

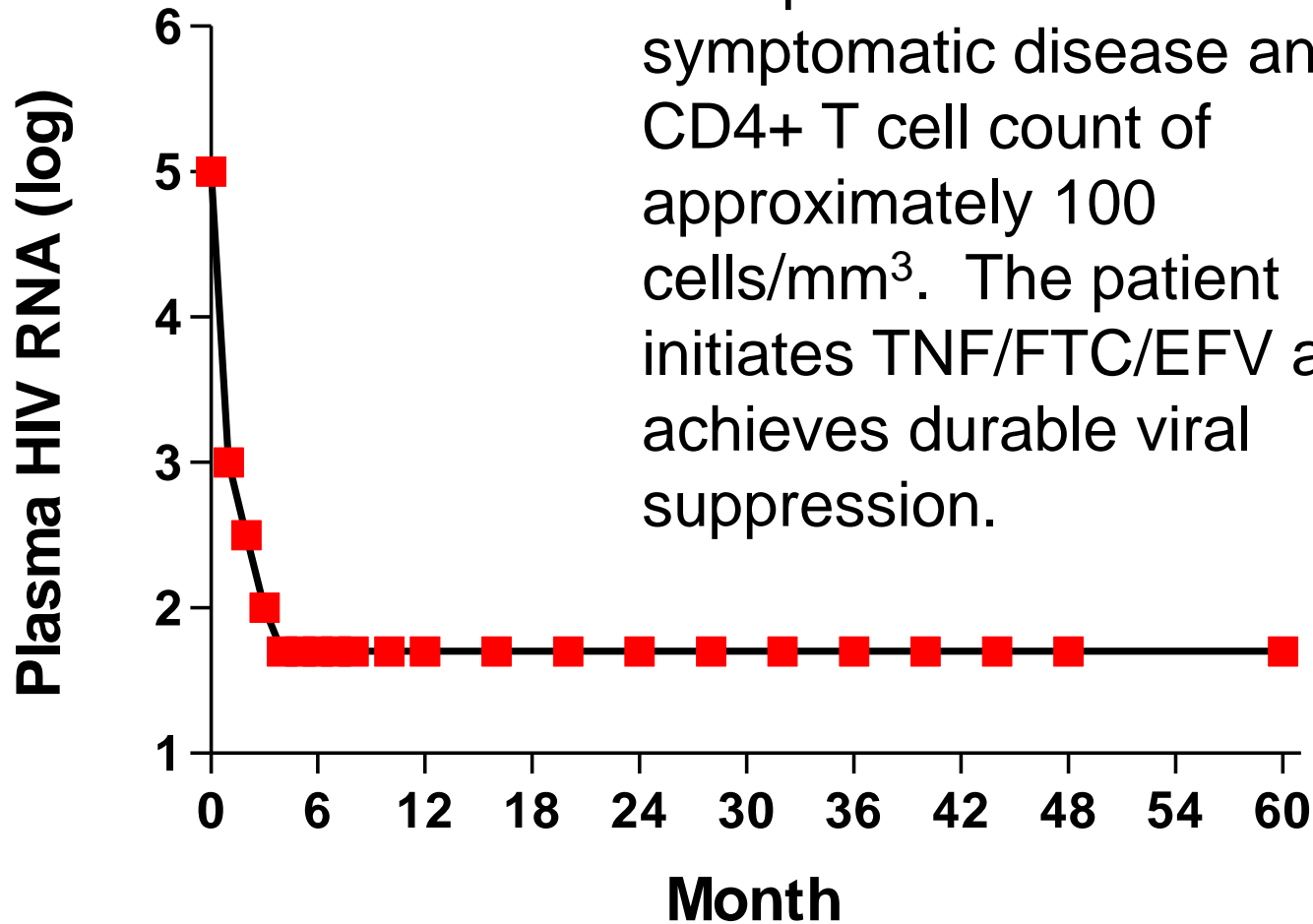
Immunologic Failure and Chronic Inflammation

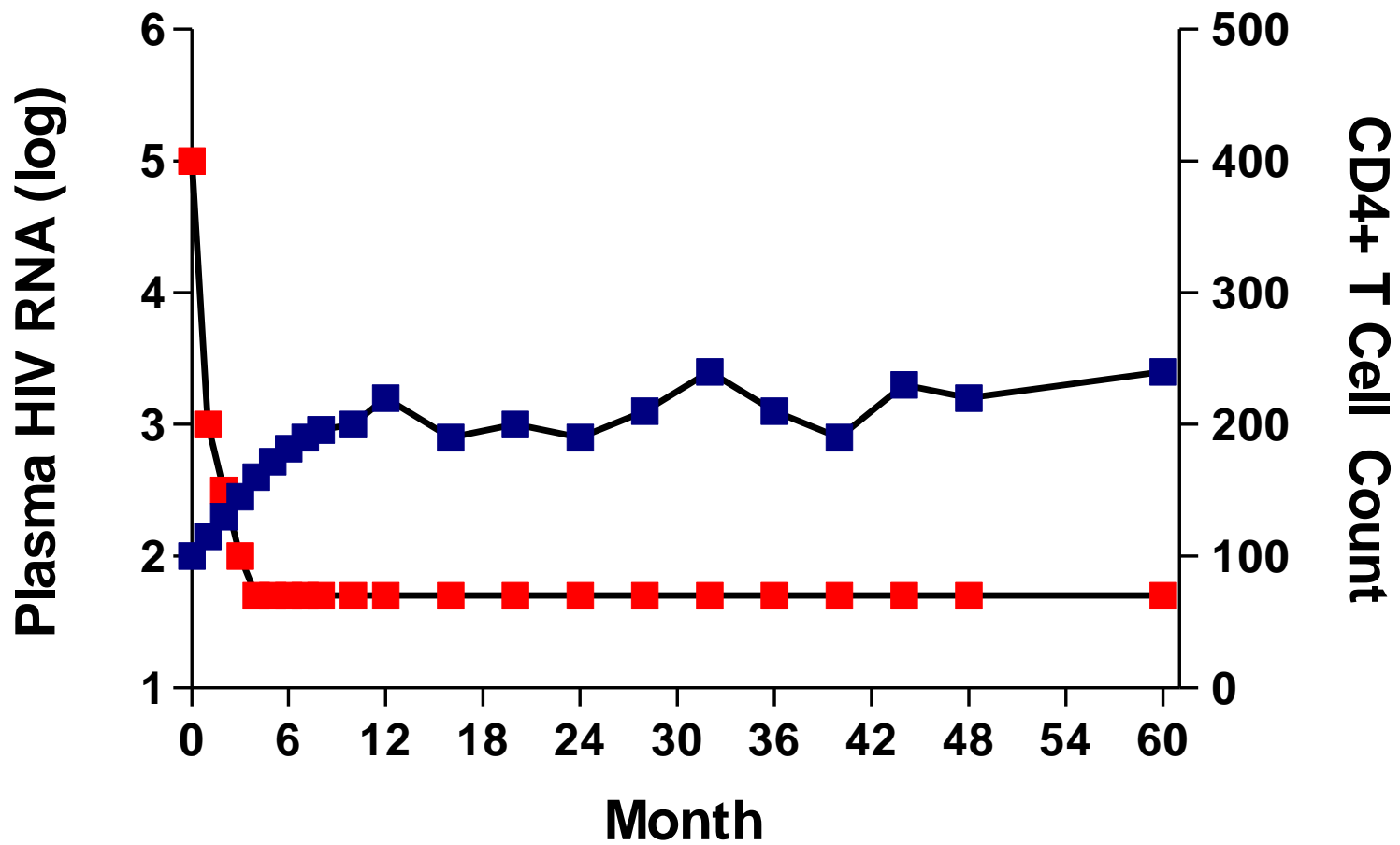
Steven G. Deeks

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/mm³. The patient initiates TNF/FTC/EFV and achieves durable viral suppression.

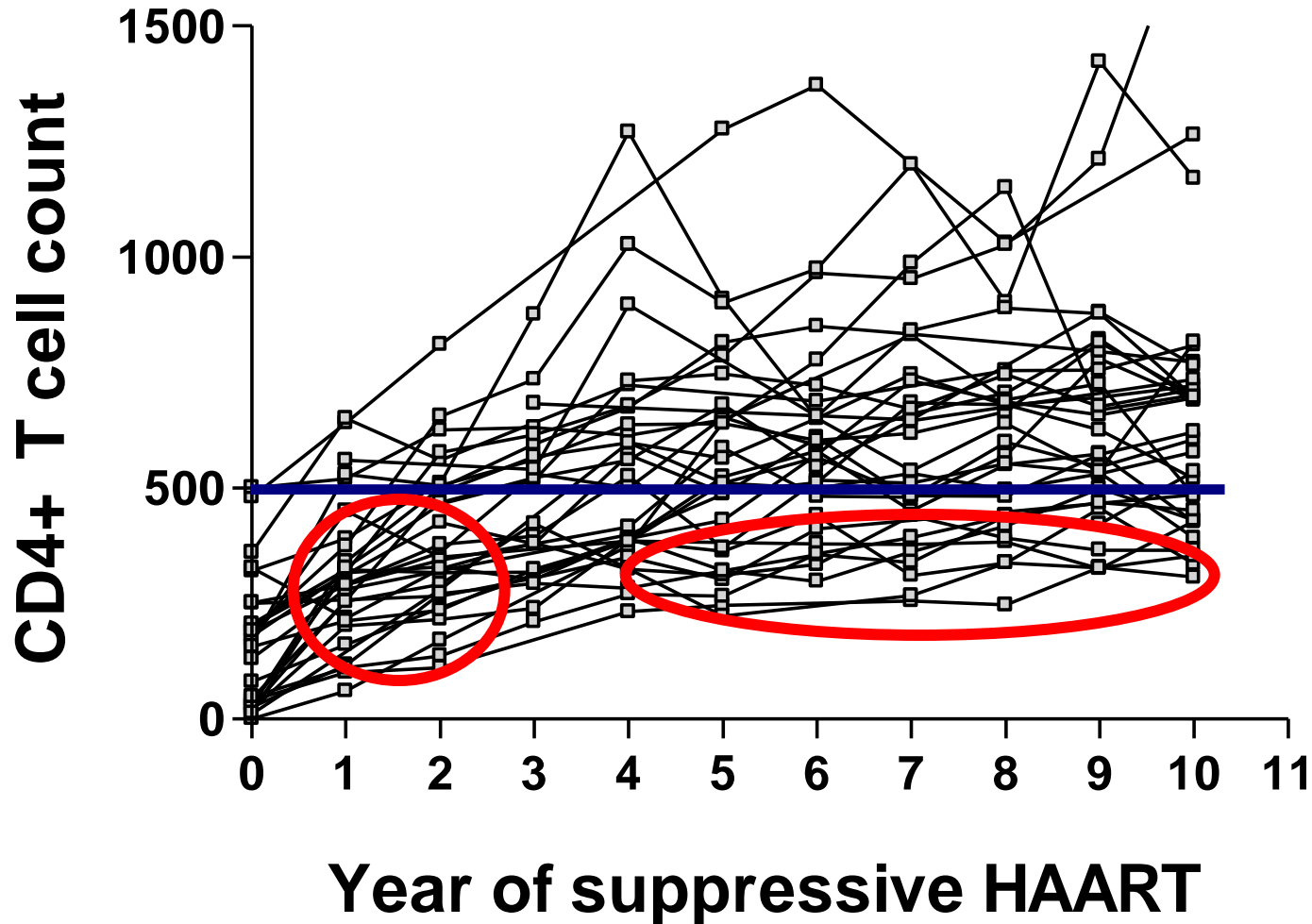




Immunologic Failure: Definition

- 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



CD4 count at start of HAART, 2003-2005

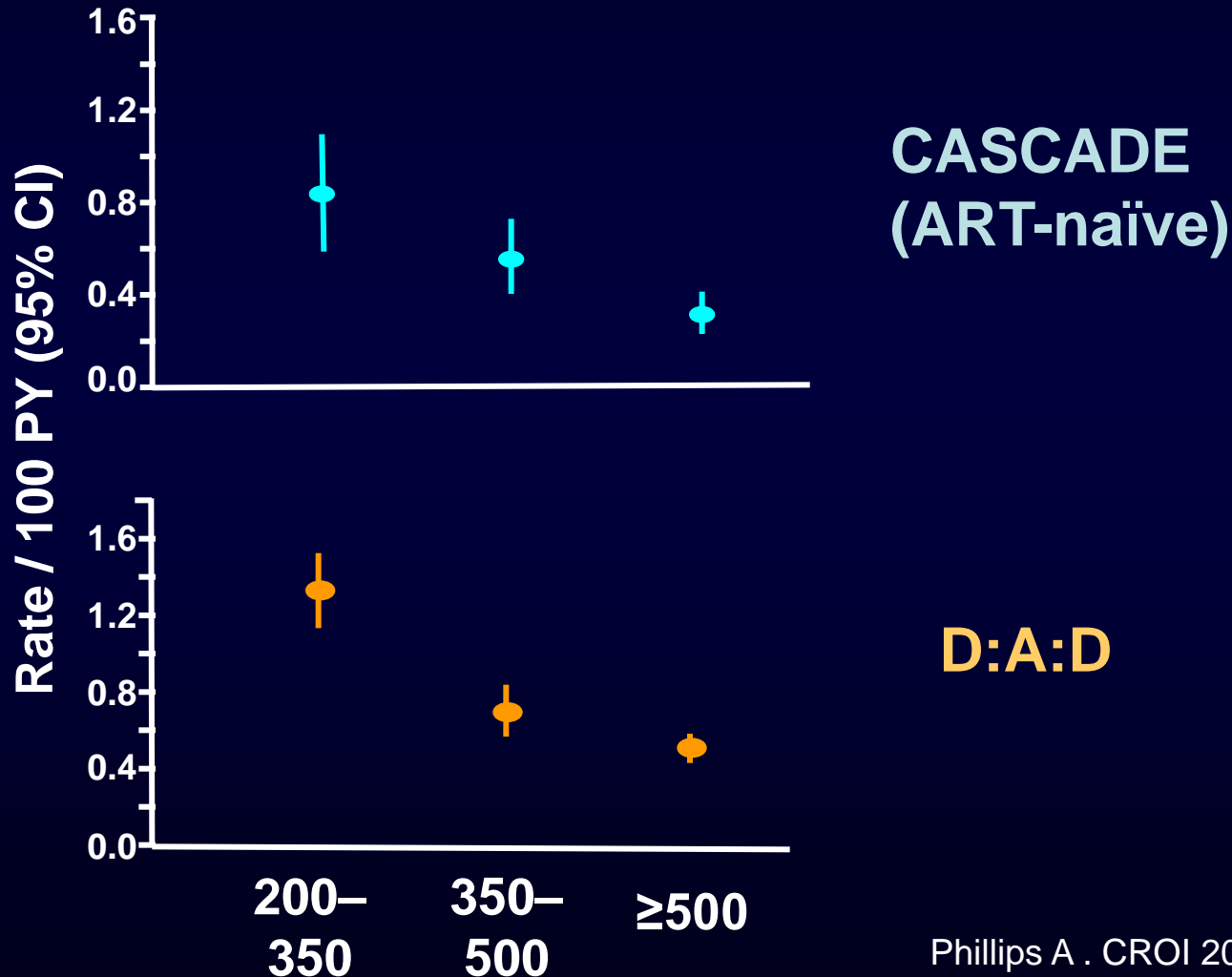


Data from 42 countries, 176 sites; n=33,008

Since 2000, CD4+ cell count at initiation has increased in Sub-Saharan Africa from 50 to 100 cells/mm³; in developed countries it has remained ~150–200 cells/mm³

**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

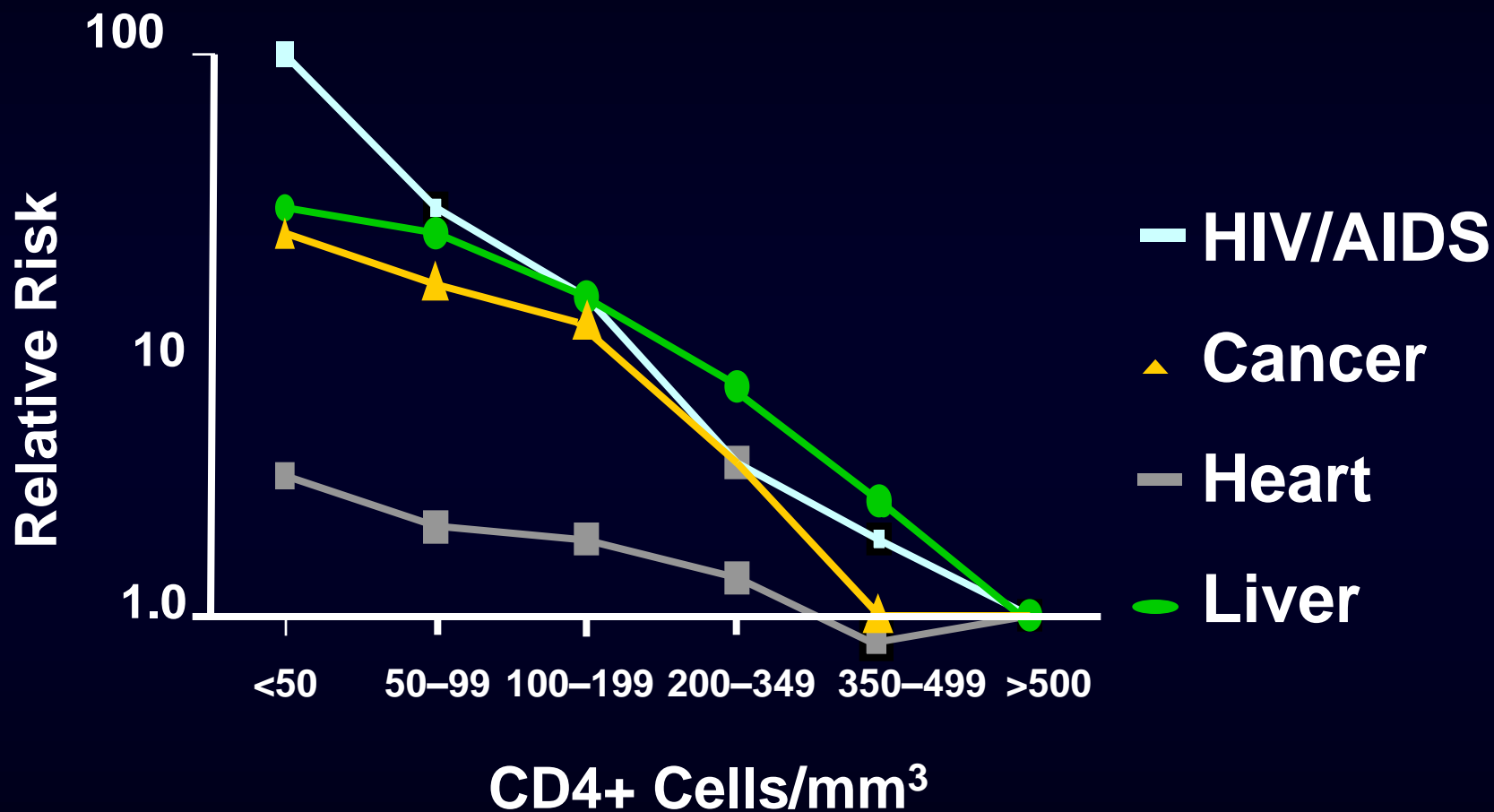


Survival of Patients with CD4 Counts \geq 500 for >5 Years is Similar to the General Population

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

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)



Weber R, et al. CROI 2005. Abstract 595.

See also: Weber R, et al. Arch Intern Med. 2006;166:1632-1641. Philips AN, et al. AIDS. 2008;22:2409-2418. Baker JV, et al. AIDS. 2008;22:841-848.

**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

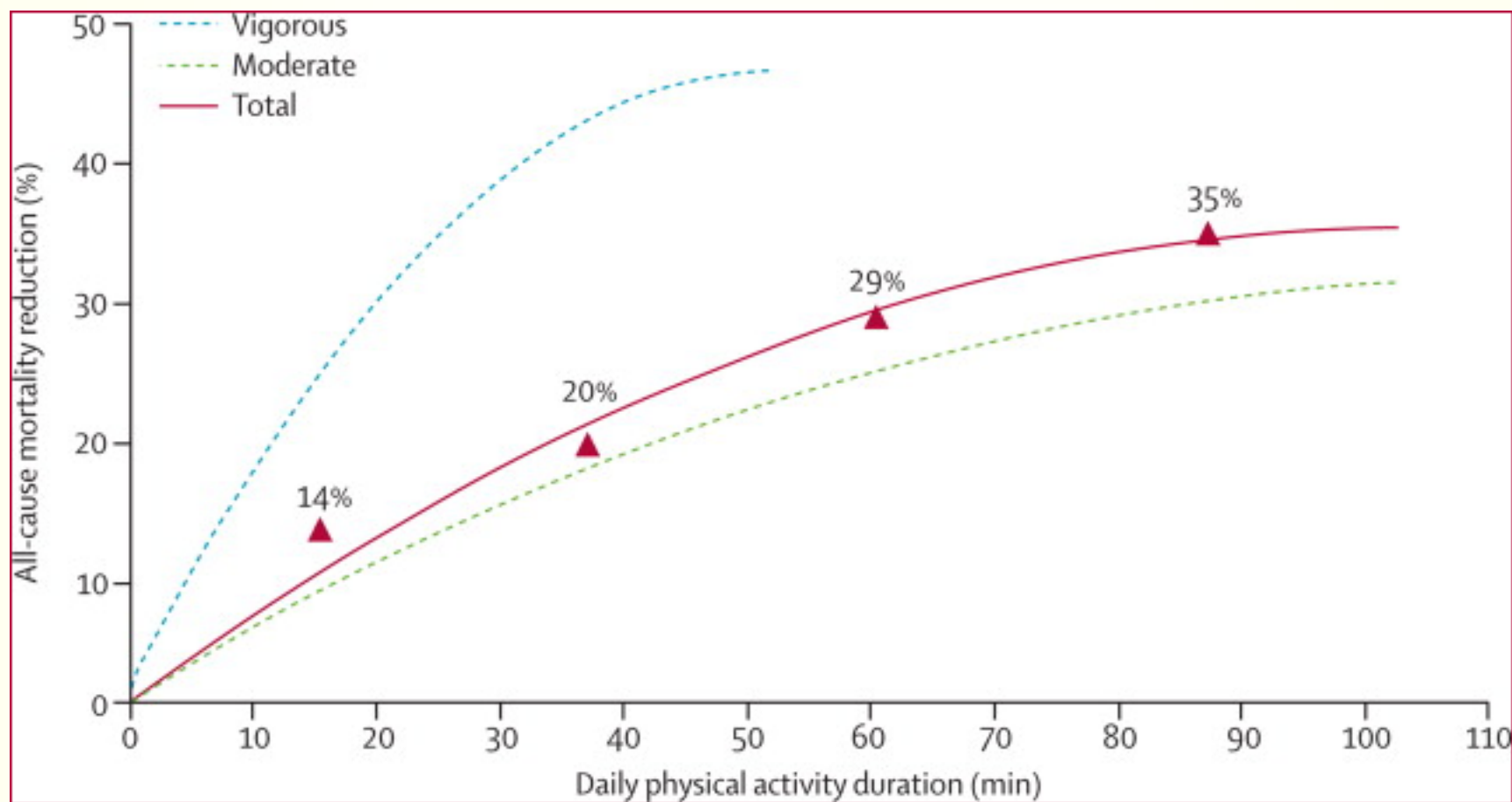
- Untreated HIV disease is associated with increased T cell activation/inflammation and these markers predict disease
- Treatment dramatically reduces but does not normalize levels inflammation
 - Inflammation on HAART predicts disease
- The degree of residual inflammation during HAART is determined in part by CD4 nadir (strong effect < 200 , less clear effect > 350)



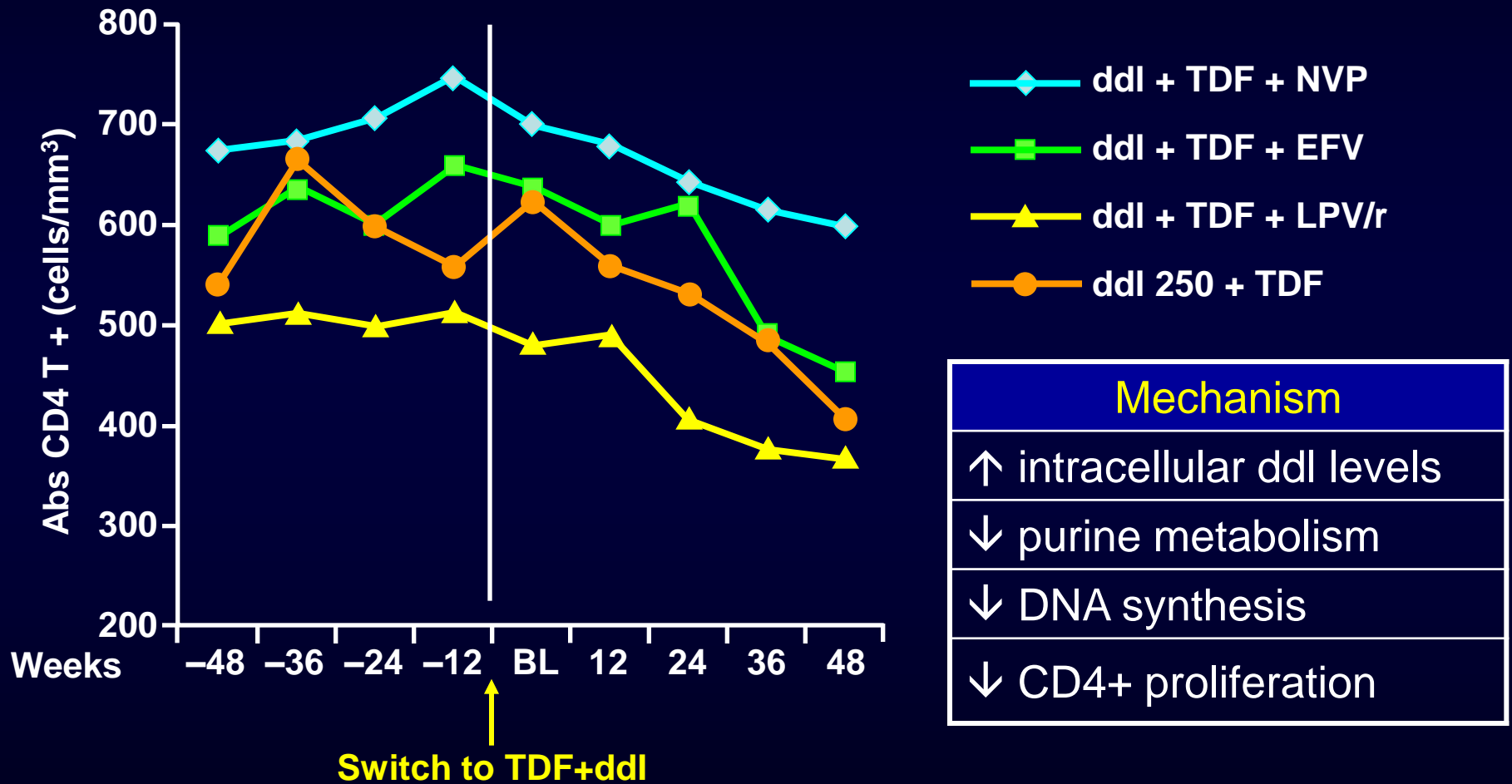
Risk factor modification
Diet
Exercise
Statins, aspirin
Vitamin D

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



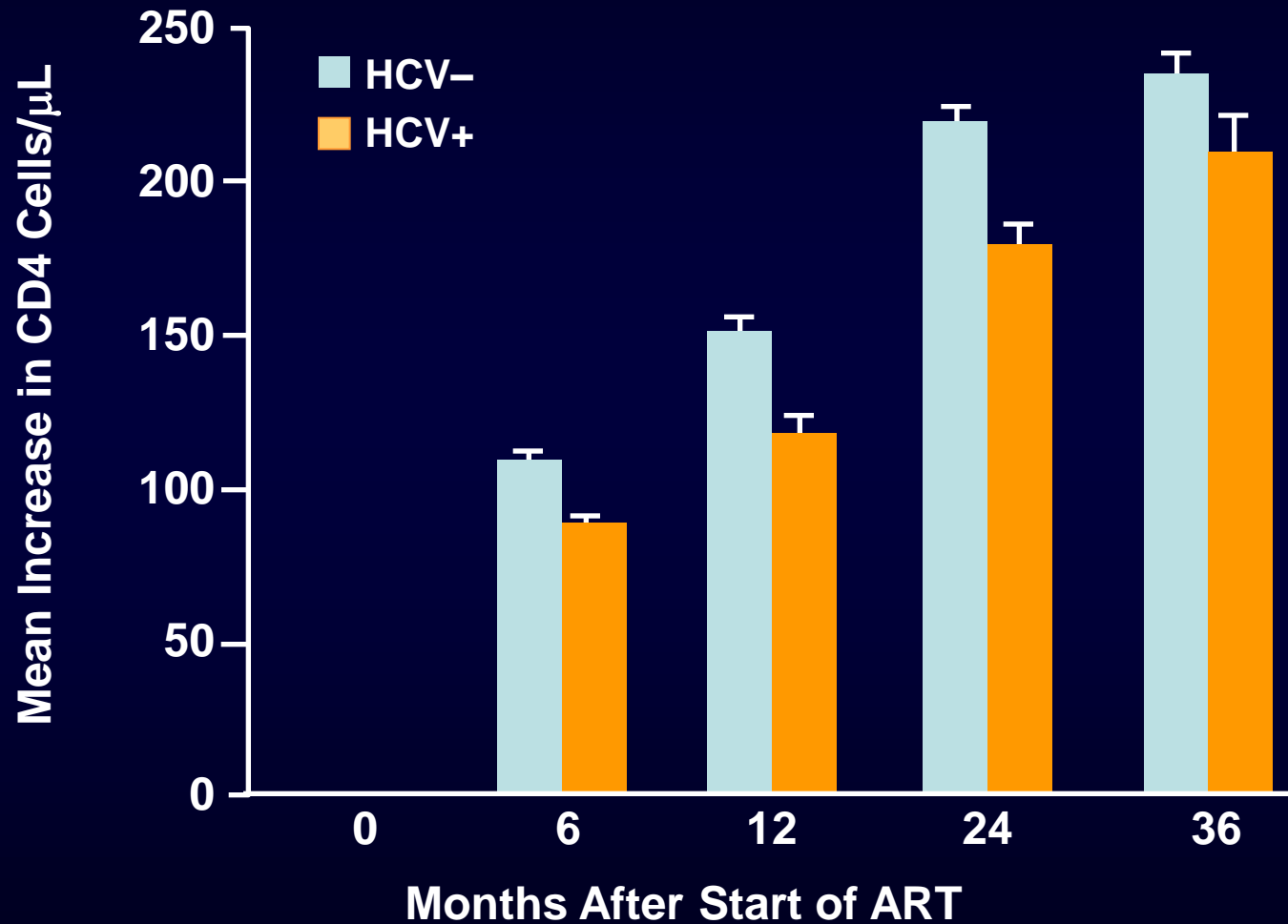
ddl+TDF Causes CD4+ Decline



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

Negredo E et al. *AIDS*. 2004;18(3):459-463; Barreiro P et al. *J Antimicro Chem*. 2006; 57(5):806-809.

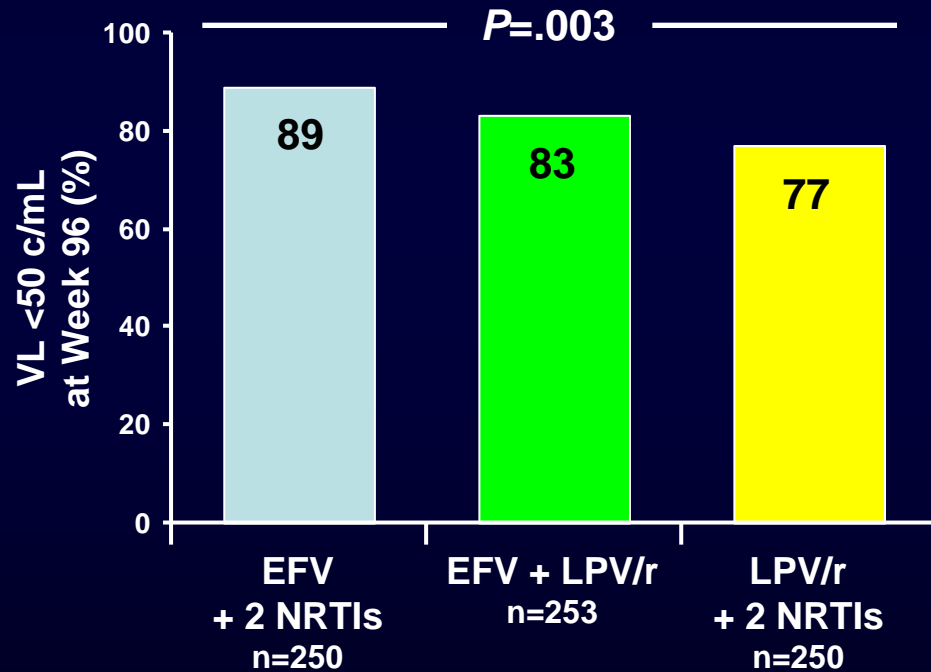
HCV Associated with Blunted CD4 Gains During HAART



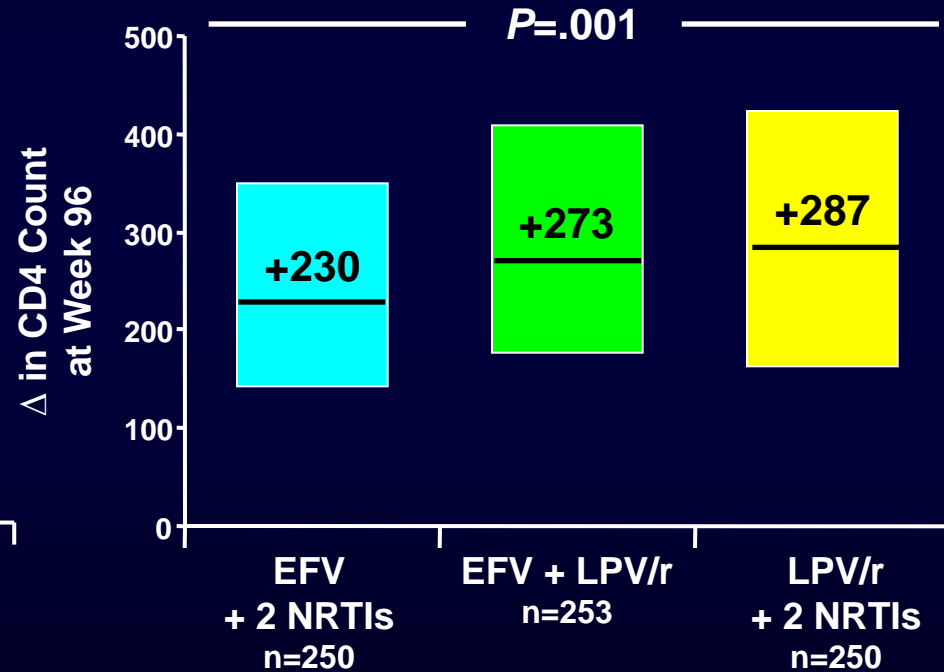
Improved CD4 Recovery with boosted PIs

ACTG 5142

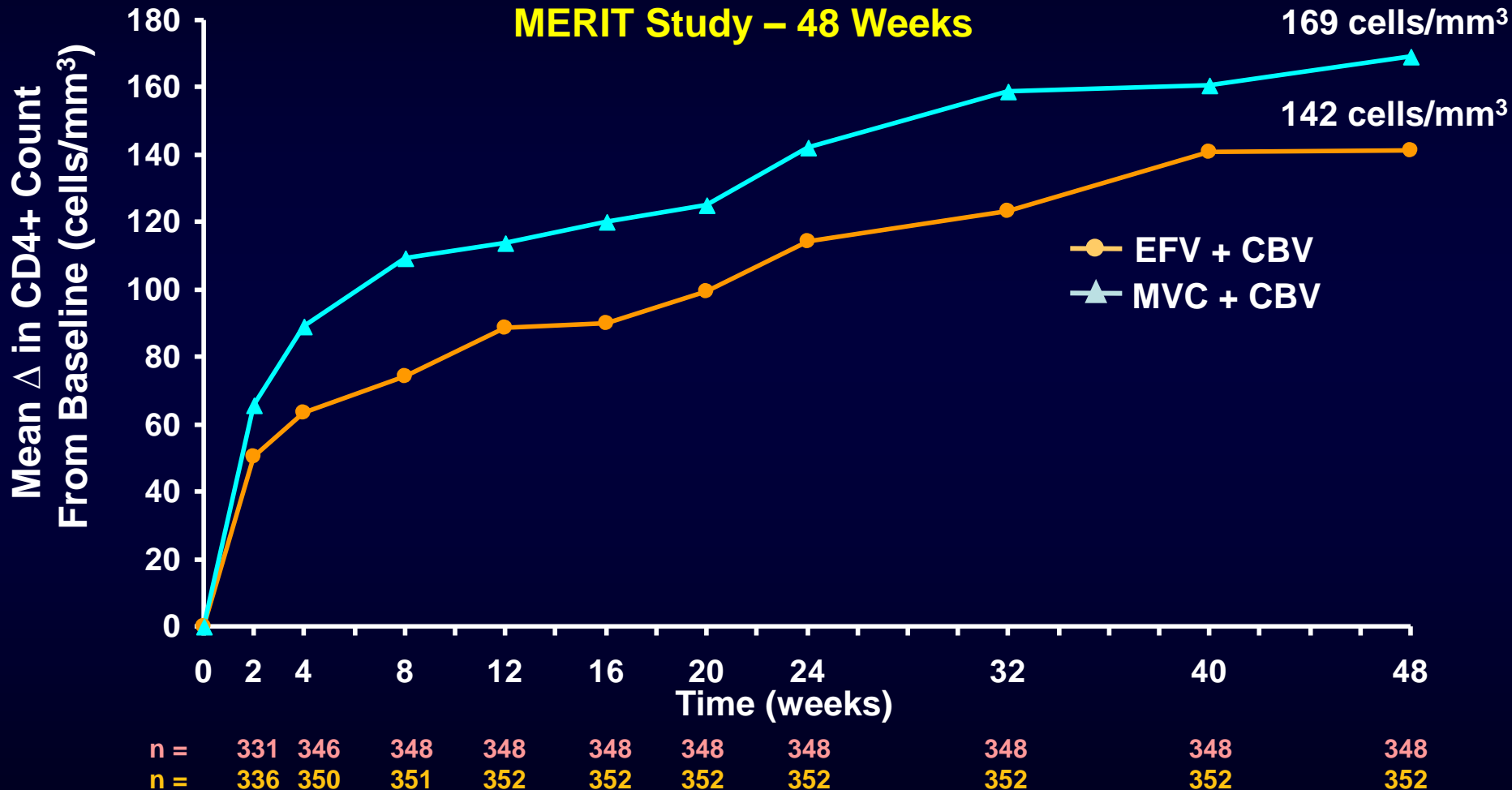
VL < 50 at Week 96



Δ CD4 at Week 96



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

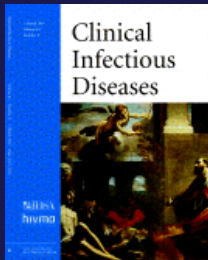


MVC = maraviroc; CBV = combivir

Saag M et al. 4th Annual IAS Meeting. Sydney, Australia: July 22-25, 2007. Abstract WESS104

Treatment intensification does not reduce residual HIV-1 viremia in patients on highly active antiretroviral therapy

J. B. Dinosa^{a,b,1}, S. Y. Kim^{a,1}, A. M. Wiegand^c, S. E. Palmer^{c,2}, S. J. Gange^d, L. Cranmer^a, A. O'Shea^e, M. Callender^a, A. Spivak^a, T. Brennan^a, M. F. Kearney^c, M. A. Proschan^f, J. M. Mican^g, C. A. Rehm^g, J. M. Coffin^{c,h,3}, J. W. Mellors¹, R. F. Siliciano^{a,j}, and F. Maldarelli^{c,3}



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

D. McMahon,¹ J. Jones,¹ A. Wiegand,² S. J. Gange,³ M. Kearney,² S. Palmer,^{2a} S. McNulty,¹ J. A. Metcalf,⁴ E. Acosta,⁵ C. Rehm,⁴ J. M. Coffin,² J. W. Mellors,¹ and F. Maldarelli²



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

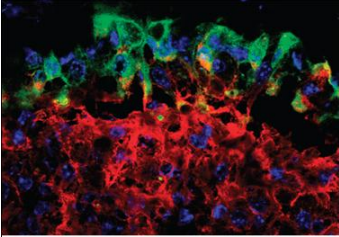
Hiroyu Hatano,¹ Timothy L. Hayes,² Viktor Dahl,³ Elizabeth Sinclair,¹ Tzong-Hae Lee,⁴ Rebecca Hoh,¹ Harry Lampiris,^{1,5} Peter W. Hunt,¹ Sarah Palmer,³ Joseph M. McCune,¹ Jeffrey N. Martin,¹ Michael P. Busch,^{1,4} Barbara L. Shacklett,² and Steven G. Deeks¹

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,¹ Mark Kelly,² Damian F. J. Purcell,³ Martyn A. French,⁴ Janaki Amin,¹ Sharon R. Lewin,^{5,6,7} Hila Haskelberg,¹ Anthony D. Kelleher,^{1,8} Roger Garsia,⁹ Mark A. Boyd,¹ David A. Cooper,^{1,8} and Sean Emery,¹ for the CORAL Study Group

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

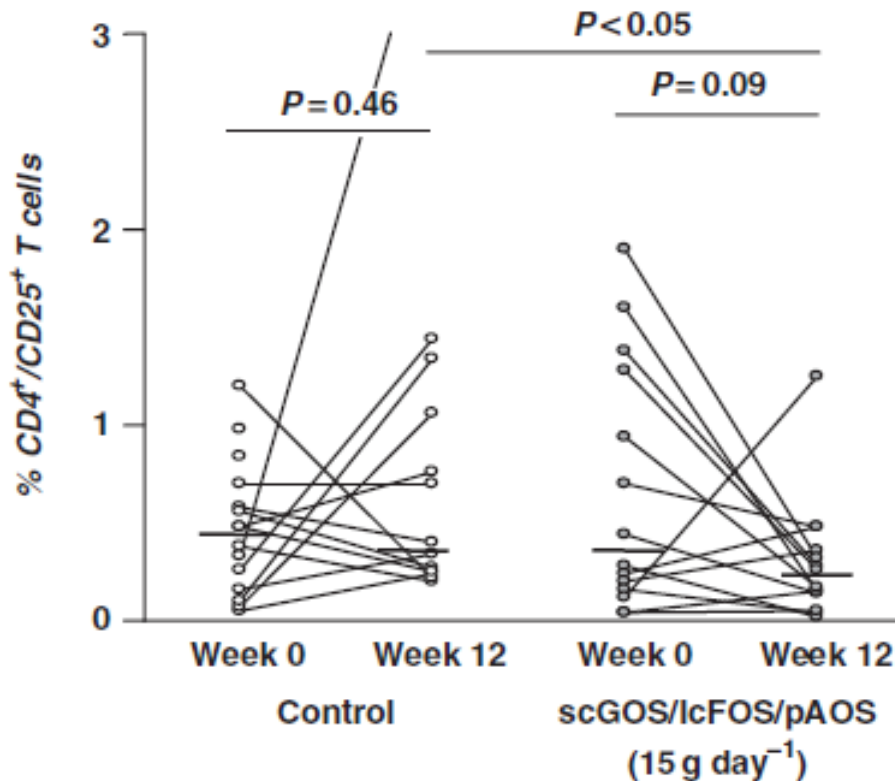
Rajesh T. Gandhi^{1*}, Lu Zheng², Ronald J. Bosch², Ellen S. Chan², David M. Margolis³, Sarah Read⁴, Beatrice Kallungal⁵, Sarah Palmer⁶, Kathy Medvik⁷, Michael M. Lederman⁷, Nadia Alatrakchi⁸, Jeffrey M. Jacobson⁹, Anne Wiegand¹⁰, Mary Kearney¹⁰, John Coffin¹¹, John W. Mellors¹², Joseph J. Eron³, on behalf of the AIDS Clinical Trials Group A5244 team[†]



T helper cells
Mucosal immunoglobulins
Vitamins and lymphocyte
migration

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 Land^{3,4}, KB Amor³, J van Schaik³, C Torti⁵, T Quirino⁶, C Tincati⁷, A Bandera¹, J Knol³, K Benlhassan-Chahour⁸, D Trabattoni⁹, D Bray⁸, A Vriesema³, G Welling¹⁰, J Garssen^{3,4} 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,¹ Mark Kelly,² Damian F. J. Purcell,³ Martyn A. French,⁴ Janaki Amin,¹ Sharon R. Lewin,^{5,6,7} Hila Haskelberg,¹ Anthony D. Kelleher,^{1,8} Roger Garsia,⁹ Mark A. Boyd,¹ David A. Cooper,^{1,8} and Sean Emery,¹ for the CORAL Study Group

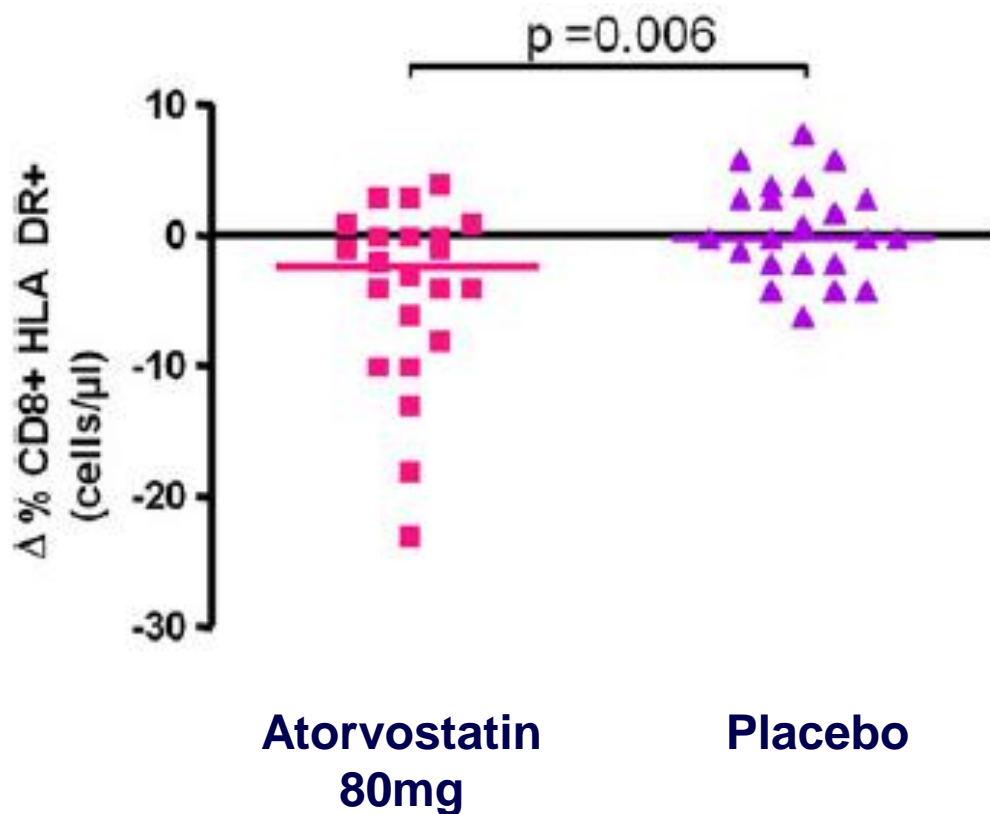
	Mean	95% CI	P value
CD4⁺ CD38⁺ HLA-DR⁺ (%)			
HIBC vs placebo	-0.03	-.22, .15	.713
RAL vs placebo	0.08	-.10, .27	.370
CD8⁺ CD38⁺ HLA-DR⁺ (%)			
HIBC vs placebo	0.16	-.72, 1.04	.719
RAL vs placebo	0.31	-.57, 1.20	.479

- 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

The Journal of
Infectious Diseases

Anuradha Ganesan,^{1,2} Nancy Crum-Cianflone,^{2,3} Jeanette Higgins,⁴ Jing Qin,⁵ Catherine Rehm,⁶ Julia Metcalf,⁷ Carolyn Brandt,³ Jean Vita,¹ Catherine F. Decker,¹ Peter Sklar,^{8,9} Mary Bavaro,³ Sybil Tasker,¹⁰ Dean Follmann,⁵ and Frank Maldarelli¹¹

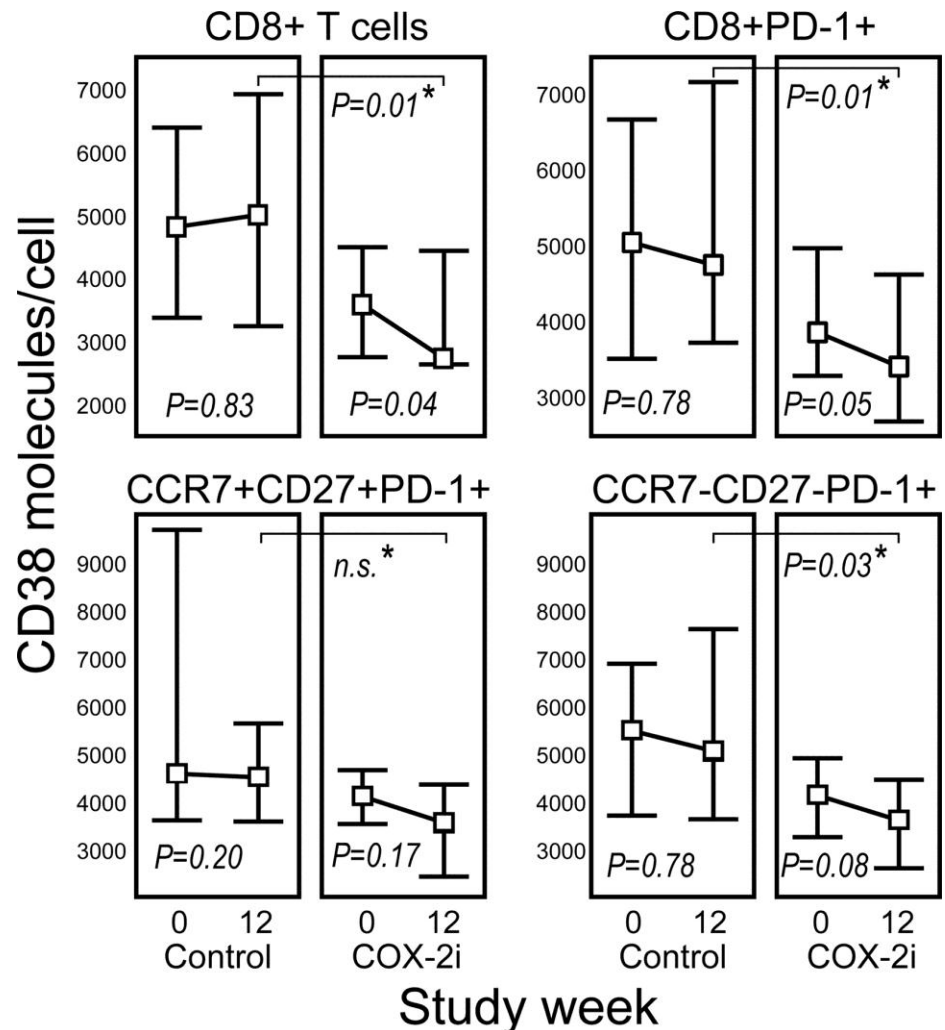


- 24 untreated subjects; cross-over
- Significant reduction in HLA-DR on CD8+ T cells
- No effect on plasma HIV RNA levels

An Exploratory Trial of Cyclooxygenase Type 2 Inhibitor in HIV-1 Infection: Downregulated Immune Activation and Improved T Cell-Dependent Vaccine Responses[∇]

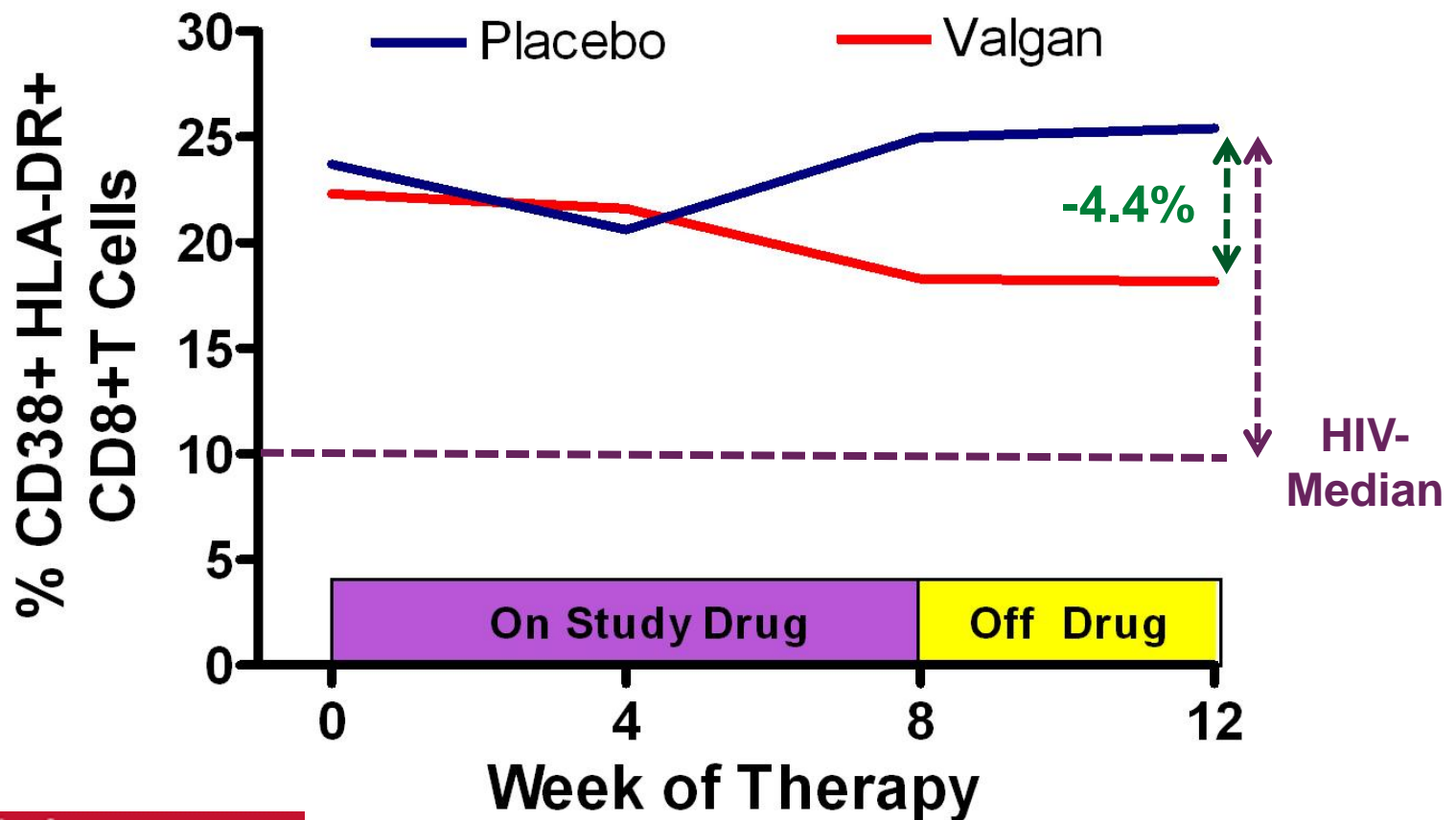
Frank O. Pettersen,^{1†} Eirik A. Torheim,^{4,5†} Anders E. A. Dahm,^{2†} Ingeborg S. Aaberge,^{6†} Andreas Lind,^{1†} Malin Holm,^{1†} Einar M. Aandahl,^{4,5†} Per M. Sandset,^{2,3†} Kjetil Taskén,^{4,5†} and Dag Kvale^{1,3†*}

- 27 untreated subjects, 12 weeks celecoxib vs. placebo.
- Reduced CD4+ and CD8+ T cell activation; reduced PD-1 expression

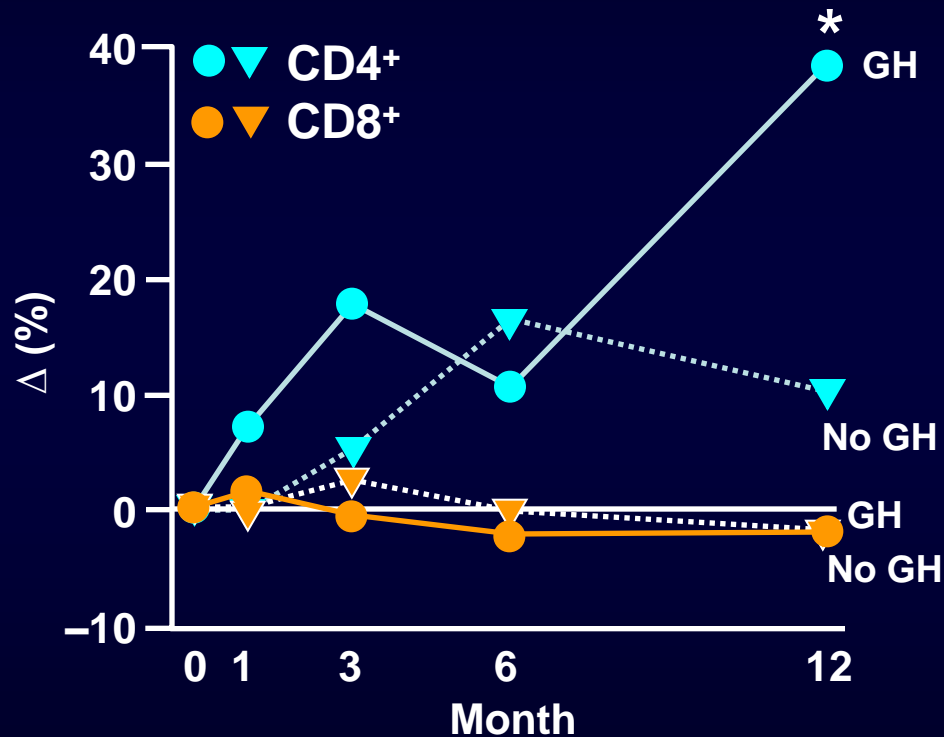


Valganciclovir Reduces T Cell Activation in HIV-infected Individuals With Incomplete CD4⁺ T Cell Recovery on Antiretroviral Therapy

Peter W. Hunt,¹ Jeffrey N. Martin,¹ Elizabeth Sinclair,¹ Lorrie Epling,¹ Juli Teague,¹ Mark A. Jacobson,¹ Russell P. Tracy,² Lawrence Corey,³ and Steven G. Deeks¹



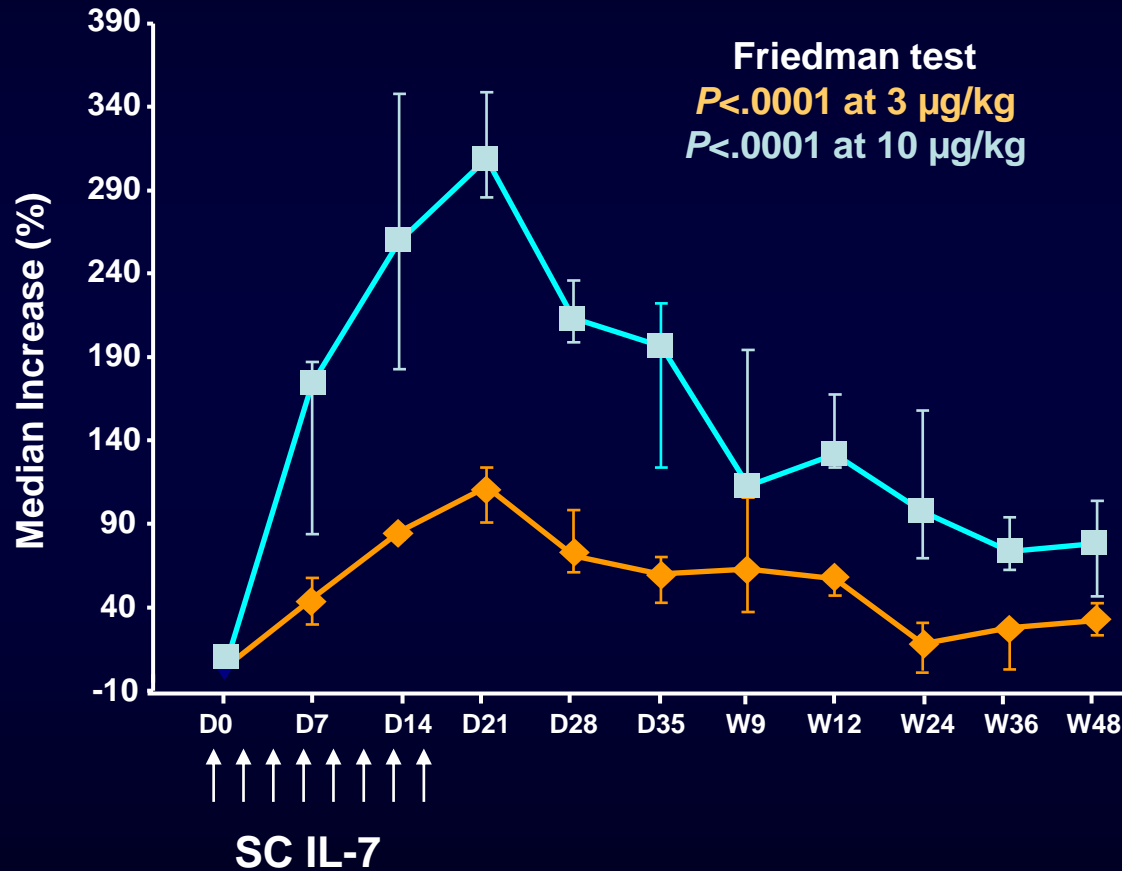
Growth Hormone Increases CD4 Counts ↑ Thymic Production of Naïve T Cells



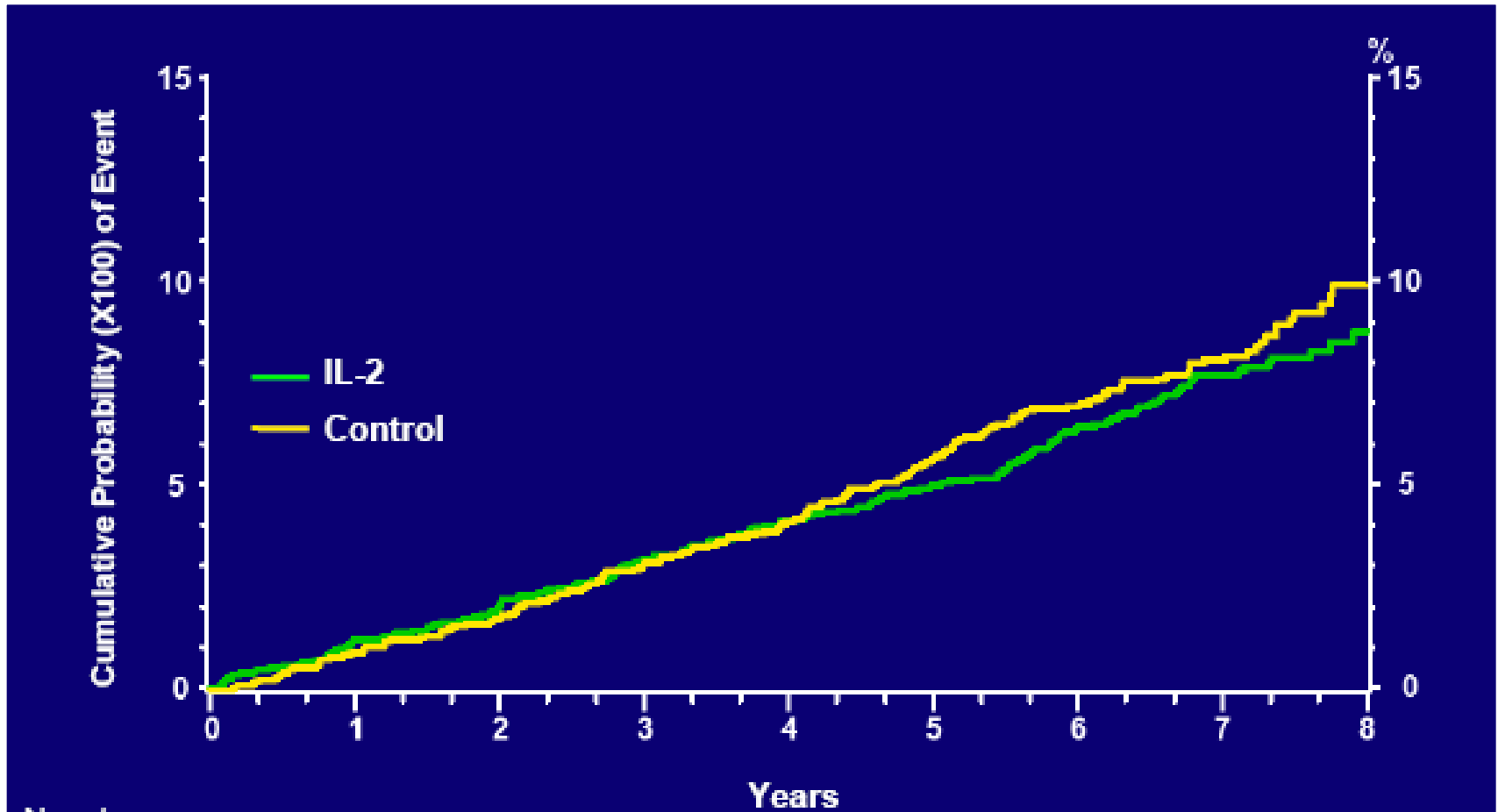
$P < .05$ GH vs no GH.

Napolitano LA et al. *J Clin Invest.* 2008; 118(3):1085-1098.

IL-7 Also Increases CD4+ Counts (Median % Increase From Baseline)



ESPIRIT: Despite causing sustained CD4 gains, IL-2 does not provide clinical benefit



Conclusions

- Immunologic 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