Activación Inmunológica y VIH/Sida: Presente y futuro, implicaciones clínicas

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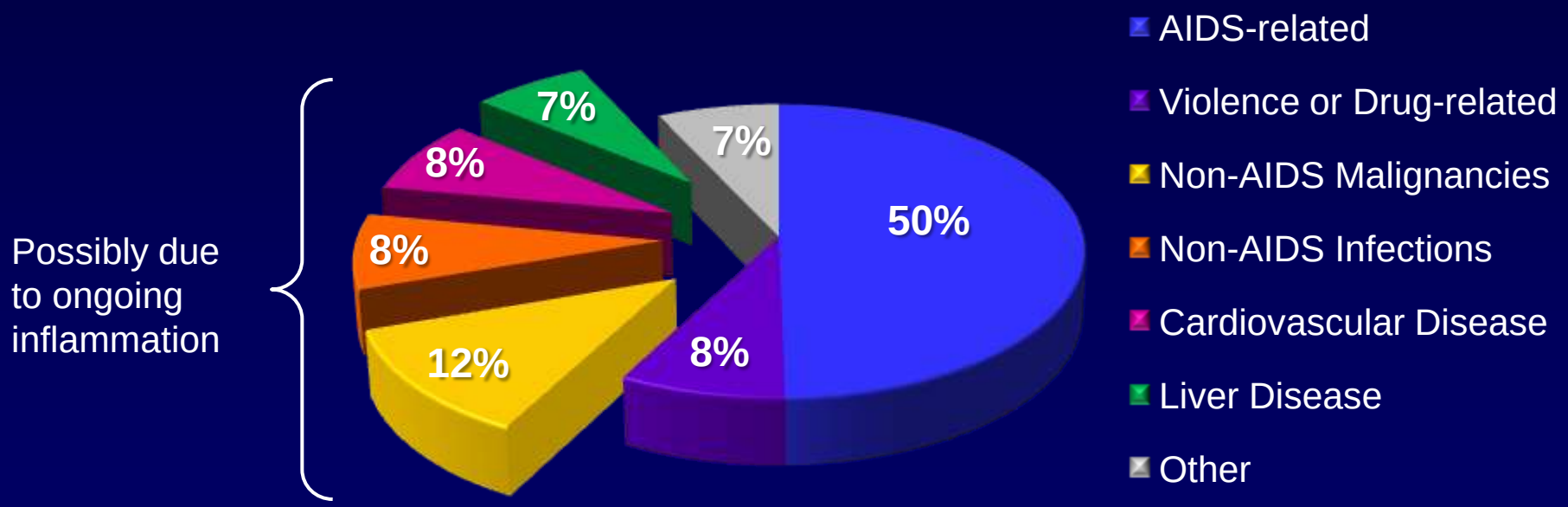
Half of Deaths in HIV-Infected Patients Now Due to Non-AIDS-Related Causes

Cause of Death in HIV+ Individuals Initiating ART (Europe and North America, 1996-2006, n=1,597*)

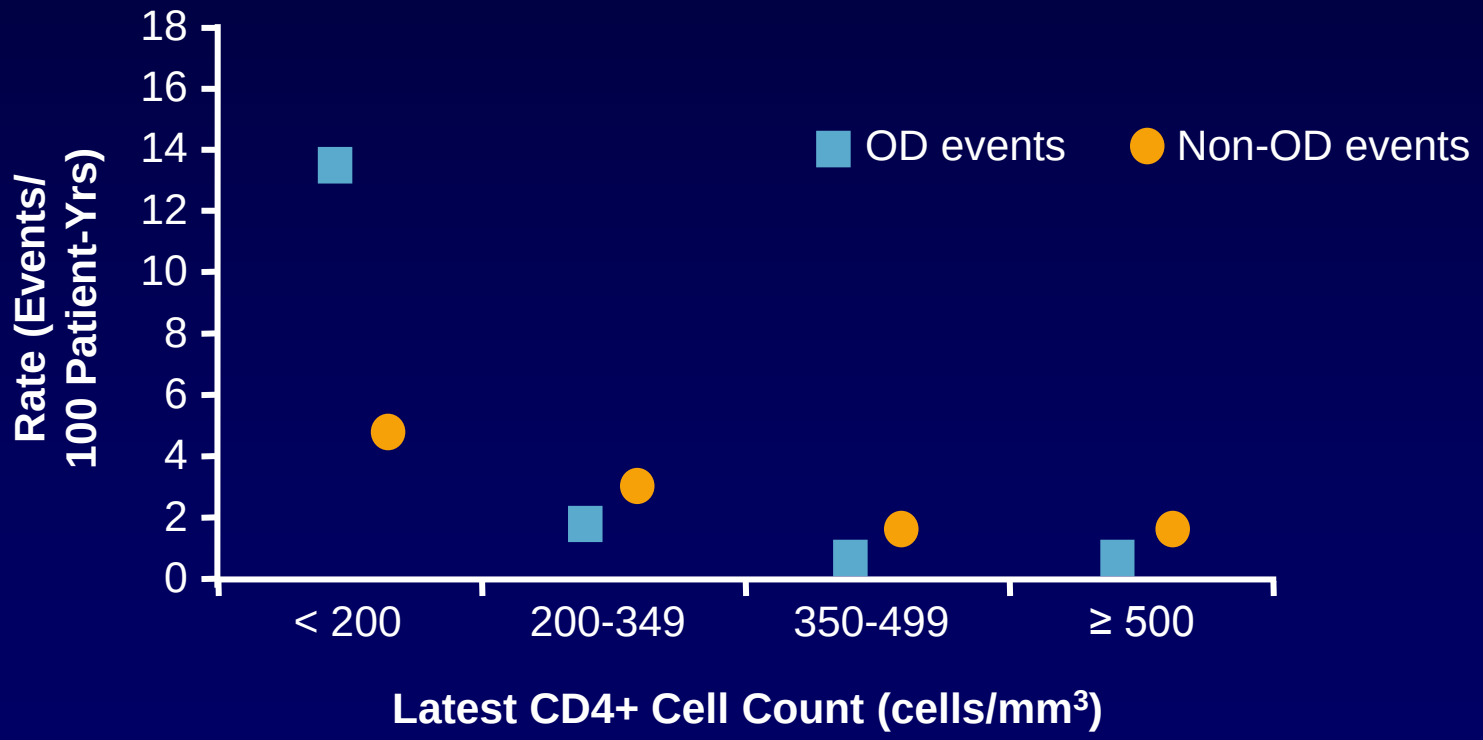


*N=39,272; total deaths=1,876.

Antiretroviral Therapy Cohort Collaboration. *Clin Infect Dis*. 2010;50:1387-1396.

FIRST: Opportunistic Diseases and Non-OD by proximal CD4 cell count

- Rates decline at higher CD4 counts
- Non-OD > OD at CD4+ cell counts > 200 cells/mm^3

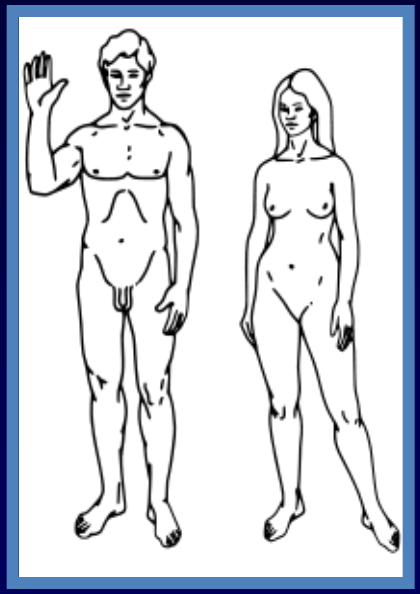


Baker J, et al. CROI 2007. Abstract 37.

SIVsm, SIVmac y HIV-2 básicamente el mismo virus

- Sooty magabey
- SIVsm
- **No causa SIDA**

- Rhesus macaque
- SIVmac
- Causa SIDA



- Humanos
- HIV-2
- Causa SIDA

¿Qué aprendimos del la infección por SIV no patogénico?

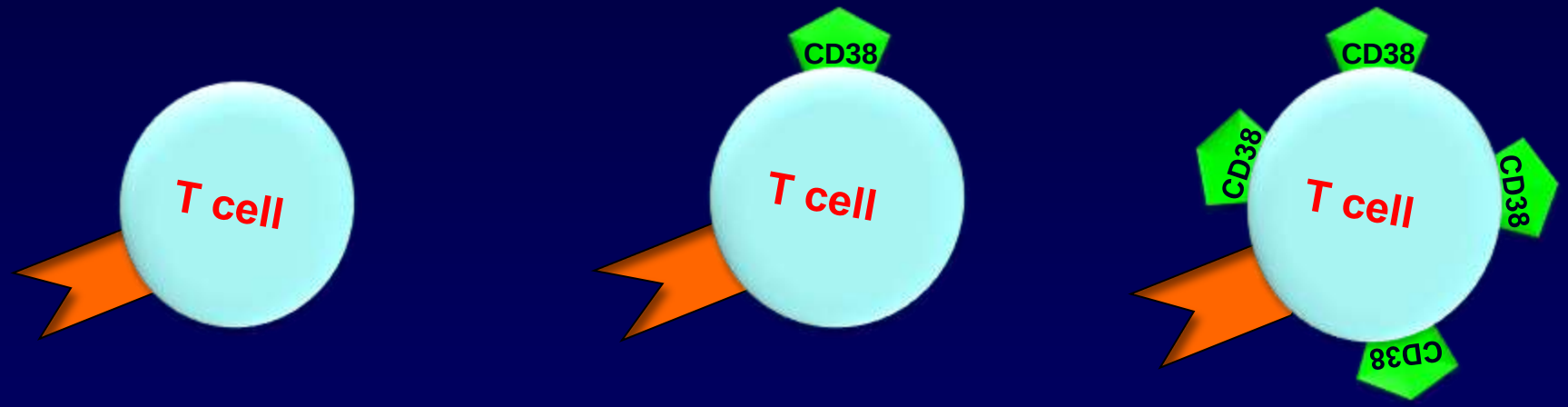
Característica	SIVmac patogénico	SIVsm no patogénico
Carga viral alta	SI	SI
Replicación rápida	SI	SI
Destrucción masiva de CD4	SI	SI
Pérdida temprana de GALT	SI	SI
Evolución del tropismo (CCR5 ➔ CXCR4)	SI	SI
Activación inmune persistente	SI	Moderada
Causa SIDA	SI	NO

What Do We Mean by Immune Activation?

1. T-cells are activated when they encounter their cognate antigens, activated phenotype:
   - Express CD69, then CD38 and HLA-DR
2. B cells show heightened spontaneous production of immunoglobulins, resulting in increased serum immunoglobulin levels
3. High serum levels of proinflammatory cytokines and chemokines:
   - Cytokines Biomarkers of inflammation: CRP, IL-6, TNF-α, IL-1β
   - Coagulation: d-Dimer
   - Endothelial dysfunction: sICAM-1, sVCAM-1
4. There is evidence of increased T-cell turnover
   - Ki67, BrdU

Adapted from Kovacs JA, et al. *J Exp Med.* 2001;194:1731-1741.

T Cell Immune Activation and Dysfunction



Naïve: non-activated

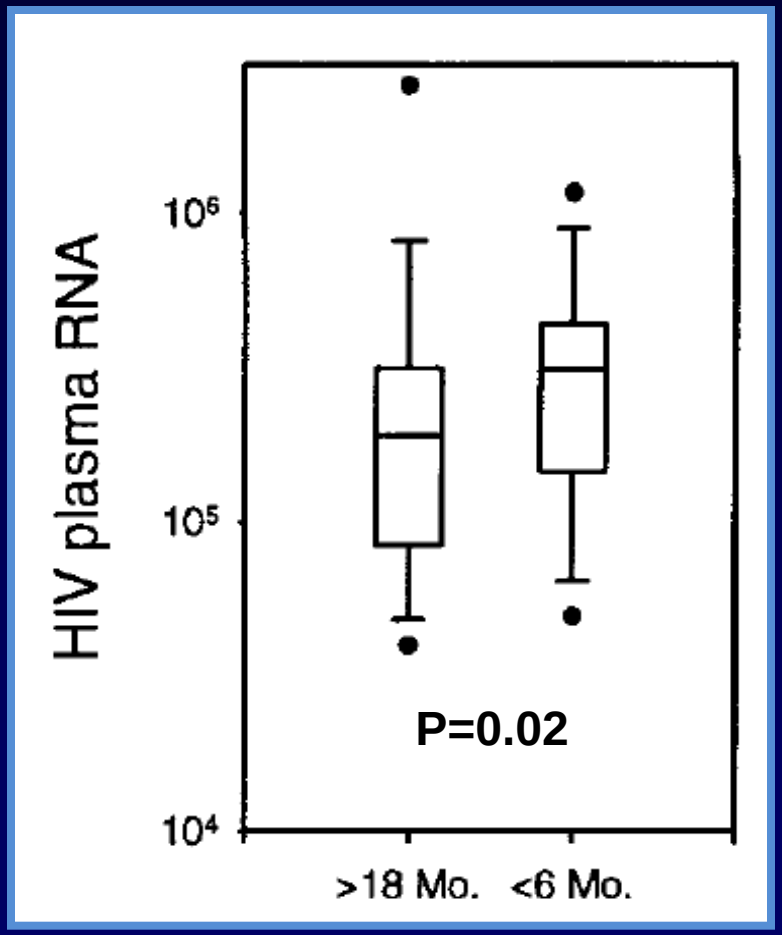
Activated

Highly-activated

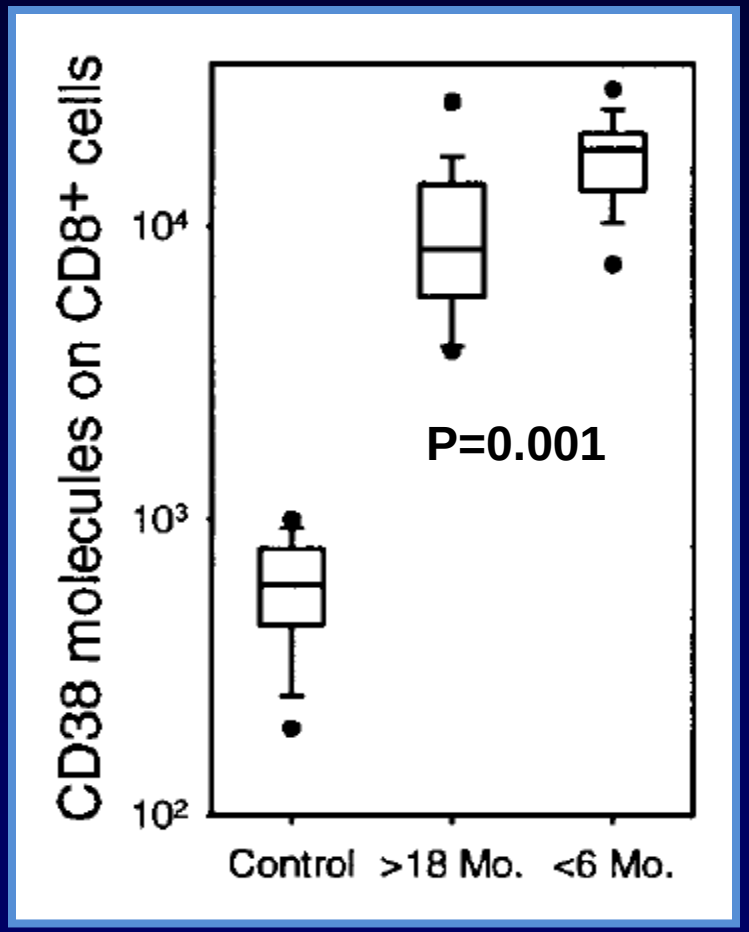
Deeks SG, et al. Blood. 2004;104;942-947.

Immune activation predicts HIV disease progression better than VL

in patients with AIDS (CD4<200)



Survival

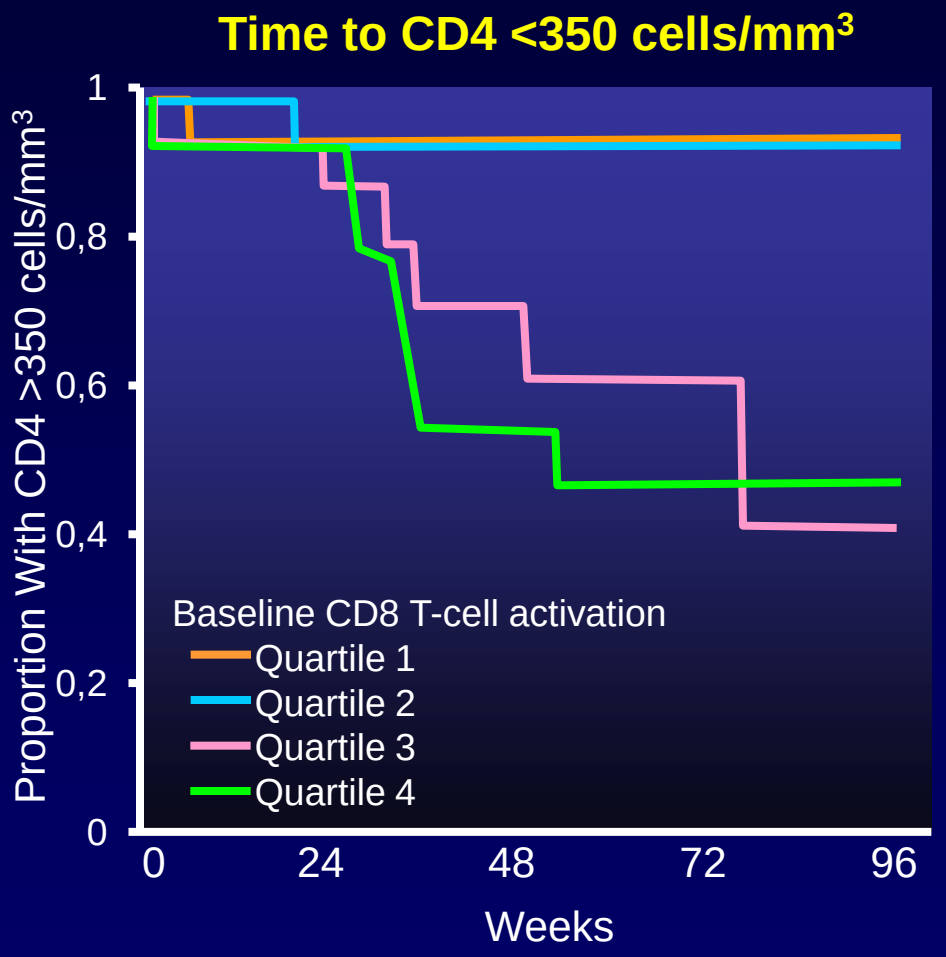


Survival

Giorgi, JID, 1999 (see also: Liu, JAIDS, 1998; Giorgi, JAIDS, 2002)

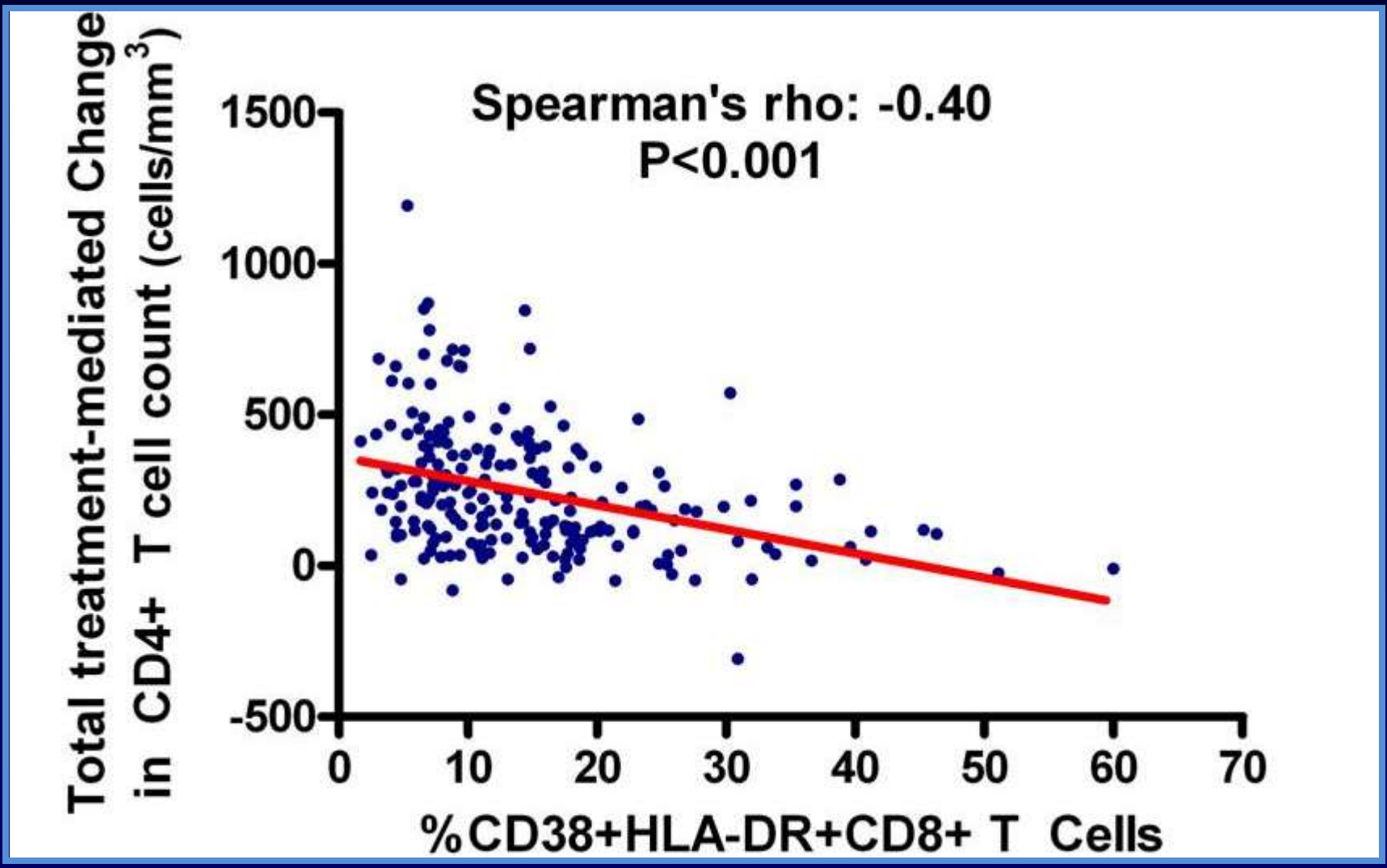
Immunologic Activation Set Point Is Established Early in HIV infection

- Recently HIV-infected patients who did not receive ART (n=68)
  - Cohort stratified into quartiles at baseline
    - Level of viremia
    - CD4 T-cell activation
    - CD8 T-cell activation
- Higher baseline CD8 T-cell activation was associated with more rapid CD4 cell decline (*P*=0.02)
  - Independent of HIV RNA levels



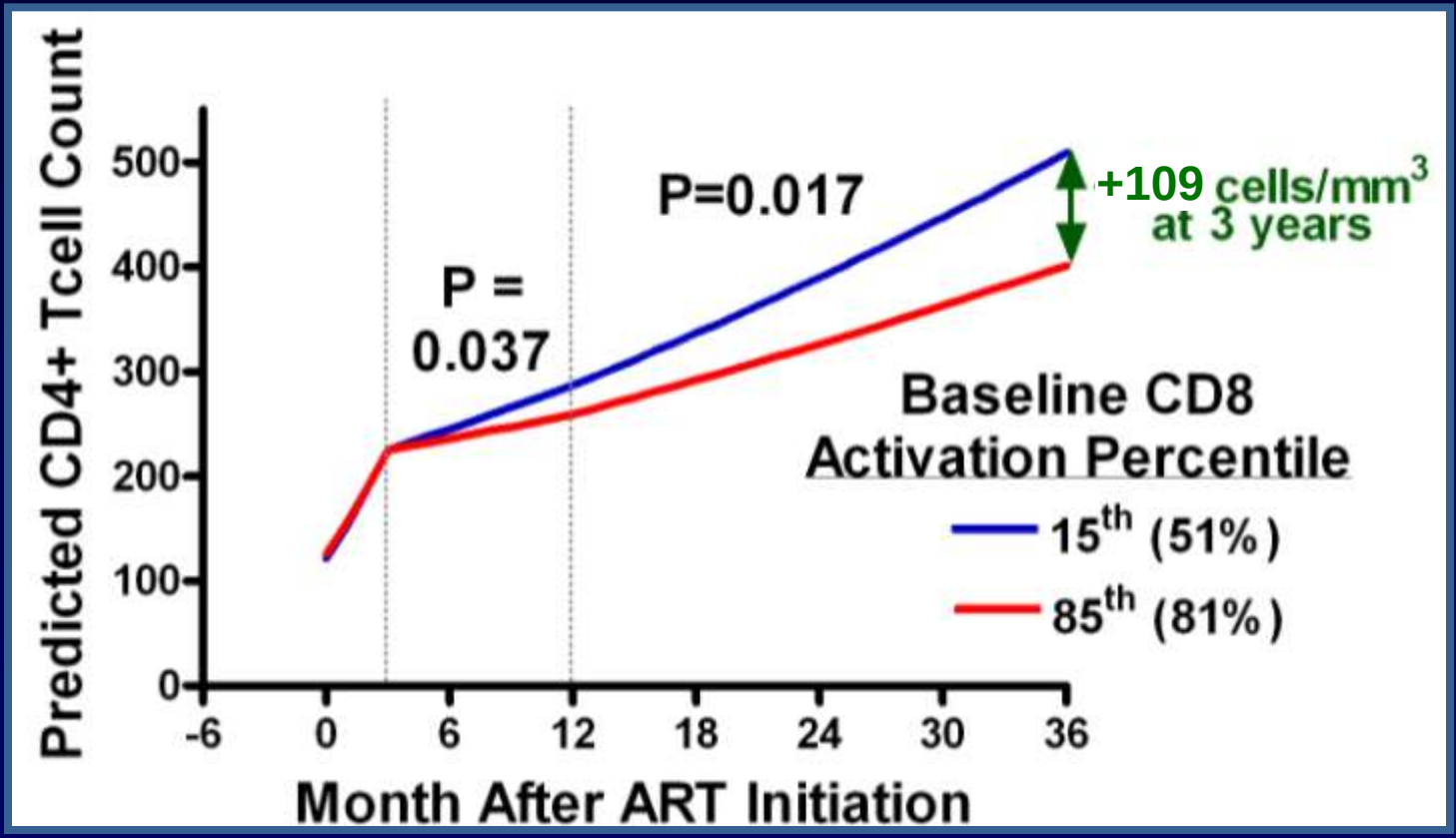
Deeks SG, et al. Blood. 2004;104;942-947.

High T Cell Activation Associated with Blunted CD4 Recovery



Hunt et al, JID, 2003; Gandhi, JAIDS, 2006; Goicoechea, JID, 2006

UARTO: High Pre-ART CD8+ T Cell Activation Predicts Poor CD4+ T Cell Recovery in Ugandans Maintaining VL<400

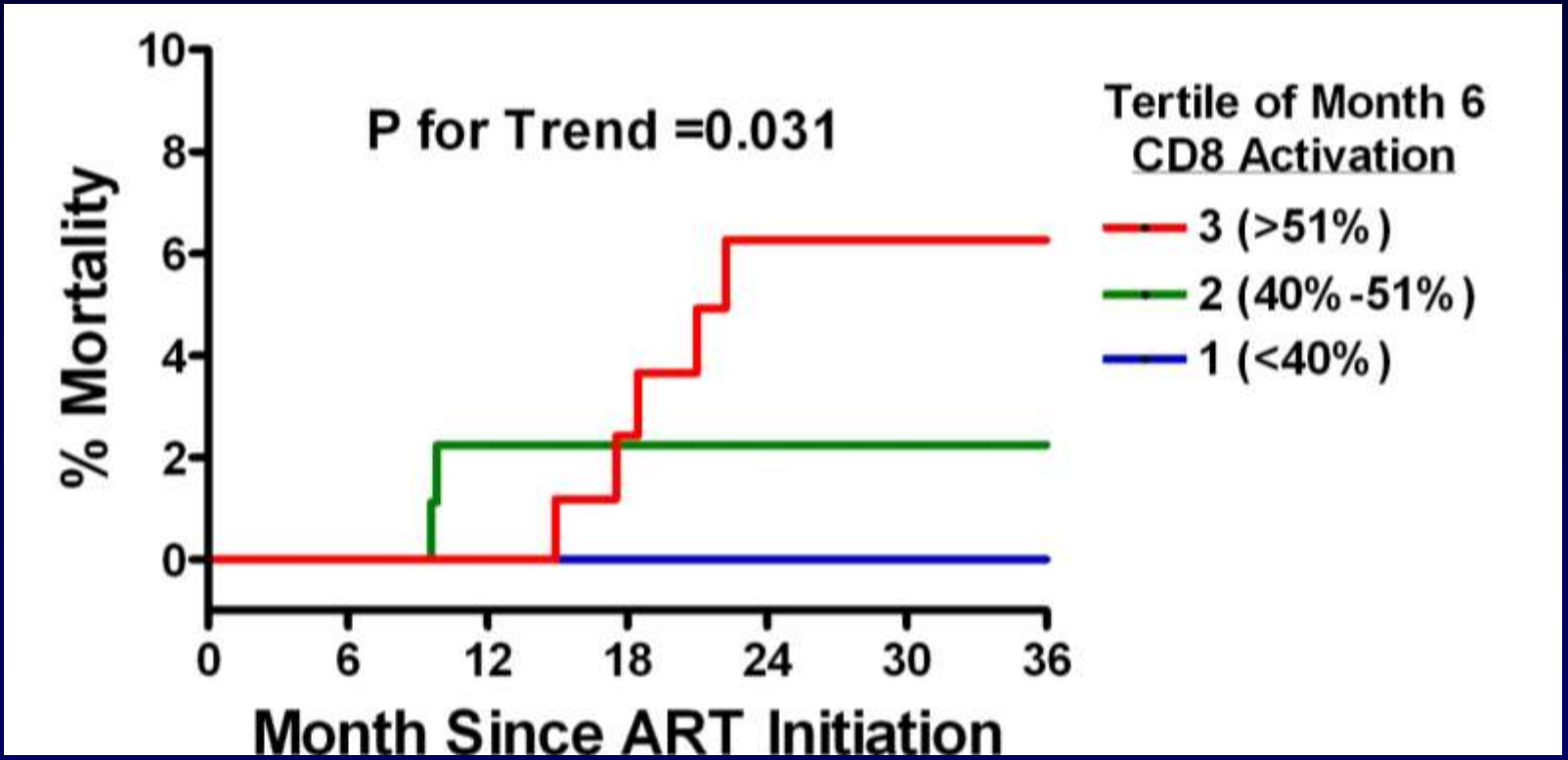


Linear mixed model adjusted for pre-ART VL, CD4 count, and gender.

Plot shows predicted CD4 changes for two prototypic patients (female, CD4 count=133, VL=126,000 c/ml) with high vs. low CD8+ T cell activation

Hunt et al, AIDS 2011;25:2123.

UARTO: High CD8+ T cell activation at month 6 of HAART predicts mortality in Ugandans with VL<400

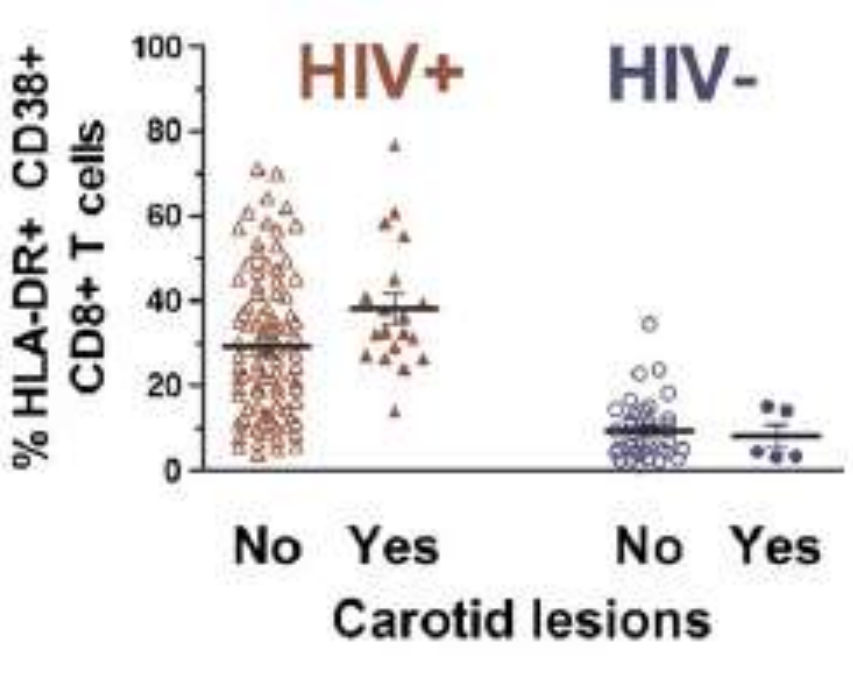


In Cox Proportional Hazards models, each 10% increase in the frequency of activated (%CD38+ HLA-DR+) CD8+ T cells was associated with an increased hazard of death even after adjustment for baseline CD4 count (HR: 1.62, P=0.048) or month 6 CD4 count (HR: 1.61, P=0.042).

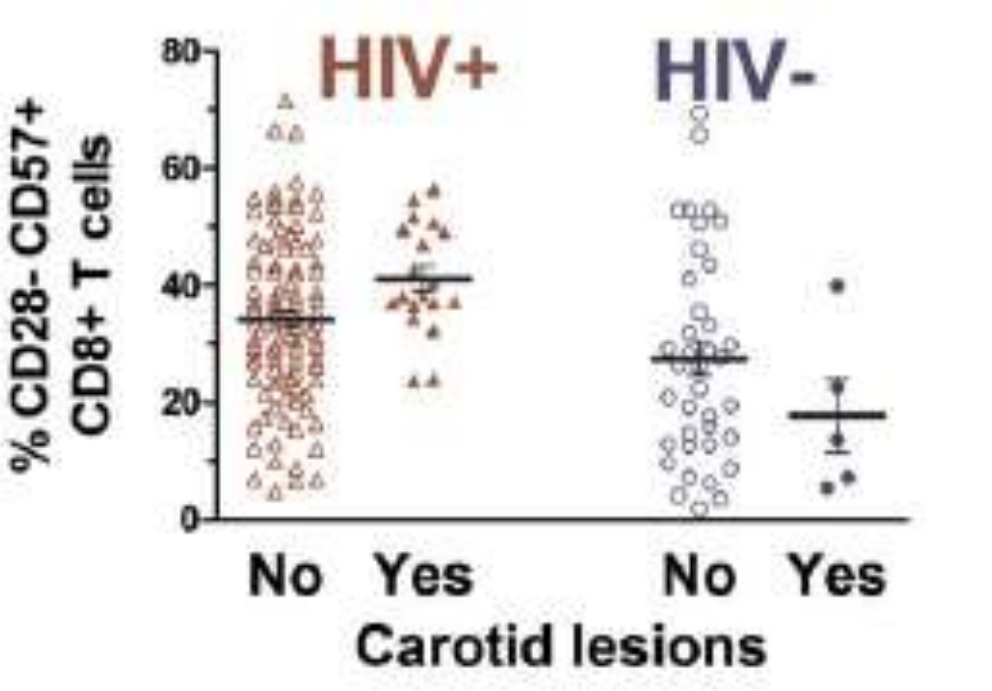
Hunt et al, AIDS 2011;25:2123.

T Cell Activation, Senescence, and Atherosclerosis

CD8 Activation
HLA-DR^{+} CD38^{+}



CD8 Senescence
CD28^{-} CD57^{+}



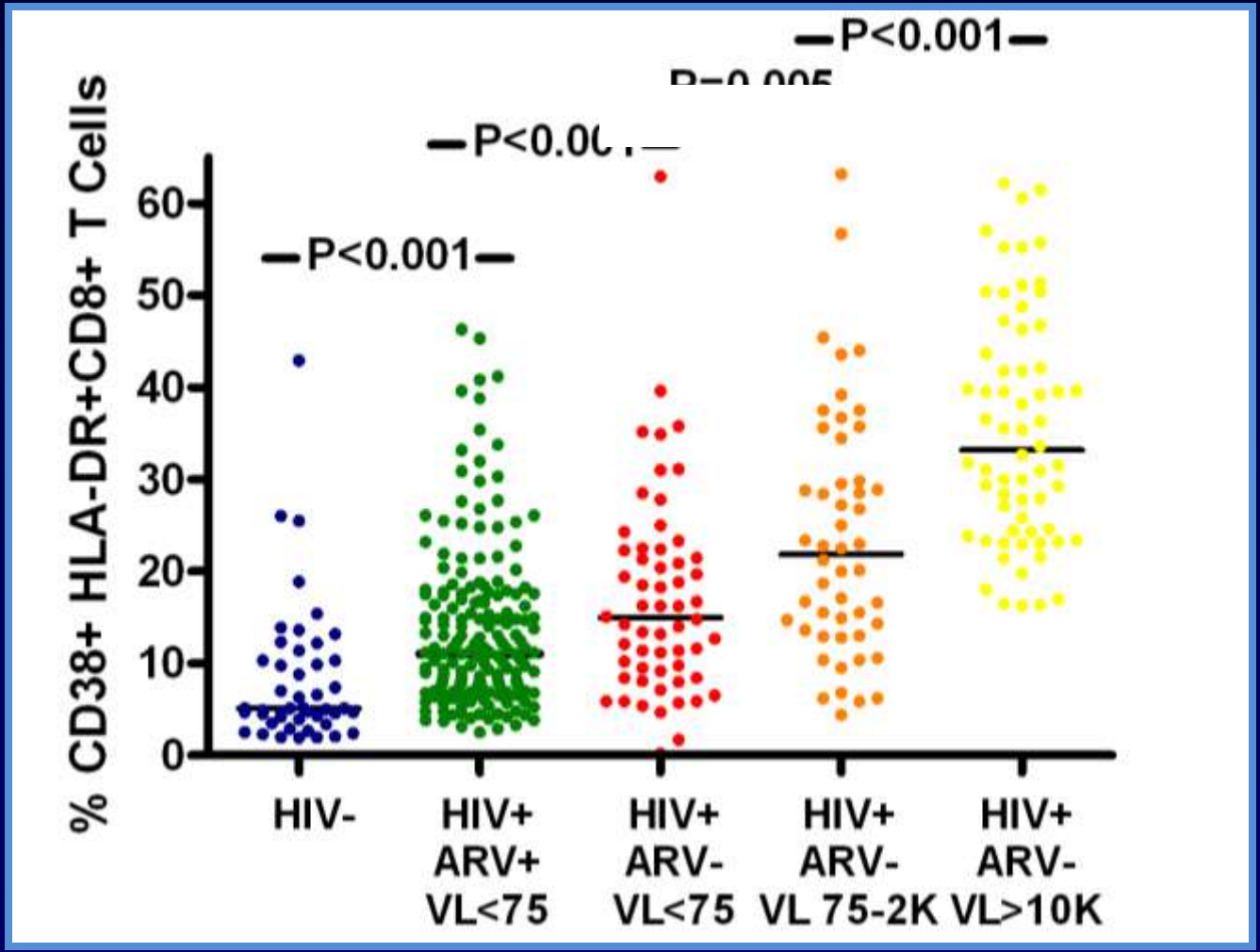
Kaplan RC et al, JID 2011;203:452.

Causes of Immune Activation/Chronic inflammation in HIV-Infection

- Residual HIV replication
- Microbial translocation
- Co-infections: CMV, HBV, HCV
- Lack of immunoregulatory responses
- Thymic dysfunction and residual defects in adaptive immune responses
- **Consequences of Immune Activation**
  - Damage to lymph nodes: fibrosis
  - Co-morbid conditions: metabolic syndrome
  - Increased T cell turn-over

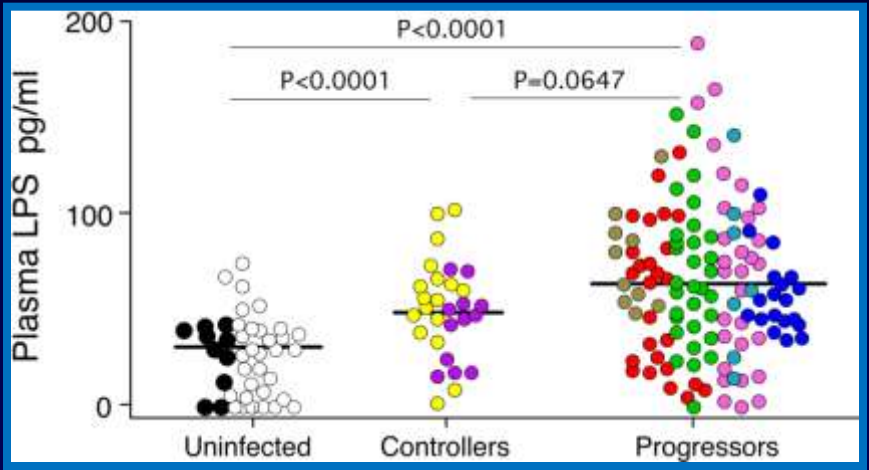
Immune Activation/Inflammation and HIV Disease: IAS 2011 symposium.

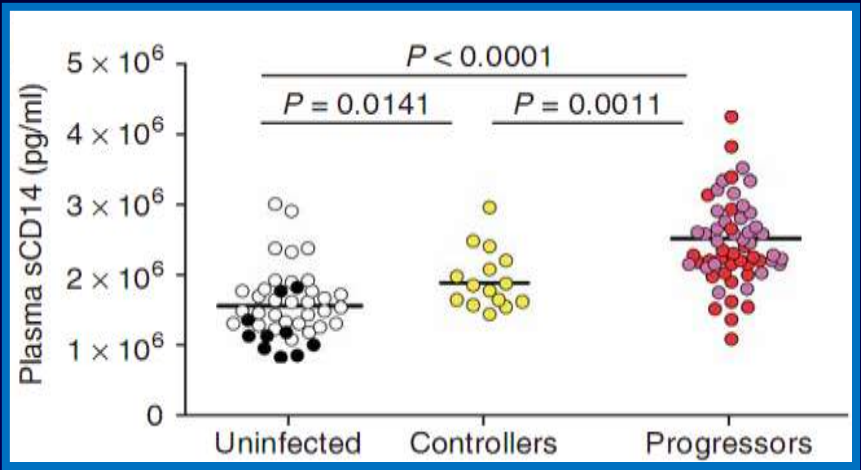
%CD38+HLA-DR+ CD8+ T Cells Discriminates Between Groups with Low Levels of Viral Replication

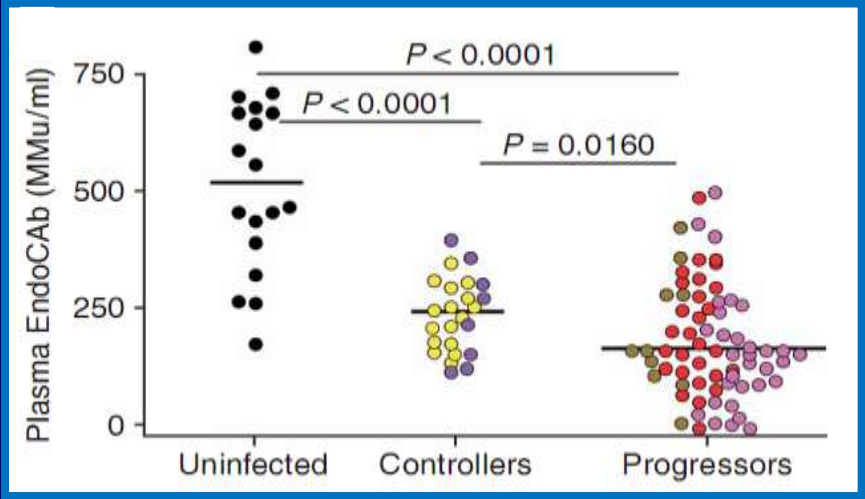


Hunt PW et al, PLOS One 2011;6:e15924.

Microbial Translocation is a cause of immune activation in chronic HIV infection

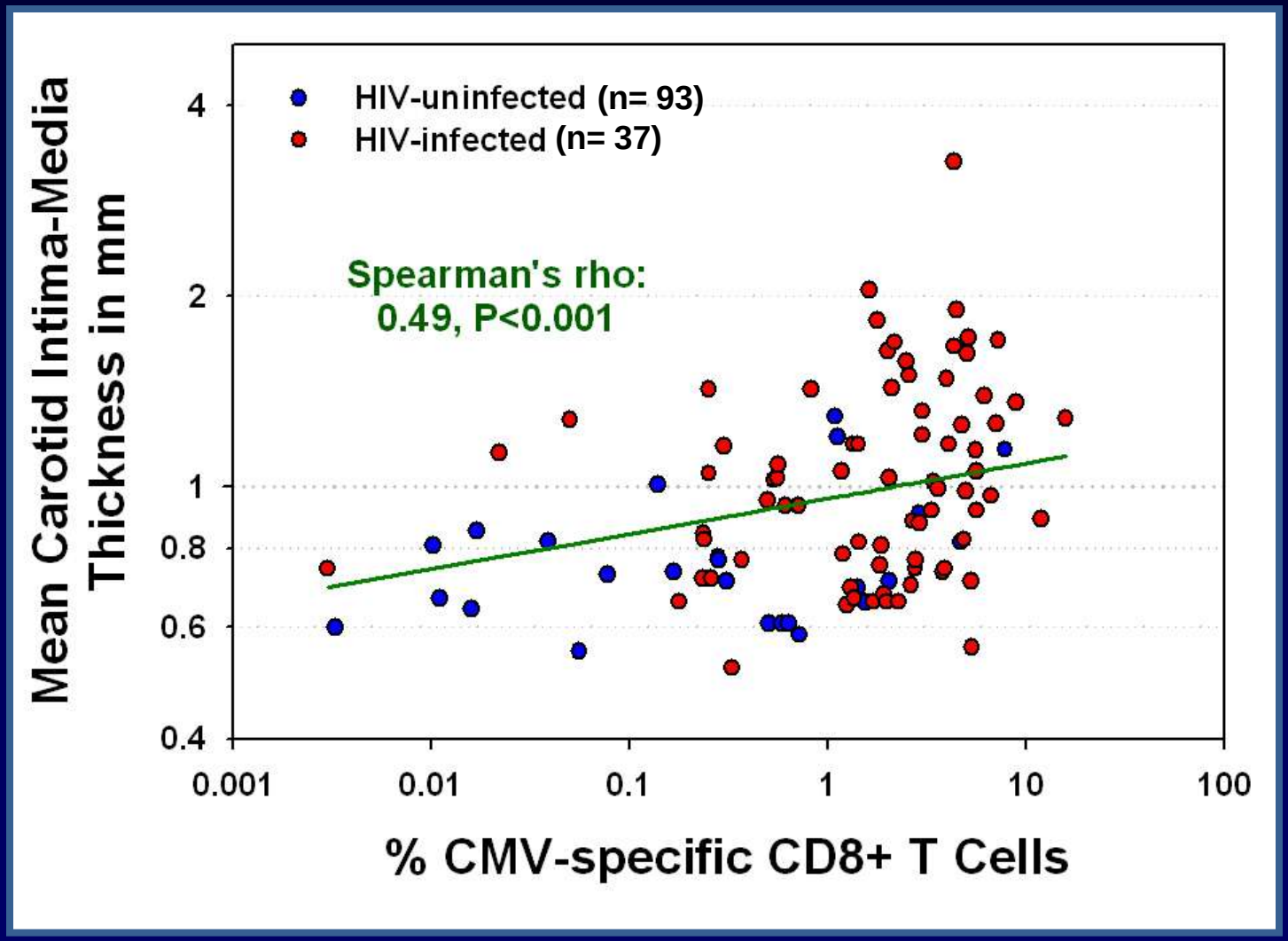






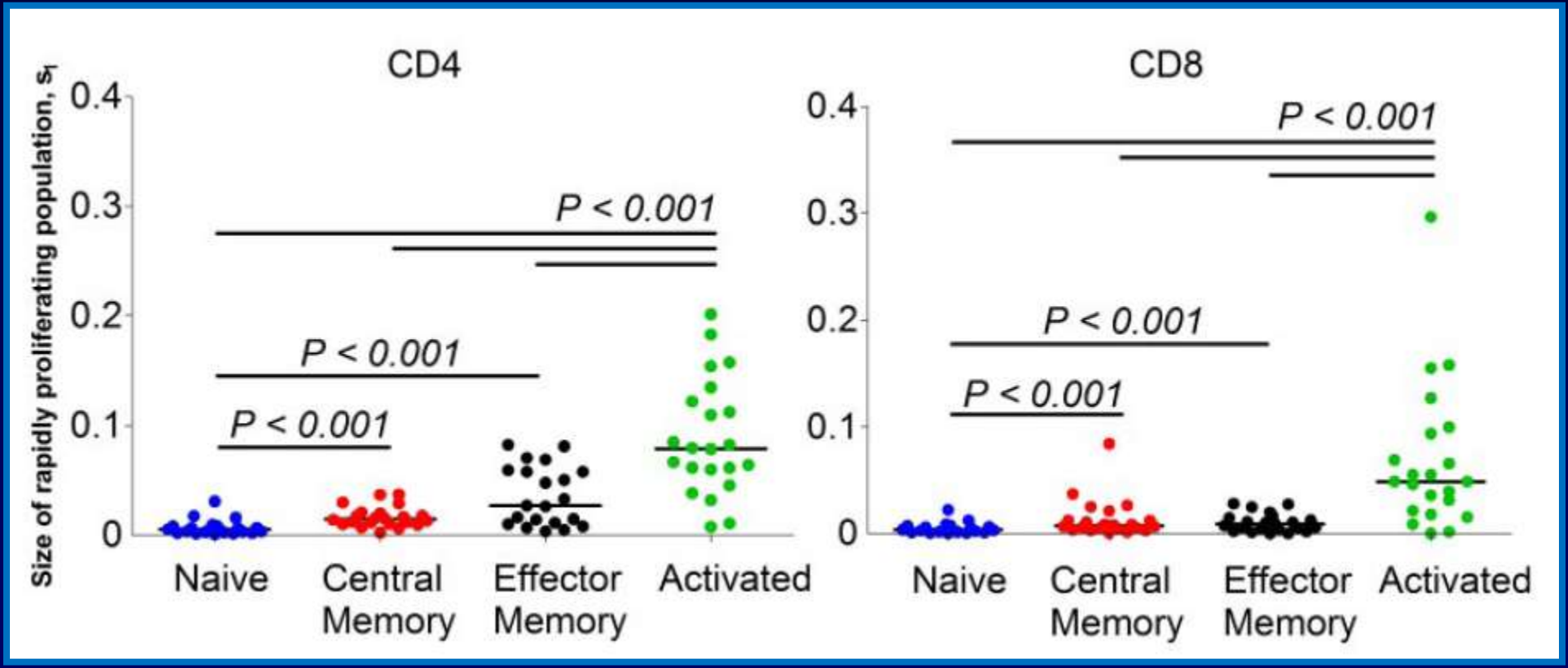
Brenchley JM et al., Nat Med 2006;12:1365–1371.

Higher CMV-specific CD8 IFN-γ Production Associated with More Atherosclerosis



Hsue PY et al, AIDS 2006;20:2275.

Activated CD38+ HLA-DR+ T cells are rapidly turning over in untreated disease



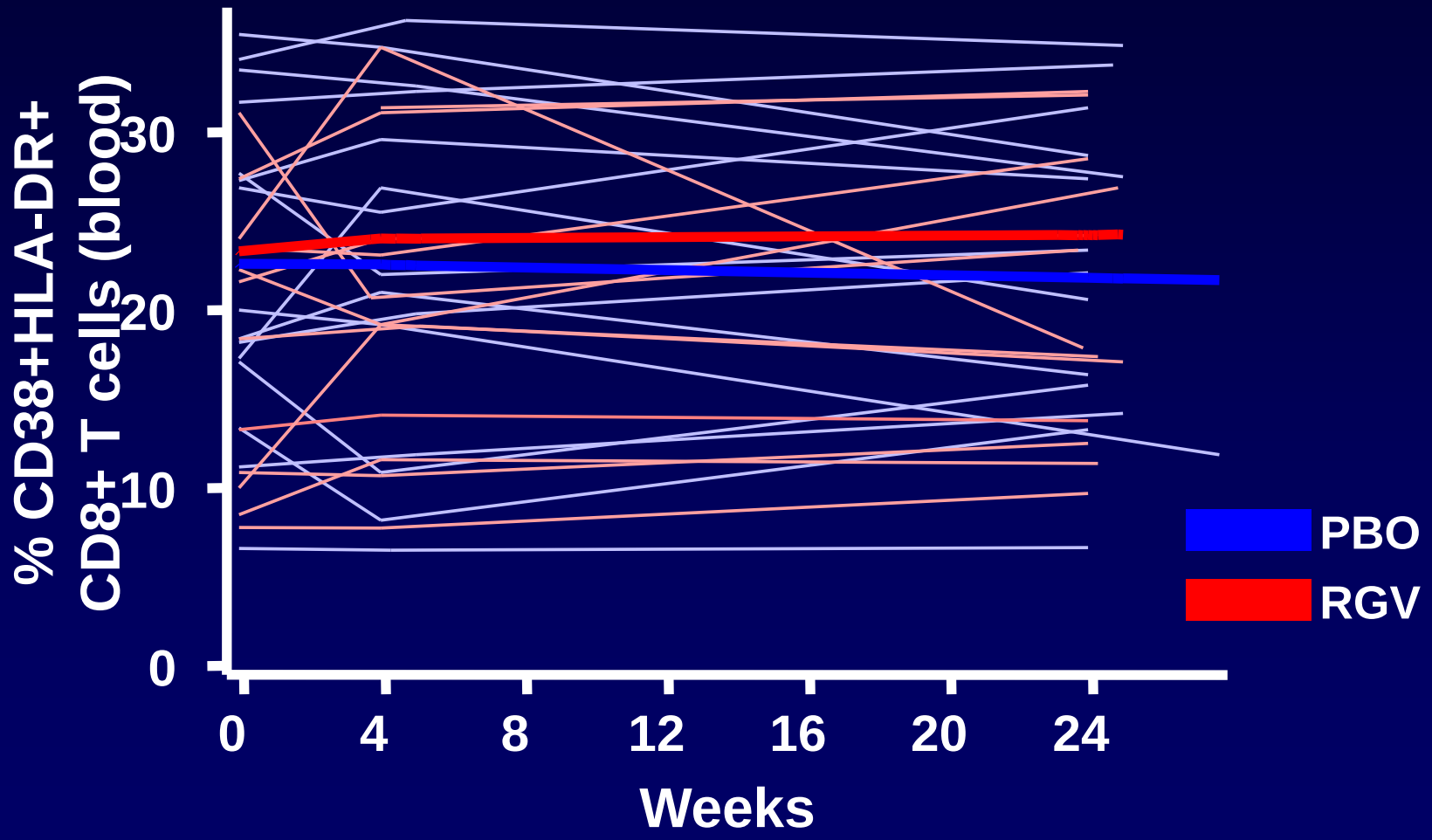
by *in vivo* labeling with bromodeoxyuridine (BrdU).

Srinivasula S et al., Blood 2011;118:262.

Managing Immune Activation

- Optimizing ARV Treatment
  - Raltegravir
- Co-Receptor Blockers
  - Maraviroc
- Anti-Inflammatory Therapy
  - COX-2 inhibitors
  - Chloroquine
  - Hydroxychloroquine
  - Salsalate (NF-κB inhibitor)
  - Pentoxifylline (TNF-α inhibitor)
  - Monoclonal antibodies against pro-inflammatory cytokines
- Immune Suppressants
  - Cyclosporine
- Statins
  - Atorvastatin
- Treatment of co-infections
  - CMV, HBV, HCV
- Lifestyle Modification
  - Smoking cessation
  - Weight loss program
  - Exercise
  - Vitamin D
  - Omega-3 fatty acids
- Bacterial Translocation
  - Rifaximin
  - Sevelamer

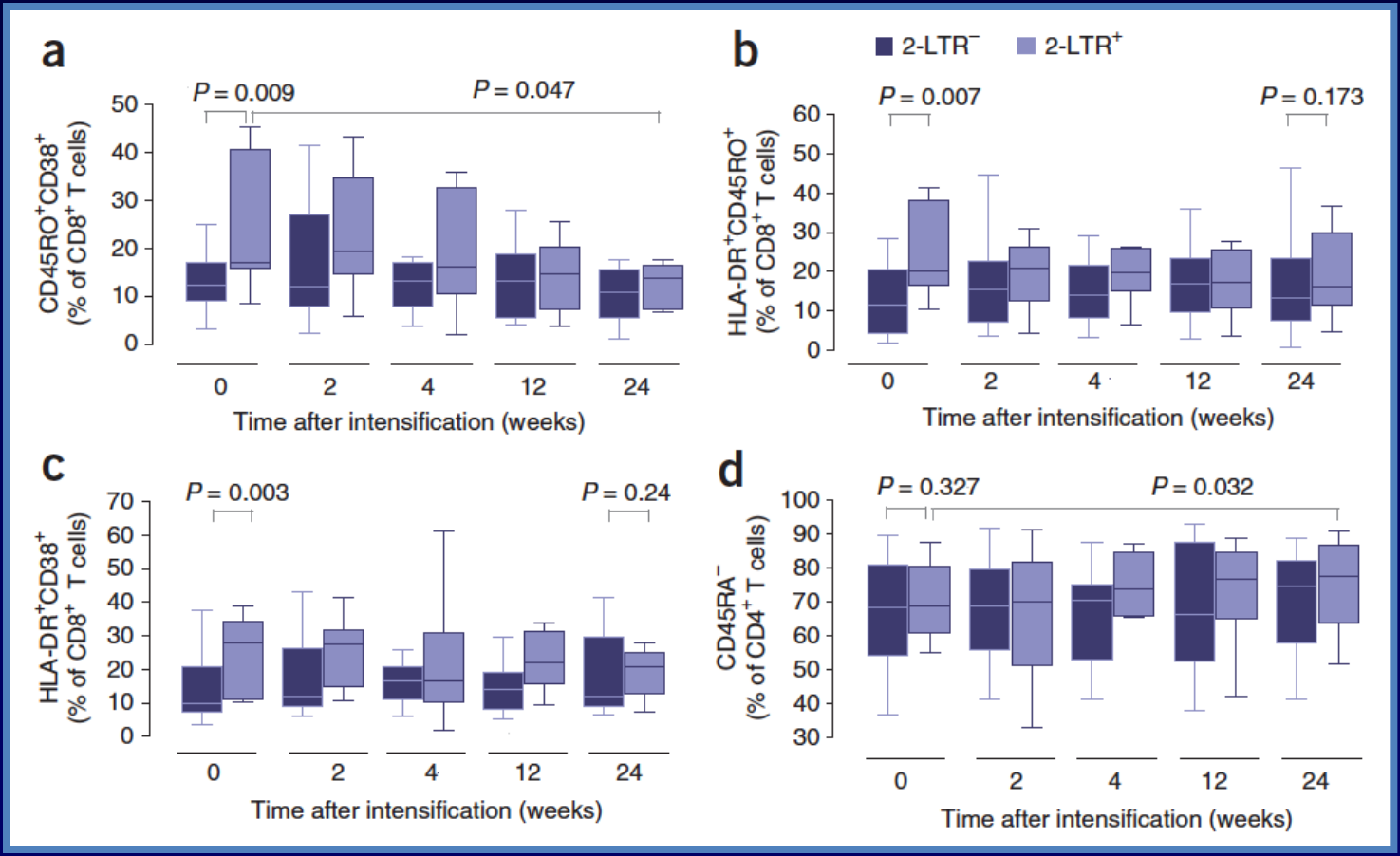
Raltegravir intensification had no effect on CD8+ T cell activation (blood and GALT) suggesting that active viral replication is not a causes of persistent inflammation



Hatano et al., JID 2011;203:960.

Efecto del raltegravir en la activación inmune en pacientes sin viremia VIH detectable

- 69 pacientes en TARV combinado y con CV <50 copias/mL por >1 año
- Randomizados a intensificar con RAL (n=45), o continuar ART (n = 24) por 48 semanas

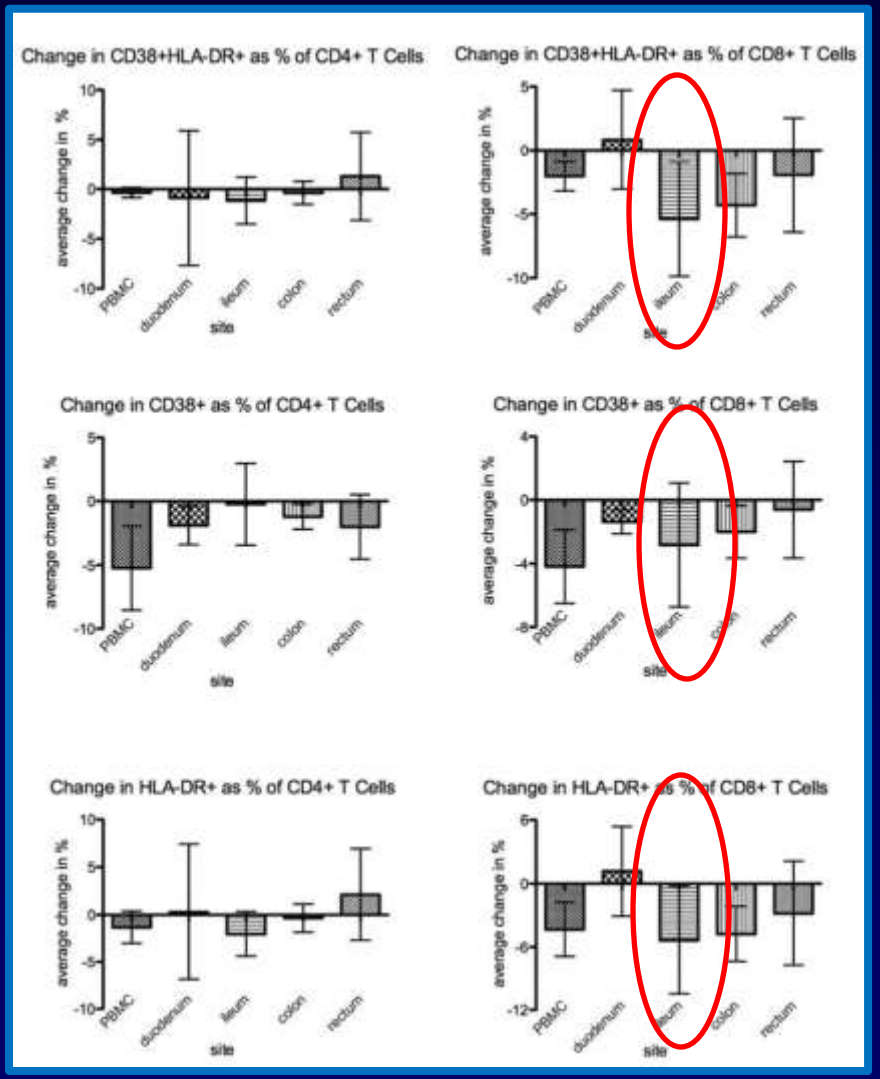


Buzón MJ et al., *Nature Medicine* 2010;16 (4):460-465.

Cambios en los niveles de activación inmune en pacientes en TARV intensificado con raltegravir

- 7 adultos en tratamiento ARV con CV <40 copias/mL por 6,7 años
- Intensificación durante 12 semanas con RAL sólo o combinado con EFV o DRV
- Biopsia de duodeno, íleo, colon, y recto
- CV plasmática, ADN y ARN en PBMC y tracto entérico, CD4 y marcadores de activación
- 5 pacientes ↓ usARN en IT
- **Tendencia a ↑ CD4 en íleo y ↓ activación en íleo y PBMC (células CD8)**

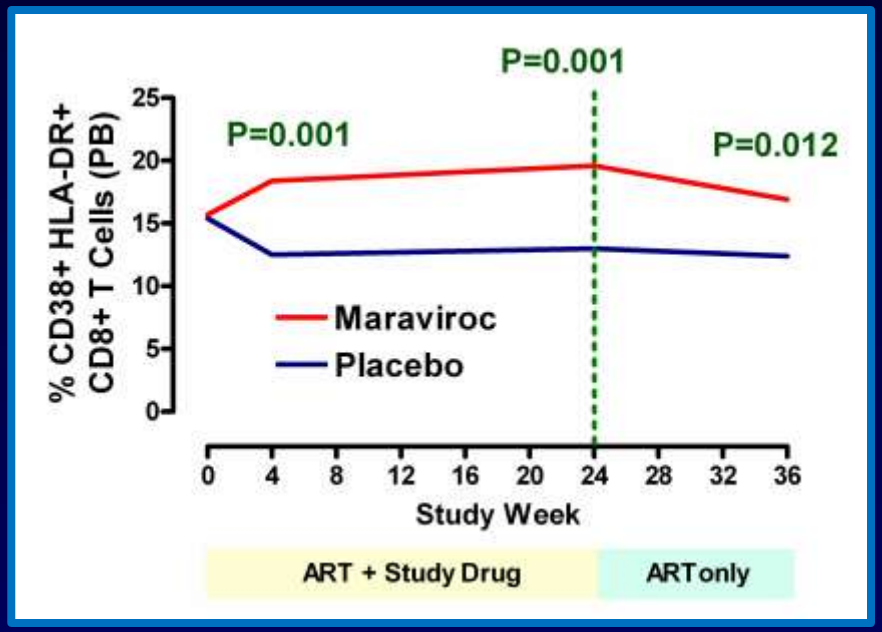
células CD4 **células CD8**



Yukl SA, et al. AIDS 2010;24:2451-2461.

Maraviroc Intensification *Increases* CD8 Activation Compared to Placebo

- Randomized, placebo controlled, 24 week study (N=45)
  - Virologically suppressed patients, on ART for >1 year with CD4 <350
- Primary outcome – change in activated CD8 T cells in peripheral blood

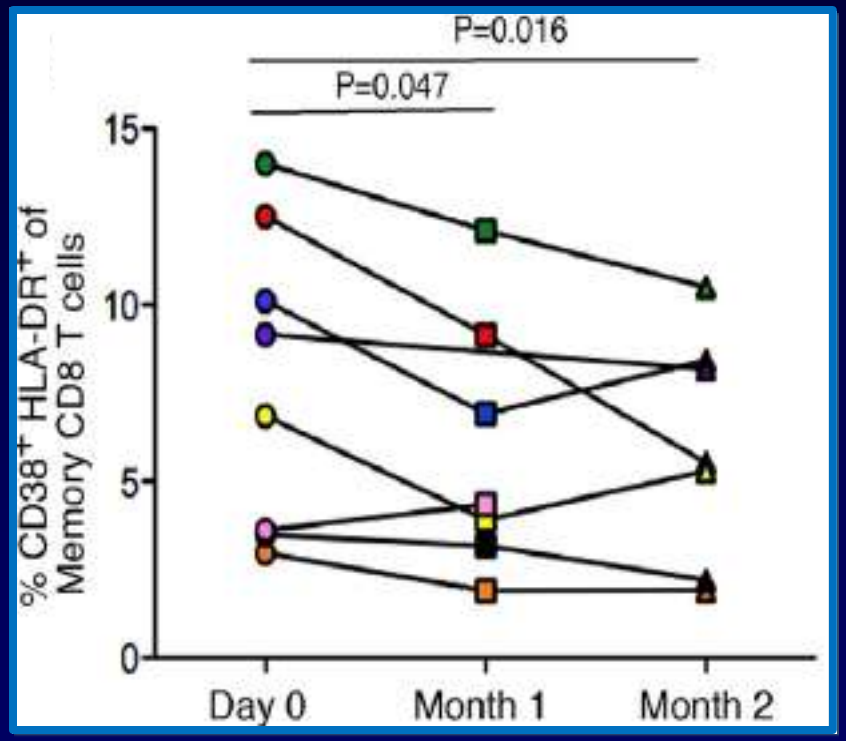


- Conclusions:
  1. T cell activation increased in gut and blood
  2. Lower LPS levels (p=0.41)
  3. sCD14 increased (p = 0.041)
  4. No impact on CD4 cell counts

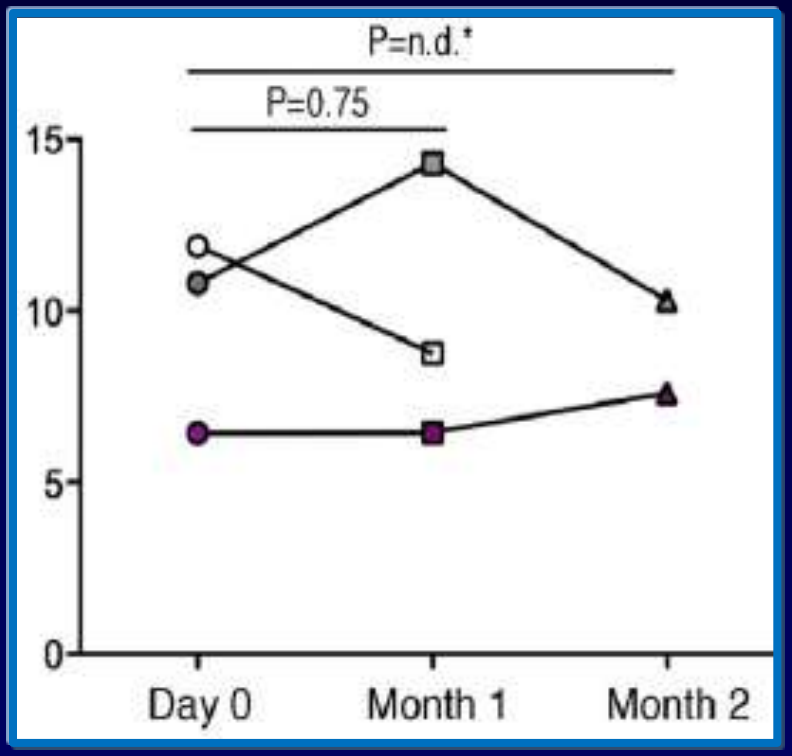
Hunt P, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 153LB.

Chloroquine Might Reduce CD8 Activation
in 13 Untreated Chronically HIV-Infected Patients

Chloroquine



Placebo



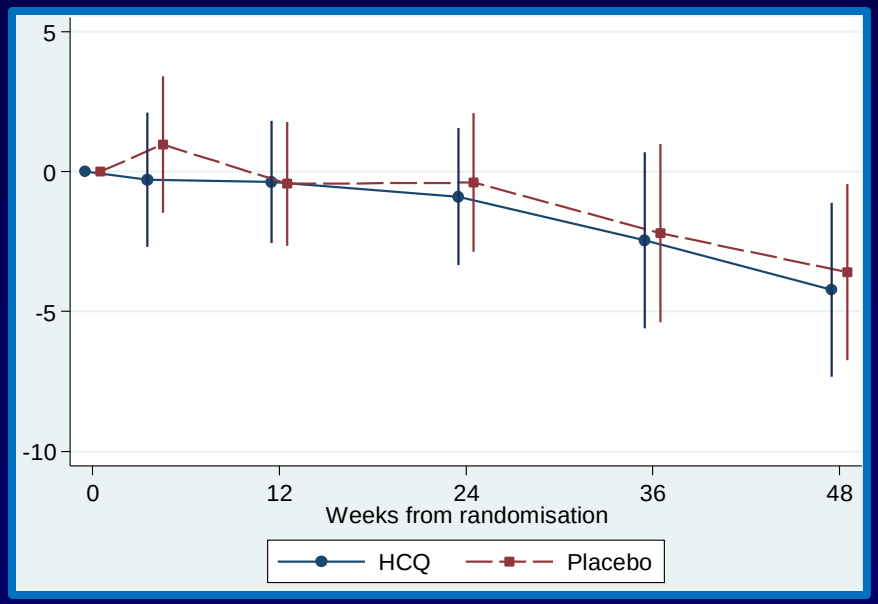
- No apparent effect on plasma HIV RNA Levels
- Decrease in plasma LPS only at month 1
- Probable mechanism: TLR inhibition (3,4,7,8,9)

Murray Sm et al, J Virol 2010;84:12082.

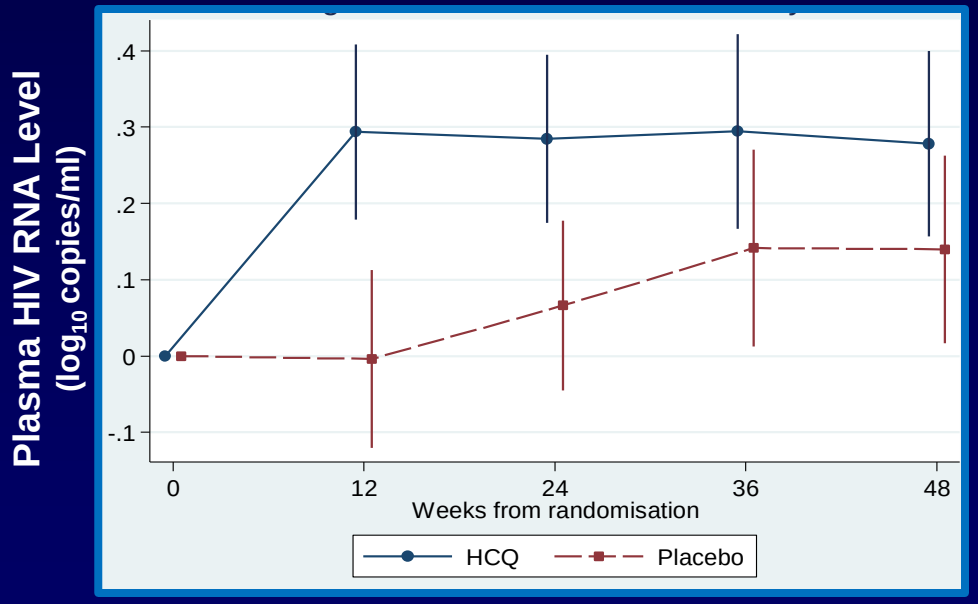
Hydroxychloroquine Did *Not* Reduce CD8 Activation in Untreated HIV+ Patients

- HCQ 400 mg vs. placebo in 80 ARV-treatment naïve patients for 48 weeks
- Activation markers, CD4 counts and HIV RNA levels tracked
- There was no difference between the groups in change from baseline in CD8CD38DR+, IL-6 or D-dimer, but the HCQ group showed a trend towards higher VL and more rapid loss of CD4 cells

%CD38+HLA-DR+ CD8s



Viral Load

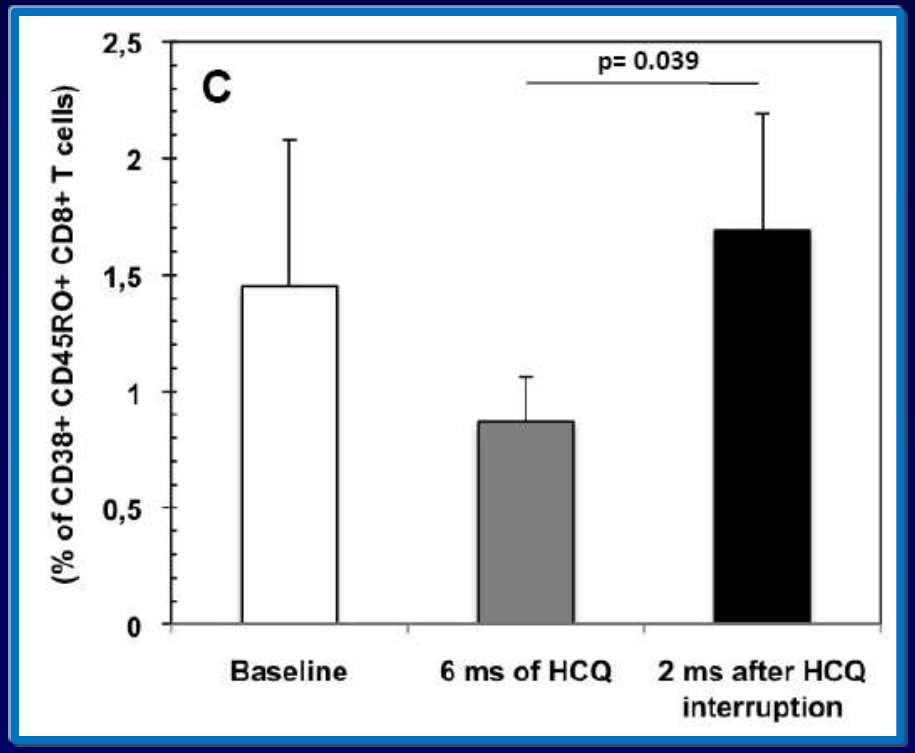


Paton NI, et al. 6th IAS; Rome, Italy; July 17-20, 2011. Abst. MOPE269.

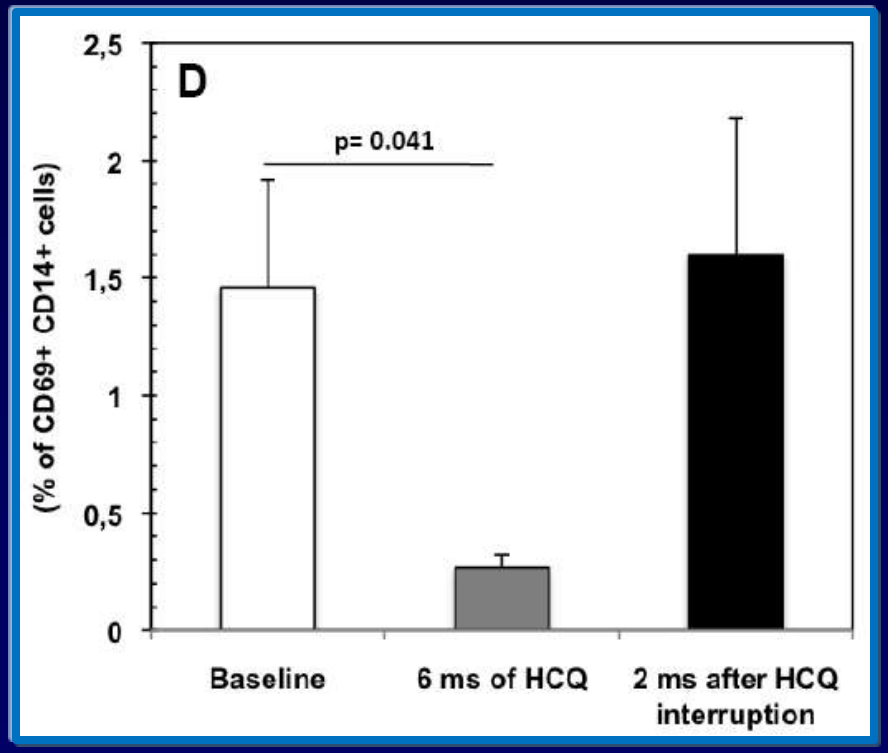
HCQ Decreases Immune Activation in ART-suppressed Immunologic Non-responders

- 20 HIV-infected immunologic nonresponders: CD4 count < 200 cells/mL or CD4 increase < 5% in the last 12 months
- HCQ 400 mg for 6 months

%CD38+ Memory CD8s



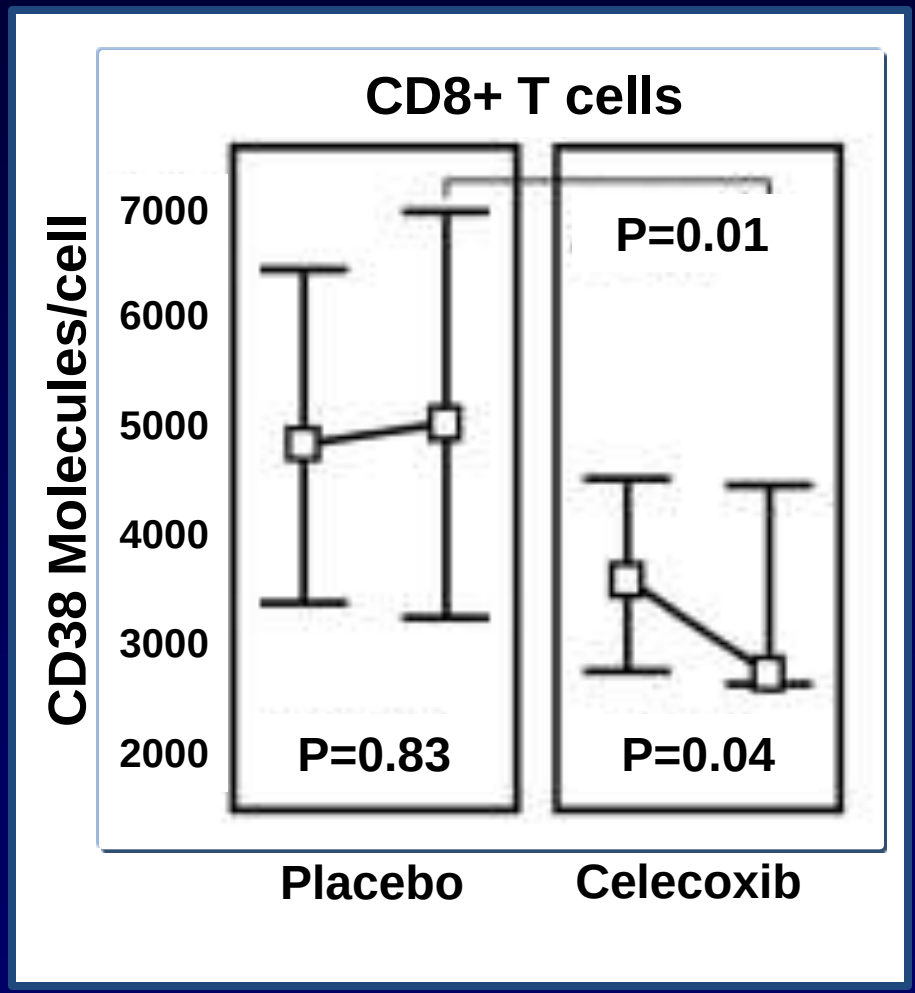
%CD69+ CD14+ Monocytes



Piconi S. et al, Blood 2011;118:3263.

COX-2 Inhibition Decreases T Cell Activation in Untreated HIV Infection

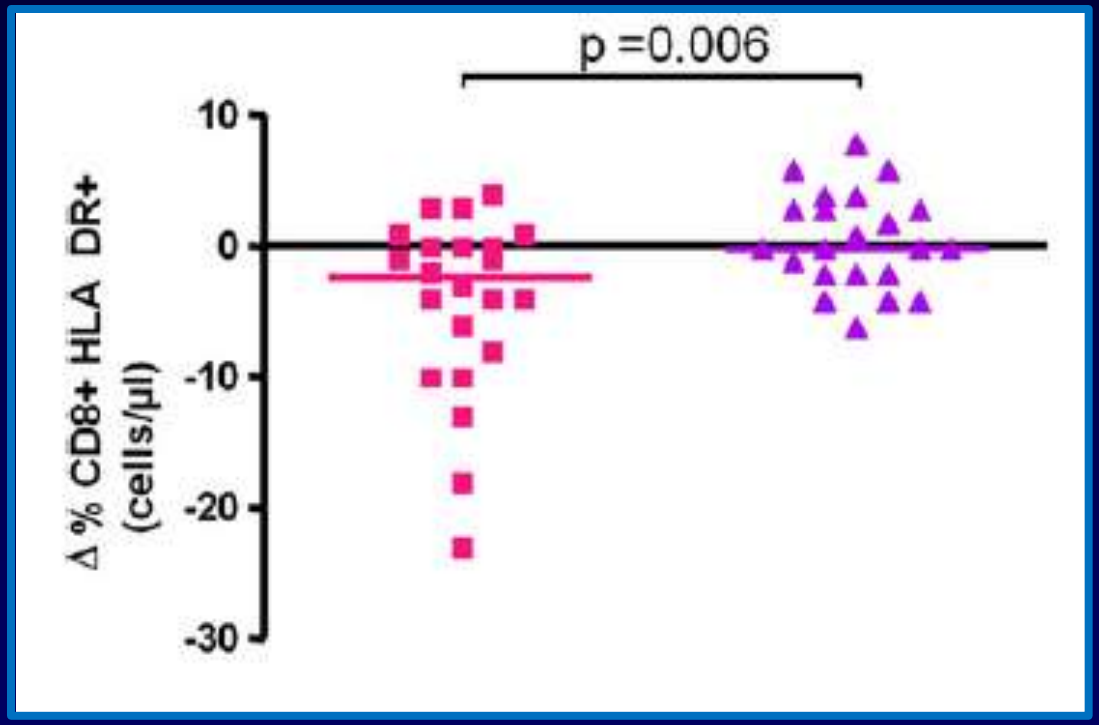
- 27 untreated patients, 12 weeks celecoxib vs. placebo
- Significant reduction in CD38 on CD8s during celecoxib therapy
- No effect on plasma HIV RNA levels
- CAD toxicity a potential problem with celecoxib



Pettersen FO et al, J Virol 2011;85:6557.

Atorvostatin Decreases T Cell Activation in Untreated HIV Infection

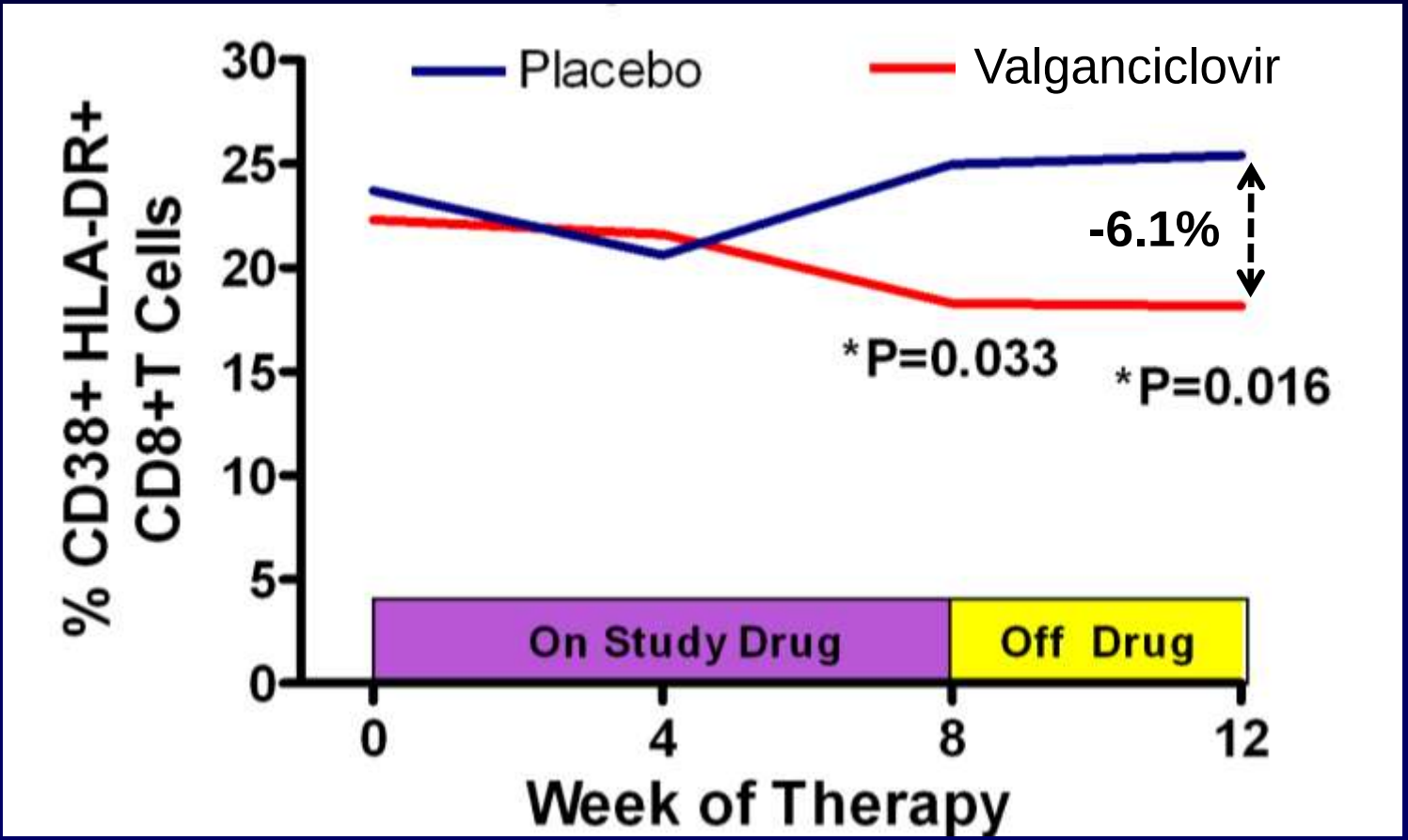
- 24 untreated patients, double-blind, cross-over design
- Significant reduction in HLA-DR on CD8s during therapy with atorvostatin
- No effect on plasma HIV RNA levels
- Studies ongoing in ART-suppressed patients



Ganesan A et al, J Infect Dis 2011;203:756.

Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation

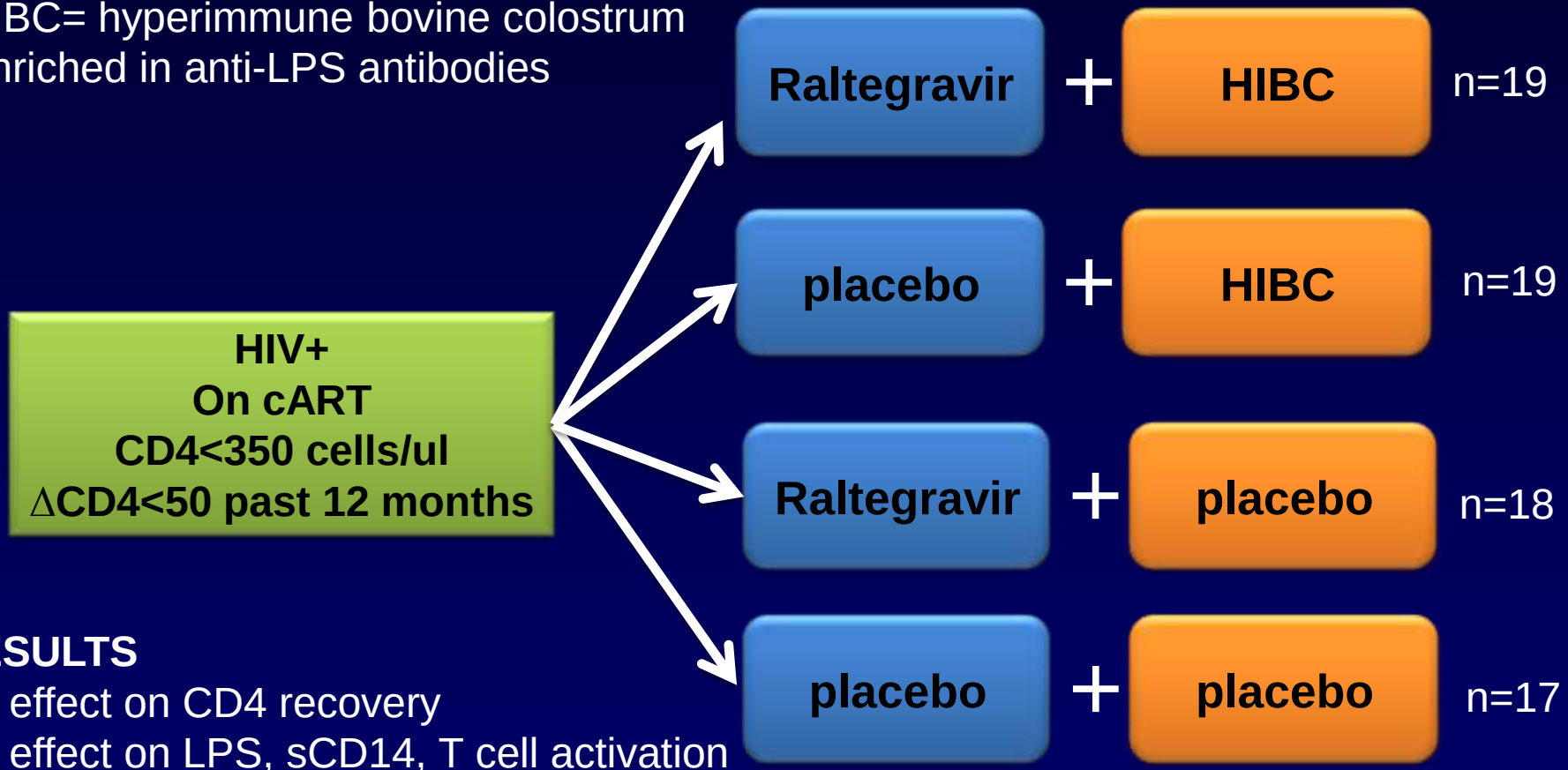
30 ARV-treated HIV-infected Patients with CD4<350



Hunt P et al, JID 2011;203:1474.

Anti-LPS antibodies have no effect on CD4 recovery: CORAL

HIBC= hyperimmune bovine colostrum
Enriched in anti-LPS antibodies



RESULTS
No effect on CD4 recovery
No effect on LPS, sCD14, T cell activation

CONCLUSION
The determinants of poor CD4 recovery following cART require further investigation

Bykawaga H et al, J Infect Dis 2011;204:1532.

Activación inmune: conclusiones

- Juega un papel principal en la patogénesis de la infección por VIH
- Tiene consecuencias clínicas evidentes sobre progresión de la infección por VIH y la emergencia de enfermedades no relacionadas con el VIH
- Conlleva al daño y envejecimiento del sistema inmune
- Principalmente relacionada con la viremia residual, translocación bacteriana y co-infecciones
- Elucidar la causa de la activación inmune permitirá el desarrollo de mejores estrategias de tratamiento