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Coronary Artery Plaque Composition and Severity Relate to the Inflammasome in HIV

646

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Background

- Despite antiretroviral therapy (ART), people with HIV (PWH) remain at higher risk for cardiovascular disease (CVD), with persistent immune activation as a major contributor to this increased risk
- The inflammasome, an innate immune complex that regulates the immunologic milieu via proinflammatory cytokines may contribute to persistent inflammation
- Priming/activation signals cause inflammasome complex formation, leading to caspase-1,which activates proinflammatory cytokines IL-1β and IL-18
- Among the general population, inflammasome activation may be causally linked to incident CVD
- Among PWH, higher inflammasome activity persists despite ART
- Limited data exist relating the inflammasome to coronary plaque in PWH

Methods

Study Design

- REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) enrolled PWH 40-75 years on stable ART with low-moderate traditional CVD risk
- A subset of US participants underwent baseline coronary computed tomography angiography (CTA) and inflammasome biomarker measurement (N=752)

Measurements

- CTAs were reviewed for coronary artery calcium (CAC) score, presence of any or vulnerable plaque
- Leaman score was calculated as an overall index of plaque burden, combining localization of coronary lesions, plaque composition, and degree of stenosis
  - Leaman score >5 is associated with incident cardiovascular events in the general population

Statistical Analysis

- Biomarker (caspase-1, IL-18, IL-1β) geometric means were compared by subgroups via ANOVA
- Relationships of log-transformed biomarkers to plaque indices were assessed by binary logistic regression, adjusted *a priori* for age, natal sex, LDL cholesterol, hypertension, current cigarette smoking, current and nadir CD4, and ART duration

IL-18 and IL-1β were independently associated with a higher odds of Leaman Score >5, a composite measure of coronary plaque burden linked to major cardiovascular events in the general population.

Participant Demographics

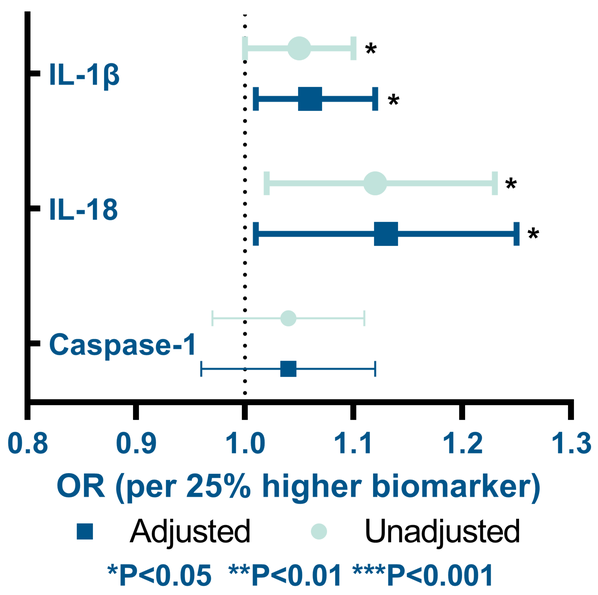
Characteristic	Total (N=752)
Age, years, median (Q1-Q3)	50 (46-55)
Female sex	133 (18%)
Race/Ethnicity	
White Non-Hispanic	280 (37%)
Black Non-Hispanic	265 (35%)
Hispanic (regardless of race)	178 (24%)
Current cigarette smoking	182 (24%)
ASCVD risk, %, median (Q1-Q3)	4.5 (2.6-6.8)
BMI, kg/m^2, median (Q1-Q3)	27.0 (24.3-30.2)

Participant HIV Characteristics

Characteristic	Total (N=752)
Current CD4, cells/mm^3, median (Q1-Q3)	601 (426-781)
Nadir CD4, cells/mm^3	
<50	162 (22%)
50-199	214 (29%)
200-349	208 (28%)
≥350	147 (20%)
HIV-1 RNA, copies/ml	
<LLQ	648 (87%)
LLQ - <400	78 (11%)
≥400	16 (2%)

Association of Inflammasome Biomarkers and Coronary Plaque Indices

Leaman Score >5



Leaman Score >5

Biomarker	Adjusted OR* (95% CI)	P Value
IL-1β	1.06 (1.01-1.12)	0.03
IL-18	1.13 (1.01-1.25)	0.03
Caspase-1	1.04 (0.96-1.12)	0.32

Presence of Plaque

Biomarker	Adjusted OR* (95% CI)	P Value
IL-1β	1.00 (0.97-1.04)	0.93
IL-18	1.02 (0.95-1.10)	0.54
Caspase-1	1.01 (0.95-1.06)	0.84

Vulnerable Plaque Features

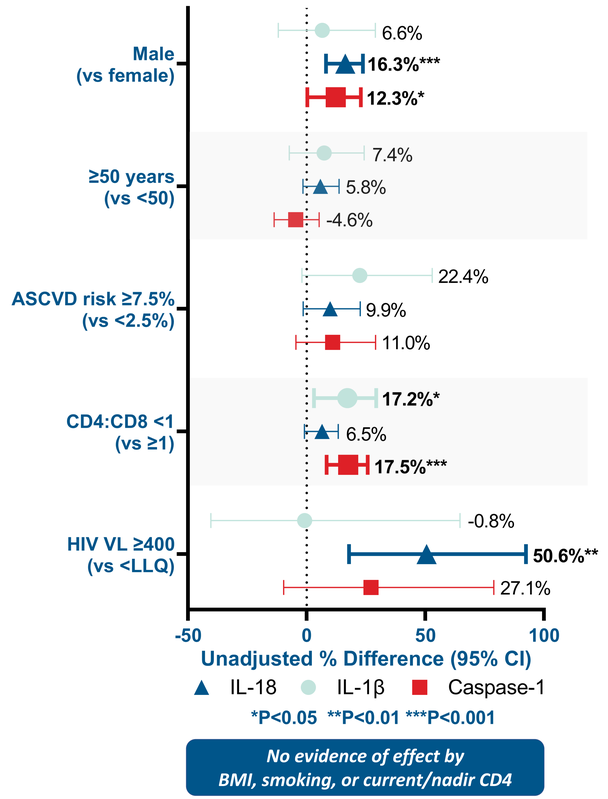
Biomarker	Adjusted OR* (95% CI)	P Value
IL-1β	1.01 (0.97-1.05)	0.63
IL-18	1.02 (0.93-1.11)	0.72
Caspase-1	0.98 (0.92-1.05)	0.58

CAC >0

Biomarker	Adjusted OR* (95% CI)	P Value
IL-1β	1.00 (0.96-1.04)	0.96
IL-18	1.01 (0.93-1.10)	0.81
Caspase-1	1.01 (0.95-1.07)	0.79

*per 25% higher biomarker

Differences in Inflammasome Biomarkers by Key Subgroups



No evidence of effect by BMI, smoking, or current/nadir CD4

Conclusions

- Among treated PWH, inflammasome activation was higher in men, persistent viremia, and CD4/CD8 <1
- Higher IL-18 and IL-1β were independently associated with Leaman score, a clinically relevant atherosclerosis index that integrates degree of stenosis and plaque location and composition
- As Leaman score >5 is associated with increased cardiovascular events in the general population, future longitudinal work is needed to determine
  1. How inflammasome activation relates to plaque progression and cardiovascular events
  2. Whether therapeutic strategies targeting the inflammasome mitigates these in PWH

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