Subclinical Atherosclerosis and Immune Activation Among US Females vs. Males With HIV

REPRIEVE
Randomized Trial to Prevent Vascular Events in HIV

CROI
Conference on Retroviruses and Opportunistic Infections

1423

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BACKGROUND

- Among people living with HIV (PWH), sex-differences in presentations of atherosclerotic cardiovascular disease (ASCVD) may be influenced by underlying differences in coronary artery plaque parameters, immune indices, or relationships therein.

METHODS

- REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV), a primary ASCVD prevention trial, enrolled anti-retroviral therapy (ART)-treated PWH globally.
- At study entry, a subset of US REPRIEVE participants underwent coronary computed tomography angiography (CCTA) and immune phenotyping (CCTA: **N=755**; CCTA + immune phenotyping: **N=725**).
- We characterized sex-differences in coronary artery plaque (log binomial regression for a relative prevalence rate [RR]) and immune indices (linear regression).
- Finally, we compared immune-plaque relationships by sex. Unless noted otherwise, analyses adjust for Pooled Cohort Equation ASCVD risk score.

RESULTS

Study Cohort

- The primary analysis cohort (N=755) included 631 (84%) males and 124 (16%) females (age 51±6 years).
- Median ASCVD risk was higher among males vs. females (4.9% [2.6–6.8] vs. 2.1% [0.9–3.7]).
- Obesity rates (BMI≥30 kg/m^2) were higher among females (48% vs. 21%).

Subclinical Atherosclerosis

- Prevalence of any coronary artery plaque and of plaques with either visible non-calcified portions and/or vulnerable plaque features (NC/V-P) was lower among females vs. males overall and controlling for ASCVD risk (**Figure 1**). **Any plaque:** RR=0.67; 95%CI: 0.50–0.92. **NC/V-P:** RR=0.71; 95%CI: 0.51–1.00) (both adjusted for ASCVD risk and BMI).
- Among those with any plaque, prevalence of NC/V-P did not differ by sex *(P=0.33).*

Females vs. males presented with:

1) Lower prevalence of coronary artery plaque
2) Lower prevalence of plaques with non-calcified portion and/or vulnerable plaque features (NC/V-P)
3) Key-differences of systemic immune activation parameters

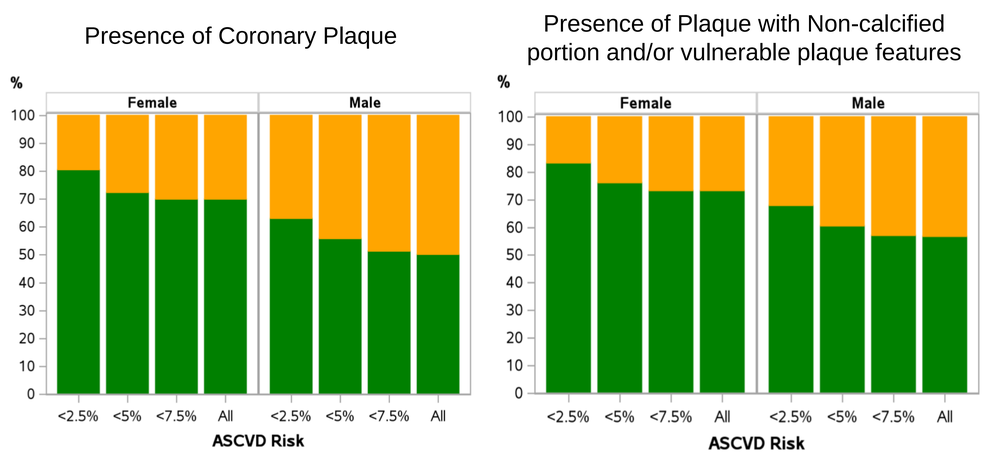
Immune Activation Indices

- **Females vs. males** showed:
  - Higher levels of IL-6, hsCRP, and D-Dimer and lower levels of LpPLA-2 (*P<0.001* for all).
  - A lower percentage of total monocytes and a shift toward a higher percentage of inflammatory/intermediate (CD14+CD16+) and patrolling/non-classical (CD14-CD16+) vs. classical (CD14+CD16-) monocyte subsets (*P<0.001* for all).

Immune-Plaque Relationships (**Figure 2**)

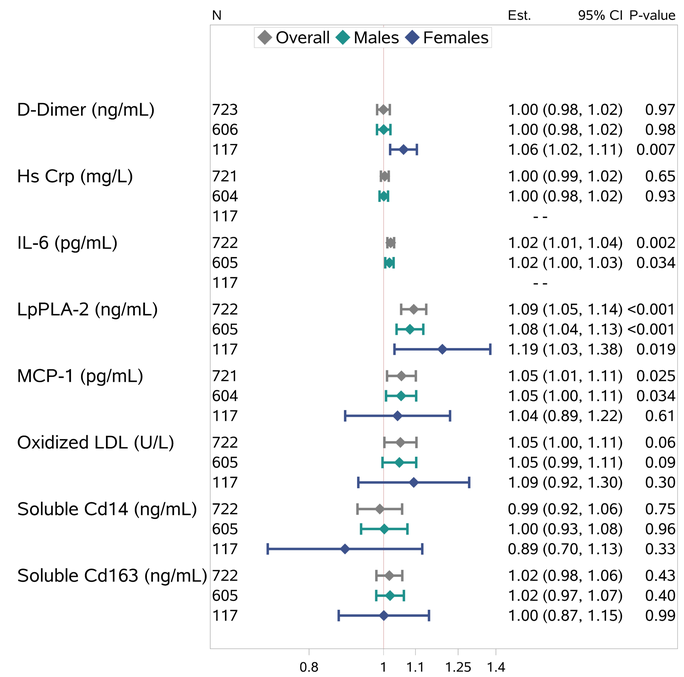
Higher levels of LpPLA-2, MCP-1, and oxidized LDL were associated with higher coronary plaque (*P<0.02*) and NC/V-P prevalence, with no differences by sex (interaction *P>0.25*) . Among females but not males, D-Dimer was associated with higher prevalence of NC/V-P (interaction *P=0.055*).

Figure 1: Prevalence of any coronary artery plaque or non-calcified plaque/ plaque with vulnerable features by ASCVD



ASCVD= atherosclerotic cardiovascular disease

Figure 2: Relationships between systemic immune indices and plaque with visible non-calcified portions or vulnerable plaque features by sex



Relevant Risk of coronary artery plaque with visible non-calcified portion or vulnerable plaque features

CONCLUSIONS

Females vs. males living with HIV had a lower prevalence of coronary artery plaque and plaque with visible non-calcified portions and/or vulnerable plaque features, as well as key differences in immune parameters. Immune-plaque relationships differed by sex for D-Dimer, but not other tested parameters. Understanding sex-specific immune drivers of subclinical coronary pathology will be key to tailoring ASCVD preventive therapies to PWH.

FUNDING Supported by NIH, NIH-LBI grants U01HL123336, to the REPRIEVE Clinical Coordinating Center, and U01HL123339, to the REPRIEVE Data Coordinating Center, and NIAID grant R01AI123001 (to MVZ and SEL), as well as funding from ViiV Healthcare, KOWA Pharmaceuticals and Gilead Sciences. NIAID has also supported this study through grants UM1 AI068636, which supports the ACTG Leadership and Operations Center; and UM1 AI106701, which supports the ACTG Laboratory..