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Non-AIDS defining malignancies (NADM) and immunosuppression: The D:A:D study

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on behalf of the D:A:D study group

Background

- HIV positive individuals are at higher risk of non-AIDS defining malignancies (NADMs)*
- An increased risk of some specific NADMs has been seen in those with a lower CD4 count**
- However, the independent associations between the magnitude/duration of immunosuppression, the latest HIV RNA level, and the development of NADM remain unclear

*Grulich, Lancet 2007, Powles ,JCO 2009, Shiels JAIDS 2009
**Silverberg, Cancer Epidemiol Biomarkers Prev 2011, Reekie Cancer 2010
Kesselring CID 2011, Bruyand CID 2009, Guiget Lancet Oncol 2009

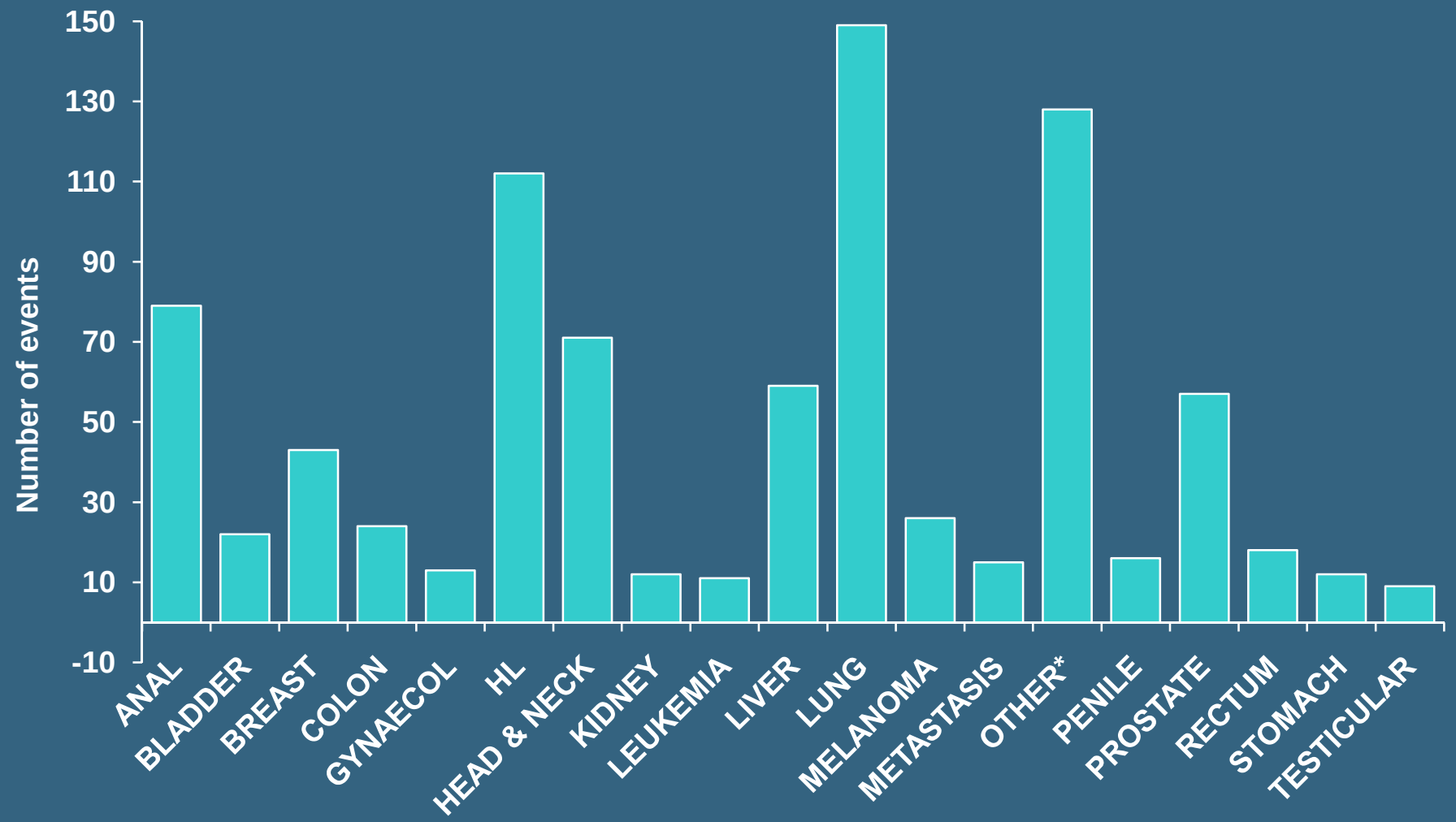
Objective

- To describe associations between the incidence rates (IR) of NADM and measures of immunosuppression and viraemia:
  - Latest CD4 count
  - Lagged CD4 count (by 6 months)
  - Nadir CD4 count
  - Time-averaged area-under-the curve (AUC) for CD4
  - Duration of immunosuppression (<100/<200 CD4 cells/mm^3)
  - Latest HIV RNA
  - AUC for HIV RNA (split into quintiles for calculating the rates)

Methods

- Information was collected on all new NADM from 1/1/2004-1/2/2010
- Events were validated centrally with information captured on cancer type/site (with data from histology report, where available)
  - NADM and ADM from before baseline was not centrally validated
- Incidence rates were calculated for NADM overall and for lung, anal and Hodgkin's lymphomas separately
- Poisson regression models were used to explore associations between each outcome and different measures of immunosuppression/HIV RNA viraemia, each modelled as a time-updated covariate

Types of NADMs and incidence



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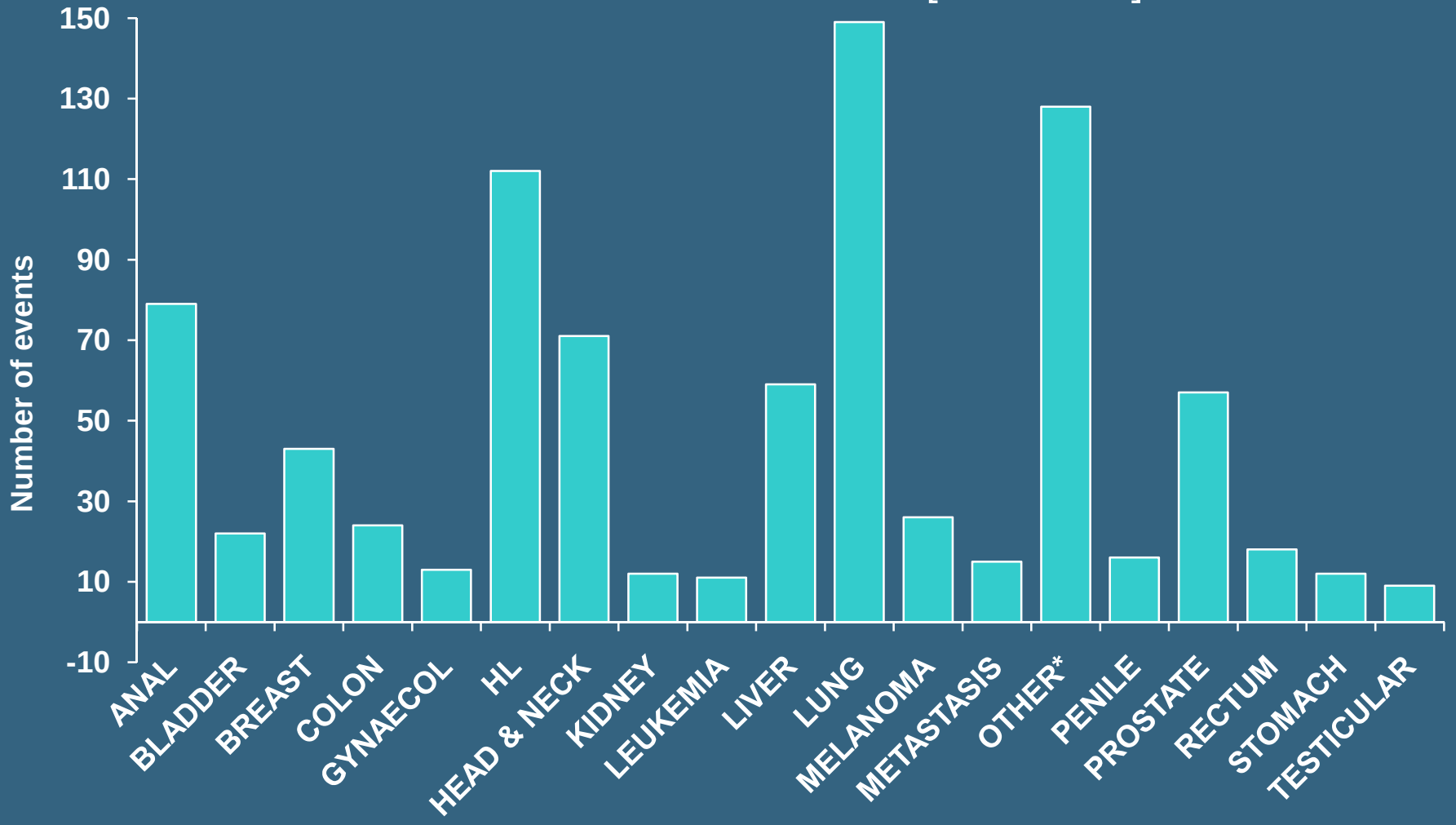
* Pancreatic cancer, esophageal cancer, gall bladder cancer

Types of NADMs and incidence

Over 176,775 person-years, 880 patients developed a new NADM
Incidence: 4.98/1000 PY, 95% CI [4.65, 5.31]



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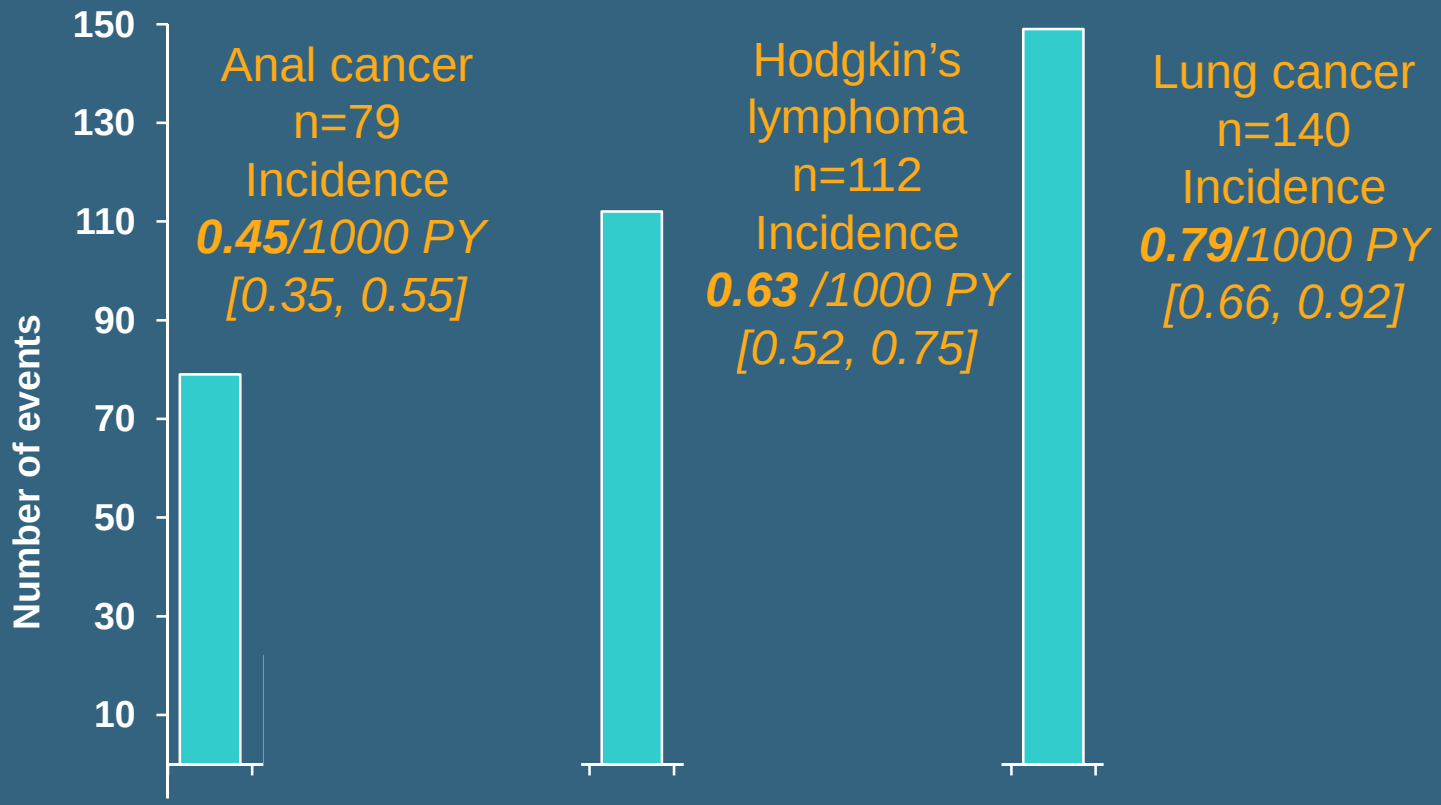
Types of NADMs and incidence

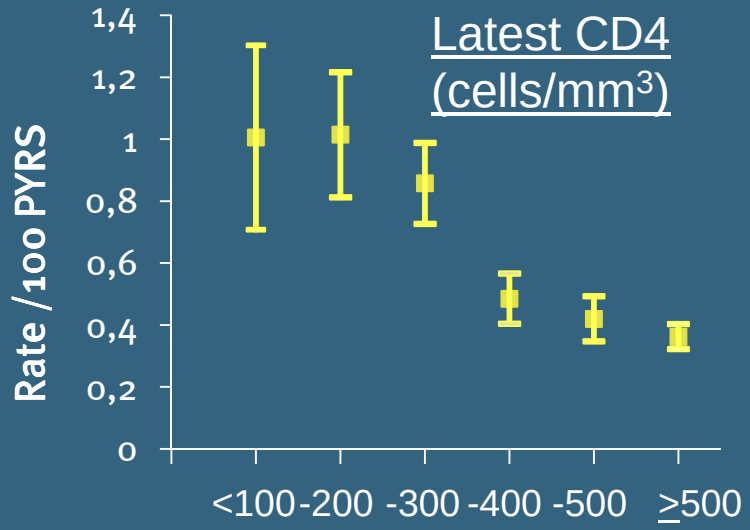


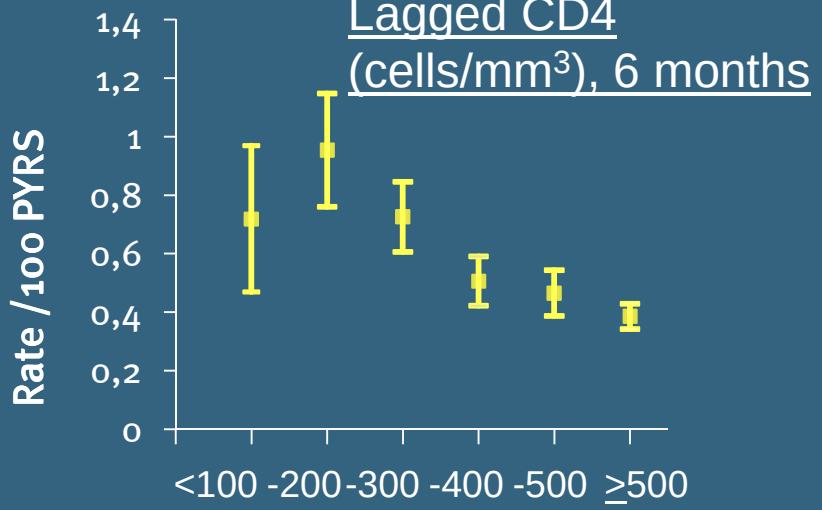
Characteristics at time of NADM diagnosis

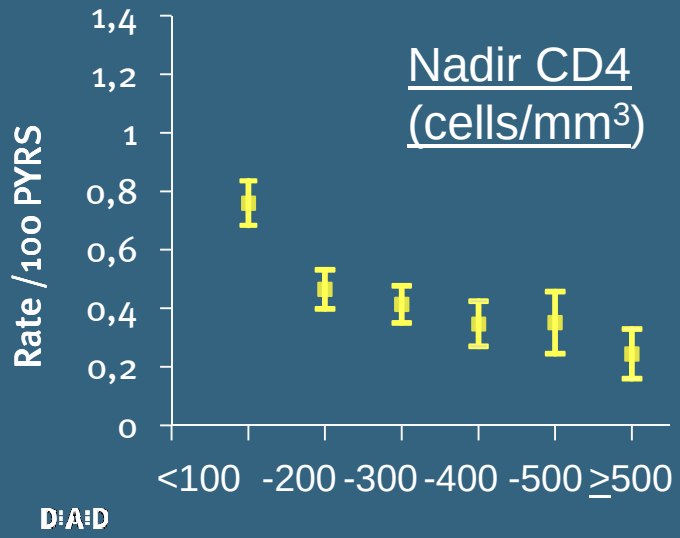
		N	% / IQR
Total number		880	100
Gender, n (%)	Male	708	80.5
Age (years)	Median (IQR)	50	44 - 59
Any use of ARV		813	92.4
CD4 count (cells/mm^3)	Median (IQR)	392	245 - 580
Nadir CD4 count (cells/m^3)	Median (IQR)	127	49 - 245
HIV RNA (log_{10} copies/ml)	Median (IQR)	1.7	1.7 - 2.4
Prior NADM, n (%)		48	5.5
Prior ADM, n (%)		91	10.3
HCV positive, n (%)*		75	8.5
HBV positive, n (%)*		55	6.3
Current smoker, n (%)		303	34.4

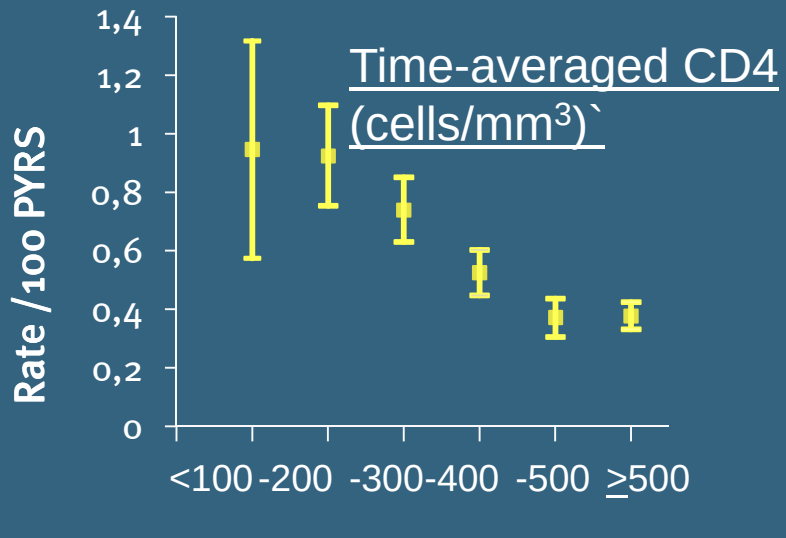
*HCV status positive: seropositive and HCV RNA positive or HCV RNA unknown; or not tested),
HBV status (positive: active infection [HB surface antigen, HB e antigen, or HBV DNA positive]; positive:

Incidence of first NADM (with 95% CI) stratified by different indicators of immunosuppression



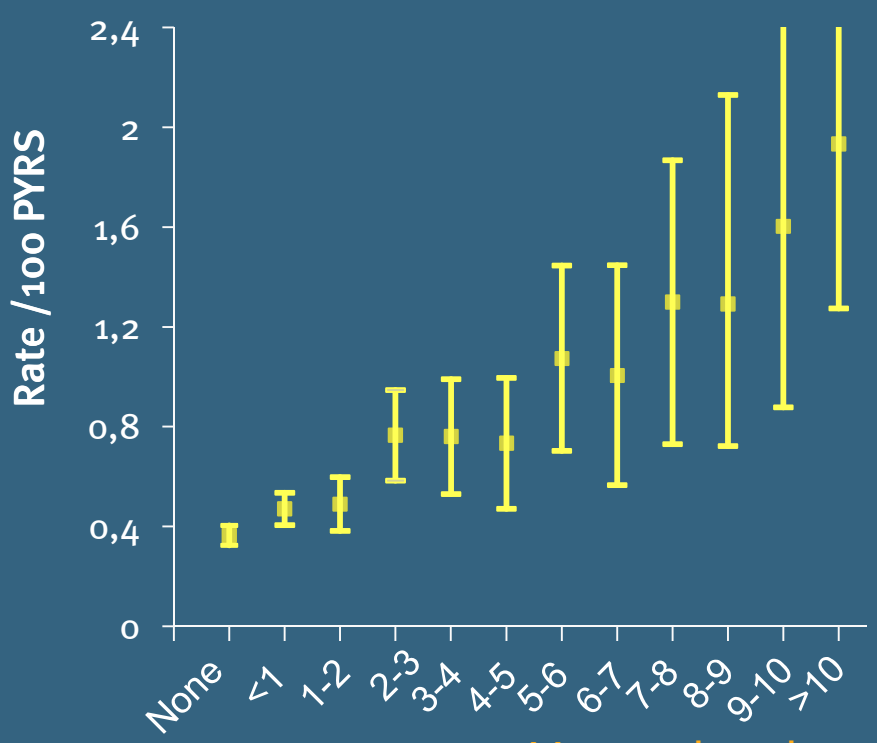






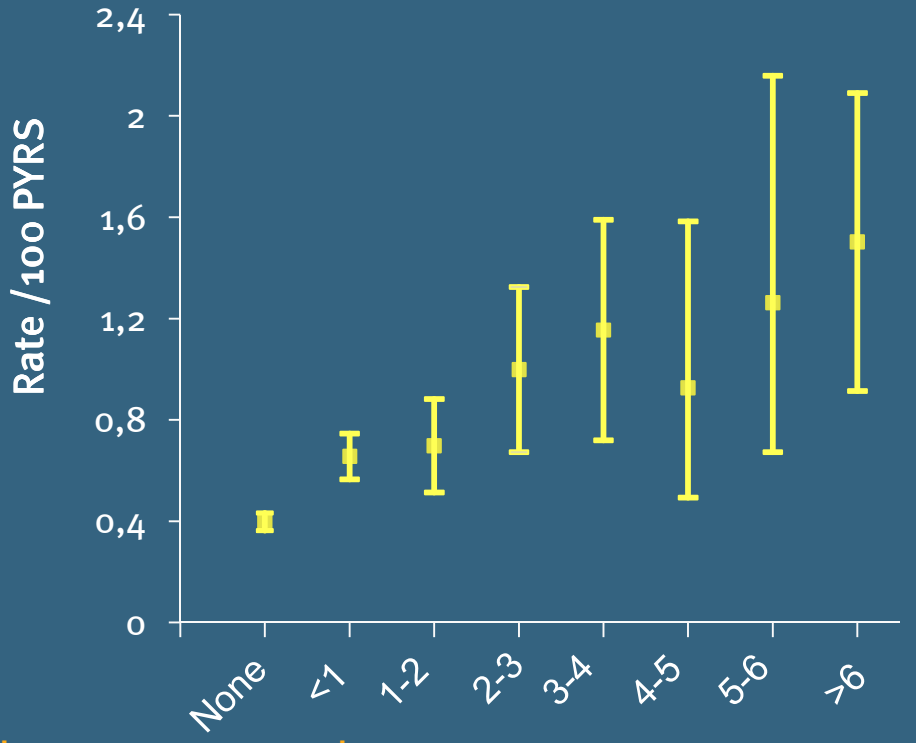
Incidence of first NADM (with 95% CI) stratified by duration of immunosuppression (years)

Cum. exposure <200 cells/mm^3



RR/ additional year:
1.05 (1.04, 1.06), p=0.0001

Cum. exposure <100 cells/mm^3



RR/ additional year:
1.05 (1.03, 1.07), p=0.0001

Years, duration of immunosupression

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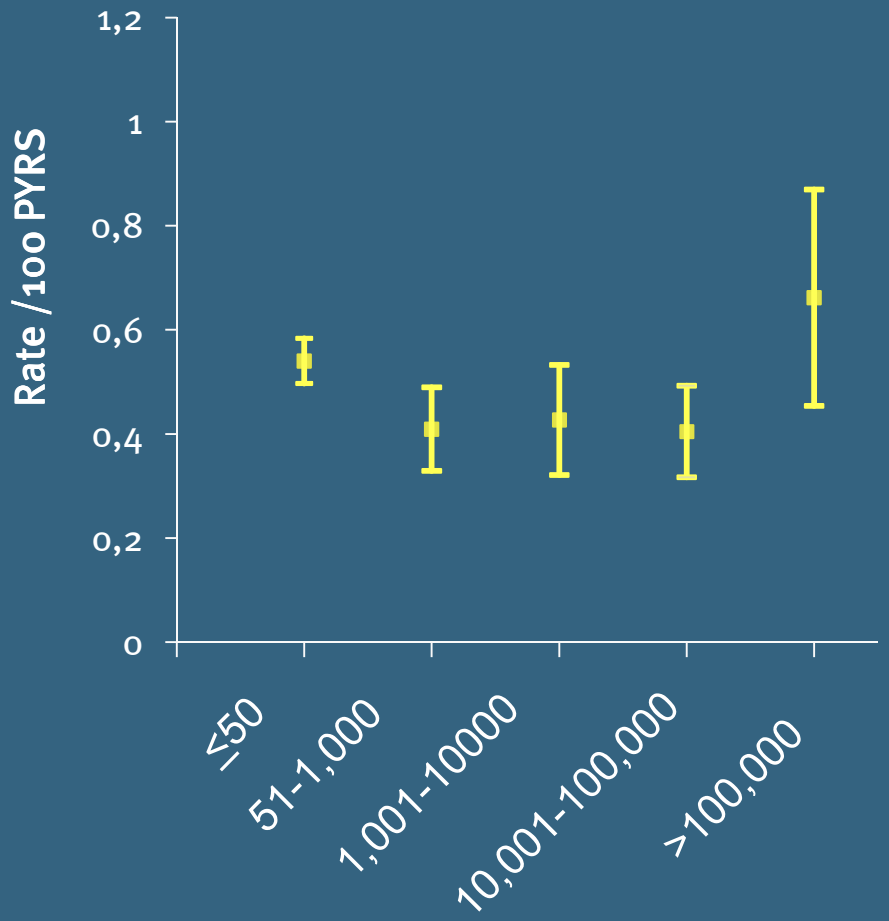
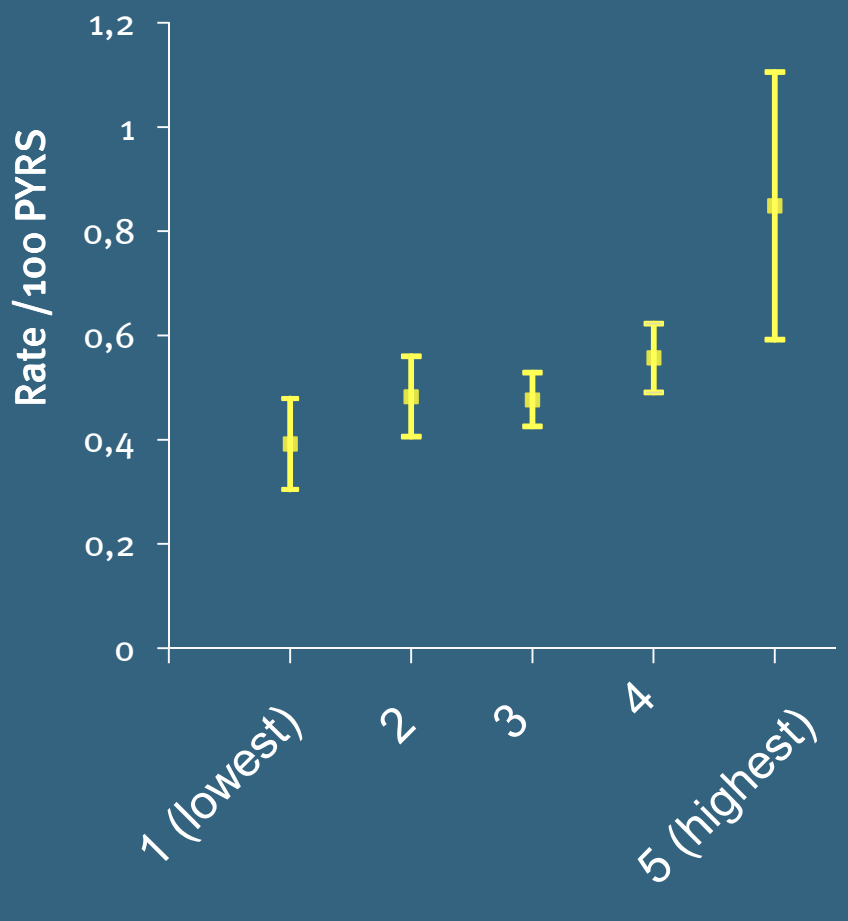
Incidence of first NADM (with 95% CI) stratified by indicators of viraemia

Latest HIV RNA



RR /log higher (log 10 copies/ml): 1.05 (0.99, 1.13), p=0.13

AUC for HIV RNA



RR /unit: 1.04 (1.00, 1.09), p=0.07

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Unadjusted associations between indicators of immunosuppression and NADM rate

Factor		RR	95% CI	P-value
Latest CD4 count	Per 50 cells/mm^3	0.96	0.94, 0.97	0.0001
Latest CD4 count 6 months ago	Per 50 cells/mm^3	0.97	0.95, 0.98	0.0001
Nadir CD4 count	Per 50 cells/mm^3	0.97	0.94, 0.99	0.01
Time-averaged CD4 count	Per 50 cells/mm^3	0.96	0.94, 0.98	0.0001

Independent associations - results from multivariable Poisson models

Factor		RR	95% CI	P-value
Latest CD4 count	Per 50 cells/mm^3	0.97	0.95, 0.98	0.0001
Nadir CD4 count	<100 cells/mm^3	1.22	1.03, 1.44	0.02
Duration of immunosuppression (<200 cells/mm^3)	Per year	1.04	1.02, 1.05	0.0001

Model also adjusted for age, sex, cohort, risk group, ethnicity, calendar year, body mass index, previous cancer, previous AIDS diagnosis, previous AIDS malignancy, HCV, HBV status as well as other immunological markers

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Analyses of specific NADM - results from multivariable Poisson models

Factor		RR	95% CI
Lung cancer (n=140)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.93**	0.89, 0.97
Hodgkin's lymphoma (n=112)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.85**	0.81, 0.89
Anal cancer (n=79)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.93**	0.89, 0.98

Models also adjusted for age, sex, MSM risk group, white ethnicity, calendar year and previous cancer

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Analyses of specific NADM - results from multivariable Poisson models

Factor		RR	95% CI
Lung cancer (n=140)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.93**	0.89, 0.97
Nadir CD4 count	<100 cells/mm^3	**1.43**	1.00, 2.04
Hodgkin's lymphoma (n=112)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.85**	0.81, 0.89
AUC RNA	Per unit higher	**1.35**	1.12, 1.63
Anal cancer (n=79)			
Latest CD4 count	Per 50 cells/mm^3 higher	**0.93**	0.89, 0.98
Duration of immunosuppression <200 cells/mm^3 / year		**1.07**	1.05, 1.08

Models also adjusted for age, sex, MSM risk group, white ethnicity, calendar year and previous cancer

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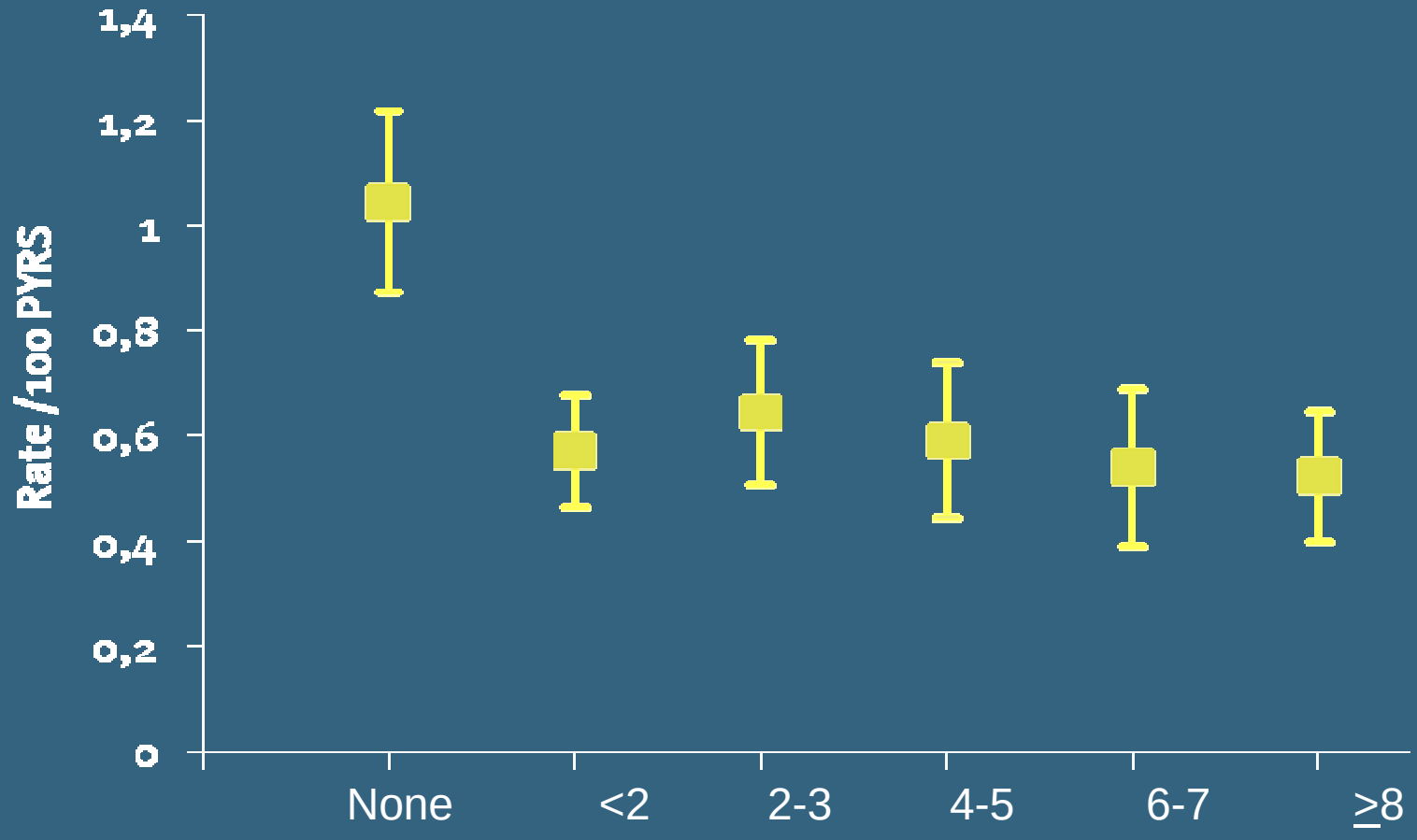
Impact of immune recovery (subgroup of patients with a prior CD4 <200 cells/mm^3)



RR per year

Before adjustment: 0.94 [0.92, 0.97], p=0.0001

After adjusting for latest CD4 count: 0.99 [0.96, 1.03], p=0.65

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Strengths and limitations

- Large dataset > 40,000 HIV positive individuals
- Events centrally evaluated, queried and classified
- Detailed data collection on several important and specific HIV-related risk factors

- Limited data on dissemination/stage of disease

Conclusions

- The risk of NADM (overall and the three most frequently observed cancers) is increased at low CD4 counts
- Whilst the risk is reduced in those who experience an increase in CD4 count (e.g. following initiation of ART), a low nadir CD4 remains associated with a persistent increase in risk
- In a subgroup of patients exploring duration of immunosuppression, data suggest that if patients recover from a prior low CD4, that nadir CD4 are no longer relevant to current risk

Conclusions

- Although exposure to HIV viraemia is associated with an increased risk of Hodgkin's lymphoma, this is not the case for anal or lung cancer
- Preventive measures should include identification and management of persons with HIV before advanced immunodeficiency has occurred
- NADM is an important differential diagnosis in patients with a low CD
  - For anal cancer, our data suggest that people at high risk with a low CD4 count should be examined

Acknowledgements

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  Additional members: N Shortman*, R Rode*, D Butcher*, B Powderly*
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