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Abbreviations: KS: Kaposi's sarcoma; NHL: non-Hodgkin lymphoma; HL: Hodgkin's lymphoma, ADCs: AIDS-defining cancers; cART: combination antiretroviral therapy; NADCs: non AIDS-defining cancers; FHDH ANRS-CO4: the French Hospital Database on HIV; ICD-9: International Classification of Diseases, Ninth Revision; ICD-10: International Classification of Diseases, Tenth Revision; HCV: hepatitis C virus; HBV: hepatitis B virus; FRANCIM: French Network of Cancer Registries; IQR: interquartile range; HR: hazard ratio.

Novelty and impact of the work (75 = 75 words): Our study examined cancer survival trends in 1992-2009 for most frequent cancers in HIV-infected individuals and provided a comparison to cancer survival estimates in the general population in France. Survival improved for Kaposi sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and liver cancer and remained stable for lung and anal cancers in the recent periods, with a survival similar to the general population for solid tumours and poorer than the general population for haematological malignancies in 2001-2004.

ABSTRACT

Although the decline in cancer mortality rates with the advent of combination antiretroviral therapy (cART) in HIV-infected individuals can be mostly explained by a decrease in cancers incidence, we looked here if improved survival after cancer diagnosis could also contribute to this decline. Survival trends were analyzed for most frequent cancers in the HIV-infected population followed in the French Hospital Database on HIV: 979 and 2760 cases of visceral and non-visceral Kaposi's sarcoma (KS), 2339 and 461 cases of non-Hodgkin lymphoma (NHL) and Hodgkin's lymphoma (HL), 446 lung, 312 liver and 257 anal cancers. Five-year Kaplan-Meier survival rates were estimated for four periods: 1992-1996, 1997-2000, 2001-2004 and 2005-2009. Cox proportional hazard models were used to compare survival across the periods, after adjustment for confounding factors. For 2001-2004, survival was compared to the general population after standardization on age and sex. Between the pre-cART (1992-1996) and early-cART (1997-2000) periods, survival improved after KS, NHL, HL and anal cancer and remained stable after lung and liver cancers. During the cART era, 5-year survival improved after visceral and non-visceral KS, NHL, HL and liver cancer, being 83%, 92%, 65%, 87% and 19% in 2005-2009 respectively, and remained stable after lung and anal cancers, being 16% and 65% respectively. Compared with the general population, survival in HIV-infected individuals in 2001-2004 was poorer for hematological malignancies and similar for solid tumors. For hematological malignancies, survival continues to improve after 2004, suggesting that the gap between the HIV-infected and general populations will close in the future.

INRODUCTION

HIV-infected individuals are at increased risk of several malignancies (1–3). Despite a decline in their incidence since the advent of combination antiretroviral therapy (cART) in 1996, AIDS-defining cancers (ADCs: Kaposi's sarcoma (KS), non-Hodgkin lymphoma (NHL) and cervical cancer) remained more frequent in HIV-infected individuals than in the general population in the recent cART period (1,2). The risk of the most frequent non AIDS-defining cancers (NADCs) also remains 3 to 47 times higher than in the general population (1–3).

Overall survival has improved since the advent of cART (4,5), due to a decline in mortality from both AIDS-defining and non AIDS-defining causes including cancers (6). Part of this decline might be explained by improved survival after cancer diagnosis. Several studies have shown improved survival after diagnosis of KS (7–9) and NHL (7,9–15) since the advent of cART. The few studies that have examined trends in cancer survival have given conflicting results for HL (16,17) and anal cancer (15,17,18), and no improvement for lung cancer (15,17). Most of these studies compared survival between the pre-cART and early cART periods (10–16). Recently, a study comparing cancer patients with AIDS with HIV-seronegative cancer patients showed that survival after cancer diagnosis had improved in the cART era, reducing the survival gap between the 2 populations from 5-fold (HR = 5.1; 95% CI [4.3-6.1]) in the pre-cART period to 3-fold (HR = 2.9; 95% CI [2.6-3.3]) in the cART period (19). However, results for AIDS patients cannot be generalized to all HIV-infected patients, as patients with AIDS in the pre-cART era differ from their counterparts in the cART era. Indeed, in the pre-cART era most individuals with HIV infection progressed to AIDS, while this is now mainly the case of only late-diagnosed patients. It is therefore important to examine temporal trends in survival after cancer diagnosis in all HIV-infected individuals.

As survival trends for ADCs and NADCs have rarely been studied, and as no data are available for individual NADCs, we examined time trends in survival after diagnosis for each of the six most frequent cancers, using data from the French Hospital Database on HIV (FHDH ANRS-CO4) collected from 1992 through 2009. We then compared survival among HIV-infected individuals to age- and sex-standardized survival in individuals with cancer in the general population in France in 2001-2004.

MATERIAL AND METHODS

The FHDH (20) is an ongoing, open, prospective cohort created in 1989, with participation by 70 general and university hospitals in France. The only inclusion criteria are HIV type 1 (HIV-1) or type 2 (HIV-2) infection and written informed consent. Among HIV-1 infected patients aged between 15 and 84 years at FHDH enrollment and followed-up between 1992 and 2009, we selected individuals diagnosed with cancer during this period. Patients who had no available CD4 cell count during the 12 months prior to cancer diagnosis were excluded. If several CD4 cell counts were available during this period, the last one was used in the analysis.

We examined the most frequent cancers diagnosed among HIV-infected individuals, namely KS, NHL, HL, and lung, liver, and anal cancer. As the prognosis of KS is worse for visceral forms, we separately analyzed visceral (mostly lung, gastrointestinal, or multiple organs) and non-visceral KS (skin, skin structures, palate and lymph nodes). The International Classification of Diseases, Ninth Revision (ICD-9) was used to code cancers in FHDH before 1997 and the Tenth Revision (ICD-10) thereafter (Supplementary table 1). For KS, NHL and HL, results of regular audits comparing data in the FHDH with those in the corresponding medical records showed that >90 % of recorded cases corresponded to histology proven cancer cases. Specific research projects implemented in the cohort showed that 95% of the recorded cases of lung cancer between 2000 and 2010 and 87% of the recorded cases of anal cancer between 1992 and 2008 were confirmed by histological findings in the medical records. For liver cancer, the diagnosis is based on liver imagery and the level of *alpha-fetoprotein*, but no validation study has been performed for this cancer. Deaths for the HIV-infected individuals were recorded in the FHDH according to the vital status in patients' medical records. Cancer diagnoses were grouped into the pre- (1992-1996), early- (1997-2000), intermediate- (2001-2004) and late-cART periods (2005-2009).

Death from all causes was the analyzed event, while patients alive at the last visit to an FHDH center or 5 years after cancer diagnosis (whichever occurred earlier) were censored. The Kaplan-Meier method was used to estimate 5-year survival after cancer diagnosis during the four periods, and the log-rank test was used to analyze differences in survival. Multivariate Cox proportional hazard models were used to evaluate the calendar-period effect on the risk of death, using the period 1997-2000 as reference. First, we adjusted Cox models for sex and age at diagnosis. Second, to determine whether changes in survival were influenced by changes in patient characteristics over time, we also included the following characteristics known to impact survival among HIV-infected individuals and which might have changed over time: sex, age at cancer diagnosis, geographic origin, HIV transmission group, region of care, hepatitis C virus (HCV) co-infection, hepatitis B virus (HBV) co-infection, AIDS status, and CD4 cell count at cancer diagnosis. Additional analyses were performed during the cART era (1997-2009), with further adjustment for viral load at cancer diagnosis. HIV viral load was not available in the pre-cART era before 1997.

Finally, to compare survival between HIV-infected individuals and the general population we used the latest data available in the French network of cancer registries (FRANCIM) in 2001-2004 (21-23). For persons with cancer in the general population, FRANCIM collected information on deaths, first by contacting the municipality of birth which compiles deaths reporting for all individuals born in the city, and the National Institute of Statistics and Economic Studies (Insee) which collects declaration of death together with the national identity number. When vital status was not known by these two queries, other sources were used as medical records, the municipality of residence or health insurance.

Because the age and sex distributions differ between the HIV-infected and general populations (1), 5-year survival in the general population was standardized for each cancer by using the direct method, based on the age and sex structure of HIV-infected patients diagnosed with the same cancer. Moreover for NHL, because histologic subtypes of NHL in HIV patients are mostly B subtypes (24), with about 44% of HIV-

infected individuals with NHL having diffuse large B-cell lymphoma (DLBCL) subtype in France (C Besson PI of the ANRS CO16 Lymphovir cohort, personal communication), we standardized survival in general population for all NHL subtypes, and also restricted the analysis to DLBCL. A *t*-test was used to compare 5-year survival between HIV-infected individuals and the French general population. For KS, this analysis was not performed because data were not available in the general population.

RESULTS

Among 99 818 HIV-1-infected individuals enrolled in the FHDH between 1992 and 2009, 6138 AIDS-defining cancers (visceral and non-visceral KS and NHL) and 1510 non AIDS-defining cancers were diagnosed. We excluded 94 individuals with cancer with no available CD4 cell count during the 12 months before diagnosis (60 with KS or NHL, of whom 50 died; and 34 with a NADC, of whom 26 died). The analysis included 979 cases of visceral KS, 2760 non visceral KS, 2339 NHL and 1476 NADCs. The HIV-infected individuals' characteristics at cancer diagnosis are shown in Table 1. Men who have sex with men accounted for most cases of KS and anal cancer, while intravenous drug users (IDU) accounted for most cases of liver cancer. The median time since HIV diagnosis was longer among patients with NADCs (11 years) than among those with ADCs (6 years). Patients with KS and NHL had a median CD4 cell count below 100/mm^3 at cancer diagnosis and also the lowest nadir CD4 cell counts. Among patients with NADCs, those with anal cancer had the lowest nadir CD4 cell counts but their median count at diagnosis was within the range of median counts among patients with other NADCs. The proportions of patients who had been on cART for at least 6 months at cancer diagnosis were below 40% for KS and NHL, and above 50% for the other cancers.

Kaplan-Meier survival distributions according to the period of cancer diagnosis are shown in Figure 1 (KS and NHL) and Figure 2 (NADCs). Five-year Kaplan-Meier survival rates and adjusted 5-year hazard ratios (HR) of death are shown in Table 2 according to the period of cancer diagnosis in the period 1992-2009, and in Table 3 for the period 1997-2009.

AIDS-defining cancers

Between the pre-cART and late cART periods, 5-year survival rates rose from 14% to 83% after visceral KS, from 36% to 92% after non visceral KS, and from 15% to 65% after NHL (Figure 1). As shown in Table 2, in analyses adjusted for age and sex, the 5-year cancer mortality declined significantly between the pre-cART and early cART periods; similar decline was observed after adjustment for all the other potential confounders, with a HR in 1992-1996 compared to 1997-2000 of 2.34 for visceral KS, 3.19 for non-visceral KS and 1.38 for NHL. The 5-year cancer mortality, adjusted for age and sex, also declined significantly during the cART era for KS whether visceral or non-visceral and for NHL (Table 3). After adjustment for all confounders, the 5-year adjusted HR of death was reduced by around 2-fold in the late-cART period compared to the early-cART period, and the reduction was significant for NHL (P_{trend} <0.0001) and non-visceral KS (P_{trend}=0.0269) and was not significant for visceral KS (P_{trend}=0.3233).

Non AIDS-defining cancers

As shown in Figure 2, between the pre-cART and late cART periods, 5-year survival increased significantly from 48% to 87% after HL and from 17% to 19% after liver cancer. For lung and anal cancers, the difference in the 5-year survival distributions was not statistically significant across the calendar periods, with an overall 5-year survival rate of 16% after lung cancer and 65% after anal cancer during the entire study period.

In analyses adjusted for age and sex, the 5-year HR of death after HL diagnosis was 1.62 (95% CI [1.04-2.53]) in the pre-cART period compared to the early cART period (Table 2), but an improvement in survival was observed during the cART era even after adjustment for all confounders including viral load at HL diagnosis (P_{trend} =0.0071) (Table 3). For lung cancer, the adjusted 5-year HR of death remained stable across the calendar periods. In analyses adjusted for age and sex, the 5-year HR of death after liver

cancer did not change significantly between the pre-cART and early cART periods (Table 2). During the cART era, survival after liver cancer diagnosis improved after adjustment for potential confounders (P_{trend} =0.0198), but was no longer significantly improved after adjustment for viral load (P_{trend} =0.2237) (Table 3). In the fully adjusted model, the 5-year HR of death after anal cancer diagnosis was 3.22 (95% CI [1.02-10.09]) in the pre-cART period compared to the early cART period (Table 2), but there was no significant change during the cART era (P_{trend} =0.7239) (Table 3).

Comparison with the general population

For cases diagnosed in 2001-2004, Table 4 shows 5-year crude survival rates for the general population in the first column, 5-year standardized survival rates for the general population in the second column and 5-year survival rates for the HIV-infected population in the third column, with respect to NHL, lung cancer, HL, liver cancer and anal cancer. For NHL, the standardized 5-year survival rate in the general population was estimated at 74% for all subtypes, being 70% for DLBCL subtype (Table 4). The age- and sex-standardized survival rate was higher in the general population than among HIV-infected individuals with respect to NHL (either for all subtypes or DLCBL subtype) and HL. Regarding solid tumors, 5-year survival rates among HIV-infected individuals were close to age- and sex-standardized rates in the general population.

DISCUSSION

Using data from FHDH with a longitudinal follow up of 20 years, we observed improved survival with the advent of cART and during the cART period among HIV-infected individuals diagnosed with KS and NHL. The advent of cART had no apparent impact on survival after HL, but survival after diagnosis of this cancer improved during the cART era. Regarding solid tumors, the only improvement in survival between the pre-cART and early cART periods concerned anal cancer. During the cART era, survival after liver cancer improved very modestly mainly because of better control of HIV viral load, while survival after lung and anal cancer was stable. Among HIV-infected individuals diagnosed with hematological malignancies in 2001-2004, survival was less favorable than in the general population, whereas survival among patients diagnosed with solid tumors during the same period was similar to that in the general population. From a methodological point of view our study highlights that accounting for the age and sex survival distribution in the general population is essential when comparing survival in HIV-infected patients to that of the general population. Table 4 nicely shows that not accounting for it would have been misleading for NHL, liver and anal cancer.

Major strengths of this work are the lengthy study period (nearly 20 years, including 15 years of cART use), the large number of cases (allowing us to study survival separately for each malignancy), the inclusion of all HIV-infected individuals (not only patients with AIDS), and the availability of many covariates known to influence the progression of HIV infection. The relationship between temporal changes in survival after cancer diagnosis and changes in cancer stage at diagnosis and cancer management could not be evaluated, as the data were not available. FHDH linkage with the French death registry is not authorized. Therefore, deaths, particularly from non AIDS-defining causes, may have

slightly been under-reported (20), leading to a slight overestimation of cancer survival in HIV-infected individuals. This bias could have a small effect on survival difference between the HIV-infected and general populations. For hematological malignancies, the survival difference may have been slightly broadened. But for lung and liver cancers, we believe that the impact of death under-notification was minimal as survival was very poor in both populations.

Another limitation of the study is not taking into account of the causes of death in the analyses, although, in patients with multiple co-morbidities, the collected causes of death could often be incorrect, incomplete or impossible to dismantle. For instance, for HIV-infected persons who have cancer, the collected cause of death could be the HIV infection, the cancer itself, the complications of the cancer treatment, or other causes. It is therefore difficult to rely on these data to ascertain the cause of death, and to determine whether differences, if any, in overall mortality between the HIV-infected and general populations are due to cancer-specific or HIV-specific mortality or both. However, the adjusted models (Table 3) give an insight of whether the improvements in survival over time, if any, are related to better cancer treatment or better treatment of HIV. Indeed, as CD4 cell count and HIV viral load depend strongly on HIV treatment adjusting for CD4 cell count and HIV viral load account for the evolution of the HIV-specific mortality that depends on the improvement in HIV treatment. Therefore, we think that the remaining effect on the evolution of survival after adjusting for CD4 cell count and HIV viral load is more likely explained by the change over time in the cancer treatment in the HIV-infected persons.

The improvement in survival after KS diagnosis is consistent with that seen in other studies comparing the pre-cART era with the cART era (7–9). Interestingly, we found that survival improved after diagnosis of both visceral and non-visceral KS. The continued improvement in survival during the cART period

among patients diagnosed with visceral KS was likely explained by the increasing proportion of HIV-infected individuals receiving antiretroviral therapy (25).

As observed in other studies, survival after NHL diagnosis improved between the pre-cART and early cART periods (9–15), and continued to improve during the cART era (until 2009). Between the pre- and early-cART periods, the improvement in survival after HL was nearly significant and survival improved during the cART era. This improvement in survival is similar to that reported by a single institution in France specialized in the treatment of lymphomas in HIV-infected individuals and had long used the same treatment protocols as for HIV-seronegative individuals (16). Two prior studies showed no change in survival after NHL or HL during the cART period (24,26), probably owing to insufficient statistical power and/or to combined analysis of HL and NHL. The improved survival observed here after diagnosis of hematological malignancies was not explained by changes in the characteristics of HIV-infected individuals over time but rather by a calendar-period effect, likely related to more often use of the same cancer treatment protocols as in HIV-uninfected individuals and to a better adherence to these protocols because of better tolerability. Despite the clear trend towards improved survival after hematological malignancies, we observed a marked difference between the HIV-infected and general populations for cases diagnosed in 2001-2004 even when restricting to DLBCL, confirming the results of previous studies (15,19,24). Although the improvement in survival could be related to better access to cancer treatment over time, suboptimal management of HIV-infected individuals with cancer likely persists in 2001-2004; indeed, HIV-seropositive cancer patients do not receive the same number of cycles or the same doses of chemotherapy as patients not infected by HIV (27). However, the improved survival found in the recent period suggests that survival will become in the future similar to that in the general population.

Survival trends after diagnosis of solid tumors differed according to the malignancy. Our analysis, based on a large number of cases of lung cancer (n=460), showed a stable overall survival rate (15%) between

1992 and 2009. This is similar to the rates observed by others during the years 1980-2000 (15). This absence of improvement could be explained by the lack of significant advances in lung cancer management and persistent high proportion of individuals diagnosed at advanced stages (28,29,30). As in other studies (31,32,33), survival among HIV-infected patients was as poor as in the general population for cases diagnosed in 2001-2004 (22).

Survival following liver cancer diagnosis did not change with the advent of cART and improved only very modestly during the cART period. The latter improvement was mainly explained by the increase over time in the proportion of patients with controlled viral load as temporal cancer survival trend was no longer significant after adjustment for viral load at cancer diagnosis. To our knowledge, survival trends after the diagnosis of liver cancer have never previously been assessed in HIV-infected patients. For cases diagnosed in 2001-2004, survival was similar among HIV-infected individuals and the general population, in agreement with a previous study (34).

Our results for anal cancer confirm those of a previous study that showed a significant improvement between the pre-cART and early cART periods (15): the 5-year HR of death in our study was 3 times higher among individuals diagnosed with anal cancer in 1992-1996 than in those diagnosed with this cancer in 1997-2000. Another study showed no such change, probably owing to the small number of cases (n=26) (18). Nevertheless, we found that survival was stable during the cART era, being similar to that of the general population for cases diagnosed in 2001-2004, as previously shown (35).

In conclusion, trends in survival after cancer depended on the type of malignancy. We showed a marked improvement in the survival of HIV-infected individuals diagnosed with KS. Survival after hematological malignancies (NHL and HL) improved over time; in 2001-2004 it remained poorer than in the general population, however, there was a considerable improvement in the recent cART period, suggesting that survival among HIV-infected individuals will gradually approach that of the general population. There was a modest improvement in survival after liver cancer diagnosis during the cART era, while survival after lung and anal cancer remained stable: survival was similar to that of the general population for cases diagnosed in 2001-2004, and remains poor for lung and liver cancers.

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Author contributions. D. C. and S. G. designed the study. M. H. performed the statistical analyses. M. H., D. C., and S. G. interpreted the data and wrote the manuscript. All the authors read and critically commented on the paper.

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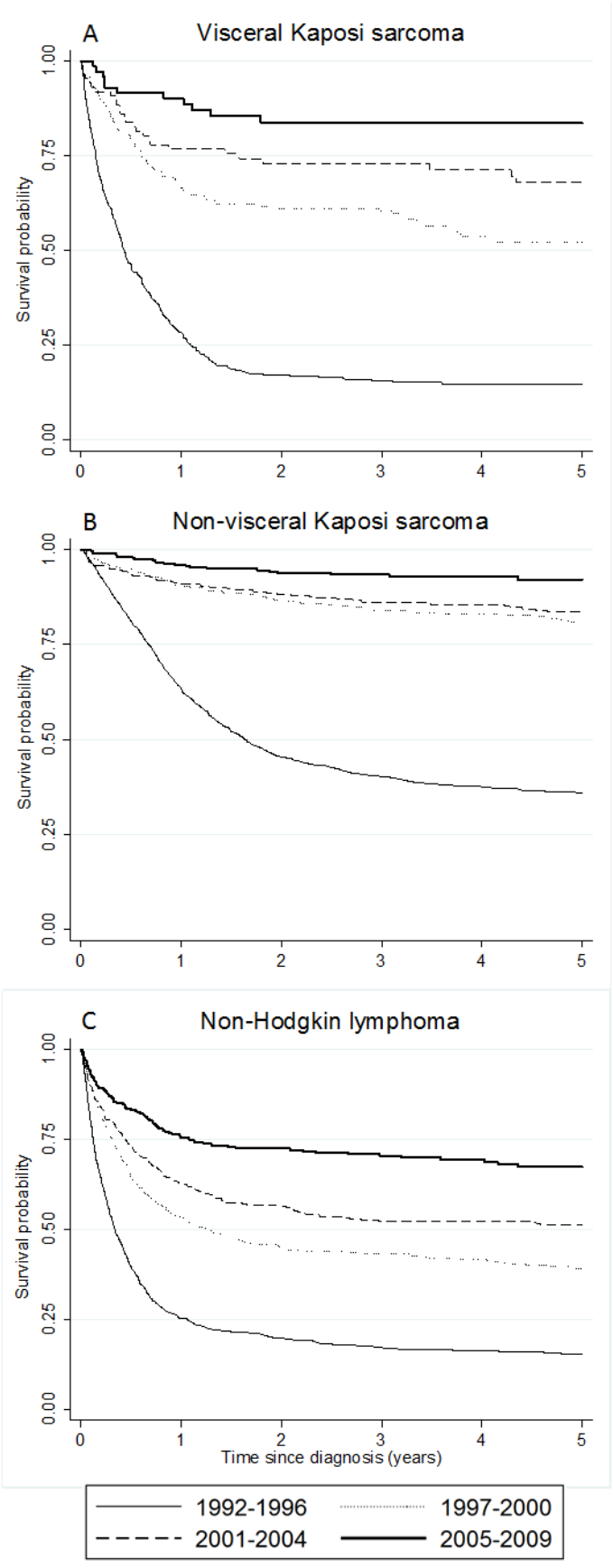
Figure legends:

Figure 1. Kaplan-Meier survival curves following diagnosis of Kaposi's sarcoma and non-Hodgkin lymphoma, stratified by calendar period of cancer diagnosis

Figure 2. Kaplan-Meier survival curves following diagnosis of four non AIDS-defining cancers (Hodgkin's lymphoma, lung, liver, anal cancer) stratified by calendar period of cancer diagnosis


A
Visceral Kaposi sarcoma
B
Non-visceral Kaposi sarcoma
C
Non-Hodgkin lymphoma
Survival probability
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Time since diagnosis (years)
1992-1996
1997-2000
2001-2004
2005-2009

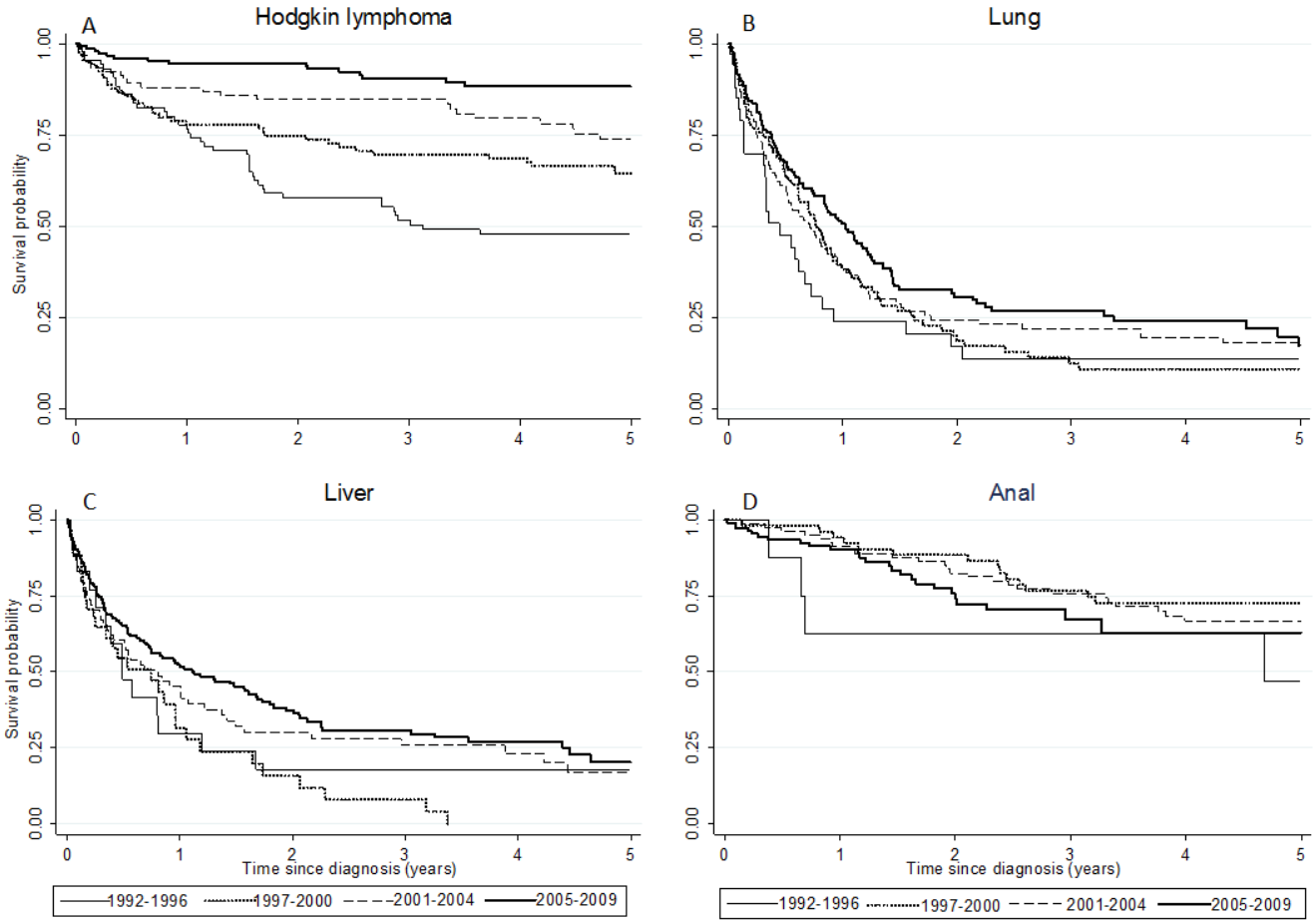

A
Hodgkin lymphoma
B
Lung
C
Liver
D
Anal
Survival probability
0.00
0.25
0.50
0.75
1.00
0
1
2
3
4
5
Time since diagnosis (years)
1992-1996
1997-2000
2001-2004
2005-2009

Table 1. Characteristics of HIV-infected individuals at cancer diagnosis.

	Visceral Kaposi sarcoma (979)	Non-visceral Kaposi sarcoma (2760)	Non-Hodgkin lymphoma (2339)	Hodgkin's lymphoma (461)	Lung (446)	Liver (312)	Anal (257)
Year of diagnosis							
1992-1996	638 (65)	1742 (63)	1088 (47)	92 (20)	36 (8)	20 (6)	8 (3)
1997-2000	176 (18)	374 (14)	516 (22)	111 (24)	107 (24)	39 (13)	54 (21)
2001-2004	90 (9)	329 (12)	359 (15)	95 (21)	131 (29)	82 (26)	83 (32)
2005-2009	75 (8)	315 (11)	376 (16)	163 (35)	172 (39)	171 (55)	112 (44)
Sex							
Men	926 (95)	2614 (95)	1955 (84)	398 (86)	382 (86)	265 (85)	234 (91)
Women	53 (5)	146 (5)	384 (16)	63 (14)	64 (14)	47 (15)	23 (9)
HIV transmission group and geographic origin							
Men who have sex with men	718 (73)	2114 (77)	1130 (48)	221 (48)	138 (31)	72 (23)	169 (66)
Injecting drug users	45 (5)	116 (4)	439 (19)	96 (21)	118 (26)	162 (52)	29 (11)
Other sub-Saharan	49 (5)	113 (4)	95 (4)	15 (3)	18 (4)	18 (6)	5 (2)
Other non-sub-Saharan	167 (17)	418 (15)	675 (29)	129 (28)	172 (39)	60 (19)	54 (21)
Age (years)	37 (33-44)	38 (33-45)	39 (33-46)	40 (34-46)	48 (42-56)	47 (42-53)	45 (39-50)
Prior AIDS							
Yes	846 (86)	1115 (40)	1157 (49)	150 (33)	150 (34)	113 (36)	133 (52)
Time since diagnosis of HIV infection (years)	4.7 (2.1-7.7)	5.5 (2.4-8.3)	6.8 (3.5-10.1)	8.1 (4.2-13.0)	9.8 (4.8-14.8)	14.2 (9.6-18.5)	13.2 (8.8-16.6)
Time since diagnosis of HIV infection < 6 months	106 (11)	262 (9)	153 (7)	21 (5)	21 (5)	9 (3)	4 (2)
HCV co-infection							
Anti-HCV antibody and/or RNA positive	77 (8)	221 (8)	415 (18)	99 (21)	121 (27)	201 (64)	38 (15)
Negative	428 (44)	1485 (54)	1093 (47)	285 (62)	240 (54)	74 (24)	162 (63)
Unknown	474 (48)	1054 (38)	831 (35)	77 (17)	85 (19)	37 (12)	57 (22)
HBV co-infection							
Hepatitis B antigen positive	78 (8)	205 (8)	203 (9)	43 (9)	47 (10)	75 (24)	36 (14)
Negative	454 (46)	1527 (55)	1260 (54)	306 (67)	289 (65)	170 (55)	164 (64)
Unknown	447 (46)	1028 (37)	876 (37)	112 (24)	110 (25)	67 (21)	57 (22)
Nadir CD4 count (cells per mm^3)	15 (5-75)	60 (15-208)	58 (10-170)	141 (43-254)	142 (47-259)	113 (40-202)	87 (18-173)
ARV at cancer diagnosis							
No current ARV	127 (13)	468 (17)	323 (14)	62 (13)	50 (11)	22 (7)	10 (4)
ARV, not cART	528 (54)	1449 (53)	1008 (43)	86 (19)	63 (14)	42 (13)	23 (9)
cART < 6 months	165 (17)	365 (13)	256 (11)	51 (11)	31 (7)	14 (5)	14 (5)
cART ≥ 6 months	159 (16)	478 (17)	752 (32)	262 (57)	302 (68)	234 (75)	210 (82)
CD4 cell count at cancer diagnosis (/mm^3)	24 (6-104)	65 (16-228)	83 (16-230)	200 (97-384)	301 (161-472)	252 (131-412)	290 (170-493)
1992-1996	11 (5-48)	34 (10-120)	25 (8-103)	166 (63-292)	175 (76-271)	82 (28-204)	302 (135-458)
1997-2000	59 (13-172)	161 (42-374)	137 (40-270)	189 (84-366)	250 (130-487)	185 (84-370)	240 (154-336)
2001-2004	107 (27-220)	160 (51-338)	162 (60-326)	182 (77-366)	278 (140-435)	241 (113-375)	296 (170-466)
2005-2009	183 (36-325)	247 (88-416)	215 (100-367)	230 (140-423)	371 (204-534)	273 (165-450)	363 (176-551)
HIV RNA load at cancer diagnosis (copies/mL)	4250 (500-164243)	11100 (500-180000)	5800 (500-130000)	500 (500-9400)	500 (500-2370)	500 (500-1672)	500 (500-7100)
1997-2000	27000 (500-225000)	28000 (500-237308)	21000 (663-187375)	1312 (500-21000)	500 (500-6000)	500 (500-15400)	1645 (500-28000)
2001-2004	2060 (500-173000)	9323 (500-198450)	4000 (500-114900)	50 (50-8600)	160 (500-6091)	139 (500-8332)	62 (500-6360)
2005-2009	198 (50-48331)	3600 (50-98501)	299 (50-64850)	50 (50-1300)	50 (50-205)	50 (50-412)	50 (50-2409)

Data are numbers (proportions) and medians (interquartile range).

Table 2. Five-year Kaplan-Meier survival rates (95% CI) and death hazard ratios (95% CI) after cancer diagnosis between 1992 and 2009.

Cancer	Diagnosis period	Cases	Deaths before 5 years	5-year srvival % (95% CI)	Death hazard ratio adjusted for age and sex (95% CI)	Death hazard ratio adjusted for all covariates* (95% CI)	Hazard Trend** P value
Visceral Kaposi	1992-1996	638	524	14.1 (11.4-17.1)	3.07 (2.42-3.90)	2.34 (1.82-3.01)	
	1997-2000	176	80	51.7 (43.8-59.1)	1(ref)	1(ref)	
	2001-2004	90	30	64.9 (53.6-74.1)	0.68 (0.45-1.03)	0.88 (0.58-1.35)	
	2005-2009	75	12	82.6 (71.3-89.7)	0.32 (0.17-0.59)	0.42 (0.23-0.77)	<0.0001
Non-visceral Kaposi	1992-1996	1742	1022	35.8 (33.5-38.2)	4.91 (3.83-6.29)	3.19 (2.47-4.10)	
	1997-2000	374	67	81.0 (76.5-84.8)	1(ref)	1(ref)	
	2001-2004	329	50	83.5 (78.8-87.3)	0.85 (0.59-1.23)	0.90 (0.63-1.31)	
	2005-2009	315	22	91.9 (87.7-94.6)	0.40 (0.25-0.65)	0.46 (0.29-0.75)	<0.0001
Non Hodgkin lymphoma	1992-1996	1088	885	14.8 (12.6-17.1)	2.04 (1.78-2.32)	1.38 (1.20-1.59)	
	1997-2000	516	301	37.8 (33.4-42.2)	1(ref)	1(ref)	
	2001-2004	359	171	48.7 (43.2-54.0)	0.76 (0.63-0.91)	0.83 (0.69-1.00)	
	2005-2009	376	115	65.1 (59.3-70.2)	0.44 (0.36-0.55)	0.52 (0.42-0.65)	<0.0001
Hodgkin lymphoma	1992-1996	92	44	47.9% (36.9-58.1)	1.62 (1.04-2.53)	1.39 (0.88-2.18)	
	1997-2000	111	38	63.3% (53.1-71.8)	1(ref)	1(ref)	
	2001-2004	95	24	72.4% (61.5-80.7)	0.67 (0.40-1.12)	0.73 (0.43-1.25)	
	2005-2009	163	17	87.2% (79.9-91.9)	0.29 (0.16-0.53)	0.33 (0.18-0.61)	<0.0001
Lung	1992-1996	36	28	13.2% (4.2-27.5)	1.10 (0.71-1.69)	1.08 (0.69-1.68)	
	1997-2000	107	85	9.9% (4.6-17.7)	1(ref)	1(ref)	
	2001-2004	131	94	16.7% (10.1-24.7)	0.95 (0.71-1.28)	0.92 (0.67-1.25)	
	2005-2009	172	114	16.4% (9.2-25.5)	0.78 (0.59-1.05)	0.78 (0.57-1.07)	0.3621
Liver	1992-1996	20	15	16.9% (4.2-36.9)	0.79 (0.43-1.46)	0.82 (0.43-1.57)	
	1997-2000	39	33	3.5% (0.3-15.2)	1(ref)	1(ref)	
	2001-2004	82	58	14.6% (6.5-25.9)	0.70 (0.46-1.08)	0.69 (0.44-1.08)	
	2005-2009	171	110	19.2% (11.5-28.5)	0.52 (0.35-0.77)	0.52 (0.34-0.80)	0.0206
Anal	1992-1996	8	4	46.9% (12.0-76.3)	2.17 (0.72-6.54)	3.22 (1.02-10.09)	
	1997-2000	54	15	71.3% (56.9-81.6)	1(ref)	1(ref)	
	2001-2004	83	25	66.7% (54.7-76.2)	1.04 (0.55-2.00)	1.13 (0.59-2.18)	
	2005-2009	112	25	62.9% (47.6-74.9)	1.26 (0.63-2.50)	1.28 (0.63-2.60)	0.2358

*Models adjusted for sex, age, geographic origin and HIV transmission group, HBV and HCV co-infection, AIDS status, and CD4 cell count at cancer diagnosis.

**P_{trend} for the fully adjusted models.

Table 3. Five-year Kaplan Meier survival rates (95% CI) and death hazard ratios (95% CI) after cancer diagnosis between 1997 and 2009.

Cancer	Diagnosis period	Cases	Deaths	5-year survival % (95% CI)	Death hazard ratio adjusted for age and sex (95% CI)	Death hazard ratio adjusted for all covariates except viral load* (95% CI)	Hazard Trend* P value	Death hazard ratio adjusted for all covariates including viral load** (95% CI)	Hazard Trend** P value
Visceral Kaposi sarcoma	1997-2000	176	80	51.7 (43.8-59.1)	1(ref)	1(ref)		1(ref)	
	2001-2004	90	30	64.9 (53.6-74.1)	0.68 (0.45-1.05)	1.03 (0.66-1.59)		1.00 (0.64-1.56)	
	2005-2009	75	12	82.6 (71.3-89.7)	0.33 (0.18-0.60)	0.56 (0.30-1.04)	0.1618	0.62 (0.33-1.18)	0.3233
Non-visceral Kaposi sarcoma	1997-2000	374	67	81.0 (76.5-84.8)	1(ref)	1(ref)		1(ref)	
	2001-2004	329	50	83.5 (78.8-87.3)	0.84 (0.58-1.22)	0.95 (0.65-1.38)		0.95 (0.65-1.40)	
	2005-2009	315	22	91.9 (87.7-94.6)	0.41 (0.25-0.66)	0.52 (0.32-0.86)	0.0312	0.50 (0.30-0.84)	0.0269
Non-Hodgkin lymphoma	1997-2000	516	301	37.8 (33.4-42.2)	1(ref)	1(ref)		1(ref)	
	2001-2004	359	171	48.7 (43.2-54.0)	0.75 (0.62-0.91)	0.83 (0.68-1.00)		0.85 (0.70-1.04)	
	2005-2009	376	115	65.1 (59.3-70.2)	0.44 (0.36-0.55)	0.54 (0.43-0.67)	<0.0001	0.58 (0.46-0.73)	<0.0001
Hodgkin lymphoma	1997-2000	111	38	63.3 (53.1-71.8)	1(ref)	1(ref)		1(ref)	
	2001-2004	95	24	72.4 (61.5-80.7)	0.70 (0.42-1.17)	0.73 (0.42-1.26)		0.79 (0.45-1.39)	
	2005-2009	163	17	87.2 (79.9-91.9)	0.32 (0.18-0.58)	0.33 (0.18-0.62)	0.0023	0.36 (0.19-0.69)	0.0071
Lung	1997-2000	107	85	9.9 (4.6-17.7)	1(ref)	1(ref)		1(ref)	
	2001-2004	131	94	16.7 (10.1-24.7)	0.94 (0.70-1.26)	0.88 (0.65-1.20)		0.88 (0.64-1.20)	
	2005-2009	172	114	16.4 (9.2-25.5)	0.77 (0.58-1.04)	0.75 (0.55-1.02)	0.1739	0.72 (0.51-1.00)	0.1330
Liver	1997-2000	39	33	3.5 (0.3-15.2)	1(ref)	1(ref)		1(ref)	
	2001-2004	82	58	14.6 (6.5-25.9)	0.70 (0.45-1.08)	0.71 (0.45-1.12)		0.72 (0.46-1.14)	
	2005-2009	171	110	19.2 (11.5-28.5)	0.51 (0.34-0.76)	0.55 (0.35-0.85)	0.0198	0.67 (0.42-1.06)	0.2237
Anal	1997-2000	54	15	71.3 (56.9-81.6)	1(ref)	1(ref)		1(ref)	
	2001-2004	83	25	66.7 (54.7-76.2)	1.03 (0.54-1.96)	1.09 (0.57-2.11)		1.13 (0.58-2.20)	
	2005-2009	112	25	62.9 (47.6-74.9)	1.23 (0.623-2.44)	1.23 (0.60-2.49)	0.8472	1.35 (0.64-2.84)	0.7239

*Cox Models adjusted for sex, age, geographic origin and HIV transmission group, HBV and HCV co-infection, AIDS status, and CD4 cell count at cancer diagnosis, and the P_{trend} for the corresponding models.

** Cox Models adjusted for sex, age, geographic origin and HIV transmission group, HBV and HCV co-infection, AIDS status, CD4 cell count and viral load at cancer diagnosis, and the P_{trend} for the corresponding models.

Table 4. Five-year survival rates (95% CI) after cancer diagnosis in the general population and in HIV-infected individuals in the period 2001-2004, in France

	5-year Kaplan Meier survival % (95% CI)			
	General population		HIV-infected population	P value**
	Crude survival †	Age- and sex-standardized survival*		
Non-Hodgkin lymphoma (all)	53 (52-54)	74 (72-76)	49 (43-54)	$<10^{-4}$
Diffuse large B-cell lymphoma	48 (45-51)	70 (65-74)	49 (43-54)	$<10^{-4}$
Hodgkin lymphoma	79 (75-83)	83 (79-87)	72 (62-81)	0.04
Lung	13 (13-14)	17 (15-18)	17 (10-25)	1.00
Liver	10 (9-12)	19 (15-24)	15 (7-26)	0.47
Anal	56 (52-61)	64 (53-76)	67 (55-76)	0.71

*Standardization based on the age and sex structure of the HIV-infected patients diagnosed with the same cancer

**t-test comparing the 5-year survival rates among HIV-infected individuals and the corresponding age- and sex- standardized survival rates in the relevant general populations in France

† From references 21, 22, 23.

Supplementary table 1: ICD-9 and ICD-10 cancer codes used in the FHDH

	FHDH	
	ICD-9 ≤ 1996	**ICD-10 >1997**
Kaposi sarcoma	176.x	C46.x
Non-Hodgkin lymphoma (NHL)	200.x	C83.3, C83.4, C83.7, C85.0, C85.1, C85.7, C85.9
Lung	162.x	C33.x, C44.x
Hodgkin lymphoma	201.x	C81.x
Liver	155.x	C22.x
Anal	Validated cases between 1992 and 2008 and C21.x in 2009	