# Session 3: Chronic Inflammation

## Abstract 3: Macrophage Arterial Infiltration Relates to Plaque Type and Immune Activation in HIV

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# Macrophage-specific arterial infiltration relates to plaque type and immune activation in HIV

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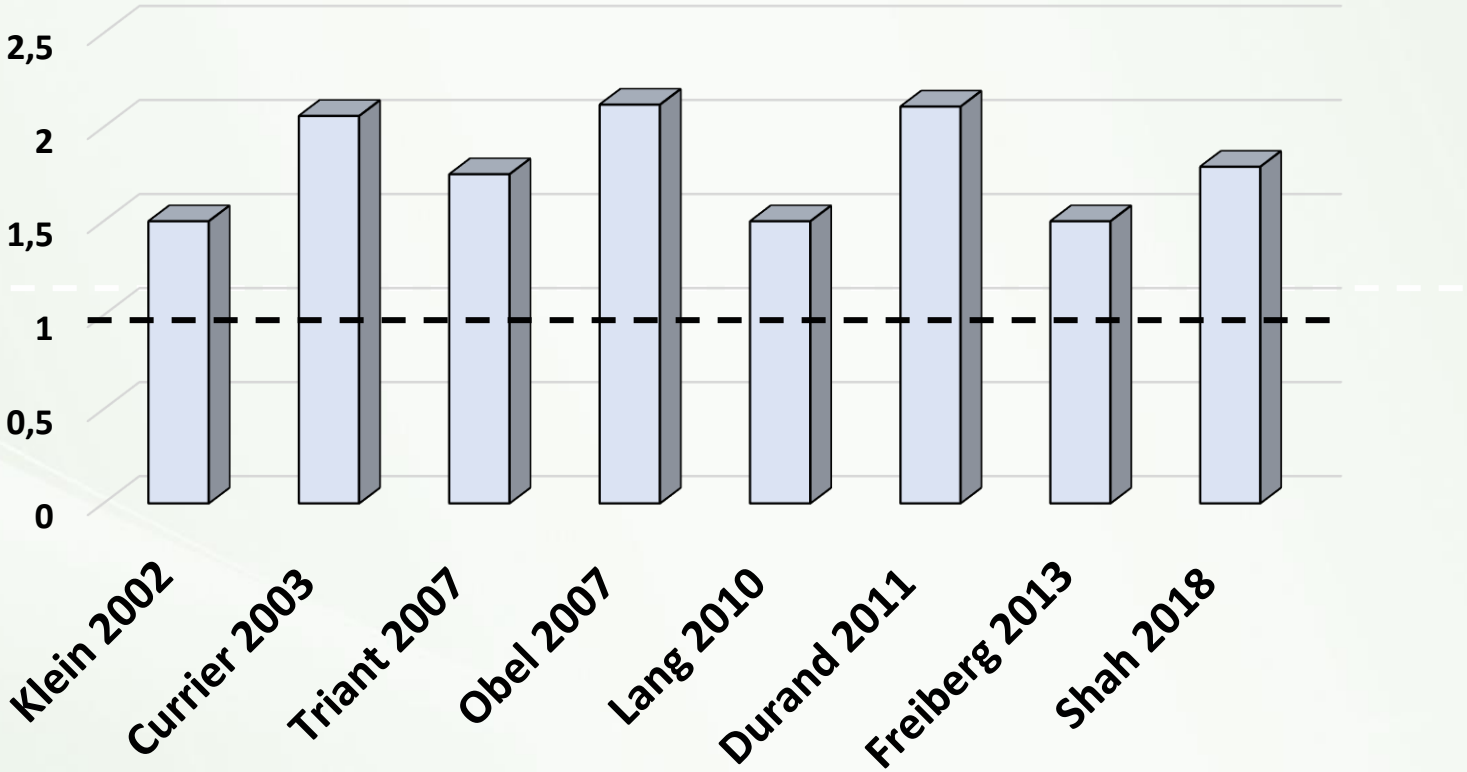
# Atherosclerotic cardiovascular disease risk is increased among PWH on ART

## Relative risk of MI in people with versus without HIV (US/European cohorts)

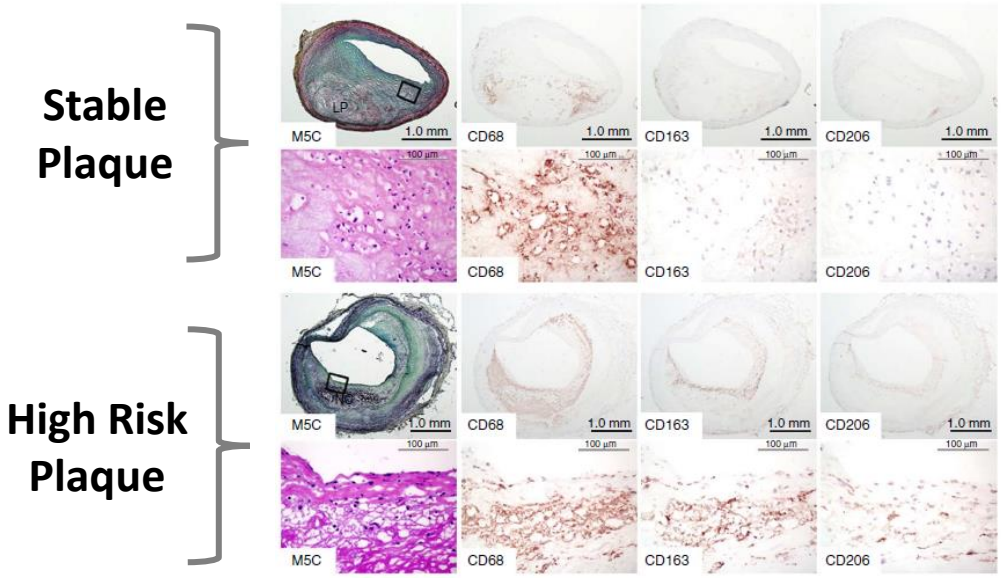


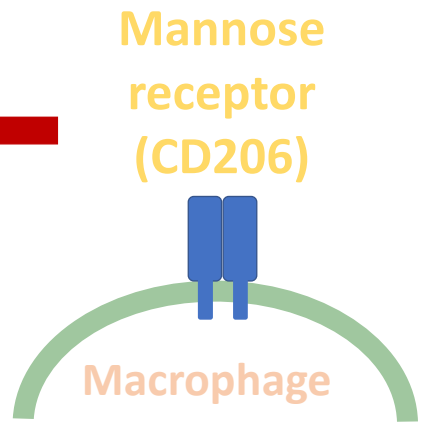

**We have hypothesized that persistent monocyte activation among PWH on ART results in downstream arterial inflammation and subsequently accelerated atherosclerosis among PWH**

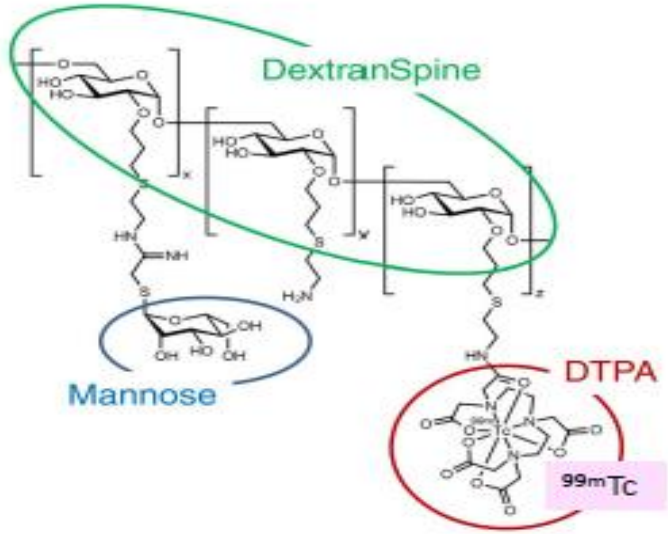
Slide adapted from Zanni/ Srinivasa /Grinspoon

# Technetium 99m tilmanocept ($^{99m}$Tc-tilmanocept) is a macrophage-specific radiotracer that binds to the macrophage mannose receptor, CD206

**Higher CD206+ macrophage infiltration in high-risk "thin-cap" atherosclerotic plaque as compared to stable "thick-cap" atherosclerotic plaque**

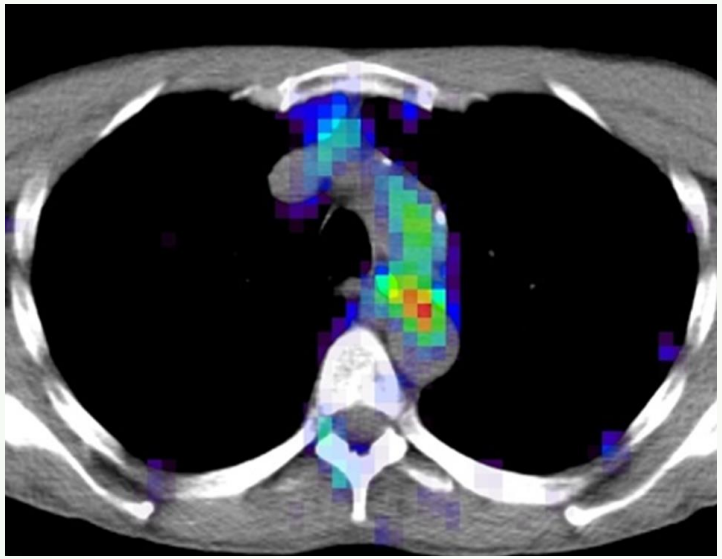


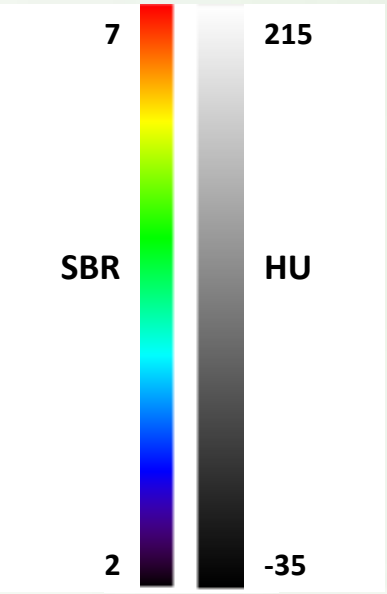




Wallace Ann Surg Oncol 2003, Tausch Onco Targets Ther 2014, Wallace Ann Surg Oncol 2013, Leong Ann Surg Oncol 2011, Marcinow JAMA Otolaryngol 2013, Tahara Nature Medicine 2012

# 99m Tc-tilmanocept SPECT/CT is a novel imaging modality that allows quantification of macrophage-specific arterial inflammation/ vascular inflammation

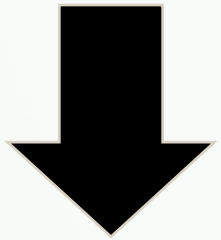





**Aortic 99mTc-tilmanocept uptake was quantified using a signal to background ratio (SBR): aortic 99mTc-tilmanocept activity to background muscle activity**

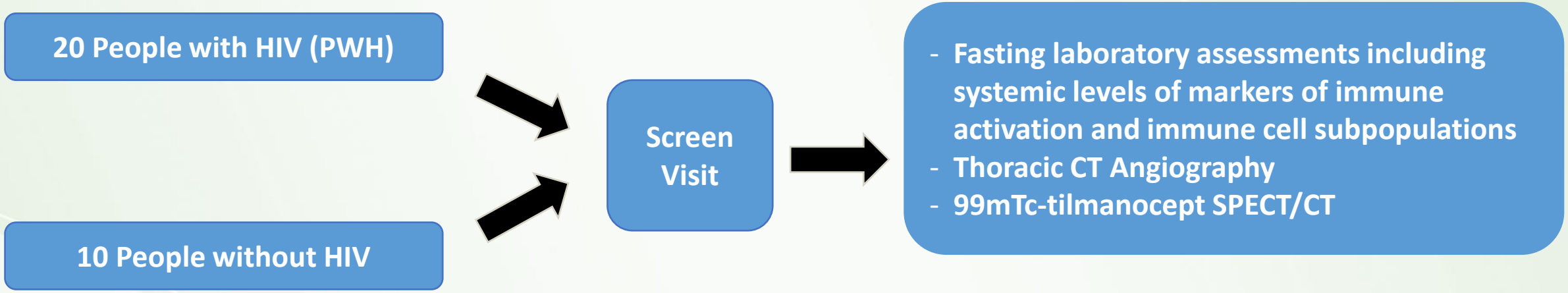
**1. What are the differences in macrophage-specific arterial inflammation among people with versus without HIV?**

**2. What is the relationship between macrophage-specific arterial inflammation, atherosclerotic plaque volume and systemic immune activation among PWH?**



**We hypothesized that PWH would have a higher level of aortic macrophage-specific arterial inflammation in relation to non-calcified aortic plaque and select immune pathways.**

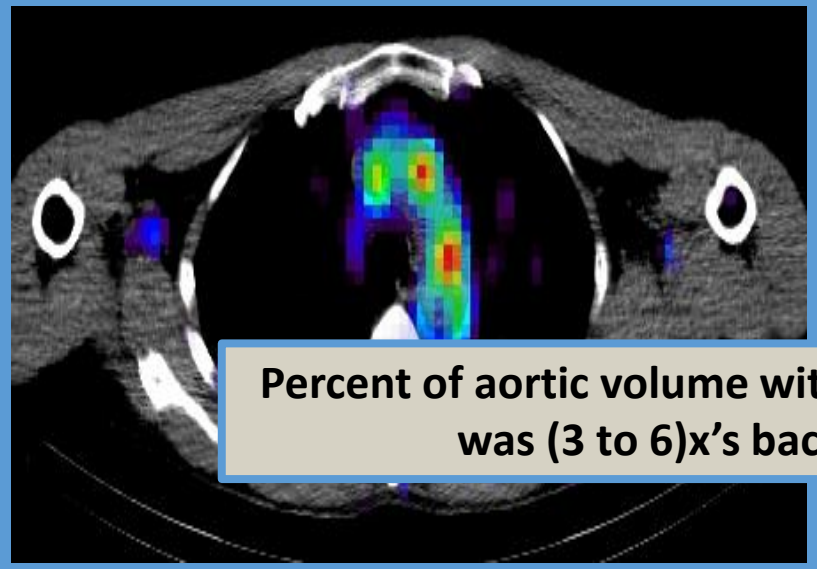
# Study Design

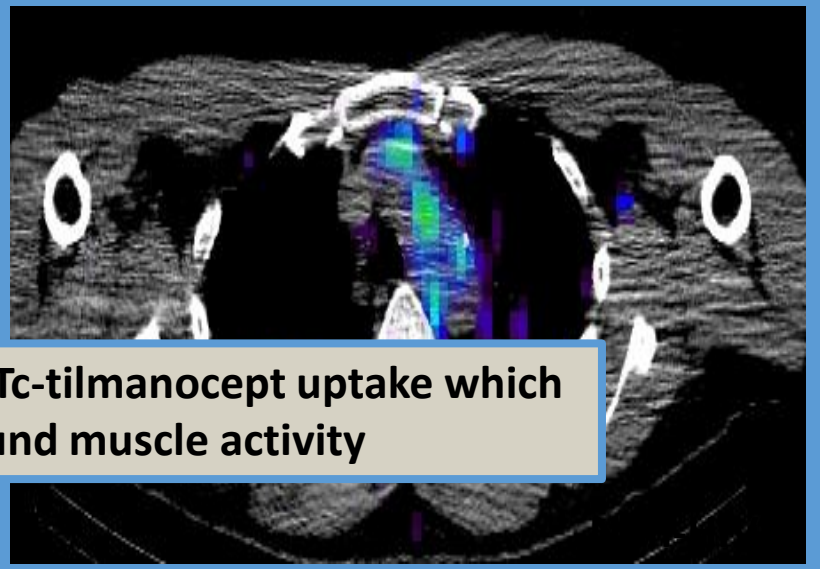


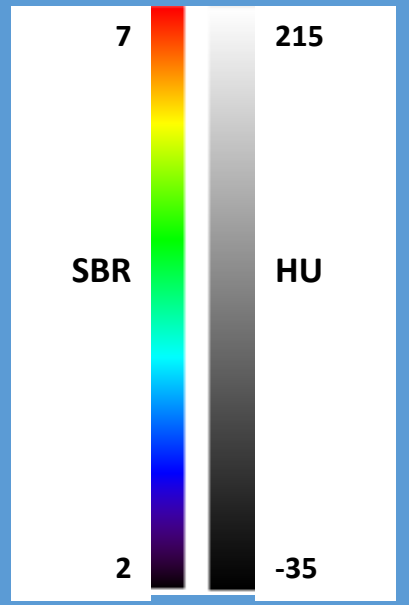

| Major Inclusion Criteria | Major Exclusion Criteria |
|---|---|
| - 18 years or older<br>- PWH: Stable ART for at least 3 months and no interruption in ART > 2 weeks over the last 3 months | - History of cardiovascular disease<br>- Use of lipid lowering agents<br>- Use of anti-inflammatory medications<br>- Contraindication to CTA or SPECT/CT imaging |

| | Participants with HIV N=20 | Participants without HIV N=10 | P-value |
|---|---|---|---|
| **Baseline Demographics** | | | |
| Age (years) | 55 ± 7 | 58 ± 4 | 0.12 |
| Sex (%)<br>Male<br>Female | <br>80 (16/20)<br>20 (4/20) | <br>80 (8/10)<br>20 (2/10) | <br>1.00 |
| Race (%)<br>White<br>Black<br>Asian<br>Other | <br>50 (10/20)<br>40 (8/20)<br>5 (1/20)<br>5 (1/20) | <br>70 (7/10)<br>30 (3/10)<br>0 (0/10)<br>0 (0/10) | <br>0.52 |
| 10 – Year ASCVD Risk Score (%) | 7.3 ± 4.7 | 8.1 ± 5.3 | 0.70 |
| BMI (kg/m$^2$) | 25.7 ± 4.7 | 27.6 ± 5.3 | 0.34 |
| LDL-C (mg/dL) | 111 ± 27 | 107 ± 33 | 0.73 |
| HDL-C (mg/dL) | 49 (42, 54) | 57 (45, 73) | 0.06 |
| Triglycerides (mg/dL) | 103 (77, 178) | 104 (77, 160) | 0.79 |
| Current HTN (%) | 15 (3/20) | 10 (1/10) | 0.70 |
| Current Smoking (%) | 30 (6/20) | 30 (3/10) | 1.00 |
| **HIV specific-parameters** | | | |
| Duration of HIV Diagnosis (years) | 22 ± 9 | -- | -- |
| CD4+ T-Cell Count (cells/mm$^3$) | 633 ± 269 | -- | -- |
| Log HIV Viral Load (copies/mL) | 1.28 (1.28, 1.42) | -- | -- |
| **Aortic atherosclerotic plaque volume on CTA** | | | |
| Total (non-calcified and calcified) aortic plaque volume (mm$^3$) | 284.5 (0.0, 578.6) | 109.1 (0.0, 350.1) | 0.45 |
| Non-calcified aortic plaque volume (mm$^3$; HU<130) | 79.8 (0.0, 481.0) | 28.1 (0.0, 206.0) | 0.42 |
| Calcified aortic plaque volume (mm$^3$; HU≥130) | 97.6 (0.0, 262.4) | 34.3 (0.0, 114.1) | 0.32 |

# Macrophage-specific arterial inflammation was higher among PWH on ART compared to matched participants of similar ASCVD risk without HIV

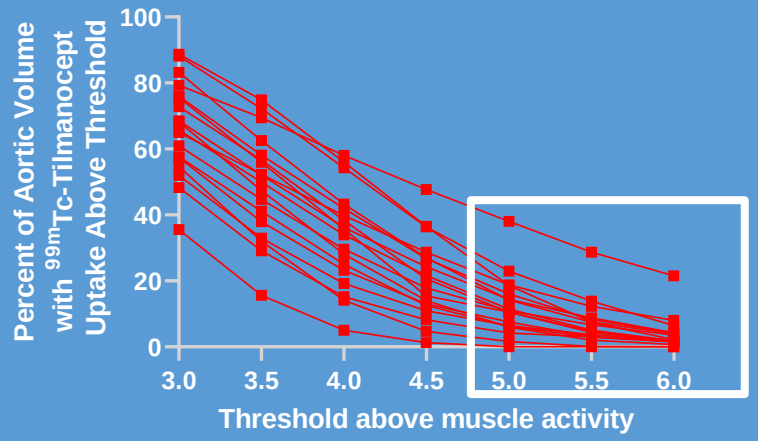




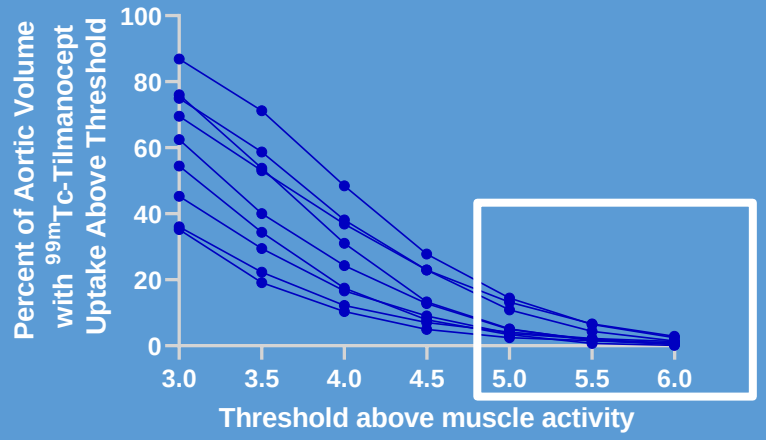



**Percent of aortic volume with $^{99m}$Tc-tilmanocept uptake which was (3 to 6)x's background muscle activity**

Patricipants with HIV

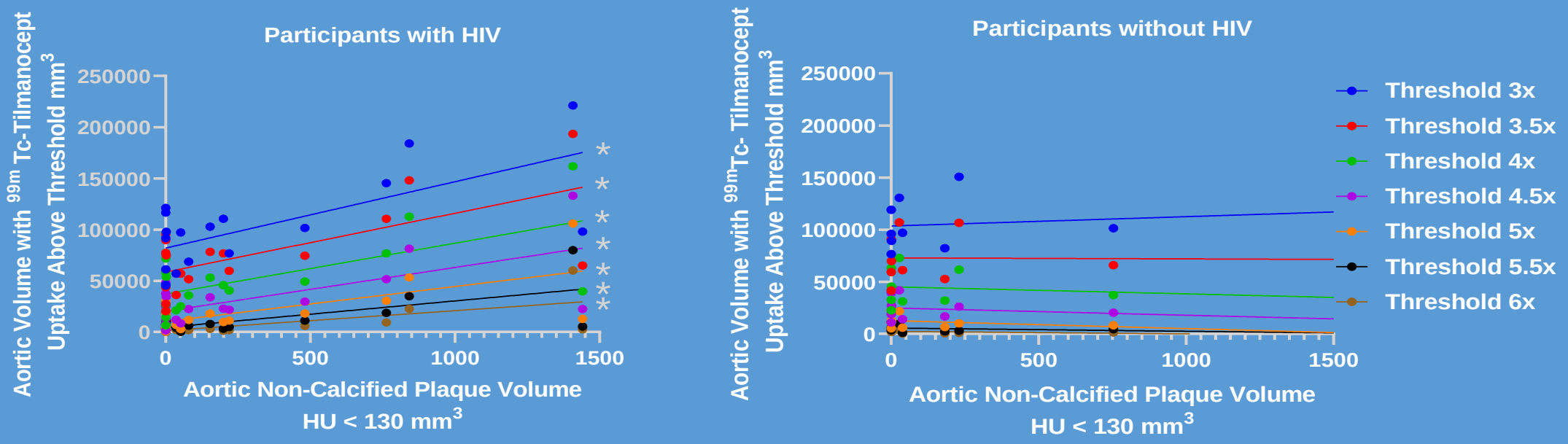



Participants without HIV




**In a repeated measures ANOVA controlling for sex, aortic $^{99m}$Tc-tilmanocept uptake was higher among PWH than in participants without HIV (P=0.02)**

# Among PWH (and not among participants without HIV), non-calcified aortic plaque volume related directly with aortic volume with $^{99m}$Tc-tilmanocept uptake




*P<0.05

In multivariable regression modelling for aortic $^{99m}$Tc-tilmanocept uptake, the interaction term between aortic plaque volume and HIV status was significant for non-calcified plaque volume (P=0.0001 for interaction) but not for calcified plaque volume (P=0.83 for interaction)

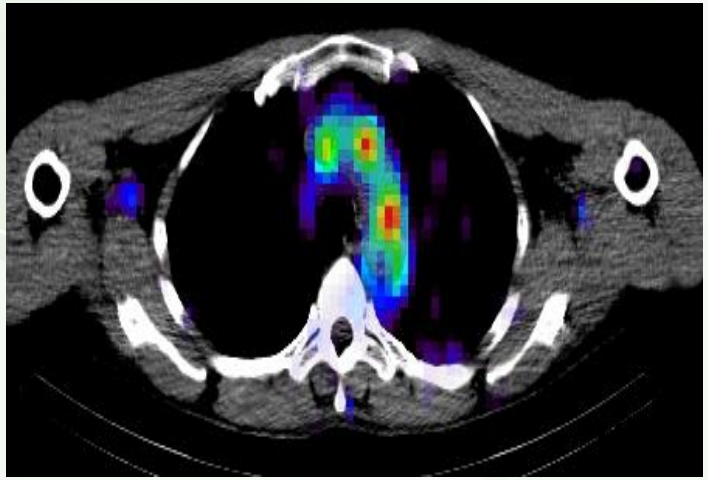
# Immune activation markers, including markers of NLRP3 inflammasome activation, were increased in HIV and related to macrophage-specific arterial inflammation

| | Participants with HIV N=19 | Participants without HIV N=9 | P-value for between group comparison | β-estimate for relationship with $^{99m}$Tc-tilmanocept uptake | P-value for relationship with $^{99m}$Tc-tilmanocept uptake |
|---|---|---|---|---|---|
| **Circulating systemic markers of immune activation** | | | | | |
| sCD14 (ng/mL) | 1653.8 ± 282.3 | 1500.8 ± 217.8 | 0.13 | 13.7 | 0.08 |
| sCD163 (ng/mL) | 617.0 (515.0, 1101.2) | 540.5 (453.8, 675.4) | 0.26 | 1.1 | 0.80 |
| MCP-1/CCL2 (pg/mL) | 217.7 ± 60.6 | 172.3 ± 34.8 | 0.02 | -161.2 | 0.0001 |
| CXCL10/IP-10 (pg/mL) | 161.4 (111.9, 230.2) | 76.7 (58.6, 87.3) | 0.0004 | -13.3 | 0.43 |
| Lp-PLA2 (ng/mL) | 131.8 ± 71.9 | 145.8 ± 65.8 | 0.61 | 22.9 | 0.44 |
| IL-18 (pg/mL) | 147.9 (101.8, 193.4) | 147.3 (97.0, 189.1) | 0.75 | -5.3 | 0.77 |
| Caspase-1 (pg/mL) | 77.3 (48.5, 97.5) | 45.6 (38.4, 55.5) | 0.01 | 137.4 | 0.004 |
| hsIL-6 (pg/mL) | 2.4 (1.5, 4.8) | 1.8 (1.0, 4.1) | 0.46 | -1160.4 | 0.13 |
| oxLDL (U/L) | 47.1 (39.7, 53.6) | 42.1 (34.8, 55.6) | 0.66 | -144.4 | 0.33 |

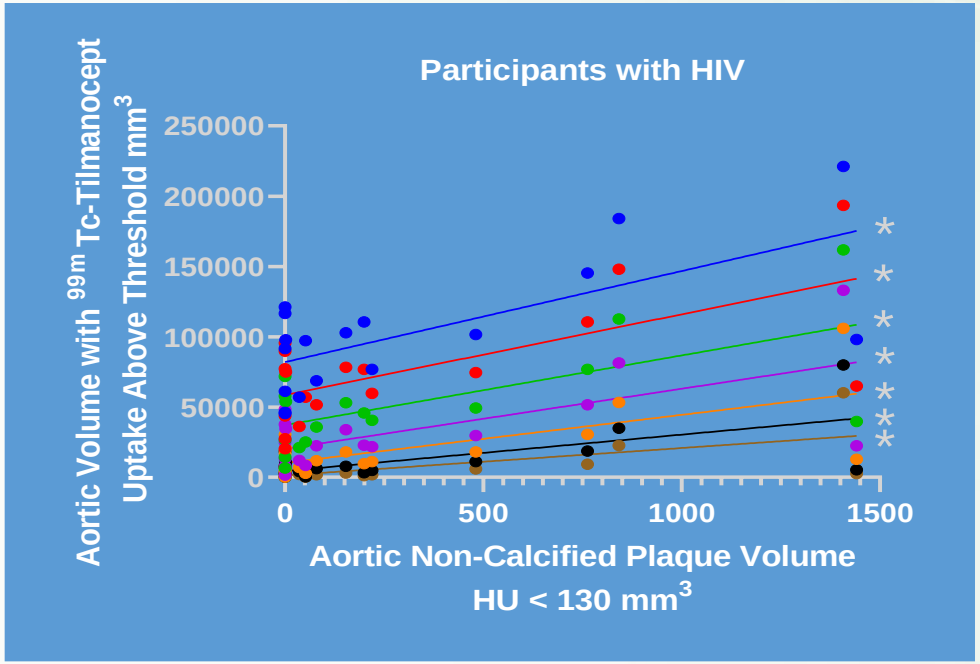
# Immune cell subpopulations differed between participants with versus without HIV and related to macrophage-specific arterial inflammation

| | Participants with HIV N=19 | Participants without HIV N=9 | P-value for between group comparison | β-estimate for relationship with $^{99m}$Tc-tilmanocept uptake | P-value for relationship with $^{99m}$Tc-tilmanocept uptake |
|---|---|---|---|---|---|
| **Circulating monocyte subpopulations** | | | | | |
| % of monocytes from total PBMCs | 7.5 ± 1.8 | 4.6 ± 1.5 | 0.0003 | 2028.9 | 0.04 |
| Absolute number of CD14+CD16- cells/µL | 310.9 (214.6, 381.7) | 241.7 (159.9, 313.1) | 0.19 | 66.9 | <0.0001 |
| Absolute number of CD14+CD16+ cells/µL | 29.8 (21.0, 40.2) | 24.4 (12.2, 30.2) | 0.07 | 202.6 | 0.08 |
| Absolute number of CD14-CD16+ cells/µL | 23.9 ± 14.2 | 14.9 ± 4.9 | 0.02 | 554.2 | 0.0004 |
| **Circulating lymphocyte subpopulations** | | | | | |
| % of lymphocytes from total PBMCs | 40.4 ± 11.5 | 28.8 ± 6.3 | 0.002 | -264.6 | 0.14 |
| % CD4+ T-cells | 31.0 (24.7, 35.8) | 53.5 (45.0, 75.7) | <0.0001 | -240.3 | 0.04 |
| Absolute number of CD4+ T-cells/µL | 569.0 (408.2, 736.9) | 728.2 (600.5, 1100.6) | 0.03 | 12.5 | 0.04 |
| % CD8+ T-cells | 43.9 (31.6, 60.6) | 20.9 (14.9, 26.3) | 0.0006 | 343.8 | 0.009 |
| Absolute number of CD8+T-cells/µL | 887.3 ± 457.7 | 366.9 ± 261.1 | 0.001 | 13.3 | 0.005 |
| CD4+/CD8+ T-cell ratio | 0.6 (0.5, 1.3) | 2.8 (1.8, 4.9) | 0.0002 | -3166.8 | 0.02 |

## PWH had higher macrophage-specific arterial inflammation



## Among PWH, macrophage-specific arterial inflammation related primarily to non-calcified plaque volume




## NLRP3 inflammasome activation, T-cell senescence, and patrolling monocytes related significantly to macrophage-specific arterial inflammation

# Thank you

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- **Study Participants**
- **MGH Metabolism Unit**
- **MGH Gordon Center for Medical Imaging**
- **MGH Cardiovascular Imaging Research Center**
- **Boston College Department of Biology**
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