Age Modifies the Association Between Sex and the Plasma Inflammatory Proteome in Treated HIV

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BACKGROUND

- Women with HIV have higher immune activation when compared to men with HIV, even when suppressed on antiretroviral therapy (ART).
- Prior work in CNICS found age played an important role in immune activation, with women above 47 years demonstrating increases in immune activation.
- Objective: determine whether there are sex differences in the plasma inflammatory proteome in people with HIV (PWH) and if the effects of sex are modified by age.

METHODS

- Analyzed 363 unique plasma proteins (Olink Inflammation Explore panel) in a randomly sampled sub-cohort of ART-suppressed adult CNICS participants.
- Assessed the relationship between natal sex and plasma proteins with linear regression adjusting for age, nadir CD4, site, race, MSM status, clinical factors (smoking, injection drug use, HCV Ab+, ASCVD risk score).
- Models were then stratified by the median age of 47.
- Mortality was assessed separately using Cox proportional hazard models adjusted for VACS index and site.
- Sex*protein interaction terms for mortality were calculated.
- P-values were adjusted for multiple comparisons by controlling for the false discovery rate (FDR) using the Benjamini-Hochberg method.

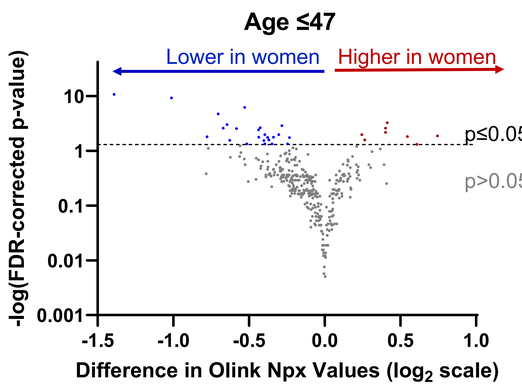
RESULTS

- Of the 968 participants sampled, 103 died over a median follow-up of 9 years.
- There was evidence of sex differences in 39 (10.7%) inflammatory proteins after FDR correction:

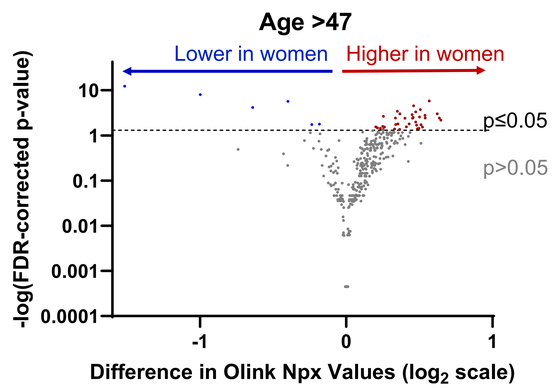
PSPN	ITGB6	ROBO1	CCL22	CD70
PROK1	HSD11B1	FLT3LG	FSTL3	CD22
GAL	ICAM4	LGALS9	COLECL12	IL6
ENPP5	DNER	PLAUR	ISM1	IL1RN
NPPC	KYNU	TNFRSF4	TNFRSF11A	EPO
LHPP	LRRN1	CD83	TREM2	MATN2
SMPDL3A	WFIKKN2	IL1RL2	IL12B	TNFRSF11B
IL17RB	PSMG3	CNTNAP2	CSF3	

[Lower in women. Higher in women]

Figure 1: Women with HIV Have Higher Inflammation than Men with HIV, Particularly at Older Ages



PSPN	ENPP5**	ICAM4	ISM1
PROK1	PKLR	IL17RB	EPO
SH2D1A	FABP9	SMPDL3A	IL1RL2
NPPC	DNPH1	KYNU	CD70
LHPP	ADA	ITGB6*	COLEC12*
GAL	GMPR	DNER	CSF3
PIK3AP1*	SIT1	CCL11*	FLT3LG
PSMG3	IL32	MERTK*	IL6*



PSPN	IL18R1*	TNFRSF11A*	CNTNAP2	CLEC7A*	IL12B
PROK1	LAMA4	TNFRSF11B*	CD83*	FSTL3*	IL1RN*
GAL	HGF*	CCL7*	TNFRSF4*	CCL22	CD22**
ENPP5**	ROBO1	NCR1*	CD70	CD79B*	TFF2*
ITGB6*	SPON1*	ISM1	COLEC12*	CD160*	CXCL10
DNER	KLRB1*	GZMA	CXCL9*	COL9A1	PLAUR*
MATN2*	LGALS9*	FCRL6	IL6*	TREM2*	CD48*

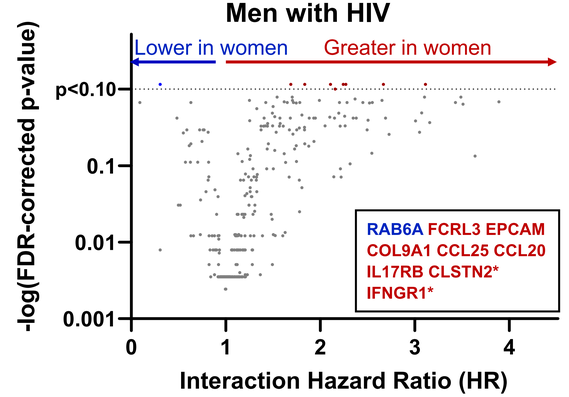
*Associated with higher mortality. **Associated with lower mortality. Lower in women. Higher in women.

Among ART-suppressed PWH, women have more inflammation than men, particularly at older ages. Many of these inflammatory proteins are associated with higher mortality.

Median or N (%)	Overall	Women	Men
N	968	169	799
Age (years)	47	47	47
Race			
White	379 (39)	28 (17)	351 (44)
Black	447 (46)	130 (77)	317 (40)
Hispanic	108 (11)	7 (4)	101 (13)
Other	34 (3.5)	4 (2)	30 (4)
BMI (kg/m^2)	26.1	30.3	25.8
CD4 Nadir (cells/mL^3)	245	244	245
ASCVD (%)	4.5	3.1	4.5
Hepatitis C Ab+	163 (17)	34 (20)	129 (16)
Ever Smoker	278 (29)	62 (37)	216 (27)
Ever IDU	166 (17)	29 (17)	137 (17)

Table: Demographic and clinical characteristics of sub-cohort

Figure 2: Relationship Between Inflammation and Mortality Tends to be Stronger in Women than in Men with HIV



(the HR for the sex-by-protein interaction term)

*Associated with overall higher mortality. Lower in women. Greater in women.

Inflammation tends to predict mortality more strongly in women than in men.

CONCLUSIONS

- Among people with ART-suppressed HIV, women have more inflammation than men, primarily at older ages.
- Many of the proteins that were elevated in midlife women with HIV are associated with mortality.
- May suggest a mechanism to explain the loss of "female advantage" in life expectancy in PWH.
- Whether menopause, which occurs around age 47 in women with HIV, is responsible for exacerbating these sex differences, requires further study.

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