Effect of immunodeficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study

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Summary

Background The relative roles of immunodeficiency, HIV viral load, and combination antiretroviral therapy (cART) in the onset of individual cancers have rarely been examined. We examined the effect of these factors on the risk of specific cancers in patients infected with HIV-1.

Methods We investigated the incidence of both AIDS-defining cancers (Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer) and non-AIDS-defining cancers (Hodgkin's lymphoma, lung cancer, liver cancer, and anal cancer) in 52 278 patients followed up in the French Hospital Database on HIV cohort during 1998–2006 (median follow-up 4·9 years, IQR 2·1–7·9; 255 353 person-years). We tested 78 models with different classifications of immunodeficiency, viral load, and cART with Poisson regression.

Findings Current CD4 cell count was the most predictive risk factor for all malignancies apart from anal cancer. Compared with patients with CD4 count greater than 500 cells per µL, rate ratios (RR) ranged from 1·9 (95% CI 1·3–2·7) for CD4 counts 350–499 cells per µL to 25·2 (17·1–37·0) for counts less than 50 cells per µL for Kaposi's sarcoma (p<0·0001), from 1·3 (0·9–2·0) to 14·8 (9·7–22·6) for non-Hodgkin lymphoma (p<0·0001), from 1·2 (0·7–2·2) to 5·4 (2·4–12·1) for Hodgkin's lymphoma (p<0·0001), from 2·2 (1·3–3·6) to 8·5 (4·3–16·7) for lung cancer (p<0·0001), and from 2·0 (0·9–4·5) to 7·6 (2·7–20·8) for liver cancer (p<0·0001). For cervical cancer, we noted a strong effect of current CD4 (RR 0·7 per $\log_2$, 95% CI 0·6–0·8; p=0·0002). The risk of Kaposi's sarcoma and non-Hodgkin lymphoma increased for current plasma HIV RNA greater than 100 000 copies per mL compared with patients with controlled viral load (RR 3·1, 95% CI 2·3–4·2, p<0·0001; and 2·9, 2·1–3·9, p<0·0001, respectively), whereas cART was independently associated with a decreased incidence (0·3, 0·2–0·4, p<0·0001; and 0·8, 0·6–1·0, p=0·07, respectively). The RR of cervical cancer for those receiving cART was 0·5 (0·3–0·9; p=0·03). The risk of anal cancer increased with the time during which the CD4 count was less than 200 cells per µL (1·3 per year, 1·2–1·5; p=0·0001), and viral load was greater than 100 000 copies per mL (1·2 per year, 1·1–1·4, p=0·005).

Interpretation cART would be most beneficial if it restores or maintains CD4 count above 500 cells per µL, thereby indicating an earlier diagnosis of HIV infection and an earlier treatment initiation. Cancer-specific screening programmes need to be assessed in patients with HIV.

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

Published Online October 8, 2009 DOI:10.1016/S1470-2045(09)70282-7

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Introduction

HIV infection is associated with an increased risk of several cancers.[1–3] Since the introduction of combination antiretroviral therapy (cART) in 1996, the incidence of AIDS-defining cancers has decreased, whereas the relative frequency of non-AIDS-defining cancers has risen.[4–6] Patients with HIV have a higher risk of both AIDS-defining and non-AIDS-defining cancers than does the general population.[4,5,7,8] HIV-infected patients and immunosuppressed organ-transplant recipients have an increased risk of developing malignancies associated with Epstein–Barr virus, human herpesvirus 8, hepatitis B and C viruses (HBV and HCV), and human papillomavirus (HPV), and both populations have a heightened risk of lung cancer.[9] Although immune deficiency is an obvious feature shared by these two populations, the effect of HIV infection itself and antiretroviral therapy on the risk of specific cancers is controversial.[2,3] We examined the incidence rates of seven specific cancers in HIV-infected patients according to the extent of immunodeficiency, viral load, and antiretroviral treatment.

Methods

Patients

The French Hospital Database on HIV (FHDH-ANRS CO4) is a large prospective hospital cohort in which enrolment is continuing.[10] Sociodemographic, clinical, therapeutic, and laboratory data are collected at least every 6 months. All participating HIV-infected patients provided written informed consent, and the database received approval by the Commission Nationale

Informatique et Liberté (CNIL). The cohort was launched in 1992 in 62 French university hospitals; however, since cART became widely available in France in 1996–97, this study included only patients followed up during 1998–2006. Clinical events were recorded with International Classification of Diseases (ICD) definitions (version 10). We included Kaposi's sarcoma, non-Hodgkin lymphoma apart from primary brain lymphoma, Hodgkin's lymphoma, lung cancer, liver cancer, anal cancer, and cervical cancer, which are the most common malignancies diagnosed in patients with HIV,[5,11] apart from cutaneous non-melanoma, which is routinely under-reported in cohorts. Patients infected with HIV-1 were eligible for this analysis if they had never received antiretroviral drugs before enrolment in the FHDH cohort, had never been included in a double-blind clinical trial, and had not been diagnosed with cancer before 1998. Patients were excluded if information about AIDS-defining events was incomplete (figure). Patients were followed up until diagnosis of cancer, death, the end of follow-up, or Dec 31, 2006, whichever occurred first.

Statistical analysis

Separate analyses were undertaken for each type of malignancy. All analyses were based on incidence rates, which were defined as the number of new cases divided by the total number of person-years at risk. We used Poisson regression with systematic adjustment for age, sex and HIV transmission group, and sub-Saharan origin. Models were tested in which immunodeficiency was defined by the CD4 cell count or the CD4 cell nadir (0–49, 50–99, 100–199, 200–349, 350–499, ≥500 cells per µL), the CD4 cell count as a continuous $\log_2$-transformed covariate, and the cumulative time during which the CD4 count was less than 200, 350, or 500 cells per µL. Viral replication was defined by the HIV RNA value (<500, 500–3·9 $\log_{10}$, 4·0–4·9 $\log_{10}$, ≥5·0 $\log_{10}$ copies per mL), the HIV RNA value as a continuous $\log_{10}$-transformed covariate, or the cumulative time during which viral load was at least 5 $\log_{10}$ copies per mL. cART was entered on an intention-to-treat approach, ignoring changes to the initial regimen. The prognostic effect of treatment was tested with a binary variable (ART-naive, dual therapy, or cART for <6 months *vs* cART for ≥6 months), or with a combination of treatment and current viral load (ART-naive, dual therapy, or cART for <6 months *vs* cART for ≥6 months with viral load >500 copies per mL *vs* cART for ≥6 months with viral load <500 copies per mL), or with the cumulative time spent on cART. All cumulative durations were calculated over the entire follow-up in the FHDH cohort and coded as none, less than 1, 1–2, 2–3, 3–4, 4–5, 5–6, and more than 6 years. Every patient's follow-up was divided into consecutive 1-month periods, and time-varying covariables were updated at the beginning of every month. The CD4 cell count and viral load were linearly interpolated, unless antiretroviral therapy was started between two measurements.

The 78 different models were successively fitted and compared with Akaike's information criterion (AIC), with the lowest AIC indicating the best fit. According to Burnham and Anderson's empirical rule,[12] a model for which the AIC is greater by 10 can be omitted from further consideration, whereas models greater by 4–7 are less strongly supported by the data, and those greater by 2 or less display a similar fit.

We undertook a number of sensitivity analyses. The first focused on patients with known HBV surface antigen or anti-HCV status, or both, since hepatitis co-infection is an important determinant of liver cancer. Because severe AIDS-defining events (excluding recurrent bacterial pneumonia, oesophageal candidiasis, herpes simplex virus disease, and pulmonary and extrapulmonary tuberculosis) could be competing risks, estimates of the risk of non-AIDS-defining cancer associated with the extent of immunodeficiency might be biased. In the second sensitivity analysis, follow-up was censored at the occurrence of the first severe AIDS-defining event. Interaction between immunodeficiency and sex were tested. Finally the robustness of our results was tested after including in the models other potential confounders such as smoking or late-stage HIV presentation. All analyses were done with SAS statistical software (version 9.1).

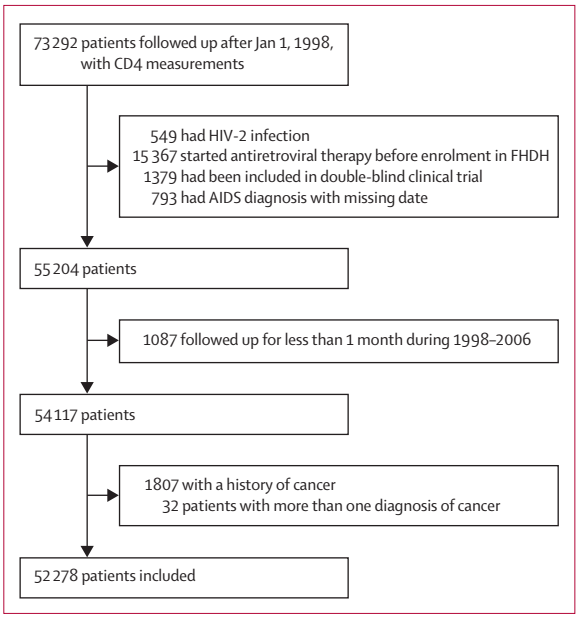

Figure: **Patient selection**
FHDH=French Hospital Database on HIV.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

We investigated the incidence of seven malignancies in 52 278 patients, with 253 353 person-years of follow-up (median 4·9 years, IQR 2·1–7·9; figure and table 1). 43 500 (83%) patients were not taking cART at study entry. In the overall population, the baseline median CD4 count was 325 cells per µL (IQR 177–491) and median viral load was 4·18 $\log_{10}$ copies per mL (3·13–4·94 $\log_{10}$). 187 468 (73%) patients received cART for the total follow-up period.

Kaposi's sarcoma was diagnosed in 565 patients (incidence 2·32 per 1000 person-years, 95% CI 2·13–2·51), non-Hodgkin lymphoma in 511 (2·09, 1·92–2·28), Hodgkin's lymphoma in 149 (0·61, 0·52–0·71), lung cancer in 207 (0·85, 0·74–0·97), liver cancer in 119 (0·49, 0·40–0·58), anal cancer in 74 (0·30, 0·24–0·38), and cervical cancer in 69 (0·93, 0·71–1·15). Table 2 shows the patients' characteristics at cancer diagnosis. Comparison with all patients enrolled in the FHDH during the same period showed the over-representation of men who have sex with men in patients with Kaposi's sarcoma and of injecting-drug users in patients with liver and lung cancer. Few patients with cancer, apart from those with Kaposi's sarcoma, originated from sub-Saharan Africa (table 2). The median known duration of HIV infection at the diagnosis of the different cancers was between 5·6 and 8·5 years, apart from for liver and anal cancer for which duration was longer than 10 years (table 2). Patients diagnosed with Kaposi's sarcoma and non-Hodgkin lymphoma had low nadir CD4 cell counts, and their median current CD4 count was less than 200 cells per µL (table 2). Although more than half the patients diagnosed with Kaposi's sarcoma or non-Hodgkin lymphoma were receiving cART, their median viral load at diagnosis suggested frequent virological failure. At least two-thirds of patients diagnosed with one of the three non-AIDS-defining cancers were receiving cART, with a high frequency of virological efficacy, although the median CD4 count was less than 300 cells per µL. Patients with anal cancer had a long history of HIV infection, a low nadir CD4 cell count, and a long cumulative period of immunodeficiency or high viral replication, or both; nearly all these patients were on antiretroviral therapy (table 2).

We systematically tested 78 models for each cancer (webappendix). The only model retained for Kaposi's sarcoma included current immunodeficiency, current viral replication, and antiretroviral therapy. The same model was retained for non-Hodgkin lymphoma. The three non-AIDS-defining cancers presented the same fitting pattern, in which the current CD4 cell count was always the most predictive factor (webappendix). The several alternative models showed that viral load and antiretroviral therapy did not clearly improve the fit (webappendix). Immunodeficiency also had a major role in the two cancers related to HPV, with very specific relations. Anal cancer was associated with the duration of both immunodeficiency and viral replication. CD4 cell count and antiretroviral therapy were associated with cervical cancer, but $\log_2$ transformation of the CD4 cell count always provided a better fit than did CD4 cell count classes (webappendix).

The risk of both Kaposi's sarcoma and non-Hodgkin lymphoma increased as the CD4 cell count fell and viral replication rose (table 3). Treated patients had a lower incidence of Kaposi's sarcoma and of non-Hodgkin lymphoma than did untreated patients (table 3). The risk of the three non-AIDS-defining cancers increased with decreasing CD4 cell counts (table 4). The risk of Hodgkin's lymphoma increased for CD4 count less than 350 cells per µL and peaked at 50–99 cells per µL. The risk

	Baseline* (n=52 278)	Follow-up (n=255 353 person-years)
Year of enrolment in FHDH		
1992–97	23 274 (44%)	..
1998–2000	10 853 (21%)	..
2001–03	10 489 (20%)	..
2004–06	7662 (15%)	..
Sex and exposure group		
MSM	16 541 (32%)	..
IDU	7393 (14%)	..
Other men	13 938 (27%)	..
Other women	14 406 (28%)	..
Migration from sub-Saharan Africa	7027 (13%)	..
Age (years)		
16–29	10 859 (21%)	26 584 (10%)
30–39	23 729 (45%)	105 435 (41%)
40–49	11 648 (22%)	81 475 (32%)
50–59	4333 (8%)	29 973 (12%)
≥60	1709 (3%)	11 886 (5%)
cART >6 months	8778 (17%)	187 468 (73%)
CD4 count (cells per µL)		
≥500	12 517 (24%)	94 096 (37%)
350–499	11 506 (22%)	62 620 (25%)
200–349	13 318 (25%)	57 981 (23%)
100–199	7471 (14%)	24 608 (9%)
50–99	3120 (6%)	7498 (3%)
0–49	4247 (8%)	6718 (2%)
Missing	2627 (5%)	1831 (1%)
HIV RNA (copies per mL)		
<500	8836 (17%)	127 082 (50%)
500–3·9 $\log_{10}$	11 824 (23%)	49 433 (19%)
4·0–4·9 $\log_{10}$	15 023 (29%)	47 396 (18%)
≥5 $\log_{10}$	10 746 (20%)	19 716 (9%)
Missing	5649 (11%)	11 725 (4%)

Data are number (%). FHDH=French Hospital Database on HIV. MSM=men who have sex with men. IDU=injecting-drug user. cART=combination antiretroviral therapy. *Baseline is the first visit after Jan 1, 1998.

Table 1: **Characteristics of patients at study entry and during follow-up from 1998 to 2006**

See Online for webappendix

	AIDS-defining cancers		Non-AIDS-defining cancers			HPV-related cancers	
	Kaposi's sarcoma (n=565)	Non-Hodgkin lymphoma (n=511)	Hodgkin's lymphoma (n=149)	Lung cancer (n=207)	Liver cancer (n=119)	Anal cancer (n=74)	Cervical cancer (n=69)
Year of diagnosis							
1998–2000	196 (35%)	191 (37%)	54 (36%)	63 (30%)	30 (25%)	19 (26%)	25 (36%)
2001–03	203 (36%)	174 (34%)	44 (30%)	66 (32%)	37 (31%)	27 (36%)	23 (33%)
2004–06	166 (29%)	146 (29%)	51 (34%)	78 (38%)	52 (44%)	28 (38%)	21 (30%)
Sex and exposure group							
MSM	343 (61%)	203 (40%)	61 (41%)	53 (26%)	25 (21%)	41 (55%)	0
IDU	24 (4%)	79 (15%)	33 (22%)	55 (27%)	54 (45%)	7 (9%)	16 (23%)
Other men	146 (26%)	143 (28%)	44 (30%)	83 (40%)	34 (29%)	21 (28%)	0
Other women	52 (9%)	86 (17%)	11 (7%)	16 (8%)	6 (5%)	5 (7%)	53 (77%)
Migration from sub-Saharan Africa	68 (12%)	35 (7%)	8 (5%)	8 (4%)	11 (9%)	4 (5%)	9 (13%)
Age (years)	40 (34–47)	40 (35–48)	39 (34–44)	46 (42–56)	46 (41–54)	44 (38–50)	39 (35-44)
Previous AIDS	157 (28%)	153 (30%)	34 (23%)	52 (25%)	37 (31%)	33 (45%)	17 (25%)
Duration of known HIV infection (years)	5·6 (1·2–10·3)	8·5 (3·5–13·0)	7·6 (3·2–12·1)	8·1 (3·8–12·5)	11·8 (6·9–16·3)	12·4 (7·8–15·2)	8·2 (4·1–11·9)
Duration of follow-up in FHDH (years)	2·7 (0·5–6·0)	4·5 (1·4–7·6)	4·2 (2·2–6·9)	5·1 (2·7–7·0)	6·4 (3·2–9·0)	6·8 (4·0–9·0)	5·0 (2·2–7·7)
Nadir CD4 count (cells per µL)	104 (28–270)	102 (32–208)	164 (62–266)	114 (43–230)	108 (40–196)	68 (18–175)	158 (83–253)
Cumulative duration with CD4 count <200 cells per µL (years)	0·1 (0–1·4)	0·6 (0–3·1)	0·2 (0–1·3)	0·5 (0–2·5)	1·0 (0·1–3·7)	2·0 (0·2–3·8)	0·2 (0–1·4)
Cumulative duration with HIV RNA >5 $\log_{10}$ copies per mL (years)	0·7 (0·1–2·9)	1·1 (0·1–2·8)	0·8 (0·2–2·6)	0·5 (0·1–1·7)	0·7 (0·1–2·2)	1·4 (0·2–3·4)	0·4 (0–1·9)
ART at cancer diagnosis							
Naive	155 (27%)	84 (16%)	17 (11%)	19 (9%)	3 (3%)	3 (4%)	12 (17%)
Dual therapy	26 (5%)	32 (6%)	12 (8%)	11 (5%)	11 (9%)	0	8 (12%)
cART <6 months	105 (19%)	43 (8%)	11 (7%)	12 (6%)	6 (5%)	2 (3%)	3 (4%)
cART ≥6 months	279 (49%)	352 (69%)	109 (73%)	165 (80%)	99 (83%)	69 (93%)	43 (67%)
CD4 count at cancer diagnosis (cells per µL)							
All patients	164 (50–359)	199 (72–338)	244 (147–420)	260 (143–420)	250 (151–384)	276 (151–435)	287 (165–465)
Patients not receiving cART*	187 (60–350)	177 (68–380)	274 (147–428)	228 (120–359)	256 (127–457)	357 (249–435)	267 (157–401)
Patients receiving cART >6 months	137 (33–366)	201 (74–337)	238 (143–420)	265 (152–422)	243 (152–381)	273 (151–382)	307 (167–474)
HIV-RNA at cancer diagnosis ($\log_{10}$ copies per mL)							
All patients	4·73 (3·07–5·44)	4·32 (2·69–5·29)	2·87 (1·69–4·38)	2·69 (1·69–4·32)	2·69 (1·69–3·98)	2·69 (1·69–4·18)	3·36 (1·85–4·51)
Patients not receiving cART	4·99 (4·00–5·58)	4·99 (3·65–5·53)	4·00 (2·69–4·85)	4·30 (2·69–4·83)	3·76 (2·88–4·43)	4·76 (4·09–4·82)	4·10 (3·71–4·74)
Patients receiving cART >6 months	4·48 (2·44–5·27)	3·95 (2·47–5·14)	2·69 (1·69–4·06)	2·62 (1·69–3·88)	2·61 (1·69–3·48)	2·47 (1·69–4·03)	2·69 (1·69–4·42)

Data are number (%) or median (IQR). FHDH=French Hospital Database on HIV. MSM=men who have sex with men. IDU=injecting-drug user. ART=antiretroviral therapy. cART=combination antiretroviral therapy.
*Patients not receiving cART included ART-naive patients, those receiving dual therapy, and those in the first 6 months of cART therapy.

Table 2: **Characteristics at diagnosis**

of lung cancer was doubled by CD4 counts in the range 350–499 cells per µL, and continued to increase thereafter as the CD4 cell count fell. The risk of liver cancer was raised at CD4 count less than 500 cells per µL, and then reached a plateau at less than 200 cells per µL (table 4). The risk of anal cancer increased with the cumulative duration of CD4 counts less than 200 cells per µL and with the cumulative duration of viral load more than 5 $\log_{10}$ copies per mL (table 5). A higher CD4 cell count was associated with lower risk of cervical cancer, whereas patients receiving cART were half as likely to develop this cancer (table 5).

These results were confirmed by sensitivity analyses. When the study population was restricted to 42 842 patients with known hepatitis virus status, of whom 2442 were co-infected with HBV, 6415 with HCV, and 947 with both viruses, the current CD4 cell count was always the most predictive factor for liver cancer, whereas hepatitis co-infection was associated with a large increase in the risk (incidence ratio 14·4, 95% CI 7·1–29·0). Co-infection with HCV did not increase the risk of non-Hodgkin lymphoma, and the associations of non-Hodgkin lymphoma with the current CD4 cell count, viral load, and cART were not modified (data not shown). When follow-up was censored at the occurrence of severe AIDS-defining events, the same models were retained for Hodgkin's lymphoma, lung cancer, liver cancer, and anal cancer. However, the increase in the risk of Hodgkin's lymphoma associated with decreasing CD4 cell counts was now more linear than bell shaped (data not shown). All interactions between

immunodeficiency and sex were non-significant. In the subsample of patients with information about tobacco use (n=10 443), smoking was an independent risk factor for lung cancer; however, the relations between immunodeficiency and increased risk of cancer were not modified after adjustment for smoking (data not shown). When late-stage HIV presentation was included among the risk factors, AIC was not improved compared with the most parsimonious model initially selected, suggesting no additional prognostic significance of this characteristic (data not shown).

Discussion

We investigated the effect of immunodeficiency, viral replication, and cART on the incidence rates of both AIDS-defining and non-AIDS-defining cancers. Current CD4 cell count was the only factor predictive of Hodgkin's lymphoma, lung cancer, and liver cancer, whereas current CD4 cell count, current viral load, and absence of cART therapy were risk factors for Kaposi's sarcoma and non-Hodgkin lymphoma. Current CD4 cell count and absence of cART were both associated with cervical cancer. Finally, the risk of anal cancer increased with the time during which the CD4 count was less than 200 cells per µL and viral load greater than 5 $\log_{10}$ copies per mL.

The greatest strength of our study is its size and length of follow-up, allowing us to investigate seven specific cancers. We included three non-AIDS-defining malignancies that were diagnosed in at least 100 patients in our cohort. Lung and liver cancers accounted for a large proportion of lethal non-AIDS-defining cancers in patients with HIV in France in 2005.[13] We also included anal cancer—an HPV-related cancer that was associated with the highest rate ratio when HIV-infected patients were compared with those uninfected.[14] The good reporting of cancers in the FHDH cohort is supported by the agreement between the standardised incidence ratios of cancers in HIV-infected patients compared with the French general population and those from others cohorts for which diagnoses were extracted from cancer registries.[4,5,7,8] Only a differential under-reporting according to the extent of immunodeficiency would distort estimates of the effect of immunodeficiency on the risk of cancer. For anal cancer, we selected only ICD codes that were validated to be highly sensitive to a diagnosis of invasive anal cancer.[15] Disease misclassification could have occurred; however, because of the magnitude of person-time in our cohort, the probability of being wrongly classified as having a malignancy will be negligible, limiting bias for the rate ratios.

The observed over-representation of men who have sex with men in patients with Kaposi's sarcoma and of injecting-drug users in patients with liver cancer and lung cancer was expected. The relation between injecting-drug use and lung cancer could be explained by the high number of smokers in this risk group. The low frequency of malignancies according to origin from sub-Saharan Africa could be related to the so-called healthy worker effect, or the origin could act as a proxy for unmeasured lifestyle factors. These sociodemographic variables were systematically included in the Poisson regression models. We did not routinely record other risk factors such as smoking. However, a sensitivity analysis confirms that it was not a confounder of immunodeficiency.

Other limitations should also be considered. First, we limited our study period to 1998–2006, when cART was widely available, and up to 80% of patients enrolled in the FHDH were being treated in 2006. A large proportion of patients still had delayed access to care, but cART was usually started promptly after enrolment.[16] This prompt start could explain the relatively short time spent with CD4 counts less than 200 cells per µL in patients diagnosed with cancer, and could have prevented us from fully exploring the duration of immunodepression. Second, we excluded 1807 patients with a diagnosis of cancer before 1998 since an AIDS-defining malignancy could have acted as competing risk, modifying the risk of non-AIDS-defining cancer

	Kaposi's sarcoma (n=565)		Non-Hodgkin lymphoma (n=511)	
	RR (95% CI)	p value	RR (95% CI)	p value
CD4 count (cells per µL)				
≥500	1·0	<0·0001	1·0	<0·0001
350–499	1·9 (1·3–2·7)	..	1·3 (0·9–2·0)	..
200–349	3·3 (2·3–4·6)	..	3·3 (2·3–4·6)	..
100–199	6·2 (4·2–9·0)	..	4·9 (3·3–7·2)	..
50–99	14·1 (9·4–21·3)	..	11·6 (7·7–17·6)	..
0–49	25·2 (17·1–37·0)	..	14·8 (9·7–22·6)	..
Viral load (copies per mL)				
<500	1·0	<0·0001	1·0	<0·0001
≥500–10 000	1·0 (0·7–1·4)	..	1·6 (1·2–2·2)	..
>10 000–100 000	1·4 (1·1–1·9)	..	1·5 (1·1–2·0)	..
>100 000	3·1 (2·3–4·2)	..	2·9 (2·1–3·9)	..
Exposure to cART >6 months	0·3 (0·2–0·4)	<0·0001	0·8 (0·6–1·0)	0·07
Age (years)				
<30	1·0	0·04	1·0	0·005
30–39	1·2 (0·9–1·7)	..	1·3 (0·9–2·0)	..
40–49	1·5 (1·0–2·1)	..	1·4 (0·9–2·2)	..
50–59	1·3 (0·9–2·2)	..	1·7 (1·1–2·8)	..
≥60	2·1 (1·2–3·4)	..	2·9 (1·7–4·9)	..
Sex and exposure group				
MSM	3·5 (2·8–4·5)	<0·0001	1·6 (1·2–2·0)	<0·0001
IDU	0·3 (0·2–0·5)	..	0·9 (0·6–1·2)	..
Not MSM, not IDU men	1·0	..	1·0	..
Not IDU women	0·4 (0·3–0·6)	..	0·8 (0·6–1·1)	..
Migration from sub-Saharan Africa	1·6 (1·2–2·2)	0·008	0·6 (0·4–0·9)	0·005

Age, CD4 cell count, viral load, and treatment are time-varying covariables. Pearson χ^2 was 1·85 (p=0·17) for Kaposi's sarcoma, and 1·68 (p=0·19) for non-Hodgkin lymphoma. RR=rate ratio. cART=combination antiretroviral therapy. MSM=men who have sex with men. IDU=injecting-drug user.

Table 3: **Multivariable analysis of factors associated with AIDS-defining cancers based on Poisson regression models**

	Hodgkin's lymphoma (n=149)		Lung cancer (n=207)		Liver cancer* (n=119)			
					Model 1		Model 2	
	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value	RR (95% CI)	p value
CD4 count (cells per μL)								
≥500	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001
350–499	1·2 (0·7–2·2)	..	2·2 (1·3–3·6)	..	2·0 (0·9–4·5)	..	1·6 (0·7–3·9)	..
200–349	2·2 (1·3–3·8)	..	3·4 (2·1–5·5)	..	4·1 (2·0–8·2)	..	4·1 (1·9–8·7)	..
100–199	4·8 (2·8–8·3)	..	4·8 (2·8–8·0)	..	7·3 (3·5–15·3)	..	5·9 (2·6–13·3)	..
50–99	7·7 (3·9–15·2)	..	4·9 (2·3–10·2)	..	6·6 (2·4–17·6)	..	5·0 (1·6–15·7)	..
0–49	5·4 (2·4–12·1)	..	8·5 (4·3–16·7)	..	7·6 (2·7–20·8)	..	4·3 (1·1–15·8)	..
Age (years)								
<30	1·0	0·16	1·0	<0·0001	1·0	<0·0001	1·0	<0·0001
30–39	1·5 (0·7–3·0)	..	2·1 (0·5–8·7)	..	2·4 (0·3–18·2)	..	1·5 (0·2–11·8)	..
40–49	1·0 (0·4–2·1)	..	7·0 (1·7–28·2)	..	6·6 (0·9–48·9)	..	4·3 (0·6–31·6)	..
50–59	0·7 (0·3–1·9)	..	14·1 (3·4–57·7)	..	15·6 (2·0–119·3)	..	14·7 (1·9–112·0)	..
≥60	1·2 (0·4–3·4)	..	28·4 (6·9–118·0)	..	26·6 (3·3–212·8)	..	25·2 (3·1–203·6)	..
Sex and exposure group								
MSM	1·0 (0·7–1·6)	<0·0001	0·7 (0·5–1·1)	<0·0001	0·8 (0·5–1·5)	<0·0001	1·0 (0·5–2·0)	<0·0001
IDU	0·8 (0·5–1·3)	..	1·6 (1·1–2·5)	..	3·8 (2·1–6·7)		1·4 (0·7–2·9)	..
Not MSM, not IDU men	1·0	..	1·0	..	1·0		1·0	..
Not IDU women	0·2 (0·1–0·4)	..	0·3 (0·2–0·6)	..	0·2 (0·1–0·5)		0·2 (0·1–0·7)	..
Migration from sub-Saharan Africa	0·7 (0·3–1·4)	0·26	0·4 (0·2–0·9)	0·005	1·8 (0·9–3·6)	0·14	2·0 (0·9–4·0)	0·14
Hepatitis co-infection	..	..	..	..	..	..	14·4 (7·1–29·0)	<0·0001

Age and CD4 cell count are time-varying covariables. Pearson χ^2 was 1·45 (p=0·23) for Hodgkin's lymphoma, 1·57 (p=0·21) for lung cancer, and 1·73 (p=0·19) for liver cancer. RR=rate ratio. MSM=men who have sex with men. IDU=injecting-drug user. *For liver cancer, two multivariable models were studied: without (model 1) or with (model 2) adjustment for hepatitis co-infection.

Table 4: **Multivariable analysis of factors associated with three non-AIDS-defining cancers based on Poisson regression models**

associated with the extent of immunodeficiency. However, in an analysis without exclusion of these people, the same models were selected for each specific cancer (data not shown). Third, HBV and HCV co-infections were not exhaustively recorded during the study period. A sensitivity analysis limited to patients whose hepatitis virus status was known confirmed the major role of HIV-associated immune deficiency in liver cancer, after adjustment for co-infection. By contrast, we noted no effect of HCV co-infection on the risk of non-Hodgkin lymphoma, as previously reported.[17] Finally, we could not address the duration of HIV infection since only a few patients in our cohort had a date of estimated seroconversion.

Immunodeficiency increased the risk of all the cancers that we investigated. These findings accord with the similar increased risk of various cancers reported for HIV-infected patients and for transplant recipients.[9] A relation has been reported between the latest CD4 cell count and the risk of death from both AIDS-defining and non-AIDS-defining cancers.[18,19] A recent review summarised the role for the immune system in the viral-associated cancers.[20] Some viruses could act with a direct transforming effect or through a facilitating process, and immune deficiency would impair the ability of the host to limit expansion of tumoral cells or viral replication at an earlier stage. In our study, HIV replication was associated with an increased risk of non-Hodgkin lymphoma, Kaposi's sarcoma, and anal cancer. Two previous studies have reported an increased risk of AIDS-related lymphoma associated with uncontrolled HIV RNA.[21,22] Since Hodgkin's lymphoma is associated with Epstein–Barr virus infection in patients infected with HIV, the small number of cases of Hodgkin's lymphoma could have prevented us detecting the effect of high viral load. Furthermore, the magnitude of risk associated with HIV RNA seems consistently lower than that associated with CD4. For Kaposi's sarcoma and anal cancer, the increased risk recorded with increased HIV RNA could indicate some interactions between HIV and their oncogenic viruses, human herpesvirus 8, and HPV, respectively. Finally, the absence of association between HIV RNA and the risk of liver cancer might suggest complex relations between HBV and HCV and HIV infection. For lung cancer not yet related to viral infection, a direct link might exist between low densities of mature dendritic cells and CD4 cells and poor clinical outcome.[23]

We noted a continuous increase in the risk of Kaposi's sarcoma and non-Hodgkin lymphoma as the CD4 cell count fell, and an increased risk associated with high viral load. The protective effect of cART was not due solely to immune restoration, since treated patients had

a lower incidence of Kaposi's sarcoma and of non-Hodgkin lymphoma after adjustment for the CD4 cell count and viral load. A protective effect of cART has previously been reported for these two malignancies, starting after 6 months of therapy.[24,25] Similarly, in the SMART trial[26] testing the strategy of intermittent antiretroviral therapy, a higher incidence of AIDS-defining cancers was recorded in the drug conservation group in which ART was stopped and restarted according to the CD4 cell count than in the group receiving continuous treatment. The effects of cART against Kaposi's sarcoma are multifactorial, and include a specific antitumoral activity of some antiretroviral drugs.[27] Another possibility would be a role of inflammation on the tumoral process, since a rise in inflammatory biomarkers was detected in the SMART trial after interruption of treatment.[28]

The severity of immunodeficiency has been associated with an excess risk of non-AIDS-defining cancers.[29] Overall, we noted that the risk increased as the CD4 cell count fell, but we detected specific relations with Hodgkin's lymphoma, lung cancer, and liver cancer. An increased incidence of Hodgkin's lymphoma has been recorded in patients with CD4 counts around 150–200 cells per µL, whereas incidence was smaller in severely immunosuppressed patients.[30] Our first analysis confirmed the finding of a higher risk in patients with moderate immunosuppression. However, this pattern disappeared in a sensitivity analysis censoring follow-up when a serious AIDS-defining event was diagnosed, and the relation between CD4 cell count and incidence of Hodgkin's lymphoma was linear. This finding might indicate that serious AIDS-defining events and Hodgkin's lymphoma are competing risks at very low CD4 cell counts.

A biological mechanism of inadequacy of growth signals that could explain the lower incidence of Hodgkin's lymphoma in patients with severe immunodepression has been postulated because of the pathway of immune response to the cytokines and chemokines expressed by the malignant Reed–Sternberg cells.[31] Specific analyses of subtypes of Hodgkin's lymphoma would be of interest to clarify the relation between CD4 cell count and the incidence of this malignancy. Even moderate immunodepression increased the risk of lung cancer by two-fold in patients with CD4 counts in the range 350–499 cells per µL compared with patients with counts 500 cells per µL or greater, according with reports of lung cancer in HIV-infected patients without severe immunodepression.[32] The effect of the CD4 cell count on the risk of liver cancer persisted after adjustment for hepatitis virus co-infection, which is a major risk factor. The absence of effect of cART on non-AIDS-defining cancers has previously been reported,[6,8] whereas findings from a study spanning the entire HIV/AIDS epidemic period suggested that antiretroviral therapy increased the risk of Hodgkin's lymphoma.[33] In our study that was restricted to the cART era, antiretroviral therapy, assessed in terms of simple cART exposure or by the cumulative duration of cART, had no effect on the risk of Hodgkin's lymphoma, lung cancer, or liver cancer. The beneficial effect of cART seemed mainly associated with the increase of CD4 cell count, but the small sample size could have prevented observation of a therapeutic benefit.

To explain the conflicting findings of low CD4 cell count associated with high-grade intraepithelial neoplasia related to HPV, but not cancer, Palefsky and Holly[34] have proposed that immune suppression would affect earlier stage of intraepithelial neoplasia related to HPV, but have a small role in progression to invasive cancer that might be related to a cumulative effect of genetic changes. Our finding that anal cancer was better predicted by the duration of immunodeficiency and of high viral load could be explained by the postulated mechanism emphasising that progression of anal intraepithelial neoplasia towards invasive cancer is not easily reversible.

Our results suggest that cART would be most beneficial if it restores or maintains the CD4 count above 500 cells per µL, thereby indicating an earlier diagnosis of HIV infection and an earlier treatment initiation. Access to cervical-cancer screening programmes should be regularly offered to all HIV-positive women, and cancer-specific screening programmes, such as for lung cancer and for anal cancer, need to be assessed in HIV-infected patients.

	Anal cancer (n=74)		Cervical cancer (n=69)	
	RR (95% CI)	p value	RR (95% CI)	p value
Duration with CD4 count <200 cells per µL (per 1 year)	1·3 (1·2–1·5)	0·0001	..	..
CD4 (per $\log_2$ increase)	..	..	0·7 (0·6–0·8)	0·0002
Duration with HIV RNA >100 000 copies per mL (per 1 year)	1·2 (1·1–1·4)	0·005	..	..
Exposure to cART >6 months	..	..	0·5 (0·3–0·9)	0·03
Age (years)				
<30	1·0	0·09	1·0	0·002
30–39	3·3 (0·5–24·6)	..	4·2 (1·0–18·3)	
40–49	3·7 (0·5–27·3)	..	7·9 (1·8–34·7)	
50–59	4·1 (0·5–32·0)	..	7·2 (1·3–38·3)	
≥60	8·0 (1·0–64·7)	..	2·6 (0·2–29·1)	
Sex and exposure group				
MSM	1·3 (0·7–2·4)	<0·0001	..	..
IDU	0·2 (0·1–0·6)	..	..	..
Not MSM, not IDU men	1·0	..	..	..
Not IDU women	0·2 (0·1–0·6)	..	..	..
Migration from sub-Saharan Africa	0·9 (0·3–2·6)	0·84	0·6 (0·3–1·5)	0·32

Age, CD4 cell count, treatment, and cumulative exposures are time-varying covariables. Pearson χ^2 was 1·25 (p=0·26) for anal cancer and 1·68 (p=0·19) for cervical cancer. RR=rate ratio. cART=combination antiretroviral therapy. MSM=men who have sex with men. IDU=injecting-drug user.

Table 5: **Multivariable analysis of factors associated with HPV-related cancers based on Poisson regression models**

Contributors
MG, FB, JC, J-ML, ER, and DC designed the study. MG and DC did the statistical analyses. MG, FB, JC, J-ML, ER, and DC interpreted the final data analyses and wrote the report. All authors read and critically commented on the paper.

Conflicts of interest
The authors declared no conflicts of interest.

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 Recherches sur le SIDA et les hépatites (ANRS), INSERM, and the French Ministry of Health.

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