SYSTEMIC AND VASCULAR INFLAMMATION PREDICT COMORBIDITIES IN TREATED HIV INFECTION

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Introduction

Although inflammation and immune dysfunction are implicated in the pathogenesis of comorbidities in people with HIV (PWH), whether an immune risk profile can predict PWH at higher risk of comorbidities is unclear.

Objectives

To determine if inflammatory profiles comprised of biomarkers reflecting different inflammatory pathways predict co-morbidities in treated PWH

Methods

In the UCD Infectious Diseases Cohort Study of PWH on antiretroviral therapy (ART), we measured 23 biomarkers using bead-based quantitative ELISA on the Luminex Magpix platform (Table 1)

Table 1: Custom Multiplex Biomarker panel*

Biomarkers functional group	Biomarkers analysed
Systemic inflammation	hsCRP, IL-2, IL-6, TNFR1, TNFR2, TNF-α, IFN-G
Coagulation	vWF, D-dimer, sCD40L
Endothelial function	E-selectin, P-selectin, sICAM-1, VCAM
Atherosclerosis	MPO, Lp-PLA2
Immune regulation	IL-1RA
Innate immune activation	MIP-1α, MCP-1, sCD163, sCD14
Microbial translocation	IL-18, LBP

***MCP, Monocyte Chemoattractant Protein ; MIP-1, Monocyte Inflammatory Protein-1; MPO, myeloperoxidase, LpPLA2, Lipoprotein associated Phospholipase A2; vWF, von Willabrand Factor; LBP, lipopolysaccharide binding protein; PD-L1, Programmed Death Ligand-1; IL, Interleukin; RA, receptor antagonisit**

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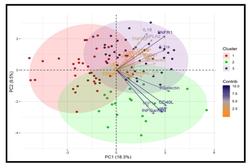
Methods Continued

Principal component analysis (PCA) was performed followed by unsupervised hierarchical clustering (HC) to partition subjects into biomarker-derived clusters.
Differences between cluster demographics was assessed using Chi-Square and Kruskal Wallis tests.
Logistic regression was used to assess associations between clusters and prevalent comorbidities [cardiovascular (CVD), kidney (CKD), liver disease (CLD), hypertension (HTN), dyslipidemia (DysL)).
Analysis was performed using SPSS ver.24 and R vers.3.6.

Results

99 PWH were included in the analysis, median age 41 (36.8, 48.0) years, 44.5% male; 54.5% African; 18.8% MSM and 8% PWID.
37 subjects had a history of comorbidities (CVD, n=5; CKD, n=2; CLD, n=15; HTN, n=20; DM, n=6) while 10 had multimorbidity.

Figure 1: Hierarchical Clustering based on PCA

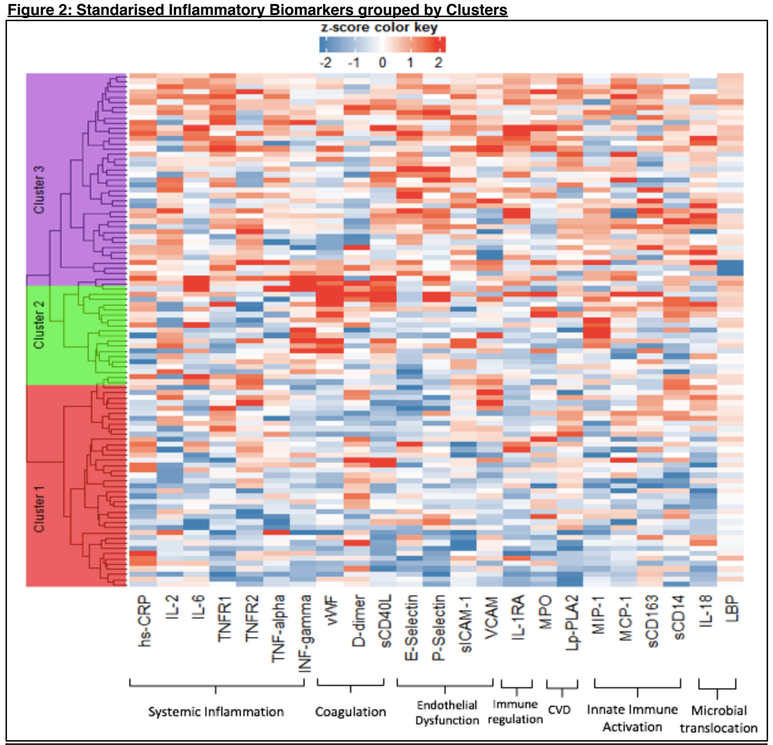


Following PCA and unsupervised HC three distinct clusters were identified (Figure 1)

Cluster 1 (n=35) was characterized by low levels of inflammation while cluster 2 by higher inflammation reflecting platelet/macrophage pathways and cluster 3, systemic, vascular and endothelial pathways (figure 2).

Subjects in Cluster 3 were more likely older, male and non-African while other demographics did not differ significantly between clusters (Table 2)
Prevalence of comorbidities was higher in cluster 2 [n= 8, (42%)] and 3 [n=22 (48.9%)] compared to cluster 1 [n= 7 (20%)], p=0.027.

Figure 2: Standarised Inflammatory Biomarkers grouped by Clusters



Cluster Characterization by Quantitative variable analysis (v-test)

Contribution Rank *	Cluster 1	Cluster 2	Cluster 3
1	Low MIP-1	High vWF	High E-Selectin
2	Low CD40-L	High IFN Gamma	High TNF R1
3	Low P-Selectin	High CD40 L	High IL 18
4	Low TNFR1	High MIP-1	High IL1-RA
5	Low E-Selectin		High s-ICAM1

Results Continued

Table 2: Demographics of Study Cohort

	Cluster 1	Cluster 2	Cluster 3	P value
N	35	19	45	
Age (IQR)	40.7 (37.6, 47.9)	40.4 (34.9, 44.5)	44.3 (39.1, 49.3)	**0.047**
Male	10 (22.7%)	8 (18.2)	26 (59.1%)	**0.032**
African	26 (74.0%)	14 (73.7%)	14 (31.1%)	**0.001**
Transmission risk				0.343
Heterosex	23 (65.7%)	13 (68.4%)	27 (60.0%)	
MSM	6 (17.1%)	2 (10.5%)	10 (22.2%)	
Smoking	6 (17.1%)	4 (21.1%)	12 (26.7%)	0.591
Nadir CD4+ count	364 (230, 526)	332 (269, 427)	363 (181, 506)	0.798
CD4/CD8 ratio	0.8 (0.5, 1.1)	0.9 (0.7. 1.3)	0.9 (0.7, 1.2)	0.353
ART duration	4.8 (1.5, 10.8)	8.2 (2.5, 10.7)	7.49 (3.7, 11.6)	0.218
CMV IgG positive	31 (88.6%)	17 (89.4%)	37 (82.3%)	0.57
HCV Ab pos.	4 (11.4%)	1 (11.1%)	8 (17.8%)	0.373
HIV RNA <40 copies/ml	34 (97.0%)	18 (94.5%)	41 (91.0%)	0.526

Cluster 3, characterized by high levels of systemic and vascular inflammation was significantly associated with prevalent comorbidities (OR 3.1 [1.09, 8.28] in logistic regression models.
Adjusting for CD4:CD8 ratio, CMV seropositivity and smoking Cluster 3 remained significantly associated with comorbidities.

Cluster 1, characterized by lower vascular, innate immune and systemic inflammation was associated with reduced risk of comorbidities (OR 0.28 [0.10, 0.74])
This association persisted after adjustment for CD4/CD8 ratio, smoking status and CMV serostatus (OR (95%CI): 0.31[0.11, 0.86] p=0.025) and again for age, gender and ethnicity (OR 0.32 [0.11, 0.90], p=0.03).

Conclusion

We have identified distinct inflammatory patterns in treated PWH that predict both enhanced and reduced risk of prevalent comorbidities.
That this association persists after adjustment for known modulators of comorbidity risk suggests alternate inflammatory pathways contributing to comorbidity pathogenesis in treat PWH
Further work is needed to examine this analytic approach in a larger cohort and assess utility of this method in prospective studies in identifying PWH at risk of comorbidities