Effect of CMV and HIV replication on T cell exhaustion and senescence during ART

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Background

- HIV-infected men who have sex with men (MSM) are nearly universally co-infected with CMV.
- HIV and CMV infections are both associated with T cell dysfunction and inflammation-related morbidities.
- We hypothesize that asymptomatic CMV replication might be associated with T cell exhaustion (PD-1) and senescence (CD57) during virologically suppressed HIV.

Objective

- To determine associations between PD-1 and CD57 expression on CD4+ and CD8+ T cell subsets by flow cytometry: naïve (CD45RA+/-CD27-CD28-), central memory (CD45RA-/CD27+CD28-), effector memory (CD4+CD45RA-/CD27-CD28+) and terminally differentiated (CD45RA-/CD27-CD28-).
- To determine associations between PD-1 and CD57 expression on CD4+ T cells and Cellular HIV RNA transcript.

Methods

- Samples: Paired seminal and blood samples from 45 CMV seropositive, chronically HIV-infected MSM on ART with suppressed HIV RNA levels in blood (<50 copies/ml, median CD4+ T cell count 644 cells/μL [range: 83-1149]).
- Data generated:
  - CMV DNA in PBMCs and seminal plasma by RT-PCR
  - Cellular HIV DNA and RNA (unspliced) by ddPCR
  - CMV DNA in PBMCs and seminal plasma by RT-PCR
  - Detection of seminal CMV DNA and higher cellular HIV RNA levels remained associated with increased PD-1 expression on total CD4 T cells (P<0.05). No other variable contributed significantly to the model.

Results

- CMV DNA was detected in 42% of seminal samples and 20% of PBMCs. Detection of CMV in PBMCs did not correlate with presence of detectable CMV DNA in semen.
- Detectable CMV DNA in semen (but not blood) was associated with increased PD-1 expression on total circulating CD4+ T cells compared to those with no detectable CMV (p=0.01), particularly in the effector and terminally differentiated subsets (p<0.05). See Figure.
- Detectable CMV DNA in semen was not associated with PD-1 expression on circulating CD8+ T cells (p=0.1) or CD57 expression on circulating CD4+ and CD8+ T cells (p=0.1).
- Higher levels of cellular HIV RNA transcripts were positively associated with increased PD-1 expression on total circulating CD4+ T cells (p=0.01), particularly in the central memory subset (p<0.05) see Table.
- Levels of cellular HIV RNA transcripts were not associated with PD-1 expression on circulating CD8+ T cells (p=0.1) or CD57 expression on circulating CD4+ and CD8+ T cells (p=0.1).
- In multivariate analysis, detection of seminal CMV DNA and higher cellular HIV RNA levels remained associated with increased PD-1 expression on total CD4 T cells (P<0.05). No other variable contributed significantly to the model.
- No associations between HIV DNA and PD-1 or CD57 expression on CD4+ T cells.

Conclusions

- Increased PD-1 on T cells has been associated with a larger immune system to adequately control HIV infection.
- Higher levels of cellular HIV RNA are associated with increased PD-1 expression on total CD4+ T cells (but not CD8+), particularly in the central memory CD4+ subset.

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Table: Associations between PD-1 Expression on T cells and Cellular HIV RNA.

<table>
<thead>
<tr>
<th>Unspliced (gag) cellular HIV RNA*</th>
<th>Spearman R</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>%PD1 of Total CD4+</td>
<td>0.41</td>
<td>0.07</td>
</tr>
<tr>
<td>%PD1 of Naïve CD4+</td>
<td>0.15</td>
<td>0.34</td>
</tr>
<tr>
<td>%PD1 of Central Memory CD4+</td>
<td>0.48</td>
<td>0.04</td>
</tr>
<tr>
<td>%PD1 of Effector Memory CD4+</td>
<td>0.30</td>
<td>0.06</td>
</tr>
<tr>
<td>%PD1 of Terminally Differentiated CD4+</td>
<td>0.23</td>
<td>0.15</td>
</tr>
<tr>
<td>%PD1 of Total CD8+</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td>%PD1 of Naïve CD8+</td>
<td>0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>%PD1 of Central Memory CD8+</td>
<td>0.12</td>
<td>0.45</td>
</tr>
<tr>
<td>%PD1 of Effector Memory CD8+</td>
<td>0.22</td>
<td>0.17</td>
</tr>
<tr>
<td>%PD1 of Terminally Differentiated CD8+</td>
<td>0.14</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* Cellular HIV RNA was normalized per ng input RNA.

Figure: PD-1 Expression on CD4+ T cells in individuals with and without CMV shedding

Presence of asymptomatic genital CMV replication is associated with higher frequency of PD-1 expression on circulating CD4+ T cells (panel A, p=0.017), particularly in the effector memory and terminally differentiated CD4+ subsets (panel B, p<0.05).