Decreased Anti-Inflammatory Tryptophan Metabolites Correlate With Higher CVD Risk in PWH

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BACKGROUND

- Distinct inflammatory profiles have been associated with increased prevalence of cardiovascular disease (CVD) in people with HIV (PWH). Alterations in tryptophan metabolism through the kynurenine pathway (KP, figure 1) have also been observed in PWH and are associated with CVD (Hoel et al Sci Rep 2018; Boyd et al OFID 2019; Bayón-Gil et al CROI 2023; Luo et al CROI 2023).
- We aimed to explore relationships between KP metabolites and inflammatory profiles of PWH.

METHODS

- In the All-Ireland Infectious Diseases (AIID) cohort, we previously identified 3 distinct inflammatory clusters using principal components analysis and hierarchical clustering on 38 plasma biomarkers. Cluster 3 (C3), denoted by higher markers of T-cell inflammation and gut endothelial dysfunction, was associated with 7-fold increased prevalence of CVD (McGettrick et al, JID 2024).
- Within this cohort, we matched (1:1:1) participants in C3 to Cluster 1 (C1) (noninflamed) and Cluster 2 (C2) (systemically inflamed) by sex-at-birth, age and ethnicity using propensity score with the nearest neighbor method (Figure 2).
- We measured the relative concentrations of ten KP metabolites (AU/mL) in plasma by UHPLC-MS/MS. We used Kruskall-Wallis to identify differences between groups followed by Dunn's multiple comparison test (with correction) to determine specific pairwise differences between clusters. Data are median (IQR) unless specified.

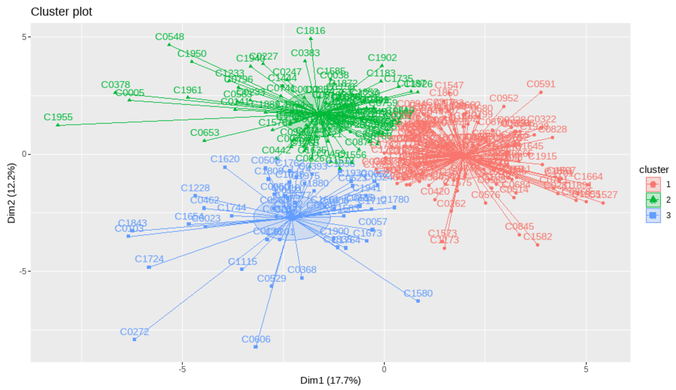


Figure 2. Cluster definition by a combination of propensity score and distance to centroid methods

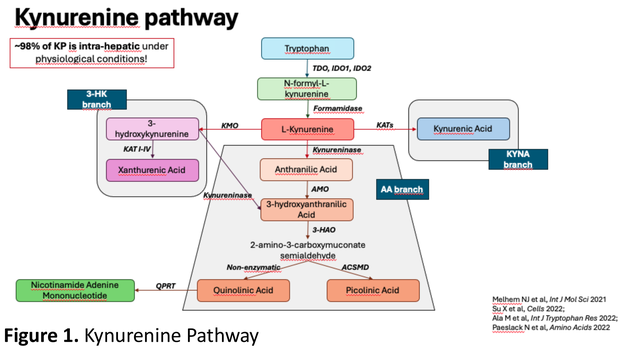


Figure 1. Kynurenine Pathway

Anti-inflammatory metabolites of the kynurenic acid branch of the KP are significantly **downregulated** in PWH with **higher CVD risk**.

RESULTS

- We included 87 PWH, 29 from each cluster. Overall, 34.5% were female, 52.3% Caucasian (table 1).

Table 1. PWH demographics. Data are median (IQR)

	Cluster 1 (n = 29)	Cluster 2 (n = 29)	Cluster 3 (n = 29)	p value
Age (yrs)	45.0 (39.7-49.5)	45.0 (39.0-50.8)	45.0 (40.0-50.0)	0.917
Time from diagnosis (yrs)	11.0 (5.0-16.0)	8.0 (5.0-13.0)	11.0 (4.0-16.0)	0.740
CD4⁺ T-cell count (cell/µL)	510 (369-712)	686 (554-782)	669 (553-934)	0.023
CD4⁺ T-cell percentage (%)	27.5 (22.0-33.5)	35.0 (29.0-42.0)	34.0 (30.0-41.0)	0.002
CD4⁺/CD8⁺ ratio	0.69 (0.53-0.84)	0.88 (0.67-1.20)	1.04 (0.65-1.21)	0.007
Total cholesterol (mmol/L)	5.30 (4.60-5.95)	5.00 (4.20-5.50)	4.40 (3.90-5.25)	0.048
HDL (mmol/L)	1.14 (0.93-1.30)	1.23 (1.00-1.34)	1.27 (1.00-1.47)	0.241
LDL (mmoL/L)	3.60 (2.90-3.95)	3.10 (2.60-3.60)	2.65 (2.37-3.35)	0.013

- Of the 10 KP metabolites we measured, four anti-inflammatory metabolites of the kynurenic acid branch of the KP were significantly downregulated in C3 (figure 3):
- All four downregulated KP metabolites correlated closely (Figure 4).

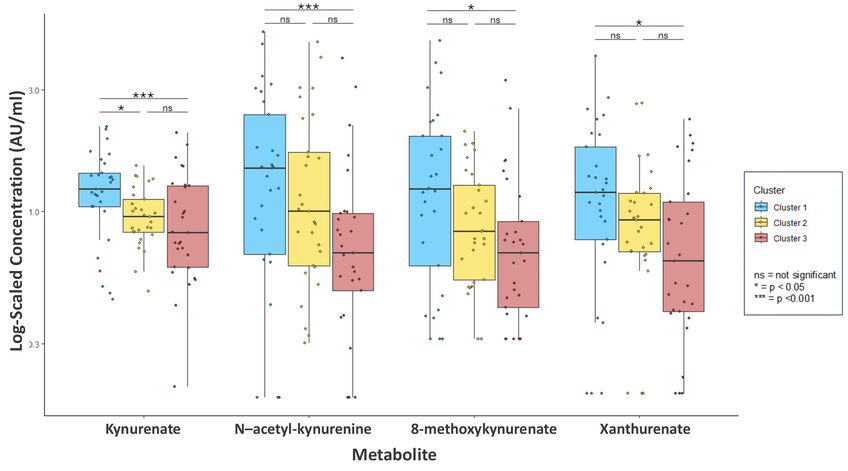
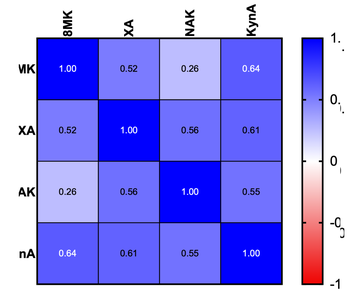


Figure 3. Four anti-inflammatory metabolites of the kynurenic acid branch of the KP, such as kynurenate (A), N–acetyl-kynurenine (B), 8-methoxykynurenate (C), and xanthurenate (D), are significantly downregulated in C3 compared with C1, while no difference has been found when comparing C2 with C1.

Abbreviations: KP, kynurenine pathway; C3, cluster 3; C1, cluster 1, C2, cluster 2.



	8-MK	XA	NAK	KynA
8-MK		< 0.001	0.024	<0.001
XA	0.001		<0.001	<0.001
NAK	0.024	<0.001		<0.001
KynA	<0.001	<0.001	<0.001	

Figure 4. Correlation plot for the downregulated KP metabolites. Correlation coefficients were calculated with Spearman's method. **Abbreviations:** 8-MK, 8-methoxy-kynurenate; XA, xanthurenic acid; NAK, N-acetyl-kynurenine; KynA, Kynurenic Acid

CONCLUSIONS

- Proinflammatory profiles associated with higher prevalent CVD in PWH are linked to coordinated downregulation in anti-inflammatory metabolites in the KP, providing insights into the pathogenesis of CVD in PWH and supporting a role for precision medicine to identify those PWH most at risk of CVD.
- Knowing more about the role of KP in CVD risk in PWH will allow to identify a strategy to reduce its influence by dietary restriction of Trp or the upregulation of Trp metabolism through other pathways.

REFERENCES

Hoel et al, Sci Rep 2018; Boyd et al, OFID 2019; Bayón-Gil et al, CROI 2023; Luo et al, CROI 2023; McGettrick et al, JID 2024

ADDITIONAL KEY INFORMATION

Other Key Information:

Measurements of the metabolites were carried out at Metabolon Inc.

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