Cytomegalovirus IgG antibody is associated with subclinical carotid artery disease among HIV-infected women

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Background

• Some HIV-infected individuals may have an increased CVD risk
  – Linked to immunodeficiency, inflammation, and immune activation

• Cytomegalovirus (CMV) is a β human herpesvirus that remains latent or persistent over the lifecourse.
  – CMV is a possible cause of T cell activation in treated HIV-infected individuals (Hunt JID 2011).
  – CMV IgG antibody has been linked with CVD and all-cause mortality in the elderly (Roberts AJE 2011)

• Hypothesis: Circulating CMV IgG is associated with subclinical measures of vascular disease in HIV-infected women.
The Women’s Interagency HIV Study (WIHS)

- WIHS cohort consists of HIV-infected women and HIV-uninfected controls enrolled at six US field centers.

- Longitudinal study ongoing since 1994, with semi-annual visits on HIV-infected and HIV-uninfected women.

- Data to be presented were obtained at a single WIHS visit completed in 2004 - 2005.
Data acquisition and methods

• Standard methods for CD4+ T cell count, HIV RNA, and CVD measures.

• CMV IgG levels using ELISA Quantitation Kit (GenWay Biotech, SD, CA).
  – Intra-assay CV ranged from 2.4%-8.0% and inter-assay CV ranged from 5.2%-9.9%

• High-resolution B-mode carotid artery ultrasound used to image the carotid arteries. Processed centrally using automated edge detection software (Hodis).
  – CV = 1.8% for intima-media thickness (cIMT)
  – CV = 2.2% for carotid diameters

• Vascular parameters included:

  Lesions: presence of cIMT > 1.5 mm in any of the imaged carotid artery segments

  Distensibility: calculated using carotid artery diameters at systole ($D_S$) and diastole ($D_D$) and brachial artery pulse pressure (PP), as:

  \[
  \text{Distensibility} = \left( \frac{2(D_S - D_D)}{D_D} \right) \times 10^6 / 133.3, \text{ in units of } (10^{-6} \times \text{Newton}^{-1} \times \text{meter}^2)
  \]

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Statistical methods

- Multivariable adjusted models relating CMV IgG with carotid artery parameters, after adjusting for confounders.

- Examined whether the association between CMV IgG and carotid parameters differed by HIV treatment status:
  - Treated/aviremic: current users of antiretroviral medications who had HIV RNA below the lower limit of detection of 80 copies/mL
  - Treated/viremic: current users of antiretroviral medications who had HIV RNA above the lower limit of detection of 80 copies/mL
  - Untreated: non-users of antiretroviral medications
Study participants

- Excluded individuals who were negative for CMV IgG
- Study population:
  - N = 601 HIV-infected women
  - N = 90 HIV-uninfected women
  - HIV-infected and HIV-uninfected groups were well-matched on age, race and smoking status
- Median age: 41-42 years
- Majority African-American/black
- Prevalence of smoking near 50%
- Mean BMI in the overweight/obese range
CMV IgG by HIV infection status

Mean (SD) serum CMV IgG levels:
25.4 (9.9) IU/mL among HIV-infected
19.4 (9.2) IU/mL among HIV-uninfected
(P < 0.01)

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## Correlates of CMV IgG level: smoking, race, diabetes

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected (n=601)</th>
<th>HIV-uninfected (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean(SD) CMV IgG</td>
<td>P</td>
</tr>
<tr>
<td>Current smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>27.5 (9.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>23.7 (10.1)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American/black</td>
<td>25.9 (9.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Other race/ethnicity</td>
<td>24.5 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27.3 (10.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>No</td>
<td>24.9 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>
Correlates of CMV IgG level: HIV parameters, C-reactive protein, BMI and age

<table>
<thead>
<tr>
<th></th>
<th>HIV-infected (n=601)</th>
<th>HIV-uninfected (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(r)</td>
<td>(P)</td>
</tr>
<tr>
<td>CD4(^+) T cell count</td>
<td>-0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Nadir CD4(^+) T cell count</td>
<td>-0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>(\log_{10}) HIV RNA</td>
<td>0.04</td>
<td>0.35</td>
</tr>
<tr>
<td>Ln C-reactive protein</td>
<td>-0.06</td>
<td>0.15</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.06</td>
<td>0.17</td>
</tr>
<tr>
<td>Age</td>
<td>0.24</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Association between CMV IgG and carotid artery parameters among HIV-infected women

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Increase in Parameter for Each 10 IU/mL Increase in CMV IgG</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid intima-media thickness (cIMT)</td>
<td>-0.7</td>
<td>-10.1 , 8.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Carotid artery distensibility</td>
<td>-1.1</td>
<td>-1.7 , -0.4</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*low values = high stiffness*

Further adjustment for CD4+ T cell count, HIV RNA, and other HIV-related and CVD-related covariates did not affect results.
Interaction term $P < .05$ after adjustment for age, race and smoking and NS after further multivariable adjustment.

Prevalence of carotid lesions = 9% in HIV-infected (7% in HIV-uninfected).

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Summary of results

• Among HIV-infected women, higher CMV IgG levels associated with:
  – Decreased carotid artery distensibility – vascular stiffness, a marker of early vascular disease.
  – Increased cIMT – asymptomatic lesion, precursor to atheroma: observed among treated/aviremic women only.

• These associations were independent of CD4, HIV RNA, and other correlates of CMV and CVD including smoking.

• No significant associations of CMV IgG with carotid artery parameters in HIV-uninfected women – possibly due to small sample size.
Conclusions

• In HIV-infected women, CMV may contribute to risk of CVD.

• Role of CMV in CVD may differ by HIV disease stage.
  – *CMV \( \uparrow \) vascular disease in patients on effective HIV treatment:* Longer survival with HIV? Immune dysregulation/reconstitution?
  – *When not on effective HAART:* HIV effect overshadows CMV effect?

• Ongoing work is examining EBV, other coinfections and hypergammaglobulinemia as predictors of CVD.

• Preliminary data did not replicate association between CD8+ T cell responses to CMV (IFN\( \gamma \)) and CVD (Hsue *AIDS* 2006).

• Translation potential of findings uncertain given available modalities directed against CMV.
CVD risk in treated HIV-infected patients: Working hypothesis

**Benefits of HAART**
- ↓ HIV replication
- ↓ Inflammation + coagulation

**Risks of HAART**
- ↑ LDL-cholesterol
- ↑ Triglycerides

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CVD risk in treated HIV-infected patients: Working hypothesis

- **CVD risks persisting with HAART**
  - ↓ Immune activation and senescence
  - Benefits of HAART
    - ↓ HIV replication
    - ↓ Inflammation + coagulation

- **Risks of HAART**
  - ↑ LDL-cholesterol
  - ↑ Triglycerides

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HAART initiation

Risk of CVD

Low

High

Time

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CVD risk in treated HIV-infected patients: Working hypothesis

CVD risks persisting with HAART

- **CMV**
- **Immune activation and senescence**

Benefits of HAART

- ↓ HIV replication
- ↓ Inflammation + coagulation

Risks of HAART

- ↑ LDL-cholesterol
- ↑ Triglycerides

Risk of CVD

- **High**
- **Low**

- **HAART initiation**

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