Matched Cohort Analysis of Carotid Artery Intimal Media Thickness Progression and Carotid Artery Plaque amongst HIV-Infected and Uninfected Adults

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Cardiovascular disease increased in HIV
- HIV infection itself
- Prevalent cardiovascular risk factors
- Anti-retroviral drugs

With an incidence of 3-5 per 1000 per year, the measurement of cardiovascular events requires very large cohorts
Measure cardiovascular risk factors
- Framingham risk score

Functional measures
- Brachial artery flow-mediated vasodilation

Measure anatomical disease progression
- CT coronary arteries
- Carotid artery ultrasound
  - Strong predictor of CV events (MI and stroke)
  - Remains poorly standardized
Objectives

To compare HIV-infected adults to non-infected adults with respect to:

1. Progression of carotid artery intima media thickness (CIMT)

2. Presence and Incidence of carotid artery plaque
Methods: Study Participants

- **Canadian HIV Vascular Study**
  - Duration: 2005-2011
  - Location: Hamilton, Toronto, Quebec, Calgary and Vancouver
  - N= 320
  - Age: 35+ years

- **The STARR (STudy of Atherosclerosis with Ramipril and Rosiglitazone)**
  - Duration: 2003-2006
  - Location: 32 centres in 9 countries, 39% N. America
  - N= 1425
  - Age= 30+years
Methods: Design

> A matched samples cohort study
> Age, gender, 1:3 matching

Baseline | Follow-up | End

145 HIV positive

430 HIV negative
Methods: Measure of CIMT

- Serially measured 12-segment CIMT readings over at least 3 years conducted by certified sonographers
- Standardized training & same imaging methods
- Validated and standardized protocols were used with high intra- and inter-observer variability (ICC: 0.90-0.96)
- Core Laboratory (Population Health Research Institute, Hamilton, Canada)
Methods: variables

- Primary Outcomes:
  - Annualized CIMT progression =
    \[
    \frac{\text{Change in CIMT (mm)}}{\text{Duration of follow-up (years)}}
    \]
  - Presence of plaque (CIMT > 1.5 mm)
  - Development of new plaque
Methods: variables

- Potential confounders:
  - smoking status; systolic blood pressure (SBP), fasting plasma glucose (FPG) and past stroke, myocardial infarction, high cholesterol
  - use of statins, angiotensin conversion enzyme inhibitors (ACEIs),
  - duration of follow-up
Methods: Statistical Analysis

- The paired t-test was used to compare the mean change in CIMT.
- Generalised linear mixed models matched group and repeated measure as random effects.
- Other parameters were fixed.
- Data was matched and analysed using IBM Statistical Package for Social Sciences (SPSS) v. 20.
## Results: Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>CHIV Cohort (n=145)</th>
<th>STARR (n=430)</th>
<th>Total (n=575)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> mean (SD)</td>
<td>46.1 (8.31)</td>
<td>46.4 (8.24)</td>
<td>46.2 (8.25)</td>
<td>0.705</td>
</tr>
<tr>
<td><strong>Gender:</strong> n(%)</td>
<td></td>
<td></td>
<td></td>
<td>&gt;=0.999</td>
</tr>
<tr>
<td>Male</td>
<td>121 (83.4)</td>
<td>359 (83.5)</td>
<td>480 (83.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (16.6)</td>
<td>71 (16.5)</td>
<td>95 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>
Results: Descriptives

- Mean (SD) age of 46.2 (8.2) years
- Mean follow-up time of 3.6 years
- Most (83.5%) were men
- Fasting glucose, history of high cholesterol, and statin use were similar between the study groups
- Current smoking was higher in the HIV cohort (31.0% vs. 13.5%)
- Body mass index was lower (25.2 vs. 29.7)
Results: CIMT progression

- Mean 12-segment carotid intima media thickness (IMT) progression was:
  - 0.019 (0.039) mm/year in HIV+ cohort
  - 0.017 (0.036) mm/year in control cohort
  - $P = 0.63$
Results: Carotid artery plaque

- Plaque (>1.5 mm in any segment) was present in:
  - 41.2% of HIV subjects
  - 2.3% of the controls (P<0.001)

- Incident plaque developed in:
  - 15.8% of HIV subjects
  - 6.2% of controls (P<0.001)

- Incident plaque development associated with:
  - HIV status
  - Current smoking, glucose and blood pressure
New plaque development: Multivariable Model

<table>
<thead>
<tr>
<th>Variables</th>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>7.69 (4.16, 14.28)</td>
</tr>
<tr>
<td>Follow-up time</td>
<td>1.17 (1.01, 1.34)</td>
</tr>
<tr>
<td>Stroke history</td>
<td>0.96 (0.00, 1.34)</td>
</tr>
<tr>
<td>MI History</td>
<td>0.00 (0.00, 1.00)</td>
</tr>
<tr>
<td>Cholesterol history</td>
<td>2.00 (1.29, 3.11)</td>
</tr>
<tr>
<td>Use of statins</td>
<td>0.77 (0.40, 1.49)</td>
</tr>
<tr>
<td>Use of ACEI</td>
<td>0.99 (0.32, 3.04)</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>1.17 (1.01, 1.37)</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>1.02 (1.01, 1.03)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>1.11 (0.71, 1.72)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>1.95 (1.22, 3.12)</td>
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<tr>
<td>Body mass index</td>
<td>0.98 (0.95, 1.02)</td>
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<tr>
<td>Lopinavir</td>
<td>0.68 (0.29, 1.62)</td>
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<tr>
<td>Stavudine</td>
<td>0.89 (0.45, 1.79)</td>
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<tr>
<td>Ritonavir</td>
<td>0.60 (0.29, 1.25)</td>
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Reduces plaque | Increases plaque
Discussion

Strengths:
- Uniform, highly-precise 12-segment CIMT by standardized protocol and centralized analysis
- Matched cohort analysis
- Robust statistical methods

Limitations
- STARR cohort not representative of general population
- Not matched by smoking or follow-up time
- Covariate interactions, residual confounding?
Conclusions:

- Progression of carotid artery IMT was similar in HIV-positive subjects and in HIV-negative controls with impaired fasting glucose and metabolic syndrome.

- Incident carotid artery plaques developed more frequently amongst the HIV cohort.

- Incident arterial plaque is a candidate outcome for future intervention trials.