Soluble Immunoregulatory Proteins Predictive for Comorbid Events in People with HIV

Thomas A. Premeaux[1], Scott Bowler[1], Courtney M. Friday[1], Carlee B. Moser[2], Alan L. Landay[3], Sara Gianella[4], and Lishomwa C. Ndhlovu[1];
for the AIDS Clinical Trials Group NWCS 411 study Team

1. Department of Medicine, Division of Infectious Disease, Weill Cornell Medicine, New York, NY 2. Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA
3. Department of Internal Medicine, Rush University Medical Center, Chicago, IL 4. Department of Medicine, University of California San Diego, CA

691

1 BACKGROUND

Despite anti-retroviral therapy (ART), people with HIV (PWH) still experience an **increased risk for non-AIDS age-related comorbid complications**, including **cardiovascular events and non-AIDS-defining cancers**, compared to the general population.[1,2] Evidence suggests that **chronic immune activation and dysfunction may be key drivers** for this increased risk of HIV-associated co-morbidities.[3] However, biomarkers of inflammation and immune dysfunction have not been implemented in routine clinical care and chronic immune dysfunction remains an elusive target. We previously identified that several soluble immunoregulatory proteins associated with diminished lymphocyte effector function are predictive of comorbid outcomes in PWH. Using a unique panel of soluble immunoregulatory proteins and a nested case-control study from the AIDS Clinical Trials Group ALLRT cohort, we aimed to identify additional predictors of comorbid events to **improve biomarker delineation** that may, in conjunction, contribute to driving disease progression.

2 APPROACH

- Study participants were evaluated at one-year post-ART at viral suppression and immediately preceding a comorbid event. Cases experienced a myocardial infarction (MI)/stroke event or cancer development. Controls were matched for age, sex, pre-ART CD4$^+$ T cell count, ART regimen at 1 year, and parent study.
- A **novel and expansive soluble immunoregulatory multiplex panel** was developed and measured by Luminex.
- Conditional logistic regression analysis assessed biomarkers as predictors for comorbid events at each timepoint. Regression for CD4 counts at year 1 and pre-event; noteworthy associations used a threshold of an effect size (odds ratio (OR) per 1 IQR) ≥1.5.
- **Machine modeling** with recursive feature elimination selection was used to assess models. Area under the curve of the receiver characteristic (AUC-ROC) were used to measure model accuracy. Models containing previously acquired biomarker measurements were compared to integrated models with newly ran immunoregulatory proteins.

3 RESULTS

3.1 Cohort Demographic and Clinical Data

Characteristic	Case	Control	Total
n	76	153	229
Age	48 [41-57]	45 [39-52]	46 [40-53]
Sex			
Male	43 (56.6%)	89 (58.2%)	132 (57.6%)
Female	33 (43.4%)	64 (41.8%)	97 (42.4%)
Race/Ethnicity			
White Non-Hispanic	54 (71.1%)	98 (64.1%)	152 (66.4%)
Black Non-Hispanic	16 (21.1%)	27 (17.6%)	43 (18.8%)
Hispanic (regardless of race)	6 (7.9%)	24 (15.7%)	30 (13.1%)
Other	0	4 (2.6)	4 (1.7%)
CD4+ T cell count (cells/μL)	225 [92-344]	236 [85-344]	228 [87-344]
log_{10} HIV-1 RNA (copies/mL)	4.7 (4.0-5.2)	4.7 (4.2-5.1)	4.7 (4.1-5.1)
Time to Event			
1-year post-ART to event (yrs)	2.8 (1.7-4.6)	-	-
Pre-event visit to event (wks)	10.5 (6.0-19.0)	-	-

*1 year pre-ART values

3.2 Unique Panel of Circulating Immunoregulatory Proteins in Predicting Comorbid Events

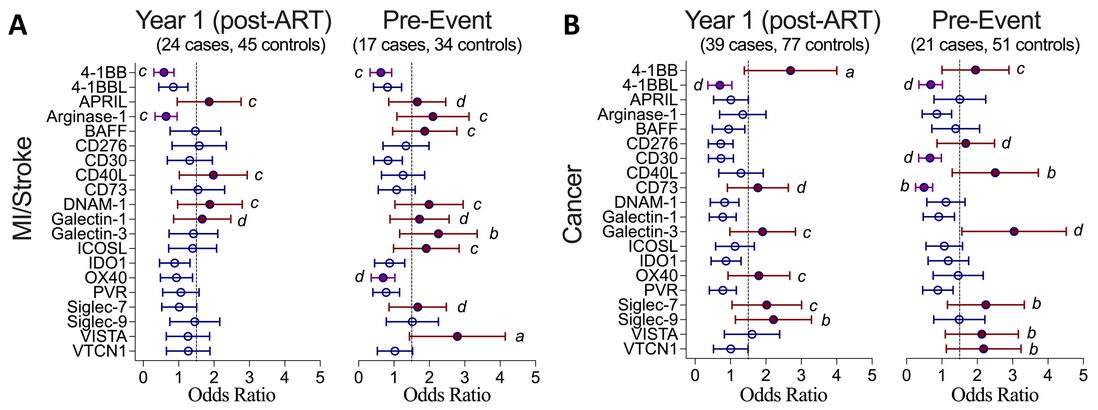

Figure 1. Soluble Immunoregulatory protein predictors of MI/stroke (A) or cancer (B) at year 1 and pre-event timepoints. Conditional logistic regression models adjusted for CD4 counts. [a]P<0.001, [b]P<0.01, [c]P<0.05, [d]P<0.1. MI=myocardial infarction.

3.3 Parameters for Machine Modeling

Demographics	Lymphocyte Activation		Microbial Translocation	
Age	**4-1BB**	**CD73**	I-FABP	BDG
Sex	**4-1BBL**	**VTCN1**	LBP	
Race/Ethnicity	**APRIL**	**VISTA**		
	BAFF	**CD276**	**Coagulopathy**	
Covariates	**CD30**	**IDO1**	D-dimer	
Chronic Hep B/C	**CD40L**	**OX40**		
Smoking Status	CD40	**ICOSL**	**Lectin Pathways**	
History of diabetes	GITR	ICOS	**Galectin-1**	**Siglec-7**
	GITRL	CD28	**Galectin-3**	**Siglec-9**
Inflammation	CD80	HVEM	Galectin-9	
IL-6 TNFR-I	CD86	BTLA		
TLR-2 TNFR-II	CD27		**Cardiovascular**	
			ST2	
Myeloid Activation	**Negative Checkpoints**		oxLDL	
Arginase-1 sCD163	**PVR**	TIM-3		
sCD14 suPAR	LAG3	PDL1		**Newly ran markers in bold**
IP-10	PD1	CTLA-4		

3.4 Improved Predictive Models for Comorbid Events

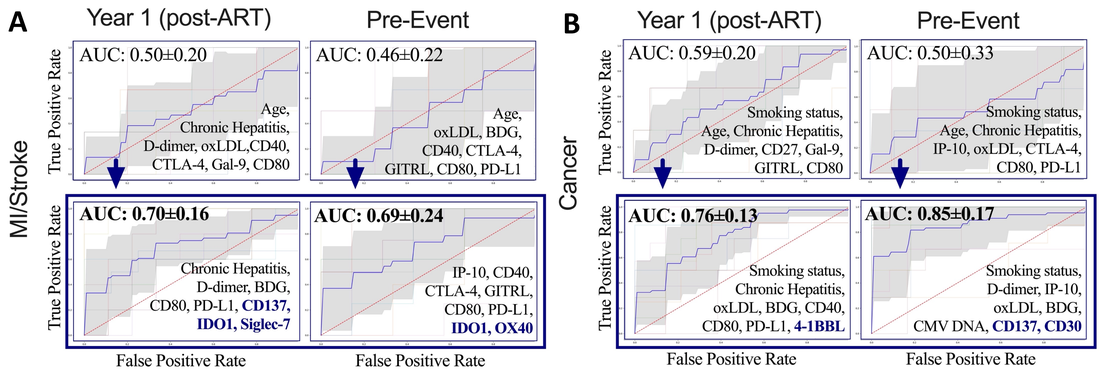

Figure 2. Support vector machine modeling of composite predictors of MI/stroke (A) or cancer (B) at year 1 and pre-event timepoints. Model parameters are listed (lower right corner) for each ROC; **inclusion of newly measured biomarkers in bold (bottom graphs)**. Blue line=mean ROC; Light grey area = ±1 standard deviation; red dotted line=chance.

4 CONCLUSIONS

- Higher levels of APRIL, CD226, and Gal-1 were significantly associated with MI/stroke at year 1 and pre-event timepoints
- Higher levels of CD137, Gal-3, and Siglec-7 were significantly associated with cancer at both timepoints
- Machine learning-based modeling showed an improvement in case classification accuracy with the inclusion of newly measured biomarkers in identifying PWH who at year 1 and pre-event would develop MI/stroke or malignancy.

We provide improved insight on immunoregulatory proteins and composite models that emerge predictive of cardiovascular and cancer events in PWH on ART

- Future directions: Single/composite predictors will be validated in test cohorts and evaluated for their efficacy in determining CVD progression and specific cancers.

5 REFERENCES

1. Deeks SG, Tracey R, & Douek DC. *Immunity* 2013, 39:633-645. **2.** Giovanni G. *et al. Clinical Infectious Diseases* 2011, 53:1120-1126. **3.** Duffau P. *AIDS* 2015, 29:2099-2108. **4.** Premeaux TA, et al. *Open Forum Infect. Dis.* 2022, 9:3 ofab570.

6 ACKNOWLEDGEMENTS

This work was supported by the National Institute of Health grants R01MH112457 (LCN), R01AI147821 (SG), DA051915 (SG), and UM1AI068634 (CBM). Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.