

HIV Infection and Accelerated Aging

Why is this happening?

*What can be done to prevent or
reverse the process?*

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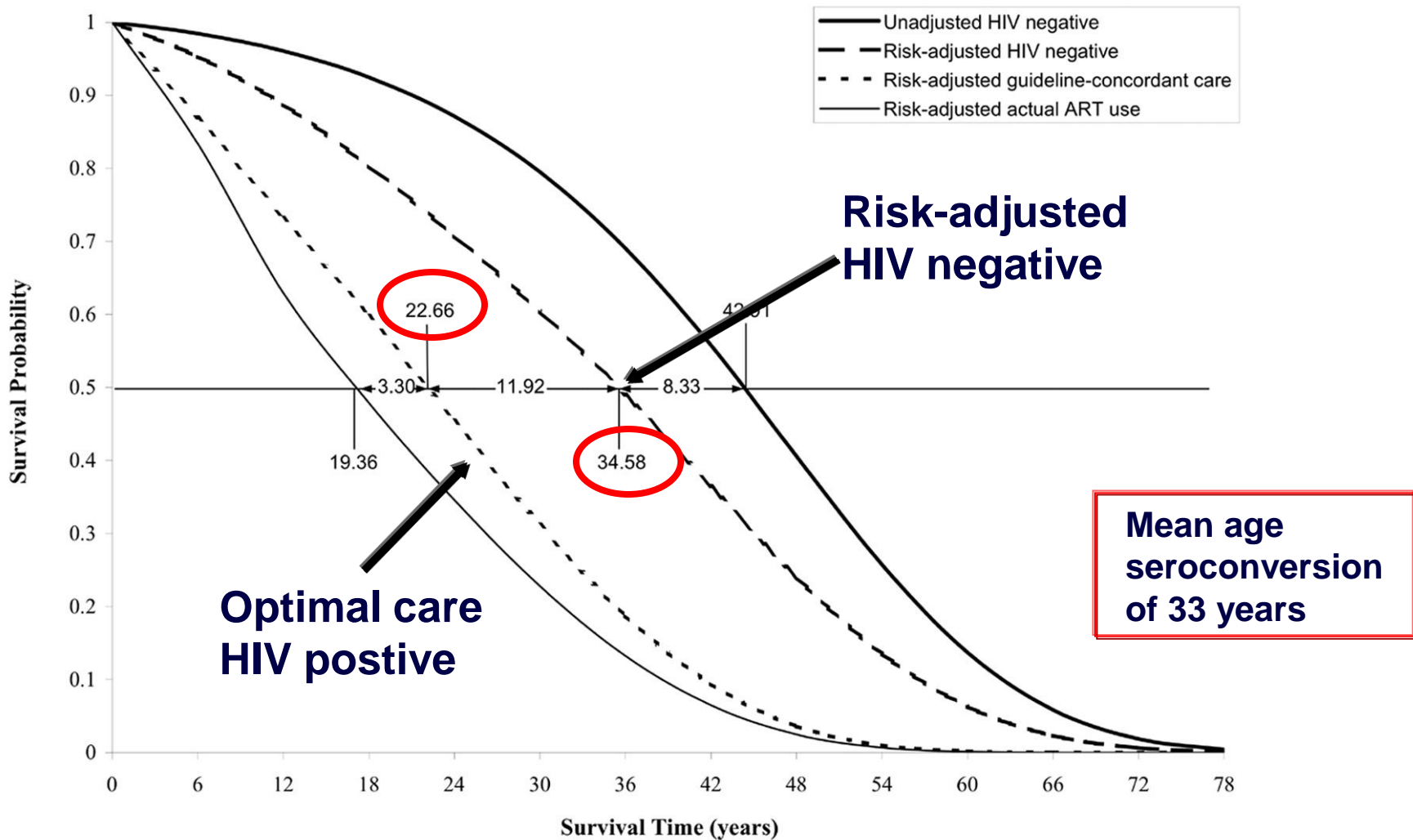
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Learning Objectives

- **Appraise the effect of untreated and treated HIV infection on T cell activation and inflammation in persons with HIV.**
- **Assess the role of inflammation and chronic T cell activation on non-AIDS morbidity and accelerated aging in your antiretroviral-treated patients.**
- **Evaluate the current evidence for potential therapeutic interventions aimed at reducing HIV-associated inflammation and/or premature “aging”.**
- **I intend to discuss ongoing research pertaining to the off-label use of FDA-approved therapies for reducing HIV-associated inflammation and/or premature “aging” during this presentation.**

Even with optimal care, well treated HIV disease may not fully restore full life expectancy



Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons

- **Cardiovascular disease**
- **Cancer (non-AIDS)**
- **Bone fractures/osteopenia**
- **Left ventricular dysfunction**
- **Liver failure**
- **Kidney failure**
- **Cognitive decline**
- **Frailty**
- ***Immune system***

Multiple factors likely explain this increased risk, including co-morbid conditions and antiretroviral drug toxicity

Questions

- **What impact does (treated) HIV infection have on immunologic factors known or thought to be involved in aging?**
- **Do these factors predict non-HIV morbidity in treated HIV infection?**
- **Can these immunologic perturbations be prevented or reversed?**
- **What implications do these data have for the “aging” and “eradication” agenda?**

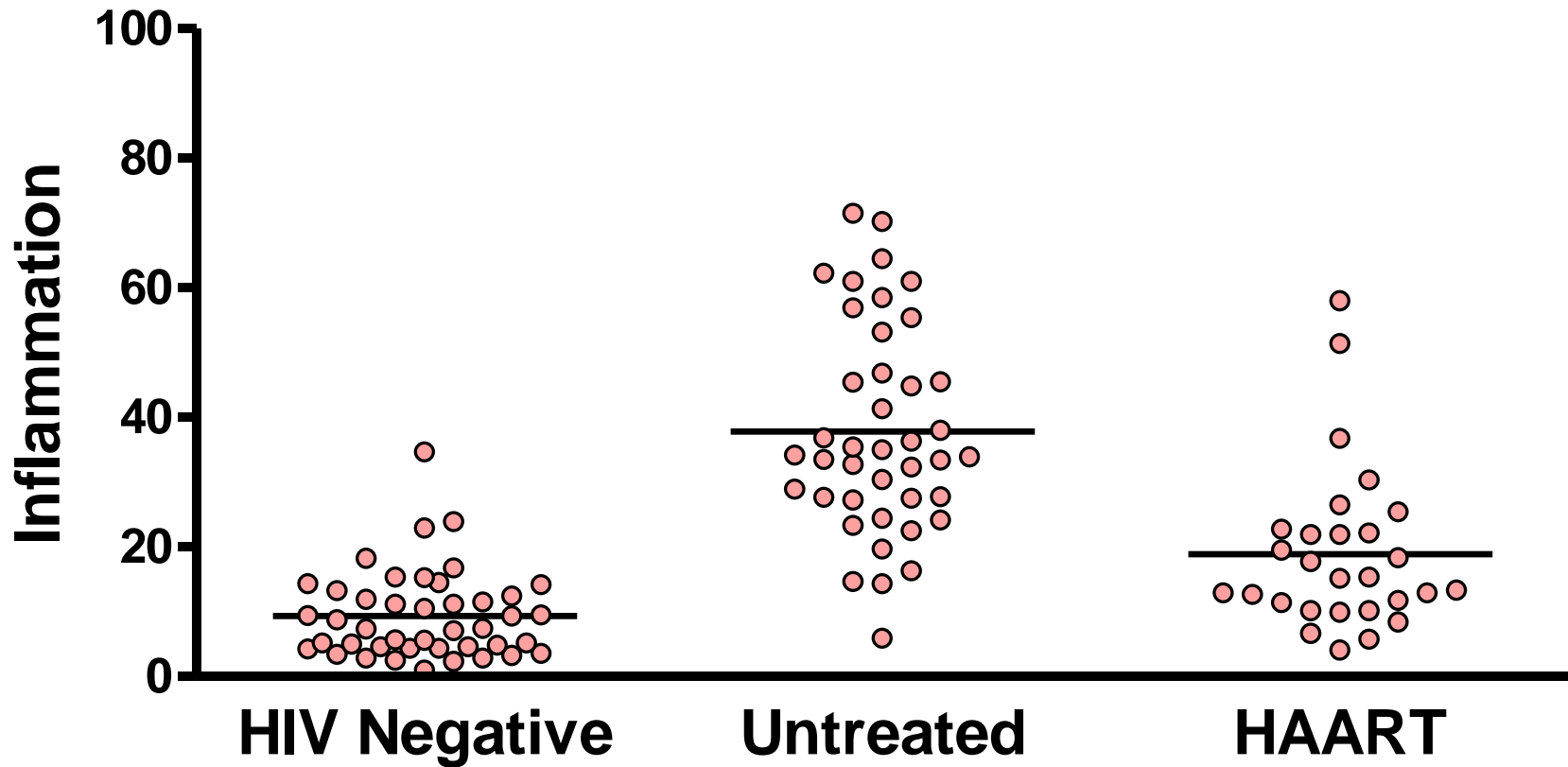
Impact of HAART on the “age” of the immune system

Aging of the Immune System (“Immunosenescence”)

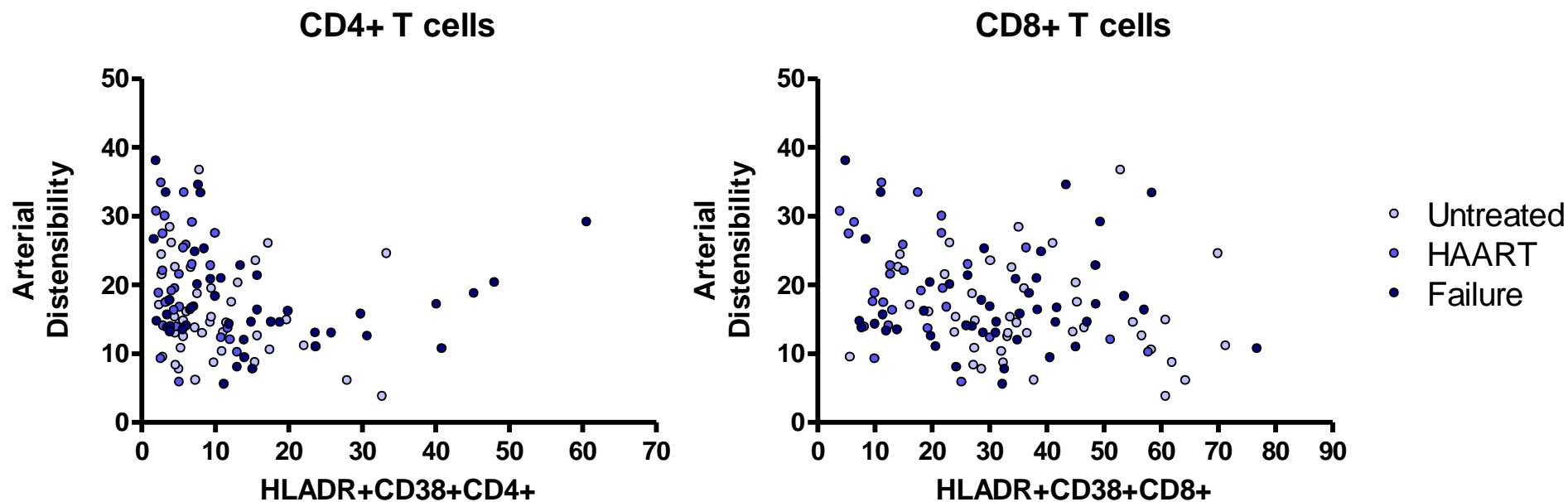
T Cell Characteristics In The Very Old That Predict Morbidity/Mortality

- **Reduced regenerative capacity (stem cells, thymus)**
- **Low naïve/memory T cell ratios**
- **Low CD4/CD8 ratio**
- **Increased T cell activation**
- **Increased in general inflammatory markers (IL6, CRP)**
- **Clonal expansion of CD28-CD57+ T cells**
- **Expanded CMV specific T cell responses**
- **Reduced T cell proliferation**

HIV infection is associated with increased inflammation and HAART only partially reverses this process



WIHS: A Higher Frequency of Activated T Cells Is Associated with Lower Arterial Distensibility (or, More Stiffness”) in Treated HIV Disease

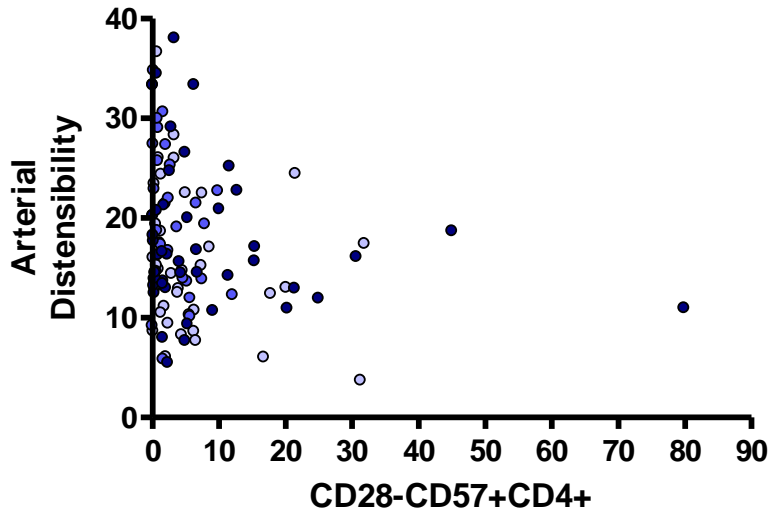


After adjustment for age and treatment exposure, the change in distensibility per SD of CD4+ T-cell activation was -1.9 (95 % CI = -3.2, -0.6, $p < 0.01$) and per SD of CD8+ T-cell activation was -1.6 (95 % CI = -2.9, -0.2, $p = 0.02$)

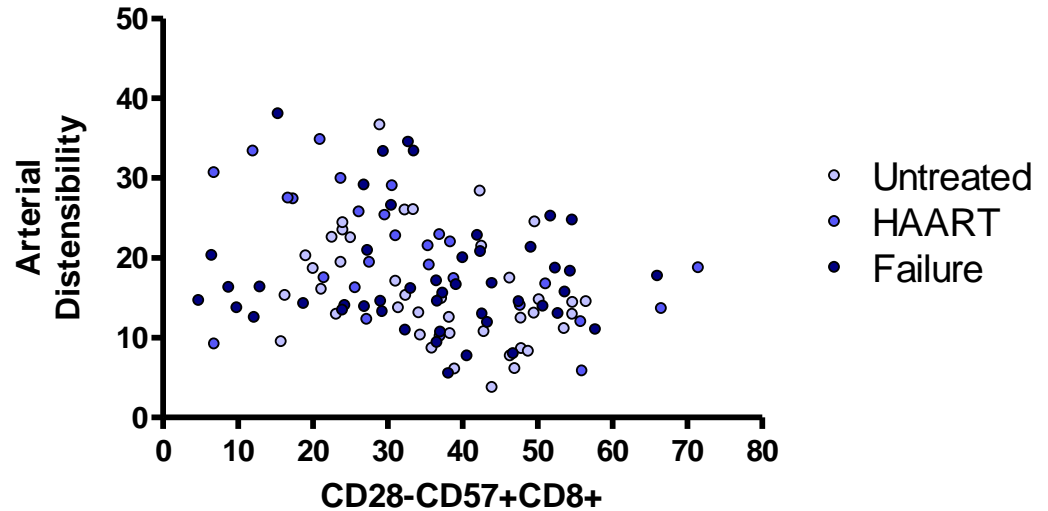
Kaplan et al (submitted)

WIHS: A Higher Frequency of CD28-CD57+ Senescent T Cells Is Associated With Lower Arterial Distensibility

CD4+ T cells



CD8+ T cells



After adjustment for age and other factors, the frequency of senescent CD4+ and CD8+ T cells was strongly and consistently associated with arterial distensibility ($P < 0.01$ for CD4 and CD8)

SMART: Inflammatory Markers Strongly Associated with Mortality and CVD Events

Biomarker	All-Cause Mortality (N=85)		Fatal or Non-fatal CVD (N=136)	
	OR	P-value	OR	P-value
hs-CRP	3.5	0.004	1.6	0.20
IL-6	12.6	<0.0001	2.8	0.003
Amyloid A	2.3	0.08	1.6	0.12
Amyloid P	1.1	0.90	2.8	0.002
D-dimer	13.3	<0.0001	2.0	0.06
F1.2	1.4	0.45	0.8	0.56

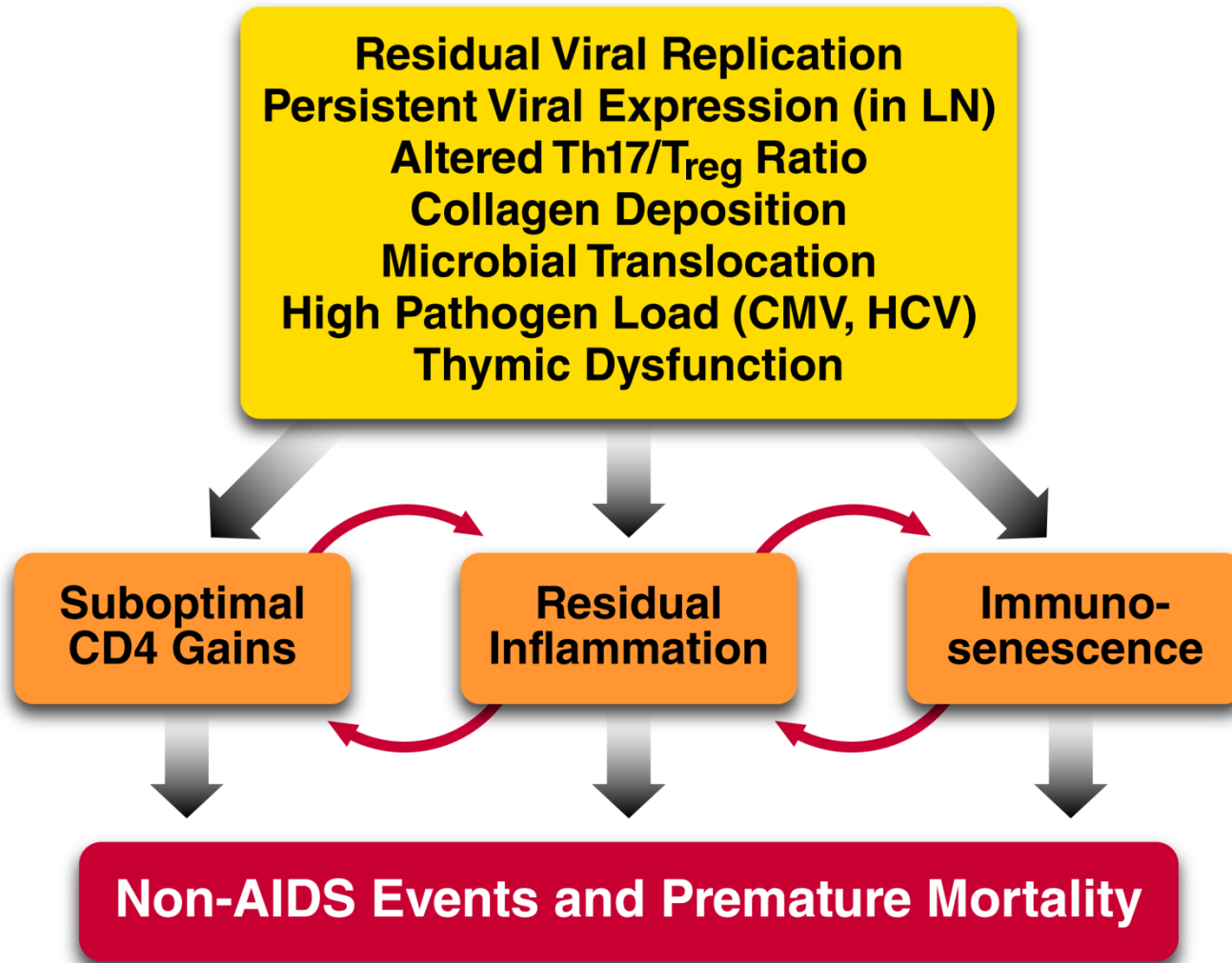
Inflammatory Biomarkers (CROI 2010)

- SMART: CD14—a marker of microbial translocation—is elevated and independently associated with mortality (OR XX) (Sander, Ab 303)
- ICONA: LPS predicts time to HAART, AIDS, death or CD4 < 200 in untreated patients with early stage disease (Marchetti, Ab 333)
- SMART: Hyaluronic acid (hepatic fibrosis) predicts non-AIDS death during treatment, and this effect is synergistic with IL6, CRP or d-dimer (Peters, Ab 660)
- NIAID: Pre-event elevations in d-dimer (but not CRP) predicts CAD event (4 month window, n=1892) (Ford, Ab 713)
- FRAM: Elevated CRP and fibrinogen—even among patients with CD4 > 500—predicts mortality (5 yr follow-up, n=922) (Tien, Ab725)
- MCP-1 and Rantes (cytokines) predicts proteinuria (Gupta, Ab 736)

Inflammatory Factors Associated with CVD Risk (CROI 2010)

- Visceral Adiposity (Guaraldi, Ab 703)
 - Observational study of 1325 HIV patients in metabolic clinic
 - Visceral adipose tissue, but not waist size or BMI was risk factor
- B-type natriuretic peptide (BNP) (Duprez, Ab 712)
 - SMART; 186 subjects with CAD event and 329 controls
 - Median BNP 48.1 in CAD group vs 25.7 in controls ($p < 0.0001$)
 - Adjusted OR for AD in highest vs. lowest quartile 2.3
- Suboptimal CD4 gains on HAART (van Lelvveld, Ab 714)
 - ATHENA cohort; 3071 patients on ART >2 years with CD4+ counts of <200 (Group A), 200-350 (B), 350-500 (C), >500 (D)
 - OR for CAD vs Group A: Group B - 0.67; Group C – 0.62; Group D – 0.47 (after adjusting for age)

Why is this happening?



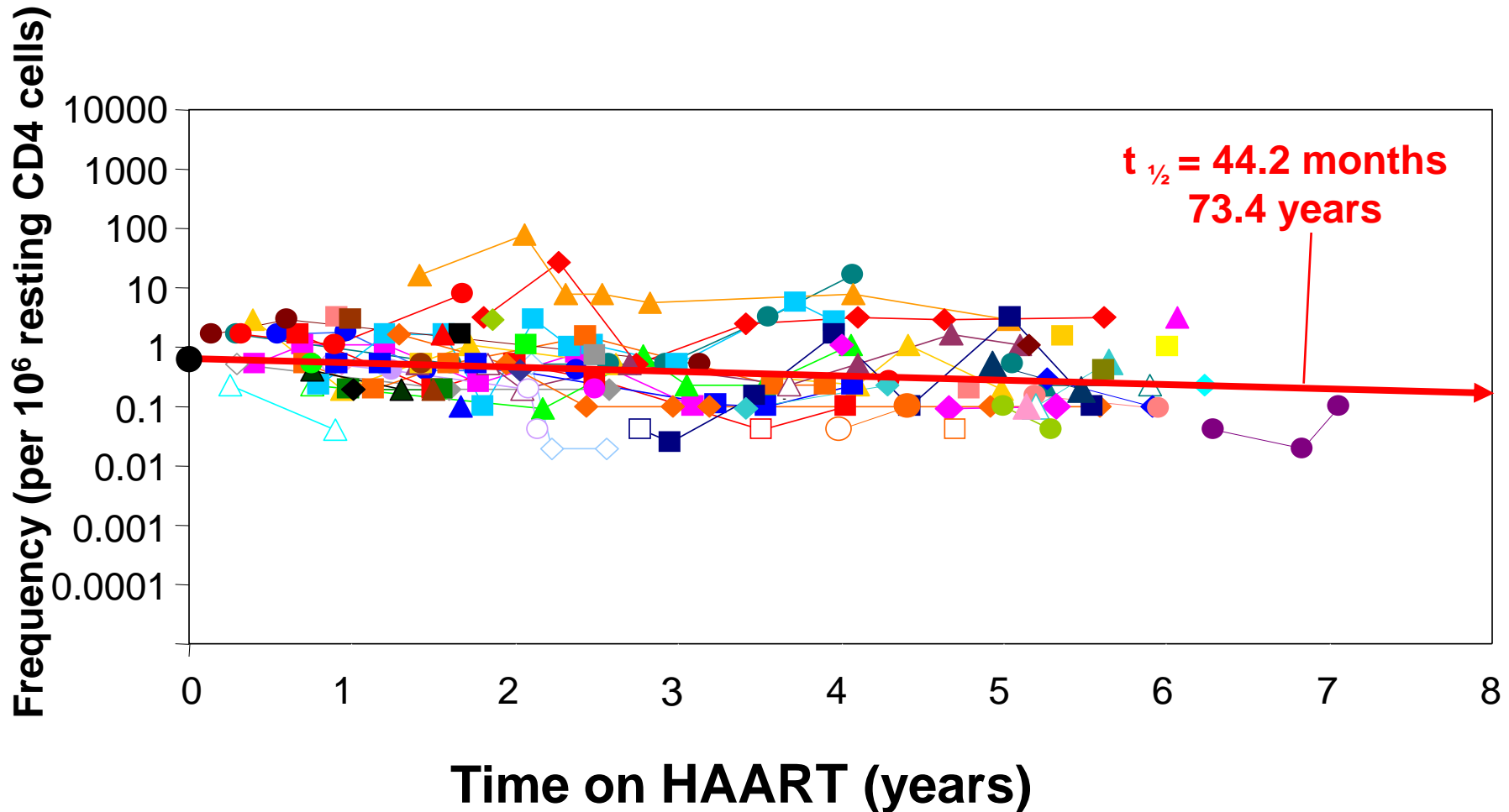
**Can HIV-associated
inflammation (or
“aging”) be treated?**

Inflammation and aging: Novel therapeutic strategies

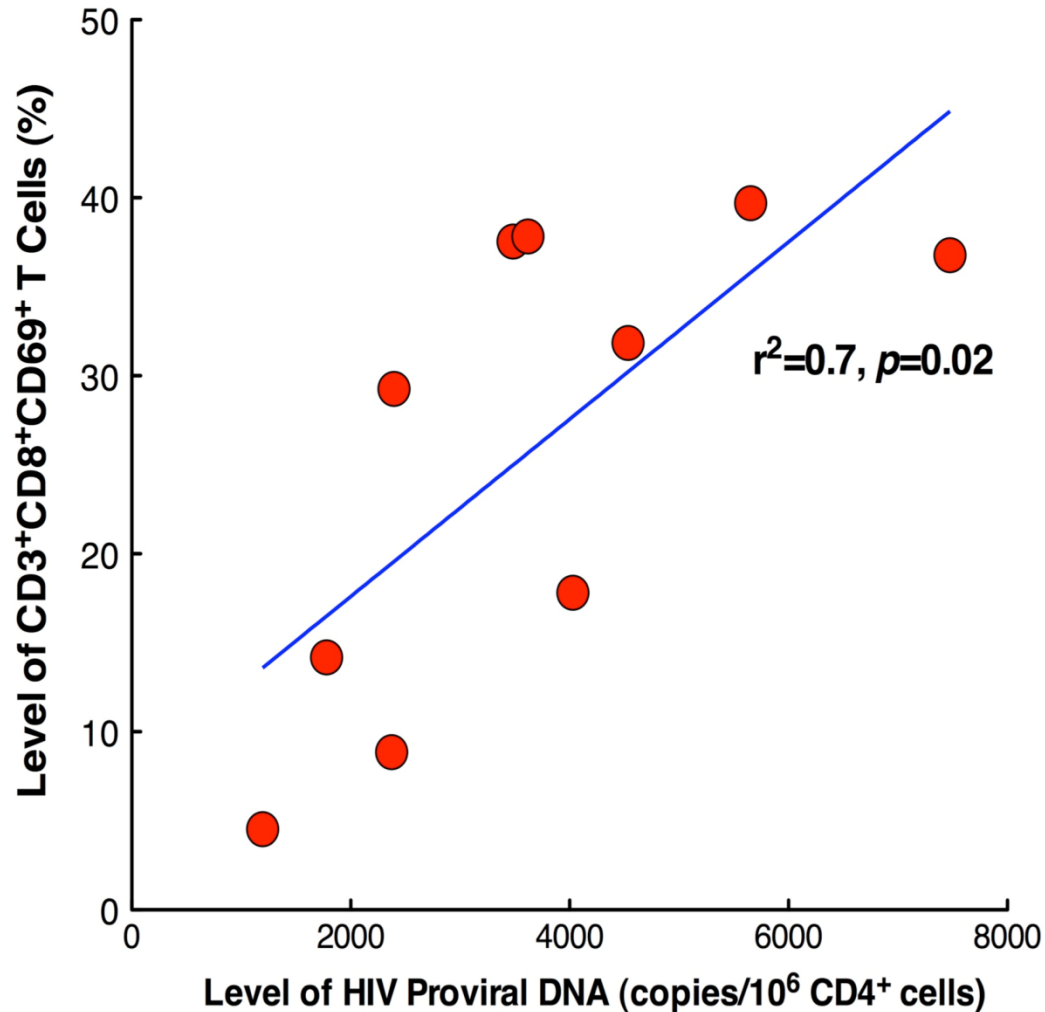
- Reduce inflammation
 - Residual HIV replication (HAART intensification)
 - Prednisone, hydroxyurea, cyclosporin, mycophenolic acid
 - Chronic/persistent co-infections (HCV, CMV)
 - Microbial translocation (sevelamer, colostrum)
 - CCR5 inhibitors
 - Chloroquine (reduced PDC mediated IFN α)
 - NSAIDs (COX-2 inhibitors)
- Enhance T cell renewal: GH, IL-2, IL-7, stem cell transplant, perfenidone, lupron
- Anti-aging interventions: Caloric restriction, sirtuin activators, telomerase activators, vitamin D, omega-3 fatty acids, rapamycin (TOR)

**Ongoing low-level
replication during
HAART as a cause or
consequence of
inflammation**

The level of replication competent HIV in resting memory T cells—presumed to be the major reservoir (but not the only reservoir)—decline over time, but the rate is very slow

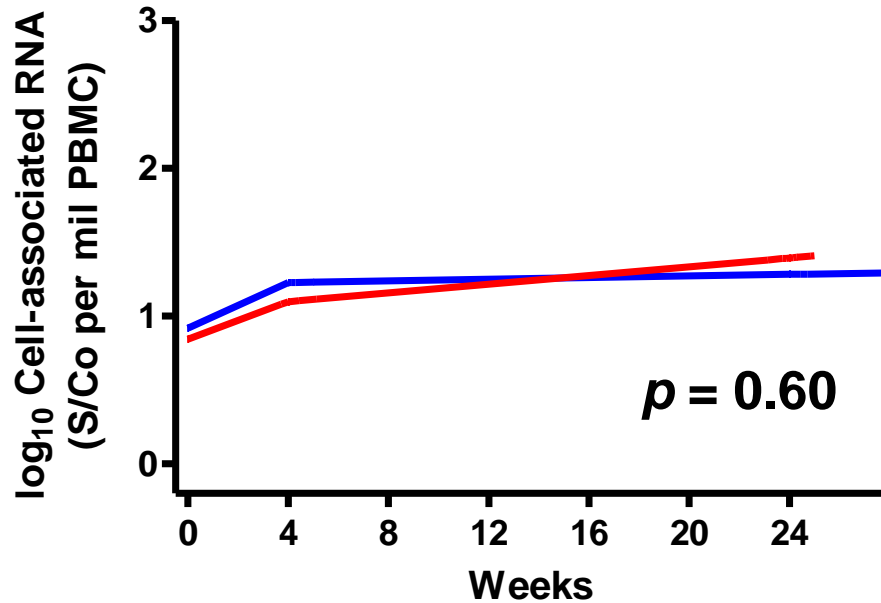


The level of latent reservoir is predicted by the frequency of activated CD8+ T cells in the gut

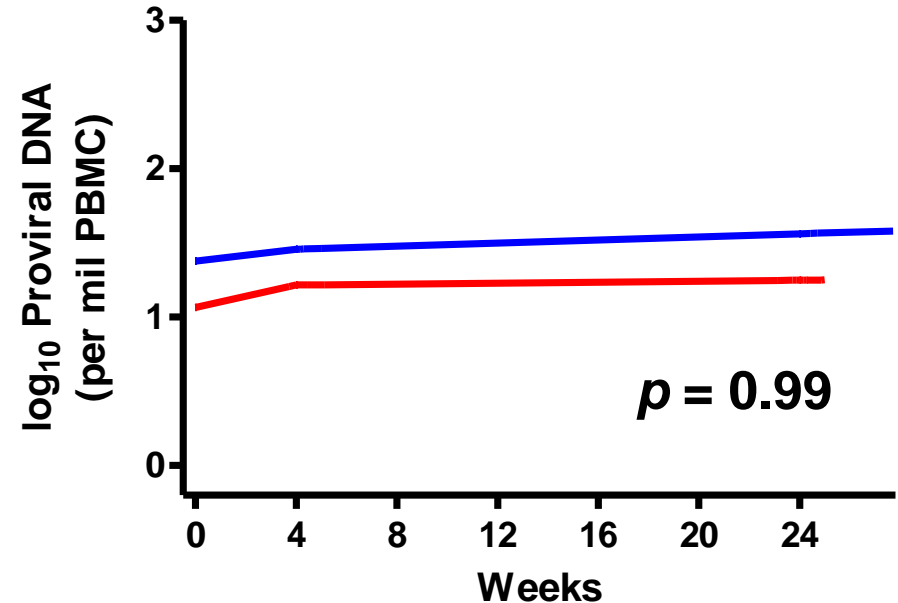


Raltegravir Intensification Had No Effect on Cell-associated RNA or Proviral DNA (Blood)

Cell-associated RNA

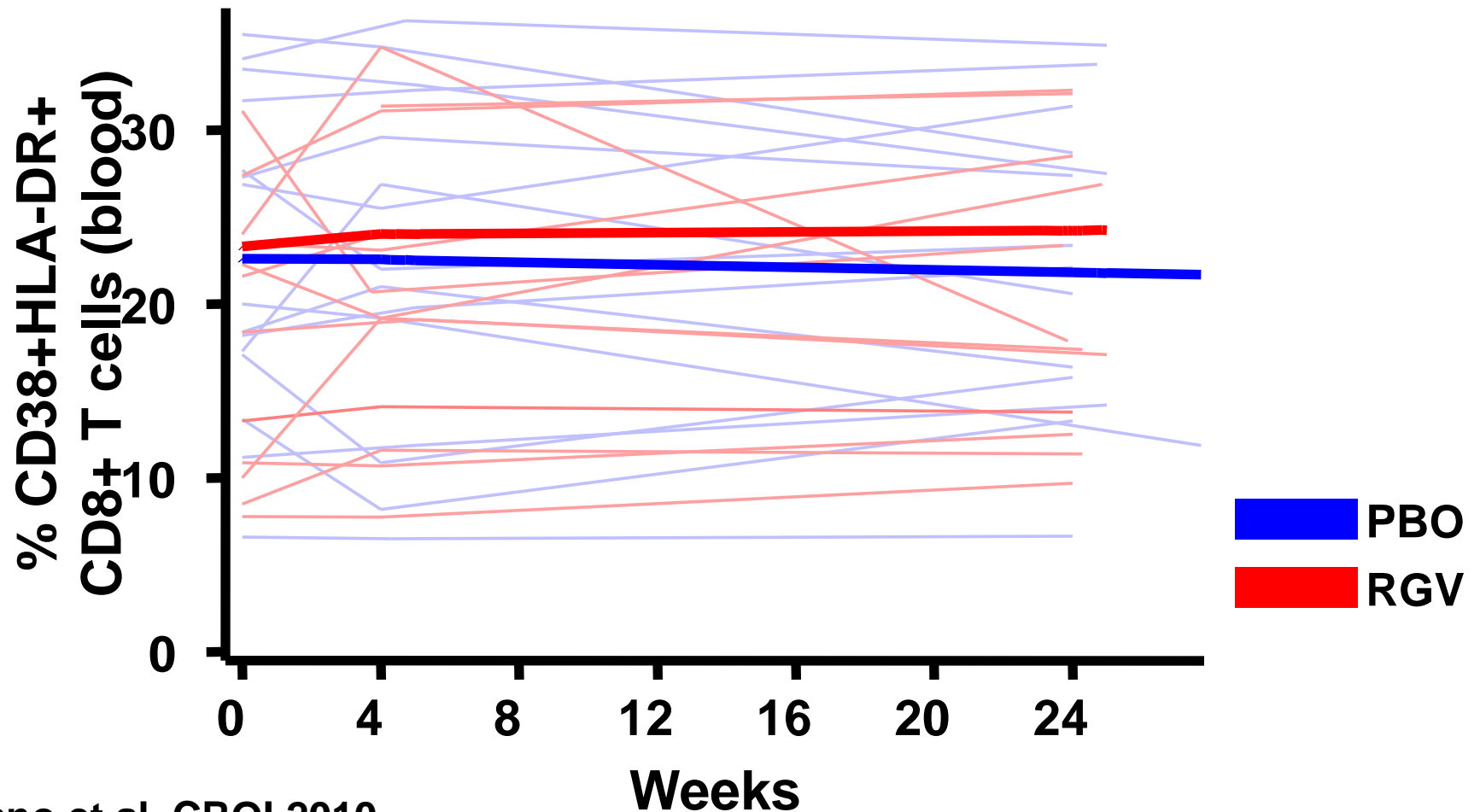


Proviral DNA



PBO
RGV

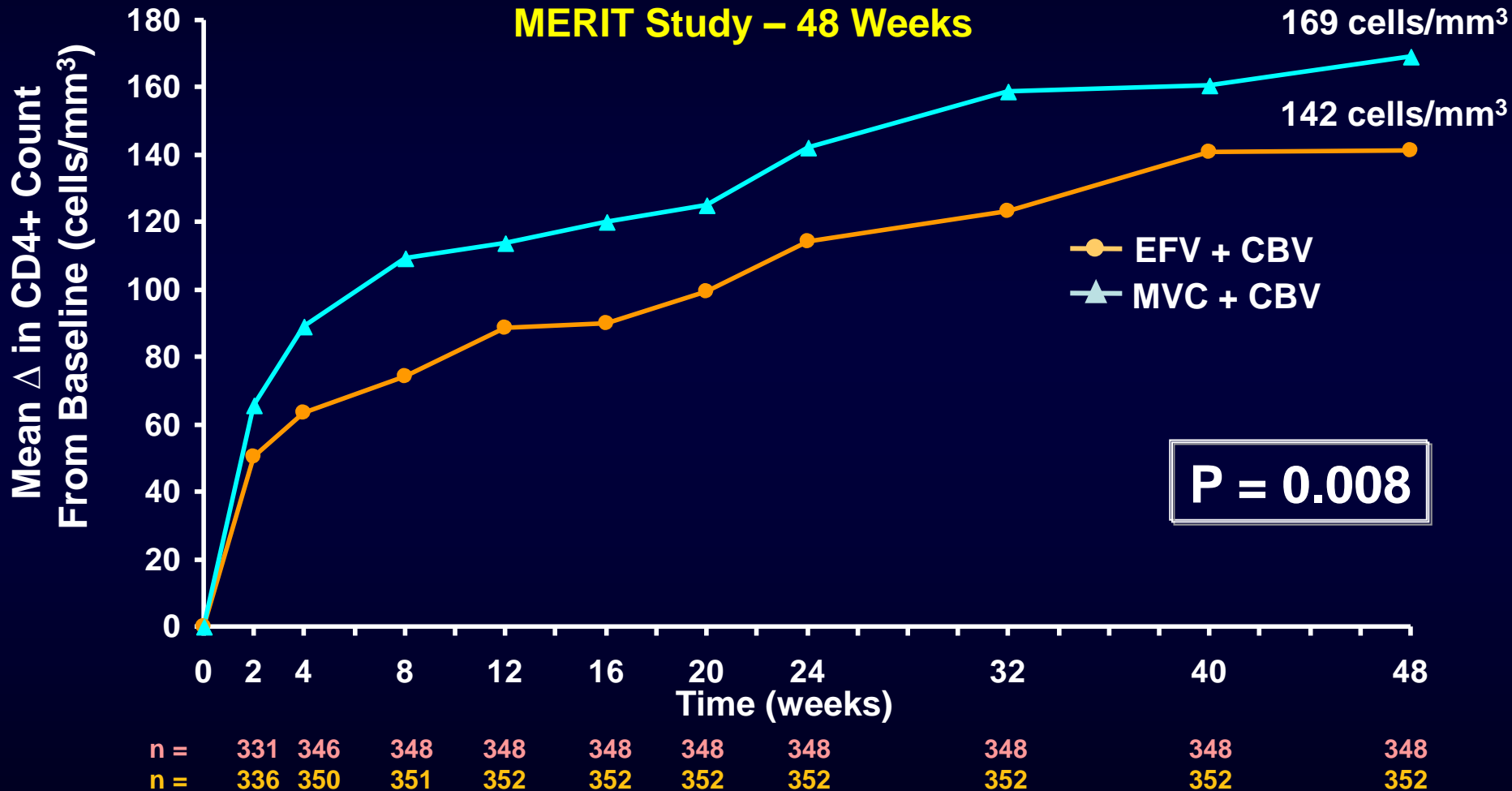
Raltegravir Intensification Had No Effect on CD8+ T Cell Activation (Blood)



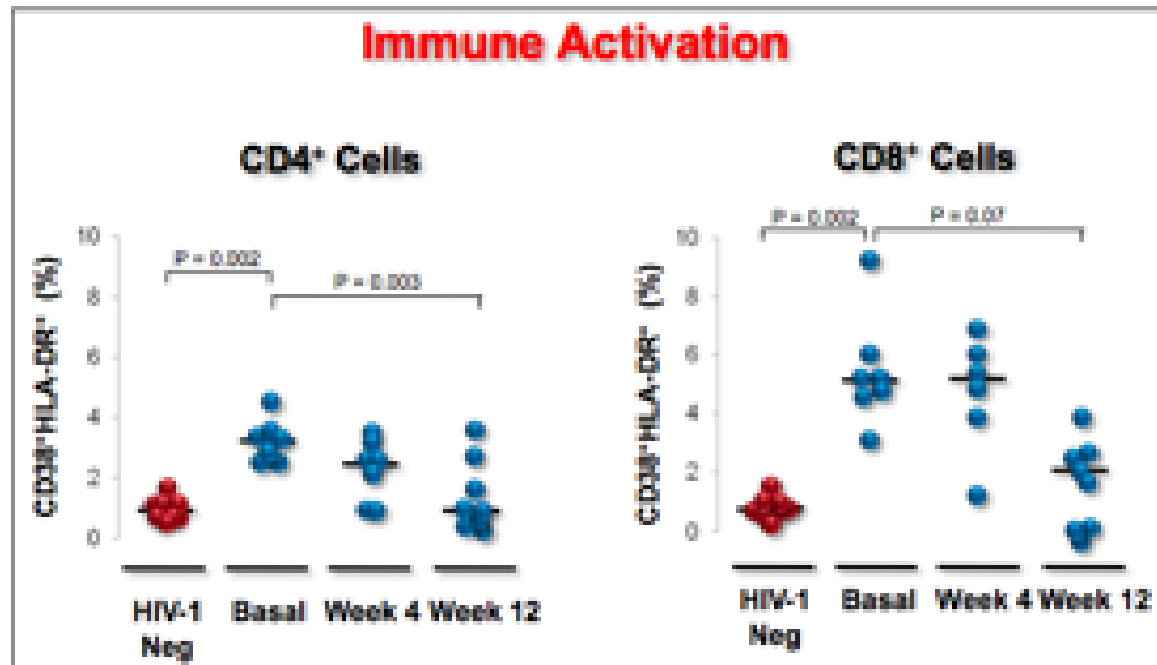
HAART Intensification

- In many studies, treatment intensification is not associated with measurable changes in plasma HIV RNA levels, immune activation, or HIV-specific responses
 - *Dinoso PNAS 09; Gandhi IAS 09; McMahon CID 10; Hatano CROI 10*
- In other studies using more precise measures of replication, an effect of intensification is often evident
 - *Buzon, CROI 10, Yuki CROI 10*
- Ongoing viral replication is not likely to be a major cause of persistent viremia, but it is possible that low-level virus replication persists and that this virus will remain a barrier to eradication

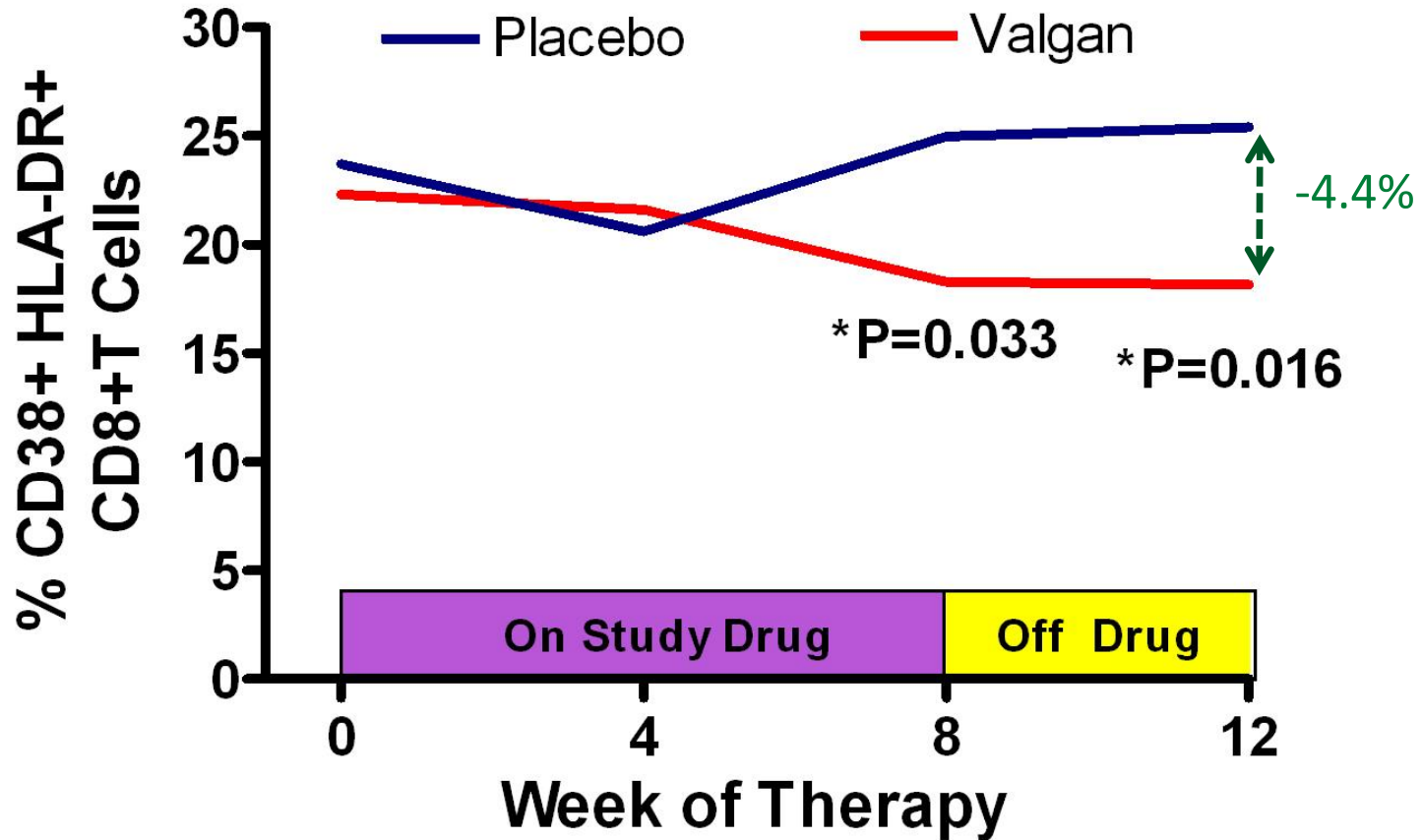
MERIT: MVC associated with ↑ CD4 recovery compared to EFV



Among HAART-suppressed subjects, maraviroc intensification was associated with a rapid decline in “activated” CD4+ and CD8+ T cells (n=9)



Valgancyclovir Decreases CD8 Activation Significantly More Than Placebo



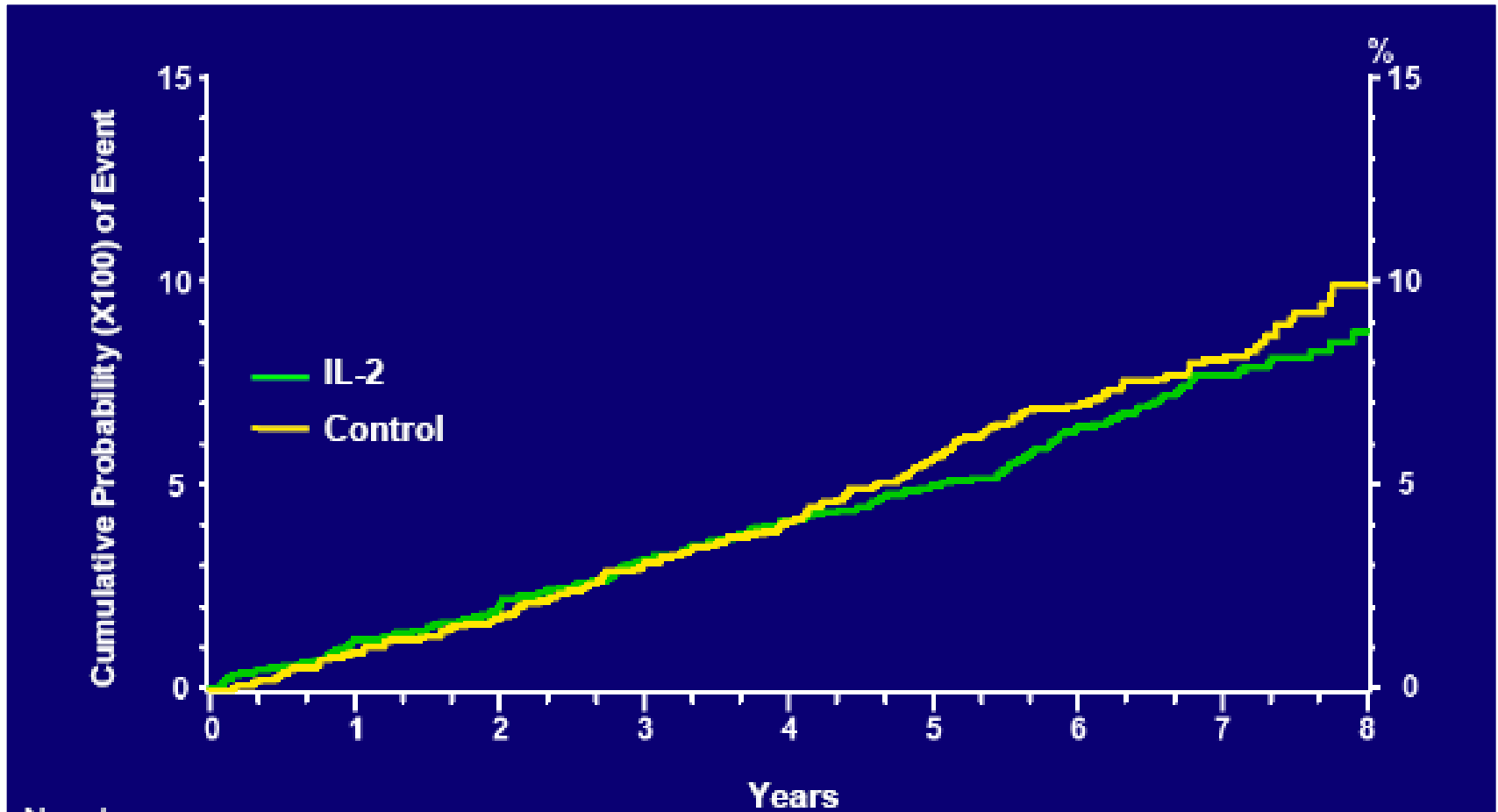
**P for difference in the change from week 0 between valgancyclovir- and placebo-treated groups.*

Altering bowel flora and/or reducing microbial translocation (BITE)

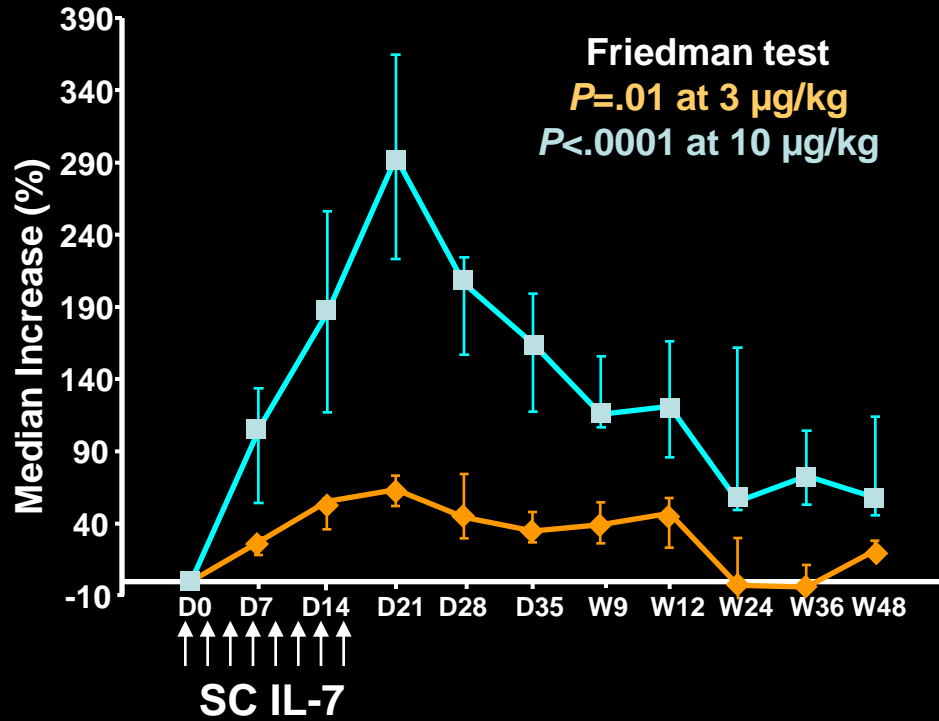
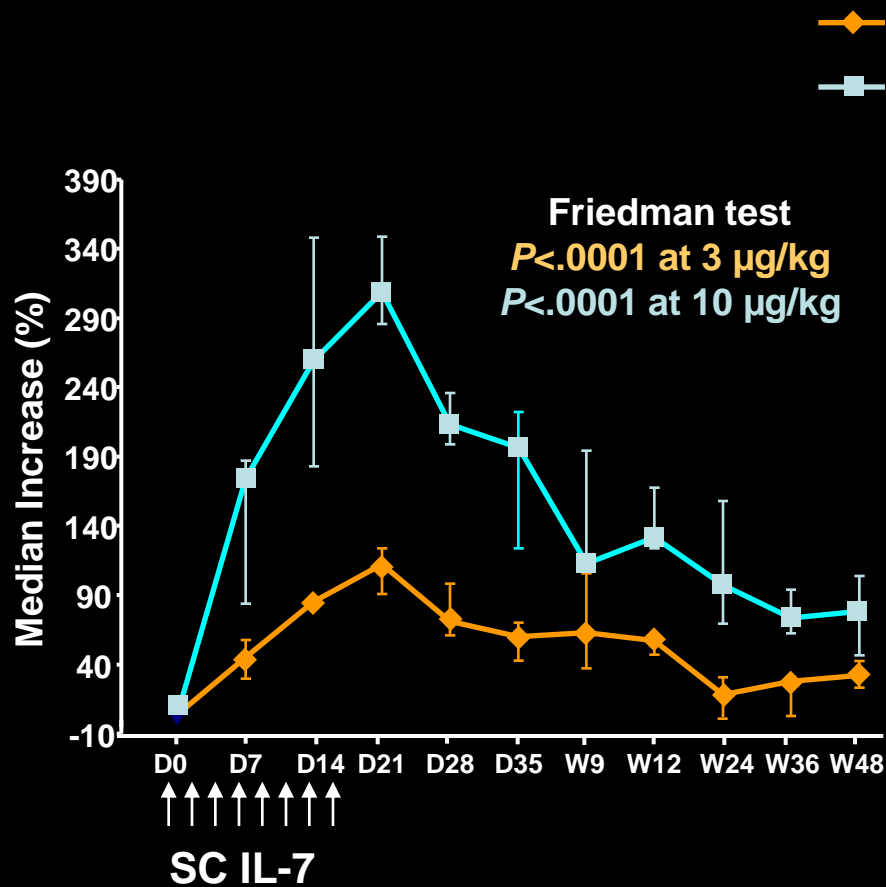
- Randomized, placebo controlled trial of NR100157 (n=340 untreated patients with early disease)
 - Bovine colostrum, oligosaccharides, polyunsaturated fatty acids, NAC

	NR100157 (n=168)	Placebo (n=172)
Completers	60	83
Started ART	25	29
AEs	30	14
CD4+ change	-28 cells*	-68 cells*

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

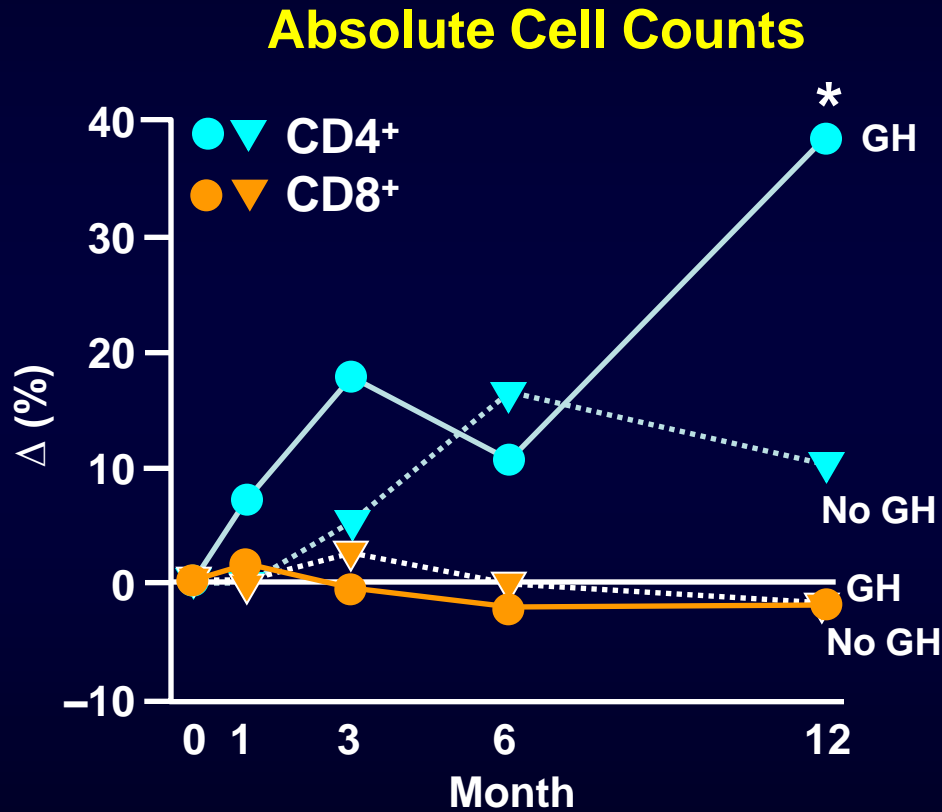


IL-7 Also Increases CD4+ Counts (Median % Increase From Baseline)



Growth Hormone Increases CD4 Counts

↑ Thymic Production of Naïve T Cells





Aggressive Screening
CAD
Bone
Cancer

Risk factor modification
Statins
Aspirin
Vitamin D

Although HIV related factors—including treatment toxicity—predict CAD, the traditional risk factors may be more important (D:A:D)

	Adjusted Model 2	
	Relative Rate (95% CI)	P Value
Exposure to PIs (per year)	1.10 (1.04-1.18)	0.002
Age (per 5 yr)	1.32 (1.23-1.41)	<0.001
Male sex	2.13 (1.29-3.52)	0.003
BMI >30 kg/m ²	1.34 (0.77-2.34)	0.31
Family history of CHD	1.40 (0.96-2.05)	0.08
Smoking status		
Current	2.92 (2.04-4.18)	<0.001
Former	1.63 (1.07-2.48)	0.02
Previous cardiovascular event	4.64 (3.22-6.69)	<0.001
Diabetes mellitus	1.86 (1.31-2.65)	<0.001
Hypertension	1.30 (0.99-1.72)	0.06
Total cholesterol (per mmol/liter increase)	1.26 (1.19-1.35)	<0.001
HDL cholesterol (per mmol/liter increase)	0.72 (0.52-0.99)	0.05

CROI 2010: Vitamin D Deficiency

- Italian cohort: Insufficient (<75 nmol/L) 54%, Deficient (<30 nmol/L) 7%
 - Associated with age, non-White and duration of ART
- Swiss Cohort: Deficiency (<30nmol/l) more prevalent in spring (42%) vs fall (14%)
 - Deficiency associated with NNRTI use and IDU
- SUN cohort: 71.6% 25 Vit D deficient
 - Associated with efavirenz, low UV exposure, Black/Latino

Vitamin D and CVD

- Associations with Vit D deficiency and CVD in cohort studies:
 - First MI increased 2 fold in men and 25 (OH) vit D < 15 ng/ml ⁽¹⁾
 - 80% increase in risk of first CVD event if 25 (OH) D < 10 ng/ml ⁽²⁾
- Meta-analysis of replacement trials 8% reduction in all cause mortality

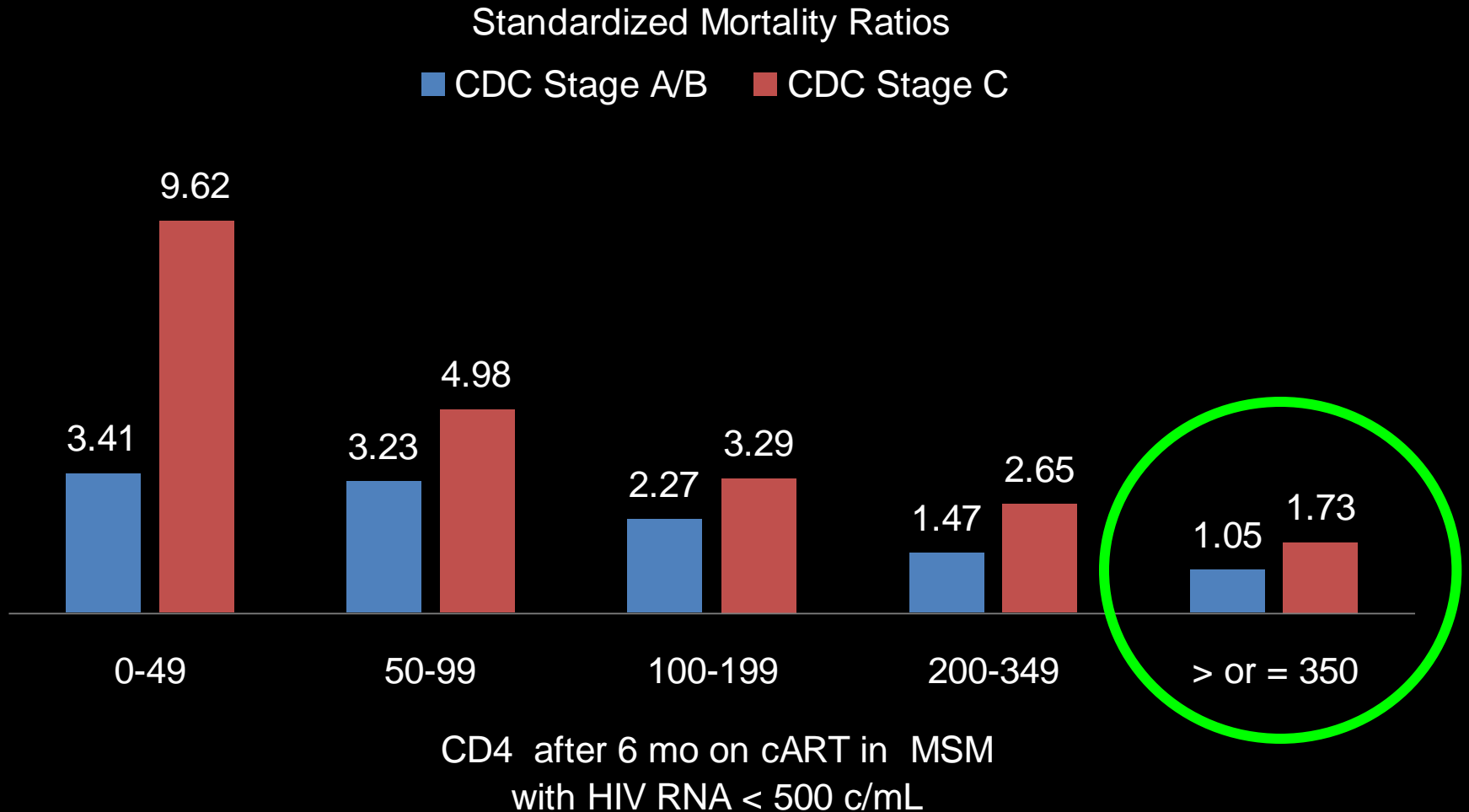
The Vitamin D and Omega-3 Trial (VITAL)

- 20,000 U.S. men and women over the age of 60 (men) or 65 (women) who have not had significant CAD or cancer
- Randomized one of four arms
 - Placebo
 - Vitamin D (~2000 IU)
 - Omega-3 fatty acids (1 gram)
 - Vitamin D plus omega-2 fatty acids
- Outcomes: CAD, stroke, cancer
- Study initiation: January 2010
- Duration of FU: 5-7 years

A mechanistic rationale (opinion) 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)

Can a normal life expectancy be restored with HAART?



Conclusions

- Even with optimal HAART, life expectancy is shorter than normal, and this appears to be predicted by lower CD4s and higher inflammation
- Many measures of T cell activation and inflammation remain higher during HAART than in seronegatives
- The phenotypic and functional characteristics of T cells during long-term HAART share many similarities with that seen in the very old
 - Unclear if this can be prevented with early therapy
 - Synergy between inflammation and T cell renewal defects
- A mechanistic appreciation of why patients are aging can influence therapy
 - Strong overlap between aging and HIV therapeutics

ARS Questions