

## Immunologic “failure” during long-term HAART

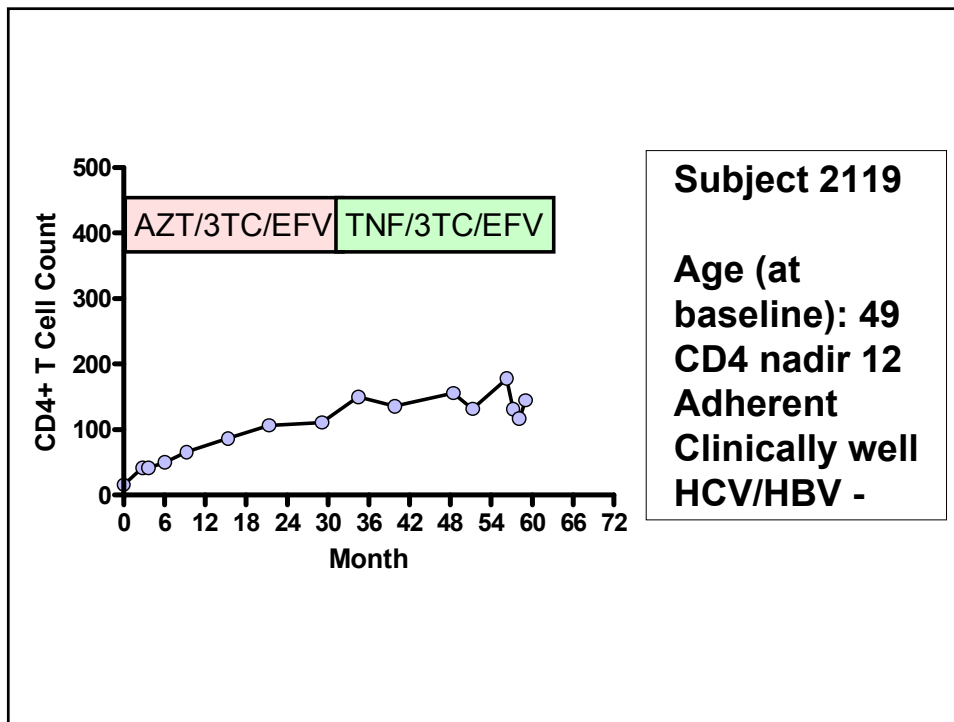
*What is it, how often does it occur, why does it happen and why we should care*

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University of California, San Francisco

### HAART: Major limitations of 1<sup>st</sup> Decade

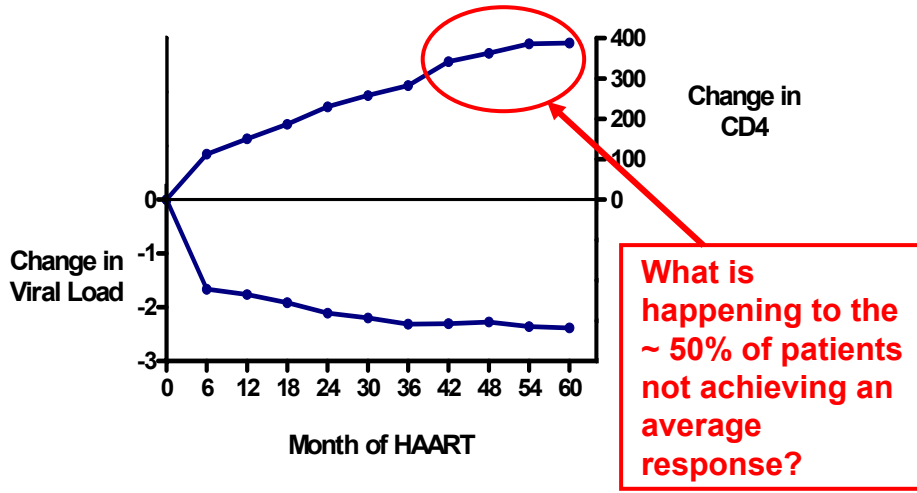
- Emergence of multi-drug resistant HIV
- Long-term complications, particularly “lipodystrophy” syndrome
- Persistent immunologic dysfunction even after years of effective viral suppression
  - “Immunologic” failure



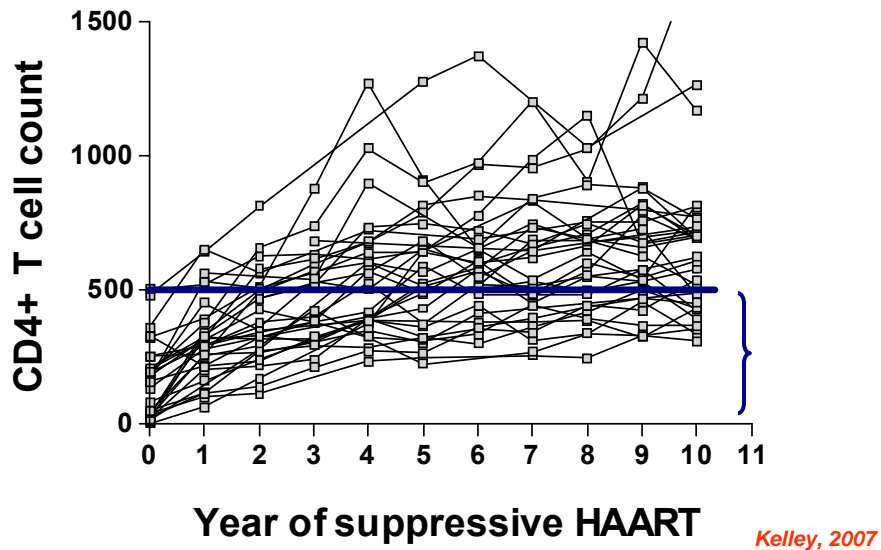
## Outline

- How common is “immunologic failure” (or, “immunologic non-response”)?
- What are the clinical implications of low CD4 during effective HAART?
  - Mortality
  - Non-AIDS events
- What are the mechanisms for immunologic failure
- What are potential therapeutic interventions?

**HAART-mediated suppression of HIV replication results in sustained CD4+ T cell gains in the average patient (SCOPE)**

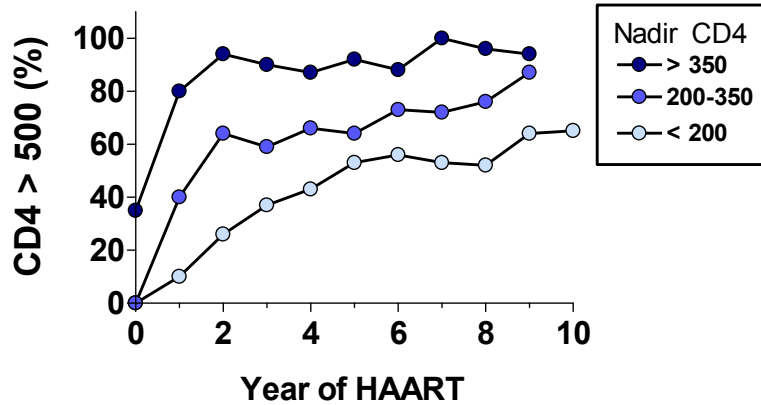


**Even after 10 years of effective HAART, many patients fail to obtain normal CD4 (n= 32)**



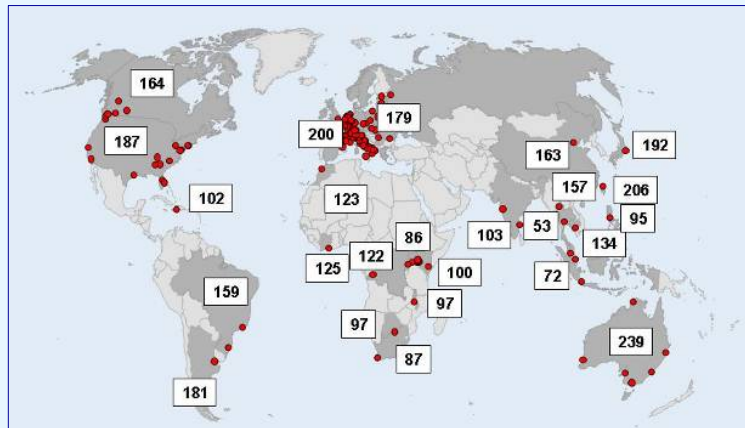
Kelley, 2007

~ 50% of patients with a CD4 < 200 who go on effective HAART fail to achieve a normal CD4+ cell count through 10 years of observation (n=300)



Kelley, 2007

### CD4 count at start of HAART, 2003–5



Data from 42 countries, 176 sites; n=33,008

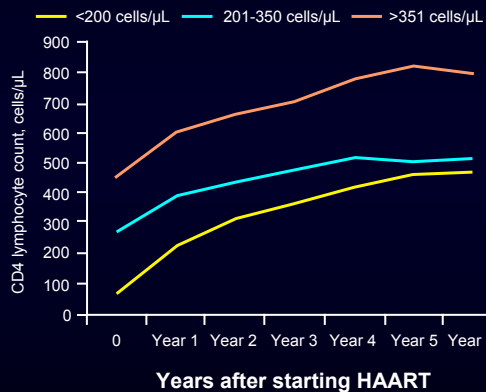
Since 2000, CD4+ cell count at initiation has increased in Sub-Saharan Africa from 50 to 100 cells/mm<sup>3</sup>; in developed countries it has remained ~150–200 cells/mm<sup>3</sup>

Egger M, et al. 14<sup>th</sup> CROI, Los Angeles 2007, #62

## CD4+ T cell counts during HAART: is there a plateau?

### Hopkins: CD4 gains during HAART suppression (n=655)

Median CD4+ cell count over time stratified by baseline CD4+ cell counts

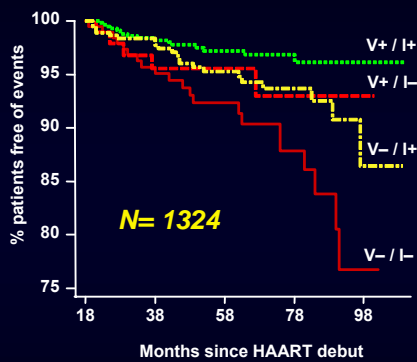


- Only patients who started HAART with baseline CD4+ cell count >350 cells/mm<sup>3</sup> returned to normal CD4+ cell counts
- Lower baseline CD4+ cell count was associated with a lower plateau, despite continued viral suppression

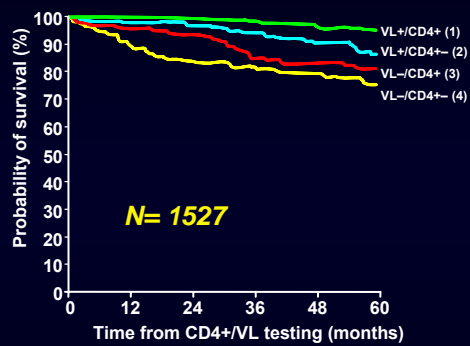
Moore RD, Keruly JC. Clin Infect Dis 2007;44:441-6

**We are the clinical implications of blunted immunologic response to HAART?**

**Italian master cohort and Hopkins Cohort:**  
*Lack of 25-50 cell increase in CD4s associated with increased risk of AIDS/mortality*



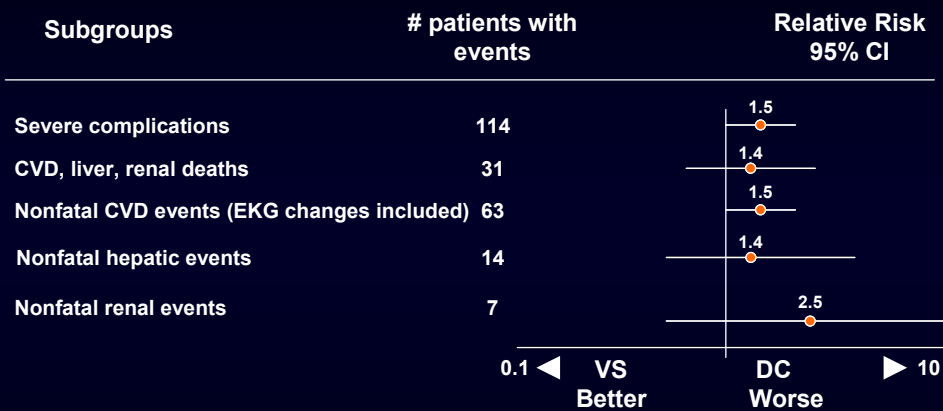
VL success: <400 c/ml  
 CD4 success: > +25



VL success: <500 c/ml  
 CD4 success: > 50 cell

## Role of CD4+ T cell count in predicting non-AIDS related complications

### SMART: Untreated HIV disease associated with increased risk of non-AIDS morbidity



*Is this related to virus replication or immunodeficiency or persistent inflammation?*

# FIRST Study Design and Follow-up

1,397 Participants Randomized

## PI Strategy

PI + NRTIs  
(N=470)

## NNRTI Strategy

NNRTI + NRTIs  
(N=463)

## 3-class Strategy

PI + NNRTI + NRTIs  
(N=464)

### Demographic Characteristics

Characteristic	Value
Age	38
Women	21%
Non-white	74%

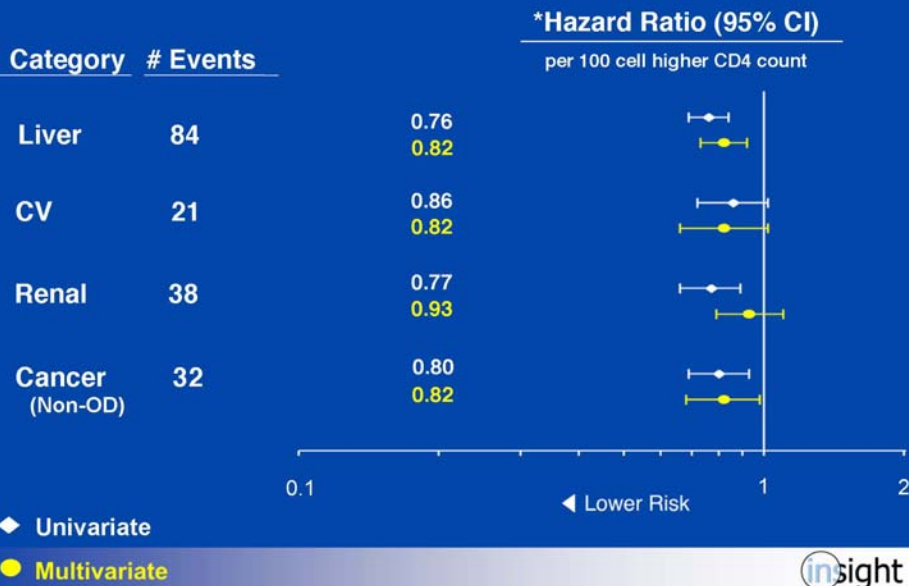
### Median Follow-up

60 months

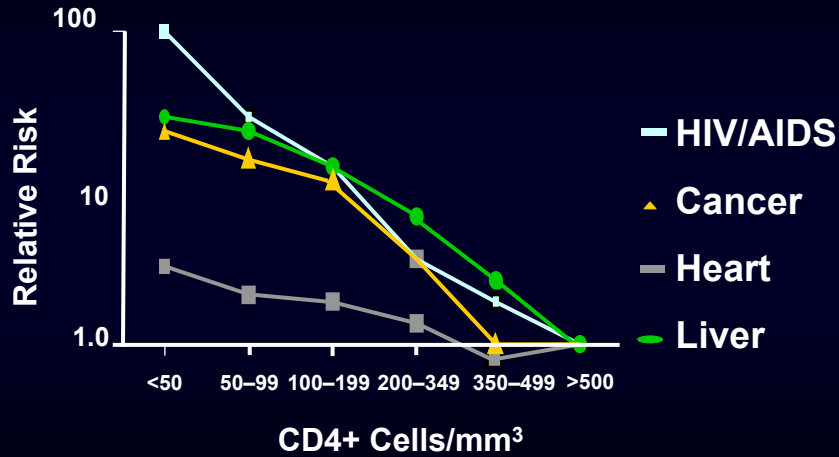
MacArthur et. al. LANCET 2006;368:9553



## Non-AIDS Morbidity is Predicted by Proximal CD4 on HAART (FIRST Study)



## CD4 on therapy predicts risk of AIDS and more importantly the risk of non-AIDS events (DAD)



*Liver-related: Chronic viral hepatitis, liver failure (other); malignancy-related: malignancy, non-AIDS hepatitis; heart-related: MI, other CVD, other heart disease*

## CD4 Count during Treatment Predicts Risk of Non-AIDS Defining Malignancies (DAD Cohort, n > 23000)

Latest CD4	Person Years	Non-AIDS defining malignancies	
		Rate (/1000 py)	RR (p)
<50	2335	6.0	15 (<0.001)
50-99	2295	9.6	19 (<0.001)
100-199	8097	6.8	10 (<0.001)
200-349	21048	2.0	3 (<0.001)
350-499	24052	1.1	2 (0.3)
≥500	46903	0.6	1

D'Arminio Monforte A, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Abst. 84.

## Summary so far

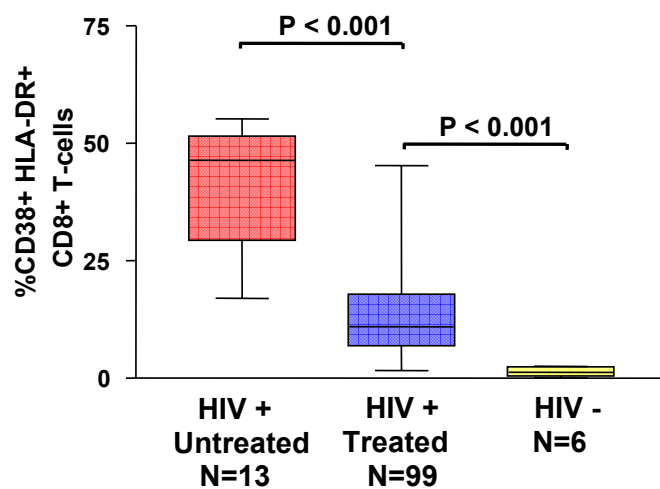
- A significant minority of HAART treated patients fail to achieve a normal CD4 during long-term HAART
  - Low pre-HAART CD4 nadir, age, HCV co-infection established predictors
  - Is there a plateau after 5 years?
- DAD and FIRST findings show consistent association between proximal CD4+ T cell counts on HAART and risk of non-AIDS defining deaths/complications
  - Differences noted even above 350 cells/mm<sup>3</sup>
- A normal life-span—which may be the real goal of therapy—requires sustained CD4 counts > 500
  - *Lewden JAIDS 07*

**Mechanisms of immunologic non-response**

## How does HIV cause CD4 depletion?

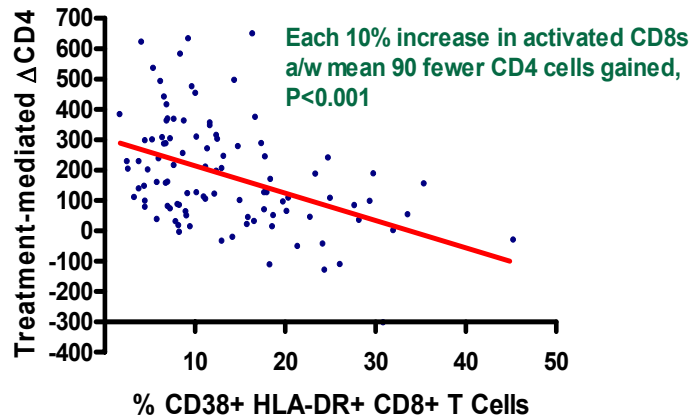
- T cell “activation”—and other measures of inflammation--predicts CD4 declines and disease progression independent of viral load
  - Accelerated turnover/immunologic exhaustion
  - Migration to tissues/virus-mediated death
  - Inflammatory changes in lymphoid infrastructure
  - T cell dysfunction/proliferation defects

CD8+ T cell activation (and other markers of inflammation) decline during HAART, but remains abnormal



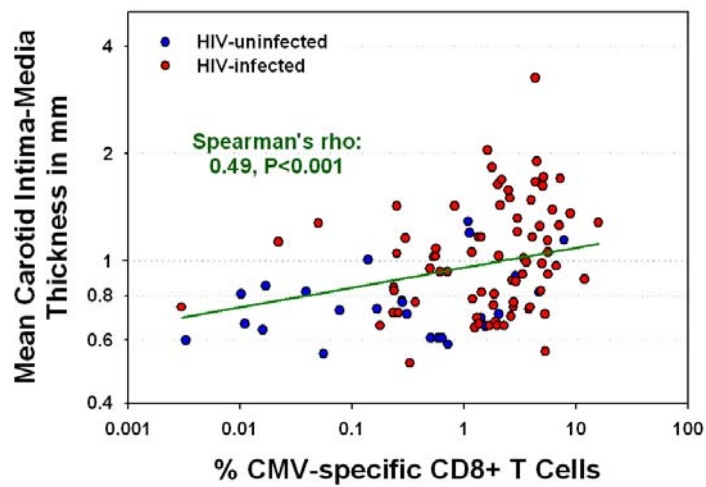
Hunt JID 2003

## Higher CD8 Activation Associated with Fewer Treatment-mediated CD4 Gains



Hunt et al, JID, 2003

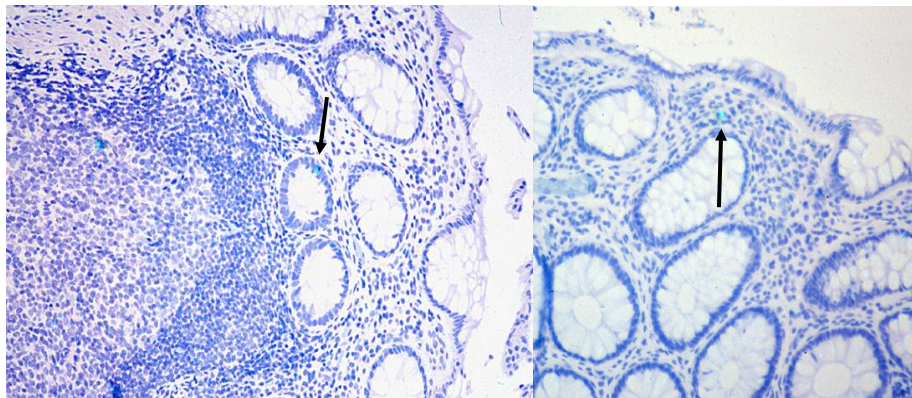
## Higher CMV-specific inflammatory changes may be driving accelerated atherosclerosis



Hsue et al, AIDS, 2006

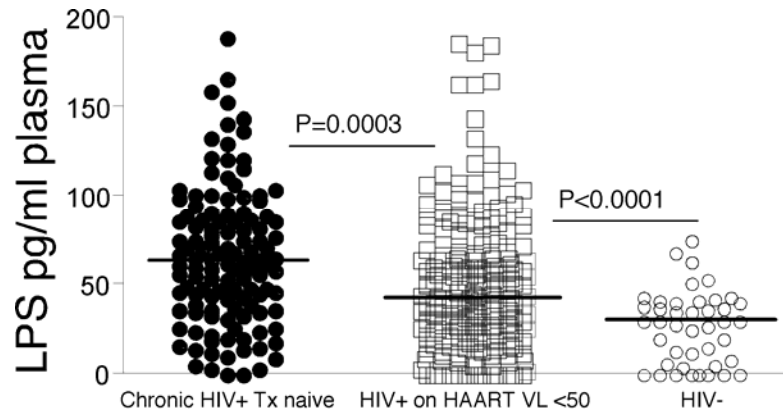
**Why is there persistent  
inflammation during  
HAART?**

Persistent HIV-1 RNA Expression in Gut  
Tissues is Commonly Observed During  
HAART and When Present Associated with  
Immune Activation and Low CD4 Density



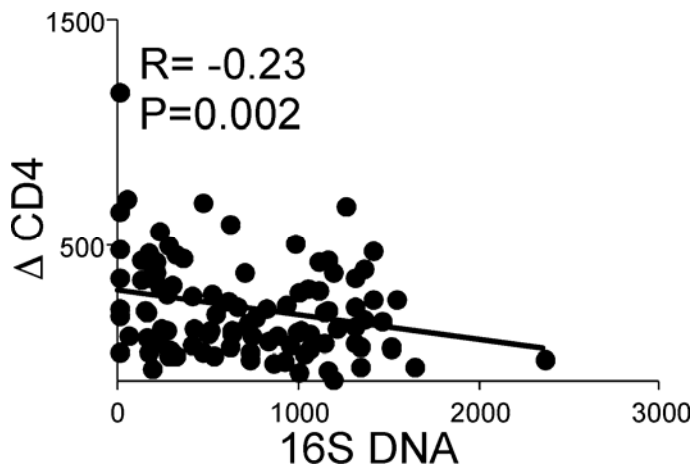
*Markowitz, 2007*

**Despite durable treatment-mediated viral suppression, endotoxin (LPS) remains high**



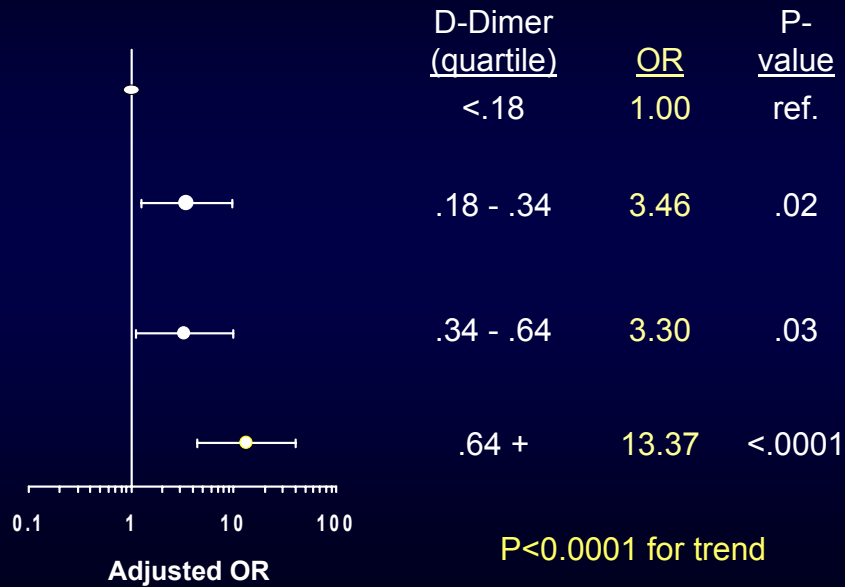
*Brenchley, 2007*

**CD4 reconstitution during HAART is negatively associated with microbial translocation**

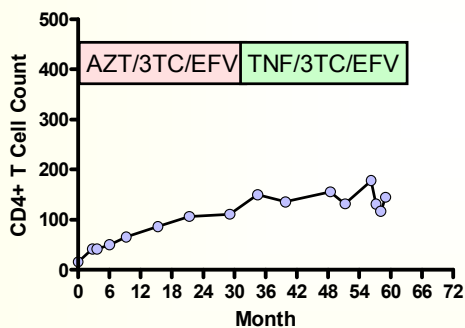


*Brenchley, 2007*

## Odds Ratios for Death by Baseline D-dimer (adjusted for viral load, CD4 and other factors)



## Therapeutic interventions

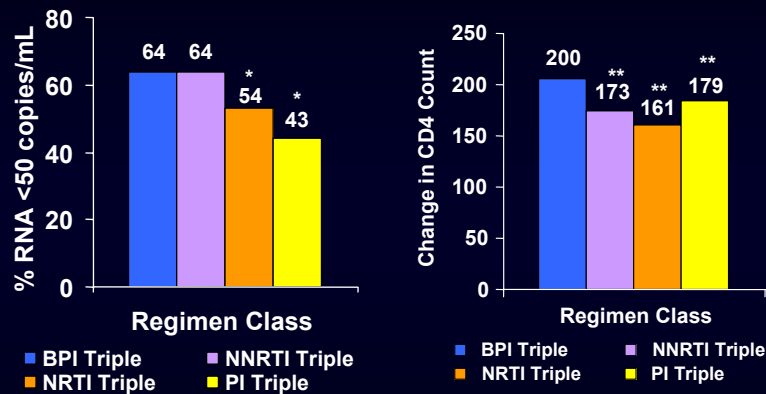


So immunologic non-responders are common in clinical practice, and its possible that normal CD4s may never be obtained in some patients, and it appears that this might predict non-AIDS morbidity, and it might be due to persistent immune activation . . . *So what to do?*

## Therapeutic Options

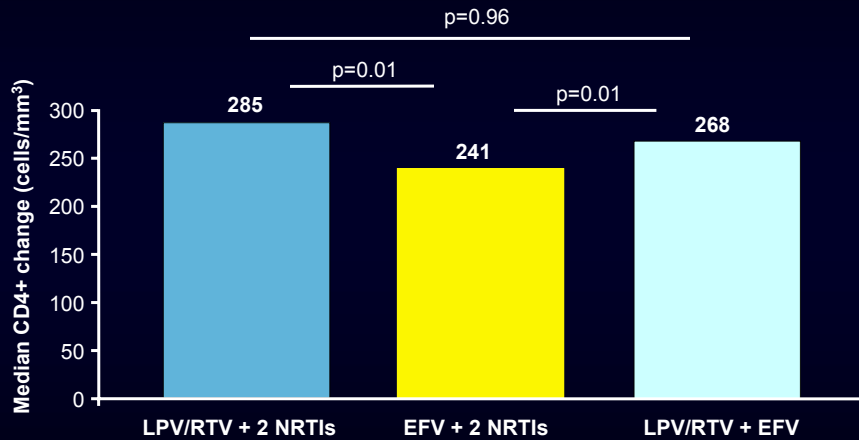
- Treatment intensification
- Growth hormone
- Cyclosporin
- Interleukin-7
- Management of co-infections (hep C, CMV)
- **Switch to protease inhibitors (the “PI” effect)**
- **Maraviroc/R5 inhibitors**
- **Interleukin-2**

Systematic overview: CD4 gains are higher in “boosted PI” treated patients compared to NNRTI treated patients (week 48)



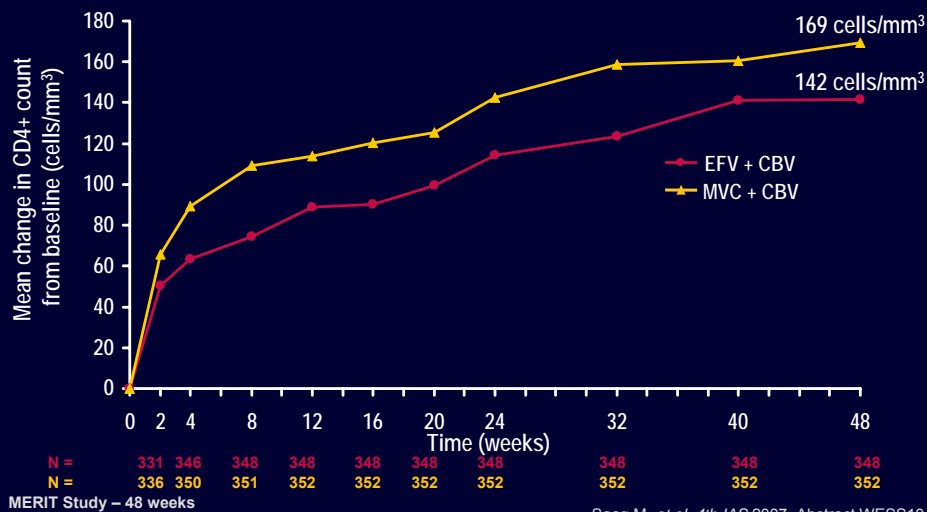
Bartlett J. *et al*, *AIDS* 2006 Oct 24;20:2051-64

## ACTG 5142: PI vs. NNRTI vs PI/NNRTI (96 weeks)

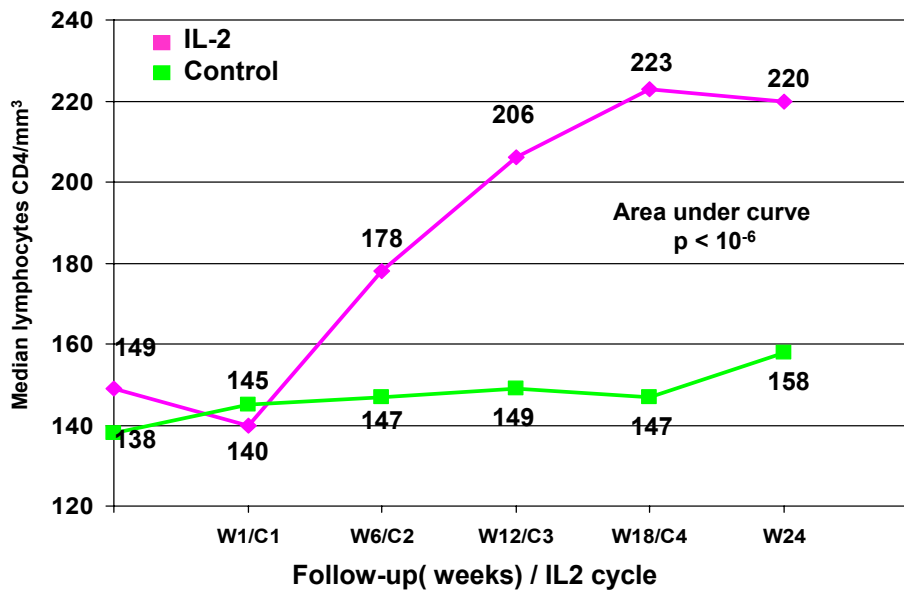


Riddler S, et al. XVI IAC, Toronto 2006, #THLB0204

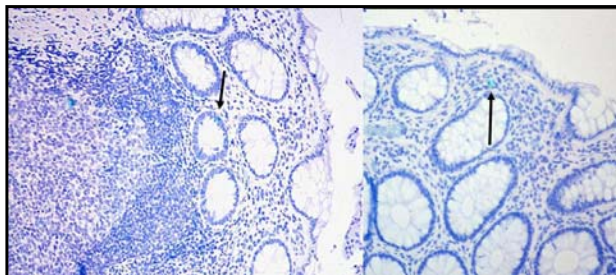
## MERIT: Greater CD4 gains among MVR-treated individuals compared to EFV-treated individuals



**ILSTIM (ANRS 082): Controlled Trial of IL-2 in persons with CD4 < 200/uL after > 6 mos of HAART**



**Incomplete Viral Suppression: Should we Intensify Therapy?**



JOURNAL OF VIROLOGY, Oct. 2008, p. 11212-11219  
 0022-5380/08/00-0 DOI: 10.1128/JVI.77.20.11212-11219.2008  
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**Productive Infection Maintains a Dynamic Steady State of Residual Viremia in Human Immunodeficiency Virus Type 1-Infected Persons Treated with Suppressive Antiretroviral Therapy for Five Years**

Diane V. Havlir,<sup>1\*</sup> Matthew C. Strain,<sup>2,3</sup> Mario Clerici,<sup>4</sup> Caroline Ignacio,<sup>5</sup> Daria Trabattoni,<sup>4</sup> Pasquale Ferrante,<sup>6</sup> and Joseph K. Wong<sup>7,8</sup>

## Summary and Conclusions I

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- Immunologic outcomes (as defined by CD4 cell count) may remain suboptimal in many HAART-suppressed patients
  - ↑ risk in those who are older, start therapy with a low CD4 nadir, and have other chronic infections
- Suboptimal CD4 gains are associated with increased risk of non-AIDS defining deaths/complications
  - Differences noted even above 350 cells/mm<sup>3</sup>

## Summary and Conclusions II

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- Long-term effective HAART reduces evidence of inflammation (immune activation) but this reduction is incomplete
  - Immune activation associated with suboptimal CD4 gains and perhaps early atherosclerosis
- Long-term effective HAART does not restore normal T cell maturation profiles
  - Proportion of “naïve” CD8 (and CD4) T cells remains low and proportion of highly differentiated effector T cells remains high
  - Profiles are c/w advanced age

## Summary and Conclusions III

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- Mechanism for persistent inflammation not known
  - Persistent HIV low level replication
  - High prevalence of other co-infections
  - Persistent microbial translocation in gut
- Mechanism for non-AIDS morbidity not known
  - Persistent inflammation
  - Persistent immunodeficiency
  - Other
    - CMV-specific CD8s are very high in treated HIV and predictive of atherosclerosis
    - D-dimers

## Summary and Conclusions IV

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- Therapeutic options for this group remain unclear as there has to this point been limited concerns
  - ? Switch to protease inhibitors in those not on these drugs
  - Immune based therapy (IL2, others)
  - Management of chronic co-infections
  - Aggressive risk management (e.g., lipid management, etc)