Inflammatory and Microbial Signatures Linked to Cardiovascular Disease Outcomes in People With and without HIV

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BACKGROUND

Chronic inflammation in people with HIV (PWH) is linked to long-term co-morbidities such as cardiovascular disease (CVD). We previously described distinct inflammatory profiles from 24 biomarkers, linked to gut and T-cell inflammation, that were associated with CVD.

This study aimed to validate these 24 biomarker associations in independent cohorts and to assess if additional biomarkers or gut microbiome signatures could potentially enhance CVD prediction in PWH.

METHODS

PWH and HIV-negative participants from three cohort studies were included[1]. 55 inflammatory biomarkers were measured using ELISA (Luminex) and chemiluminescence (MesoScale Devices).

Principal component analysis (PCA) and hierarchical clustering (HC) was performed on the original 24 biomarkers. A recursive feature addition (RFA) model was used to assess the stepwise addition of 31 additional biomarkers, selecting those that enhanced the model for repeat PCA and HC. Multinomial logistic regression explored associations between clusters and CVD outcomes.

Microbiota composition was analysed by 16S rRNA amplicon sequencing of stool samples, with differentially abundant (DA) species between clusters identified by Analysis of Compositions of Microbiomes with Bias Correction (ANCOM-BC) and correlated to biomarkers using Spearman correlation.

Distinct inflammatory profiles in people with and without HIV are strongly linked to CVD, and *integrating additional* biomarkers and gut microbiome signatures improves CVD prediction.

RESULTS

408 participants (median age 50 [IQR] 43–58) years; 83% male; 68% White; 78% PWH) were included. PCA of the baseline 24 biomarkers revealed 3 clusters. Cluster 3 showed higher inflammation markers (IL1-β, IL-6, TNF-α), immune regulation (TSLP, MIP1-α), and T-cell differentiation (IL2, IL12, IFN-γ). After RFA, 13 of the 31 additional biomarkers were added to the PCA (yellow stars, Fig 1) and showed a stronger association with CVD (Fig 2).

Table 1.

	Cluster 1, N = 192[1]	**Cluster 2**, N = 178[1]	**Cluster 3**, N = 38[1]	**p-value**[2]
Age	49 (38, 56)	51 (45, 60)	54 (47, 56)	0.011
Sex, Male	156 (82%)	148 (83%)	33 (87%)	0.78
Race, white	120 (63%)	125 (70%)	30 (81%)	0.23
MSM practice	123 (68%)	109 (66%)	19 (66%)	0.95
BMI	25.6 (23.4, 29.1)	26.5 (23.2, 29.7)	27.2 (24.3, 28.8)	0.29
Diabetes	9 (4.7%)	19 (11%)	1 (2.6%)	0.058
Dyslipidemia	78 (41%)	84 (47%)	15 (39%)	0.43
History of CVD	54 (28%)	64 (36%)	18 (47%)	0.044
CVD parameters				
Total Cholesterol, mmol/L	5.03 (4.40, 5.71)	4.90 (4.10, 5.50)	5.05 (4.23, 5.70)	0.27
LDL, mmol/L	3.00 (2.31, 3.60)	2.80 (2.10, 3.35)	3.00 (2.37, 3.59)	0.12
HDL, mmol/L	1.33 (1.04, 1.56)	1.22 (1.04, 1.45)	1.20 (0.98, 1.42)	0.035
Triglycerides, mmol/L	1.21 (0.90, 1.80)	1.52 (1.00, 2.20)	1.82 (1.21, 2.51)	0.001
HIV Parameters				
HIV Positive	145 (76%)	148 (83%)	25 (66%)	0.035
ART Duration, yrs	10 (6, 15)	11 (6, 17)	13 (5, 21)	0.15
CD4 Count cells/mm³	623 (483, 822)	606 (475, 788)	599 (527, 767)	0.66

HDL, high density lipoprotein; LDL, low density lipoprotein;. [1]Median (IQR); n (%), [2]Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test

Figure 1.

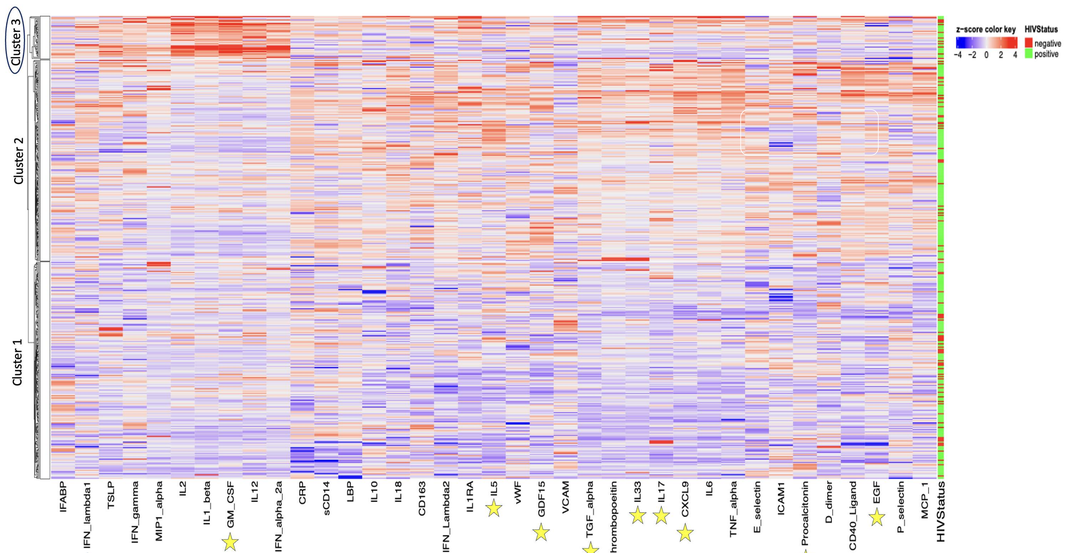
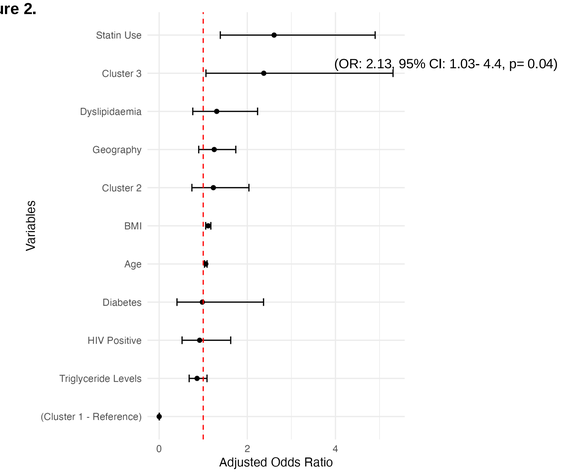


Figure 2.



ANCOM-BC revealed enrichment of 5 and depletion of 7 gut microbial species in cluster 3. Correlation analysis found several biomarkers identified in cluster 3 (IFN-λ2, MIP-1 α, MCP-1, CD40-ligand, TGF-α) associated with a depletion of short-chain fatty acid- producing species (*Bacteroides coprocola, Bacteroides massiliensis, Fusobacterium mortiferum and Dialister invisus*) that are linked to inflammation regulation and CVD outcomes.

CONCLUSIONS

Distinct inflammatory clusters, enhanced by RFA modelling are associated with CVD parameters and altered gut microbiome signatures.

ADDITIONAL KEY INFORMATION

1. The All-Ireland Infectious Diseases Cohort (AIID), the Understanding the Pathology of Comorbid Disease in HIV-Infected Individuals With Coronary Artery Disease (HIV UPBEAT CAD) study and the Co-morbidities in relation to HIV/AIDS (COBRA) study.

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