Lipidome abnormalities and altered macrophage phenotype may contribute to cardiovascular disease risk in the aging HIV population

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Cardiovascular disease risk is increased for people with HIV

Friis-Moller et al NEJM 2003
Combination antiretroviral therapy and the risk for myocardial infarction.

Currier et al JAIDS 2003
Coronary heart disease in HIV-infected individuals.

Bozzette et al NEJM 2003
Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection.

Increased Acute Myocardial Infarction Rates and Cardiovascular Risk Factors among Patients with Human Immunodeficiency Virus Disease
-health care system-based cohort study, looking for MI rates in HIV+ and HIV- patients
PWH have significantly altered lipidome composition

- Traditional lipid measurements (TC, LDL, TG) were not significantly different among HIV- and HIV+ groups
- 37.1% of all lipidome species were significantly altered
- Lipid profiles linked to CVD in the general population
Lipids classes associated with CVD tend to be increased in older PWH

- Older PWH (Over 55) tend to have increased concentrations of CERs, DAGs, FFAs, TAGs
- CER levels correlate with inflammatory plasma biomarkers in older, but not younger PWH
PWH have increased levels of coronary artery calcification

<table>
<thead>
<tr>
<th>CAC Value</th>
<th>Calcification Grade</th>
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<tbody>
<tr>
<td>0</td>
<td>No Calcification</td>
</tr>
<tr>
<td>0-10</td>
<td>Minimal</td>
</tr>
<tr>
<td>11-100</td>
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<tr>
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<td>Severe</td>
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<tr>
<td>&gt;1000</td>
<td>Very Severe</td>
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</tbody>
</table>

A. Young (<55) B. Old (>55)
Arterial age estimates are increased in PWH compared to uninfected controls

**Arterial Age Calculation Factors**
- Coronary Artery Calcium Score
- Age
- Sex
- Total Cholesterol
- HDL
- Systolic Blood Pressure
- Smoking Status
- Use of Anti-Hypertensive Meds

The Multi-Ethnic Study of Atherosclerosis

Arterial Age as a Function of Coronary Artery Calcium (From the Multi-Ethnic Study of Atherosclerosis [MESA])

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Monocyte-derived macrophage (MDM) differentiation

- Markers of inflammation and myeloid cell activation, and microbial products are increased in serum from PWH
MDMs from PWH have an ‘activated’ phenotype

- HLA-DR MFI
- CD300e MFI
- MFI TLR4
- % Positive CD163

HIV - vs HIV +

* p < 0.05
** p < 0.01
MDMs from PWH display increased propensity to form foam cells

- Bodipy: Intracellular lipid stain detected by flow cytometry
- Dil-OxLDL uptake assay: MDMs incubated with labeled oxLDL for 4h and Dil fluorescence measured by flow cytometry

MDMs from HIV+ and HIV- individuals display differential patterns of gene expression.

Pathway Analyses:
- Innate immune signaling
- Cell cycle regulation
- Lipid transport and fatty acid metabolism
- Reduced antioxidant pathway activation
- Mitochondrial dysfunction

Differentially Expressed Genes, (p<0.05) = 811

Agilent Seahorse Analyzer
Biomarkers associated with morbidity and mortality in HIV infection correlate with unique DGE signatures

sCD14

Top 50 DEPs by P.Value sCD14

*Levels of serum inflammatory biomarkers are directly associated with inflammatory signaling pathway activation

Correlations with lipids associated with CVD

- Free Fatty Acids
- Ceramides
- Triacylglycerides
- Saturated Fatty Acids
Exposure to pooled serum from HIV+ donors is sufficient to alter macrophage phenotype

A. 

- **HLA DR MFI**
  - *Differentially expressed genes (p<0.05) = 2675

B. 

- **CD163 % Positive**

C. 

- **Bodipy MFI**
  - HIV Pool
  - HIV+ Pool

* Differentially expressed genes (p<0.05) = 2675
Conclusions – Altered lipids and macrophage phenotype in PWH may enhance cardiovascular disease risk

- Coronary calcification levels are increased in PWH
  - Severe risk in older PWH
- Broad changes in MDM transcriptome and signaling pathway activation
- Increased lipid uptake and inflammatory foam cell phenotype
- Altered lipidome composition in PWH may play a role in driving pro-atherogenic macrophage phenotype
  - Detailed lipid analyses may better predict CVD risk
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