Transcriptional Signatures Underlying Cardiovascular Disease in Persons Living With HIV

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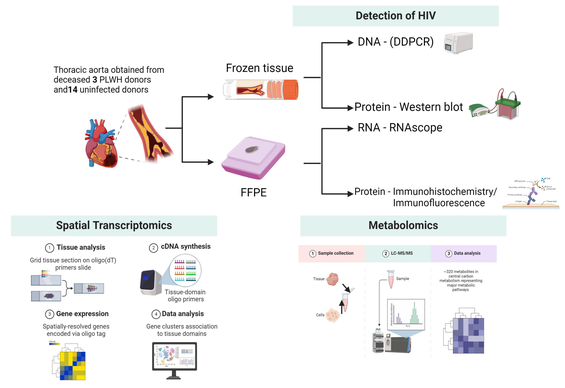
BACKGROUND

- HIV infection has been associated with increased risk of cardiovascular disease (CVD).
- Aortic abnormalities have been observed in individuals with HIV, including aortic dilation and increased stiffness.
- The pathogenesis of CVD in persons living with HIV (PLWH) is not well understood, but chronic inflammation and immune activation are thought to play a role.
- Retinoic acid has potential to decrease the incidents CVD.
- Apolipoprotein D (ApoD) is involved in lipid metabolism and immune regulation and is elevated in the serum of PLWH.
- To our knowledge the role of ApoD in aortic abnormalities in PLWH has not been studied.

METHODS



In an unsupervised approach:

- We used droplet digital polymerase chain reaction
- (ddPCR), and immunohistochemistry to detect and quantify HIV.
- Spatial transcriptomics (Visium) and metabolomics were used to define differences in aorta by HIV status.
- Differentially expressed genes were identified using Loupe Browser 6 software.
- Statistical significance and fold change values were computed using the negative binomial test. Genes with adjusted p-values, FDR < 0.05, were considered significantly different.
- Global metabolomic profiling of aorta was performed using mass spectometry, and over 320 metabolites were detected in both (+) and (-) modes.Analysis was performed using the Metaboanalyst 5.0 software.

The aorta of PLWH have increased ApoD transcripts & lower concentration of retinoic acid compared to people without HIV.

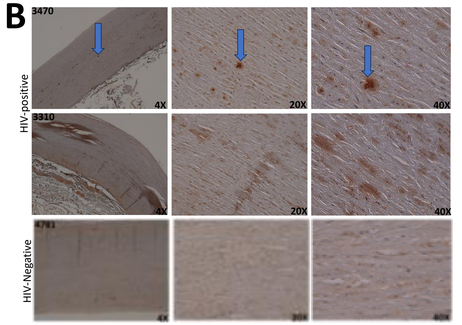
RESULTS

A

	PLWH n=5	Without HIV n=17
Age, yrs.	64.0 [44.0 – 68.5]	66.0 [60, 70.5]
Gender, % Male	4 (80%)	11 (64.7%)
Race, % Caucasian	4 (80%)	15 (88.2%)
BMI, Kg/m²	23.8 [20.3, 30.6]	30.9 [24.6, 40.2]
With Diabetes	1 (20%)	1 (0.06%)
Smoking history	1 (20%)	9 (52.9%)
Aorta Characteristics		
Location of Aorta	Thoracic aorta (4) Not specified (1)	Thoracic aorta (10) Not specified (6) Abdominal (1)
Time to processing, hrs.	14.7 [11.9, 21]	13.3 [10.2, 16.4]
Cause of death	Respiratory arrest, Pulmonary edema Cancer HIV Respiratory failure (PEs) Cardiac arrest	Self-inflicted GSW Natural cardiac death CVA/Stroke (6) Intracranial hemorrhage Cardiopulmonary arrest (5) Respiratory failure Trauma End-stage COPD

Abbreviations: BMI, body mass index; yrs., years; hrs., hours; GSW, gunshot wound; CVA, cerebral vascular accident

B



C

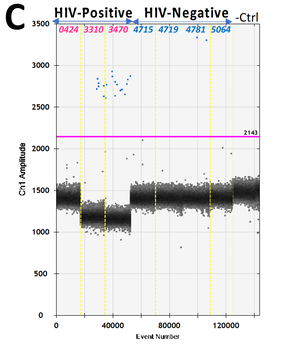


Figure 1. Aorta from PLWH have detectable HIV RNA. Table on the **left** shows the characteristics of the cohort of participants included in this study obtained from the National Disease Research Interchange (NDRI) (A). The **middle** panel shows IHC slides highlighting p24 expression on sample from PLWH. We extracted RNA from aorta of PLWH and persons without HIV samples and performed ddPCR using the LTR primer (**right** panel).

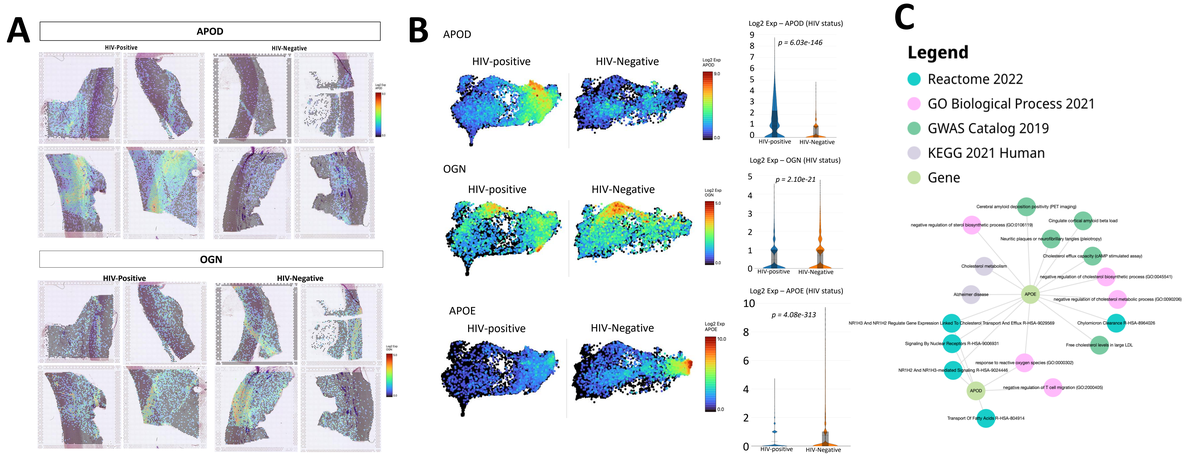
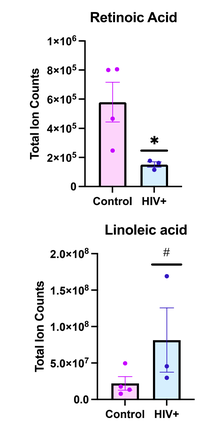


Figure 2. Spatial profiling of aorta provides insights on differences by HIV. The RNA transcripts that were different by HIV status are shown. APOD, osteoglycin (OGN), and apolipoprotein E (APOE) are differentially expressed by HIV status as shown spatially (A), UMAPs with combined data comparing gene expression in 4 PLWH and people without HIV (B). Subnetwork plot shows associations such as APOD, and APOE both respond to reactive oxygen species (C).

A



B

Partial Spearman adjusted
Showing correlation with HIV status
Adjusted for recovery time and age

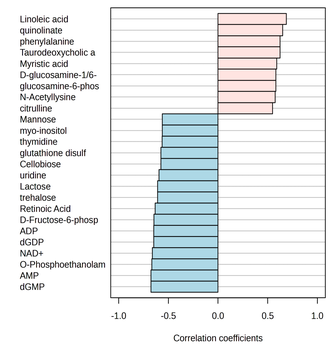


Figure 3. Aorta from PLWH have altered metabolic profiles. Bar plots show differential expression of retinoic acid and linoleic acid by HIV status (A). Using partial Spearman rank correlation analysis adjusted for recovery time and age, several cytokines are associated with HIV status (B).

CONCLUSIONS

- ApoD, a lipocalin may be associated with premature atherosclerosis and poor outcomes in PLWH.
- Low levels of retinoic acid in PLWH may contribute to the chronic state of inflammation. Detection of low retinoic acid in aorta suggests a role for this difference in the inflammatory response within the aorta.

FUTURE DIRECTIONS

- Further investigation into the mechanisms underlying APOD and retinoic acid involvement in HIV-associated atherosclerosis is warranted.
- Exploring the impact of aging, antiretroviral therapy and lifestyle interventions on APOD expression and cardiovascular outcomes in PLWH will be crucial.

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