Original Article

Relationship Between Current Level of Immunodeficiency and Non-Acquired Immunodeficiency Syndrome-Defining Malignancies

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BACKGROUND: In the combined antiretroviral therapy (cART) era, non–acquired immunodeficiency syndrome (AIDS)-defining malignancies account for more morbidity and mortality in human immunodeficiency virus-infected patients than AIDS-defining malignancies. However, conflicting data have been reported on the relationship between immunodeficiency and the development of some non–AIDS-defining malignancies. **METHODS:** A total of 14,453 patients from the prospective, multinational EuroSIDA cohort were included. Malignancies were classified as virus-related, non–virus-related epithelial, and other. The incidence of non–AIDS-defining malignancies was calculated stratified by current CD4 count. Poisson regression was used to investigate factors associated with the development of non–AIDS-defining malignancies. **RESULTS:** A total of 356 non–AIDS-defining malignancies occurred, with an incidence rate of 4.3 per 1000 person years of follow-up (95% confidence interval [CI], 3.8-4.7); 172 (48.3%) were virus-related, 135 (37.9%) were non–virus-related epithelial, and 49 (13.7%) were classified as other. Anal (69 cases), lung (31 cases), and melanoma (13 cases), respectively, were the most common non–AIDS-defining malignancies within each group. After adjustment, current CD4 was associated with virus-related non–AIDS-defining malignancies (incidence rate ratio [IRR], 0.81 per doubling; 95% CI, 0.75-0.88; $P < .0001$) and non–virus-related epithelial non–AIDS-defining malignancies (IRR, 0.84; 95% CI, 0.75-0.95; $P = .004$), but not with other non–AIDS-defining malignancies (IRR, 1.04; 95% CI, 0.83-1.31; $P = .73$). Current CD4 count was also associated with anal cancer (IRR, 0.86; 95% CI, 0.75-0.99; $P = .03$), Hodgkin lymphoma (n = 52; IRR, 0.83; 95% CI, 0.73-0.95; $P = .005$), and lung cancer (IRR, 0.76; 95% CI, 0.64-0.90; $P = .0002$). **CONCLUSIONS:** A low current CD4 count was associated with an increased incidence of certain non–AIDS-defining malignancies. Starting cART earlier to reduce the proportion of patients with a low CD4 count may decrease the rate of developing many common non–AIDS-related malignancies. A randomized trial to explore this strategy is urgently needed. ***Cancer* 2010;116:5306–15.** © *2010 American Cancer Society.*

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Three different types of cancer have been classified as acquired immunodeficiency syndrome (AIDS)-defining malignancies: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and more recently, cervical carcinoma.[1] Combined antiretroviral therapy (cART) has decreased the incidence of AIDS-defining malignancies in human immunodeficiency virus (HIV)-infected patients, along with other AIDS-defining illnesses.[2] The decrease has been noted particularly for NHL and KS,[3] whereas some studies have reported that the incidence of cervical cancer has not varied over time.[3-5]

Many non-AIDS defining malignancies have been found at a higher incidence in HIV patients than in the general population.[6,7] The incidences of Hodgkin lymphoma (HL) and malignancy of liver, lung, anus, and oral cavity/pharynx have all been found to be higher among the HIV-infected population than the general population,[8,9] as well as melanoma, leukemia, and vaginal, colon, rectal, and kidney cancer in some studies.[8] Several oncogenic viruses are thought to cause AIDS-defining malignancies; human herpesvirus 8 is associated with KS, Epstein-Barr virus (EBV) is associated with the 2 most common NHL subtypes, and the human papillomavirus (HPV) is associated with cervical cancer.[10-12] Also, several non–AIDS-defining malignancies have been associated with viruses, including HL,[13,14] anal cancer,[15] and hepatocellular carcinoma (HCC).[16]

The increasing incidence of some non–AIDS-defining malignancies and the decrease in AIDS-defining malignancies in the cART era has meant that non–AIDS-defining malignancies now account for more morbidity and mortality in HIV-infected patients than AIDS-defining malignancies.[6] There are many possible reasons for a higher incidence in HIV-infected persons, including direct or indirect viral oncogenesis, immunodeficiency, drug toxicities, and chemical agents.[17,18] Some other cancer risk factors, such as smoking[19] or alcohol consumption, are also highly prevalent in HIV-infected populations.[20]

There is growing interest in the correlation between immunodeficiency and non–AIDS-defining malignancies. Previous studies support the theory that non–AIDS-defining malignancies become more frequent in immunodeficient patients with or without HIV infection.[21-23] The aim of this study was therefore to investigate the incidence of non–AIDS-defining malignancies across Europe in HIV-infected patients and the risk factors associated with the development of non–AIDS-defining malignancies. In particular, we sought to determine whether current CD4 count was independently associated with risk of non–AIDS-defining malignancies after accounting for associated risk factors measured in EuroSIDA.

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Table 1. Cancers Included in Each Category

Virus Related, n = 172	Non–Virus-Related Epithelial, n = 135	Other, n = 49
HPV related	Lung (31)	Unspecified (20)
Anal (69)	Breast (17)	Melanoma (13)
Oral (12)	Prostate (15)	Brain (4)
Pharynx (2)	Rectal (12)	Multiple myeloma (4)
Larynx (8)	Colon (11)	Myeloid leukemia (3)
Vulval (5)	Pancreas (7)	Leukemia (3)
Penile (2)	Stomach (7)	Liposarcoma (1)
EBV related	Esophagus (6)	Lymphoid leukemia (1)
Hodgkin (52)	Kidney (6)	
HBV and HCV related	Bladder (6)	
Liver (22)	Testicular (4)	
	Lip (2)	
	Thyroid (2)	
	Uterine (2)	
	Ovarian (2)	
	Urinary unspecified (2)	
	Nasopharynx (1)	
	Gall bladder (1)	
	Gastric (1)	

HPV indicates human papillomavirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

MATERIALS AND METHODS

Patients

EuroSIDA is a large prospective study with >100 centers across Europe, Israel, and Argentina. Details of the study have been published elsewhere.[24] At each follow-up visit, details on all CD4 counts and HIV RNA measurements since last follow-up are recorded as well as the date of starting or stopping any antiretroviral drug, the use of any prophylaxis against opportunistic infections, the date and type of development of any AIDS-defining illnesses, non-AIDS defining illness, or opportunistic infection, and death. Data are collected and updated at 6-month intervals. These updates include data on all visits and laboratory measurements in the previous 6 months. This analysis includes follow-up data to a median date of September 2008.

All EuroSIDA patients who had a CD4 count measured before enrollment into EuroSIDA and some prospective follow-up were included in the analysis.

Statistical Methods

Baseline was defined as the date of enrollment into EuroSIDA. Patients were followed until either death or their last recorded visit in EuroSIDA. Therefore, patients could develop >1 distinct non–AIDS-defining malignancy while under follow-up. Any non–AIDS-defining malignancy diagnosed before enrollment into EuroSIDA was classified as a prior non–AIDS-defining malignancy, and recurrences of the same non–AIDS-defining malignancy were excluded.

Non–AIDS-defining malignancies were classified using the International Classification of Diseases and Related Health Problems, 10th edition code classification system. Non–AIDS-defining malignancies were categorized a priori into 3 categories: virus-related, non–virus-related epithelial, and other cancers, as shown in Table 1. Nonmelanoma skin cancer was excluded, as it is not systematically ascertained and not thought to cause significant morbidity or mortality.[2] Virus-related cancers included all cancers whose development was known to be virus related,[11,25] including anal cancer, HL, and HCC. Non–virus-related epithelial cancer included all epithelial cancers that have not been shown to be related to a particular virus. Cancers included in the "other" category were those that did not fit clearly into either of the 2 groups or were not well defined in the database, for example, malignant melanomas, leukemia, multiple myeloma, and brain (non-NHL) cancer.

The incidence of non–AIDS-defining malignancies per 1000 person years of follow-up was calculated and stratified by current (time-updated) CD4 count. Person years of follow-up accrued within current CD4 count strata, and person years of follow-up were censored when the most recent CD4 count was >6 months old. Poisson regression analysis was used to determine the factors associated with the development of non–AIDS-defining malignancies; appropriate adjustments were made to

account for repeated events within patients. Factors investigated included sex, age, race, exposure group, region of Europe, and nadir CD4. In addition, CD4 count, viral load, year of follow-up, smoking status, hepatitis B and C status, starting cART, and diagnosis of any AIDS-defining malignancies were included as time-updated covariates. Starting cART was defined as any regimen including $\geq$3 antiretrovirals. Patients were classed as hepatitis B positive if they had a positive hepatitis B virus (HBV) surface antigen test recorded and hepatitis C positive if they had a positive hepatitis C virus (HCV) antibody test. Factors that were significant in univariate analysis ($P < .1$) were included in multivariate analyses. The analysis was performed on all non–AIDS-defining malignancies combined and separately for each non–AIDS-defining malignancy group. Where there was a sufficient number of events (>30) for specific non–AIDS-defining malignancies, the analysis was repeated for the individual non–AIDS-defining malignancies. In addition, previous studies have shown that rates of breast, prostate, and colorectal cancers are not raised in people with HIV[21]; therefore, an additional subgroup analysis focused on these 3 cancers combined.

All analysis was performed using SAS 9.1 (SAS institute, Cary, NC).

RESULTS

There were 14,453 patients included in the analysis. Table 2 gives the baseline characteristics for patients included in the study. Patients were mainly male (75.3%), of white ethnic origin (88.7%), and homosexual (41.3%), with a median age of 36 years (interquartile range, 31-44); 9772 (67.6%) patients were on cART at baseline, 3486 (24.1%) had experienced at least 1 AIDS-defining illness (not including AIDS-defining malignancies) before baseline, and 680 (4.7%) had previously been diagnosed with a malignancy (either AIDS-defining or non–AIDS-defining).

A total of 338 patients developed 1 non–AIDS-defining malignancy while under follow-up, and 9 patients developed 2 different non–AIDS-defining malignancies; thus, a total of 356 non–AIDS-defining malignancies were included in analyses, as shown in Table 1, during 83,398 person years of follow-up, to give an incidence rate of 4.3 per 1000 person years of follow-up (95% confidence interval [CI], 3.8-4.7). A total of 172 were classed as virus-related, 135 as non–virus-related epithelial non–AIDS-defining malignancies, and 49 as other malignancies. There was a decreasing incidence rate of all non–AIDS-defining malignancies combined with increasing current CD4 count (Fig. 1). For example, at a current CD4 count of $\leq$200/mm^3, the incidence rate was 6.4 per 1000 person years of follow-up (95% CI, 5.1-7.7) compared with 3.4 per 1000 person years of follow-up (95%

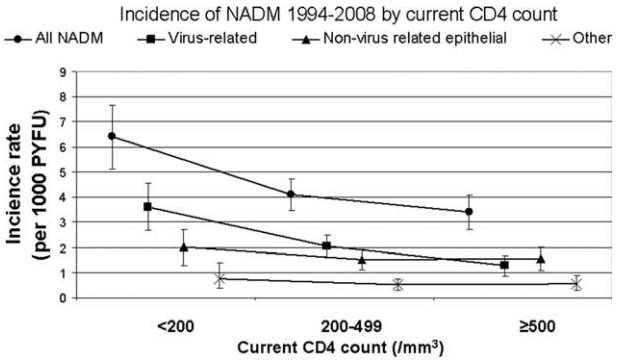
Table 2. Patients Characteristics at Enrollment Into EuroSIDA

Characteristics	No.	%
All patients	14,453	100
Male sex	10,879	75.3
White ethnic origin	12,822	88.7
Exposure group		
Homosexual	5965	41.3
IDU	3488	24.1
Heterosexual	4017	27.8
Other	983	6.8
Region of Europe		
South/Argentina	4571	31.6
Central	3374	23.3
North	3724	25.8
East	2784	19.3
Hepatitis B status		
Negative	9194	63.6
Positive	645	4.5
Unknown	4614	31.9
Hepatitis C status		
Negative	6263	43.3
Positive	2782	19.3
Unknown	5409	37.4
Treatment		
Naive	1569	10.9
ART	3112	21.5
cART	9772	67.6
Prior diagnosis of AIDS or malignancy		
None	10,287	71.2
Prior AIDS, not ADM	3486	24.1
Prior malignancy, ADM or NADM	680	4.7
Smoking status		
Current	2809	19.4
Previous	890	6.2
Never	1510	10.4
Unknown	9244	64.0

	Median	IQR
Age, y	36	31-44
CD4 per mm^3	300	153-453
CD4 nadir per mm^3	177	64-302
Viral load[a] per $\log_{10}$ copies	2.70	1.70-4.23
Recruitment	January 99	January 96-January 04

IDU indicates intravenous drug user; ART, antiretroviral therapy; cART, combined ART; AIDS, acquired immunodeficiency syndrome; ADM, AIDS-defining malignancy; NADM, non–AIDS-defining malignancy; IQR, interquartile range.

[a] A total of 9389 patients had viral load data available at enrollment.



Current CD4 count	<200	200-499	≥500
Number of events			
All NADM	99	159	98
Virus-related	56	79	37
Non-virus related epithelial	31	59	45
Other	12	21	16

Figure 1. Incidence of cancer is shown by current CD4 count. NADM indicates non-acquired immunodeficiency syndrome-defining malignancies; PYFU, person years of follow-up.

CI, 2.7-4.1) at a current CD4 count of >500/mm^3 ($P <$ .0001). As shown in Figure 1, there is a clear decrease in the incidence rate of virus-related non–AIDS-defining malignancies with increasing CD4 count, from 3.6 at CD4 counts of ≤200/mm^3 (95% CI, 2.7-4.6) to 1.3 at CD4 counts of >500/mm^3 (95% CI, 0.9-1.7; $P <$ .0001). The incidence of non–virus-related epithelial cancer showed a small but not statistically significant decrease as current CD4 count increased, whereas that of other cancers was similar at different current CD4 count levels ($P =$ .38).

Table 3 shows the results of the multivariate Poisson regression analysis. For any non–AIDS-defining malignancy, after adjustment, a higher current CD4 count was associated with a lower incidence of non–AIDS-defining malignancies (incidence rate ratio [IRR], 0.87 per doubling; 95% CI, 0.82-0.94; $P <$ .0001). Nadir CD4 count was not found to be significant after adjustment (IRR, 1.03; 95% CI, 0.98-1.09; $P =$ .26). Hepatitis B antigen-positive patients had double the incidence rate of non–AIDS-defining malignancies compared with those who were hepatitis B antigen negative (IRR, 2.14; 95% CI, 1.58-2.90; $P <$ .0001). A previous diagnosis of AIDS increased the incidence of non–AIDS-defining malignancies by 39% (IRR, 1.39; 95% CI, 1.09-1.78; $P =$ .007), and a prior malignancy almost doubled the incidence of non–AIDS-defining malignancies (IRR, 1.84; 95% CI, 1.30-2.59; $P =$ .0005) compared with no prior diagnosis. Age and ethnicity were also associated with the incidence of non–AIDS-defining malignancies; nonwhite patients had a 51% lower incidence of non–AIDS-defining malignancies (IRR, 0.49; 95% CI, 0.32-0.77; $P =$ .002), and older patients had a 51% increased incidence per 10 years older (IRR, 1.51; 95% CI, 1.37-1.67; $P <$ .0001).

In the virus-related group, there was a significantly decreased incidence of non–AIDS-defining malignancies associated with higher current CD4 counts (IRR per doubling, 0.84; 95% CI, 0.77-0.91; $P <$ .0001). Higher current CD4 count was also associated with a lower incidence of non–virus-related epithelial cancers (IRR, 0.84; 95% CI, 0.75-0.95; $P =$ .004). However, current CD4 count was not a significant factor in predicting the incidence in the other non–AIDS-defining malignancies group (IRR, 1.04; 95% CI, 0.83-1.31; $P =$ .73). Nadir CD4 count was not associated with development of any of the cancer groupings after adjustment for current CD4 count. A prior malignancy diagnosis (IRR, 2.45; 95% CI, 1.56-3.84; $P <$ .0001) and a hepatitis B-positive diagnosis (IRR, 2.53; 95% CI, 1.69-3.77; $P <$ .0001) were associated with an increased incidence of virus-related cancers. Older age was associated with a higher incidence of non–virus-related epithelial (IRR, 2.02; 95% CI, 1.77-2.36; $P <$ .0001) and other (IRR, 1.35; 95% CI, 1.05-1.73; $P =$ .02) cancers. Year of follow-up was also associated with an increased rate of non–virus-related epithelial cancer (IRR, 1.06; 95% CI, 1.01-1.11; $P =$ .01).

Figure 2 shows the incidence rate ratio per 2-fold increase in current CD4 count, after adjustment, for each of the non–AIDS-defining malignancies groupings and for specific non–AIDS-defining malignancies. The 3 most frequently observed cancers (anal cancer [n = 69], HL [n = 52], and lung cancer [n = 31]) were also investigated separately. For anal cancer, after adjustment, there was a significantly decreased incidence with increasing current CD4 count (IRR, 0.86 per doubling; 95% CI, 0.75-0.99; $P =$ .03); nadir CD4 count was also found to be marginally significant (IRR, 0.93 per doubling; 95% CI, 0.84-1.01; $P =$ .09). Homosexual transmission group had a higher incidence of anal cancer compared with patients infected via heterosexual transmission (IRR, 2.96; 95% CI, 1.40-6.24; $P =$ .04). Patients with a prior malignancy diagnosis (IRR, 3.25; 95% CI, 2.71-6.16; $P =$ .0003), who were hepatitis B antigen positive (IRR, 2.29; 95% CI, 1.25-4.18; $P =$ .007), and who had a later year of follow-up (IRR, 1.10; 95% CI, 1.02-1.18; $P =$ .01) also had a higher incidence of anal cancer. As there is some uncertainty about the association of HL at intermediate levels of immunodeficiency and debate over whether

Table 3. Multivariate Poisson Regression Analysis

Characteristics	All NADM			Virus Related			Non–Virus-Related Epithelial			Other		
	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*	IRR	95% CI	*P*
Sex												
Male	1.00	—	—	1.00	—	—				1.00	—	—
Female	1.08	0.78-1.50	.64	0.87	0.52-1.46					0.18	0.04-0.77	.02
Race												
White	1.00	—	—	1.00	—	—	1.00	—	—			
Other	0.49	0.32-0.77	.002	0.43	0.21-0.86	.02	0.65	0.34-1.23	.18			
Exposure group												
Homosexual	1.00	—	—	1.00	—	—				1.00	—	—
IDU	1.01	0.69-1.50	.94	1.12	0.75-1.65	.58				0.55	0.12-2.44	.43
Heterosexual	0.74	0.54-1.03	.07	1.51	0.29-0.88	.02				1.34	0.66-2.75	.42
Other	0.80	0.53-1.22	.30	0.47	0.22-1.02	.06				1.40	0.53-3.69	.50
Region of Europe												
South/Argentina	1.00			1.00	—	—	1.00	—	—	1.00	—	—
Central	1.22	0.94-1.62	.14	1.40	0.96-2.04	.08	0.91	0.58-1.43	.67	2.36	0.91-6.11	.08
North	1.11	0.84-1.45	.47	1.04	0.71-1.53	.85	1.07	0.76-1.63	.76	2.38	0.95-5.96	.06
East	0.59	0.36-0.97	.04	0.30	0.12-0.76	.01	0.53	0.25-1.15	.11	3.13	0.92-10.62	.07
Hep B status												
Negative	1.00	—	—	1.00	—	—	1.00	—	—			
Positive	2.14	1.58-2.90	<.0001	2.53	1.69-3.77	<.0001	1.77	1.03-3.04	.04			
Unknown	0.71	0.50-1.03	.07	0.68	0.42-1.12	.13	0.75	0.44-1.28	.29			
Hep C status												
Negative	1.00	—	—							1.00	—	—
Positive	0.95	0.66-1.37	.79							0.59	0.18-1.94	.39
Unknown	1.03	0.67-1.59	.88							1.62	0.42-6.30	.49
Ever smoked												
Never	1.00	—	—							1.00	—	—
Current	1.37	0.99-1.90	.06							5.01	1.15-21.87	.03
Previous	1.39	0.97-1.98	.07							4.32	0.93-20.01	.06
Unknown	1.75	1.23-2.48	.002							12.31	2.81-53.82	.0009
Prior diagnosis												
None	1.00	—	—	1.00	—	—				1.00	—	—
AIDS (nonmalignancy)	1.39	1.09-1.78	.007	1.40	0.97-2.01	.07				1.79	0.94-3.40	.07
Malignancy	1.84	1.30-2.59	.0005	2.45	1.56-3.84	<.0001				1.78	0.64-4.95	.27
Age, per 10 years	1.51	1.37-1.67	<.0001	1.13			2.02	1.77-2.36	<.0001	1.35	1.05-1.73	.02
CD4 doubling	0.87	0.82-0.94	<.0001	0.84	0.78-0.91	<.0001	0.84	0.75-0.95	.004	1.04	0.83-1.31	.73
CD4 nadir	1.03	0.98-1.09	.26	1.01	0.95-1.09	.65				0.97	0.84-1.12	.65
Year of follow-up							1.06	1.01-1.11	.01			
Ever started cART	1.52	1.10-2.11	.01	1.48	0.93-2.33	.09				2.26	0.81-6.28	.12

NADM indicates non–AIDS-defining malignancy; IRR, incidence rate ratio; CI, confidence interval; IDU, intravenous drug user; Hep, hepatitis; AIDS, acquired immunodeficiency syndrome; cART, combined antiretroviral therapy.

a linear relationship exists, the association of current CD4 count was initially investigated at different CD4 count strata. In univariate analysis compared with patients with a current CD4 count of $\geq 500/mm^3$, patients with a current CD4 count of $<200/mm^3$ had a 6× higher incidence of HL (IRR, 6.40; 95% CI, 2.76-14.84; $P < .0001$), and those with a CD4 count of between 200 and $499/mm^3$ had double the incidence of HL (IRR, 2.23; 95% CI, 0.95-5.24; $P = .06$), indicating a linear relationship. Therefore, in adjusted analysis current CD4 count was included as a continuous variable. Higher current CD4 count was associated with a lower incidence of HL (IRR, 0.83 per doubling; 95% CI, 0.73-0.95; $P = .005$), whereas a prior AIDS diagnosis (IRR, 1.78; 95% CI, 0.94-3.37; $P = .08$) was marginally associated with a higher incidence of HL. The incidence of lung cancer was significantly decreased with a higher current CD4 count (IRR, 0.76; 95% CI, 0.64-0.90; $P = .0002$). Being a

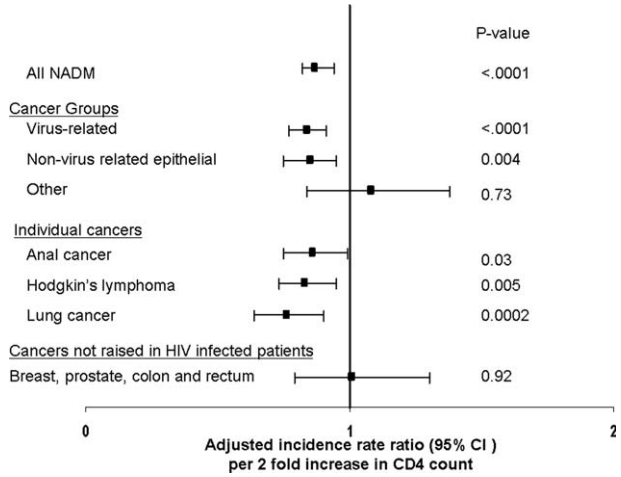


Figure 2. Incidence rate of non–acquired immunodeficiency syndrome (AIDS)-defining malignancies (NADM) is shown by current CD4 count. The all non–AIDS-defining malignancies model was also adjusted for sex, ethnic origin, human immunodeficiency virus (HIV) exposure group, region of Europe, hepatitis B and C status, smoking status, prior AIDS diagnosis, age, CD4 nadir, and started combined antiretroviral therapy (cART). The virus-related model was also adjusted for sex, ethnic origin, HIV exposure group, region of Europe, hepatitis B status, prior AIDS diagnosis, age, nadir CD4, and started cART. The non–virus-related epithelial model was also adjusted for ethnic origin, region of Europe, hepatitis B status, age, and year of follow-up. The "other" model was also adjusted for sex, HIV exposure group, region of Europe, hepatitis C status, smoking status, prior AIDS diagnosis, age, and started cART. The anal cancer model was also adjusted for sex, ethnic origin, HIV exposure group, region of Europe, hepatitis B and C status, prior AIDS diagnosis, nadir CD4, and year of follow-up. The Hodgkin lymphoma model was also adjusted for sex, HIV exposure group, region of Europe, prior AIDS diagnosis, and year of follow-up. The lung cancer model was also adjusted for smoking status, prior AIDS diagnosis, and age. The combined breast, prostate, colon, and rectum cancer model was also adjusted for HIV exposure group, region of Europe, hepatitis B and C status, smoking status, age, and year of follow-up. CI = confidence interval.

current smoker compared with having never smoked (IRR, 16.80; 95% CI, 2.23-126.2; $P = .0006$) and older age (IRR, 2.79 per 10 years older; 95% CI, 2.22-3.50; $P < .0001$) also significantly increased the rate of lung cancer.

There were 55 diagnoses of breast, colon, or prostate cancer (Table 1). There was no significant relationship with the incidence of these cancers combined and current CD4 count (IRR, 1.01 per doubling; 95% CI, 0.79-1.30; $P = .92$). Older age (IRR, 1.87 per 10 years older; 95% CI, 1.48-2.35; $P < .0001$) and increasing year of follow-up (IRR, 1.15 per year; 95% CI, 1.06-1.25; $P = .0005$) were associated with an increased rate of these combined cancers.

DISCUSSION

The incidence of non–AIDS-defining malignancies in EuroSIDA from 1994 to 2007 was 4.3 per 1000 person years of follow-up. After adjustment, a higher current CD4 count was independently associated with a decreased incidence of non–AIDS-defining malignancies. In addition, an increased rate of virus-related cancers and non–virus-related epithelial cancers was found in immunodeficient patients. HL, anal cancer, and lung cancer were all found at a higher rate in patients with lower current CD4 counts after adjustment for other demographic and traditional risk factors.

Our findings confirm results from other studies that have found a link between immunodeficiency and certain non–AIDS-defining malignancies,[18,21,23,26-29] although others have not found an association.[22,30] However, only a few of these studies focused on CD4 count as a measure of immunodeficiency.[18,28,29] It is important to distinguish between CD4 count nadir and current CD4 count; the former measures the lowest point the CD4 count has reached and will address the long-term risk of non–AIDS-defining malignancies. In contrast, the current CD4 count measures the short-term risk of non–AIDS-defining malignancies, based on the latest information, and takes account of increases in CD4 count that are associated with starting cART. In this study, current CD4 count and not CD4 nadir was found to be important for the development of non–AIDS-defining malignancies, a finding also found by the Swiss HIV Cohort Study, where the latest CD4 count was associated with the risk of HCC, but CD4 nadir was insensitive in predicting the risk of HCC.[28]

There was a significant increase in non–AIDS-defining malignancies with increasing calendar year of follow-up, as reported by previous studies.[3,31,32] There are several potential explanations for the suggested increase in non–AIDS-defining malignancies. Centers participating in the study may have become more aware of the importance of non-AIDS diagnoses and have recorded more non–AIDS-defining malignancies in recent years, although EuroSIDA has an extensive quality assurance program, and the data on non–AIDS-defining malignancies have been part of the quality assurance exercise since 2003. In addition, patients with HIV are now living longer[24] and aging, which may allow other comorbidities such as non–AIDS-defining malignancies to develop.

Because of the small number of individual non–AIDS-defining malignancies, 3 groups of non–AIDS-defining malignancies were defined: virus-related, non–virus-related epithelial, and other. These groups were

defined a priori before starting analyses and after review by several study group clinicians. Several viral infections are considered to be the causative organism of certain cancers in humans, with nearly 15% of all cancers thought to have an infectious agent in their etiology.[33] HL in patients infected with HIV is virtually always EBV-associated.[13,14] HCC almost invariably occurs in the context of HBV or HCV chronic coinfection in HIV-infected patients.[16] Large retrospective cohort studies of HIV-infected patients followed up during the cART era have not found an increase in HCC without hepatitis coinfection.[34] The principal risk factor for anal cancer is HPV infection.[15] In addition, studies have found that vulva, vagina, penile, oral cavity, and pharynx cancers are caused by HPV, with limited association with cancer of the larynx.[11,21,25,35] Interestingly, previous studies have found a link between virus-related cancers such as HL,[27] HCC,[28] and anal cancer[26] with immunodeficiency determined by time to AIDS diagnosis[26,27] or CD4 count within 1 year of diagnosis.[28] The most common non–virus-related epithelial cancers (eg, lung and prostate) remain difficult to treat, and the majority remain incurable, with very little improvement in survival over the past decade[36]; in addition, based on oncoepidemiologic studies, risk of epithelial cancers starts to increase at about the age of 30 years and increases progressively by age.[37] Therefore, all non–virus-related epithelial cancers were grouped together. The final group "other" included leukemia, myeloma, brain tumors, and melanoma as well as any cancers that were not well defined within the database.

Our results confirmed the findings from a previous meta-analysis that immunodeficient patients, irrespective of cause, are at an increased risk of developing virus-related cancers.[21] In particular, our study found that HL and anal cancer were both found at a higher rate in patients with lower CD4 counts after adjustment for other demographic and traditional risk factors. Some studies support our results.[21,38] Biggar et al found that the incidence of HL is highest at moderate CD4 counts (150-199 cells/mm^3),[38] and another study[39] found that the risk of HL increased for CD4 counts of $<$350 cells/mm^3 and peaked at 50 to 99 cells/mm^3. We found a linear relationship between with decreasing CD4 count and increasing incidence of HL. Other studies, however, have found no association.[22] The mechanisms through which infection with these viruses leads to increased risk of cancer are not fully understood, but it is thought that advancing immunodeficiency may result in losing control of the oncogenic virus.

Non–virus-related epithelial cancers were also associated with an increased rate in immunodeficient patients. A meta-analysis by Grulich et al[21] comparing rates of cancer in HIV-infected patients and transplant patients found little evidence of an increased risk of epithelial cancers in either group compared with the general population, whilst a decreased rate was found in prostate cancer. The combined analysis looking at prostate, breast, rectum, and colon cancer found no relationship between immune deficiency and the development of these cancers, which supports findings that these have not been found at an increased rate in HIV-infected patients.[21] However, Grulich et al[21] did report an increase in rates of lung cancer, which was the most common cancer in the epithelial group in our study and was found to be associated with current CD4 count, although it is worth noting that we did not have complete data on smoking status, 1 of the main risks for lung cancer.[40]

We found several predictors of virus-related cancers. Prior malignancy diagnosis was associated with an increased incidence of virus-related malignancies, the majority being AIDS-defining malignancies (87%), which are caused by pro-oncogenic viruses.[10,11] This may be an indicator that if you lose immunosurveillance that otherwise protects you against pro-oncogenic viruses, you are at an increased risk of all types of cancer caused by pro-oncogenic viruses. The HIV transmission group was also associated with an increased incidence of virus-related cancers, particularly when focusing on anal cancers. Studies before the HIV epidemic found an increased risk of HPV-related anal cancer in homosexual men.[41,42] This increased risk has been found to be even higher in those infected with HIV.[10,42,43] Older age was a strong predictor in the development of any non–AIDS-defining malignancies; in particular, age was a significant predictor in the non–virus-related epithelial and other cancer groups. This is not surprising, given that around 77% of all cancers are diagnosed in patients older than 55 years.[44,45]

The EuroSIDA study is a diverse and heterogeneous patient population initiated in 1994 that provides an ideal opportunity for considering the development of non–AIDS-defining malignancies over many years of follow-up. Unlike the recent DAD study,[18] this study includes both fatal and nonfatal non–AIDS-defining malignancies. In addition to looking at all non–AIDS-defining malignancies, the effects of immunodeficiency of specific cancer types were also investigated, as well as individual cancer types where there was sufficient data.

There are several limitations of our work. As with all cohort studies, we can only adjust for the data that we have collected. Excessive alcohol use has been shown to be significant in predicting the risk of developing cancer,[44] as has smoking, both of which have been found at an increased level in the HIV-infected population compared with the general population.[46] We were able to adjust for smoking status in patients with this data recorded, but did not find it was a significant predictor; however, we do not currently collect data on alcohol intake. In addition, the centers included in EuroSIDA may not be representative of all clinics in Europe. Patients in EuroSIDA are those attending clinics for routine outpatient appointments; they have good access to care and may be monitored more frequently than other HIV-infected patients. We grouped the non–AIDS-defining malignancies into 3 categories a priori, as we did not have sufficient power to consider them all individually. This has the advantage that we can look in detail in 3 broad categories that have many features in common, but the main disadvantage is that the groupings are heterogeneous, particularly in the "other" group.

Cohorts and clinical trials need to collect data on both AIDS-related and non–AIDS-related illnesses to obtain a better understanding of the incidence and risk factors for the development of non-AIDS illnesses, including cancer. Greater understanding of how these cancers develop and their risk factors may help in the prevention and treatment of malignancies in both the HIV-infected and uninfected populations. Although this study is not based on a strategic trial, and cannot establish that increasing the CD4 counts after starting cART caused the decrease in non–AIDS-defining malignancies, it does suggest that earlier treatment may be beneficial for reducing the incidence of non–AIDS-defining malignancies. This is supported also by recent data from the Strategies for Management of Antiretroviral Therapy study, where patients in the drug conservation arm who interrupted treatment had a higher rate of AIDS-defining malignancies,[47] which was thought to be because of lower CD4 cell counts and higher viral loads. The Strategic Timing of Antiretroviral Therapy trial to determine whether starting cART early (before CD4 drops to <500 cells/mm^3), rather than waiting until CD4 drops to <350 cells/mm^3 as current guidelines recommend, reduces the occurrence of serious morbidity and mortality, will also explore whether cART protects against non–AIDS-defining malignancies.[48]

Our study has shown a link with immunodeficiency and the development of certain non–AIDS-defining malignancies. Starting cART earlier to reduce the proportion of patients with a low CD4 count may decrease the rate of developing many common non–AIDS-related malignancies.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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