Sex Differences in Subclinical Coronary Atherosclerotic Plaque Among Individuals with HIV on Antiretroviral Therapy

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Disclosures

• The speaker has nothing to disclose

• S.E.L.
  – Non-paid board member of the community non-profit organization Healing Our Community Collaborative

• J.L.
  – Medical Affairs Advisory Board for Gilead Sciences
  – Study drug donation from Shire for an NIH-funded study

• M.V.Z.
  – Scientific Advisory Board Meeting for Roche Diagnostics
  – Research funding to her institution for an investigator-initiated study from Gilead
Women with HIV are at particularly high risk for myocardial infarction (MI).

Relative Risk of MI in HIV vs. Non-HIV

- **Women**: 2.98 (2.33, 3.75)
- **Men**: 1.40 (1.16, 1.67)

Bars show mean, error bars show 95% CI

Triant, *JCEM 2007*
Background

A Major Mechanism of MI: Acute Plaque Rupture

Coronary Computed Tomography Angiography (CTA) Can Distinguish Features Predictive of Plaque Rupture

Composition

Non-calcified plaque
Calcified plaque

High-Risk Morphology

Positive remodeling
Low attenuation

Tabas, Nature Reviews Immunology 2010
Central Objective

While women and men with HIV have similar rates of MI, are the mechanisms underlying MI similar between sexes?

Here, we utilize coronary CTA to compare the prevalence and burden of coronary plaque and high-risk morphology plaque between women and men with HIV and no known cardiac disease.

**Sex-Specific Mechanisms of MI**

- Similar Plaque Phenotype
- Similar MI Rates in Women vs. Men with HIV
Study Design

HIV+ women and men, 18-60 years old, Stable ART (> 3 months), No known CVD
- Coronary computed tomography angiography (CTA)
- Detailed metabolic and immune phenotyping

Major Endpoints
Presence and burden of:
- Any plaque
- Non-calcified or calcified plaque
- High-risk morphology plaque features
- Obstructive plaque

HIV+ Women (n = 48) vs. HIV+ Men (n = 97)
HIV+ Women with Plaque (n = 17) vs. HIV+ Men with Plaque (n = 60)
## Demographics and Traditional Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>HIV+ Women (n = 48)</th>
<th>HIV+ Men (n = 97)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y (median [IQR])</strong></td>
<td>48 [41, 54]</td>
<td>48 [42, 52]</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Race/Ethnicity, %</strong></td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>White</td>
<td>25</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>60</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Current hypertension, %</strong></td>
<td>13</td>
<td>27</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Current diabetes, %</strong></td>
<td>19</td>
<td>7</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Current smoking, %</strong></td>
<td>50</td>
<td>40</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>History of IVDU, %</strong></td>
<td>25</td>
<td>20</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>History of cocaine use, %</strong></td>
<td>56</td>
<td>71</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Current statin use, %</strong></td>
<td>10</td>
<td>17</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Overall Sample
# Traditional Cardiovascular Disease Risk Factors

<table>
<thead>
<tr>
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<th>HIV+ Women (n = 48)</th>
<th>HIV+ Men (n = 97)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>181 [156, 210]</td>
<td>175 [155, 203]</td>
<td>0.35</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>105 ± 37</td>
<td>101 ± 31</td>
<td>0.51</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>57 [44, 72]</td>
<td>45 [38, 55]</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hemoglobin A1c, %</td>
<td>5.6 [5.4, 5.8]</td>
<td>5.3 [5.0, 5.7]</td>
<td>0.0005</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.5 ± 5.2</td>
<td>26.2 ± 4.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Visceral fat, cm²</td>
<td>75 [34, 119]</td>
<td>138 [80, 258]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Subcutaneous fat, cm²</td>
<td>278 [195, 406]</td>
<td>166 [103, 233]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>sCD163, ng/mL</td>
<td>1509 [1084, 2457]</td>
<td>1062 [693, 1548]</td>
<td>0.0003</td>
</tr>
<tr>
<td>sCD14, ng/mL</td>
<td>2023 [1312, 2661]</td>
<td>307 [157, 443]</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Mean ± SD for normally distributed continuous variables, median [IQR] for non-normally distributed continuous variables
# HIV-Related Parameters

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<th>HIV+ Men (n = 97)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Time since diagnosis, y</td>
<td>14.6 ± 5.9</td>
<td>13.8 ± 6.5</td>
<td>0.46</td>
</tr>
<tr>
<td>CD4⁺ T cell count, cells/mm³</td>
<td>535 [411, 759]</td>
<td>462 [303, 744]</td>
<td>0.10</td>
</tr>
<tr>
<td>Viral load undetectable, %</td>
<td>84</td>
<td>85</td>
<td>0.83</td>
</tr>
<tr>
<td>Hepatitis C co-infection, %</td>
<td>29</td>
<td>23</td>
<td>0.40</td>
</tr>
<tr>
<td>Total duration ART, y</td>
<td>8.9 [3.9, 11.8]</td>
<td>8.0 [4.5, 11.0]</td>
<td>0.51</td>
</tr>
<tr>
<td>NRTI use, %</td>
<td>94</td>
<td>97</td>
<td>0.38</td>
</tr>
<tr>
<td>NNRTI use, %</td>
<td>17</td>
<td>49</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PI use, %</td>
<td>63</td>
<td>55</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Mean ± SD for normally distributed continuous variables, median [IQR] for non-normally distributed continuous variables.

Overall Sample
Sex Differences in Coronary Plaque Prevalence

Overall Sample

* $P \leq 0.01$
§ $P \leq 0.05$
Sex Independently Predicts Coronary Plaque

Odds ratios adjusted for age, race, hypertension, diabetes, HDL-C, visceral fat, ART regimen

Overall Sample
Sex Differences in Coronary Plaque Burden

Bars show mean, error bars show SD

* $P \leq 0.01$
Despite comparable rates of MI in women and men with HIV, HIV-infected ART-treated women had a lower prevalence and burden of any plaque and of positively remodeled plaque compared to men.

Among the subset of individuals with plaque, is the phenotype more severe in women versus men?
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**Study Design**

**HIV+ men and women, 18-60 years old, Stable ART (> 3 months), No known CVD**
- Coronary computed tomography angiography (CTA)
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**Major Endpoints**
Presence and burden of:
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- **HIV+ Women** (n = 48)
- **HIV+ Men** (n = 97)

- **HIV+ Women with Plaque** (n = 17) vs. **HIV+ Men with Plaque** (n = 60)
No Sex Difference in Total Plaque Segments

Total Number of Coronary Segments with Plaque

Bars show mean, error bars show SEM
No Sex Differences in Coronary Plaque Prevalence

- Non-calcified: Women 94%, Men 76%
- Positively Remodeled: Women 71%, Men 82%
- Low Attenuation: Women 41%, Men 37%
- Obstructive: Women 0%, Men 8%

All N.S.
Sex Differences in Plaque Composition

Non-calcified and Calcified Plaque

**Number of Segments**

- **Non-calcified**
  - Women: [Graph Data]
  - Men: [Graph Data]

- **Calcified**
  - Women: [Graph Data]
  - Men: [Graph Data]

**Proportion of Plaque Segments**

- **Non-calcified**
  - Women: [Graph Data]
  - Men: [Graph Data]

- **Calcified**
  - Women: [Graph Data]
  - Men: [Graph Data]

Bars show mean, error bars show SEM

*Individuals with Plaque*
Sex Differences in Plaque High-Risk Morphology

Low Attenuation and Positive Remodeling

Number of Segments

- Low Attenuation
- Positively Remodeled

Proportion of Plaque Segments

- Low Attenuation
- Positively Remodeled

Bars show mean, error bars show SEM

Individuals with Plaque
Summary – Individuals with Plaque

• Compared to men, HIV-infected ART-treated women with coronary plaque have
  – No difference in number of affected segments or prevalence of high-risk morphology features
  – Higher burden of non-calcified plaque
  – Lower burden of positively remodeled plaque

While the absence of macroscopic plaque among women with HIV may not necessarily be reassuring, the presence of plaque in this group could be particularly worrisome
Clinical Implications

• Despite the similar rates of MI in women and men with HIV, in an analysis of asymptomatic individuals on ART, women had a lower prevalence and burden of coronary plaque and high-risk morphology plaque compared to men.

• Mechanisms beyond macroscopic plaque rupture may underlie MI in women.

• Only by further elucidating the mechanisms of MI among women with HIV can we appropriately tailor cardiovascular disease prevention and management to this population.
Limitations

- Relatively small sample size
- Men and women were not explicitly matched
- By design, individuals with MI or angina symptoms were not assessed
Future Directions: Potential Mechanisms of MI in Women with HIV

- Coronary plaque erosion
- Coronary vasospasm
- Microvascular disease
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