Clinical Infectious Diseases Advance Access published July 29, 2013

Risk of AIDS-defining cancers among HIV1-infected patients in France between 1992 and 2009: Results from the FHDH-ANRS CO4 cohort

Mira Hleyhel[1,2], Aurélien Belot[3,4,5], Anne Marie Bouvier[6], Pierre Tattevin[7], Jérôme Pacanowski[8], Philippe Genet[9], Nathalie De Castro[10], Caroline Dupont[11], Armelle Lavolé[12], Christian Pradier[13], Dominique Salmon[14,15], Anne Simon[16], Valérie Martinez[17], Dominique Costagliola[1,2,18], Sophie Grabar[1,15,19], on behalf of the FHDH-ANRS CO4 cohort*

[1]INSERM UMR S 943, Paris, France

[2]UPMC Paris Univ 06 UMR S 943, Paris, France

[3]Hospices Civils de Lyon, Service de Biostatistique, F-69003, Lyon, France

[4]Institut de Veille Sanitaire, Département des maladies chroniques et traumatismes, F-94410, Saint-Maurice, France

[5]FRANCIM

[6]INSERM UMR 866, Registre Bourguignon des cancers digestifs, FRANCIM, CHU Dijon, Dijon, France

[7]Centre Hospitalier Universitaire de Rennes, Hôpital Pontchaillou, Service de maladies infectieuses, Rennes, France

[8]Assistance Publique Hôpitaux de Paris (AP-HP), Hôpital Saint Antoine, Service de maladies infectieuses et tropicales, Paris, France

[9]Centre Hospitalier d'Argenteuil, Service d'hématologie-SIDA, Argenteuil, France

[10]AP-HP, Hôpital Saint Louis, Service de maladies infectieuses et tropicales, Paris, France

[11]AP-HP, Hôpital Ambroise-Paré, Service de médecine interne, Boulogne, France

[12]AP-HP, Hôpital Tenon, Service de pneumologie, Paris, France

[13]Centre Hospitalier Universitaire de Nice, Hôpital de l'Archet, Département de santé publique, Nice, France

[14]AP-HP, Groupe hospitalier Cochin Broca Hôtel-Dieu, Service de médecine interne et centre de référence maladies rares, Paris, France

[15]Université Paris Descartes, Sorbonne Paris cité, Paris, France

[16]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de médecine interne, Paris, France

[17]AP-HP, Hôpital Antoine Béclère, Service de médecine interne – immunologie clinique, Clamart, France

[18]AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Service de maladies infectieuses et tropicales, Paris, France

[19]AP-HP, Groupe hospitalier Cochin Broca Hôtel-Dieu, Unité de biostatistique et d'épidémiologie, Paris, France

Corresponding author: Mira Hleyhel, INSERM UMR S 943, 56 Boulevard Vincent Auriol, BP 335, 75625 Paris cedex 13, Tel. 33 (1) 42 16 42 94, Fax. 33 (1) 42 16 42 61, mhleyhel@ccde.chups.jussieu.fr

[*]Members are listed at http://www.ccde.fr/main.php?main_file=fl-1171464013-677.html

Summary of the article main point: Although the decrease in the incidence of ADC over time, the risk remained high in 2005-2009. Patients with stably restored immunity on cART had an elevated risk for KS and risk similar to that of the general population for NHL.

Abstract

Background. We examined trends in the incidence of the 3 AIDS-defining cancers (ADC) (Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical cancer) among HIV-infected patients relative to the general population between 1992 and 2009 in France, focusing on age at ADC diagnosis and on patients with controlled viral load and restored immunity on combined antiretroviral therapy (cART).

Methods. Age- and sex- standardized incidence rates were estimated in patients enrolled in the French hospital database on HIV, and in the general population in France during 4 calendar periods (1992-1996, 1997-2000, 2001-2004, and 2005-2009). Standardized incidence ratios (SIR) were calculated for all periods and separately for patients on cART, with CD4 cell counts $\geq 500/mm^3$ for at least 2 years and viral load ≤ 500 copies/ml.

Results. Although the incidence of ADC fell significantly across the calendar periods, the risk remained constantly higher in HIV-infected patients than in the general population. In patients with restored immunity, the relative risk remained significantly elevated for KS [SIR= 35.4 (95% CI; 18.3-61.9)], and was similar to that of the general population for NHL [SIR= 1.0 (95% CI; 0.4-1.8)]. ADC were diagnosed at a younger age in HIV-infected patients, with a particularly marked difference for NHL (-11.3 years, $p<0.0001$).

Conclusions. The incidence of all ADC continued to fall, including cervical cancer, in the cART period, but the risk remained higher than in the general population in 2005-2009. In patients with stably restored immunity, KS remained significantly more frequent than in the general population.

Introduction

The three AIDS-defining cancers (ADC) namely Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL) and cervical cancer were added to the list of AIDS-defining conditions by the Centers for Disease Control and Prevention [1] because of their association with immunodeficiency [2-5]. The three ADC are known to be associated with viral infections [6], namely human herpes virus 8 (HHV-8) for KS, Epstein–Barr virus (EBV) for most cases of NHL in HIV-infected patients and human papilloma virus (HPV) for cervical cancer. Compared to the general population, a meta-analysis of studies conducted mainly in the pre-combined antiretroviral therapy (cART) era suggested that the risk in HIV-infected patients was 3640-fold higher for KS, 77-fold higher for NHL and 6-fold higher for cervical cancer [7].

Since the advent of cART in 1996, several studies have shown a large fall in the incidence of KS and NHL [8-17], while the results for cervical cancer are heterogeneous [9, 11, 12, 16, 17], mainly owing to the small number of cases. These studies did not extend beyond the year 2006, and some of them involved only patients with AIDS rather than all patients living with HIV [9, 11, 15, 17]. The number of HIV-infected patients with CD4 cell counts above 500 cells/mm^3 has increased since the advent of cART, and it is therefore interesting to investigate whether the elevated risk of ADC persists in patients with restored immunity.

Age-related comorbidities have been found to occur much earlier in patients infected with HIV than in uninfected individuals [18, 19]. However, Shiels et al. [20], studying age at diagnosis of non AIDS-defining cancers, with adjustment for the difference in age distribution between patients with AIDS and the general population, found that differences in median age at diagnosis were modest and that few of them were statistically significant. This "premature aging" hypothesis has not been tested for ADC.

The aim of this study was to evaluate long-term trends in the incidence of each ADC among patients enrolled in the French Hospital Database on HIV (FHDH ANRS CO4), one of the largest cohorts of HIV-infected patients, by comparison with the general population in France during the period 1992-2009. We also estimated standardized incidence ratios (SIR), both overall and for the subset of patients with controlled viral load and restored immunity on cART. Differences in age at ADC diagnosis between the HIV-infected and general populations were also evaluated.

METHODS

Study population

Created in 1989, FHDH is a nationwide, open, prospective cohort of HIV-infected adults managed in 70 hospitals, representing 50% of patients living with HIV in care in France in 2010 [21] and 56% of newly diagnosed AIDS cases in France between 2004 and 2006 [22]. The only inclusion criteria of the cohort are HIV-1 or HIV-2 infection and written informed consent. We included in this analysis all patients with HIV-1 infection who were between 15 and 84 years of age at FHDH enrolment and were followed-up between January 1st, 1992 and December 31st, 2009. Patients from French overseas territories were not eligible because data in the general population were not available for this study. Patients were included if they had at least 2 follow-up visits or if they died before their second follow-up visit or hospitalization, and if they had at least one CD4 cell count during follow-up. ADC were coded in FHDH using the International Classification of Diseases ICD-9 (9th revision) before 1997 and ICD-10 (10th revision) thereafter (see Supplementary table 1). Patients with history of ADC at FHDH enrolment were excluded from the analysis of the relevant ADC.

ADC incidence rates (IR) in the general population were obtained from the association of the French network of Cancer Registries (FRANCIM), which gathers data from 21 population-based regional French cancer registries covering about 20% of the population. All the new cases of cancers diagnosed and registered using the International Classification of Diseases for Oncology ICD-O-3 (3rd edition) (see Supplementary table 1) between 1992 and 2009 were considered in this study.

Statistical methods

The study was divided into pre-cART (1992-1996), early-cART (1997-2000), intermediate-cART (2001-2004) and late-cART (2005-2009) periods. For each calendar period the number of person-years (PY) at risk for each patient was calculated from the date of cohort entry or the start date of the period, whichever occurred later, until the date of cancer diagnosis, death, 6 months after the last visit, or the end of the period, whichever occurred first. Because of the aging of the HIV-infected population during the study period and for purposes of comparison (within the HIV-infected population and between the HIV-infected and general populations), crude IRs were standardized for age (in 5-year increments) and gender by using the direct standardization method based on the age and sex structure of the FHDH population followed between 1997 and 2009 (see Supplementary table 2). Standardized IRs and their 95% confidence intervals (CI) in the HIV-infected and general populations were calculated for all calendar periods. Trends in standardized IRs between the pre-cART and cART periods and within cART periods were tested by using linear regression models with the standardized IR as the outcome and the calendar period as the covariate.

To compare the risk of ADC in HIV-infected patients to that in the general population, two estimators were calculated [23]. First, the excess IR was estimated in additive fashion by subtracting the standardized IR in the general population from that in the HIV-infected patients; the 95% CIs for the excess IRs were computed assuming a Poisson distribution for the excess cases [24]. Second, the SIR was used to compare, in multiplicative fashion, the observed number of cases in HIV-infected patients with that expected in the general population. The expected number of cases was estimated by weighting the age- and sex- specific IR for the general population by the number of PY in the corresponding stratum of the HIV-infected population in all calendar periods. In addition, to evaluate the risk of ADC in the subset of HIV-infected patients with restored immunity, SIRs were estimated for patients on cART whose CD4 cell count had been ≥500/mm^3 continuously for at least 2 years and with controlled viral load (≤500 copies/ml) at the last assessment before cancer or the last follow up. CIs for the SIRs were calculated with an exact method based on the Poisson distribution [25].

Age at cancer diagnosis was compared between the HIV-infected and general populations after adjusting for the difference in the age- and sex- distribution (Figure 1) by using the indirect standardization method as in Shiels et al. [20]. The median age at cancer diagnosis among the expected cases in the general population was estimated and compared, using Brown Mood test [26], with the median age at cancer diagnosis in HIV-infected patients between 1997 and 2009.

RESULTS

Patients' characteristics

This analysis included 99309 HIV1-infected patients contributing to 687336 PY and corresponding to a mean follow-up of 6.9 years (Figure 2). The patients' characteristics at entry in each calendar period are shown in Table 1. Median age increased across the study periods. The

proportion of patients with HIV RNA ≤500 copies/ml increased from 24% in the early-cART period to 54% in the late-cART period and that of patients with CD4 cell count of ≥500/mm^3 from 20% in the pre-cART period to 37% in the late-cART period, in line with the increase in the proportion of patients on cART during the overall study period. We excluded 2781 prevalent cases of KS, 753 prevalent cases of NHL and 50 prevalent cases of cervical cancer (Figure 2). Between 1992 and 2009, 5890 incident ADC were reported, comprising 3366 cases of KS, 2344 cases of NHL and 180 cases of cervical cancer. The majority of cases (n= 3265, 55%) occurred in the pre-cART, followed by 1015 cases (17%) in the early-cART, 807 cases (14%) in the intermediate-cART, and 803 cases (14%) in the late-cART period.

Trends in the incidence of ADC and comparison with the general population

Age- and sex- standardized IRs for each ADC in the HIV-infected and general populations are shown in Figure 3, and the corresponding excess IRs relative to the general population are shown in Table 2. Regarding KS (Figure 3a), HIV-infected men who have sex with men (MSM) continued to have the highest risk during all the calendar periods. The incidence of KS fell significantly between the pre-cART and cART periods ($p<0.0001$), and continued to fall significantly in the cART era ($p<0.0001$), except among HIV-infected women ($p=0.1560$). Relative to the general population, the incidence of KS in the HIV-infected population was higher in all sex and HIV transmission groups during all the cART periods. The excess IR for KS during the late-cART period was 286 cases per 100000 PY among HIV-infected MSM, 105 cases per 100000 PY among other HIV-infected men, and 59 cases per 100000 PY among HIV-infected women.

The incidence of NHL among HIV-infected patients (Figure 3b) fell significantly across the calendar periods ($p<0.0001$) and also over the cART period ($p<0.0001$). The incidence in both

HIV-infected men and women was higher than in the general population during all the calendar periods. In the late-cART period, the excess IR for NHL was 159 cases per 100000 PY in HIV-infected men and 87 cases per 100000 PY in HIV-infected women.

The incidence of cervical cancer (Figure 3c) fell significantly both among HIV-infected women and in the general female population across the calendar periods ($p<0.0001$). The decline among HIV-infected women was also significant during the cART period ($p=0.0005$). The incidence of cervical cancer was higher in HIV-infected women than in the general population, with an excess IR of 51 cases per 100000 PY in the late-cART period.

Standardized incidence ratios compared to the general population

SIRs calculated according to sex, the HIV transmission group and the calendar period are shown in Table 3. Although a 2.5-fold decline in KS was observed during the study period, the relative risk (RR) remained >300 during all the calendar periods. A marked decline (13-fold) in NHL was observed during the study period, but the RR remained 9-fold higher in HIV-infected patients than in the general population during the late-cART period. The RR for cervical cancer declined 2-fold during the study period, but remained 5-fold higher in HIV-infected patients than in the general population in the late-cART period. Compared with the general population, patients on cART with CD4 cell counts $\geq 500/mm^3$ for at least 2 years and HIV RNA ≤ 500 copies/ml still had a significantly higher risk of KS (SIR=35.4 [18.3-61.9]), but there was no statistical difference for NHL (SIR=1.0 [0.4-1.8]) (Table 4). The SIR for cervical cancer could not be estimated because of the small number of observed and expected cases.

Age at cancer diagnosis

HIV-infected patients were diagnosed with ADC much earlier than the general population, with a median difference ranging from -13 years for cervical cancer to -17 years for KS and -31 years for NHL. After adjusting for the difference in age and sex structure between the two populations, the "real" difference was smaller but remained significant for KS (-2.2 years), cervical cancer (-3.2 years), and NHL (-11.3 years) (Table 5).

DISCUSSION

Even if the incidence of the three ADC among HIV-infected patients in France fell between the pre-cART and cART periods and continued to decline during the cART period, the risks remained significantly higher than in the general population during all the calendar periods. Patients with restored immunity for at least 2 years and controlled viral load on cART still had a strongly elevated risk of KS (35-fold), while the risk of NHL was similar to that of the general population. Age at KS and cervical cancer diagnosis was only slightly different between HIV-infected and general populations (-2 and -3 years respectively), while the difference was more marked for NHL (-11 years).

The main strengths of this study are the large number of HIV-infected patients included and the large number of incident cancers recorded in each calendar period. This allowed us to estimate IRs and SIRs separately for each period and each cancer. As summarized by Chaturvedi et al. [27], in most instances, the SIR reasonably approximates the RR. But when HIV prevalence is high and/or cancer incidence in HIV-infected patients relative to non-infected persons is high, the SIR tends to underestimate the RR. This could have been the case for KS which is rare among individuals not infected with HIV. However, because there are no cancer registries in the French

regions with the highest prevalence of HIV infection (Paris area and Provence-Alpes-Côte d'Azur), this phenomenon is minimized. Another possible limitation of our study is the incomplete ADC ascertainment. Indeed, we previously showed that the ADC ascertainment rate was 73% in 2006 [28], and verified that it was independent of the geographic origin and the CD4 cell count (not shown). Based on the results of regular audits comparing data in the FHDH database with those in the corresponding medical records, AIDS-defining events have been reported in consistent fashion since the launch of the database, and it is therefore unlikely that changes in the ascertainment rate over time would affect our results. Even if we underestimated the RRs with respect to the general population, this could not explain the excess risks observed here.

Between the pre- and early-cART periods [9-12, 14-17, 29] and also during the cART period [9-12, 14, 16, 17], most studies have shown a fall in the incidence of KS and NHL. This was also the case in our study, where the incidence of KS and NHL continued to decline until 2009. As previously showed [8], the elevated incidence of KS among HIV-infected women is likely due to the high proportion of women of sub-Saharan origin (26%), who are more at risk of KS. Indeed, in 2005-2009, the incidence of KS in HIV-infected women of sub-Saharan origin was 105.0 (63.6-146.5) per 100000 PY, while the incidence in other HIV-infected women was 36.0 (19.5-52.5) per 100000 PY. For cervical cancer, although most previous studies, which included limited numbers of cases (from 8 to 74), showed no change in the incidence [9, 11, 12, 15, 16], a study with 1276 cases [17] showed a decline among women with AIDS between 1991 and 2005. In the current study, which included all women infected with HIV and not only those with AIDS, and analyzed a large number of cases (n=180) with lengthy follow-up, the incidence of cervical cancer also declined over time.

The comparison of SIR values between different studies can be problematic as SIR estimation is not based on a common standard. Indeed, SIR values vary with the relative sizes of the different strata that compose the study population, such as sex, age and the transmission group [13, 30]. However, as in other studies [12, 13, 15, 16, 31], we observed a higher risk for all ADCs among HIV-infected patients compared to the general population during all the calendar periods. Furthermore, despite the decline in the RRs over time, the risk of the three ADC remained higher than in the general population during the late-cART period (300-fold for KS, 9-fold for NHL and 5-fold for cervical cancer). SIRs and excess IRs may lead to different interpretations of the risk according to the type of cancer and the baseline risk in the general population. For instance, in 2005-2009, the SIR was 150 for KS in HIV-infected men other than MSM, and 9 for NHL in all HIV-infected men, whereas the excess IRs were respectively 105 and 159 cases per 100000 PY. This illustrates the fact that, in addition to the RR, it is important to take the absolute risk into account. In the study population, the median CD4 cell count rose from 259/mm^3 in the pre-cART era to 413/mm^3 in the late-cART period, in line with the rise from 3.5% to 86% in the proportion of patients on cART. This is likely to account in large part for the decrease in the burden of the three ADC. However, the magnitude of the fall differed according to the cancer, gender and HIV transmission group. The reason for this heterogeneity is unclear, but it might involve differences in the relation between immunodeficiency and cancer risk, or differences in the proportion of persons co-infected with the relevant oncogenic virus.

In patients with restored immunity, the risk remained elevated for KS (SIR=35) and was not increased for NHL (SIR=1). The RR for cervical cancer could not be estimated due the relatively small number of PY of follow-up for women in this analysis. A previous study showed elevated RRs for KS and NHL (60 and 4 respectively) among HIV-infected individuals with current CD4

cell counts ≥500/mm^3 compared to a group of HIV-uninfected individuals, after adjustment for several cancer risk factors [4]. Immune restoration was defined differently in the current analysis: instead of the current CD4 cell count, we used a continuous period of at least 2 years with high CD4 cell counts. The difference in the definition of the immune restoration could be an explanation for the different results observed in the two studies.

The younger age at ADC diagnosis among HIV-infected patients compared to the general population may be linked to 3 non-exclusive factors: (1) an earlier acquisition of oncogenic virus infection (HHV-8, EBV and HPV), (2) a closer medical surveillance of HIV-infected patients, leading to an earlier diagnosis, and/or (3) a specific effect of HIV infection. Due to the small difference in the age at diagnosis of KS (-2 years) and cervical cancer (-3 years), the third factor is not necessary to explain our results. In the case of NHL, the much larger difference (-11 years) cannot be explained only by the first 2 factors.

In conclusion, the increase of cART use and CD4 cell counts was associated with a further decline in the risk of AIDS-defining cancers, even for the cervical cancer, during the cART period. However, the risk remained higher than in the general population, even during the most recent period. Our results do not favor the hypothesis of premature aging in HIV patients for KS and cervical cancer. Among treated patients with immunological (i.e. CD4 count ≥500/mm^3 during at least two years) and virological success, the risk was not increased for NHL but remained higher than in the general population for KS. This suggest that cART would be most beneficial to prevent the risk of cancer in HIV-infected patients, if it restores or maintains CD4 count above 500/mm^3, thereby indicating the need for an earlier diagnosis of HIV infection and an earlier treatment initiation.

Author Contributions:

DC and SG designed the study. MH did the statistical analyses. MH, DC and SG interpreted the data and wrote the manuscript. All authors read and critically commented on the paper.

Funding:

Agence Nationale de Recherche sur le SIDA et les hépatites virales (ANRS), INSERM, and the French Ministry of Health.

Potential conflicts of interest:

No author has any financial or personal relationships with people or organizations that could inappropriately influence this work, although several members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

Acknowledgments:

We thank all the participants and research assistants of the French Hospital Database on HIV. The French Hospital Database on HIV is supported by Agence Nationale de Recherche sur le SIDA et les hépatites virales (ANRS), INSERM, and the French Ministry of Health.

1.Schneider E, Whitmore S, Glynn KM, et al. Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years--United States, 2008. MMWR Recomm Rep **2008**; 57: 1-12.

2.Clifford GM, Polesel J, Rickenbach M, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst **2005**; 97: 425-432.

3.Guiguet M, Boue F, Cadranel J, Lang JM, Rosenthal E, Costagliola D. Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol **2009**; 10: 1152-1159.

4.Silverberg MJ, Chao C, Leyden WA, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiol Biomarkers Prev **2011**; 20: 2551-2559.

5.Frisch M, Biggar RJ, Engels EA, Goedert JJ, Group AI-CMRS. Association of cancer with AIDS-related immunosuppression in adults. JAMA **2001**; 285: 1736-1745.

6.Schulz TF. Cancer and viral infections in immunocompromised individuals. Int J Cancer **2009**; 125: 1755-1763.

7.Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet **2007**; 370: 59-67.

8.Grabar S, Abraham B, Mahamat A, Del Giudice P, Rosenthal E, Costagliola D. Differential impact of combination antiretroviral therapy in preventing Kaposi's sarcoma with and without visceral involvement. J Clin Oncol **2006**; 24: 3408-3414.

9.Biggar RJ, Chaturvedi AK, Goedert JJ, Engels EA. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst **2007**; 99: 962-972.

10.Polesel J, Clifford GM, Rickenbach M, et al. Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS **2008**; 22: 301-306.

11.Polesel J, Franceschi S, Suligoi B, et al. Cancer incidence in people with AIDS in Italy. Int J Cancer **2010**; 127: 1437-1445.

12.Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003. Ann Intern Med **2008**; 148: 728-736.

13.Franceschi S, Lise M, Clifford GM, et al. Changing patterns of cancer incidence in the early- and late-HAART periods: the Swiss HIV Cohort Study. Br J Cancer **2010**; 103: 416-422.

14.Franceschi S, Maso LD, Rickenbach M, et al. Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer **2008**; 99: 800-804.

15.Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980-2002. AIDS **2006**; 20: 1645-1654.

16.Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer **2008**; 123: 187-194.

17.Shiels MS, Pfeiffer RM, Gail MH, et al. Cancer burden in the HIV-infected population in the United States. J Natl Cancer Inst **2011**; 103: 753-762.

18.Brock MV, Hooker CM, Engels EA, et al. Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care. J Acquir Immune Defic Syndr **2006**; 43: 47-55.

19.Puoti M, Bruno R, Soriano V, et al. Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. AIDS **2004**; 18: 2285-2293.

20.Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Ann Intern Med **2010**; 153: 452-460.

21.Supervie V and Costagliola D. The Spectrum of Engagement in HIV Care in France: Strengths and Gaps. 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, USA **2013**; Abstract 1030.

22.Spaccaferri G, Cazein F, Lievre L, et al. Estimation of completeness of AIDS surveillance with capture-recapture method, France, 2004–2006. BEH **2010**; 313–315.

23.Lewden C, Bouteloup V, De Wit S, et al. All-cause mortality in treated HIV-infected adults with CD4 ≥ 500/mm3 compared with the general population: evidence from a large European observational cohort collaboration. Int J Epidemiol **2012**; 41: 433-445.

24.Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott Williams & Wilkins **1998**.

25.Breslow N, Day N. Statistical methods in cancer research. Lyon: IARC Scientific Publications, **1987**.

26.Brown GW, Mood AM. On median tests for linear hypotheses. Proc Second Berkeley Symp on Math Statist and Prob **1951**; 159-166.

27.Chaturvedi AK, Mbulaiteye SM, Engels EA. Underestimation of relative risks by standardized incidence ratios for AIDS-related cancers. Ann Epidemiol **2008**; 18: 230-234.

28.Lanoy E, Spano JP, Bonnet F, et al. The spectrum of malignancies in HIV-infected patients in 2006 in France: the ONCOVIH study. Int J Cancer **2011**; 129: 467-475.

29.Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. Blood **2001**; 98: 2339-2344.

30.Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. J Clin Oncol **2008**; 26: 4834-4842.

31.Dal Maso L, Polesel J, Serraino D, et al. Pattern of cancer risk in persons with AIDS in Italy in the HAART era. Br J Cancer **2009**; 100: 840-847.

Table 1. Patients' characteristics at entry in each calendar period*.

	Pre-cART 1992-1996	Early-cART 1997-2000	Intermediate-cART 2001-2004	Late-cART 2005-2009
Number of HIV-1 infected patients with at least one visit during the period	46203 (100)	49030 (100)	56634 (100)	67546 (100)
Age	33.0 (28.8-39.2)	35.5 (31.1-41.5)	38.3 (33.3-44.4)	40.9 (35.1-47.2)
Sex and HIV transmission group				
Men who have sex with men	18027 (39.0)	18154 (37.0)	20229 (35.7)	24155 (35.8)
Other men	16862 (36.5)	17506 (35.7)	19262 (34.0)	21952 (32.5)
Women	11314 (24.5)	13370 (27.3)	17143 (30.3)	21439 (31.7)
Origin				
Sub-Saharan men	791 (1.7)	1520 (3.1)	2595 (4.6)	3901 (5.8)
Sub-Saharan women	922 (2.0)	2156 (4.4)	4401 (7.8)	6708 (9.9)
Non sub-Saharan men	34098 (73.8)	34140 (69.6)	36896 (65.1)	42206 (62.5)
Non sub-Saharan women	10392 (22.5)	11214 (22.9)	12742 (22.5)	14731 (21.8)
Prior AIDS-defining opportunistic infections	6039 (13.1)	7017 (14.3)	9023 (15.9)	11376 (16.8)
HIV RNA copies/mL**		9100 (549-65000)	1085 (500-27100)	126 (50-18058)
HIV RNA ≤ 500 copies/mL		11647 (23.8)	25134 (44.4)	36443 (54.0)
CD4 cells/mm^3***	259 (98-447)	306 (165-470)	400 (234-595)	413 (262-597)
CD4 cell counts ≥ 500 cells/mm^3	9164 (19.8)	10585 (21.6)	20056 (35.4)	24733 (36.6)
Treatment				
Naïve	4545 (9.8)	2094 (4.3)	2636 (4.7)	4231 (6.3)
Previous ARV, no current ARV	8215 (17.8)	3715 (7.6)	5494 (9.7)	3497 (5.2)
ARV, not cART	31815 (68.9)	17683 (36.1)	4342 (7.7)	1718 (2.5)
cART****	1628 (3.5)	25538 (52.1)	44162 (88.0)	58100 (86.0)
Number of person-years of follow-up				
Men who have sex with men	42335	56645	65967	89922
Other men	40712	51578	59788	80363
Women	29198	39484	52205	79139

*A given patient may be followed-up in more than one period.

Data are presented as counts (proportions) and medians (Inter-Quartile Range).

Abbreviations: cART combined antiretroviral therapy, ARV antiretroviral drugs

**HIV RNA data were available for 47464 patients (96.8%) in the early cART period, 55390 patients (97.8%) in the intermediate cART period, and 66154 patients (98.0%) in the late cART period

***CD4 cell count data were available for 45675 patients (98.9%) in pre-cART period, 48403 patients (98.7%) in the early cART period, 55827 patients (98.6%) in the intermediate cART period, and 66753 patients (98.8%) in the late cART period

****cART is defined as boosted protease inhibitor monotherapy, whatever the protease inhibitor; dual therapy with two boosted protease inhibitors or one boosted protease inhibitor plus one non-nucleoside reverse transcriptase inhibitor; or at least one boosted protease inhibitor or with an integrase inhibitor and/or an anti-CCR5 drug; or a combination of 3 or more drugs.

Table 2. Excess incidence rates per 100000 person-years in HIV-infected patients relative to the general population in different calendar periods.

Cancer type		Pre-cART 1992-1996	Early-cART 1997-2000	Intermediate-cART 2001-2004	Late-cART 2005-2009
Kaposi's sarcoma	Women	272.2 (188.1-356.2)	80.6 (50.1-111.1)	72.9 (49.6-96.2)	59.1 (41.4-76.7)
	MSM	4932.9 (4664.0-5201.9)	570.4 (501.8-639.0)	406.6 (356.0-457.2)	286.1 (247.8-324.4)
	Other men	1326.6 (1147.3-1505.8)	278.0 (223.6-332.3)	191.7 (155.7-227.7)	104.5 (80.1-128.8)
Non-Hodgkin's lymphoma	Women	622.5 (500.8-744.3)	209.3 (159.9-258.7)	117.9 (87.2-148.6)	86.8 (65.0-108.5)
	Men	1336.3 (1231.1-1441.4)	413.2 (369.1-457.3)	226.5 (198.9-254.1)	158.5 (138.1-178.9)
Cervical cancer	Women	134.4 (75.5-193.3)	112.6 (74.5-150.7)	59.5 (36.2-82.8)	51.1 (34.1-68.1)

The excess incidence rate (95% CI) per 100000 person-years was estimated as the difference between the standardized incidence rates between HIV-infected patients and the general population.

Abbreviations: cART combined antiretroviral therapy, MSM men who have sex with men

Table 3. Standardized incidence ratios (SIR) according to the calendar period.

Cancer type		Pre-cART 1992-1996		Early-cART 1997-2000		Intermediate-cART 2001-2004		Late-cART 2005-2009	
		O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Kaposi's sarcoma	Women	73/0.05	1446.0 (1133.4-1818.2)	32/0.03	1059.9 (724.9-1496.4)	38/0.03	1113.1 (787.6-1527.9)	45/0.07	657.7 (479.6-880.0)
	MSM	1738/1.24	1399.9 (1334.9-1467.3)	300/0.56	534.5 (475.7-598.6)	251/0.47	531.6 (467.9-601.6)	232/0.56	414.1 (365.1-474.4)
	Other men	337/1.44	234.4 (210.1-260.9)	124/0.58	212.5 (176.8-253.4)	112/0.48	235.7 (194.1-283.6)	84/0.56	149.8 (119.5-185.5)
	All	2148/2.73	787.0 (754.1-821.0)	456/1.17	388.1 (353.3-425.4)	401/0.98	408.6 (369.6-450.6)	361/1.19	304.5 (273.9-337.6)
Non-Hodgkin's lymphoma	Women	162/1.44	112.5 (95.9-131.3)	85/2.54	33.5 (26.7-41.4)	66/4.21	15.7 (12.1-19.9)	77/7.99	9.6 (7.6-12.0)
	Men	916/7.80	117.5 (110.0-125.4)	426/12.67	33.6 (30.5-37.0)	302/19.67	15.4 (13.7-17.2)	310/34.38	9.0 (8.0-10.1)
	All	1078/9.24	116.7 (109.9-123.9)	511/15.21	33.6 (30.8-36.6)	368/23.88	15.4 (13.9-17.1)	387/42.37	9.1 (8.3-10.1)
Cervical cancer	Women	39/3.20	12.2 (8.7-16.6)	48/5.17	9.3 (6.9-12.3)	38/7.01	5.4 (3.8-7.5)	55/10.27	5.4 (4.0-7.0)

Abbreviations: cART combined antiretroviral therapy, O observed cases, E expected cases, SIR standardized incidence ratio, CI confidence interval, MSM men who have sex with men

Table 4. Standardized incidence ratios (SIR) for AIDS-defining cancers in HIV-infected patients on cART, with CD4 cell count ≥ 500/mm^3 for at least 2 years and controlled viral load.

Cancer type	O/E	Number of PY of HIV+ patients	IR in HIV+ patients (95% CI) per 100000 PY	IR in general population* (95% CI) per 100000 PY	SIR (95% CI)
Kaposi's sarcoma	12/0.34	55 633	21.6 (11.2-37.7)	0.6 (0.5-0.6)	35.4 (18.3-61.9)
Non-Hodgkin's lymphoma	9/9.48	56 493	15.9 (7.3-30.2)	13.8 (13.5-14.1)	1.0 (0.4-1.8)
Cervical cancer	3/2.20	14 825	20.2 (4.2-59.1)	12.9 (12.5-13.4)	-

*Incidence rate standardized for the age and sex structure of the HIV-infected population 1997-2009.

Abbreviations: O/E observed/expected, PY person-years, IR incidence rate, SIR standardized incidence ratio, CI confidence interval

Table 5. Age at cancer diagnosis among patients with HIV infection and in the general population in France between 1997 and 2009.

Cancer type	Observed age HIV+ population	Observed age General population	Observed difference (years)	Expected age general population	Real difference (years)	P-value**
Kaposi's sarcoma	40.3 (34.7-47.2)	57.5 (42.5-72.5)	-17.2	42.5 (37.5-47.5)	-2.2	$<10^{-4}$
Non-Hodgkin's lymphoma	41.2 (35.9-48.2)	72.5 (57.5-77.5)	-31.3	52.5 (42.5-57.5)	-11.3	$<10^{-4}$
Cervical cancer	39.3 (35.7-45.5)	52.5 (42.5-67.5)	-13.2	42.5 (37.5-47.5)	-3.2	$<10^{-4}$

Age at cancer diagnosis is presented as the median (Inter-Quartile Range).

*Real difference estimated as the difference between observed age at cancer diagnosis in the HIV-infected population and expected age at cancer diagnosis in the general population.

**P value for the comparison of median age for cancers observed in people with HIV and expected cases in the general population.

Expected cases are adjusted for age and sex.

Figure 1. Age and sex distribution of the HIV-infected and general populations.

Figure 2. Flow chart of patients' inclusion in the study

Abbreviations: FHDH French Hospital Database on HIV, KS Kaposi's sarcoma, NHL non-Hodgkin's lymphoma, PY person-years

Figure 3. ADC standardized incidence rates in the HIV-infected and general populations per calendar period. Standardization is based on the age and sex distribution of HIV-infected patients between 1997 and 2009. (a) Kaposi's sarcoma; (b) non-Hodgkin's lymphoma; (c) cervical cancer.