Differences in associations of CD4/CD8 ratio, sex, and age on risk of mortality in HIV-infected adults on ART


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Abstract #16
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Background

In elderly, HIV-uninfected populations, low CD4/CD8 ratio:
- associated with mortality, neurocognitive decline, & frailty
- characterized by expansion of CD8 T cell clonal populations and loss of CD28 expression on CD8 T cells (senescence)
- associated with male sex

In HIV-infected adults:
- Low CD4/CD8 ratio correlates with measures T cell activation and senescence
- Low CD4/CD8 ratio associated with HANA outcomes, particularly CVD
- The effects of sex and age on CD4/CD8 ratio and its associated clinical outcomes have not been described

Hypothesis

We hypothesized aging HIV-infected women would have higher CD4/CD8 ratio compared to men and this difference would be associated with decreased risk of mortality.
Methodology

- Vanderbilt Comprehensive Care Clinic
- Adult (> 18 years) who enrolled in care between January 1, 1998, and December 31, 2012
- Followed until death; December 31, 2012; or last clinic visit if gap in care > 1 year
- Inclusion criteria:
  - Two provider visits within first year
  - HIV-1 RNA <400 copies/mL for 1 year, documented by at least 2 laboratory values <12 months apart ("baseline" defined by this time point)
  - CD4 and CD8 cell counts available and HIV-1 RNA <400 copies/mL within 6 months of baseline
<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Men</th>
<th>Women</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>1554 (77)</td>
<td>452 (23)</td>
<td></td>
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<tr>
<td>Age in years, median (IQR)</td>
<td>42 (25-48)</td>
<td>40 (32-47)</td>
<td>0.004(^a)</td>
</tr>
<tr>
<td>Non-white race (%)</td>
<td>589 (38)</td>
<td>278 (62)</td>
<td>&lt;0.001(^b)</td>
</tr>
<tr>
<td>History of HCV infection (%)</td>
<td>215 (14)</td>
<td>73 (16)</td>
<td>0.22(^b)</td>
</tr>
<tr>
<td>History of HBV infection (%)</td>
<td>136 (9)</td>
<td>14 (3)</td>
<td>&lt;0.001(^b)</td>
</tr>
<tr>
<td>Anemia(^c) at baseline (%)</td>
<td>345 (24)</td>
<td>93 (22)</td>
<td>0.57(^b)</td>
</tr>
<tr>
<td>Duration of ART in years, median (IQR)</td>
<td>1.4 (1.1-3.2)</td>
<td>1.3 (1.1-2.4)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>CD4/CD8 ratio, median (IQR)</td>
<td>0.54 (0.32-0.82)</td>
<td>0.67 (0.46-96)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm(^3)), median (IQR)</td>
<td>450 (294-634)</td>
<td>528 (384-766)</td>
<td>&lt;0.001(^a)</td>
</tr>
<tr>
<td>CD8 cell count (cells/mm(^3)), median (IQR)</td>
<td>833 (626-1139)</td>
<td>790 (568-1083)</td>
<td>0.004(^a)</td>
</tr>
</tbody>
</table>

\(^a\) Wilcoxon ranksum test for comparison of continuous variables

\(^b\) Chi\(^2\) test for comparison of categorical variables

\(^c\) Anemia defined as hemoglobin <11.8 (g/dL) for women and <14 (g/dL) for men.
Sex differences in median CD4/CD8 ratio, CD4 count, and CD8 count by age

** Comparison of men vs. women = $P < 0.01$
Sex differences in median CD4/CD8 count ratio, CD4 count, and CD8 count by age

* Comparison of men vs. women = $P < 0.10$

** Comparison of men vs. women = $P < 0.01$
Cox Proportional Hazards Models for Mortality

• No sex disparity in mortality was observed (aHR 1.08 [95% CI: 0.68-1.72])
• CD4/CD8 ratio no longer associated with mortality in adjusted models (aHR 0.97 [0.91-1.03])
• Interaction term for age and CD4/CD8 ratio suggestive of effect modification ($p = 0.06$)

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>HR [95% CI] per 0.1 increase in CD4/CD8 ratio</th>
<th>$P$ value</th>
<th>aHR* [95% CI] per 0.1 increase in CD4/CD8 ratio</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years (27 deaths)</td>
<td>0.86 [0.76-0.98]</td>
<td>0.02</td>
<td>0.86 [0.74-1.02]</td>
<td>0.08</td>
</tr>
<tr>
<td>40-49 years (64 deaths)</td>
<td>0.95 [0.89-1.02]</td>
<td>0.15</td>
<td>1.01 [0.94-1.09]</td>
<td>0.73</td>
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<tr>
<td>≥ 50 years (38 deaths)</td>
<td>0.94 [0.85-1.04]</td>
<td>0.20</td>
<td>0.94 [0.83-1.07]</td>
<td>0.34</td>
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</table>

* Adjusted models included sex and CD4 cell count
Limitations

1. Single clinic cohort and limited number of outcomes

2. Used a single time point for CD4/CD8 ratio rather than time-updated

3. CMV serologic data not routinely collected in our clinic

4. Did not include cause of death data
Conclusions

- For both men and women, CD4/CD8 ratio decreased with increasing age.
- Across all ages, women had consistently higher CD4/CD8 ratio values compared to men.
- Women did not have improved survival compared to men after accounting for this difference.
- Low CD4/CD8 ratio was not associated with mortality in older patients but may be predictive of mortality in the youngest HIV-infected adults, even after adjusting for CD4 cell count.
Acknowledgements

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Patients

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“Baseline” definition

1.) HIV-1 RNA >400 cps/mL

2.)

3.)

4.) HIV-1 RNA <400 cps/mL

Baseline

Clinic Entry

Cohort Entry

1 year

Observation time
Sex differences in median change over time in CD4 count, CD8 count, and CD4/CD8 ratio by age

Among 530 patients with consistent HIV-1 RNA suppression 3 years baseline

- **CD4 count**
- **CD8 count**

<table>
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<th>Age Categories</th>
<th>CD4 Count</th>
<th>CD8 Count</th>
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<tbody>
<tr>
<td>&lt;40 years (n=218)</td>
<td></td>
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<tr>
<td>40-49 years (n=212)</td>
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<tr>
<td>50+ years (n=123)</td>
<td></td>
<td>**</td>
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** Comparison of men vs. women = $P < 0.01$