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Immunodeficiency as Risk Factor for Non-AIDS Defining Malignancies in HIV-1 Infected Patients on cART: the Athena Cohort

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BACKGROUND

The incidence of certain non-AIDS defining malignancies (NADM) has been found to be higher among the HIV infected population than in the general population. The reasons for this increase remain elusive. Confounding by traditional risk factors, such as smoking, alcohol use and co-infection account for some of the increased risk but not all.

AIM

The aim of this study was to explore the role of immunodeficiency and viraemia in the treated HIV population as risk factors for NADM, while adjusting for traditional risk factors.

METHODS

- Patients starting cART >1 Jan 1996 were selected from the Netherlands observational ATHENA cohort. Patients were either ART naïve or had prior mono/duo NRTI exposure.
- Follow up started at cART initiation until last available CD4 or HIV RNA measurement or February 1st 2009, whichever came first.
- Cases were extracted from patient records. Definition of cases according to D:A:D protocol. (Not including basal cell carcinoma and squamous cell carcinoma skin).
- Only non-AIDS defining malignancies occurring after initiation of cART were taken into account.
- Time-updated Cox regression models were used to investigate time to diagnosis of first NADM. CD4 and VL measurements were updated in 3 month periods. If the CD4 or VL measurement was missing, the previous observation was carried forward.
- Models were adjusted for gender, region of origin, mode of HIV-acquisition, nadir and baseline CD4 count, prior AIDS diagnosis, alcohol abuse, tobacco use, HBV and HCV co-infection and estimated duration of HIV infection prior to the start of cART.
- Age and exposure to cART were included in the models as time-updated variables. Exposure to cART was modeled as cumulative exposure to PIs, NNRTIs and NRTIs.
- Immunodeficiency was taken into account as latest CD4 count (lagged 6 months) and as cumulative exposure to CD4 counts below certain thresholds, i.e. below 200, 350 and 500 cells/mm³.
- Viraemia was investigated similarly, as latest viral load, latest viral load lagged 6 months and as cumulative time of viraemia above 50, 400, and 1000 cp/ml.

RESULTS

Table 1 shows the baseline characteristics. In total, follow-up time was 67,179 person years (PY), with a median follow-up time of 5.5 years (IQR 2.2-8.3). Median time on CART was 4.8 years (IQR 1.9-8.2). One-fifth (13,971 PY) of follow-up was contributed by patients with detectable HIV-1 RNA levels.

232 non-AIDS defining malignancies were diagnosed during follow-up. 100 (43%) of these cancers were potentially related to an infectious cause (mostly anal (n=37), laryngeal (n=20), hepatocellular cancers (n=16), and Hodgkin's lymphoma (n=20)) and 132 (57%) of these cancers were not infection-related (mostly lung (n=44), hematological (n=17), prostate (n=16), breast (n=12), and colon cancer (n=10)). Characteristics of patients diagnosed with a NADM are shown in **Table 2**.

In multivariate Cox models, longer exposure to CD4 counts below 200 cells, and to a lesser extend between 200 and 350 cells were associated with a higher risk of non-AIDS defining malignancies, HR 1.12, (95% CI 1.03-1.22), HR 1.08 (0.99-1.18) respectively, per year longer. Longer exposure to detectable viraemia was not associated with non-AIDS defining malignancies, neither were latest viral load nor latest CD4 count **(Figure 1).**

Significant risk factors for non-AIDS defining malignancies were a longer estimated duration of HIV infection prior to starting cART, HBV co-infection, older age, prior AIDS diagnosis and being from Western origin.

In analyses stratified according to infection-related and not infection-related malignancies, longer exposure to CD4 counts below 200 cells/mm³ was associated with malignancies with a possible infection-related cause (HR 1.16, CI 1.03-1.31), but this association was not seen in other types of cancers (HR 1.07, CI 0.95-1.21). No significant effect of viraemia was seen in either group of cancers **(Figure 2).**

CONCLUSION

In HIV-1 infected patients on cART, immunodeficiency was found to be an independent predictor for non-AIDS defining malignancies, specifically malignancies with an infection-related cause. Factors that remain important to consider when assessing cancer risk in HIV-infected patients, apart from immunodeficiency, are higher age, concomitant infection with oncogenic viruses and tobacco use. Our results support starting cART above 350 cells/mm³ to decrease the risk of developing malignancies. Screening for anal HPV infections and pre-malignant lesions, counseling patients to quit smoking and vaccination against hepatitis B virus could further reduce the incidence of non-AIDS malignancies in the treated HIV-1 infected population.

Table 1. **Baseline characteristics**

N		**11459**	
Gender, N (%)	**Male**	**8816**	**(77 %)**
Age, median (IQR)		**38**	**(32-45)**
Region of origin, N (%)	**W-Eur/N-Am**	**7250**	**(63 %)**
Exposure Group, N (%)	**MSM**	**6003**	**(52 %)**
	Hetero	**3958**	**(35 %)**
	IDU	**541**	**(5 %)**
Prior ART, N (%)		**2240**	**(20 %)**
Prior AIDS, N (%)		**3079**	**(27 %)**
Nadir CD4, median (IQR)	**cells/mm³**	**150**	**(55-240)**
HIV RNA, median (IQR)	**log_{10}cps/ml**	**4.9**	**(4.3-5.3)**
HCV, N (%)	**Antibody**	**561**	**(5 %)**
HBV, N (%)	**Surface antigen**	**531**	**(5 %)**
Alcohol Abuse, N (%)		**797**	**(7 %)**
Smoking status, N (%)	**Ever**	**4745 / 6701**	**(71 %)**
	Missing	**4758**	**(42 %)**

Table 2. **Characteristics of patients with NADM**

N	**232**	
Age at diagnosis, median (IQR)	**43**	**(38 - 51)**
Prior to start cART		
Prior mono/duo NRTI, N (%)	**89**	**(39 %)**
Prior AIDS, N (%)	**89**	**(39 %)**
Prior NADM , N (%)	**2**	**(0.9 %)**
6 months prior to NADM diagnosis		
CD4 (/mm³) , Median (IQR)	**340**	**(210 - 540)**
cART, N (%)	**205**	**(89 %)**
Undetectable VL, N (%)	**169**	**(75 %)**
HBV , N (%)	**17**	**(7 %)**
HCV, N (%)	**14**	**(6 %)**
Smoking, N (%)	**120**	**(77 %)**
Alcohol abuse, N (%)	**23**	**(10 %)**

Figure 1. **Multivariate Cox regression model**

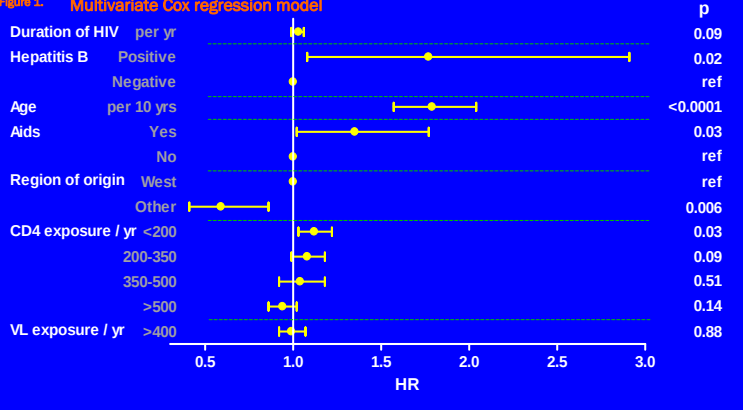

Figure 2. **Effect of immunodeficiency on malignancies due to infection-related and other causes**