (median of 231 CD4/mm³ in 2005 versus 157 CD4/mm³ in 2000). Thirty-eight percent of patients had excessive alcohol consumption. Among AIDS events, the proportion of NHL-associated deaths (n = 103, including 16 primary brain NHL) was not different between 2000 and 2005 (11 and 10%, respectively) with CD4 cell count in the same magnitude (median: 86/mm³ in 2000 versus 76/mm³ in 2005, for systemic NHL). However, 32% of the patients who died from NHL had CD4 cell count above 200/mm³ at time of death. The proportion of lethal Kaposi sarcoma and cervical cancer remained similar during the two periods of survey.
Discussion

In this large national prospective survey specifically designed to assess the primary cause of death in HIV-infected patients, we showed that malignancies accounted for more than one third of the cause of death in this population of patients with a statistically significant progression since 2000. The proportion of non-AIDS cancers also significantly increased from 2000 to 2005 although these patients had a median CD4 count at a similar level (218/mm³ in 2000 versus 205/mm³ in 2005). These results are consistent with those of the D:A:D study which showed that immunosuppression, as reflected by the latest CD4 count, was strongly associated with the risk of death from non-AIDS-defining malignancies, with a median CD4 cell count at 211/mm³ at time of death [15]. The risk of non-AIDS cancer is higher in HIV-infected patients than in the general population [16, 17]. The increasing proportion of lethal non-AIDS-defining malignancies may be related first to this subpopulation ageing (46 years in 2000 versus 49 years in 2005) but also to a bad control of risk factors (ie, tobacco for respiratory cancers, Human papillomavirus infection for 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) observed in this survey as well as that of lethal breast cancers (7 patients in 2005 versus none in 2000) are to be underlined.

The role of cART is still a matter of debate. Burgi et al showed that cART appeared to be beneficial in protecting against the development of malignant disease [18], whereas conflicting results have been reported in the D:A:D study especially for Hodgkin's disease [15]. This issue is thus to be specifically addressed in further studies in order to provides evidence-based recommendations for cART treatment in those patients. The beneficial role of
cART might be delayed for non-AIDS-defining causes of death, especially cancers. In this way, mortality rate was shown to reach a similar level to the general population in a subgroup of HIV-infected persons whose CD4 cell count was above 500/mm$^3$, after several years of cART treatment [19]. Over this five-year period, the proportion of hepatitis-related hepatocarcinoma significantly increased confirming data observed in other series [20]. However, the proportion of hepatitis B-related hepatocarcinoma remained stable while a 3-fold increase was observed for hepatitis C-related hepatocarcinoma during the same time. The widespread use of antiretrovirals (eg, emtricitabine, tenofovir) efficient against hepatitis B virus might explain this discordant change over time. On the other side, we noticed an increased proportion of HCV-related hepatocarcinoma in this ageing population despite a better control of HIV disease (median CD4 count at 231/mm$^3$ in 2005 versus 157/mm$^3$ in 2000) suggesting that control of HCV is insufficient among HIV-infected patients.

Despite the widespread use of cART and improved management of long-term antiretroviral treatments, the proportion of AIDS-defining cancers and particularly NHLs did not decrease over time. NHL remained the most frequent AIDS-defining event leading to death. The incidence of NHL has decreased dramatically since the introduction of cART but less than the other opportunistic infections and remains stable since 1996 [21]. Moreover, the response rate and the survival rate remain poor (around 75%) particularly in patients with CD4 less than 100/mm$^3$, history of previous opportunistic infections and poor general status [22]. As the risk of NHL occurrence clearly decreases as the CD4 count increases, the best way to prevent NHL could be to reach or maintain a high level of CD4 count [23]. However, other factors independent of immunosuppression like HIV and EBV replication may also have an impact on NHL occurrence risk [21-24].
In conclusion, this study showed a stable proportion of AIDS-cancers leading to death between 2000 and 2005 meanwhile an increasing proportion of patients dying from non-AIDS cancers was noticed in HIV-infected patients. These include lung cancers, nose and throat cancers, digestive and pancreas cancers, skin cancers, breast cancers and anal cancers. Cancer prevention, screening, early diagnosis and improved management should be included in routine long-term follow-up of HIV-infected patients and could have some immediate impact on mortality. Moreover, as the median CD4 level was below 250/mm$^3$ in this population of HIV-infected patients, the therapeutic goal should be to maintain or to reach a CD4 count level as high as possible in addition to other usual prevention policy systematically implemented in this population, in order to prevent cancer-related deaths.
References


<table>
<thead>
<tr>
<th></th>
<th>Hepatitis-related hepatocellular carcinoma</th>
<th>Non-AIDS non-hepatitis cancers</th>
<th>Non-cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NHL</strong></td>
<td>(N = 84)</td>
<td>(N = 173)</td>
<td>(N = 676)</td>
</tr>
<tr>
<td>Gender male (%)</td>
<td>81</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>Duration of HIV infection (years, median, IQR)</td>
<td>9.6 [9.5-15.0]</td>
<td>15.4 [10.5-17.9]</td>
<td>11.7 [6.6-16.1]</td>
</tr>
<tr>
<td>AIDS stage (%)</td>
<td>43</td>
<td>100</td>
<td>62</td>
</tr>
<tr>
<td>CD4 count (mm$^3$, median, IQR)</td>
<td>76 [20-239]</td>
<td>231 [116-367]</td>
<td>205 [75-360]</td>
</tr>
<tr>
<td>CD4 &gt; 500/mm$^3$ (%)</td>
<td>11</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Previous antiretroviral treatment (%)</td>
<td>88</td>
<td>7.8 [0.8-12.1]</td>
<td>8.2 [5.3-10.9]</td>
</tr>
<tr>
<td>ARV treatment duration (years, median, IQR)</td>
<td>48</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>HIV-RNA &lt; 500 copies/ml (%)</td>
<td>69</td>
<td>62</td>
<td>23</td>
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<tr>
<td>Intravenous drug use (%)</td>
<td>78</td>
<td>23</td>
<td>29</td>
</tr>
<tr>
<td>Hepatitis C (%)</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Hepatitis B (%)</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Poor socio-economic conditions (%)</td>
<td>25</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Alcohol (%)</td>
<td>13</td>
<td>38</td>
<td>26</td>
</tr>
<tr>
<td>Tobacco (%)</td>
<td>39</td>
<td>39</td>
<td>56</td>
</tr>
</tbody>
</table>

Table 2: Cancer-related causes of death. The Mortalité 2000 and the Mortalité 2005 surveys.

<table>
<thead>
<tr>
<th></th>
<th>Mortalité 2000</th>
<th>Mortalité 2005</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented deaths (reported)</td>
<td>924 (964)</td>
<td>1013 (1042)</td>
<td></td>
</tr>
<tr>
<td>Cancer-related causes of death</td>
<td>269 (29%)</td>
<td>344 (34%)</td>
<td>0,02</td>
</tr>
<tr>
<td><strong>Cancer aetiology</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>149 (55%)</td>
<td>134 (39%)</td>
<td>-</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>17 (6%)</td>
<td>37 (11%)</td>
<td>0,03*</td>
</tr>
<tr>
<td>Non-AIDS/non-hepatitis-related</td>
<td>103 (38%)</td>
<td>173 (50%)</td>
<td>0,01*</td>
</tr>
<tr>
<td><strong>AIDS</strong></td>
<td>n=149</td>
<td>n=134</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>105 (11%)</td>
<td>103 (10%)</td>
<td></td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>40 (4%)</td>
<td>25 (3%)</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>4 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hepatitis-related</strong></td>
<td>n=17</td>
<td>n=37</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>8 (1%)</td>
<td>28 (3%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>7 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>2 (&lt;1%)</td>
<td>3 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Non-AIDS/non-hepatitis-related</strong></td>
<td>n=103</td>
<td>n=173</td>
<td></td>
</tr>
<tr>
<td>Respiratory Lung</td>
<td>50 (5%)</td>
<td>65 (6%)</td>
<td></td>
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<tr>
<td>Nose and throat</td>
<td>44</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Digestive</td>
<td>6 (&lt;1%)</td>
<td>13 (3%)</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (&lt;1%)</td>
<td>11 (1%)</td>
<td></td>
</tr>
<tr>
<td>Anal</td>
<td>6 (&lt;1%)</td>
<td>11 (1%)</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>2 (&lt;1%)</td>
<td>10 (1%)</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>12 (1%)</td>
<td>9 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Other hemopathies</td>
<td>5 (&lt;1%)</td>
<td>8 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>3 (&lt;1%)</td>
<td>7 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>4 (&lt;1%)</td>
<td>6 (&lt;1%)</td>
<td></td>
</tr>
<tr>
<td>Others**</td>
<td>12 (1%)</td>
<td>33 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

*Comparisons are adjusted on age and gender
**See Appendix for details
Appendix

“Other” causes of death observed in the Mortalité 2000 and Mortalité 2005 studies.
Mortalité 2000: 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), bladder (N=1).
Mortalité 2005: 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), mandible (N=1).

Mortalité 2005 (ANRS EN19) Group, in collaboration with Mortavic Group

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CMIT Collège des Universitaires de Maladies infectieuses et Tropicales
SFLS Société Française de Lutte contre le Sida
SNFMI Société Nationale Française de Médecine Interne
SPILF Société de Pathologie Infectieuse de Langue Française
ADELF Association des Epidémiologistes de Langue Française
GERMIVIC Groupe d’Etude et de Recherche en Médecine Interne et Maladies Infectieuses sur le Virus de l’hépatite
FPRRH Fédération des Pôles de Références et Réseaux Hépatites
AFEF Association Française Etude du Foie
SRLF Société de Réanimation de langue Française
SPLF Société de Pneumologie de Langue Française
Mortalité 2005 (ANRS EN19) in collaboration with Mortavic, List of participants


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