#552

Distinct Cancers Have Distinct Inflammatory Predictors in Treated HIV

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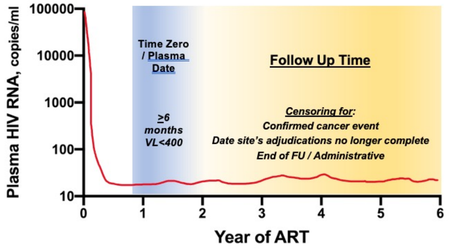
Background

- Despite ART, people with HIV (PWH) remain at higher risk for infection-related and lung cancers and lower risk for prostate cancer than the general population.
- Persistent inflammation may plausibly contribute to these risk differences, but the pathways that predict these cancers in treated HIV remain unclear.

Methods

- **Case-cohort design within CNICS network**
  - **Cohort**: 9,430 PWH identified with VL<400 c/ml for ≥ 6 months on ART and an available plasma specimen (closest to 1 year sampled).
  - **Sub-cohort**: Random sample of cohort (n=968)
  - **Cases:** All adjudicated events occurring after plasma sample sampled from cohort
    - Anal cancer
    - Lung Cancer
    - Non-Hodgkin Lymphoma
    - Prostate Cancer
- **Biomarkers** assessed by ELISA or Electro-chemiluminescence in duplicate
  - K/T ratio by LC-MS (in singlicate)
- **Analysis:** Cox proportional hazards, weighting sub-cohort observations according to sampling ratio

Case-cohort Design Schematic

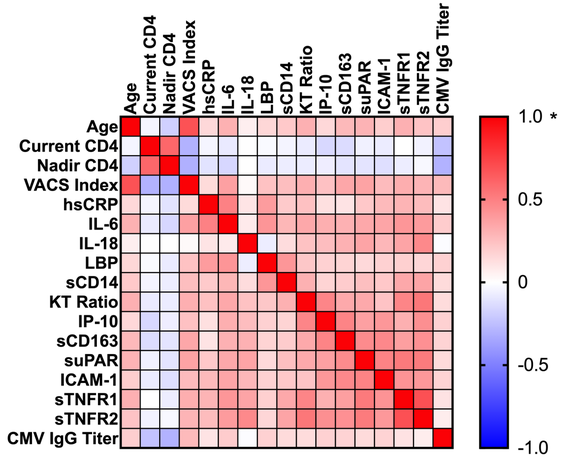


Characteristics of ART-suppressed CNICS Participants

Characteristic	Sub-Cohort N=968	Anal Cancer N=36	Lung Cancer N=37	Non-Hodgkin Lymphoma* N=19	Prostate Cancer N=36
	Median (IQR)				
Age, years	47 (39-53)	47 (43-50)	58 (50-64)	50 (43-57)	53 (50-61)
% Male natal sex	83	89	80	100	100
% Non-White Race	61	66	43	53	70
Current CD4 count, cells/mm³	573 (401-801)	426 (213-677)	523 (316-688)	341 (196-460)	632 (452-890)
Nadir CD4 count, cells/mm³	245 (81-398)	79 (14-191)	143 (69-266)	61 (27-185)	252 (56-445)
% Plasma HIV RNA <400 c/ml	100	100	100	100	100
% Ever Smoker	29	49	63	29	39
% CMV IgG+	97	100	97	82	100
VACS Index	12 (6-24)	16 (6-21)	27 (12-45)	22 (16-33)	22 (12-33)
Years Follow Up	3.8 (1.5-6.2)	3.0 (1.4-4.3)	2.5 (1.2-3.8)	1.6 (0.4-2.8)	2.9 (1.2-4.7)

*Burkitt's (n=5), PCNSL (n=2), Follicular (n=1), Large Cell (n=11)

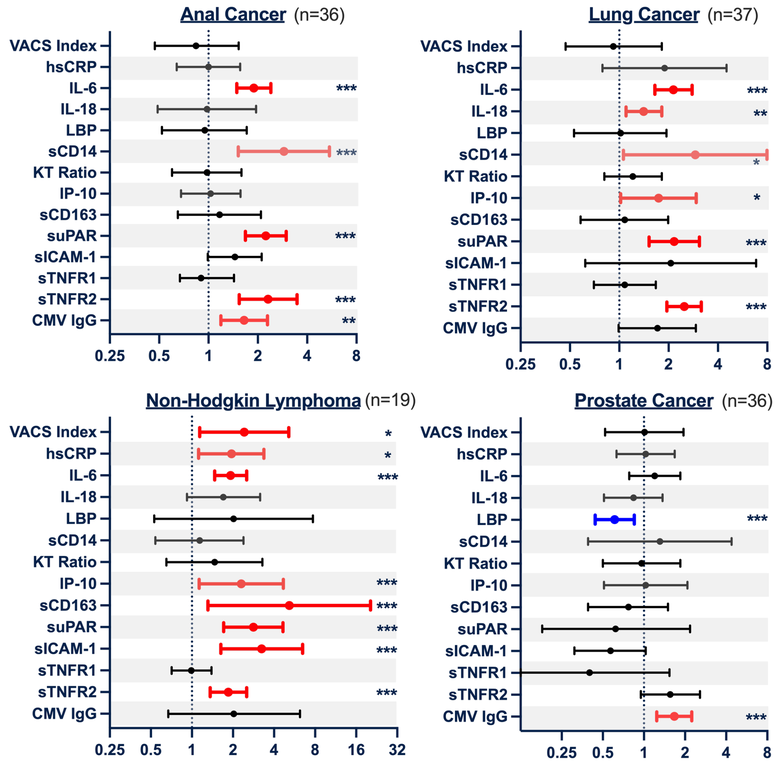
Correlations among Clinical and Immunologic Biomarkers in Sub-Cohort



*Spearman's correlation coefficients are plotted

Results

Biomarker Predictors of Non-AIDS Cancers



Adjusted Hazard Ratio per IQR increase (95% CI)

***P<0.05, **P<0.01, ***P<0.001**

Models adjusted for age, natal sex, and smoking

Principal findings from sensitivity and post-hoc analyses:
- *Most associations remained significant after CD4 count adjustment.*
- *Biomarker-NHL associations markedly attenuated when restricting to events >1y after sampling.*
- *Association between VACS index & NHL no longer significant after adjustment for either sTNFR2 or IL-6.*
- *Higher sCD14 and CMV IgG titers were more strongly associated with increased prostate cancer risk after adjustment for LPS binding protein.*

Conclusions / Implications

- **Inflammatory markers (particularly suPAR) generally predicted cancers that are increased in HIV, but not prostate cancer.**
  - *Consistent with inflammation as a potential mechanism explaining HIV-associated cancer risk.*
- **Distinct Non-AIDS cancers have distinct immunologic predictors in treated HIV.**
  - *Interventions targeting discrete inflammatory pathways may affect risks of some cancers more than others.*
- **Inflammatory markers were more consistent predictors of cancer than VACS index.**
  - *VACS index may not reflect the specific pathways that affect risk of many non-AIDS cancers in treated HIV.*
- **CMV IgG titer tended to predict most cancers.**
  - *Consistent with CMV playing a role in cancer risk among PWH (Hodowanec, Path Imm, 2019)*
- **Higher LPS binding protein (LBP) predicted a decreased prostate cancer risk in treated HIV.**
  - *Consistent with established effects of LPS in suppressing testosterone levels in healthy men (Tremellen, Am J Physiol Endocrin Metb, 2017)*
  - *May explain why prostate cancer is decreased in HIV*

This work was supported by P30CA082103-21S5, P30AI027763, K24AI145806, R01HL126538, R24AI067039, R01DK112304, R56HL160457.