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Relationship between Current Level of Immunodeficiency and Non-AIDS Defining Malignancies

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INTRODUCTION

Incidence of non-AIDS defining malignancies (NADM) may be elevated in patients with HIV. Among others the incidence of Hodgkin's lymphoma, leukemia, cancer of the liver, lung, anus, colon or rectum, and kidney have all been found to be higher among the HIV infected population than the general population. The reasons for this increase remain elusive. Confounding by some traditional risk factors, such as smoking, alcohol use and co-infection account for some of the increased risk but not all. There appears to be a relationship between immunodeficiency and non-AIDS malignancies, but evidence of the relationship between current CD4 count, i.e. the most recently measured, and the risk of NADM is still limited.

AIM

The aim of this analysis was to investigate whether current CD4 count was independently associated with the risk of NADM after accounting for traditional and other HIV-associated risk factors.

METHODS

- 12,865 patients with a CD4 count prior to enrollment and some propective follow- up in EuroSIDA were included
- Patients were followed until either death or their last recorded visit in EuroSIDA
- NADM were classified using the ICD-10 classification system. All skin cancers were excluded from the analysis
- The CD4 count, viral load and antiretroviral treatment ever started before each NADM were determined, measurements must have been within 6 months prior to diagnosis
- The incidence of NADM per 1,000 person years of follow-up was calculated, and stratified by current CD4 count i.e. time updated as the most recently measured CD4 count
- Poisson regession was used to determine factors related to the development of NADM. Models adjusted for year of follow-up, gender, exposure group, race, region of Europe, time on cART, age, hepatitis B and C, nadir CD4, and whether or not patient ever smoked

Table 1
Baseline characteristics

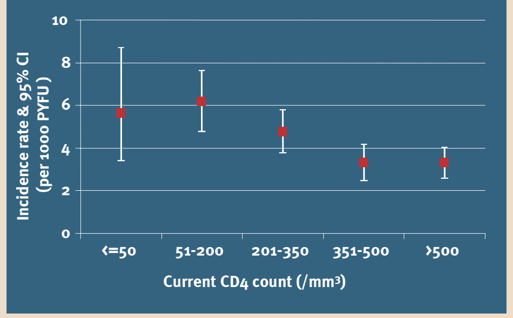
		Developed NADM during prospective follow-up			
		No		Yes	
		N	%	N	%
All patients		12556	97.6	309	2.4
Gender	Male	9552	76.1	255	82.5
Ethnic origin	White	11037	87.8	287	92.9
Prior AIDS		3575	28.5	92	29.8
Prior NADM		101	0.8	8	2.6
ARV Treatment	Naïve	1286	10.2	30	9.7
	ART	2823	22.5	121	39.2
	cART	8447	67.3	158	51.1
		Median	IQR	Median	IQR
Age		36	31-44	42	34-50
CD4		287	142-440	230	127-360
Nadir CD4		170	60-297	147	667-250
Baseline		06/97	12/95-03/02	02/97	05/94-04/98

Table 2
Characteristics at time of NADM diagnosis

	Lung Cancer N=24	Anal Cancer N=58	Haematological N=60*	Urinary& Genital N=40	Digestive Organs N=55Ψ	Other N=80
CD4 count Median (IQR)						
Current	304 (197-467)	285 (190-522)	272 (140-428)	393 (195-553)	287 (214-420)	324 (188-570)
Nadir	63 (10-170)	55 (18-132)	89 (122-235)	152 (30-236)	114 (43-201)	120 (47-208)
Viral load N (%)						
VL data	23 (95.8)	53 (91.4)	51 (85.0)	32 (80.0)	48 (80.0)	60 (75.0)
VL<500	17 (73.9)	32 (55.2)	35 (50.0)	20 (50.0)	28 (58.6)	46 (57.5)
Treatment N (%)						
Naïve	0 (0)	1 (1.7)	6 (10.0)	2 (5.0)	1 (1.8)	2 (2.5)
ART	2 (8.3)	3 (5.2)	8 (13.3)	6 (15.0)	8 (14.6)	15 (18.8)
cART	22 (91.7)	54 (93.1)	43 (76.7)	32 (80.0)	46 (83.6)	63 (78.7)

*49 Hodgkin's cancer, Ψ14 Liver cancer

Figure 1
Incidence of NADM 1994-2007 by current CD4 count



RESULTS

Table 1 shows the baseline characteristics, comparing those who developed a NADM to those who did not. Patients developing NADM were more likely to be male (p=0.01), older (p<0.0001), have a lower CD4 count (p=0.0001), have had a prior NADM (p=0.01) and have been enrolled in EuroSIDA earlier (p<.0001).

317 NADM were recorded over 75,234 person years with an incidence rate of 4.2 per 1000 PYFU 95%CI (3.7-4.7). 301 patients developed one and 8 patients developed two different NADM whilst under follow-up. **Table 2** shows the patient characteristics at time of diagnosis for different NADM. Patients with anal or haematological cancer were younger and had lower CD4 counts. 24% (95%CI 18, 30) and 40% (95% CI 33, 47) were estimated to have died at 12 and 24 months after diagnosis of NADM using Kaplan Meier estimation.

Figure 1 shows the relationship between current CD4 count and incidence of NADM. There was an increasing incidence of NADM as current CD4 count decreases.

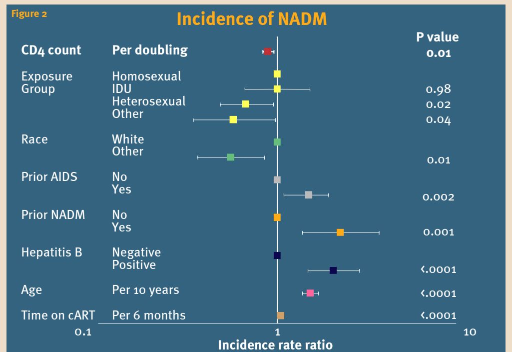
Figure 2 shows that after adjustment there was a decreasing rate of NADM with increasing CD4 count. For each doubling of the CD4 count there was an 11% decreased incidence of developing a NADM. In addition ethnicity, prior AIDS diagnosis, prior NADM diagnosis, time on cART, hepatitis B status, and age were all significant predictors of developing NADM.

Figure 3 shows the relationship between current CD4 count and the incidence of specific NADM was consistent for the different diagnoses, except the less common, NADM (grouped as other), but due to the small number of events and limited power was only significant for anal (p=0.02) and digestive cancers (p=0.003).

CONCLUSION

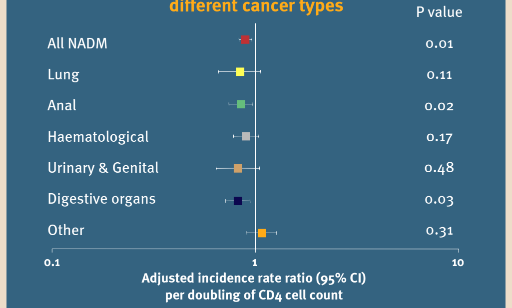
Current immunodefiencency was associated with an excess risk of NADM. One possible explanation is enhanced oncogenic potential by pro-oncogenic viruses (e.g. HPV and anal cancer). An infectious oncogenesis has only been established for a few of NADM linked with immunosuppression in this study and other mechanisms may also contribute. As the immunosuppression may be reversed by cART, HIV is a suitable candidate model for improving our understanding of how immunosuppression affects oncogenic transformation.

Figure 2
Incidence of NADM



Multivariate regression analysis also adjusted for gender, region of Europe, Hepatitis C status, CD4 nadir and smoking status which were non significant.

Figure 3
Incidence rate of NADM by current CD4 for different cancer types



Multivariate regression analysis adjusted for gender, exposure group, race, prior AIDS, prior NADM, region of Europe, hepatitis B & C status, time on cART, nadir CD4 and smoking status

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