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?

Patient Mr. RL: 2005

- **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

Date	Viral Load	CD4	CD4%	Comment
Jan 2007	220,000	2	0.4	
June 2007	<50	8	2	Prednisone taper begun
Jan 2008	<50	24	3	
June 2008	<50	48	4	
Dec 2008	<50	88	8	Off prednisone
June 2009	<50	95	8	
Dec 2009	<50	102	9	
June 2010	<50	118	11	

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”

Patient RL: Clinical Course

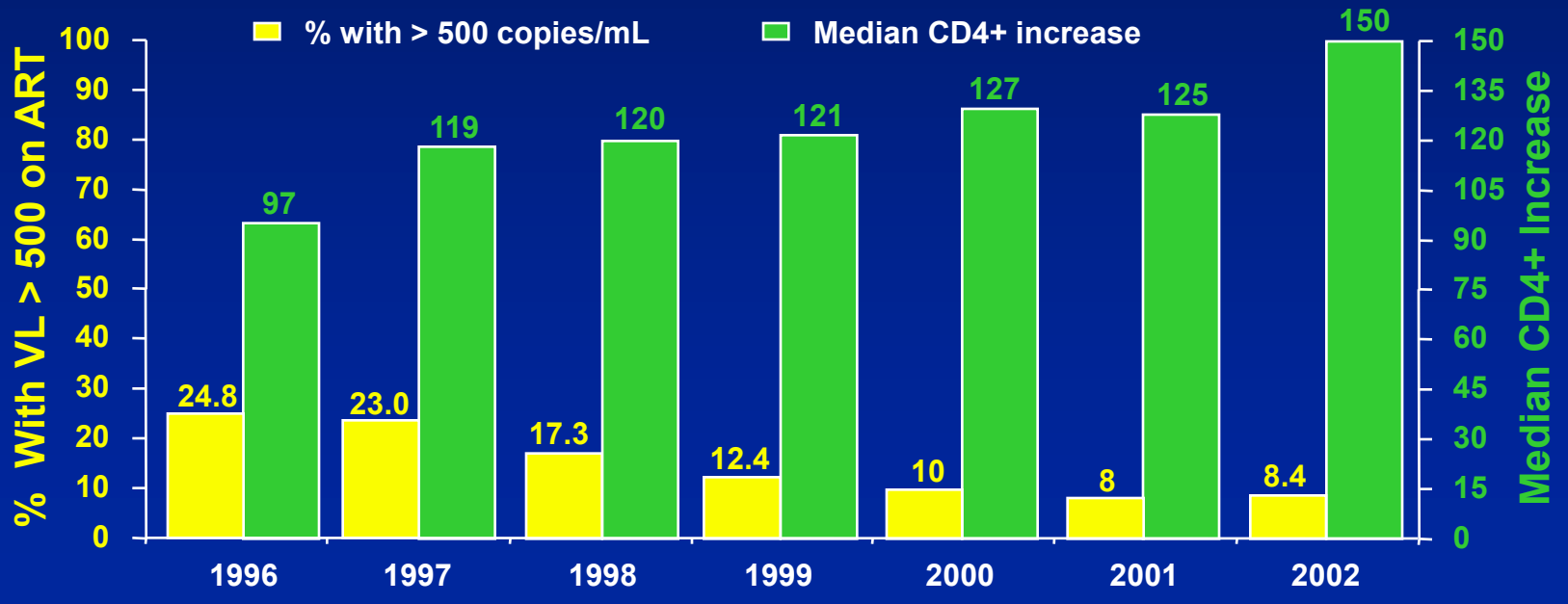
- **2009: Arthralgias of large and small joints, R knee pain and swelling with new effusion with 40,000 WBC in fluid (90% PMNs) All stains and cultures negative.**
  - Rheumatoid Factor strongly positive
  - Responded to tap and one synovial triamcinolone injection and plaquenil
  - “Rheumatoid IRIS!”

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

CD4 Counts in HIV

- **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

Percent of Patients with CD4 >500 at 10 years, stratified by CD4 before HAART

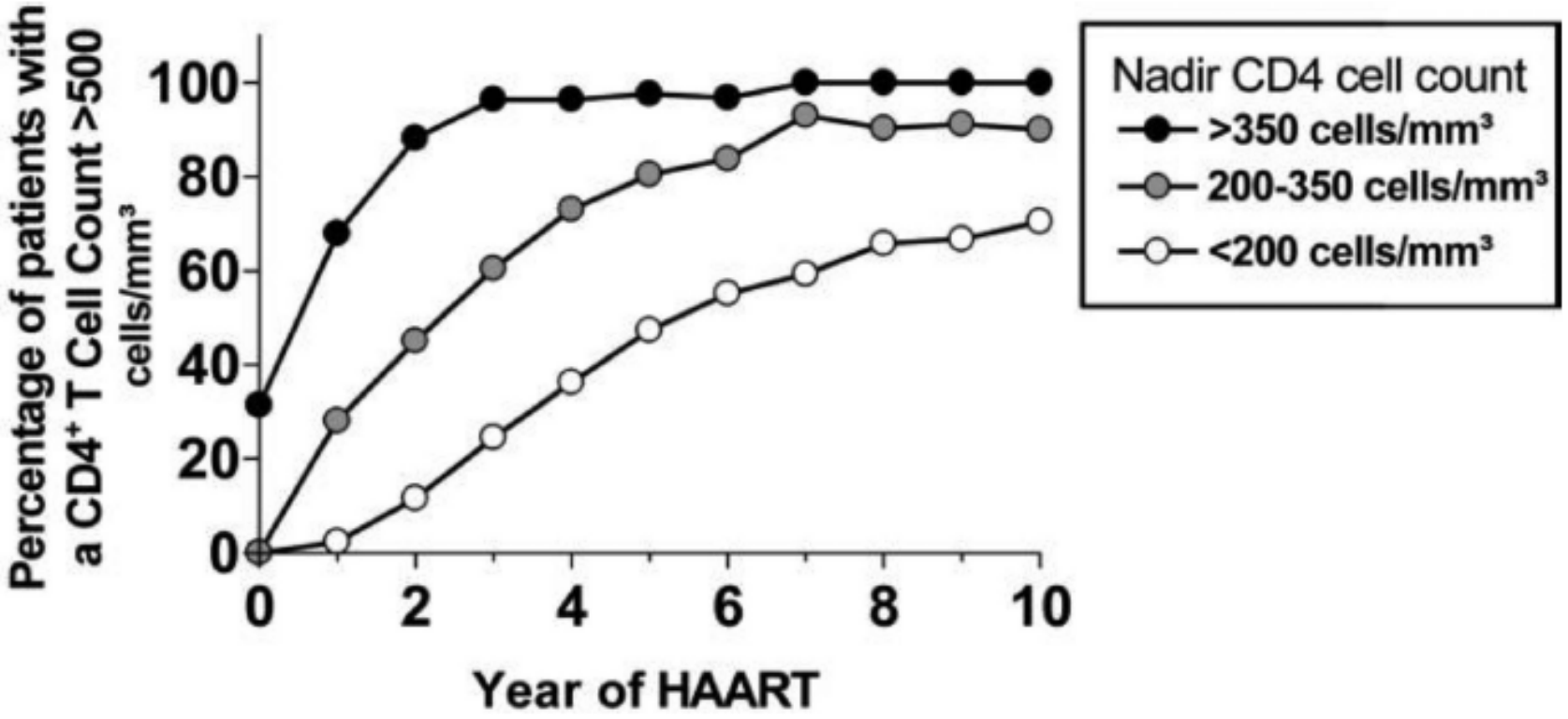


Figure 4.
The percentage of patients with a $CD4^+$ cell count in the normal range (>500 cells/mm^3) over time, stratified by $CD4^+$ cell count before initiation of therapy. Patients were censored after year 4 when plasma HIV RNA levels increased to >1000 copies/mL for any reason.

Kelley et al CID. 48: (6) 787, 2009.

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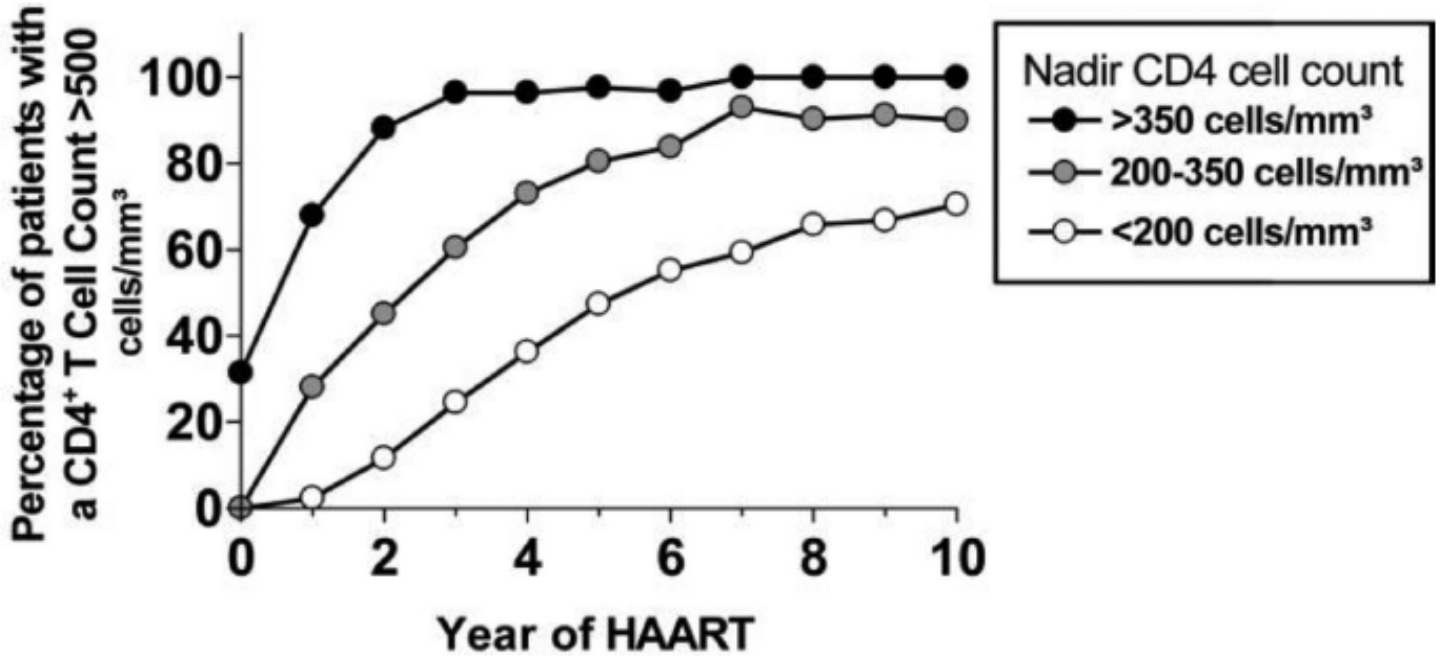

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WHO?

WHY?

Kelley et al CID. 48: (6) 787, 2009.

Predictors of CD4 Count <200 at 4 Years of Effective HAART

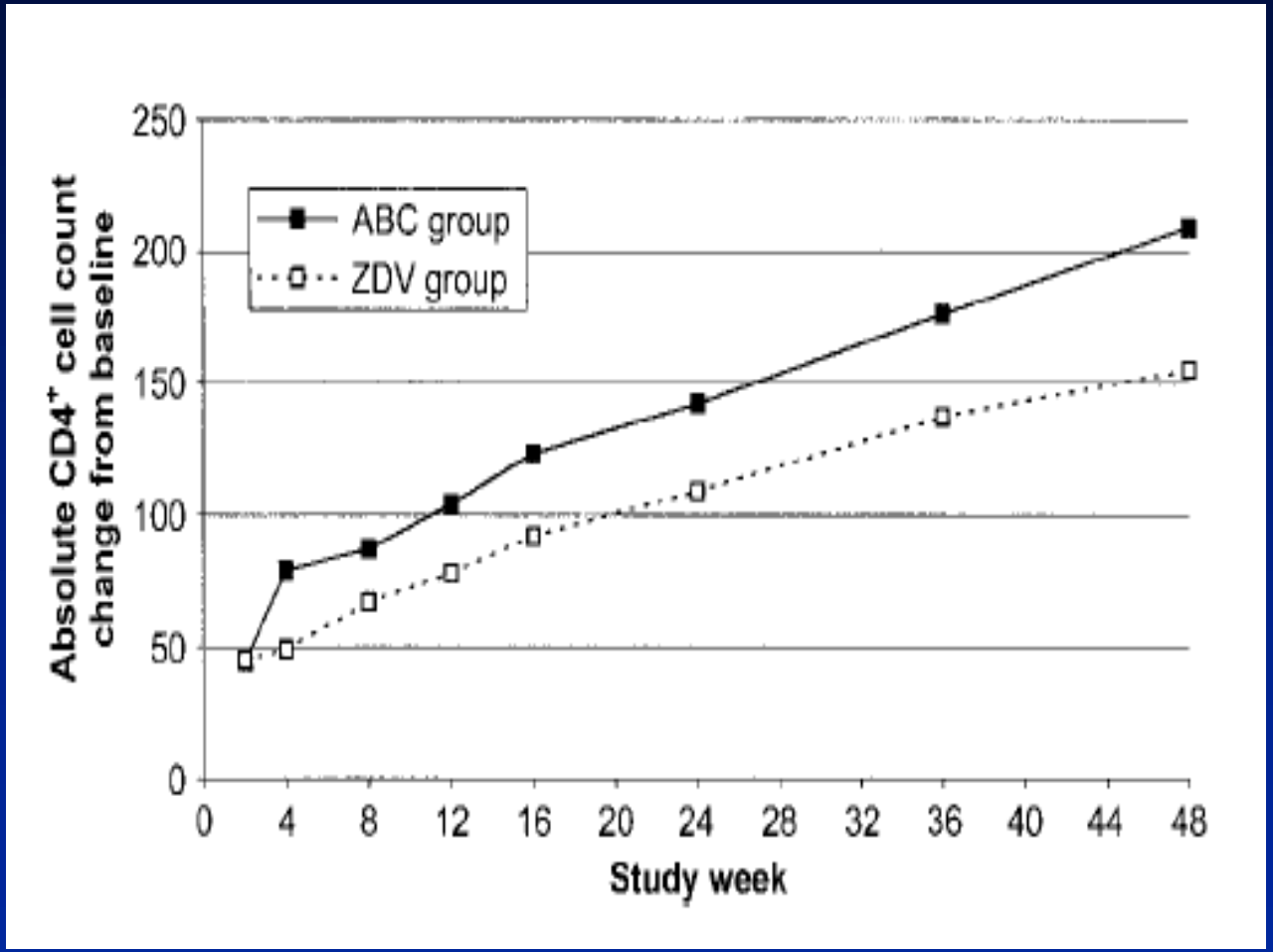
Parameter
Increasing age
Longer duration of HIV infection
More advanced CDC stage (clinical stage) at diagnosis*
Lower nadir CD4 count before HAART
Hepatitis C antibody positive
Treatment with nucleoside analogues
Therapy interruptions

*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

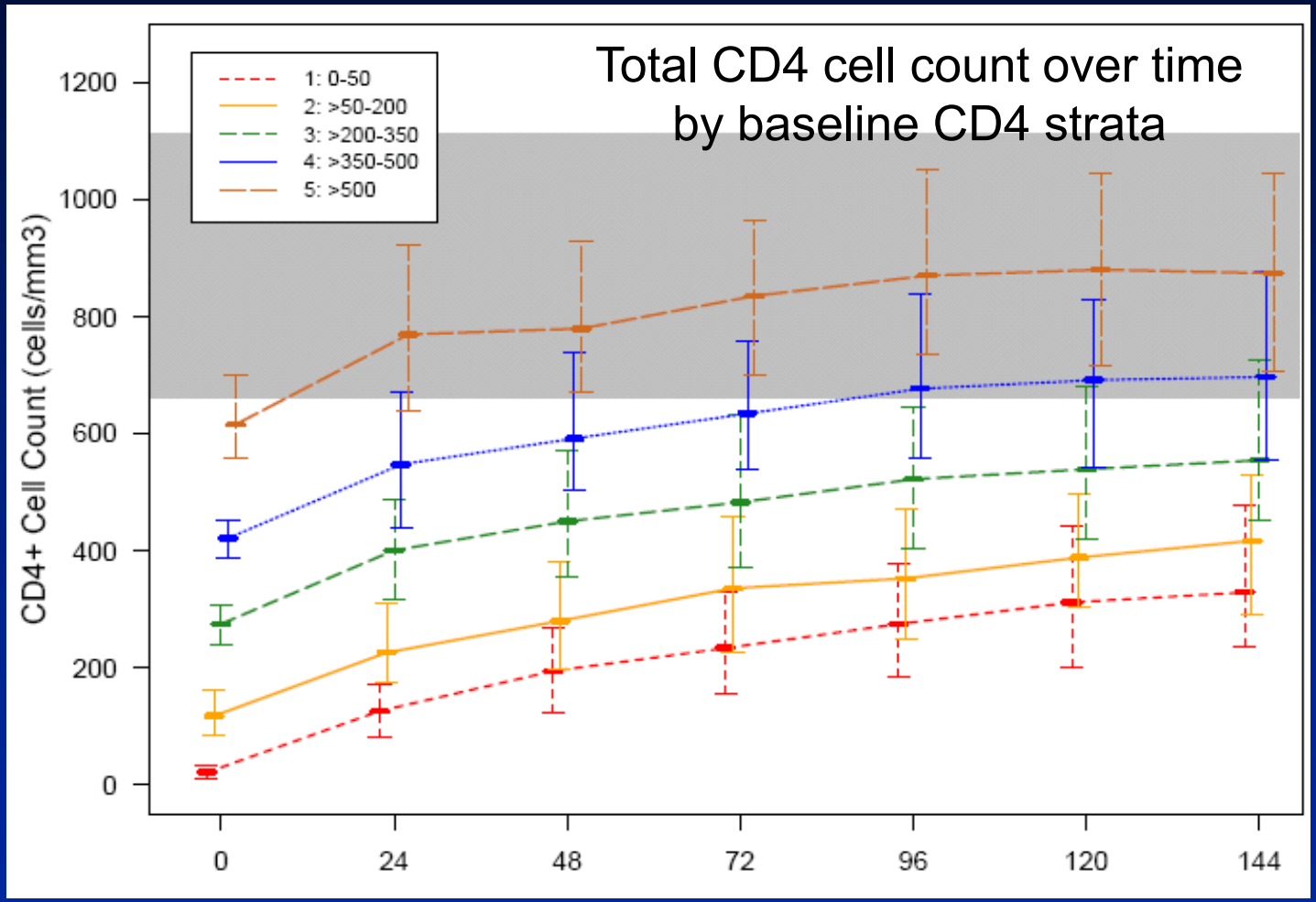
Other Factors Impacting CD4 Count

- **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**

Information on CD4 Reconstitution from ACTG 384

- **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



Baseline CD4

>500

351-500

201 - 350

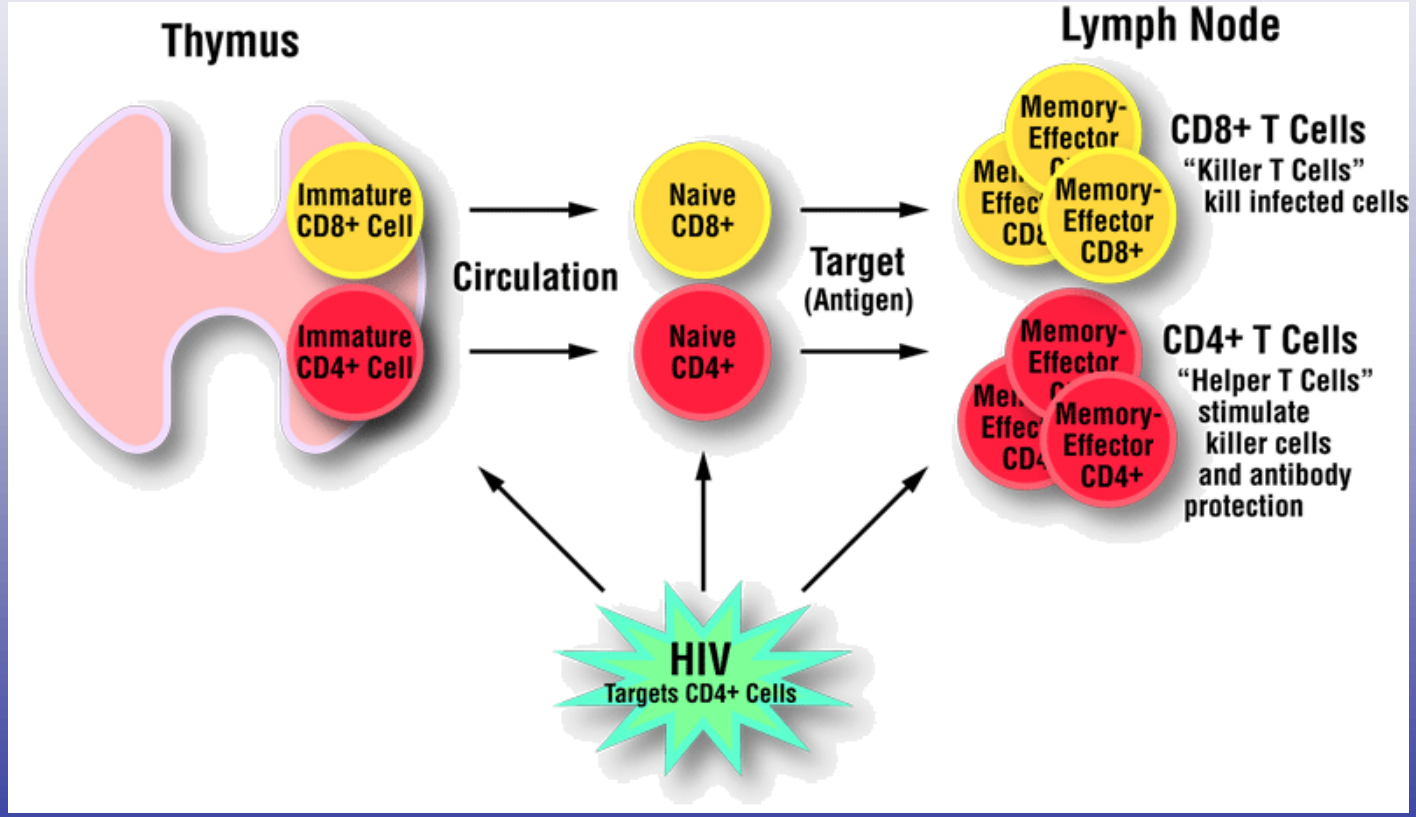
51 - 200

0 - 50

Shaded area represents normal HIV-negative volunteers

Robbins, CID 2009

Previous Model of HIV Pathogenesis: HIV-Mediated Lysis of CD4 cells



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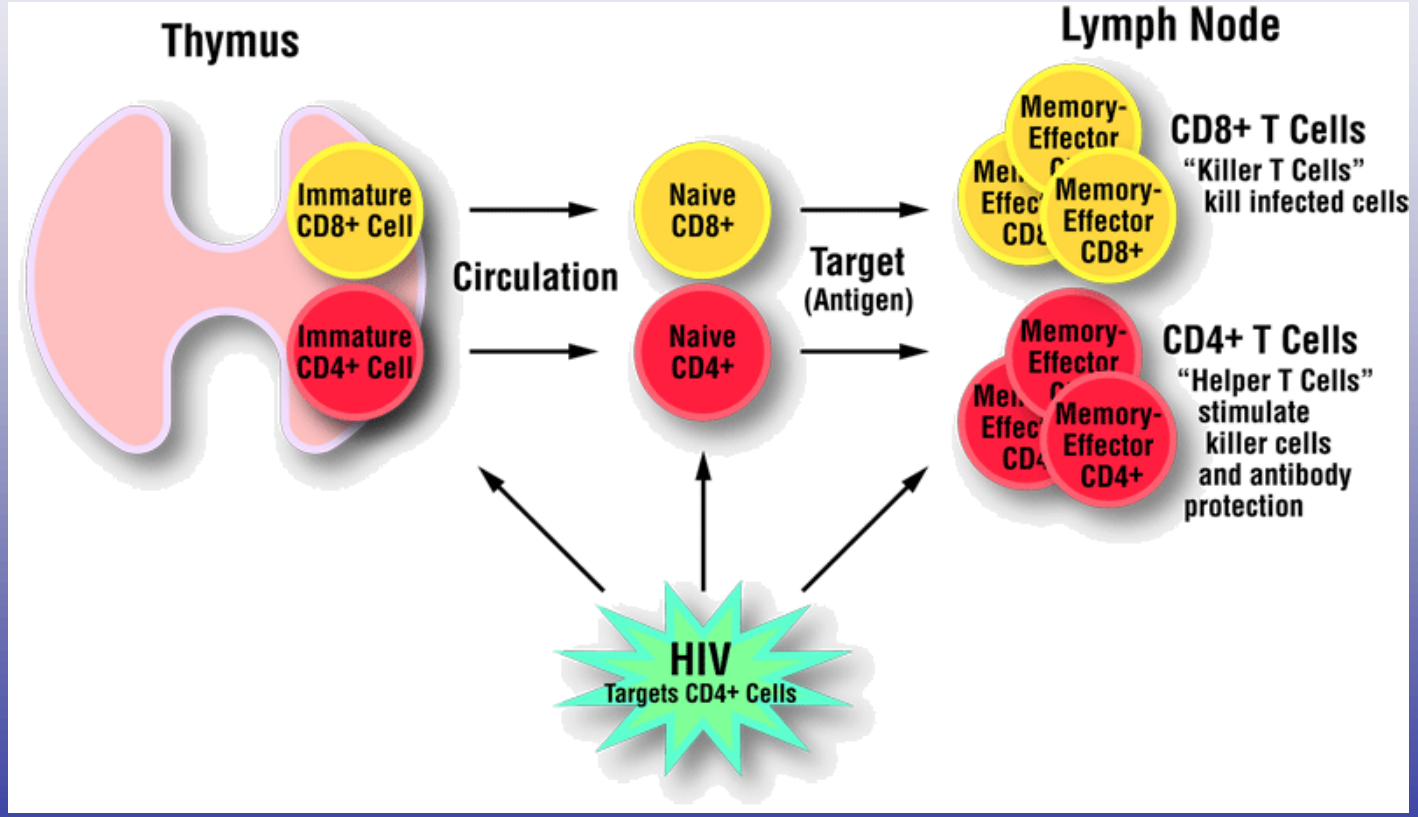


Problems with this hypothesis:

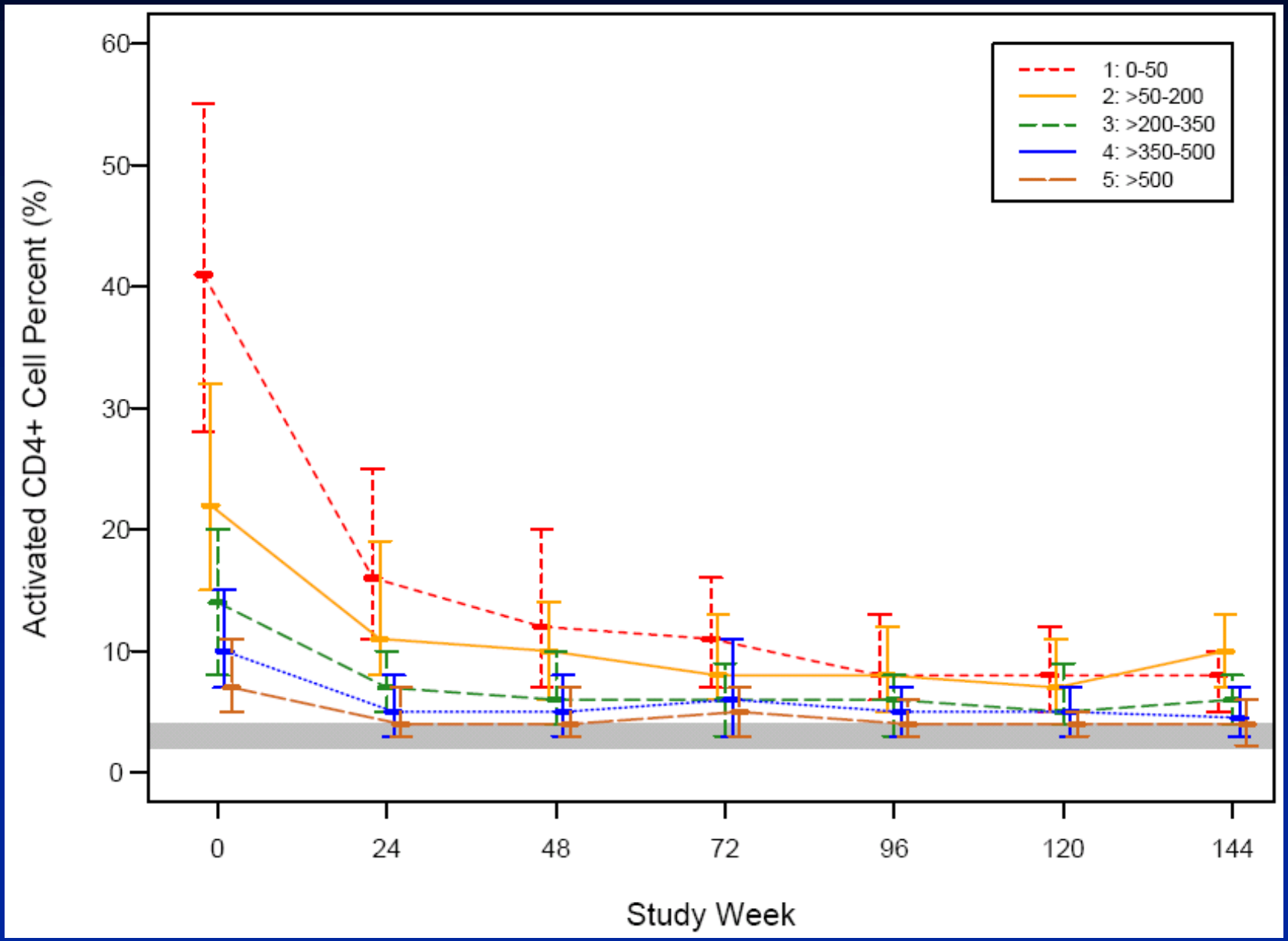
Not all dying cells are HIV infected.

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



Stratum 1 (CD4 <50)

activated CD4	****	4 (40%)
non-activated CD4	******	6 (60%)

Stratum 5 (CD4 >500)

activated CD4	**	40 (8%)
non-activated CD4	** ** ** ** ** ** ** ** ** ** ** ********************	460 (92%)

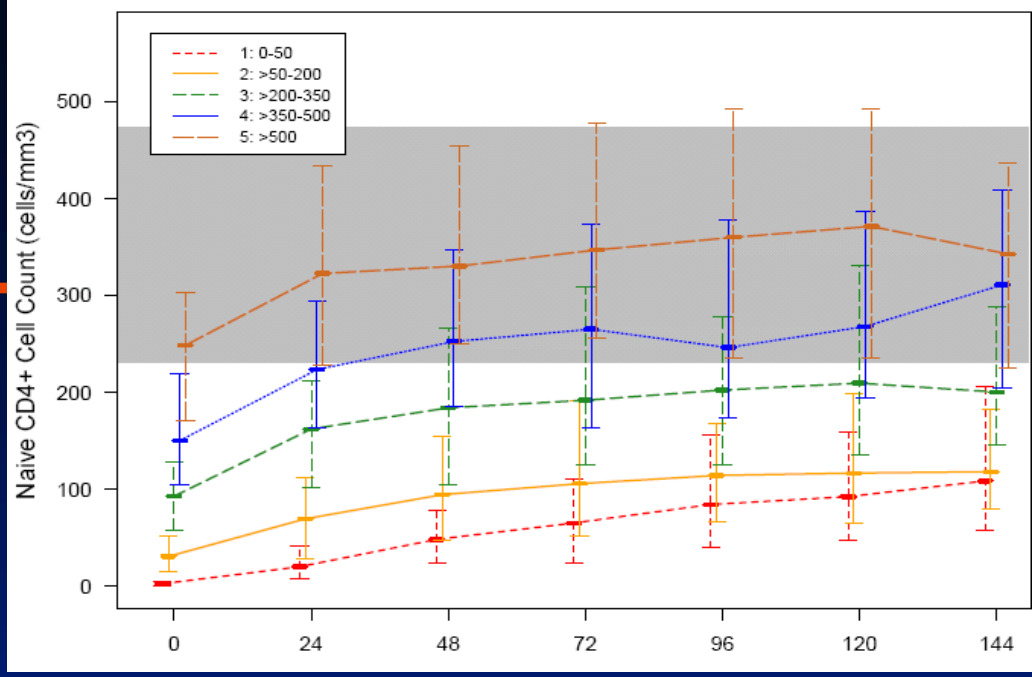
Current Model of Pathogenesis

- **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)**

Hellerstein J Clin Investig 112:956, 2003

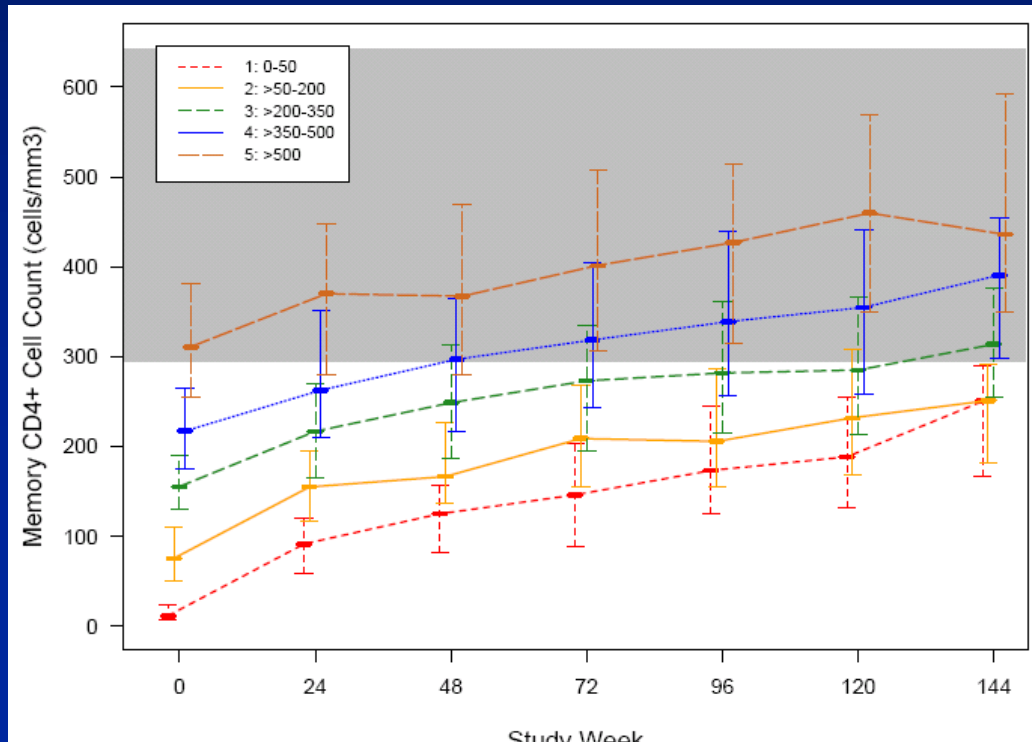
Median Naive CD4

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

Baseline CD4	N/M cell ratio Baseline	Week 144
≤50	0.21 →	0.43
50-199	0.45 →	0.50
200-349	0.57 →	0.68
350-499	0.66 →	0.80
>500	0.81 →	0.8/0.69

HIV(-) controls N/M ratio = 0.8

Current Model of Pathogenesis

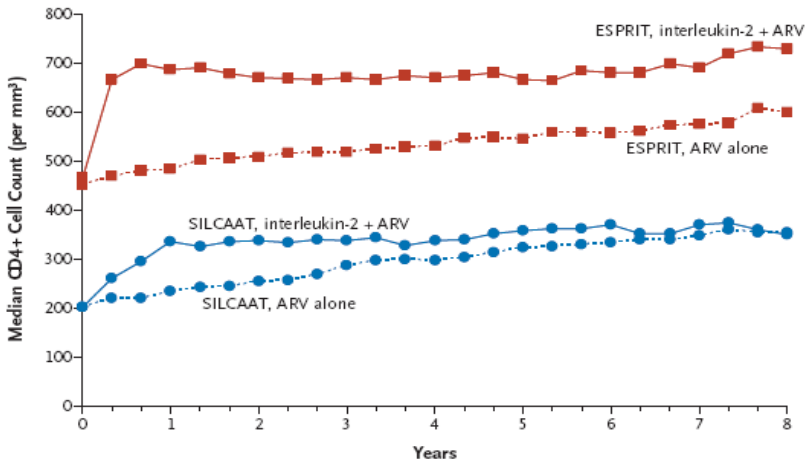
- **Accelerated T cell turnover as a result of chronic immune activation**
  - Increased T cell proliferation
  - Increase in programmed T cell death (apoptosis)
- **Accelerated turnover of specific T cell populations**
  - Short lived, memory T cells (both CD4 and CD8)
- **Pathogenic Implications: impaired capacity of host to generate new immune responses through naïve T cell pathways**

Clinical Implications of Persistently Low CD4 while on Suppressive HAART

- **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

Moore et al. AIDS 20:371, 2006
Monforte et al. AIDS 22:2143:2008

Pharmacologic Strategies for Improving CD4: Interleukin-2 (IL-2)



No. of Patients									
SILCAAT, interleukin-2 + ARV	849	722	650	635	648	623	597	447	254
SILCAAT, ARV alone	845	754	679	666	632	632	603	453	233
% Receiving interleukin-2 during yr	97.8	39.8	23.6	18.4	14.8	12.0	7.5	4.2	
ESPRIT, interleukin-2 + ARV	2071	1890	1842	1809	1768	1732	1415	887	297
ESPRIT, ARV alone	2040	1928	1862	1803	1740	1649	1349	831	255
% Receiving interleukin-2 during yr	96.2	37.9	28.7	22.3	17.7	13.7	12.5	9.6	

Figure 1. Median CD4+ Cell Counts during the Study Period, According to Study and Treatment Group.
The median CD4+ cell counts are shown for the groups receiving interleukin-2 plus antiretroviral therapy (ARV) and the groups receiving ARV alone in the SILCAAT study and ESPRIT. The counts during the first 30 days after a cycle of interleukin-2 are not stable and therefore were excluded. Also shown are the percentages of patients assigned to receive interleukin-2 who were taking the drug during each year of the study.

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 efavifenz in the STARTMRK study
  - Maroviroc 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

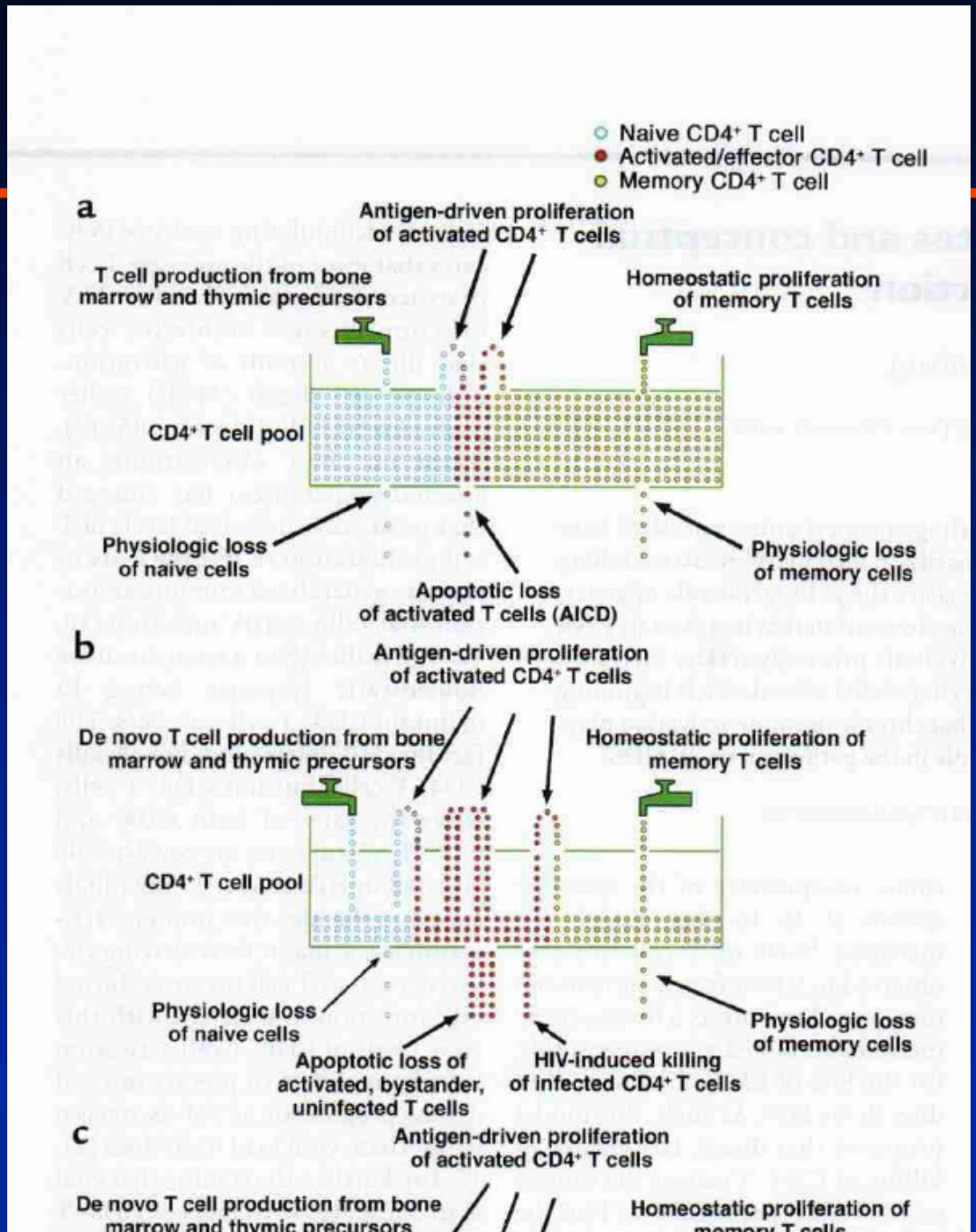
- **He remains stable with a CD4 count in the 120 range after > 3 years of suppressive HAART**
  - On Bactrim but not fluconazole
- **Last CT scan shows decrease in size and necrosis of thoracic and abdominal nodes**
  - His mycobacterial therapy has been cut back to “secondary prophylaxis” with clarithromycin 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**



Silvestri and Feinberg. JCI 112:821, 2003