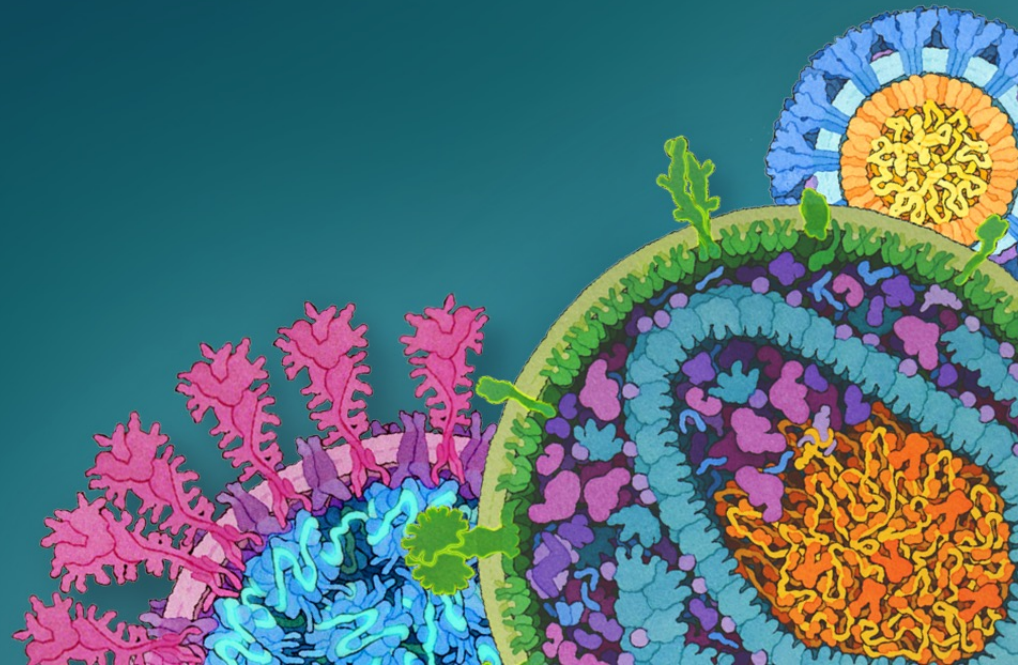


POTENTIAL BIOLOGIC MECHANISMS OF AGING IN HIV

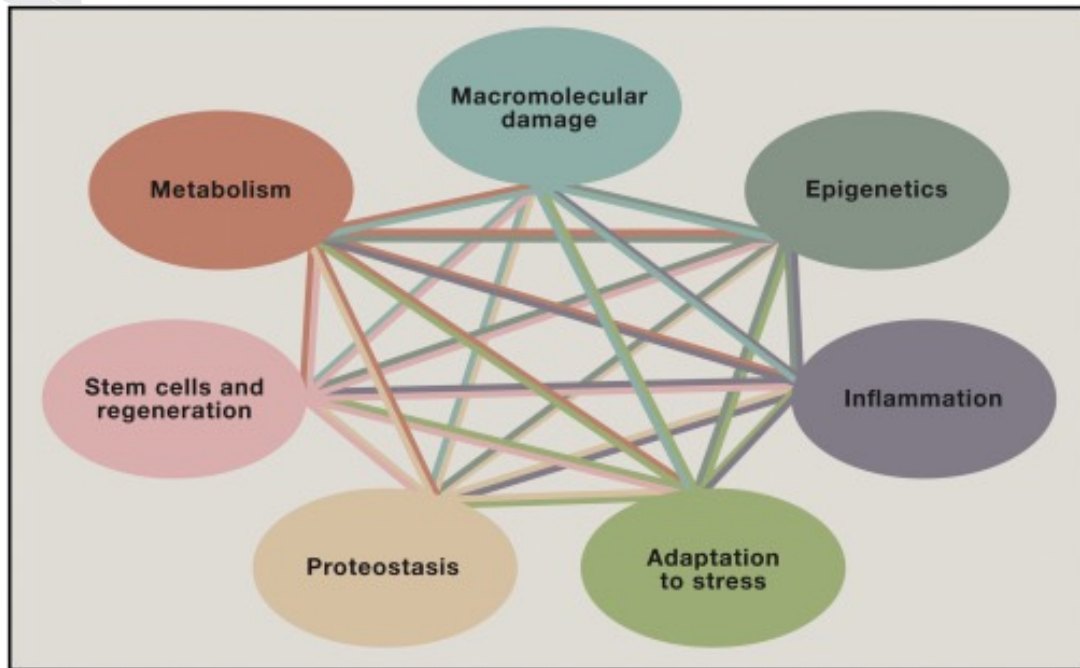
Nicholas Funderburg PhD

*Ohio State University
School of Health and Rehabilitation Sciences
Columbus, Ohio, United States*

Disclosure: Dr. Funderburg has served as a consultant for Gilead.



Aging is a key risk factor in many chronic diseases and PWH have increased risk of many aging related comorbidities



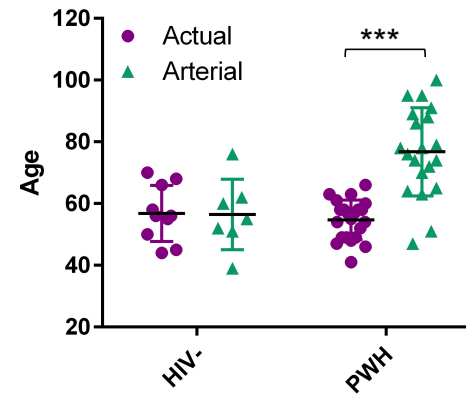
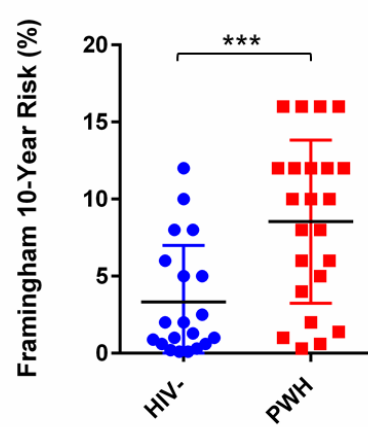
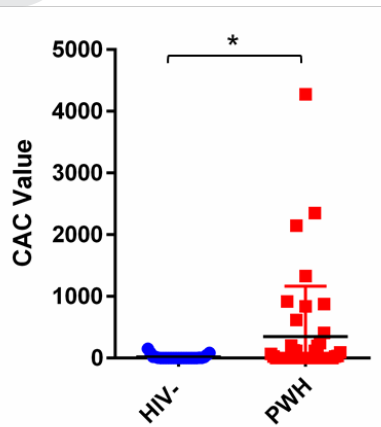
The 7 pillars of Aging

Kennedy Cell 2014

Does HIV or its treatment with ART accelerate these pillars of aging in people with HIV?

If so, what are the mechanisms?

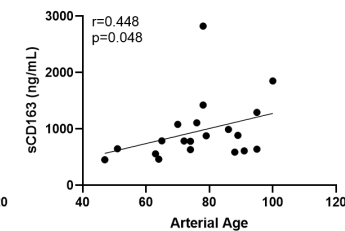
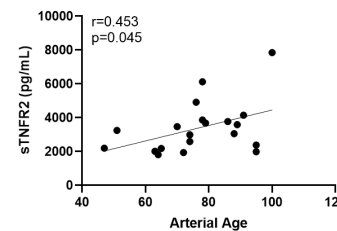
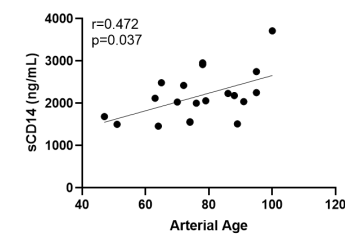
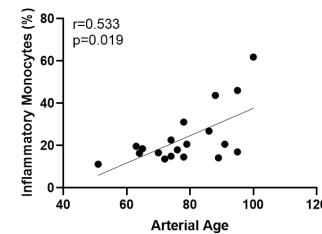
PWH have increased coronary calcium scores and arterial ages compared to a demographically similar group of people without HIV



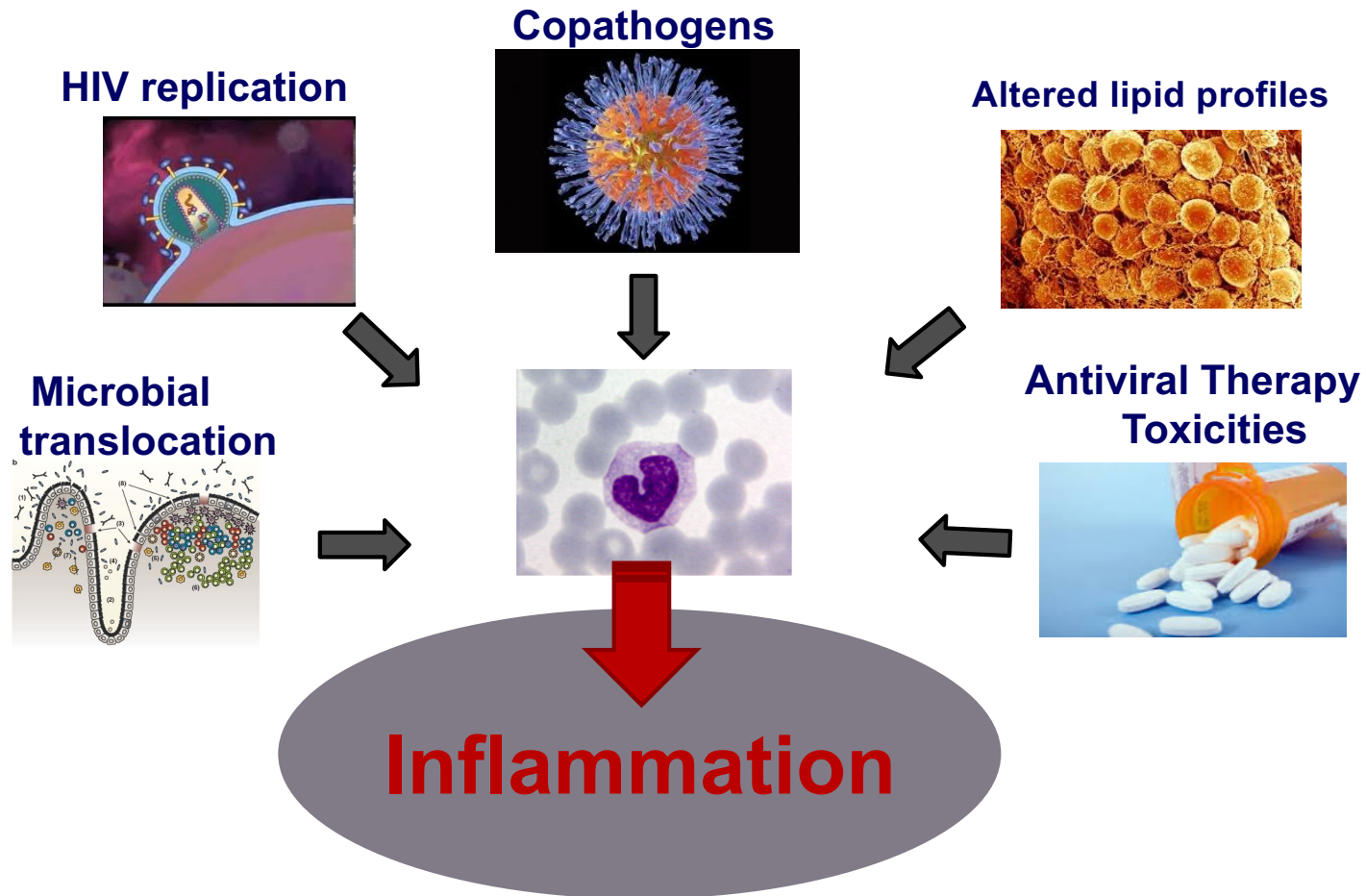
Inflammation

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

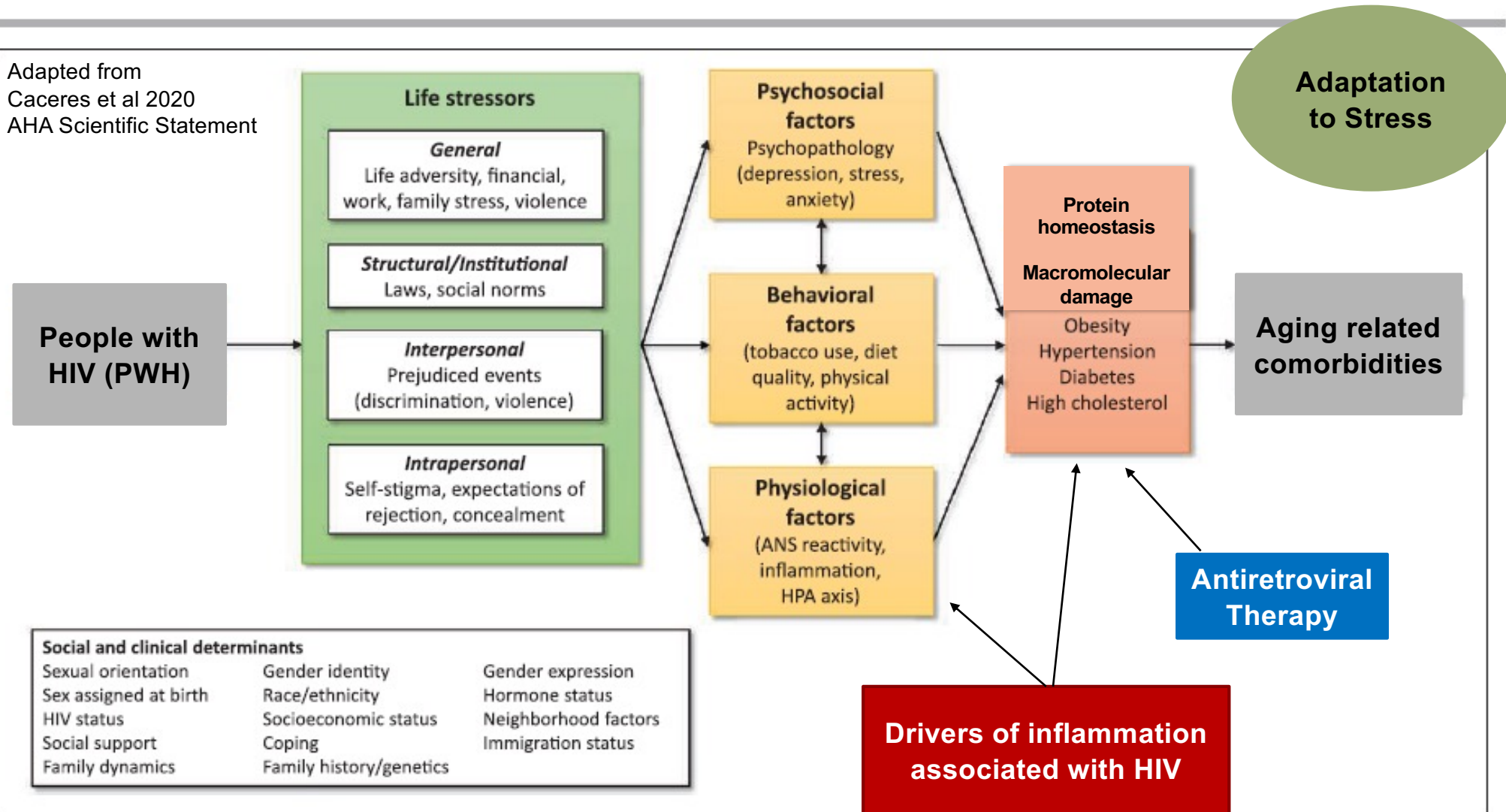
McClelland et al *Am J Cardiol* 2009



What are the underlying biological mechanisms that influence inflammation and promote age-related comorbidities in PWH?



Adapted from
Caceres et al 2020
AHA Scientific Statement



Stem cell hematopoiesis may be altered by Inflammation

Physiology

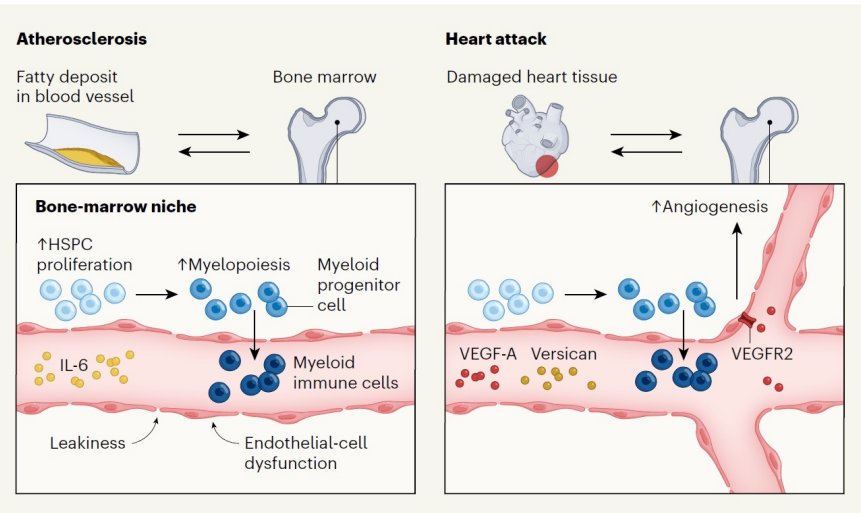
Cardiac disease disrupts the bone-marrow niche

Tomer Itkin & Shahin Rafii

The production of blood cells, including some immune cells, relies heavily on the bone-marrow microenvironment. Cardiovascular diseases are now found to corrupt this niche, leading to imbalances in blood-cell production.

- CHIP Figure

Stem Cells and regeneration



Trained immunity regulates innate immune responses to repeat exposures to TLR ligands and may contribute to inflammatory conditions.

nature
microbiology

ARTICLES

PUBLISHED: 19 DECEMBER 2016 | VOLUME: 2 | ARTICLE NUMBER: 16246

Microbial stimulation of different Toll-like receptor signalling pathways induces diverse metabolic programmes in human monocytes

Ekta Lachmandas^{1†}, Lily Boutens^{1,2†}, Jacqueline M. Ratter^{1,2†}, Anneke Hijmans¹, Guido J. Hooiveld², Leo A. B. Joosten¹, Richard J. Rodenburg³, Jack A. M. Fransen⁴, Riekelt H. Houtkooper⁵, Reinout van Crevel¹, Mihai G. Netea^{1*} and Rinke Stienstra^{1,2*}

RESEARCH ARTICLE

IMMUNOGENETICS

Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity

Sadia Saeed,^{1*} Jessica Quintin,^{2*} Hindrik H. D. Kerstens,^{1*} Nagesha A. Rao,^{1*} Ali Aghajani-Refah,^{1*} Filomena Matarese,¹ Shih-Chin Cheng,² Jacqueline Ratter,² Kim Berentsen,¹ Martijn A. van der Ent,¹ Nilofar Sharifi,¹ Eva M. Janssen-Megens,¹ Menno Ter Huurne,¹ Amit Mandoli,¹ Tom van Schaik,¹ Aylwin Ng,^{3,4} Frances Burden,^{5,6} Kate Downes,^{5,6} Mattia Frontini,^{5,6} Vinod Kumar,⁷ Evangelos J. Giamarellos-Bourboulis,⁸ Willem H. Ouwehand,^{5,6} Jos W. M. van der Meer,² Leo A. B. Joosten,² Cisca Wijmenga,⁷ Joost H. A. Martens,¹ Ramnik J. Xavier,^{3,4} Colin Logie,^{1†} Mihai G. Netea,^{2†} Hendrik G. Stunnenberg^{1†}

Epigenetics

Metabolism

Inflammation

Differential Responsiveness to TLR ligands in PWH

Brenchley *Nat Med* 2006

Meier et al *Nat Med* 2009

Jalbert et al *PLoS One* 2013

Petrov et al *Immunology* 2013

Merlini et al *Front Immunol* 2016



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WEXNER MEDICAL CENTER

Effect of HIV infection and antiretroviral therapy on immune cellular functions

Marek Korenca, ... , Brian K. Agan, Hendrik Streeck

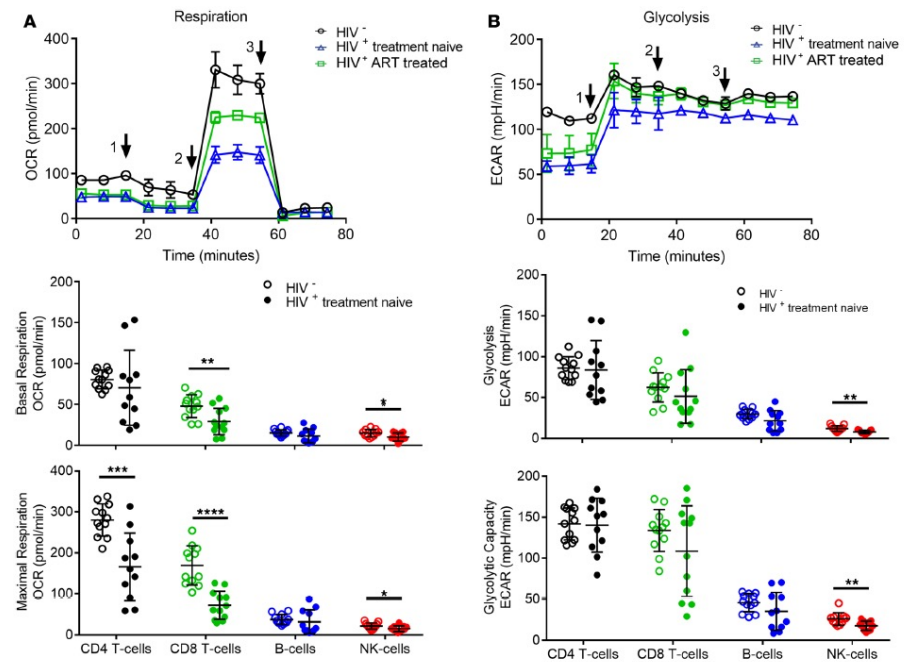
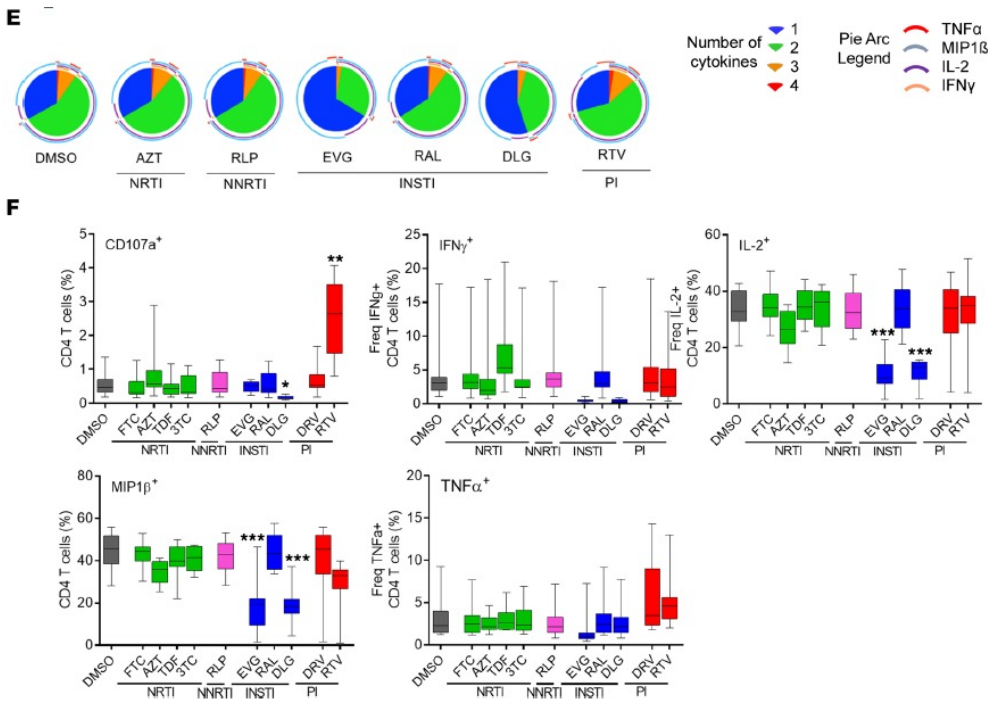
JCI Insight. 2019;4(12):e126675. <https://doi.org/10.1172/jci.insight.126675>.

Research Article | AIDS/HIV | Immunology

Adaptation to Stress

Macromolecular damage

Inflammation



Antiretroviral Therapy may alter immune cell function by modulation of mitochondrial function, telomere length, and oxidative stress.

Adaptation to Stress

Macromolecular damage

Circulation

ORIGINAL RESEARCH ARTICLE

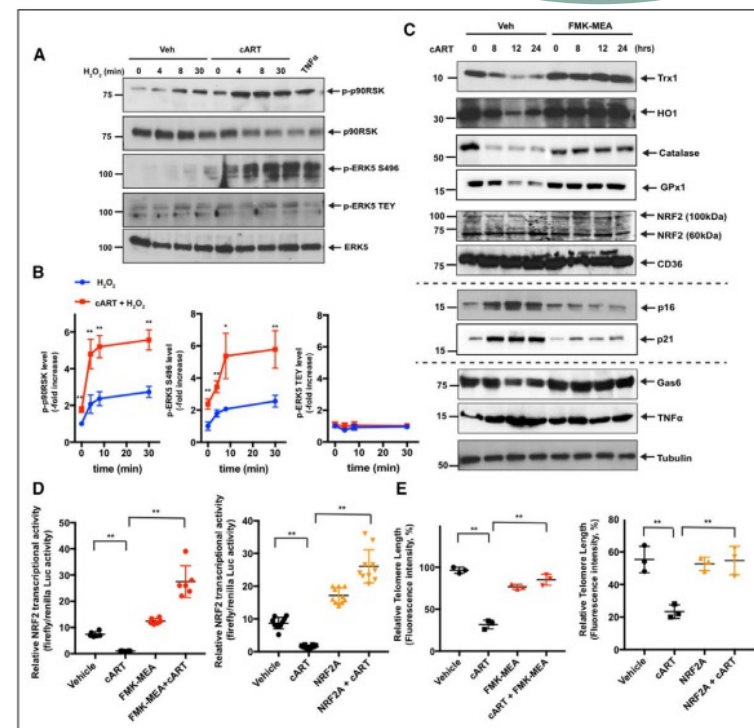
Senescent Phenotype Induced by p90RSK-NRF2 Signaling Sensitizes Monocytes and Macrophages to Oxidative Stress in HIV-Positive Individuals Implications for Atherogenesis

BACKGROUND: The incidence of cardiovascular disease is higher in HIV-positive (HIV+) patients than it is in the average population, and combination antiretroviral therapy (cART) is a recognized risk factor for cardiovascular disease. However, the molecular mechanisms that link cART and cardiovascular disease are currently unknown. Our study explores the role of the activation of p90RSK, a reactive oxygen species-sensitive kinase, in engendering senescent phenotype in macrophages and accelerating atherogenesis in patients undergoing cART.

Meera V. Singh, PhD*
Sivareddy Kotla, PhD*
Nhat-Tu Le, PhD*
Kyung Ae Ko, DVM*
et al

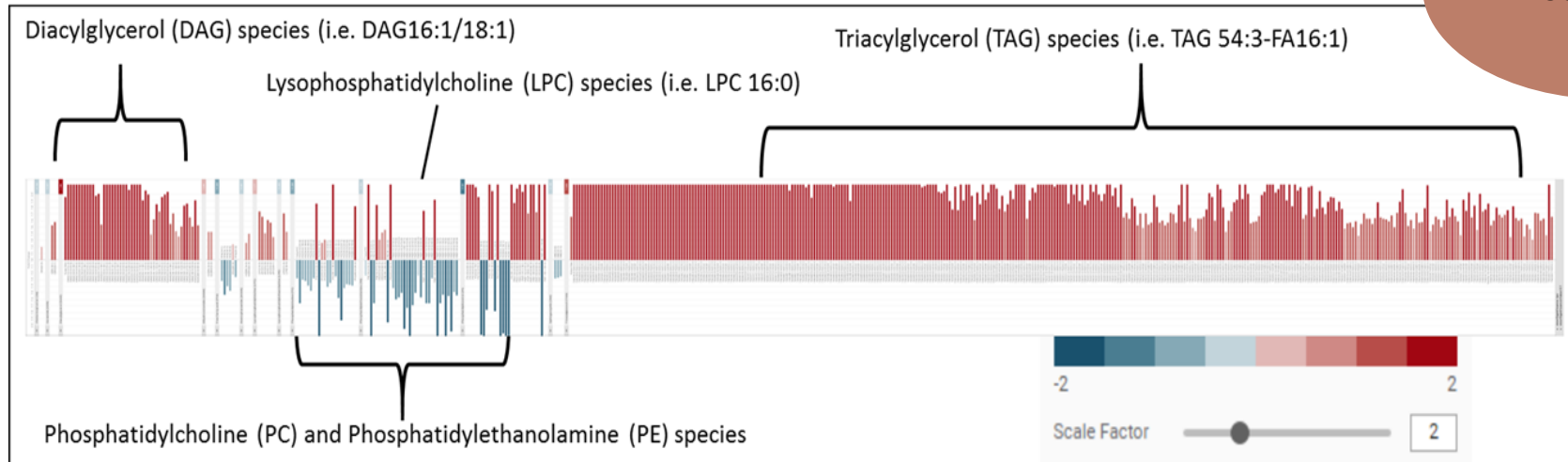
Mitochondrial Dysfunction

- Martin et al *AAC* 2004 –mitochondrial DNA synthesis
- Morse et al *JID* 2012 -mitochondrial dysfunction in adipose tissue
- Kirmse et al *PIDJ* 2013 abnormal mitochondrial function in ART exposed infants
- McComsey et al *JID* 2013 -fat mitochondrial DNA
- Willig et al *Redox Biology* 2017- monocyte bioenergetics and body composition
- Bowman et al *AAC* 2020 – PBMCs, monocytes, MDMs, Tcells, mt dysfunction and ROS
- van der Heijden et al *Scientific Reports* 2021- platelet mitochondrial dysfunction



HIV and ART alter the concentration and composition of lipid profiles

Metabolism



- Traditional lipid measurements (TC, LDL) were not dramatically different among HIV- and HIV+ groups
- Red- lipids increased in PWH
Blue- lipids decreased in PWH

Lipid species have been associated with CVD and diabetes

Stegemann et al *Circulation* 2014
Meikle et al *ATVB* 2011
Fernandez et al *PlosOne* 2013
Wong et al *PlosOne* 2014
Haus et al *Diabetes* 2009
Toledo et al *Am J Clin Nutr* 2017
Razquin et al *Diabetes Care* 2018

Belury et al *Pathogens and Immunity* 2017

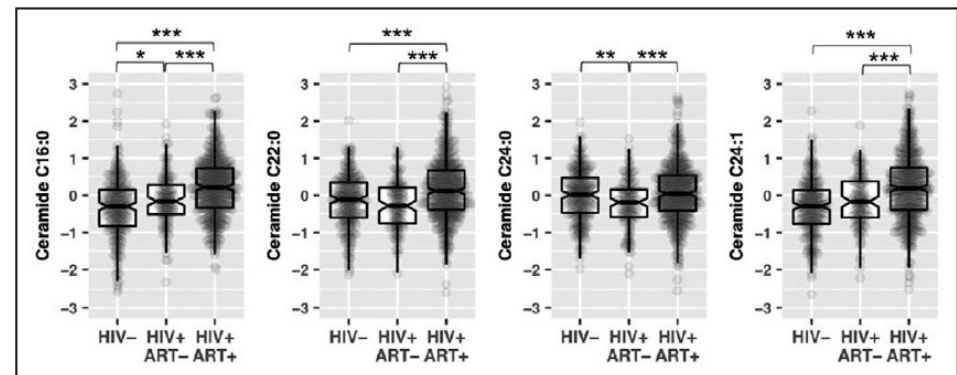
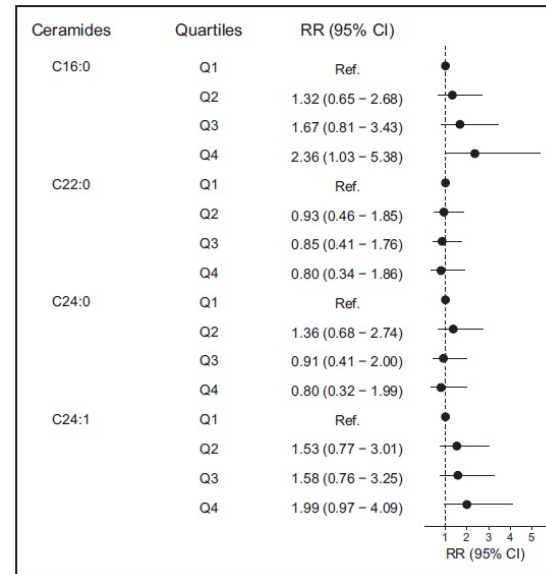
Elevated Plasma Ceramides Are Associated With Antiretroviral Therapy Use and Progression of Carotid Artery Atherosclerosis in HIV Infection

BACKGROUND: Ceramides have been implicated in the pathophysiology of HIV infection and cardiovascular disease. However, no study, to our knowledge, has evaluated circulating ceramide levels in association with subclinical cardiovascular disease risk among HIV-infected individuals.

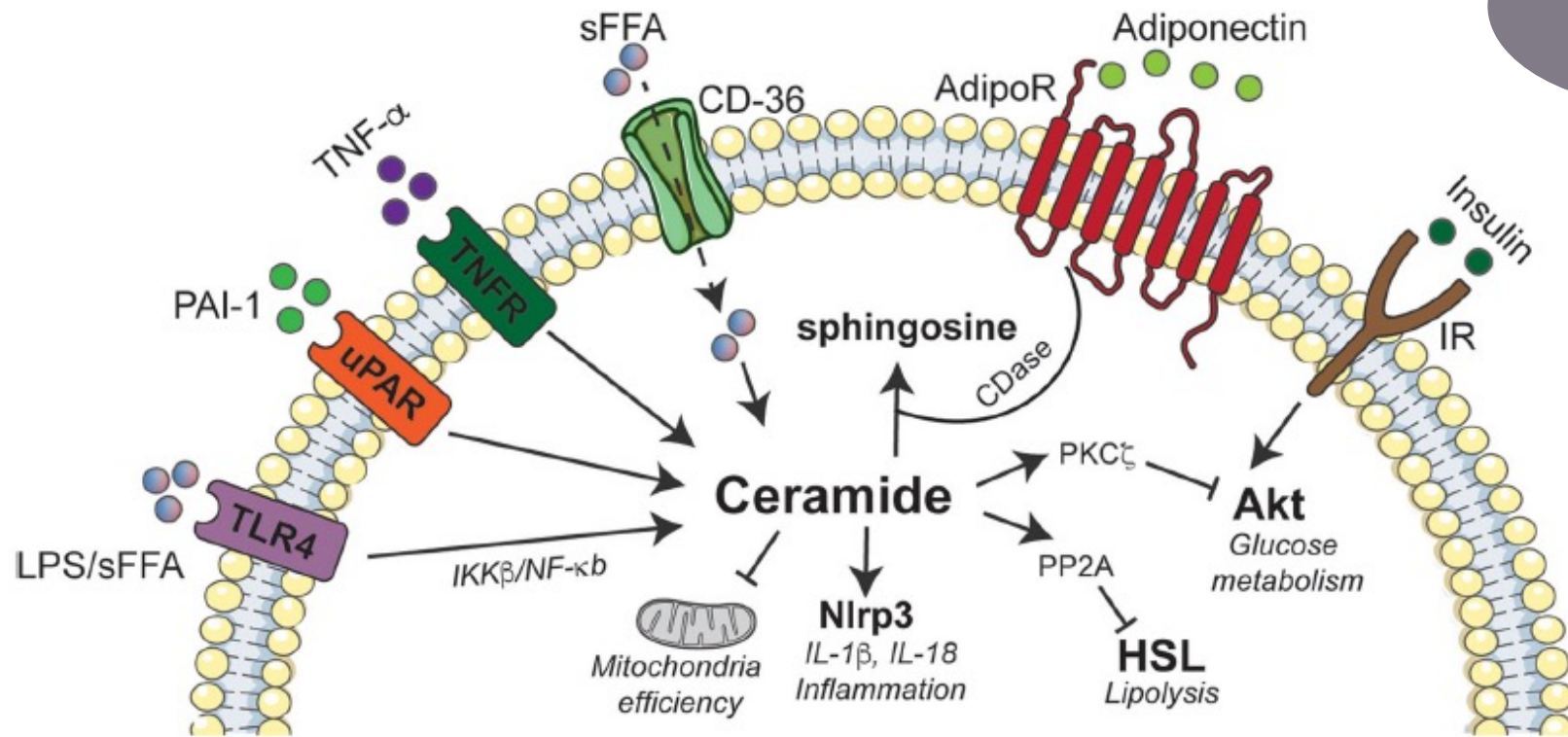
METHODS: Plasma levels of 4 ceramide species (C16:0, C22:0, C24:0, and C24:1) were measured among 398 women (73% HIV+) and 339 men (68% HIV+) without carotid artery plaques at baseline from the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. We examined associations between baseline plasma ceramides and risk of carotid artery plaque formation, assessed by repeated B-mode carotid artery ultrasound imaging over a median 7-year follow-up.

RESULTS: Plasma levels of C16:0, C22:0, and C24:1 ceramides were significantly higher in HIV-infected individuals compared with those without HIV infection (all $P < 0.001$), and further analysis indicated that elevated ceramide levels were associated with antiretroviral therapy use, particularly protease inhibitor use, in HIV-infected individuals (all $P < 0.001$). All 4 ceramides were highly correlated with each other ($r = 0.70-0.94$; all $P < 0.001$) and significantly correlated with total-cholesterol ($r = 0.42-0.58$; all $P < 0.001$) and low-density lipoprotein cholesterol ($r = 0.24-0.42$; all $P < 0.001$) levels. Of note, C16:0 and C24:1 ceramides, rather than C22:0 and C24:0 ceramides, were more closely correlated with specific monocyte activation and inflammation markers (eg, $r = 0.30$ between C16:0 ceramide and soluble CD14; $P < 0.001$) and surface markers of CD4⁺ T-cell activation. A total of 112 participants developed carotid artery plaques over 7 years, and higher levels of C16:0 and C24:1 ceramides were significantly associated with increased risk of carotid artery plaques (relative risk [95% CI] = 1.55 [1.29, 1.86] and 1.51 [1.26, 1.82] per standard deviation increment, respectively; both $P < 0.001$), after adjusting for demographic and behavioral

Wei Zhao, MS*
 Xueyin Wang, PhD*
 Amy A. Deik, BA
 David B. Hanna, PhD
 Tao Wang, MD, PhD
 Sabina A. Habermen, PhD
 Sanjiv J. Shah, MD
 Jason M. Lazar, MD
 Howard N. Hodis, MD
 Alan L. Landay, PhD
 Bing Yu, PhD
 Deborah Gustafson, PhD
 Kathryn Anastos, MD
 Wendy S. Post, MD
 Clary B. Clish, PhD
 Robert C. Kaplan, PhD
 Qibin Qi, PhD



Ceramides can contribute to inflammation, mitochondrial dysfunction, and insulin resistance.



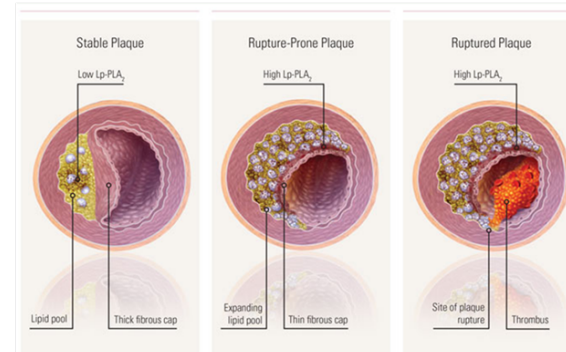
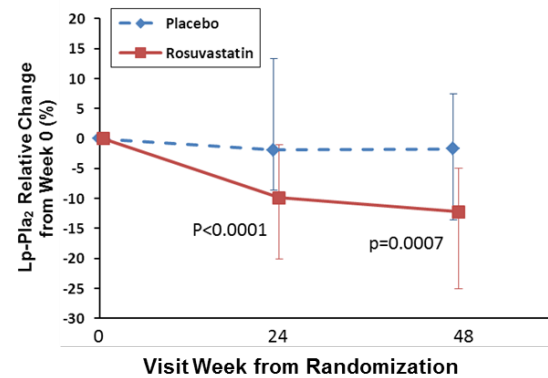
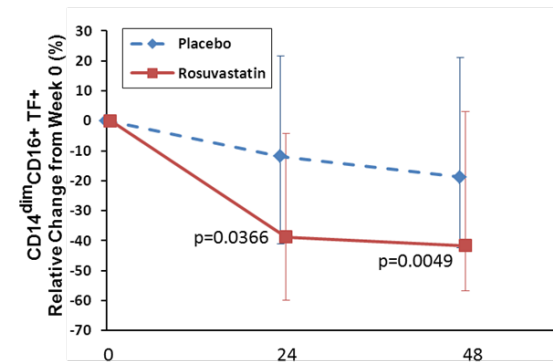
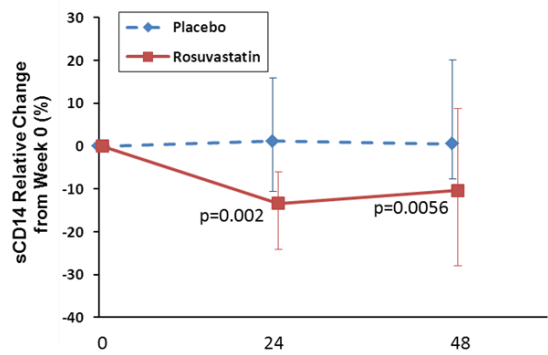
Metabolism

Inflammation

Chaurasia et al *Frontiers in Immunology* 2020

Statin treatment decreases monocyte activation and inflammation in PWH.

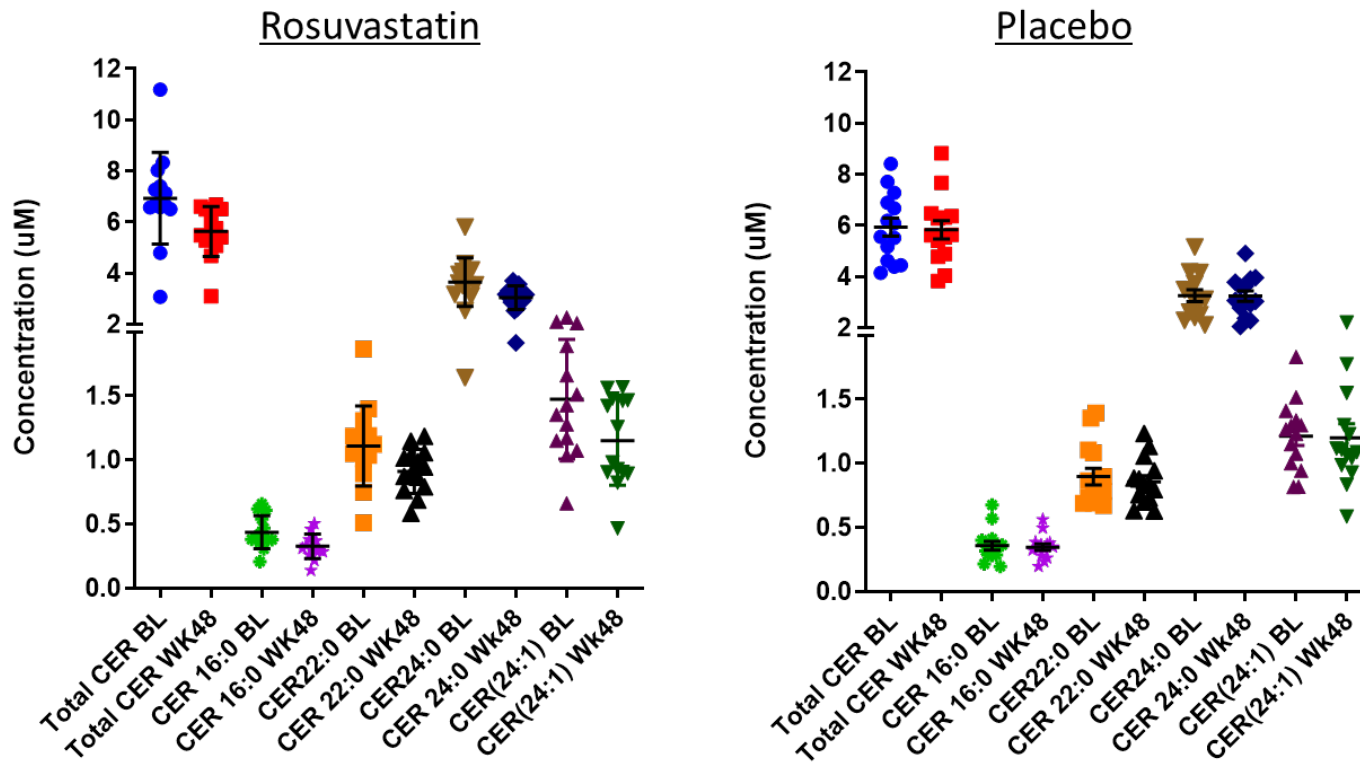
SATURN HIV Study



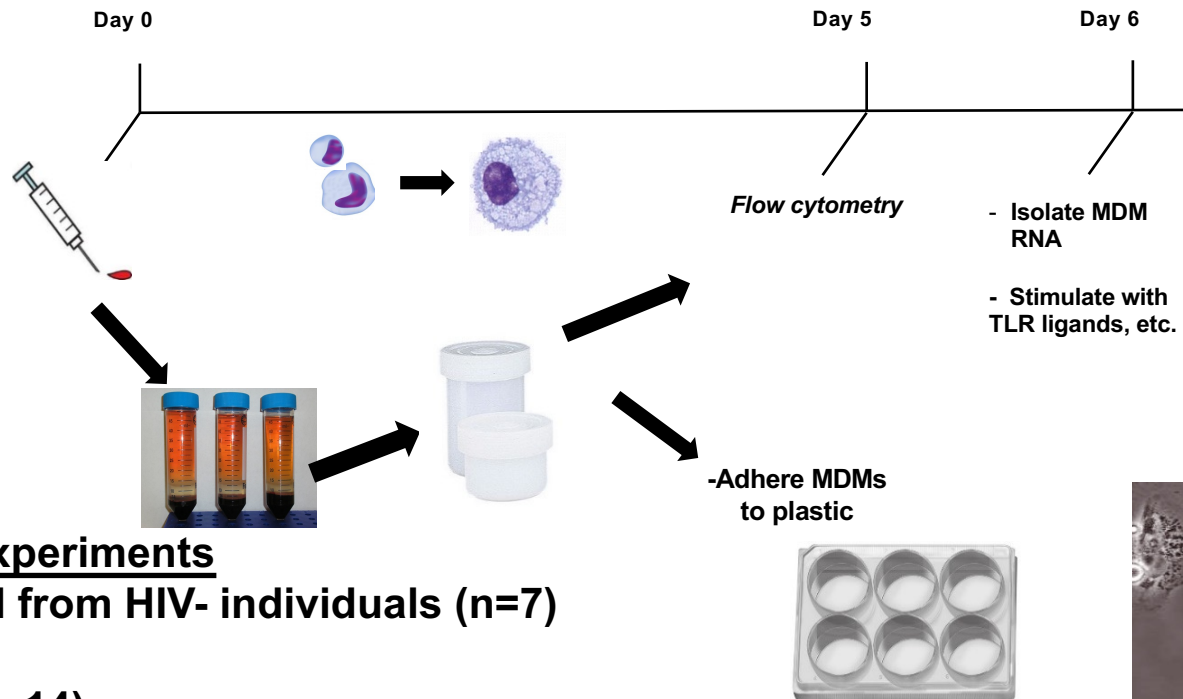
Funderburg et al *CID* 2014 and *JAIDS* 2015, Eckard *JID* 2014, Hileman et al *AIDS* 2016, Funderburg *P&I* 2016

Statin treatment decreases monocyte activation, inflammation, and ceramide levels in PWH.

SATURN HIV Study



Monocyte derived macrophage (MDM) are a model for tissue/plaque macrophages and are activated by their environment.

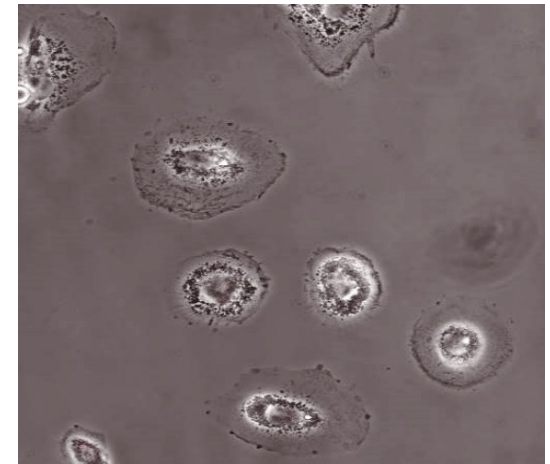


Pooled Serum Experiments

PBMCs collected from HIV- individuals (n=7)

Pooled Serum (n=14)

- 1) SATURN statin users Baseline
- 2) SATURN statin users Week 48
- 3) SATURN placebo users Baseline
- 4) SATURN placebo users Week 48



Statin therapy may reduce CVD events in PWH and improve “biological age?”

Table 3. Comparison of Demographic and Clinical Parameters by Presence of Plaque (continued)

Parameter	Participants, No./total No. (%)			P value
	All participants (n = 755)	Coronary plaque		
		None (n = 387)	Present (n = 368)	
Inflammation and immune activation biomarkers, median (IQR)				
Insulin, µU/mL	6.7 (4.5-11.7)	6.7 (4.4-11.7)	6.8 (4.7-11.8)	.29
sCD14, ng/mL	1817 (1527-2184)	1838 (1549-2188)	1786 (1468-2176)	.18
sCD163, ng/mL	842 (625-1089)	839 (615-1107)	842 (628-1087)	.67
MCP-1, pg/mL	185 (146-242)	180 (139-229)	194 (155-252)	<.001
IL-6, pg/mL	1.58 (0.99-2.79)	1.45 (0.96-2.60)	1.71 (1.05-3.04)	.008
LpPLA2, ng/mL	130 (92-168)	120 (85-157)	136 (103-177)	<.001
oxLDL, mU/L	53.1 (41.9-69.9)	50.4 (40.4-64.2)	56.6 (45.0-73.3)	<.001
hsCRP, mg/dL	0.18 (0.08-0.36)	0.16 (0.08-0.34)	0.19 (0.08-0.40)	.10
hsCRP categories				
Lower risk, <0.10	219/742 (29.5)	121/380 (31.8)	98/362 (27.1)	.17
Average risk, 0.10-0.30	301/742 (40.6)	155/380 (40.8)	146/362 (40.3)	
Higher risk, 0.31-1.00	161/742 (21.7)	80/380 (21.1)	81/362 (22.4)	
Highest risk, >1.00	61/742 (8.2)	24/380 (6.3)	37/362 (10.2)	

Metabolism

Inflammation



Randomized Trial to Prevent Vascular Events in HIV

Hoffman et al *JAMA Open Network* 2021

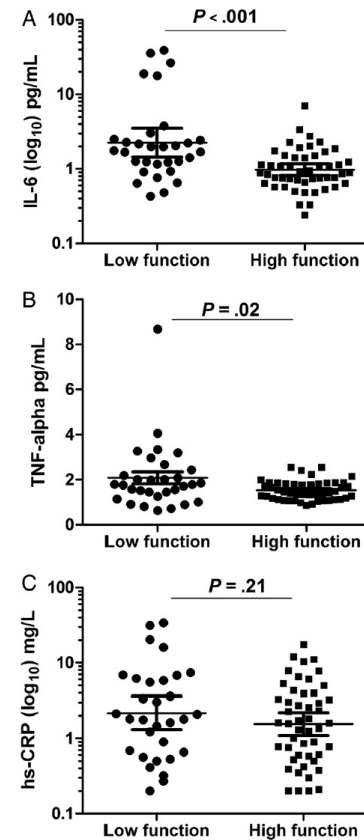
Frailty and functional impairments are also associated with aging and inflammation

Inflammation

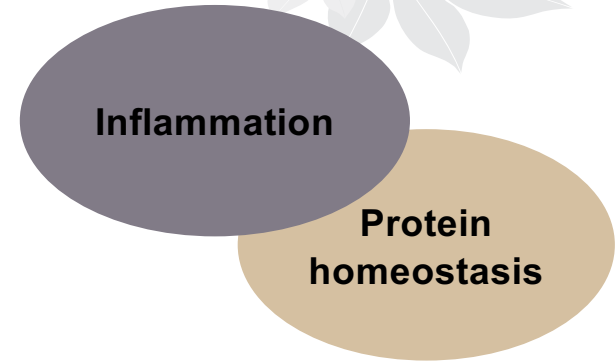
Association of Functional Impairment with Inflammation and Immune Activation in HIV Type 1-Infected Adults Receiving Effective Antiretroviral Therapy

Kristine M. Erlandson,^{1,2} Amanda A. Allshouse,³ Catherine M. Jankowski,² Eric J. Lee,¹ Kevin M. Rufner,⁴ Brent E. Palmer,⁵ Cara C. Wilson,¹ Samantha MaWhinney,³ Wendy M. Kohrt,² and Thomas B. Campbell¹

¹Division of Infectious Diseases, ²Division of Geriatric Medicine, ³Department of Biostatistics and Informatics, University of Colorado, Denver, ⁴Division of Gastroenterology and Hepatology and ⁵Division of Allergy and Clinical Immunology, Department of Medicine,



Muscle quality is related to inflammation in PWH

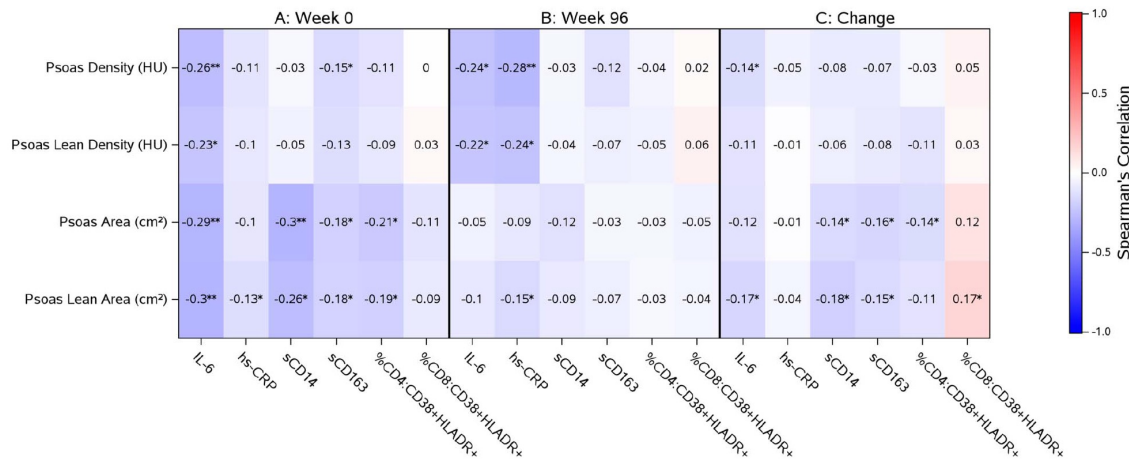


Poorer Muscle Quality and Quantity With ART Initiation Is Associated With Greater Inflammation and Immune Activation

Arianna Kousari, MD,^a Carlee Moser, PhD,^b Maxine Olefsky, MS,^b Todd T. Brown, MD, PhD,^c Judith S. Currier, MD,^d Grace A. McComsey, MD,^e Ann Scherzinger, PhD,^f James H. Stein, MD,^g Jordan E. Lake, MD, MSc,^h and Kristine M. Erlandson, MD, MSⁱ

Kousari et al

J Acquir Immune Defic Syndr • Volume 88, Number 4, December 1, 2021

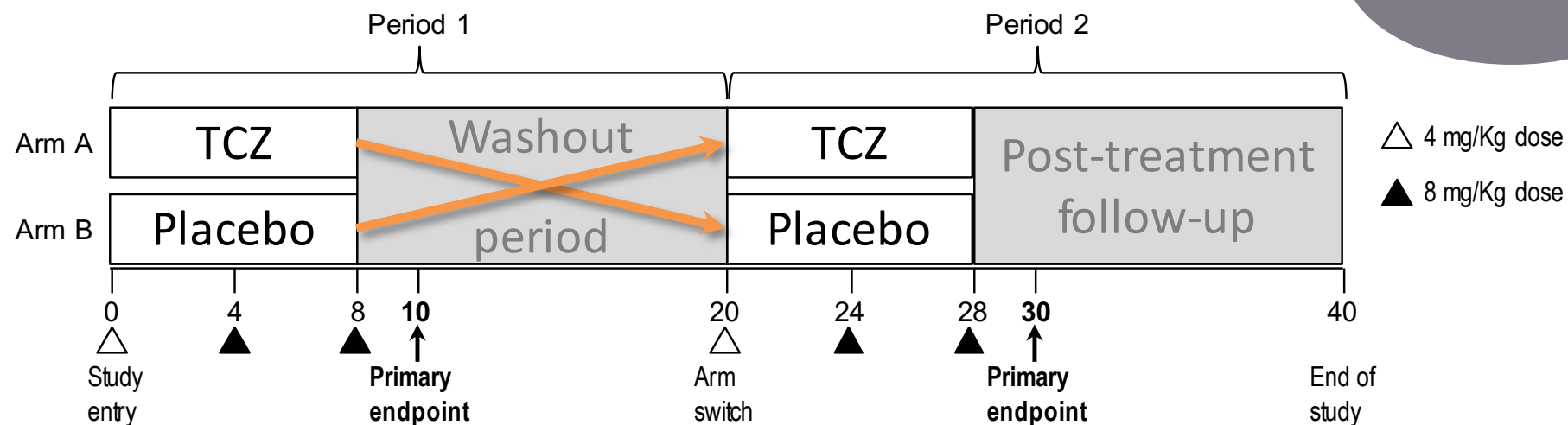


IL-6 may modulate protein homeostasis

- STAT3 and ubiquitin proteasome activation
- mTOR inhibition and decreased protein synthesis

IL-6 receptor blockade with Tocilizumab (TCZ) in people with HIV

CROI 2020 Abstract 113

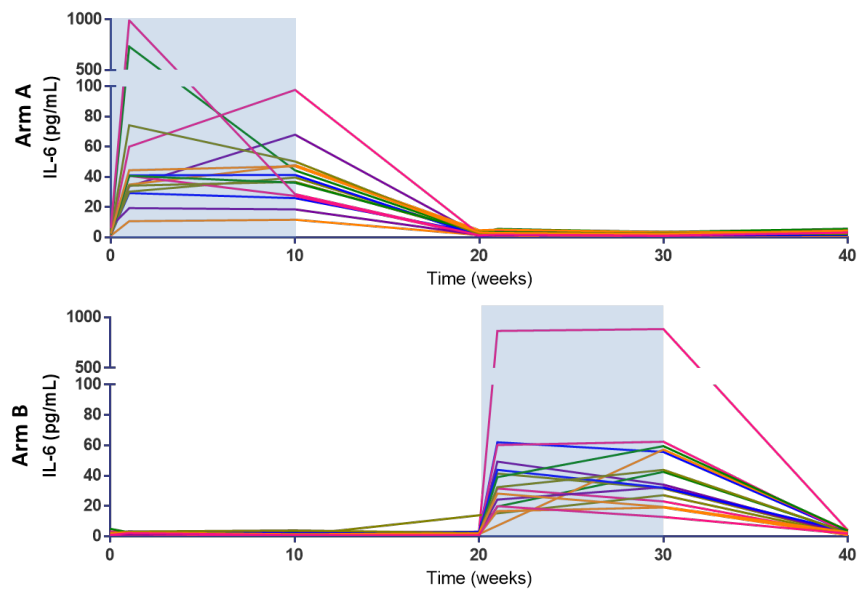


Inflammation

- Participants were HIV+, aged 18-60 with suppressed viremia on stable ART, CD4+ T cells between 350 and 1,000, and no active major comorbidities
- Intervention: IV Tocilizumab, 4 mg/Kg X 1 then 8 mg/Kg x 2 every 4 weeks or matching placebo

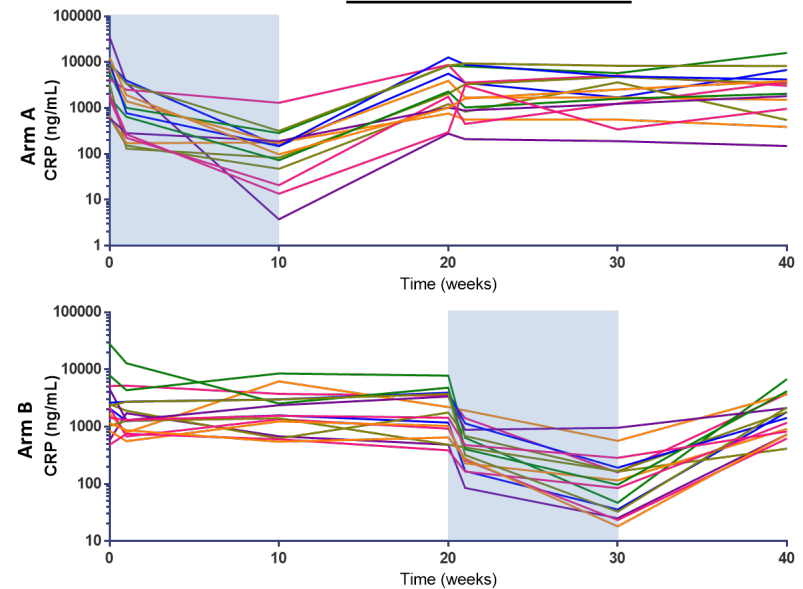
Tocilizumab (TCZ) treatment in PWH reduces markers of inflammation and immune activation that are associated with morbidity and mortality

IL-6 Levels



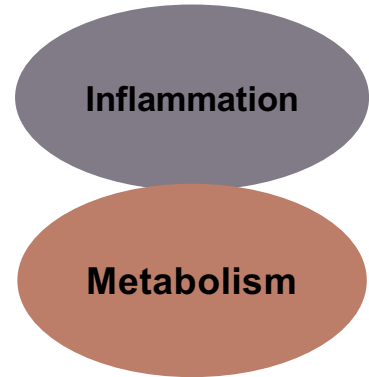
Blue area= TCZ treatment

CRP Levels

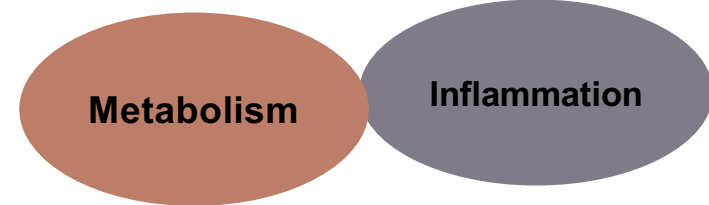
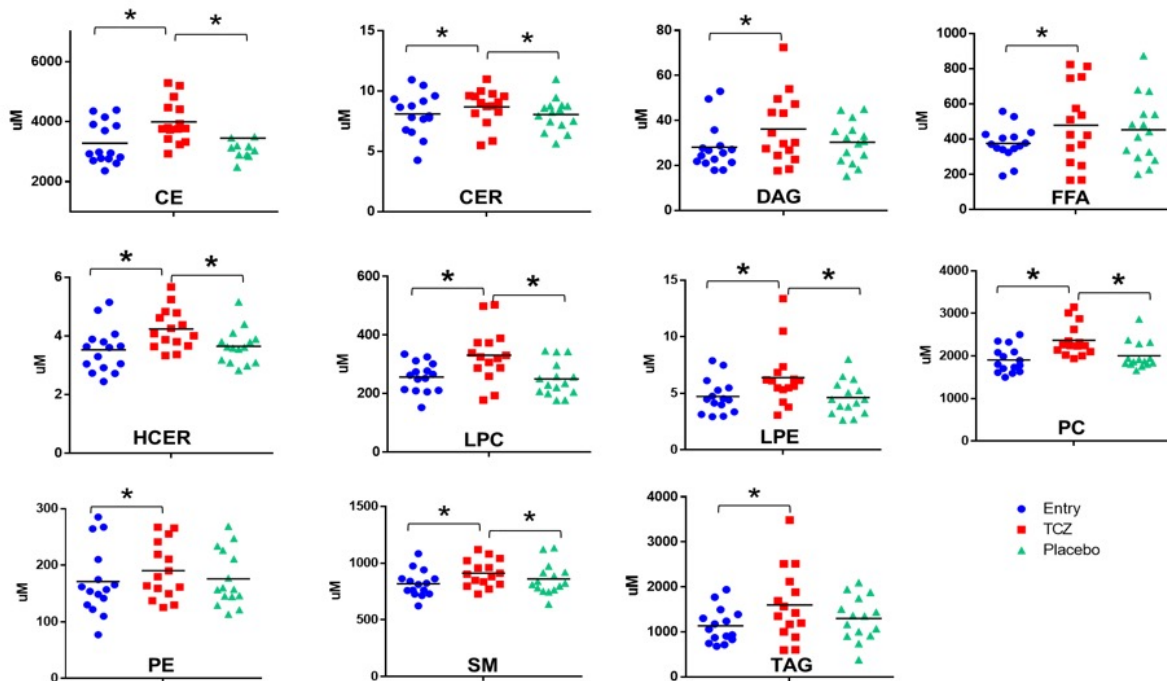


IL-6 blockade with TCZ in PWH reduces markers of inflammation and immune activation, but also increases the concentration of multiple lipid species

Activity	Est. effect	P-value
sCD14	-312 ng/mL	<0.001
sCD40L	-466 pg/mL	<0.001
sTNFR1	-106 pg/mL	0.002
D-dimer	-47 ng/mL	<0.001
sTNFR2	-168 pg/mL	0.04
sCD163	61 ng/mL	0.06
IP10	14 pg/mL	0.13
IL-22	-0.44 pg/mL	0.83
I-FABP	171 pg/mL	0.48
Zonulin	-1.33 ng/mL	0.33



IL-6 blockade with TCZ in PWH reduces markers of inflammation and immune activation, but also increases the concentration of multiple lipids



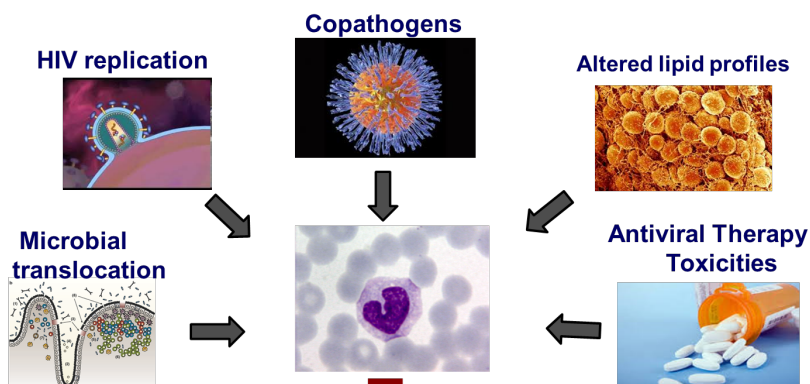
	Estimate (95% CI)	Effect size	p
CE	541.4 (361.9, 712.1)	0.73	<0.0001
CER	0.56 (0.086, 1.14)	0.43	0.0167
DAG	6.22 (2.32, 12.08)	0.55	0.0015
DCER	0.13 (0.036, 0.23)	0.47	0.0076
FFA	55.4 (-38.3, 158.8)	0.21	0.2474
HCER	0.52 (0.31, 0.73)	0.74	<0.0001
LCER	0.16 (-0.073, 0.39)	0.23	0.2023
LPC	56.5 (29.4, 83.1)	0.60	5.00E-04
LPE	1.24 (0.43, 2.30)	0.49	0.0051
PC	386.8 (249.2, 517.1)	0.76	<0.0001
PE	20.3 (7.9, 34.5)	0.54	0.0022
SM	61.8 (24.0, 107.2)	0.56	0.0012
TAG	365.0(164.7, 617.8)	0.59	5.00E-04

What are the underlying biological mechanisms that influence inflammation and promote age-related comorbidities in PWH?

Epigenetics

Stem Cells
and
regeneration

Adaptation to
Stress



Metabolism

Macromolecular
damage

Protein
homeostasis

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The Funderburg Lab

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Aya Cannon Undergraduate student

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Morgan Boucher M.S.
Brandon Snyder B.S.
Frances Avila-Soto B.S.
Lane Hornsby B.S.

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Jesse Kwiek, Abbie Norris-Turner,
Thura Harfi, Namal Liyanage,
Carlos Malvestutto, Ethan Morgan,
Shaurya Prakash, Chris Taylor, Randy Wexler

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R01HL134544, R01HL158592



Outside Collaborators

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- Dr. Michael Lederman and Dr. Scott Sieg
- Drs. Grace McComsey, Corri Hileman, Chris Longenecker, Sahera Dirajlal-Fargo and the SATURN HIV Team
- Dr. Michael Freeman and Dr. Soumya Panigrahi
- Drs. David Zidar, Mukesh Jain, Jeff Jacobson and Robert Asaad
- Dr. Nehal Mehta and team at NHLBI
- Dr. Jordan Lake - UT Houston
- Dr. Nichole Klatt – University of Minnesota
- Dr. Kristine Erlandson – CU
- Drs. Amanda Willig and Turner Overton UAB
- Dr. Matthew Feinstein Northwestern
- Members of the HIV and Aging Working group in the ACTG
- Dr. Larry Schlesinger- Texas Biomed Macrophage protocol

All of the blood donors, clinicians, and community members



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