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Incidence of HIV-Related Anal Cancer Remains Increased Despite Long-Term Combined Antiretroviral Treatment: Results From the French Hospital Database on HIV

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ABSTRACT

Purpose
To study recent trends in the incidence of anal cancer in HIV-infected patients receiving long-term combined antiretroviral treatment (cART) compared with the general population.

Patients and Methods
From the French Hospital Database on HIV, we identified 263 cases of invasive anal squamous cell carcinoma confirmed histologically between 1992 and 2008. We compared incidence rates of anal cancer across four calendar periods: 1992-1996 (pre-cART period), 1997-2000 (early cART period), and 2001-2004 and 2005-2008 (recent cART periods). Standardized incidence ratios (SIRs) were calculated by using general population incidence data from the French Network of Cancer Registries.

Results
In HIV-infected patients, the hazard ratio (HR) in the cART periods versus the pre-cART period was 2.5 (95% CI, 1.28 to 4.98). No difference was observed across the cART calendar periods (HR, 0.9; 95% CI, 0.6 to 1.3). In 2005-2008, HIV-infected patients compared with the general population had an excess risk of anal cancer, with SIRs of 109.8 (95% CI, 84.6 to 140.3), 49.2 (95% CI, 33.2 to 70.3), and 13.1 (95% CI, 6.8 to 22.8) for men who have sex with men (MSM), other men, and women, respectively. Among patients with CD4 cell counts above 500/μL for at least 2 years, SIRs were 67.5 (95% CI, 41.2 to 104.3) when the CD4 nadir was less than 200/μL for more than 2 years and 24.5 (95% CI, 17.1 to 34.1) when the CD4 nadir was more than 200/μL.

Conclusion
Relative to that in the general population, the risk of anal cancer in HIV-infected patients is still extremely high, even in patients with high current CD4 cell counts. cART appears to have no preventive effect on anal cancer, particularly in MSM.

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INTRODUCTION

Several studies showed an increased risk of anal cancer among HIV-infected patients before the advent of combination antiretroviral therapy (cART).[1-4] The incidence of anal cancer was reported to be twice as high in HIV-infected men who have sex with men (MSM) as in their HIV-seronegative counterparts,[1,2] and 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.[3] Some studies[4-7] have shown no positive impact of cART-induced immune restoration on the prevalence or incidence of anal human papillomavirus (HPV) infection and anal squamous intraepithelial lesions (SILs) that are precursors of invasive anal cancer, although other data suggest a favorable effect of long-term cART on the incidence of anal SILs.[8,9] Overall, the incidence of anal cancer appears to have risen with the widespread use of cART.[4,10-17]

Several studies[14,15,18-22] have compared the risk of anal cancer, among other malignancies, in HIV-infected patients to that observed in the general population in North America and Europe and have shown an excess risk in the HIV-infected population. However, except for one recent study,[23] these studies involved small numbers of anal malignancies (between 18 and 80) and could not account for HIV transmission groups or degree of immunodeficiency nor did they clearly conclude whether anal cancer occurs at an earlier age in HIV-infected patients.[24]

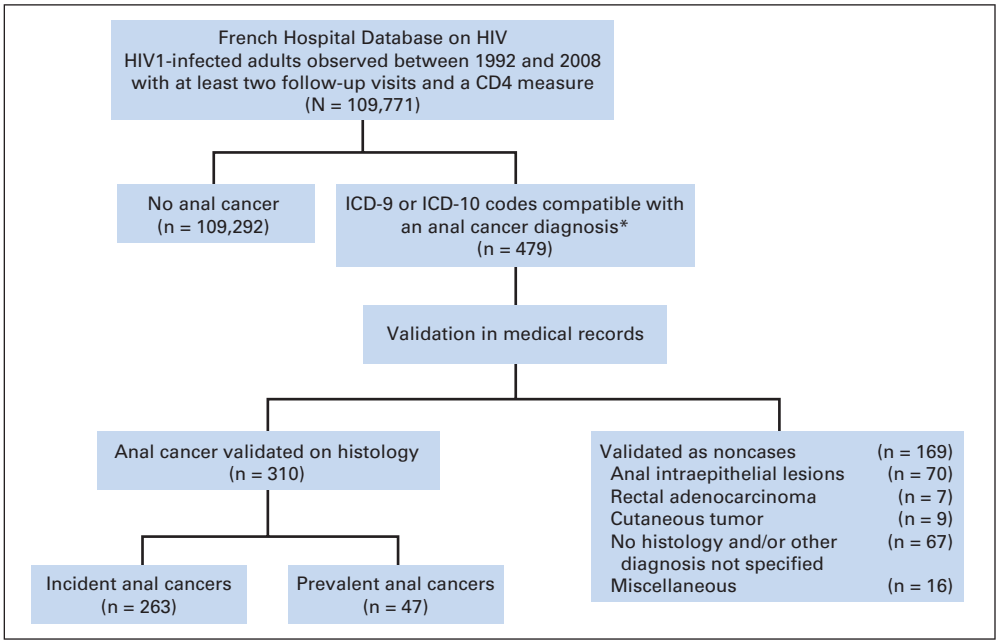

Fig 1. Flow chart. (*) International Classification of Diseases, 9th revision (ICD-9) codes: 154.2, 154.3, 230.5, 230.6, 232.5, 235.5; ICD, 10th revision (ICD-10) codes: C21.0, C21.1, C21.2, C21.8, C44.5, D01.3, D04.5, D37.7, D48.5.

Here, we analyzed the incidence of anal cancer in a large French cohort of HIV-infected patients in both the pre-cART era and the cART era (until 2008), according to the HIV transmission group, current and past immunodepression, and age. The aim was to study temporal trends in anal cancer incidence rates in HIV-infected patients between 1992 and 2008 to determine the impact of long-term cART. Trends in this population were compared with those in the general French population.

PATIENTS AND METHODS

Study Population

Patients were selected from the French Hospital Database on HIV-Agence Nationale de Recherches sur le SIDA et les hépatites virales FHDH-ANRS CO4, a nationwide hospital-based cohort[25] created in 1989. Sixty-nine clinical centers in teaching hospitals across France currently 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 collected clinical, biologic, and therapeutic data at least every 6 months from medical records by using specialized software. The FHDH was approved by the French data protection authority (Commission Nationale de l'Informatique et des Libertés). Patients were not eligible for this study if they were younger than age 13 years, were not observed between January 1992 and December 2008, had less than 6 months of follow-up, or had a history of anal cancer or ongoing anal cancer at FHDH enrollment. A previous analysis of the FHDH focused on the period 1992-2004.[4] This study updates this analysis to 2008, adding 131 new incident cases of anal cancer to the 132 cases previously studied, and it compares incidence rates to those reported in the general population in France.

General Population in France

Reference data for the incidence of anal cancer in the general population in France were obtained from the French Network of Population-Based Cancer Registries (FRANCIM [France-cancer-incidence et mortalité]) for 1992 to 2006 (141,819,554 person-years [PY]). Fifteen cancer registries covering 18 French administrative regions and corresponding to 19% of the French population were considered for this study. Incident cases were defined as cancer with C21 topography according to the International Classification of Diseases for Oncology (ICD-O). Lymphomas were excluded. All incident cases of anal cancer diagnosed between 1992 and 2006 were considered.

Definition of Anal Cancer

Cases of anal cancer were extracted from the FHDH by using a large spectrum of ICD codes that could potentially correspond to a diagnosis of anal cancer. Codes from the ICD-9 (9th revision) were used before 1997 and codes from the ICD-10 (10th revision) were used thereafter. Overall, 479 patients with such ICD codes between 1992 and 2008 were retrieved from the database. For each patient, we confirmed the diagnosis of anal cancer by examining histologic findings reported in the medical records. We considered only invasive anal squamous cell carcinoma and excluded all cases of carcinoma in situ. Details of the selection process are provided in Figure 1.

Statistical Analysis

Follow-up was measured from FHDH enrollment or January 1992, if the date of enrollment was before 1992, until diagnosis of anal cancer, death, the last follow-up visit, or December 31, 2008, whichever occurred first. Incidence rates of anal cancer were calculated for four calendar periods: the pre-cART period (1992-1996) and the cART era divided into three periods: early (1997-2000), intermediate (2001-2004) and recent (2005-2008). For the general population, incidence rates were directly standardized on the basis of the age (5-year age groups) and sex distribution of the HIV-infected population enrolled onto the FHDH during the cART period (1997-2008).

The observed number of incident anal cancers in the HIV-infected patients was divided by the expected number of anal cancers, yielding a standardized incidence ratio (SIR) estimate. Expected numbers were obtained by multiplying the patient-years at risk in each 5-year age group in the HIV-infected population by the corresponding sex- and age-specific incidence rates in the general population for each period studied. CIs for SIRs were calculated with an exact method based on the Poisson distribution.[26] To explore a potential age acceleration effect, which would be indicated by higher SIRs at younger rather than older ages,[14] SIRs were estimated for several age groups (25 to 34, 35 to 44, 45 to 54, 55 to 64, and $\geq$ 65 years) during the cART period (1997-2008). Finally, to explore the impact of the severity and duration of immunodeficiency, SIRs were estimated for patients with current CD4 cell counts $\geq 500/\mu L$ for at least 2 years before diagnosis, according to whether the CD4 nadir was more than $200/\mu L$ or less than $200/\mu L$ for more or less than 2 years.

Factors associated with the risk of anal cancer in HIV-infected patients were identified by using a multivariable Cox proportional hazards model that

included only variables with *P* values below .2 in univariable analysis. These comprised age at inclusion in the FHDH, sex, the HIV transmission group (MSM, non-MSM, and women), the CD4 cell nadir, AIDS status before anal cancer or at the end of follow-up, and the calendar periods that were used as a proxy of treatment exposure. For the calendar periods, either the pre-cART period or the early cART period was used as reference. The CD4 cell nadir was estimated from FHDH enrollment until the first event (anal cancer, death, or last follow-up visit). We used the 1993 Centers for Disease Control and Prevention clinical AIDS case definition. AIDS diagnosis was considered as a time-dependent covariate.

All tests were two-sided, and *P* values below .05 were considered to denote statistical significance. Statistical analyses were done with SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

Patients' Characteristics

Between 1992 and 2008, 109,771 patients enrolled onto the FHDH cohort were eligible for the study and contributed 705,518 PY at risk of anal cancer. Of these, 263 patients had a confirmed diagnosis of incident invasive anal cancer (Fig 1). Patient characteristics are provided in Table 1. Among the 263 cases of anal cancer recorded in the FHDH cohort, 195 occurred in the recent cART period (2001-2008), and these were evenly distributed between the two recent subperiods. Men accounted for 91% of cases and MSM for 65% of cases. Median age at diagnosis of anal cancer was 46 years among men and 42 years among women ($P = .02$). The median CD4 cell count at diagnosis of anal cancer was 310/μL. The median CD4 cell count nadir was 95/μL. Only 11% of the patients had not received cART before the onset of anal cancer. An AIDS-defining event had occurred in 51% of patients before diagnosis of anal cancer.

In the French cancer registries, 2,012 cases of invasive anal cancer were recorded between 1992 and 2006, with 1,433 cases (71%) in women and 579 (39%) in men. The median age at diagnosis was 67 years (interquartile range [IQR], 52-77 years) among men and 72 years (IQR, 57 to 77 years) among women.

Trends in the Incidence of Anal Cancer Over Time

The incidence of anal cancer observed in the FHDH cohort and in the FRANCIM database is shown in Figure 2 according to the calendar period and HIV transmission group. The incidence increased six-fold between the pre-cART and cART periods, from 8.5 (95% CI, 3.5 to 13.4) per 100,000 PY in 1992-1996 to 53.2 (95% CI, 43.0 to 63.3) per 100,000 PY in 2005-2008. This increase was noted in all the HIV transmission groups, and it stabilized during the cART period. Substantially higher incidence rates were found among MSM in all the periods studied.

Comparison With the General Population

SIRs according to sex, the HIV transmission group, and the calendar period are depicted in Table 2. A significant increase in SIRs was observed in the cART period compared with the pre-cART period. This increase was observed in all HIV transmission groups but was particularly marked among MSM, with SIRs of 41 in the pre-cART period ranging from 95 to 131 in the cART periods.

SIRs are shown in Figure 3 according to sex and age between 1997 and 2008. Regardless of sex, SIRs were much higher at younger ages than at older ages (P for trend $< .001$). Among men, the SIRs were 419 (95% CI, 265 to 627) for those age 25 to 34 years and 75 (95% CI, 61 to 92) for those age 45 to 54 years. The corresponding SIRs in women were 83 (95% CI, 9 to 300) and 8 (95% CI, 2 to 17).

Table 1. Characteristics of Patients With Invasive Anal Cancer

Characteristic	HIV-Infected Population From the FHDH (n = 263)				General Population From FRANCIM (n = 2,012)			
	No.	%	Median	IQR	No.	%	Median	IQR
Sex and HIV transmission group								
Women	23	8.7			1,433	71		
Men	240	91.3			579	29		
MSM	172	65.4						
Other men	68	25.9						
Period of diagnosis								
1992-1996	11	4.2			511	25		
1997-2000	57	21.7			554	28		
2001-2004	89	33.8			596	30		
2005-2008*	106	40.3			351	17		
Age at diagnosis, years								
MSM			46	39-51				
Other men			46	40-50			67	52-77
Women			42	37-47			72	57-77
AIDS prior to diagnosis	135	51.3						
CD4 cell count at diagnosis, cells/μL			310	195-509				
CD4 nadir, cells/μL			95	21-176				
cART at diagnosis	235	89.4						
Duration of cART at diagnosis, months			65	26-105				

Abbreviations: cART, combined antiretroviral treatment; FHDH, French Hospital Database on HIV; FRANCIM, French Network of Cancer Registries; IQR, interquartile range; MSM, men who have sex with men.
*Period 2005-2006 for the FRANCIM data.

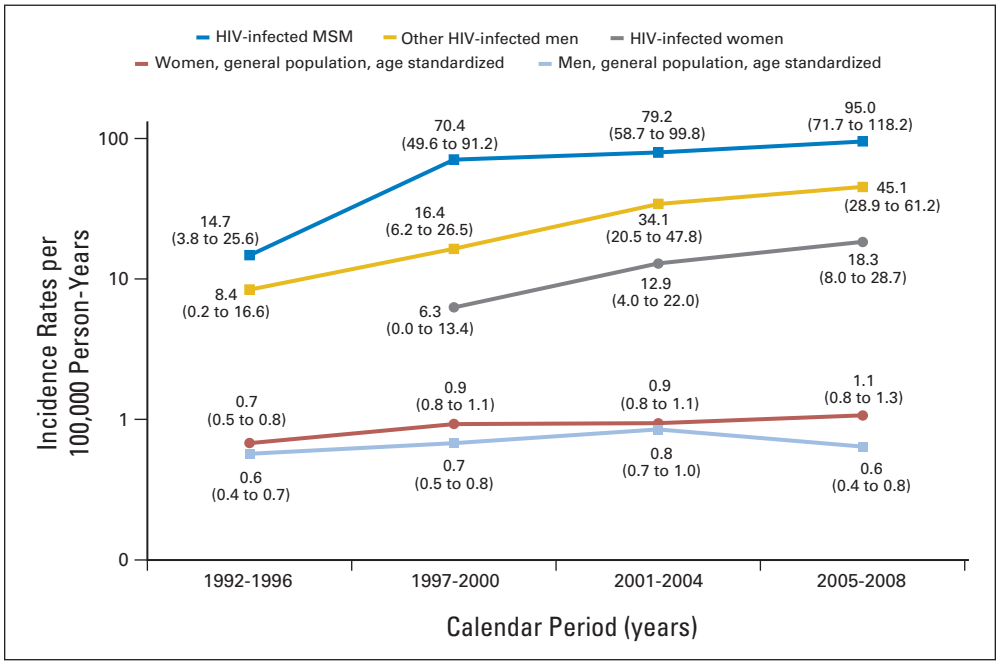

Fig 2. Incidence of anal cancer according to sex, HIV transmission group, and calendar period. For the general population, incidence rates were standardized by 5-year age groups on the basis of the age and sex distribution of the HIV-infected population in the French Hospital Database on HIV in the combined antiretroviral treatment period (1997-2008). Incidence rates are expressed per 100,000 person-years with 95% CIs in brackets. MSM, men who have sex with men.

In patients with current CD4 $\geq$ 500/μL for at least 2 years before the diagnosis of anal cancer (371,354 PY), the SIR was 25 (95% CI, 17 to 34) when the CD4 nadir had been more than 200/μL and 22 (95% CI, 13 to 34) when the CD4 nadir had been less than 200/μL for less than 2 years, but it was much higher when the CD4 nadir had been less than 200/μL for more than 2 years (SIR, 68; 95% CI, 41 to 104).

Factors Associated With the Risk of Anal Cancer in HIV-Infected Patients

The main characteristics of the HIV-infected patients with and without anal cancer are compared in Table 3. Anal cancer was more likely to occur in older patients, men (particularly MSM), patients with a prior diagnosis of AIDS, and patients with lower CD4 cell nadirs. Men had a higher risk of anal cancer than women (adjusted HR, 5.5 for MSM and 2.1 for other men). A significant increase in the incidence of anal cancer was observed in the cART era as compared with the pre-cART era, with an HR of 2.5 (95% CI, 1.3 to 5.0). No difference was found across the three cART periods, with an HR of 0.9 (95% CI, 0.6 to 1.3) relative to the 1997-2000 period.

DISCUSSION

Over an 18-year period (705,519 PY) during which cART was widely available for the last 12 of those years (575,288 PY), we found that the

Table 2. SIR According to Sex, HIV Transmission Group, and Calendar Period

Cases	1992-1996	SIR	95% CI	1997-2000	SIR	95% CI	2001-2004	SIR	95% CI	2005-2008	SIR	95% CI
No. of person-years	130,230			171,465			204,423			199,401		
Women		0			8.4	1.7 to 24.6		13.8	5.9 to 27.1		13.1	6.7 to 22.8
Observed	0			3			8			12		
Expected	0.13			0.36			0.58			0.92		
MSM		41.3	16.5 to 85.1		131.4	95.5 to 176.4		95.0	71.9 to 123.0		109.8	84.6 to 140.3
Observed	7			44			57			64		
Expected	0.17			0.33			0.60			0.58		
Other men		29.6	8.0 to 75.8		31.4	15.0 to 57.7		39.8	25.5 to 59.2		49.2	33.2 to 70.3
Observed	4			10			24			30		
Expected	0.13			0.32			0.60			0.61		
Overall		25.2	12.6 to 45.2		56.4	42.7 to 73.1		49.8	40.0 to 61.3		50.2	41.1 to 60.8
Observed	11			57			89			106		
Expected	0.44			1.01			1.79			2.11		

Abbreviations: MSM, men who have sex with men; SIR, standardized incidence ratio.

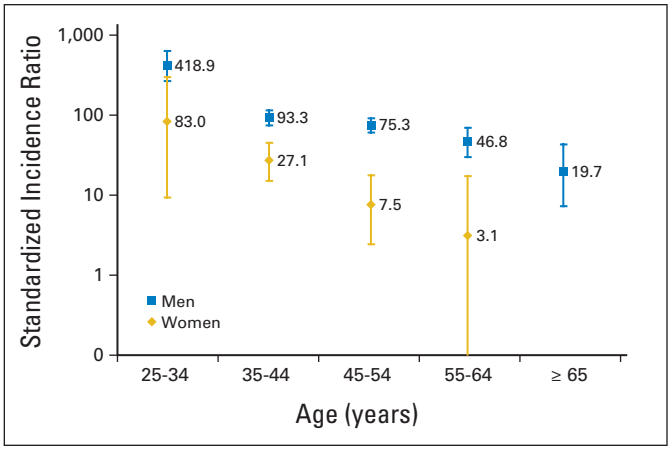

Fig 3. Standardized incidence ratios of anal cancer according to sex and age between 1997 and 2008. *P* values for trend across age class are < .001 for both men and women. Vertical bars represent 95% CIs.

incidence of anal cancer increased markedly between the pre-cART and cART periods and then remained at that level but stable during the cART period. We confirmed the large excess risk of anal cancer reported in HIV-infected patients, particularly MSM, compared with that in the general population. We found that anal cancer occurred earlier in HIV-infected patients than in the general population and that even in HIV-infected patients whose CD4 cell counts remained above 500/μL for more than 2 years before diagnosis, the risk was more than 20-fold higher.

Strengths and Limits

This study has three important strengths: (1) inclusion of a large population from a nationwide study in which patients belonging to various HIV transmission groups were prospectively recruited both before and after the advent of cART; (2) the large number of person-years of follow-up, especially during the cART era; and (3) to the best of our knowledge for the first time in France, a comparison with the general population. All 263 cases of anal cancer recorded in the FHDH were histologically validated, representing the largest series of anal cancer for which the risk could be studied individually according to sex. Previous studies pooled anal cancer with other non–AIDS-defining malignancies and/or included relatively few cases, and only one evaluated the risk in women.[23] One limitation of our study is the potential under-reporting of anal cancer in the FHDH.[27] This might have led to an underestimation of incidence rates, but there is no evidence that the rate of under-reporting differed according to the CD4 cell count or age. Our comparison with the general population did not allow us to adjust for individual characteristics other than age and sex, such as lifestyle and smoking.

Temporal Trends

As previously observed,[4] we found that the incidence of invasive anal cancer increased in all HIV transmission groups after the introduction of cART in France. Moreover, during the 12-year period of widespread use of cART, the incidence remained high in all HIV transmission groups (especially MSM), with no trend toward a decline in the most recent period. The HR was 2.5 (95% CI, 1.28 to 4.98) for the cART versus pre-cART period and 0.9 (95% CI, 0.6 to 1.3) for the recent cART period (2001-2008) versus the early cART period (1997-2000). When cART was individually analyzed in the Cox regression model, the HR of cART was significantly increased (HR, 1.8; 95% CI, 1.1 to 2.7) and can probably be explained by the longer survival associated with cART rather than by a direct effect of cART.

Most, if not all, previous studies also showed a rise in the incidence of anal cancer between the pre-cART and cART periods. Although some studies suggested a stabilization,[23,28] as observed here, two[16,21] showed a continued increase during the cART period. It should be noted, however, that these two studies involved few cases of anal cancer (n = 19[16]) or a shorter period of trend estimation.

Table 3. Risk of Anal Cancer in HIV-Infected Patients (FHDH) From Multivariable Cox Regression Analyses

Variable	Anal Cancer (n = 263)				No Anal Cancer (n = 109,461)				Multivariable Analysis Model			
	No.	%	Median	IQR	No.	%	Median	IQR	HR (1992-1996)	95% CI	HR (1997-2000)	95% CI
									Per 10 years			
Age at enrollment, years			36	31-44			35	29-42	1.2	1.1 to 1.4		
Sex and transmission group												
Women	23	8.7			33,082	30.2			1			
MSM	172	65.4			39,477	36.1			5.5	3.5 to 8.6		
Other men	68	25.9			36,902	33.7			2.1	1.3 to 3.5		
Nadir CD4 cell count, cells/μL*			95	21-176			169	45-300	0.87	0.82 to 0.93		
									Per log2			
AIDS*†	135	51.3			36,723	33.5			2.0	1.5 to 2.6		
Period												
1992-1996	11								1		0.4	0.2 to 0.8
1997-2000	57								2.7	1.3 to 5.3	1	
2001-2004	89								2.4	1.2 to 5.0	0.9	0.6 to 1.3
2005-2008	106								2.3	1.1 to 4.9	0.9	0.6 to 1.3
cART*†	235	89.4			77,975	71.2						

Abbreviations: cART, combined antiretroviral treatment; FHDH, French Hospital Database on HIV; HR, hazard ratio; IQR, interquartile range; MSM, men who have sex with men.
*Before diagnosis of anal cancer in patients with anal cancer and before the end of follow-up for patients without anal cancer.
†Time-dependent variable.

Our comparison with the general population highlights the higher risk of anal cancer in HIV-infected patients, regardless of sex, the HIV transmission group, and the calendar period. The SIRs increased between the pre-cART and cART periods in all the groups studied. During the cART era, the risk of anal cancer among MSM was nearly 100-fold higher than in the general male population. The risk was about 50-fold higher in other men and 13-fold higher in women relative to the general female population. Note that the relative risks are likely to be even higher, because SIRs tend to underestimate the relative risk when the prevalence of HIV/AIDS is high.[29]

Overall, our results are in keeping with those of previous studies, indicating that the risk of invasive anal cancer is increased in HIV-infected individuals, not only in the pre-cART era[1-3] but also in the cART era[4,10-13,15-17,23,30] and relative to the general population.[14,15,18,20-23]

One possible explanation for the excess risk of malignancies associated with HIV infection is provided by the premature aging hypothesis (ie, the occurrence of cancer at younger ages in HIV-infected patients). This hypothesis was recently tested by Shiels et al,[14] who used an elegant method that takes into account the difference in the age distribution between the HIV-infected population and the general population. These authors found that age at cancer diagnosis did not differ between HIV-infected patients and the general population, with a few exceptions among which are anal cancer and lung cancer. Median age at diagnosis of anal cancer was significantly lower in HIV-infected patients than would have been expected in the general population (42 *v* 45 years; $P < .001$).[14] Likewise, we found that SIRs for anal cancer were markedly increased in HIV-infected men, particularly between the ages of 25 and 34 years (SIR, 419). These higher SIRs observed at younger ages are compatible with earlier acquisition of HPV infection among HIV-infected individuals as well an age-accelerated carcinogenesis in HIV-infected patients.

Risk of Anal Cancer According to the CD4 Cell Count at Diagnosis

Risk factors for invasive anal cancer in this study were older age, the HIV transmission group (MSM *v* others), prior AIDS, the cART calendar period, and a low CD4 cell nadir. An association between immunodepression and anal cancer has also been reported elsewhere.[4,31-33] Here, the incidence of anal cancer was still high despite long-term cART, and even in patients who had been on effective cART for more than 2 years and had relatively high CD4 cell counts ($> 500/\mu L$), the risk of anal cancer was still far higher than in the general population (SIR > 20). The SIR rose to 67 when the nadir CD4 cell count had been below $200/\mu L$ for more than 2 years, suggesting that not only the CD4 nadir but also the duration of low CD4 cell counts is associated with the risk of anal cancer.[31] Therefore, to reduce this excess risk of anal cancer, ART should not only restore but also durably maintain near-normal immune function.

Recent guidelines on the treatment of HIV-infected patients in industrialized countries recommend ART for asymptomatic patients with CD4 cell counts below $500/\mu L$.[34] If these recommendations are broadly applied, the incidence of anal cancer is likely to fall in the future, because patients would be able to avoid low CD4 cell nadirs and AIDS-defining events.

Our findings are in agreement with those of previous studies indicating that cART-associated immune restoration is not associated with a reduction in the incidence of anal HPV infection or anal SILs, precursors of invasive anal cancer.[4,6,7,9,35] cART, despite increasing the CD4 T-cell count and restoring immunity to several opportunistic pathogens,[36-38] does not appear to enhance the control of HPV, measured in terms of anti-E6 and anti-E7 HPV-16 lymphoproliferative responses, and has been associated with progression of HPV-related anal SILs.[7] Immunodepression may accelerate progression from high-grade SILs to invasive anal cancer. Indeed, the CD4 cell nadir and AIDS onset, two markers of immunodeficiency, were independent risk factors for anal cancer in our study, and the risk grew as the CD4 cell nadir fell.

In conclusion, this study shows that the risk of HPV-associated invasive anal cancer is markedly increased in all groups of HIV-infected patients and especially in MSM and that this cancer occurs earlier in these patients groups than in the general population. The incidence of anal cancer remained increased in the recent cART period (2005-2008), indicating that long-term cART does not prevent this malignancy. These results emphasize the need to assess the clinical efficacy and cost-effectiveness of anal cancer screening and earlier treatment of HIV infection.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Christophe Piketty, Murielle Mary-Krause, Dominique Costagliola, Sophie Grabar
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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