Memory loss: T cell subsets associated with mortality in HIV+ and HIV− veterans

Wyatt J. McDonnell¹, Meredith S. Duncan¹, John R. Koethe¹, Margaret Doyle², Simon Mallal¹, Amy Justice³, Matthew S. Freiberg¹

1 Vanderbilt University Medical Center, Nashville, TN, USA
2 University of Vermont, Burlington, VT, USA
3 Yale University, New Haven, CT, USA

9th International Workshop on HIV & Aging
New York, NY, 2018
Today, we’ll discuss:

• Some background: HIV and immune activation, T cells, “inflammaging”
• Study design/sample collection in VACS (Veterans Aging Cohort Study)
• Preliminary analyses of T cell subsets and mortality in HIV+ and HIV− veterans
HIV and immune activation

Immune activation
HIV and immune activation

Immune activation

HIV replication
HIV and immune activation

HIV replication

Immune activation

Vascular damage

A little background: HIV and chronic immune activation
HIV and immune activation

- HIV replication
- Vascular damage
- Microbial translocation

A little background: HIV and chronic immune activation
HIV and immune activation

13 September 2018

A little background: HIV and chronic immune activation
HIV and immune activation

A little background: HIV and chronic immune activation

Co-infection (HCV, CMV, etc.)

HIV replication

Immune activation

ARV therapy

Vascular damage

Microbial translocation
T cells: from naïve to memory

Naïve T cells
T cells: from naïve to memory

Naïve T cells

Effector T cells

T cells: from naïve to memory


A little background: T cell differentiation
T cells: from naïve to memory

Naïve T cells → Effector T cells

T cells: from naïve to memory


A little background: T cell differentiation
T cells: from naïve to memory

A little background: T cell differentiation

T cells: from naïve to memory

T cells: from naïve to memory

Naïve T cells

Effector T cells

\(T_{CM}\) cells

\(T_{EM}\) and \(T_{EMRA}\) cells

Long-lived classical memory

T cells: from naïve to memory

T cells: from naïve to memory

Naïve T cells → Effector T cells → \( T_{CM} \) cells → \( T_{EM} \) and \( T_{EMRA} \) cells

Long-lived classical memory

T cells: from naïve to memory

- Naïve T cells
- Effector T cells
- Long-lived classical memory
- TCM cells
- TEM and TEMRA cells

Transcription
- T-bet^{hi}
- Eomes^{low}

Co-stimulation
- 4-1BB^{hi} (CD137)
- CD27^{low}
- CD28^{low}
- IL-7R^{low}

Long-lived non-classical memory

T_{EM} and T_{EMRA} cells

T cells: from naïve to memory

T cells: from naïve to memory

Transcription
- T-bet\textsuperscript{hi}
- Eomes\textsuperscript{low}

Co-stimulation
- 4-1BB\textsuperscript{hi} (CD137)
- CD27\textsuperscript{low}
- CD28\textsuperscript{low}
- IL-7R\textsuperscript{low}

Functionality
- Granzyme B\textsuperscript{hi}
- Perforin\textsuperscript{hi}
- PD-1\textsuperscript{low}

Tissue homing
- CX\textsubscript{3}CR1\textsuperscript{hi}
- CD62L\textsuperscript{low}
- CCR7\textsuperscript{low}

Long-lived non-classical memory

The main question

2337 veterans from VACS:
• 1518 HIV+
• 819 HIV−

Methods: cohort design
13 September 2018
The main question

2337 veterans from VACS:
• 1518 HIV+
• 819 HIV−

2005-2007: PBMCs banked

Methods: cohort design
The main question

2337 veterans from VACS:
• 1518 HIV+
• 819 HIV−

Methods: cohort design

2005-2007: PBMCs banked

2015-2017: 80 immune cell subsets via FACS
The main question

2337 veterans from VACS:
• 1518 HIV+
• 819 HIV−

Methods: cohort design

2005-2007: PBMCs banked

2015-2017: 80 immune cell subsets via FACS

Naive
CD45RA+CCR7+

Activated
CD38+

Memory
CD45RO+CCR7+

Effector memory
CD45RO+CCR7−CD45RA+CCR7−CD57+

TEMRA

Methods: cohort design

13 September 2018
CD27 & cardiovascular mortality in HIV− populations

Newcastle 85+ study:
- 749 individuals
- 641 CMV+
- No differences in gender, CVD risk factors, age-related disease
- HR 1.78 [1.27-2.48]

The main question

Naive CD45RA+CCR7+

Activated CD38+

Memory CD45RO+CCR7+

Effector memory CD45RO+CCR7−

TEMRA CD45RA+CCR7−CD57+
The main question

Naive
CD45RA+CCR7+

Activated
CD38+

Memory
CD45RO+CCR7+

Effector memory
CD45RO+CCR7−

T_{EMRA}
CD45RA+CCR7−CD57+

September 2015

Methods: cohort design
The main question

Methods: cohort design

September 2015

Naive CD45RA+CCR7+
Activated CD38+
Memory CD45RO+CCR7+
Effector memory CD45RO+CCR7−
TEMRA CD45RA+CCR7−CD57+

Alive
Dead

September 2015
The main question

- Naive: CD45RA+CCR7+
- Activated: CD38+
- Memory: CD45RO+CCR7+
- Effector memory: CD45RO+CCR7−
- TEMRA: CD45RA+CCR7−CD57+

- Alive: HIV+ HIV−
- Dead: HIV+ HIV−

September 2015
The main question

Methods: cohort design

Naive
CD45RA+CCR7+

Activated
CD38+

Memory
CD45RO+CCR7+

Effector memory
CD45RO+CCR7−

T_EMRA
CD45RA+CCR7−CD57+

Alive
HIV+
HIV−

Dead
HIV+
HIV−

Cox model:
• Age
• Sex
• Race
• ART

September 2015
## Cohort characteristics by HIV status at baseline

<table>
<thead>
<tr>
<th></th>
<th>HIV+ n=1518</th>
<th>HIV- n=819</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>97</td>
<td>90</td>
</tr>
<tr>
<td>African American race, %</td>
<td>69</td>
<td>67</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>72</td>
<td>83</td>
</tr>
<tr>
<td>High LDL cholesterol (≥160 mg/dL), %</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>Hepatitis C, %</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>Hazardous drinking, %</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>CD4 cell count/mm³ (median)</td>
<td>392</td>
<td>–</td>
</tr>
<tr>
<td>HIV-1 RNA copies/mL (median)</td>
<td>75</td>
<td>–</td>
</tr>
</tbody>
</table>
# Baseline CD4 subsets and risk of mortality

<table>
<thead>
<tr>
<th>T Cell</th>
<th>HIV+ (n=1055)</th>
<th></th>
<th>HIV-neg (n=578)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>p-value</td>
<td>Hazard Ratio</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>[95% CI]</td>
<td></td>
<td>[95% CI]</td>
<td></td>
</tr>
<tr>
<td>CD4+ Naïve</td>
<td>0.71 [0.56, 0.91]</td>
<td>0.007</td>
<td>0.69 [0.47, 1.01]</td>
<td>0.05</td>
</tr>
<tr>
<td>CD4+CD38+ (activated)</td>
<td>1.47 [1.24, 1.75]</td>
<td>&lt;0.001</td>
<td>0.77 [0.56, 1.06]</td>
<td>0.10</td>
</tr>
<tr>
<td>CD4+CD45RO+ (memory)</td>
<td>0.88 [0.74, 1.05]</td>
<td>0.16</td>
<td>1.16 [0.91, 1.50]</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Hazard ratios refer to one interquartile range increase in T cell subset
Baseline CD4 subsets and risk of mortality

<table>
<thead>
<tr>
<th>T Cell</th>
<th>HIV+ (n=1055)</th>
<th>HIV-neg (n=578)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio [95% CI]</td>
<td>p-value</td>
</tr>
<tr>
<td>CD4+ Naïve</td>
<td>0.71 [0.56, 0.91]</td>
<td>0.007</td>
</tr>
<tr>
<td>CD4+CD38+ (activated)</td>
<td>1.47 [1.24, 1.75]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4+CD45RO+ (memory)</td>
<td>0.88 [0.74, 1.05]</td>
<td>0.16</td>
</tr>
<tr>
<td>CD4+ T&lt;sub&gt;EM&lt;/sub&gt;</td>
<td>1.05 [0.91, 1.22]</td>
<td>0.52</td>
</tr>
<tr>
<td>CD4+ T&lt;sub&gt;EMRA&lt;/sub&gt;*</td>
<td>1.12 [1.04, 1.22]</td>
<td><strong>0.005</strong></td>
</tr>
<tr>
<td>CD4+ T&lt;sub&gt;EMRA&lt;/sub&gt;†</td>
<td>1.17 [1.10, 1.24]</td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

Hazard ratios refer to one interquartile range increase in T cell subset

* CD4+ T<sub>EMRA</sub> cells defined as CD45RA<sup>+</sup>CD28<sup>−</sup>CD57<sup>+</sup>

† CD4+ T<sub>EMRA</sub> cells alternately defined as CD45RA<sup>+</sup>CD27<sup>−</sup>
## Baseline CD8 subsets and risk of mortality

<table>
<thead>
<tr>
<th>T Cell</th>
<th>HIV+ (n=1238)</th>
<th>HIV-neg (n=700)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>p-value</td>
</tr>
<tr>
<td></td>
<td>[95% CI]</td>
<td></td>
</tr>
<tr>
<td>CD8+ naïve</td>
<td>0.75 [0.56, 0.99]</td>
<td>0.04</td>
</tr>
<tr>
<td>CD8+CD38+ (activated)</td>
<td>1.32 [1.10, 1.59]</td>
<td>0.002</td>
</tr>
<tr>
<td>CD8+CD45RO+ (memory)</td>
<td>1.25 [1.07, 1.45]</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Hazard ratios refer to one interquartile range increase in T cell subset.
# Baseline CD8 subsets and risk of mortality

<table>
<thead>
<tr>
<th>T Cell</th>
<th>HIV+ (n=1238)</th>
<th>HIV-neg (n=700)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td></td>
<td>[95% CI]</td>
<td>[95% CI]</td>
</tr>
<tr>
<td>CD8+ naïve</td>
<td>0.75 [0.56, 0.99]</td>
<td>0.87 [0.61, 1.23]</td>
</tr>
<tr>
<td>CD8+CD38+ (activated)</td>
<td>1.32 [1.10, 1.59]</td>
<td>0.79 [0.59, 1.07]</td>
</tr>
<tr>
<td>CD8+CD45RO+ (memory)</td>
<td>1.25 [1.07, 1.45]</td>
<td>1.24 [0.96, 1.58]</td>
</tr>
<tr>
<td>CD8+ T\text{EM}</td>
<td>1.13 [0.96, 1.32]</td>
<td>1.03 [0.73, 1.44]</td>
</tr>
<tr>
<td>CD8+ T\text{EMRA}*</td>
<td>0.85 [0.72, 1.01]</td>
<td>0.91 [0.74, 1.11]</td>
</tr>
<tr>
<td>CD8+ T\text{EMRA}\†</td>
<td>0.97 [0.83, 1.14]</td>
<td>0.92 [0.76, 1.13]</td>
</tr>
</tbody>
</table>

Hazard ratios refer to one interquartile range increase in T cell subset

* CD8+ T\text{EMRA} cells defined as CD45RA\textsuperscript{+}CD28\textsuperscript{−}CD57\textsuperscript{+}

† CD8+ T\text{EMRA} cells alternately defined as CD45RA\textsuperscript{+}CD27\textsuperscript{−}
**T\textsubscript{EMRA} and HIV status**

- In the HIV+ subjects, higher CD4+ T\textsubscript{EMRA} cells defined by two different surface markers were associated with increased risk of death.
- These T\textsubscript{EMRA} cells were 2-fold higher in the HIV+

<table>
<thead>
<tr>
<th>Age</th>
<th>CD4+CD45RA+CD28-CD57+ T\textsubscript{EMRA}</th>
<th>CD4+CD45RA+CD27- T\textsubscript{EMRA}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV+</td>
<td>HIV-neg</td>
</tr>
<tr>
<td>&lt;45</td>
<td>5.4%</td>
<td>2.0%</td>
</tr>
<tr>
<td>45-55</td>
<td>4.3</td>
<td>2.3</td>
</tr>
<tr>
<td>&gt;55</td>
<td>4.7</td>
<td>2.4</td>
</tr>
</tbody>
</table>
$T_{EMRA}$ and HIV status

CD4 $T_{EMRA}$ (CD28-CD57+) by suppression and age groups

HIV
HIV+ suppressed
HIV+ viremic

Group
CD4+CD45RA+CD28 CD57+ as % CD4

<45 yo 45-55 yo >55 yo <45 yo 45-55 yo >55 yo <45 yo 45-55 yo >55 yo
$T_{EMRA}$ and HIV status

CD4 $T_{EMRA}$ (CD28-CD57+) by suppression and age groups

<table>
<thead>
<tr>
<th>Group</th>
<th>HIV-</th>
<th>HIV+ suppressed</th>
<th>HIV+ viremic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 yo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-55 yo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;55 yo</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results

13 September 2018
CMV and $T_{EMRA}$ cells


Also of note...
Acknowledgments

John Koethe, MD  Simon Mallal, MBBS  Matthew Freiberg, MD  Meredith Duncan, MS

Jeffrey Blume, PhD  Melissa Wellons, MD  Sarah Felter Loch, BA
Acknowledgments

Amy Justice, MD, PhD  Kathleen McGinnis, PhD  Margaret Doyle, PhD  Russell Tracy, PhD

NIAAA U10 AA013566  NIAAA U24 AA020794  NIAAA U01 AA020790  NHLBI R01 HL125032  NIDDK R56 DK108352
Thank you for your attention!