



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

ER Bowman¹, M Kulkarni¹, J Gabriel¹, A Kettelhut¹, M Cichon¹, K Reidl¹, S Koletar¹, B Richardson², C Cameron², M Cameron², NT Funderburg¹

¹The Ohio State University, Columbus, OH, USA; ²Case Western Reserve University, Cleveland, OH, USA

Emily Bowman PhD

The Ohio State University
School of Health and Rehabilitation Sciences



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.

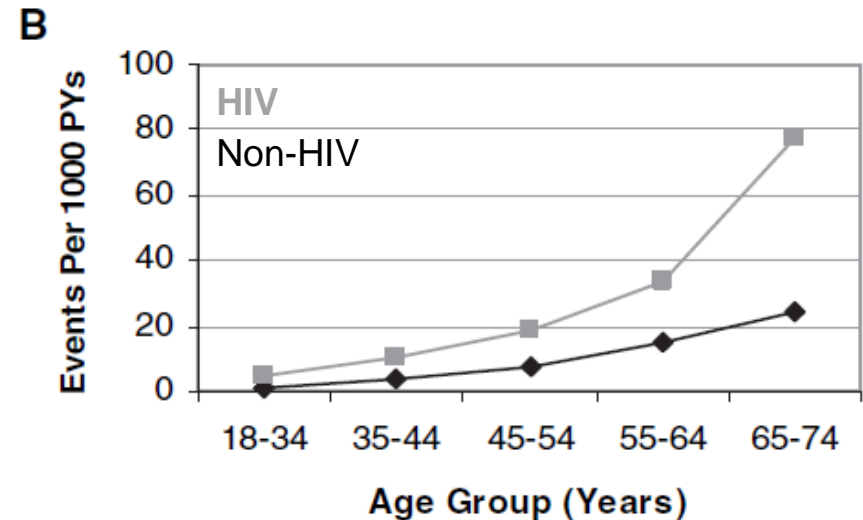
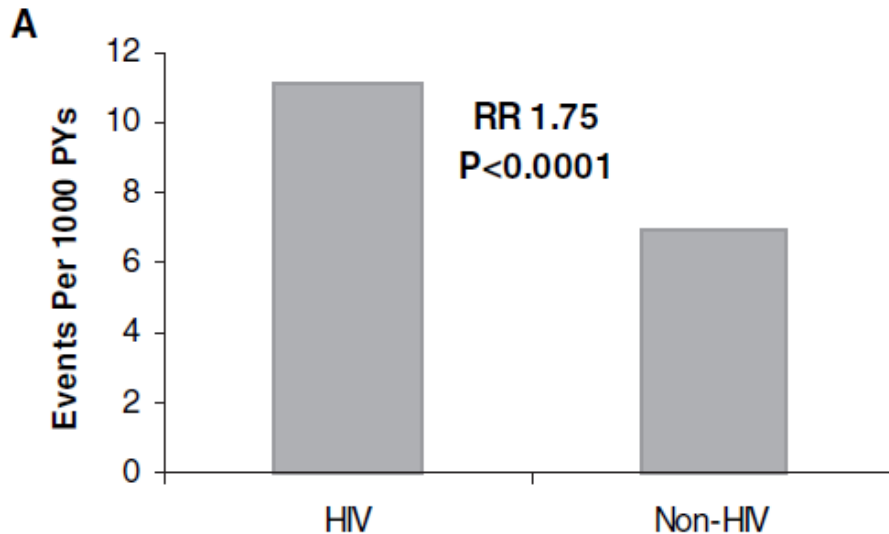
Bozzette et al *NEJM* 2003

Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection.

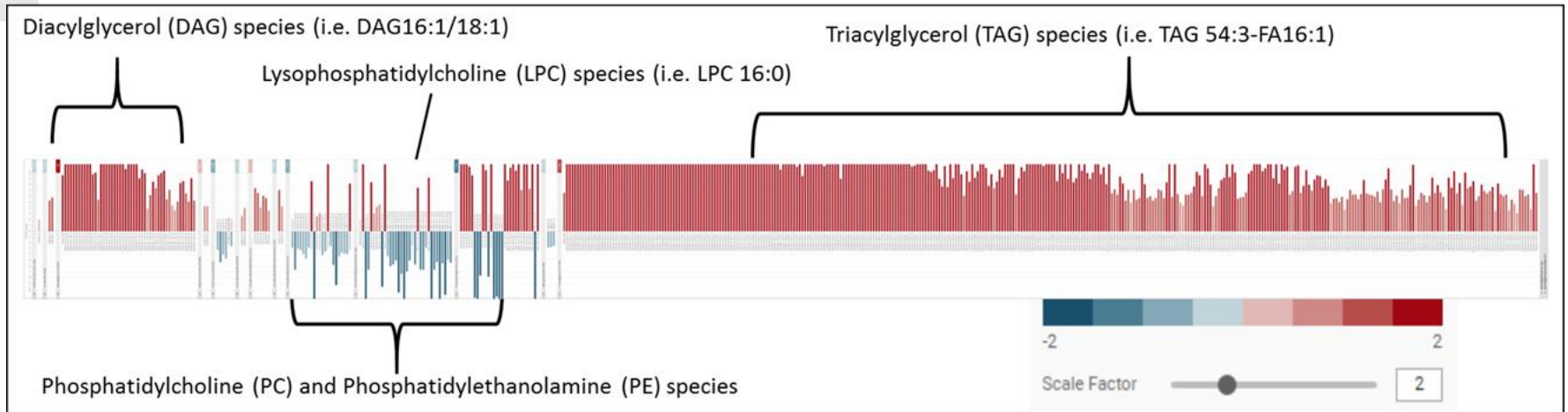
Triant et al *J Clin. Endo. Met.* 2007

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

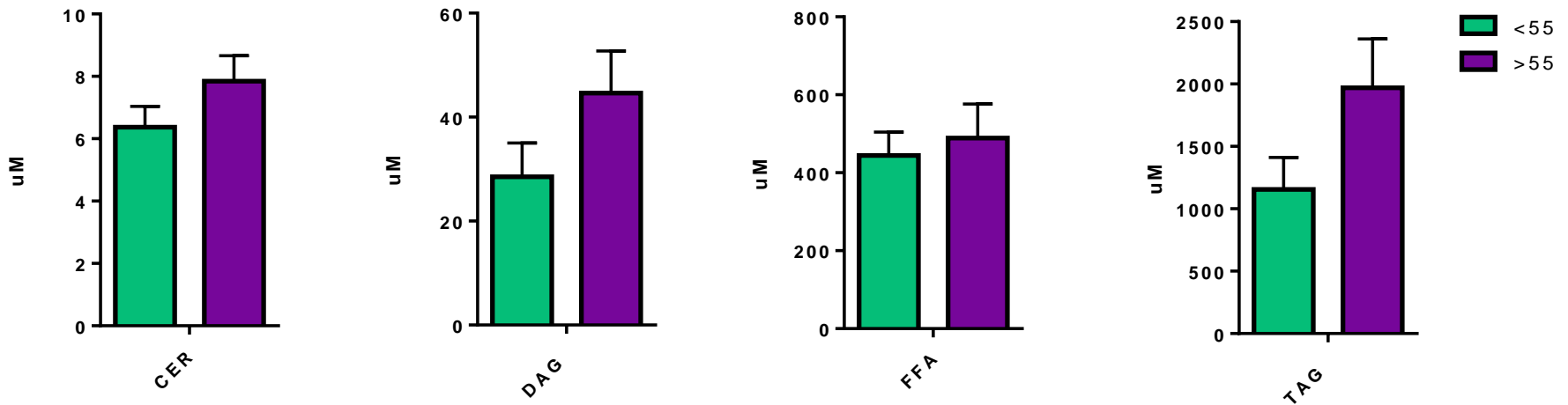


PWH have significantly altered lipidome composition



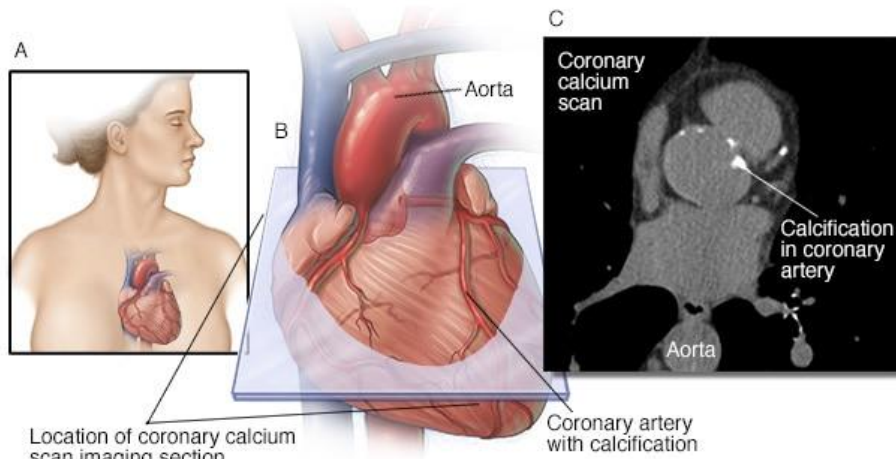
- Traditional lipid measurements (TC, LDL, TG) were not significantly different among HIV- and HIV+ groups
- 37.1% of all lipidome species were significantly altered
- Lipid profiles linked to CVD in the general population

Lipids classes associated with CVD tend to be increased in older PWH



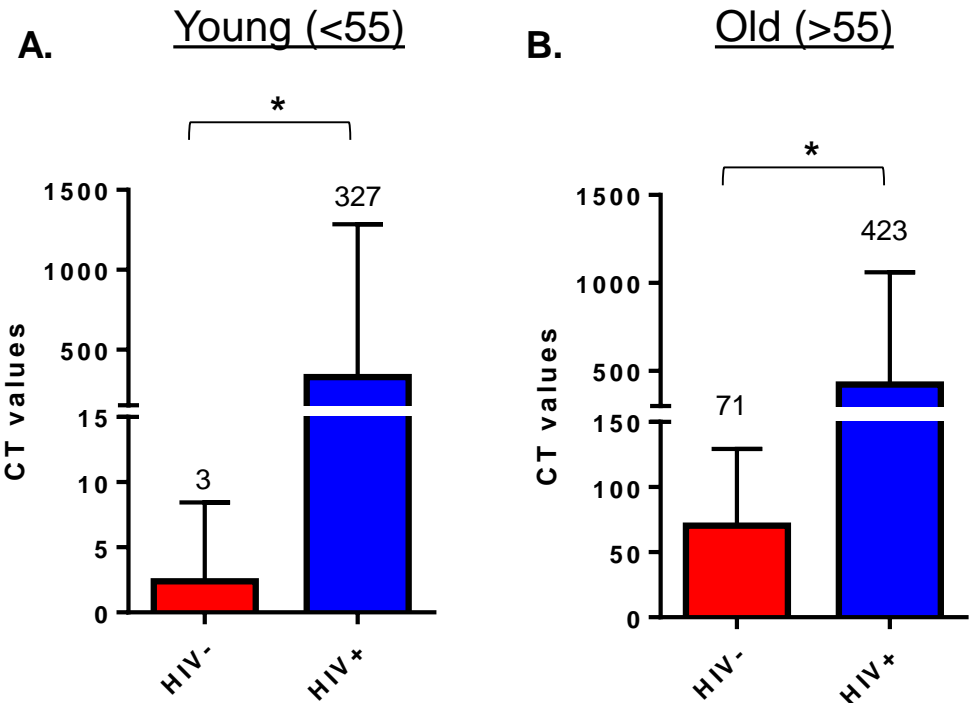
- Older PWH (Over 55) tend to have increased concentrations of CERs, DAGs, FFAs, TAGs
- CER levels correlate with inflammatory plasma biomarkers in older, but not younger PWH

PWH have increased levels of coronary artery calcification



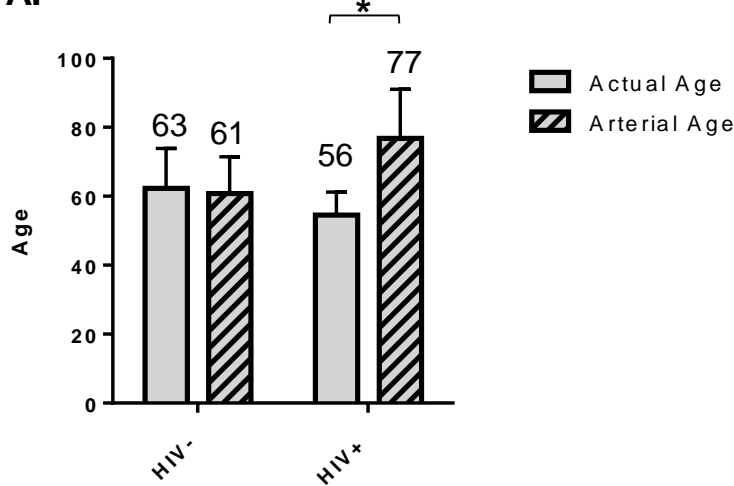
© MAYO FOUNDATION FOR MEDICAL EDUCATION AND RESEARCH. ALL RIGHTS RESERVED.

<u>CAC Value</u>	<u>Calcification Grade</u>
0	No Calcification
0-10	Minimal
11-100	Mild
101-400	Moderate
401-1000	Severe
>1000	Very Severe

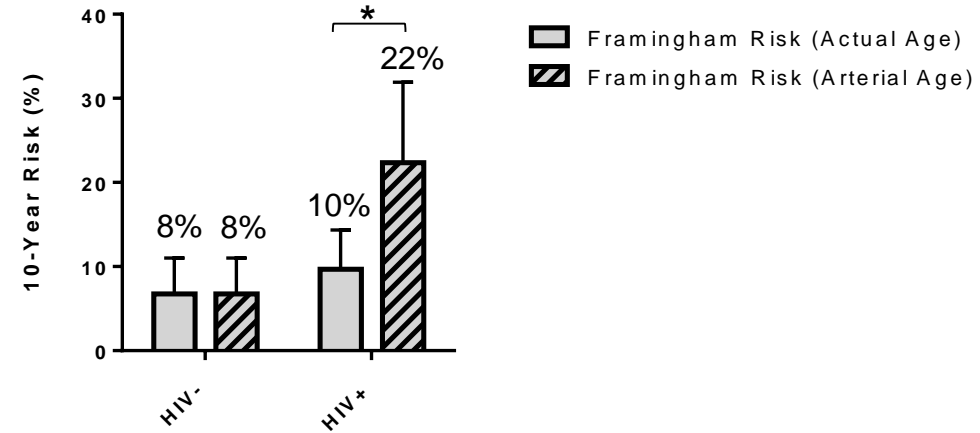


Arterial age estimates are increased in PWH compared to uninfected controls

A.



B.



Arterial Age Calculation Factors

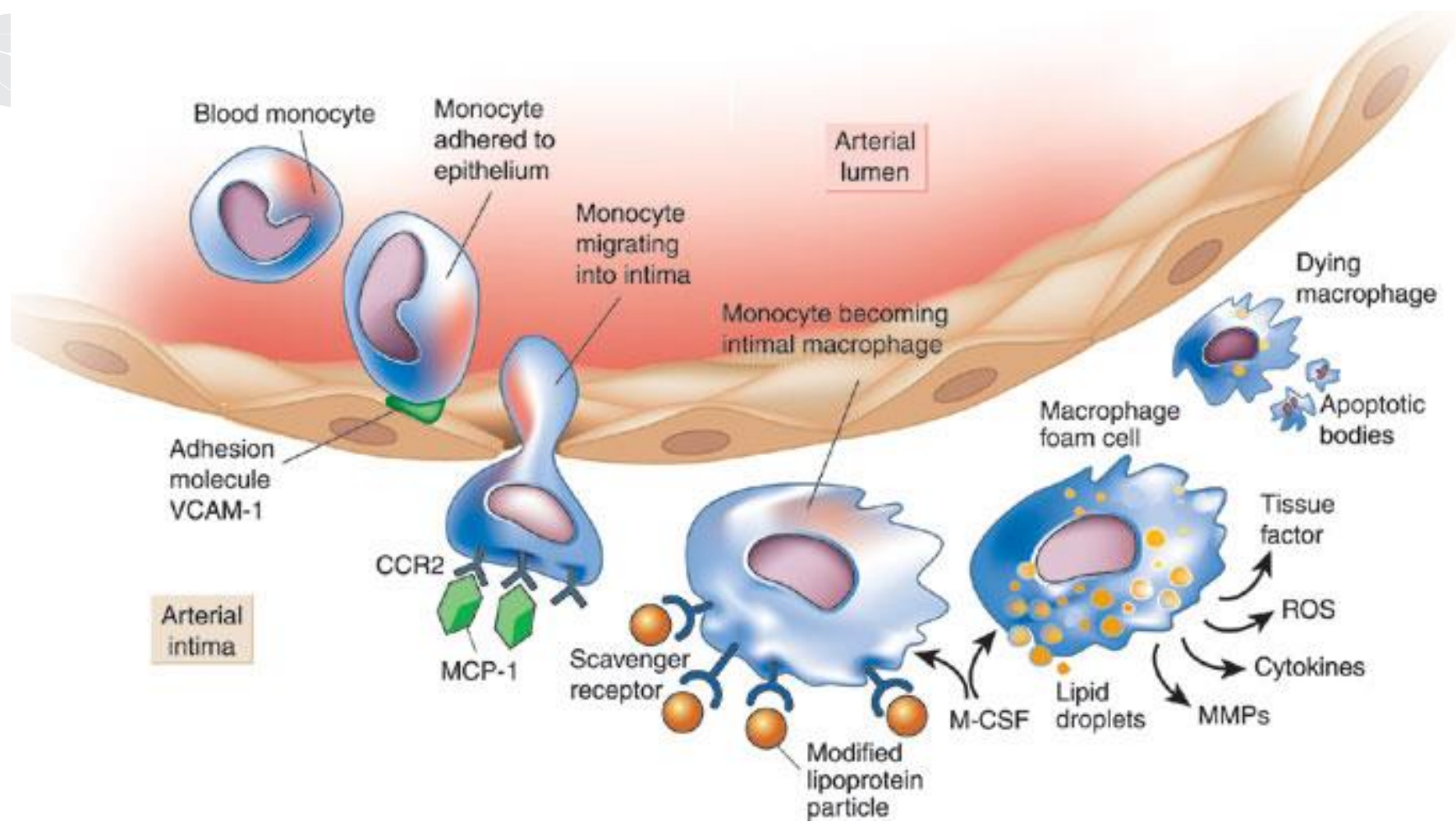
- Coronary Artery Calcium Score
- Age
- Sex
- Total Cholesterol
- HDL
- Systolic Blood Pressure
- Smoking Status
- Use of Anti-Hypertensive Meds



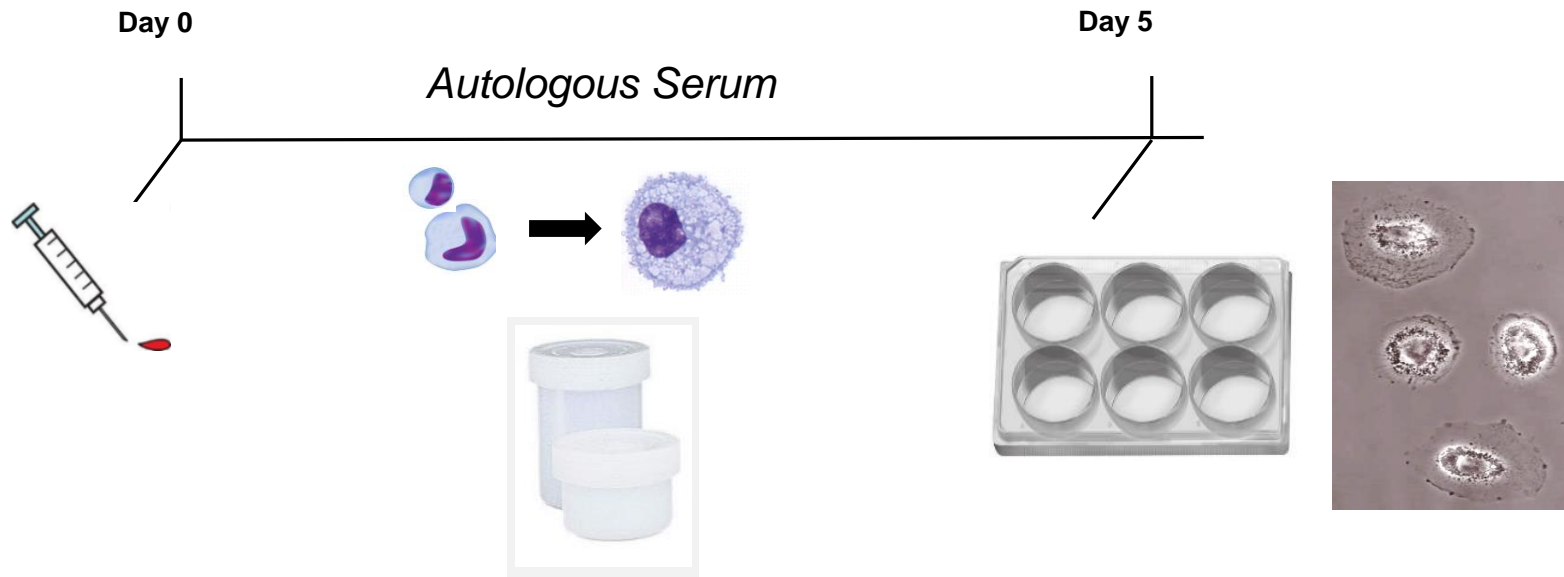
The Multi-Ethnic Study of Atherosclerosis

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

Robyn L. McClelland, PhD^a, Khurram Nasir, MD MPH^b, Matthew Budoff, MD^c, Roger S. Blumenthal, MD^d, and Richard A. Kronmal, PhD^a

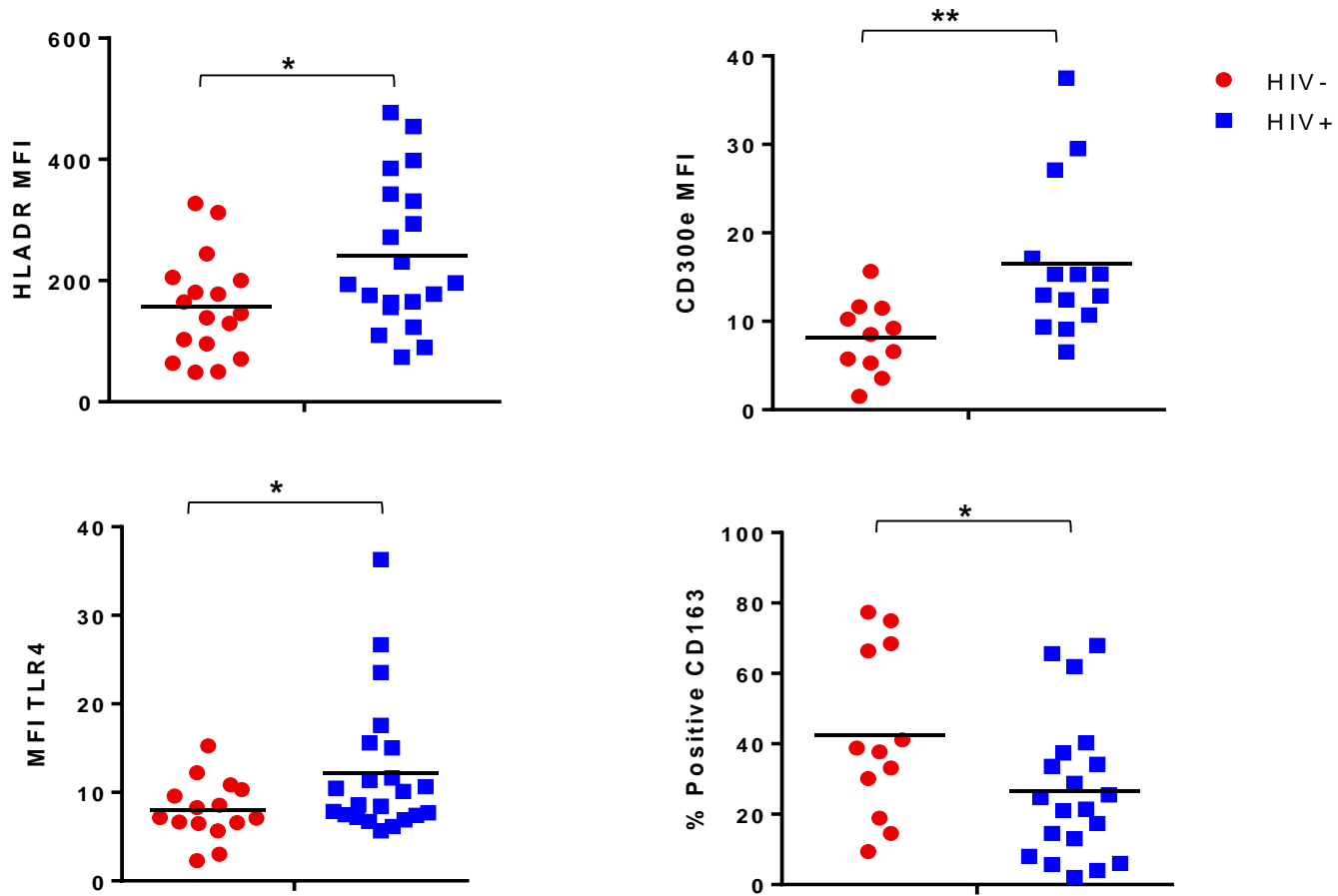


Monocyte-derived macrophage (MDM) differentiation

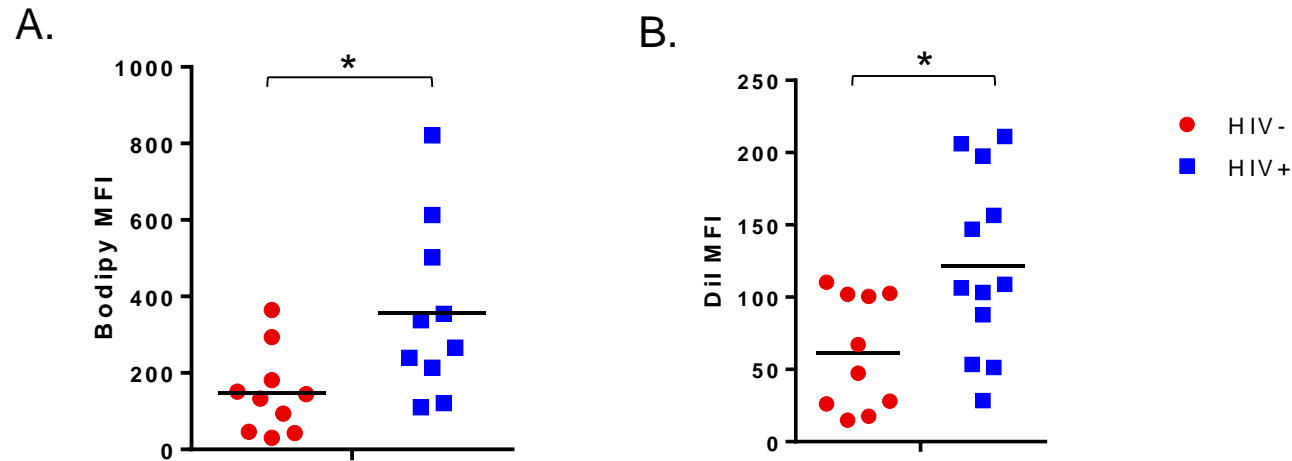


- Markers of inflammation and myeloid cell activation, and microbial products are increased in serum from PWH

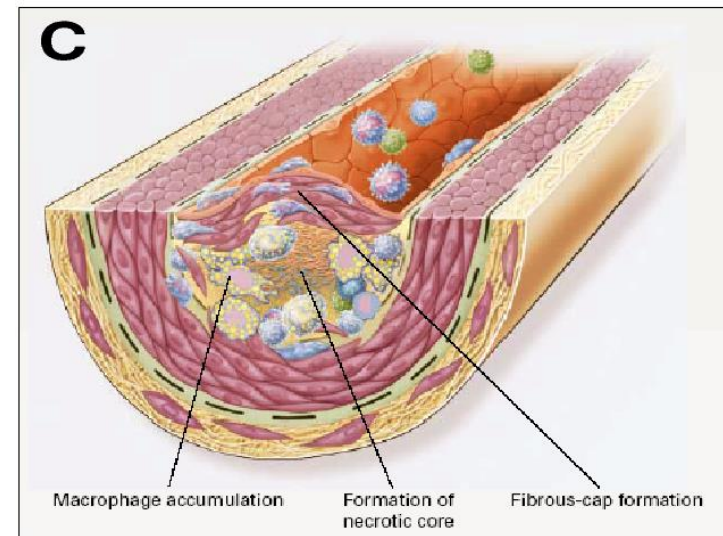
MDMs from PWH have an 'activated' phenotype



MDMs from PWH display increased propensity to form foam cells



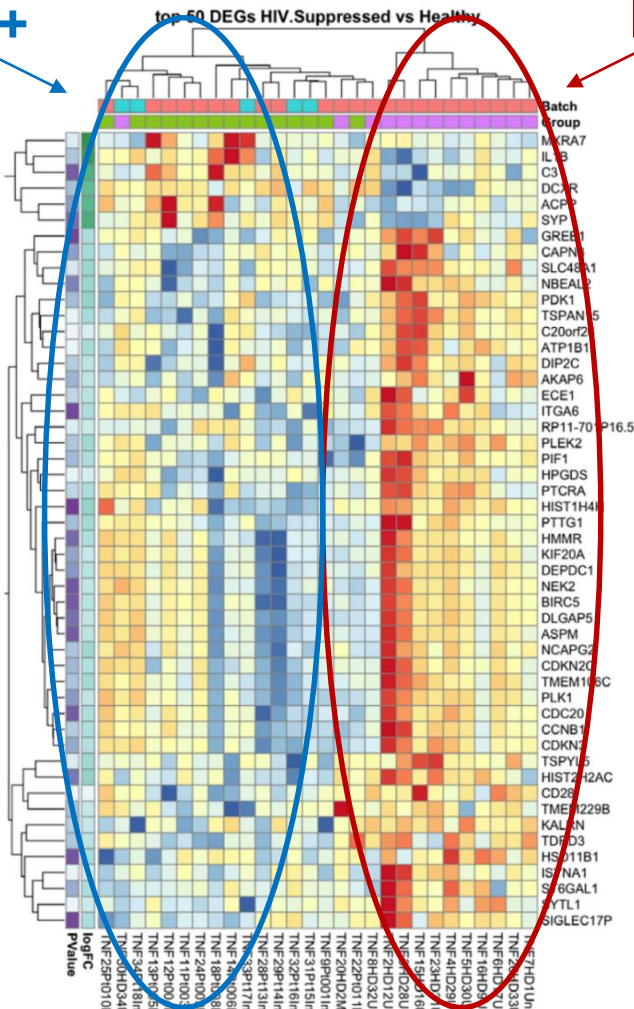
- Bodipy: Intracellular lipid stain detected by flow cytometry
- Dil-OxLDL uptake assay: MDMs incubated with labeled oxLDL for 4h and Dil fluorescence measured by flow cytometry



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

HIV+

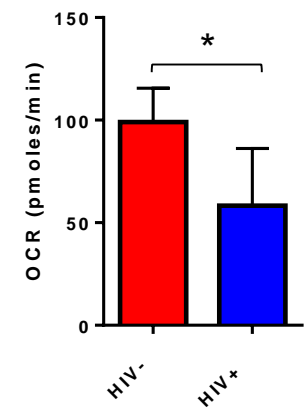
HIV-



Pathway Analyses:

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

Maximal Mitochondrial Respiration

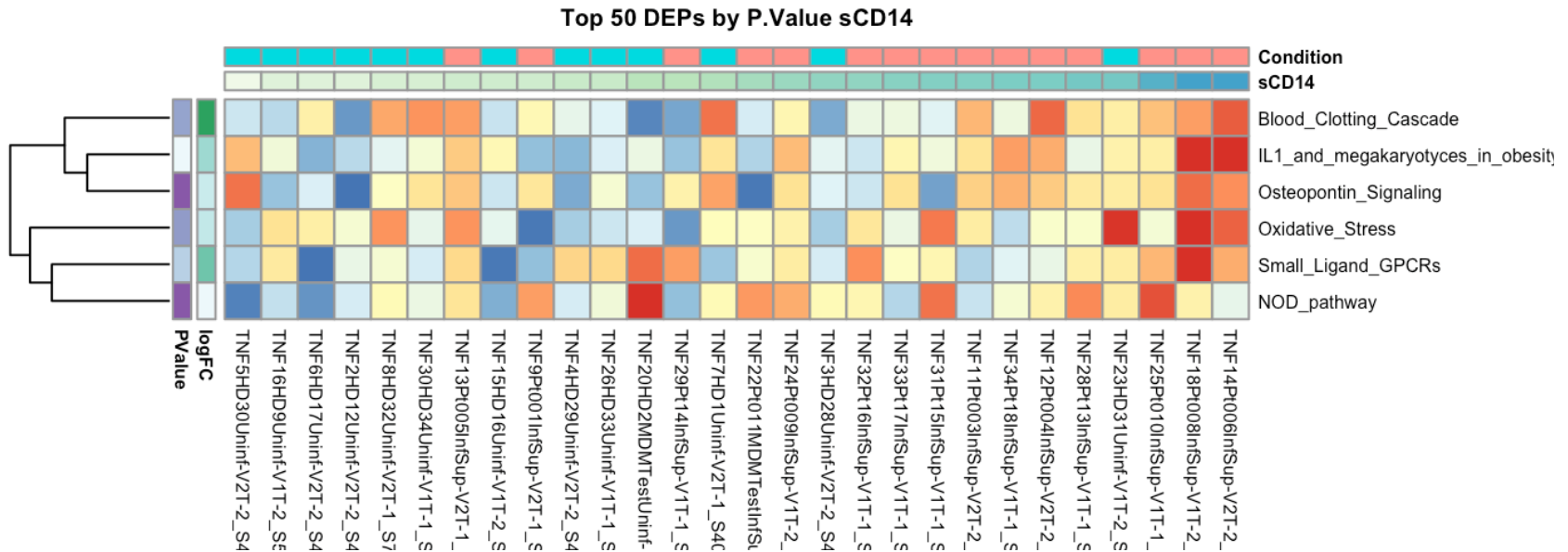


Agilent Seahorse Analyzer

Differentially Expressed Genes, (p<0.05) = 811

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

sCD14

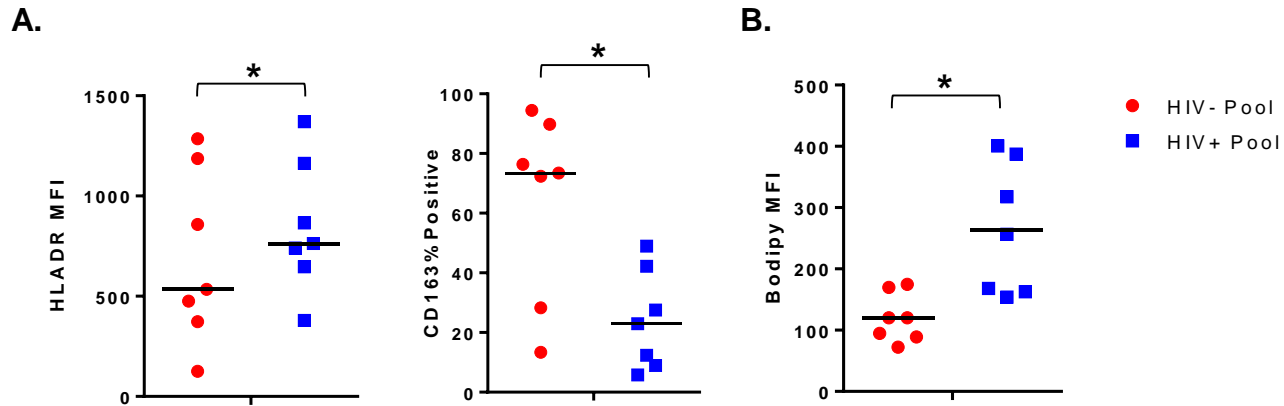


Correlations with lipids associated with CVD

- Free Fatty Acids
- Ceramides
- Triacylglycerides
- Saturated Fatty Acids

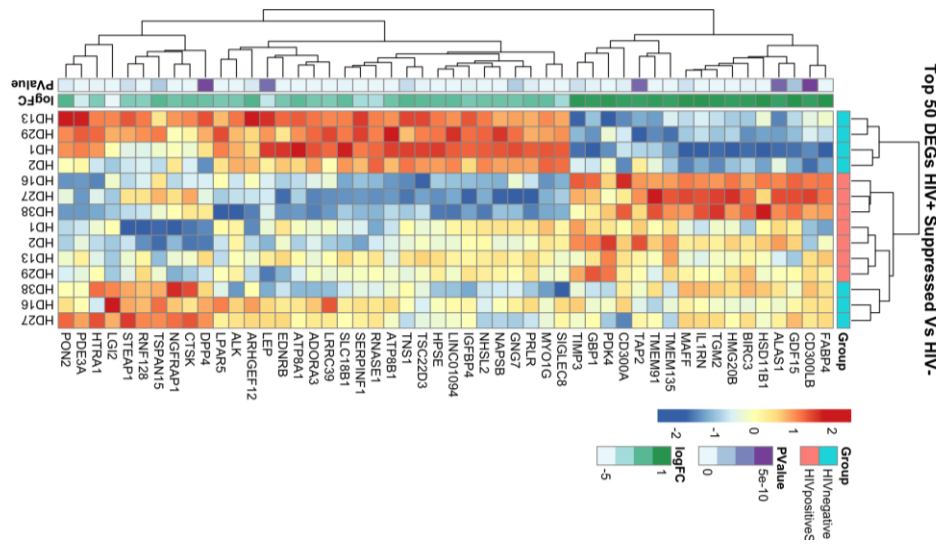
*Levels of serum inflammatory biomarkers are directly associated with inflammatory signaling pathway activation

Exposure to pooled serum from HIV+ donors is sufficient to alter macrophage phenotype



*Differentially expressed genes ($p < 0.05$) = 2675

C.



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

Acknowledgements

Nick Funderburg Lab

- Manjusha Kulkarni, PhD
- Janelle Gabriel, MS
- Aaren Kettlehut (MD/PhD Student)
- Francis Avila-Soto (Undergraduate)
- Lane Hornsby (Undergraduate)

Ohio State Collaborators

- Susan Koletar, MD
- Ohio State Genomics Core
- MDM protocol – Larry Schlesinger, PhD
- Lipidomics - Morgan Cichon, PhD

Ken Riedl, PhD



Case Western Reserve University

- Mark Cameron, PhD
- Cheryl Cameron, PhD
- Brian Richardson, PhD
- Applied Functional Genomics Core

- *All of the blood donors*

Funding

- NHLBI R56 HL126563
- R01HL134544
- R00HL108743

