Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy

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Objective: To describe the cases of anal cancer that appeared in the French Hospital Database on HIV between 1992 and 2004 and to study risk factors of anal cancer.

Methods: We examined the incidence rates of anal cancer between 1992 and 2004 and the risk associated among 86 322 HIV-infected patients included in the French Hospital Database on HIV.

Results: We identified 132 cases of anal cancer, including 124 cases in men (94%), of whom 75% had sex with men. Median age at diagnosis was 42.8 years (interquartile range: 36.9–49.4). At diagnosis, 103 patients (78%) were receiving combination antiretroviral therapy for a median of 37.1 months (interquartile range: 4.5–59.8). Median survival after anal cancer diagnosis was 5 years. The respective overall incidence rates of anal cancer per 100 000 person-years between 1992 and March 1996, April 1996 to 1998 and between 1999 and 2004 were 11 (95% confidence interval, 4–17), 18 (95% confidence interval, 10–27) and 40 (95% confidence interval, 32–47). The risk of anal cancer was higher among men who have sex with men. After adjustment for age at inclusion in the study, as well as gender, the HIV transmission group, the nadir CD4 cell count and AIDS status, the incidence was higher in the years 1999–2004 than in between 1992 to March 1996 (hazard ratio, 2.5; 95% confidence interval, 1.2–5.3), with no change in the years 1999–2004.

Conclusion: The incidence of anal cancer has increased among HIV-infected patients in France since 1996. Although an ascertainment bias cannot be excluded, data indicate that combination antiretroviral therapy does not prevent anal cancer in these patients. This supports the urgent need for developing anal cancer screening programs for HIV-infected men who have sex with men.

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Keywords: anal cancer, cancer, combination antiretroviral therapy, HIV infection, human papillomavirus infection, immune restoration, papillomavirus

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Introduction

The prevalence and incidence of anogenital human papillomavirus (HPV) infection and HPV-related anal intraepithelial neoplasia (AIN), the precursors of anal cancer, were found to be higher in HIV-seropositive individuals than in HIV-seronegative ones before the advent of combination antiretroviral therapy (cART) [1]. In addition, several studies showed an increased risk of anal cancer in HIV-infected patients in the precART era [2–4]. The incidence of anal cancer was reported to be two-fold higher in HIV-infected men who have sex with men (MSM) than in HIV-seronegative MSM [2,3], whereas the relative risk of anal cancer among HIV-seropositive men and HIV-seropositive MSM was 37-fold and 59-fold higher, respectively, than in the general population [4]. Anal cancer is 14 to 175 times more frequent in HIV-infected patients than in the general population [5–9], and the prevalence of HPV infection is also higher in the former. In a recent study, Chiao *et al.* [10] found that anal cancer tended to be diagnosed at a younger age in HIV-infected patients and particularly in men, whereas in the general population, anal cancer is more frequent in women and usually occurs during the sixth decade of life. In the cART era, some data show no positive impact of cART-induced immune restoration on the prevalence or incidence of anal HPV infection and AIN [11–13]. Few data are available on the incidence of anal cancer since the advent of cART, and some point to an increase and some not [5,14–16]. In the present study, we analysed the incidence of anal cancer among French HIV-infected patients during different periods defined by antiretroviral availability.

Methods

Study population

Patients were selected from the French Hospital Database on HIV (FHDH), a nationwide hospital-based cohort [17]. This epidemiological network was created in 1989, and currently, 62 French teaching hospitals across France contribute data on HIV-infected patients. The only FHDH inclusion criteria are HIV-1 or HIV-2 infection and written informed consent. Trained research assistants prospectively collect clinical, biological and therapeutic data from medical records by using a specialized software (DMI2, property of the French Ministry of Health). A follow-up form is completed at least every 6 months or at each visit or hospital admission during which a new clinical manifestation is diagnosed, a new treatment is prescribed or a change in biological markers is noted. In each centre, AIDS diagnoses are validated by an HIV/AIDS expert physician. Patients were not eligible for this study if they were less than 13 years of age, if they were not followed between January 1992 and December 2004, if they had less than 6 months of follow-up, if they had a history of anal cancer or ongoing anal cancer at FHDH enrolment, or if they were receiving antiretroviral treatment in a double-blind trial. Overall, 86 332 patients were eligible for the study.

The FHDH was approved by the French data protection authority (Commission Nationale de l'Informatique et des Libertés, CNIL). The study was approved by the scientific committee of the Clinical Epidemiology Group of the FHDH.

Definition of anal cancer

The International Classification of Diseases (ICD) codes are currently used by the FHDH (ICD9 prior to 1997 [18] and ICD10 [19] thereafter).

For the purpose of the present study and to assess the sensitivity of the coding in the database, we first selected all FHDH patients with ICD codes who could potentially correspond to a diagnosis of anal cancer. These codes selected patients with carcinoma *in situ* as well as invasive carcinoma. Overall, 207 patients with an ICD code possibly corresponding to a diagnosis of anal cancer were retrieved from the database between 1992 and 2004. For each patient with this ICD code, we then collected data from the medical record on the histology of cancer and the underlying cause of death for patients who died. We used the available histological information to validate the diagnosis of invasive anal cancer and excluded all cases of carcinoma *in situ*. Eight cases were classified as presumptive because no histological data were available, but they were included in the analysis because they corresponded to the ICD codes validated as invasive anal cancer in more than 90% of cases in our study. Presumptive cases were pooled together with cases of confirmed invasive cancer, and sensitivity analyses were carried on confirmed cases only. The detail of the screening process is depicted in Fig. 1.

Statistical analysis

The date of entry to this study was defined as 1 January 1992 for patients who were enrolled in the FHDH before this date and were still alive, and as the date of enrolment in the FHDH for subjects enrolled after this date. Follow-up was measured from study entry until initial diagnosis of anal cancer, death, the last follow-up visit or 31 December 2004, whichever occurred first. The incidence of anal cancer per 100 000 patient-years was calculated for five calendar periods, according to cART availability in France, as follows: the precART period was defined as the period between January 1992 and March 1996, the early cART period was between April 1996 and December 1998 and the recent cART era was divided into three periods to investigate the evolution of incidence over these periods: 1999–2000, 2001–2002 and 2003–2004.

The characteristics of patients diagnosed with anal cancer were compared across the three calendar periods by using

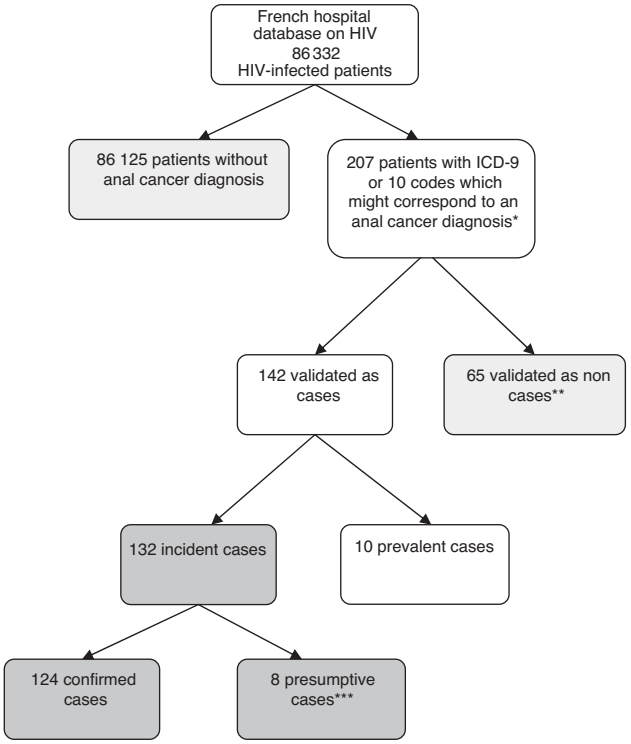

Fig. 1. Flow chart. *ICD-9 codes: 154.2, 154.3, 230.5, 203.6, 232.5, 235.5. ICD-10 codes: C21.0, C21.1, C21.2, C21.8, C44.5, D01.3, D04.5, D37.7, D48.5. **Mainly anal squamous intraepithelial lesion. ***No histological information to validate the cases, but ICD-9 or 10 codes with good sensitivity. ICD, International Classification of Diseases.

the χ^2 test for categorized variables or Kruskal–Wallis test for continuous variables.

Factors associated with the risk of anal cancer were identified by using a multivariable Cox proportional hazards model including only those variables with *P* values below 0.2 in univariable analysis. These comprised age at inclusion in the study, gender, the HIV transmission group, nadir CD4 cell count and the AIDS status prior to anal cancer or at the end of follow-up. To take into account the possible impact of cART on the incidence of anal cancer, either of the five calendar periods were introduced in the model (model 1) and used as a proxy for treatment exposure or cART exposure itself was used (model 2) including all data. An analysis of sensitivity was done with the model 2 when the variable cART was taken into account, with the study period restricted to the years 1998–2004. The CD4 cell nadir was obtained from enrolment in the FHDH until the occurrence of the first event (anal cancer, death or last follow-up visit). We used the 1993 Centers for Disease Control and Prevention's revised clinical AIDS case definition [20]. AIDS diagnosis and cART initiation were considered as time-dependent covariates. All analyses were based on an intent-to-continue-treatment approach and thus ignored subsequent treatment changes, including interruptions and terminations. As the risk of HPV lesions and cancer was higher in MSM, we used a variable based on a cross-classification of sexes and the transmission group (MSM, non-MSM and women).

The overall survival between diagnosis of anal cancer and June 2005 was analysed by using Kaplan–Meier estimates. Factors associated with the risk of death after anal cancer were identified by using a multivariable Cox proportional hazards model adjusted for age, gender, the HIV transmission group, CD4 cell count at anal cancer, the AIDS status and the period of cART availability in France, and were as follows: the precART period was defined as the period between January 1992 and March 1996, the cART period was between April 1996 and December 2004.

All tests were two sided, and *P* values below 0.05 were considered statistically significant. Statistical analyses were done with the SAS software package, version 9.1 (SAS Institute, Cary, North Carolina, USA).

Role of the funding source

The funding sources had no role in the collection, analysis or interpretation of the data or in the decision to submit the paper for publication.

Results

Among 86 322 patients included in the analysis, 132 had a diagnosis of anal cancer, which was confirmed and presumptive in 124 (93.9%) and eight cases, respectively (Fig. 1). The characteristics of patients with confirmed and presumptive diagnoses were not different (data not shown).

The characteristics of patients with incident invasive anal cancer are shown in Table 1. Among the 132 cases of anal cancer, 102 occurred in the recent cART period (1999–2004), and these were evenly distributed among the three sub-periods. Men accounted for 93.9% of cases and MSM for 70.5% of cases. Median age at diagnosis of anal cancer was 42.8 years [interquartile range (IQR), 36.9–49.4), with no difference according to sex and the HIV transmission group ($P = 0.29$). The median CD4 cell count at anal cancer diagnosis increased with time from 188 cells/μl in the precART period to 288 cells/μl in the recent cART period. Nearly one-quarter of the patients had not received cART before the onset of anal cancer. An AIDS-defining event was notified in 41.7% of cases prior to anal cancer diagnosis (Table 2).

Fifty-three of the 132 patients died, 34 (64.2%) of anal cancer. The survival curve with anal cancer is shown in Fig. 2. The 2-year survival rates in the cART and the precART period were 79.8% [95% confidence interval

Table 1. Characteristics of patients with diagnosis of anal cancer.

	Overall $n=132$	PrecART $n=11$ (8.3%)	Early cART $n=19$ (14.4%)	Recent cART $n=102$ (77.3%)	P value
Diagnosis					0.1252
Confirmed[a]	124 (93.9%)	10 (90.9%)	16 (84.2%)	98 (96.1%)	
Presumptive[b]	8 (6.1%)	1 (9.1%)	3 (15.8%)	4 (3.9%)	
Gender and group of transmission, *n* (%)					0.1399
MSM[c]	93 (70.5%)	7 (63.6%)	17 (89.5%)	69 (67.6%)	
Other men	31 (23.5%)	4 (36.4%)	1 (5.3%)	26 (25.5%)	
Women	8 (6.0%)	0 (0.0%)	1 (5.3%)	7 (6.9%)	
Period of diagnosis, *n* (%)					
1992–March 1996	11 (8.3%)	11 (100%)			
April 1996–1998	19 (14.4%)		19 (100%)		
1999–2000	37 (28.0%)			37 (36.3%)	
2001–2002	32 (24.2%)			32 (31.4%)	
2003–2004	33 (25.0%)			33 (32.3%)	
Age at diagnosis (year), median (IQR)					
Overall	42.8 (36.9–49.4)	35.9 (31.4–43.3)	36.9 (32.6–43.4)	41.2 (36.0–47.5)	0.5294
MSM ($n=93$)	42.8 (36.8–49.4)	44.7 (31.6–46.6)	39.4 (34.8–50.2)	42.9 (37.7–49.4)	0.6132
Other men ($n=31$)	44.2 (37.3–50.3)	38.5 (36.0–46.4)	42.9 (42.9–42.9)	46.6 (37.4–50.3)	0.7816
Women ($n=8$)	40.4 (36.6–42.0)		41.1 (41.1–41.1)	39.7 (35.6–42.2)	0.8273
CD4 cell count at diagnosis					
Median (cells/μl) (IQR)	265 (15–434)	188 (45–320)	227 (65–290)	288 (188–463)	0.0265
Unknown, *n* (%)	10 (7.6%)	0 (0.0%)	3 (15.8%)	7 (6.9%)	
Death	53	8	10	35	
Death related to anal cancer	32 (60.4%)	4 (50%)	4 (40%)	24 (68.8%)	0.2146

cART, combination antiretroviral therapy; IQR, interquartile range; MSM, men who have sex with men.
[a]Confirmed by histological information retrieved from medical records. [b]No histological information but ICD codes, clinical data and treatment information suggestive of anal cancer.

(CI), 72.2–87.4] and 45.5% (95% CI, 16.0–74.9), respectively. In a multivariable Cox model, patients diagnosed with anal cancer in the precART period had a higher risk of death than those diagnosed in the cART period [hazard ratio, 14.1; 95% CI, 5.2–38.6].

The main characteristics of the patients in the groups with and without anal cancer are shown in Table 2. In addition, patients with anal cancer were exposed to cART for a median duration of 37.1 months before the diagnosis of anal cancer (IQR, 4.5–59.8)) and patients without

Table 2. Characteristics of the French Hospital Database on HIV study population.

	Anal cancer $n=132$	No anal cancer $n=86\,190$	Multivariable analysis HR with Model 1[c] (95% CI)	Multivariable analysis HR with Model 2[d] (95% CI)
Age at enrolment (years)			1.2 (1.0–1.5)	1.2 (1.0–1.5)
Median (IQR)	36.5 (31.4–44.2)	34.2 (29.3–41.01)	Per 10 years	Per 10 years
Gender and transmission group, *n* (%)				
Women	8 (6.0%)	24 249 (28.1%)	1	1
MSM	93 (70.5%)	30 164 (35.0%)	7.7 (3.74–15.95)	7.4 (3.6–15.3)
Other men	31 (23.5%)	31 777 (36.9%)	2.6 (1.2–5.6)	2.6 (1.2–5.6)
Nadir CD4 cell count before event (cells/μl), *n* (%)			0.9 (0.8–1.0)	0.9 (0.8–1.0)
Median (IQR)	75 (19–164)	150 (31–291)	Per log2	Per log2
AIDS before event[a,b], *n* (%)	55 (41.7%)	24 228 (28.1%)	2.3 (1.5–3.4)	2.2 (1.5–3.3)
Period				
1992–March 1996			1	
April 1996–1998			1.5 (0.7–3.4)	
1999–2000			2.9 (1.3–6.3)	
2001–2002			2.1 (0.9–4.9)	
2003–2004			2.2 (1.0–5.3)	
cART before event[a,b], *n* (%)	103 (78.0%)	52 169 (60.5%)		1.7 (1.1–2.8)

cART, combination antiretroviral therapy; HR, hazard ratio; MSM, men who have sex with men.
[a]Event, diagnosis of anal cancer, death, end of follow-up or 31 December 2004, whichever occurred first. [b]Time-dependent variable. [c]Model 1, adjusted for age at inclusion in the study, gender, the HIV transmission group, nadir CD4 cell count and AIDS status prior to anal cancer or at the end of follow-up, and the five calendar periods. [d]Model 2, adjusted for age at inclusion in the study, gender, the HIV transmission group, nadir CD4 cell count and AIDS status prior to anal cancer or at the end of follow-up, and the exposition to cART before event or end of the follow-up.

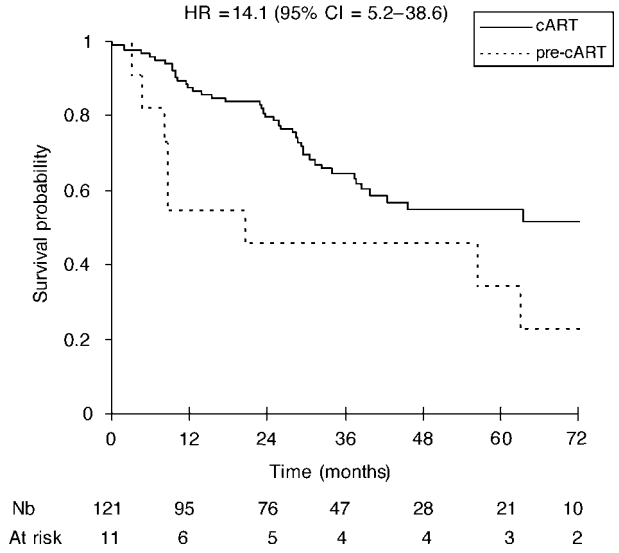

Fig. 2. Kaplan–Meier estimates of survival after anal cancer diagnosis in HIV-infected patients enrolled in the French Hospital Database, according to the cART periods. cART, combination antiretroviral therapy; CI, confidence interval; HR, hazard ratio.

anal cancer for a median duration of 14.5 months (IQR, 0.0–59.6) before death or the end of follow-up. Whatever the multivariable model (Table 2), anal cancer was more likely to occur in older patients, in MSM, in patients with a prior AIDS diagnosis and in patients with lower nadir CD4 cell counts. For example, in model 1 adjusted on the period, men had a higher risk of anal cancer than women (hazard ratio, 7.7 and 2.6 for MSM and non-MSM, respectively). MSM were more at risk of anal cancer than were non-MSM (hazard ratio, 3.0; 95% CI, 2.0–4.5). No relationship between sex, the HIV transmission group and the study period was found. A significant increase in the incidence of anal cancer was observed in the recent cART era as compared with the precART period, with adjusted hazards ratios of 2.9 (95% CI, 1.3–6.3), 2.1 (95% CI, 0.9–4.9) and 2.2 (95% CI, 1.0–5.3), respectively. Compared with the period of 1999–2000, hazard ratio was 0.8 (95% CI, 0.5–1.2) in the years 2001–2002 and 0.8 (95% CI, 0.5–1.3) in the years 2003–2004, indicating no significant increase in the incidence of anal cancer in the three sub-periods of the recent cART era. In the model 2 adjusted on cART, exposure to cART was associated with a higher risk of anal cancer (hazard ratio, 1.7; 95% CI, 1.1–2.8). When the analysis was restricted to the years 1998–2004, the hazard ratio associated with the exposure to cART was similar (hazard ratio, 1.7; 95% CI, 0.9–3.2).

The overall incidence of anal cancer per 100 000 person-years increased between the precART and the cART period (Fig. 3). In the precART, the early cART and the

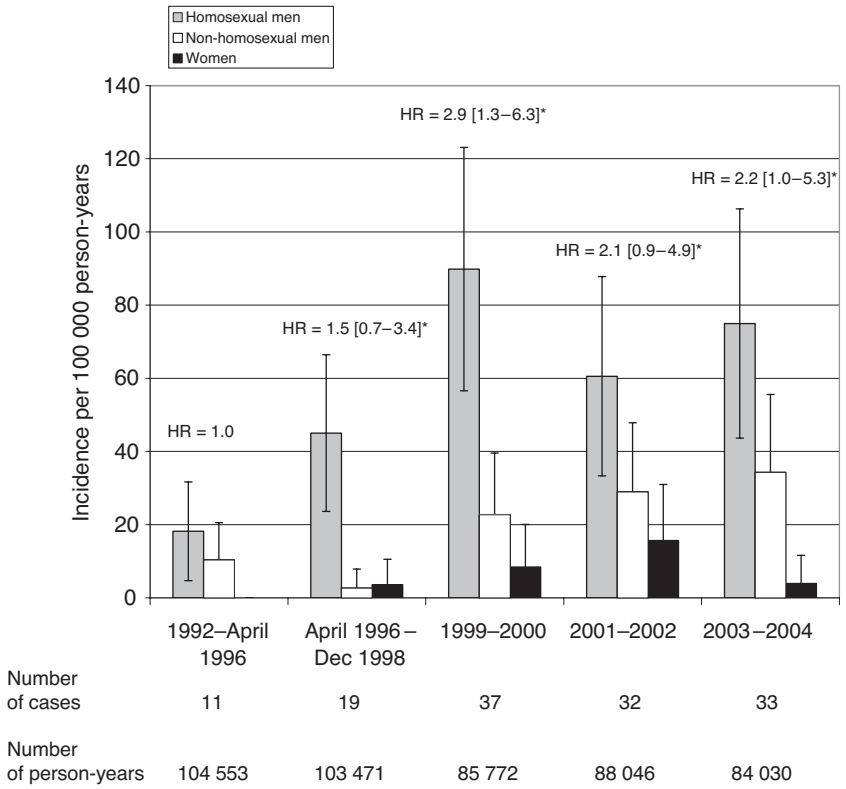

Fig. 3. Change in the incidence of anal cancer according to gender, HIV transmission group and calendar period. HR, hazard ratio. *Adjusted for age, sex, HIV transmission group, CD4 nadir, and AIDS.

three sub-periods of the recent cART era (1999–2000, 2000–2001 and 2002–2003), the incidences of anal cancer were 10.5 (95% CI, 4.3–16.7), 18.4 (95% CI, 10.1–26.6), 43.1 (95% CI, 29.2–57.0), 36.3 (95% CI, 23.8–48.9) and 39.3 (95% CI, 25.9–52.7) per 100 000 person-years, respectively. The increase was noted in all HIV transmission groups with a hazard ratio of 2.5 (95% CI, 1.2–5.3) between 1999 and 2004 and between 1992 and March 1996, even if absolute risk was higher in MSM than in the other transmission groups. The incidence of anal cancer in MSM was 18.2 per 100 000 (95% CI, 4.7–31.7) in the precART period, 45.0 (95% CI, 23.6–66.4) in the early cART period and 75.1 (95% CI, 57.4–92.8) between 1999 and 2004. Among other men and among women, the incidence of anal cancer in the recent cART era was 28.6 and 9.4 per 100 000 person-years, respectively.

All cases of anal cancer were validated, and 93.9% of diagnoses were histologically confirmed. The primary analysis included both confirmed and presumptive diagnoses, but the results were similar when presumptive cases were excluded. For instance, as compared with the precART period, the adjusted hazard ratio was 2.5 (95% CI, 1.2–5.3) in the years 1999–2004 in the analysis, which included presumptive diagnoses and hazard ratio was 2.5 (95% CI, 1.1–5.6) in the analysis, which only included confirmed diagnoses.

Discussion

The present study shows that anal cancer in HIV-infected patients occurred in MSM and at around 40 years of age, with an increase in the incidence since the introduction of cART in France. This increase affected all HIV transmission groups, although the absolute risk was higher in MSM.

Two important strengths of the present study are the inclusion of a large population from a nationwide study, which included prospectively studied individuals from various transmission groups both before and after the advent of cART, and the large number of person-years of follow-up (465 872 person-years).

As anal cancer is not an AIDS-defining illness, it is likely that some cases, especially of micro-invasive cancer, were not recorded in the database. However, this possible undernotification should have been fairly stable with time. Even if several studies documented an increased risk of anal cancer in HIV-infected patients in the precART era [2–4], national recommendations on AIN screening were introduced in France in 2002 [21], possibly resulting in over-reporting in the later period of the study. If this ascertainment bias was major, however, one would have expected the risk of anal cancer to increase more markedly after 2003. This was not the case; the increase was observed after 1996 in MSM and after the years 1999–2000 in non-MSM and women. In addition, the small number of cases observed between 1992 and April 1996 could be explained by a weak survival of HIV-infected patients and, therefore, insufficient time for anal cancer to develop.

Several studies showed an increased risk of anal cancer among HIV-infected patients in the precART era [2–4]. In contrast, few data on the incidence of anal cancer have been published since cART became widely available in industrialized countries. Moreover, comparisons between studies are difficult because the incidence depends upon age, immunodepression, AIDS, ethnicity, sex and the HIV transmission group. Nevertheless, it is possible to compare incidence trends over time. The AIDS and cancer registries for San Diego County were recently matched from 1988 to 2000 [14]. The average annual incidence of invasive anal cancer precART was 49 per 100 000 men aged 25–64 years, compared with 144 per 100 000 post-cART. In this latter study, the high proportion of MSM and the restriction of the study population to patients with AIDS probably explain the much higher incidence rates of invasive anal cancer than found in our study (roughly 40/100 000 in the cART period). However, the incidence increased 2.9 fold between the two periods of this study, which is similar to what we observed. Similar increased ratios were found in two European cohorts [5] and a US registry [22]. In contrast, the recently published study by Engels *et al.* [16] did not report such an increase.

Most of these studies examined two calendar periods (precART era compared with cART era) in order to indirectly measure the potential effect of cART on the incidence of anal cancer. In our study, cART was associated with an increase in the incidence of anal cancer. However, it is difficult to separate the effect of cART itself (individual effect) from that of the calendar period (population effect). As pointed out by Palefsky [23], several mechanisms may account for the increased frequency of HPV-associated diseases in HIV-seropositive individuals. One is the modulation of the immune response to HPV. Despite increasing the CD4 T-cell count and restoring immunity to several opportunistic pathogens [24–26], cART does not appear to enhance the control of HPV and has been associated with the progression of HPV-related AIN, the precursor of anal cancer [11–13]. Thus, the cART-induced increase in the survival of HIV-infected patients may allow sufficient time for AIN to progress to invasive anal cancer. The observed difference in the incidence between the precART and the cART periods could be due to differences in survival times between these two periods. Prior to cART, survival time was so short that it was insufficient for progression to anal cancer, whereas after the use of cART, the survival increased and the cancers

became manifest. The incidence of anal cancer in our study remained stable during the recent cART period, likely because after an initial improvement in the survival associated with the advent of cART in the HIV-infected population, there has been no improvement in most recent periods [27].

One possible reason for heterosexual men having anal cancer would be the under-reporting of men-men sex. Nevertheless, recent data suggest that opportunistic HPV infection and AIN may occur in the anal canal of immunocompromized patients who have not practiced receptive anal intercourse [28,29]. This is in line with the increase in invasive anal cancer in nonhomosexual patients in our study.

Anal cancer shares many biological characteristics with cervical cancer, including a similar histopathologic appearance and association with HPV infection. The incidence of cervical cancer in HIV-infected patients is much lower than that of anal cancer [15] and its incidence remained unchanged or tended to increase slightly since the introduction of cART [15,30,31]. One may speculate that this different pattern could be explained by the fact that HIV-infected women undergo a regular cervical cancer screening program.

Immunosuppression may accelerate the progression from high-grade AIN to invasive anal cancer as CD4 cell nadir and AIDS onset, which are markers of immunosuppression, were independent risk factors for anal cancer in our study. However, Frisch *et al.* [4] did not found any association between anal malignancies and levels of immunosuppression in a study of HPV-associated cancers among 309 365 patients with HIV infection in the US.

The overall 2-year survival rate with anal cancer in the cART period was 79%, in keeping with the results of Biggar *et al.* [32] or Chiao *et al.* [10] who found no difference with the general population. Some other studies have suggested a lower survival rate than in the general population [5,33–36] but this concerns a very small number of cases, and some of them did not have a long period under cART. So, it seems that cART improved survival which became similar to that in HIV-negative individuals as showed by Chiao *et al.* [10].

In conclusion, given the cost-effectiveness of screening for anal AIN in HIV-infected MSM [37], our findings strongly suggest that screening for AIN should be implemented in HIV-infected MSM, whether or not they are using cART. Taking into account the lower level of incidence among other men and women, we recommend making such a cost-effectiveness evaluation before implementing screening in these groups.

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