Immunologic Failure and Chronic Inflammation

Steven G. Deeks
Professor of Medicine
University of California, San Francisco
52 year old HIV+/HCV+ man presents with symptomatic disease and a CD4+ T cell count of approximately 100 cells/mm$^3$. The patient initiates TNF/FTC/EFV and achieves durable viral suppression.
Immunologic Failure: Definition

- No CD4+ T cell gains (flat “slope”)
- Persistent CD4+ T cell count below some threshold
  - 350 cells/mm³
  - 500 cells/mm³
  - 800 cells/mm³
- High level immune activation/inflammation
- Vaccine unresponsiveness
Limitations: Biology associated with low CD4+ T cells on early HAART (most of whom will eventually reconstitute an effective immune system) may prove to be different than long-term immunologic non-responders.
Data from 42 countries, 176 sites; n=33,008

Since 2000, CD4+ cell count at initiation has increased in Sub-Saharan Africa from 50 to 100 cells/mm$^3$; in developed countries it has remained ~150–200 cells/mm$^3$

What are the clinical implications of immunologic failure?
Risk of Death due to Non-AIDS causes (cancer, CVD, others) is predicted in part by proximal CD4 on therapy.

Rate / 100 PY (95% CI)

≥500

200–350

350–500

≥500

Survival of Patients with CD4 Counts ≥ 500 for >5 Years is Similar to the General Population

<table>
<thead>
<tr>
<th>Duration of Follow-up with CD4 ≥ 500 cells/mm³ (Yrs)</th>
<th>N</th>
<th>Deaths n</th>
<th>Standardized Mortality Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1208</td>
<td>37</td>
<td>2.5 (1.8-3.5)</td>
</tr>
<tr>
<td>1</td>
<td>1156</td>
<td>29</td>
<td>2.1 (1.4-3.1)</td>
</tr>
<tr>
<td>2</td>
<td>1083</td>
<td>26</td>
<td>2.2 (1.4-3.2)</td>
</tr>
<tr>
<td>3</td>
<td>1031</td>
<td>22</td>
<td>2.1 (1.3-3.2)</td>
</tr>
<tr>
<td>4</td>
<td>967</td>
<td>18</td>
<td>2.1 (1.3-3.4)</td>
</tr>
<tr>
<td>5</td>
<td>864</td>
<td>12</td>
<td>1.9 (1.0-3.2)</td>
</tr>
<tr>
<td>6</td>
<td>763</td>
<td>2</td>
<td>0.5 (0.1-1.6)</td>
</tr>
<tr>
<td>7</td>
<td>610</td>
<td>1</td>
<td>0.5 (0.0-2.6)</td>
</tr>
</tbody>
</table>

Standardized Mortality Ratio = Mortality in HIV-infected patients / Mortality in General Population

Low CD4 on therapy predicts risk of AIDS and more importantly the risk of non-AIDS events (D:A:D)

What are mechanisms of immunologic failure?
Multiple immunologic abnormalities are observed in immunologic failure

- Reduced thymic function
- Increased fibrosis in lymph nodes
- Loss of gut mucosal integrity
- Reduced T cell proliferation
- Reduced naïve T cells
- Increased T cell activation (CD38, HLA-DR)
- Increased T cell dysfunction (PD-1)
- Increased inflammatory biomarkers
- Elevated pro-coagulant state
- Dramatic expansion of CMV-specific cells
- Increased T cell dysfunction (PD-1)
- Higher proviral DNA
What are the therapeutic approaches for immunologic failure?
A mechanistic rationale for starting therapy as early as possible

- Untreated HIV disease is associated with increased T cell activation/inflammation and these markers predict disease.
- Treatment dramatically reduces but does not normalize levels of inflammation.
  - Inflammation on HAART predicts disease.
- The degree of residual inflammation during HAART is determined in part by CD4 nadir.
  (strong effect < 200, less clear effect > 350)
Risk factor modification
Diet
Exercise
Statins, aspirin
Vitamin D
Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi Pang Wen*, Jackson Pui Man Wai*, Min Kuang Tsai, Yi Chen Yang, Ting Yuan David Cheng, Meng-Chih Lee, Hui Ting Chan, Chwen Keng Tsao, Shan Pou Tsai, Xifeng Wu
ddI+TDF Causes CD4+ Decline

TDF = Tenofovir Disoproxil Fumarate  ddl = didanosine;  NVP = nevirapine;  EFV = efavirenz.


**Mechanism**

- ↑ intracellular ddl levels
- ↓ purine metabolism
- ↓ DNA synthesis
- ↓ CD4+ proliferation

Switch to TDF+ddl
HCV Associated with Blunted CD4 Gains During HAART


![Graph showing mean increase in CD4 cells/μL over time for HCV-negative (HCV−) and HCV-positive (HCV+) individuals. The graph indicates a blunted CD4 gain in HCV-positive individuals compared to HCV-negative individuals.](image-url)
Improved CD4 Recovery with boosted PIs
ACTG 5142

VL<50 at Week 96

\[ P = .003 \]

\begin{align*}
\text{VL <50 c/mL at Week 96} & \\
\text{EFV + 2 NRTIs} & = 89 & n=250 \\
\text{EFV + LPV/r} & = 83 & n=253 \\
\text{LPV/r + 2 NRTIs} & = 77 & n=250
\end{align*}

\[ P = .001 \]

\[ \Delta \text{CD4 at Week 96} \]

\[ +230 \]

\[ +273 \]

\[ +287 \]

MERIT: MVC associated with ↑ CD4 recovery than EFV despite worse VL response

MERIT Study – 48 Weeks

Mean Δ in CD4+ Count From Baseline (cells/mm³)

Time (weeks)

0 2 4 8 12 16 20 24 32 40 48

EFV + CBV
MVC + CBV

169 cells/mm³
142 cells/mm³

n = 331 346 348 348 348 348 348 348 346 350 351 352 352 352 352 352 352 352 352 348

MVC = maraviroc; CBV = combivir
Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy


Short-Course Raltegravir Intensification Does Not Reduce Persistent Low-Level Viremia in Patients with HIV-1 Suppression during Receipt of Combination Antiretroviral Therapy


A Randomized, Controlled Trial of Raltegravir Intensification in Antiretroviral-treated, HIV-infected Patients with a Suboptimal CD4+ T Cell Response

Hinuyo Hatano, Timothy L. Hayes, Viktor Dahl, Elizabeth Sinclair, Tong-Hae Lee, Rebecca Hoh, Harry Lempiris, Peter W. Hunt, Sarah Palmer, Joseph M. McCune, Jeffrey N. Martin, Michael P. Busch, Barbara L. Shacklett, and Steven G. Deeks

Intensification of Antiretroviral Therapy With Raltegravir or Addition of Hyperimmune Bovine Colostrum in HIV-Infected Patients With Suboptimal CD4+ T-Cell Response: A Randomized Controlled Trial

Helen Byakwoaga, Mark Kelly, Damian F. J. Parcell, Martyn A. French, Junsaki Amin, Sharon R. Lewis, Hille Hasko-Berg, Anthony D. Kelleher, Roger Garsia, Mark A. Boyd, David A. Cooper, and Sean Emerg

The Effect of Raltegravir Intensification on Low-level Residual Viremia in HIV-Infected Patients on Antiretroviral Therapy: A Randomized Controlled Trial

Rajesh T. Gandhi, Lu Zheng, Ronald J. Bosch, Ellen S. Chan, David M. Margolis, Sarah Read, Beatrice Kallungal, Sarah Palmer, Kathy Medvik, Michael M. Lederman, Nadia Alatrakchi, Jeffrey M. Jacobson, Anne Wiegand, Mary Kearney, John Coffin, John W. Mellors, Joseph J. Eron, on behalf of the AIDS Clinical Trials Group A5244 team
Specific prebiotics modulate gut microbiota and immune activation in HAART-naive HIV-infected adults: results of the “COPA” pilot randomized trial

A Gori¹, G Rizzardini², B van’t Land³, KB Amor⁴, J van Schaik⁵, C Torti⁵, T Quirino⁶, C Tincati⁷, A Bandera¹, J Kno³, K Benlhassan-Chahour⁸, D Trabattoni⁹, D Bray⁸, A Vriesema³, G Welling¹⁰, J Garssen³,⁴ and M Clerici¹¹

- Randomized, double-blind study of oligosaccharide (designed to modify intestinal microbiota toward “beneficial” bacteria)
- Reduced sCD14, activated CD25+ CD4+ T cells
Intensification of Antiretroviral Therapy With Raltegravir or Addition of Hyperimmune Bovine Colostrum in HIV-Infected Patients With Suboptimal CD4⁺ T-Cell Response: A Randomized Controlled Trial

Helen Byakwaga, Mark Kelly, Damian F. J. Purcell, Martyn A. French, Janaki Amin, Sharon R. Lewin, Hila Haskelberg, Anthony D. Kelleher, Roger Garcia, Mark A. Boyd, David A. Cooper, and Sean Emery, for the CORAL Study Group

- 75 treated subjects (immunologic failure)
- 4 arms: RTG intensification, bovine colostrum
- No effects on CD4, activation, sCD14, LPS, HIV RNA
High Dose Atorvastatin Decreases Cellular Markers of Immune Activation without Affecting HIV-1 RNA Levels: Results of a Double-Blind Randomized Placebo Controlled Clinical Trial

- 24 untreated subjects; cross-over
- Significant reduction in HLA-DR on CD8+ T cells
- No effect on plasma HIV RNA levels
• 27 untreated subjects, 12 weeks celecoxib vs. placebo.

• Reduced CD4+ and CD8+ T cell activation; reduced PD-1 expression
Valganciclovir Reduces T Cell Activation in HIV-infected Individuals With Incomplete CD4⁺ T Cell Recovery on Antiretroviral Therapy

Peter W. Hunt, Jeffrey N. Martin, Elizabeth Sinclair, Lorrie Epling, Juli Teague, Mark A. Jacobson, Russell P. Tracy, Lawrence Corey, and Steven G. Deeks

The Journal of Infectious Diseases
Growth Hormone Increases CD4 Counts

Thymic Production of Naïve T Cells

P<.05 GH vs no GH.
IL-7 Also Increases CD4+ Counts (Median % Increase From Baseline)

Friedman test

$P < .0001$ at 3 µg/kg

$P < .0001$ at 10 µg/kg
ESPIRIT: Despite causing sustained CD4 gains, IL-2 does not provide clinical benefit

Abrams et al; NEJM 2009
Conclusions

- Immunological failure (defined based on CD4+ T cell counts, inflammation and immune dysfunction) is largely predicted by CD4+ T cell count nadir, as well as age.
- Consistent increased risk of non-AIDS events and mortality.
- The phenotypic and functional characteristics of T cells during long-term HAART share many similarities with that seen in the very old.
- Prevented by starting therapy early.
- Traditional approaches to risk reduction seem warranted (exercise, diet, weight loss).
- Multiple experimental studies are in progress.
  - Regulatory pathway unclear.