Early initiation rather than prolonged duration of antiretroviral therapy in HIV infection contributes to the normalization of CD8 T-cell counts: Relevance for clinical outcome

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Abstract

Background: Elevation of CD8 T-cells occurs during primary HIV infection (PHI) and persists following long-term antiretroviral therapy (ART), which has been associated with increased risk of non-AIDS-related morbidity and mortality independently of CD4 T-cell recovery. We examined factors associated with trajectories of CD8 T-cells counts in PHI and assessed influence of early vs. chronic ART initiation on CD8 T-cell elevation over time.

Methods: 280 individuals were enrolled during PHI and 251 were followed for 24 months, where 84 started ART before 6 months of infection (eART), 49 between 6 and 24 months of dART) and 118 remained untreated (nART). Plasma viral load, CD4 and CD8 T-cells were assessed at each study visit. CD8 T-cell counts were also examined in 182 age-matched HIV-infected individuals who initiated ART during chronic infection and maintained undetectable plasma viral load for at least 5 years.

Results: At PHI baseline, higher CD8 T-cell counts were associated with more recent infection (p=0.019), higher CD4 T-cell counts (p=0.001) and higher viral load (p=0.001). The CD8 T-cell count in the eART group decreased from 797 to 588 cells/µl over 24 months (p=0.001), to a level lower than that of untreated PHI (834 cells/µl, p=0.004) or long-term treated chronic individuals (743 cells/µl, p=0.047). More prominent CD8 T-cell recovery was observed in the eART group compared to the dART group.

Conclusions: ART initiation in early HIV infection is associated with improved resolution of CD8 T-cell elevation compared to long-term ART initiated in chronic infection. Early ART may contribute to reducing the risk of non-AIDS-related events by alleviating CD8 T-cell elevation.

Background

HIV infection is featured by profound immune dysfunction and skewed T-cell homeostasis. Elevation of CD8 T-cells occurs during PHI and persists following long-term ART, which has been associated with increased risk of non-AIDS-related events independently of CD4 T-cell recovery. Mechanisms underlying CD8 persistence remain unclear, and may include immune activation, alteration of lymph node architecture, gut mucosal dysfunction, microbial translocation and T-cell trafficking or redistribution. Whether an early approach could ameliorate ongoing elevation of CD8 T-cell counts remains unknown. Here we examined factors associated with trajectories of CD8 T-cell counts in early HIV infection. By comparing individuals receiving early vs. delayed ART, we also assessed the impact of timing and duration of ART on CD8 T-cell elevation over time.

Study population

• 280 Cohort from Montreal Primary HIV Infection Study Cohort (Montreal, Quebec, Canada) from May 1996 to December 2012, who were recruited before 6 months of infection and had been followed for 24 months (Figure 1). Plasma viral load (VL), CD4 and CD8 T-cell counts measured at a maximum interval of 3 months.

• 182 age-matched HIV-1-infected adults who started ART during chronic infection and maintained undetectable VLs for at least 5 years. The CD4 and CD8 T-cell counts measured each calendar year after VLs became undetectable were examined.

• 40 age-matched uninfected healthy controls.

Methods

Figure 1. Enrollment of PHI participants

Table 1. Characteristics of PHI participants, chronically infected individuals and uninfected controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PHI</th>
<th>PHI</th>
<th>PHI</th>
<th>Chronic</th>
<th>Uninfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD count, cells×10^6</td>
<td>eART</td>
<td>dART</td>
<td>nART</td>
<td>Long-term ART</td>
<td>Controls</td>
</tr>
<tr>
<td>N=64</td>
<td>N=49</td>
<td>N=118</td>
<td>N=112</td>
<td>N=49</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>37.0 (8.7)</td>
<td>36.0 (10.4)</td>
<td>38.0 (6.6)</td>
<td>50.2 (5.3)</td>
<td>45.6 (7.4)</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>74 (11.9)</td>
<td>74 (14.9)</td>
<td>72 (6.6)</td>
<td>75 (16.8)</td>
<td>72 (6.5)</td>
</tr>
<tr>
<td>CD8 at enrollment, median (IQR)</td>
<td>81 (75-131)</td>
<td>81 (75-131)</td>
<td>81 (75-131)</td>
<td>81 (75-131)</td>
<td>81 (75-131)</td>
</tr>
<tr>
<td>ART at enrollment, median (IQR)</td>
<td>85 (75-125)</td>
<td>85 (75-125)</td>
<td>85 (75-125)</td>
<td>85 (75-125)</td>
<td>85 (75-125)</td>
</tr>
</tbody>
</table>

| HIV viral load, median (IQR) | 1.6 (1.0-3.1) | 3.5 (1.1-5.8) | 6.4 (6.2-9.3) | 7.0 (6.5-9.5) | Non-detectable |
| CD4 T-cell count, median (IQR), cells/µl | 770 (532-1341) | 780 (680-1209) | 825 (685-1182) | 771 (680-1182) | 678 (570-1080) |
| CD4/CD8 ratio, median (IQR) | 0.5 (0.2-0.8) | 0.6 (0.3-0.8) | 0.8 (0.6-0.9) | 0.7 (0.5-0.8) | 2.1 (3.1-0.2) |

Table 2. Curvilinear and multivariate analyses of factors associated with CD8 T-cell levels for PHI individuals at baseline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Participants N=64</th>
<th>CD8 T-count &lt;2000 cells/µl</th>
<th>P Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>37.0 (8.7)</td>
<td>0.22</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>74 (11.9)</td>
<td>0.01</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>CD8 at enrollment, median (IQR)</td>
<td>81 (75-131)</td>
<td>0.01</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Trajectories of CD8 T-cells over time in early treated primary HIV infection and chronic long-term treated chronic infection (median, IQR)

HIV RNA log10 viral load

-3 | 70 (75-125) | 70 (75-125) |
-2.5 | 72 (75-125) | 72 (75-125) |
-2 | 55 (75-125) | 55 (75-125) |
-1.5 | 50 (75-125) | 50 (75-125) |
-1 | 45 (75-125) | 45 (75-125) |

Figure 3. Trajectories of CD4 and CD8 T-cell counts and CD4/CD8 ratio over time in PHI (Median)

(A) CD8 T-cell count in eART group was higher than in dART group (p=0.01) at 24 months.
(B) CD8 T-cell count in nART group remained stable, at 24 months, CD8 T-cell counts in eART group were lower than those of the nART group (p=0.04), though still elevated compared to the control group (p=0.01).
(C) CD4/CD8 ratio in the eART group declined over time, the ratio in the nART group was higher than that of the eART group (p=0.01) at 24 months.

Figure 4. Dynamics of CD8 T-cell counts during the course of HIV infection

Elevation of CD8 T-cell counts in HIV infection could be divided into two major compartments, the fast-response and slow-to-respond compartments. The fast-response compartment may mainly include activated T-cells such as CD8+VDR +CD28- and is associated with viral antigenic stimulation, which could be controlled by effective ART. The slow-to-respond compartment may associate with gut mucosal damage, acquired ‘immunologizing’, and impaired distribution and homing capacity of T-cells.

Conclusions

Early ART initiation in PHI was associated with a significant decrease in CD8 T-cell counts coupled with VL reduction and CD4 T-cell recovery, which was even more prominent when ART was initiated within 6 months of infection. In contrast, although prolonged ART initiation in chronic HIV infection was associated with more recovery in CD4 T-cell counts and CD4/CD8 ratio, CD8 T-cell counts remained persistently elevated, and were higher than those observed with ART initiation in PHI. Timing rather than duration of ART appears to be more crucial for normalization of CD8 T-cell counts in HIV infection. In addition to the recovery of CD4 cells and delay in disease progression, ART initiation during PHI may further contribute to reducing future risks of non-AIDS morbidity and mortality by alleviating CD8 T-cell elevation.

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