Longitudinal CD4:CD8 ratio and CD8 counts and risk of AIDS and non-AIDS defining malignancies in antiretroviral treated people with HIV: The RESPOND Cohort Consortium

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Background

- Modern antiretroviral therapy (ART) led to a major reduction in AIDS events and an increase life expectancy in people living with HIV (PLHIV)[1]
- Chronic inflammation can persist even in virally suppressed individuals and may promote the development of malignancies
- Evidence gap: **Low CD4:CD8 ratio has been proposed as proxy for inflammation[2]. Its prognostic role in terms of malignancy risk remains unclear**

Methods

Eligibility:

- Analysis within the international cohort consortium of infectious diseases (RESPOND)[3], a collaboration of 17 observational studies across Europe and Australia with more than 36,000 PLHIV
- Inclusion criteria for this analysis: ART-treated PLHIV ≥18 years; followed for a minimum of 12 months between 01.01.2012 and 31.12.2020, with CD4, CD8, and viral load measurement at baseline (the later of cohort entry and 01.01.2012)
- Exclusion criteria: pre-baseline history of malignancy and development of malignancy within the first 12 months of follow-up

Analyses:

- Cox proportional hazard models with time-dependent exposures of immunological and virological risk factors
- Time-updated variables are updated at the end of each follow-up month and missing information is extrapolated using the last observation carried forward
- Time-dependent exposures of immunological and virological risk factors are observed 12 months prior a given follow-up (12 months lagged exposures) to avoid risks of detecting associations that reflect reverse causality.

Results

Non-AIDS defining malignancy	**n**	**%**
Lung	73	11.97
Anal	60	9.84
Prostate	54	8.85
Malignant melanoma	41	6.72
Head and neck cancer	40	6.56
Bladder	32	5.25
Pancreas	31	5.08
Colorectal	26	4.26
Hodgkin lymphoma	24	3.93
Liver	24	3.93
Breast	16	2.62
Kidney	16	2.62
Gynecological	15	2.46
Rectum	12	1.97
Connective tissue	8	1.31
Penile	8	1.31
Testicular	8	1.31
Gall bladder	7	1.15
Oesophageal	6	0.98
Leukemia	6	0.98
Lip	5	0.82
Multiple myeloma	4	0.66
Brain	2	0.33
Stomach	2	0.33
Bone	1	0.16
Other/unclassified	89	14.59
Total	*610*	*100*

AIDS defining malignancy	**n**	**%**
Non-hodgkin lymphoma	73	52.52
Kapsoi sarcoma	56	40.29
Cervical	10	7.19
Total	*139*	*100*
Infection-related malignancy		
Non-hodgkin lymphoma	71	19.19
Anal	60	16.22
Kaposi sarcoma	55	14.86
Liver	24	6.49
Hodgkin lymphoma	22	5.95
Cervical	10	2.70
Penile	8	2.16
Oesophagal	6	1.62
Stomach	2	0.54
Total	*258*	*100*

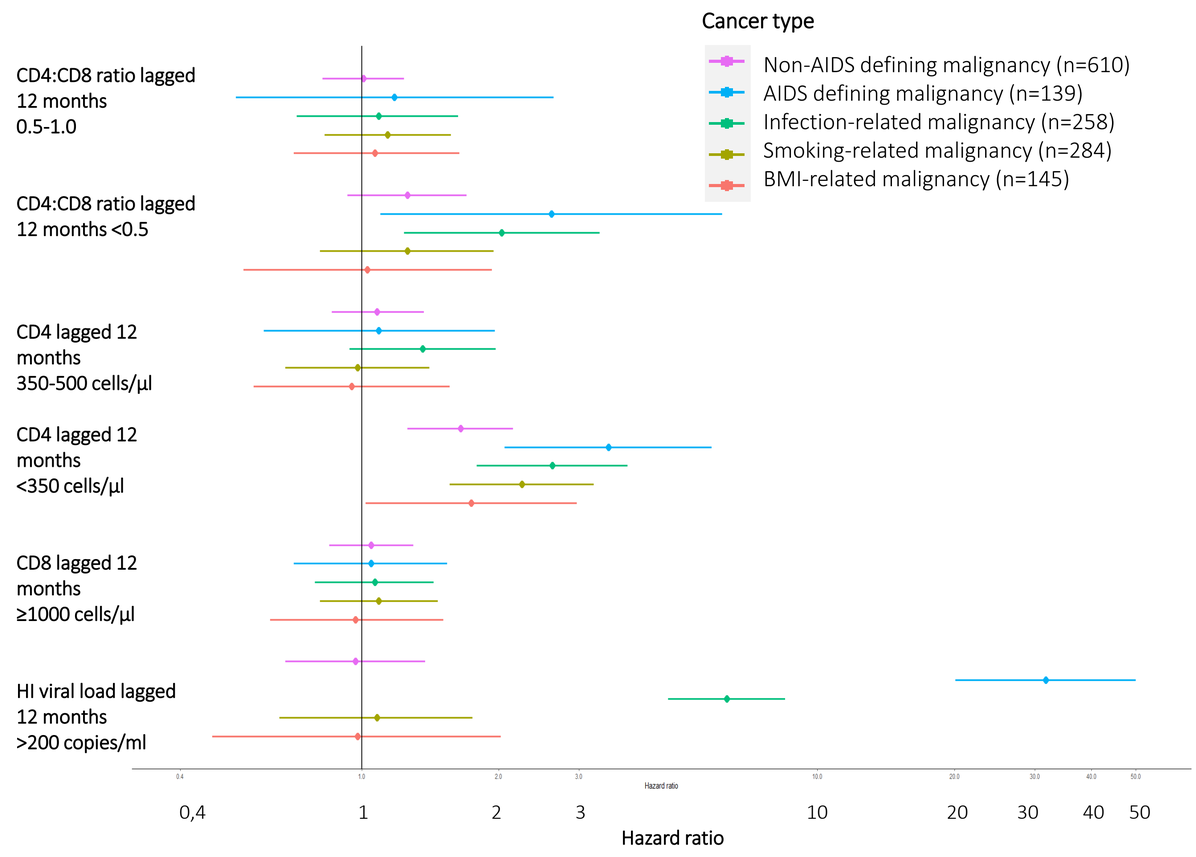
Smoking-related malignancy	**n**	**%**
Lung	78	27.46
Head & neck cancer*	37	13.03
Bladder	34	11.97
Pancreas	32	11.27
Colon	27	9.51
Liver	24	8.45
Kidney	16	5.63
Rectum	12	4.23
Cervical	10	3.52
Oesophageal	6	2.11
Lip	6	2.11
Stomach	2	0.70
Total	*284*	*100*
BMI-related malignancy	**n**	**%**
Pancreas	32	22.07
Colorectal	28	19.31
Liver	24	16.55
Breast	17	11.72
Kidney	16	11.03
Rectum	12	8.28
Gall bladder	7	4.83
Oesophageal	6	4.14
Thyroid	3	2.07
Total	*145*	*100*

*Smoking-related head & neck malignancies include oral cavity, hypopharyngeal, laryngeal, oropharyngeal, saliva gland, sino/nasal cavity and unspecified sub-types.

Table: Classification of malignancies

- A total of 19,247 PWHIV were included for analyses
- 730 PWHIV developed a first malignancy over 105,469 person-year; incidence rate (95% confidence interval (CI)): 6.92 (6.44-7.44) per 1,000 person-year.
- Non-AIDS defining malignancies are associated with low CD4 cell counts <350 cells/µl (adjusted hazard ratio (aHR): 1.65; 95% CI: 1.26-2.15)
- **AIDS-defining malignancies** are associated with viral loads ≥200 copies/ml (aHR 31.71; 95%CI 20.10-50.01), **low CD4 cell counts <350 cells/µl** (aHR 3.48; 95%CI 2.06-5.86) and low CD4:CD8 ratios <0.5 (aHR 2.61; 95%CI 1.10-6.19)
- **Infection-related malignancies** are asscociated with **low CD4 cell counts <350 cells/µl** (aHR 2.62; 95%CI 1.79-3.83), low CD4:CD8 ratios <0.5 (aHR 2.03; 95%CI 1.24-3.33) and HI viral loads ≥ 200 copies/ml (aHR 6.33; 95%CI 4.71-8.51)
- Smoking-related and Body Mass Index-related (BMI) malignancies are associated with low CD4 cell counts <350 cells/µl (aHR 2.25; 95%CI 1.56-3.23 and aHR 1.74; 95%CI 1.02-2.97, respectively)

Figure: Adjusted hazard ratios together with 95% confidence interval for non AIDS defining, AIDS defining, infection, smoking and body mass related malignancies



All models are adjusted for age, sex, mode of HIV acquisition, and ethnic group. The model for infection-related malignancy is further adjusted for baseline hepatitis C and B status. The model for smoking-related malignancy is further adjusted for 12 months lagged smoking status. Body mass-related model is adjusted for baseline body mass index.

Limitations

- No adjustment for important risk factors such as bacterial pneumonia, cytomegalovirus, human papillomavirus infection and alcohol consumption was possible
- Missclassification bias due to extrapolation of time-updated variables between follow-up visits cannot be ruled out

Conclusions

- Low CD4:CD8 ratios are related with increased risk of infection-related malignancy and AIDS-defining malignancy
- High CD4 cell counts reduce the risk of all groups of malignancy studied in this analysis
- Viral suppression is important to prevent both AIDS-defining and infection-related malignancies
- Clinical implication: Maintenance of high CD4 cell counts and viral suppression remain the key to reducing the risk of malignancies. Low CD4:CD8 ratios may inform targeted cancer screening programs and improve early diagnosis, especially for infection-related cancers

References: 1: Antiretroviral Therapy Cohort Collaboration. Lancet, 2008, 2: Bruno et al. AIDS Rev; 2017, 3: The RESPOND Study Group. Microorganisms; 2020

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