CD4 Responses of Patients on Effective Highly Active Antiretroviral Therapy (HAART)

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CD4 Responses in the Era of Highly Active Antiretroviral Therapy (HAART)

- Case of patient RL
- What are normal CD4 counts?
- How does the CD4 count respond on HAART?
- What factors impact the CD4 response?
- How has our paradigm for CD4 depletion and reconstitution changed?
- How should a clinician manage a patient with viral suppression but little or no CD4 reconstitution?
46 year old man who presents for a yearly exam complaining of malaise, myalgias, weight loss, without fevers.

Physical exam reportedly unremarkable

Laboratories: Elevated hepatic transaminases (SGPT 150’s, SGOT 120s).

- Denies a history of viral hepatitis or high risk behavior for viral hepatitis or HIV. Has 2-6 beers/week. No family history of liver disease.
- Hep B sAg negative, sAb and cAb positive. Hep C Ab and RNA negative. Hep A Ab negative. Screen for hemachromatosis negative. ANA negative. AMA negative
Patient Mr. RL

- Liver biopsy with inflammation without fibrosis or other abnormalities, reported as “autoimmune hepatitis.”
- Patient begun on 60 mg of prednisone a day with remission of symptoms, weight gain, and over 2 months, normalization of hepatic transaminases.
- Two attempts at slow prednisone taper failed when the patient got below 20 mg a day.
Patient Mr. RL: 2006

- Progressive cough with scant sputum, dyspnea on exertion and one episode of hemoptysis
- Smoker, born and lived in Boston area his whole life, worked in sales, no known TB or other exposures
- Chest x-ray: large left upper lobe cavity with surrounding consolidation. CT confirms this and hilar lymphadenopathy
- Sputum studies unrevealing
- Left upper lobectomy performed and cultures grow Mycobacterium kansasii and mycobacterium avium complex (MAC)
Patient Mr. RL: 2006

- Infectious Disease consulted
- They note a history of odonophagia with oral candidiasis on exam
- Blood cultures for mycobacteria sent and turn positive 20 days later for MAC
- HIV Ab test positive, HIV RNA 210,000 copies, CD4 2 (0.4%)
Patient RL: 2007

- Patient begun on fluconazole and Bactrim
- Also begun on isoniazid, rifabutin, ethambutol and clarithromycin
- Referred for HIV care
  - No additional history
  - Exam shows resolution of oral candida
- Begun on Atripla (tenofovir, FTC and efavirenz) at first visit with us, about 3 weeks in mycobacterial treatment
## Patient RL Viral Load and CD4

<table>
<thead>
<tr>
<th>Date</th>
<th>Viral Load</th>
<th>CD4</th>
<th>CD4%</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jan 2007</td>
<td>220,000</td>
<td>2</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>June 2007</td>
<td>&lt;50</td>
<td>8</td>
<td>2</td>
<td>Prednisone taper begun</td>
</tr>
<tr>
<td>Jan 2008</td>
<td>&lt;50</td>
<td>24</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>June 2008</td>
<td>&lt;50</td>
<td>48</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dec 2008</td>
<td>&lt;50</td>
<td>88</td>
<td>8</td>
<td>Off prednisone</td>
</tr>
<tr>
<td>June 2009</td>
<td>&lt;50</td>
<td>95</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Dec 2009</td>
<td>&lt;50</td>
<td>102</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>June 2010</td>
<td>&lt;50</td>
<td>118</td>
<td>11</td>
<td></td>
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</table>
Patient RL: Clinical Course

- 2007: bone densitometry shows osteoporosis, begun on alendronate and calcium and Vit D
  - 2008: painful vertebral compression fractures

- 2008: CT scan of chest and abdomen for follow up of lymphadenopathy showed much larger nodes with necrotic centers, including a group of nodes abutting a modest sized abdominal aortic aneurysm. No fevers, chills, abdominal pain.
  - Fine needle aspirate showed acid fast bacilli but cultures were negative
  - Presumed subclinical “mycobacterial IRIS”
2009: Arthralgias of large and small joints, R knee pain and swelling with new effusion with 40,000 WBC in fluid (90% PMNs) All stains and cultures negative.

- Rheumatoid Factor strongly positive
- Responded to tap and one synovial triamcinolone injection and plaquenil
- “Rheumatoid IRIS!”
CD4 Counts in HIV

“Normal” counts form a bell shaped curve ranging from approximately 350 to 1500. Correlation with CD4%:

- CD4 > 500: CD4% > 30%
- CD4 200-500: CD4% 14-28%
- CD4 <200: CD4% <14%

CD4 calculated from 3 measured variables: WBC, % lymphocytes, % lymphocytes that are CD4+

- Large individual variability: 18% variability for CD4% and 25% for CD4 count
Viral Load and CD4 Responses Improving Over Time

- 4143 subjects from 5 clinic cohorts in Europe and Canada
- Treatment-naive; started HAART from 1996-2002
- ↓ risk of virologic failure, ↑ median CD4+ increase in later years

Lampe S, et al. 12th CROI Abstract 593
In untreated HIV, there is a general correlation between viral load “set point” and CD4 decline.

- This correlation is strongest at a population level.
- At the level of the individual, viral load is a poor predictor of CD4 decline, accounting for <10% of individual variation in CD4.
Figure 4.
The percentage of patients with a CD4$^+$ cell count in the normal range (>500 cells/mm$^3$) over time, stratified by CD4$^+$ cell count before initiation of therapy. Patients were censored after year 4 when plasma HIV RNA levels increased to >1000 copies/mL for any reason.
Percent of Patients with CD4 >500 at 10 years, stratified by CD4 before HAART

Figure 4.
The percentage of patients with a CD4+ cell count in the normal range (>500 cells/mm^3) over time, stratified by CD4+ cell count before initiation of therapy. Patients were censored after year 4 when plasma HIV RNA levels increased to >1000 copies/mL for any reason.
Predictors of CD4 Count <200 at 4 Years of Effective HAART

<table>
<thead>
<tr>
<th>Parameter</th>
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<tr>
<td>Increasing age</td>
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<tr>
<td>Longer duration of HIV infection</td>
</tr>
<tr>
<td>More advanced CDC stage (clinical stage) at diagnosis*</td>
</tr>
<tr>
<td>Lower nadir CD4 count before HAART</td>
</tr>
<tr>
<td>Hepatitis C antibody positive</td>
</tr>
<tr>
<td>Treatment with nucleoside analogues</td>
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<td>Therapy interruptions</td>
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*May include bone marrow infiltration with opportunistic mycobacteria or other infections, less commonly tumor

Kaufmann et al Arch Int Med 163:18, 2003
Mocroft et al AIDS 20 (8) 1141:2006
AZT-Containing Regimens and CD4 Count
CAN 30024: abacavir /3TC vs zidovudine/3TC

deJesus et al Clin Infect Dis 2004
Other Factors Impacting CD4 Count

- **Medications:**
  - Corticosteroids or other bone marrow suppressive therapies
  - Chemotherapy
  - Interferon or PEG-Interferon

- **Other Infections**
  - HTLV-1 (Brazil, Caribbean, Japan)
  - Other viral infections including CMV, Epstein-Barr Virus

- **Malnutrition**

- **Major medical illness or surgery**

- **Pregnancy (hemodilution)**

- **Sex, race, psychological or physical stress have little or no effect**
Randomized trial of initial ARV strategies (drugs included nucleotides, PIs and NNRTIs)

- Clinical and lab outcomes have been previously presented.

2009: using data from 978 subjects (621 with comprehensive immunologic assessments), the study team compared CD4, CD4 naïve and memory, CD4 activation, CD8, CD8 activation, B- and NK- cells among subjects in different baseline CD4 cell count strata.
CD4 Count by Baseline CD4 Stratum Over Time

Total CD4 cell count over time by baseline CD4 strata

1: 0-50
2: >50-200
3: >200-350
4: >350-500
5: >500

Baseline CD4
>500
351-500
201 - 350
51 - 200
0 - 50

Shaded area represents normal HIV-negative volunteers

Robbins, CID 2009
Previous Model of HIV Pathogenesis: HIV-Mediated Lysis of CD4 cells
Previous Model of HIV Pathogenesis: HIV-Mediated Lysis of CD4 cells

Problems with this hypothesis:

Not all dying cells are HIV infected.

Not only CD4, but CD8 cells show increased proliferation and turnover.
Current Model of Pathogenesis: “Friendly Fire” or “Innocent Bystander” Model

- Accelerated T cell turnover as a result of chronic immune activation
  - Increased T cell proliferation
  - Increase in programmed T cell death (apoptosis)
Activated CD4 cell (CD4+/CD38+/HLA-DR+) percent by baseline CD4 stratum over time
<table>
<thead>
<tr>
<th>Stratum 1 (CD4 &lt;50)</th>
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<tbody>
<tr>
<td><strong>activated CD4</strong></td>
<td>****</td>
<td>4 (40%)</td>
</tr>
<tr>
<td><strong>non-activated CD4</strong></td>
<td>*****</td>
<td>6 (60%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stratum 5 (CD4 &gt;500)</th>
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<tbody>
<tr>
<td><strong>activated CD4</strong></td>
<td>40 (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>non-activated CD4</strong></td>
<td>460 (92%)</td>
<td></td>
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</table>
Current Model of Pathogenesis

- Accelerated T cell turnover as a result of chronic immune activation
  - Increased T cell proliferation
  - Increase in programmed T cell death (apoptosis)

- Accelerated turnover of specific T cell populations: Short lived, memory T cells (both CD4 and CD8)

Median Naive CD4
by CD4 stratum

Median Memory CD4
by CD4 stratum

ACTG 384; Robbins, CID 2009
### Median Naïve/Memory CD4 ratios Fail to Normalize in Lower CD4 Strata in ACTG 384

<table>
<thead>
<tr>
<th>Baseline CD4</th>
<th>N/M cell ratio Baseline</th>
<th>Week 144</th>
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</thead>
<tbody>
<tr>
<td>≤50</td>
<td>0.21</td>
<td>0.43</td>
</tr>
<tr>
<td>50-199</td>
<td>0.45</td>
<td>0.50</td>
</tr>
<tr>
<td>200-349</td>
<td>0.57</td>
<td>0.68</td>
</tr>
<tr>
<td>350-499</td>
<td>0.66</td>
<td>0.80</td>
</tr>
<tr>
<td>&gt;500</td>
<td>0.81</td>
<td>0.8/0.69</td>
</tr>
</tbody>
</table>

HIV(-) controls  N/M ratio = 0.8
Current Model of Pathogenesis

- Accelerated T cell turnover as a result of chronic immune activation
  - Increased T cell proliferation
  - Increase in programmed T cell death (apoptosis)
- Accelerated turnover of specific T cell populations
  - Short lived, memory T cells (both CD4 and CD8)

Pathogenic Implications: impaired capacity of host to generate new immune responses through naïve T cell pathways
A persistently low CD4 count while on suppressive HAART is associated with a small but measurable increased risk of AIDS and non-AIDS related morbidity and mortality (compared to those with rising CD4 counts)

- Compared to those with same CD4 without suppressive HAART, magnitude of risk smaller

Should guidelines for primary or secondary prophylaxis use different CD4 counts if the patient is on long term suppressive HAART?

- Currently no evidence to recommend this
Pharmacologic Strategies for Improving CD4: Interleukin-2 (IL-2)

SILCAAT and ESPRIT studies:
IL-2 increased CD4 but was toxic, expensive and did not impact any clinical endpoints
Pharmacologic Strategies for Improving CD4

- Some limited evidence (not always consistent) for better CD4 responses with some ARV regimens than others
  - Boosted protease inhibitors as compared to NNRTIs (specifically, lopinivir/ritonavir vs efavirenz in ACTG 5142)
  - Raltegravir vs efavirenz in the STARTMRK study
  - Maraviroc vs efavirenz in the MERIT study

- Other than NNRTI to boosted PI, most clinicians do not feel that the potential added benefit of other switches is worth the cost ($$ as well as inconvenience to the patient of switching regimens)
Back to Our Patient RL

- He remains stable with a CD4 count in the 120 range after > 3 years of suppressive HAART
  - On Bactrim but not fluconazole

- Last CT scan shows decrease in size and necrosis of thoracic and abdominal nodes
  - His mycobacterial therapy has been cut back to “secondary prophylaxis” with clarithromycin and ethambutol

- He remains underweight and we have worked on nutrition

- He still smokes but we nag him relentlessly

- We debated a switch from Atripla to a boosted PI regimen, but he talked us out of it
Conclusions: I

- Patients who begin suppressive HAART at lower CD4s are less likely to reach CD4 >500
- Immune activation and altered T cell kinetics are important in CD4 loss
  - They improve but do not resolve with suppressive HAART, particularly in the low CD4 strata
- Patients on suppressive HAART with lower CD4 counts have a slightly increased risk of AIDS and non AIDS morbidity and mortality compared to those with higher CD4 counts
Conclusions: II

- In these patients, clinicians should:
  - Prevent treatment interruptions
  - Address nutrition and other treatable infectious or noninfectious conditions
  - Consider a switch from AZT to another nucleoside/nucleotide
  - Possibly consider a switch from an NNRTI to a boosted PI
  - Continue primary and secondary prophylaxis per guidelines

- Use coping skills developed from experience in this field!

- Thank you