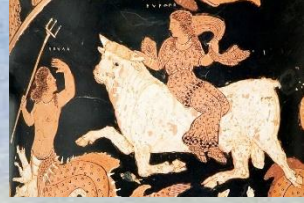
Scuola Medica Salernitana

Azienda Ospedaliera Universitaria
San Giovanni di Dio e Ruggi d'Aragona - Salerno
La Città d'Ippocrate

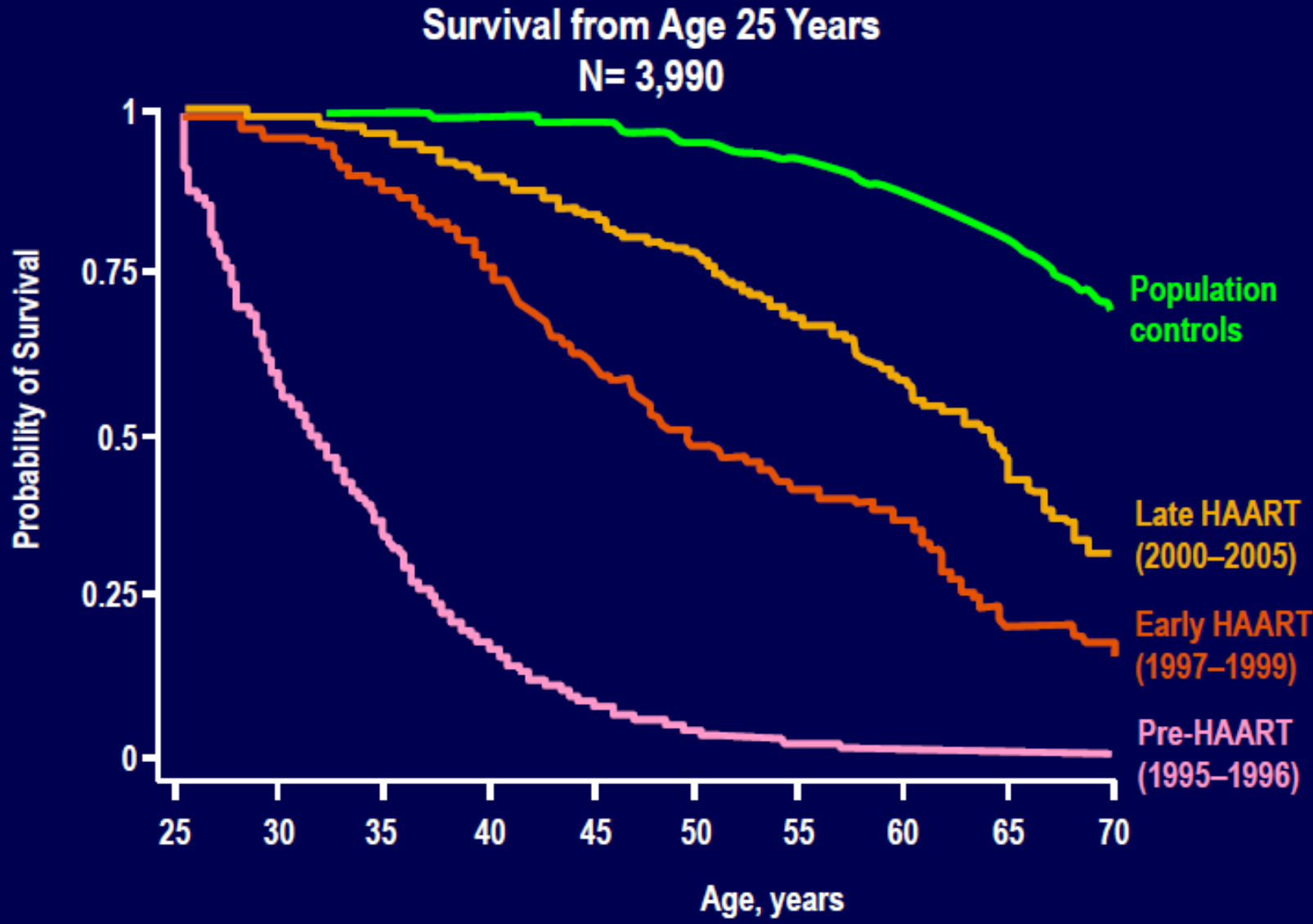


"Infiammazione, immunoattivazione e senescenza in corso di infezione da HIV"

Nicola Boffa
UOSD Virologia Clinica
UOC Malattie Infettive

6th *Infec*TO Paestum 13-15 maggio 2014

Late HAART Era Patients Still Have a 10y Shorter Life Expectancy than HIV- Controls

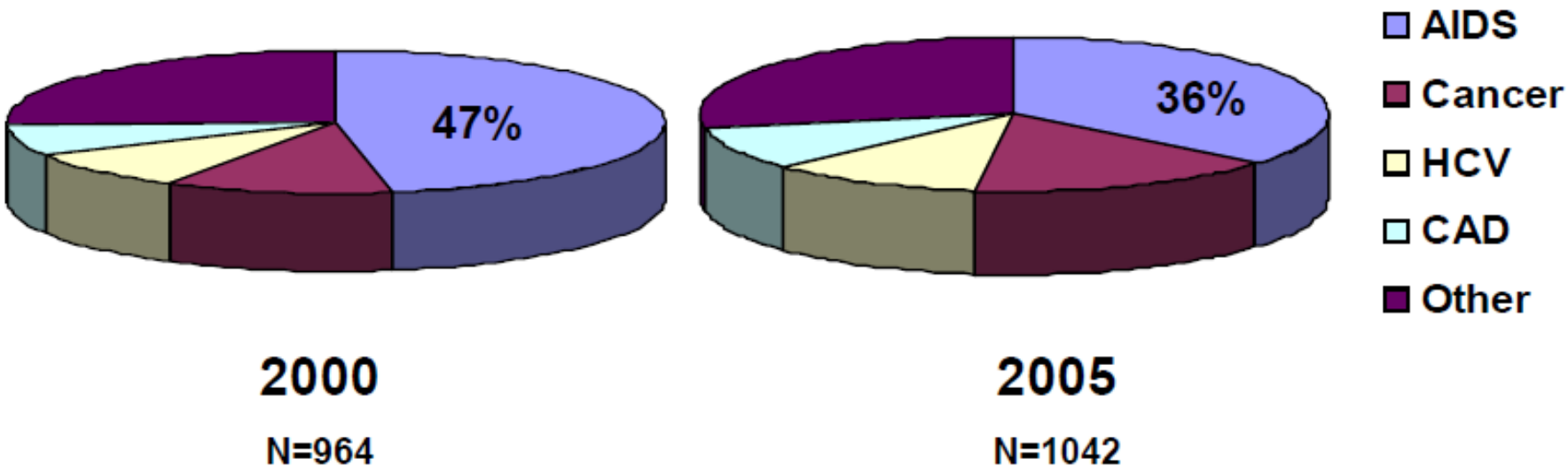


Adapted from Lohse N, et al. Ann Intern Med 2007;146:87–95

(See Also: ART-CC, Lancet, 2008; Lewden, JAIDS, 2007)

Almost 2/3 of All Deaths in Late HAART Era Are Non-AIDS-associated

ANRS E19



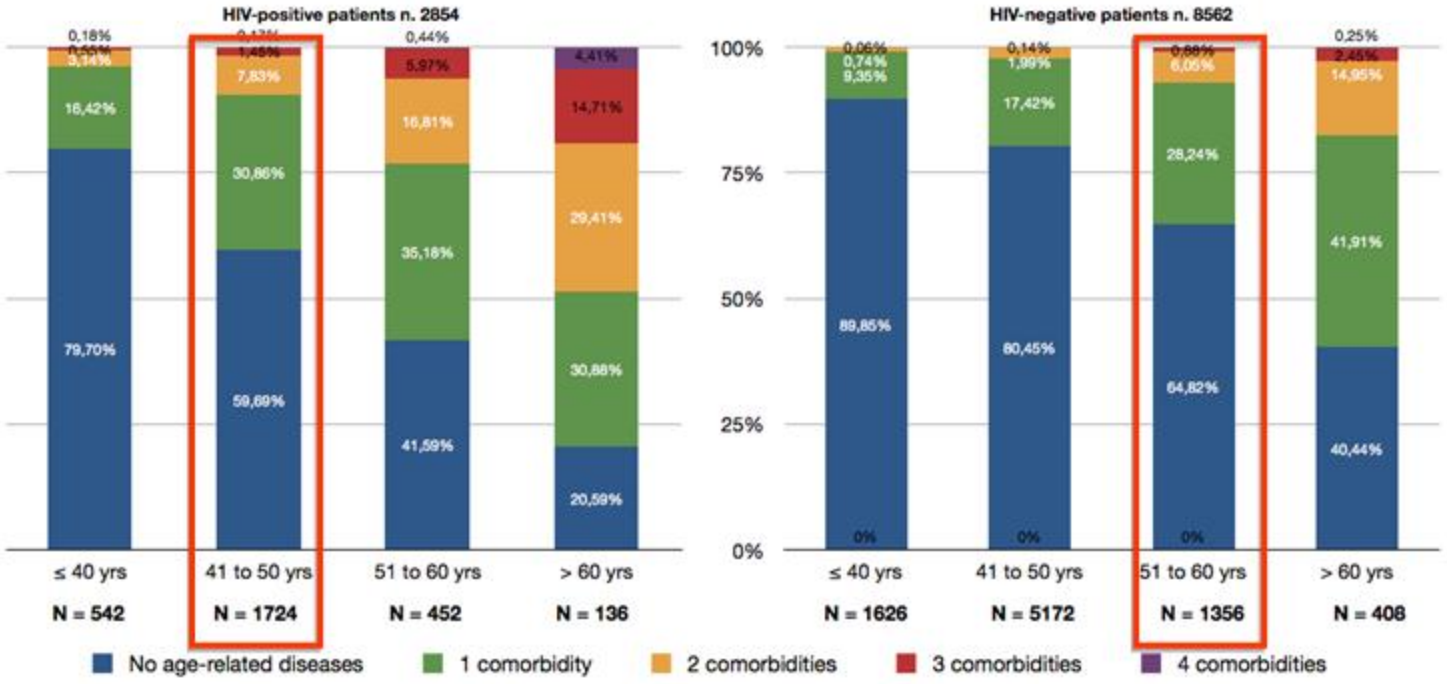
Lewden et al. JAIDS, 2008

Many morbidities associated with aging also appear to be increased in treated HIV disease

- Cardiovascular disease [1-3]
- Cancer (non-AIDS) [4]
- Bone fractures / osteoporosis [5,6]
- Liver failure [7]
- Kidney failure [8]
- Cognitive decline [9]
- Frailty [10]

1. Klein D, et al. J Acquir Immune Defic Syndr. 2002;30:471-477. 2; Hsue P, et al. Circulation. 2004;109:316-319. 3. Grinspoon SK, et al. Circulation. 2008;118:198-210. 4. Patel P, et al. Ann Int Med, 2008;148:728-736. 5. Triant V, et al. J Clin Endocrinol Metab. 2008;93:3499-3504. 6. Arnsten JH, et al. AIDS. 2007 ;21:617-623. 7. Odden MC, et al. Arch Intern Med. 2007;167:2213-2219. 8. Choi A, et al. AIDS, 2009;23(16):2143-49. 9. McCutchan JA, et a. AIDS. 2007 ;21:1109-1117. 10. Desquilbet L, et al. J Gerontol A Biol Sci Med Sci. 2007;62:1279-1286

Poly-pathology prevalence in cases and controls, stratified by age categories

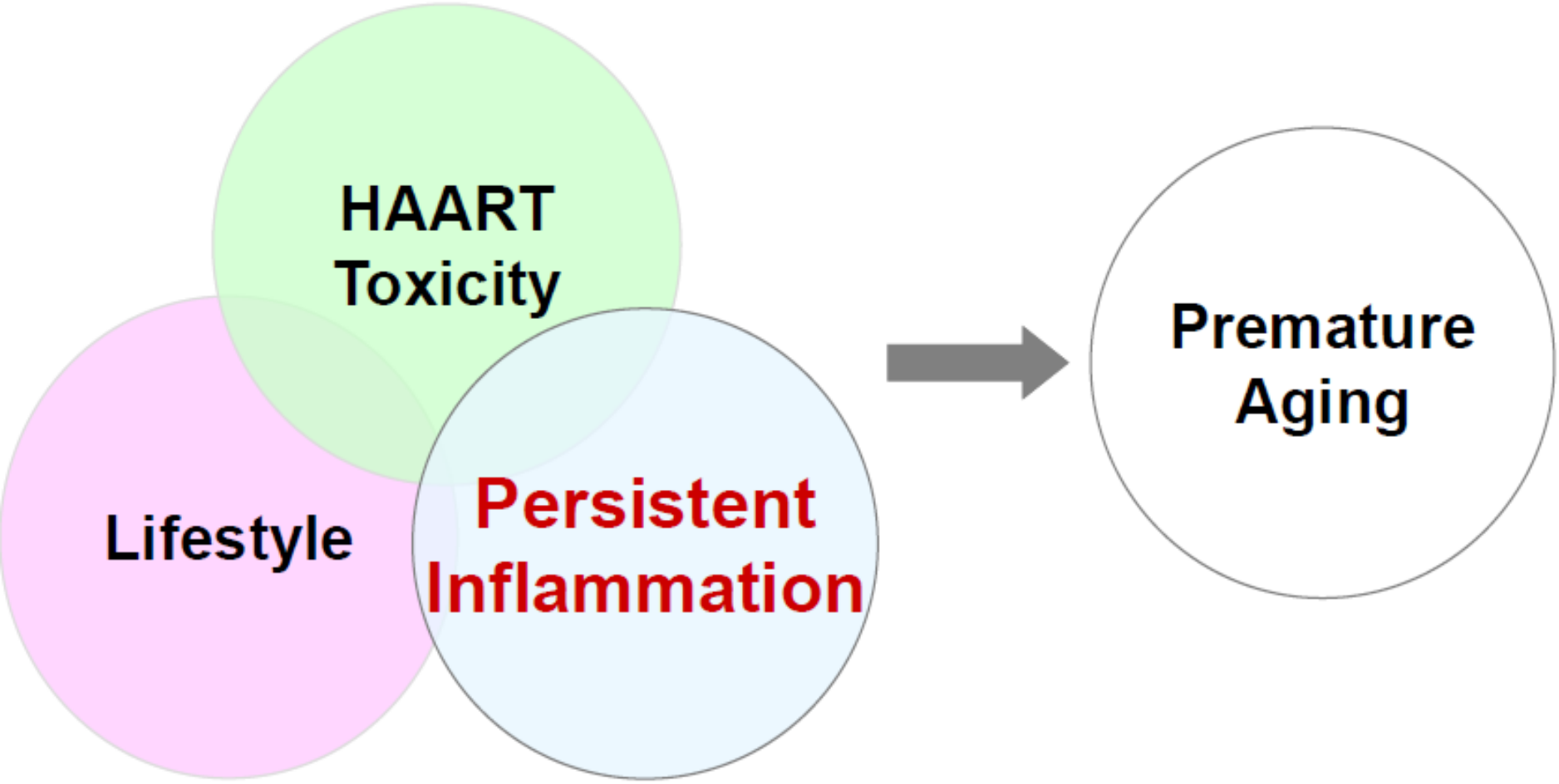


Pp 3.9% 9.0% 20.0% 46.9% **Pp 0.5% 1.9% 6.6% 18.7%**

Pp prevalence was higher in cases than controls in all age strata (all p-values <0.001)
Pp prevalence seen cases aged 41-50 was similar to that observed among controls aged 51-60 controls (p=0.282)

Guaraldi et al IWADRL 2010,London

Non-AIDS events are more common in HIV disease, even after adjustment for age, HAART exposure and traditional risk factors



Deeks and Phillips, BMJ, 2009

OPEN ACCESS Freely available online October 2008 | Volume 5 | Issue 10 | e203 PLOS MEDICINE

Inflammatory and Coagulation Biomarkers and Mortality in Patients with HIV Infection

Lewis H. Kuller[1], Russell Tracy[2], Waldo Belloso[3], Stephane De Wit[4], Fraser Drummond[5], H. Clifford Lane[6], Bruno Ledergerber[7], Jens Lundgren[8], Jacqueline Neuhaus[9], Daniel Nixon[10], Nicholas I. Paton[11], James D. Neaton[9*], for the INSIGHT SMART Study Group

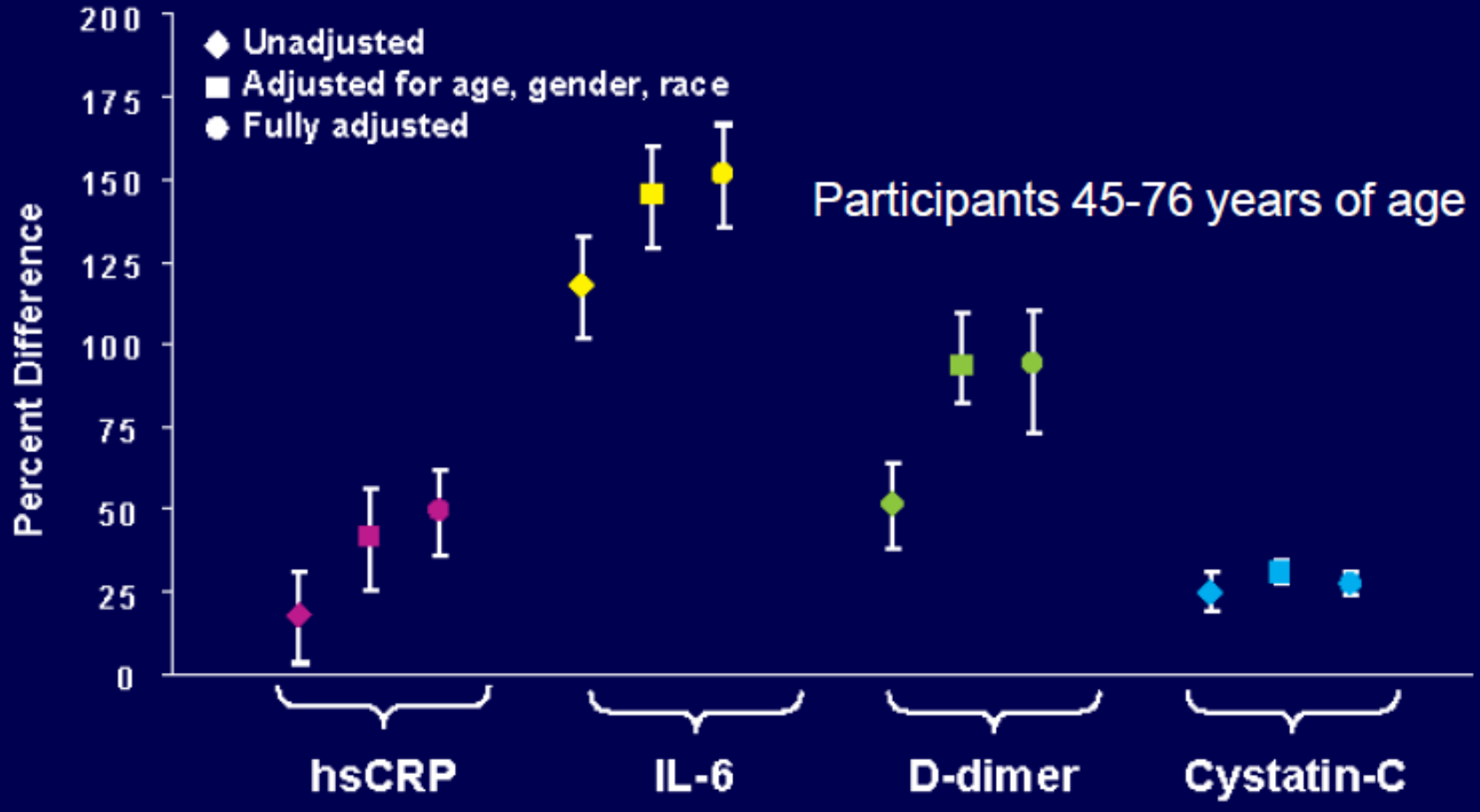
1 University of Pittsburgh, Pittsburgh, Pennsylvania, United States of America, **2** University of Vermont, Burlington, Vermont, United States of America, **3** Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, **4** Saint-Pierre Hospital, Brussels, Belgium, **5** National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, Sydney, Australia, **6** National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, United States of America, **7** University Hospital, Zurich, Switzerland, **8** University of Copenhagen, Copenhagen, Denmark, **9** University of Minnesota, Minneapolis, Minnesota, United States of America, **10** Virginia Commonwealth University, Richmond, Virginia, United States of America, **11** Medical Research Council Clinical Trials Unit, London, United Kingdom

Biomarker and All-Cause Mortality Associations

Baseline Level	OR ($4^{th}/1^{st}$ QRT) Univariate	*P-value*
D-dimer	**12.4**	<0.0001
IL-6	**8.3**	<0.0001
hsCRP	**2.0**	0.05

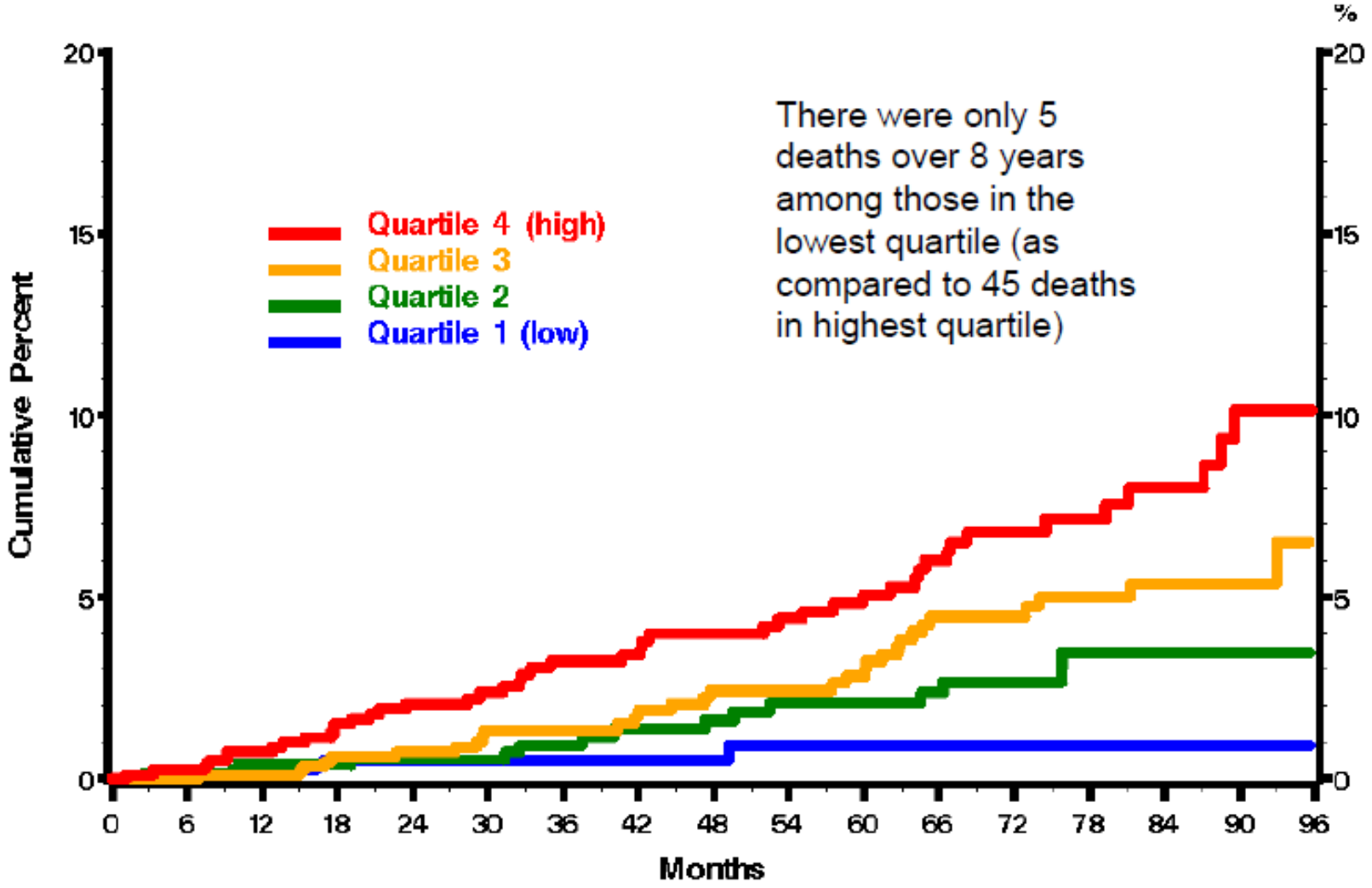
Inflammatory markers are higher in treated HIV disease compared with HIV seronegatives, adjusted for demographics and CV risk factors

SMART versus MESA



Neuhaus J, et al., JID, 2010. Abstract 740. (also see: French, JID, 2009)

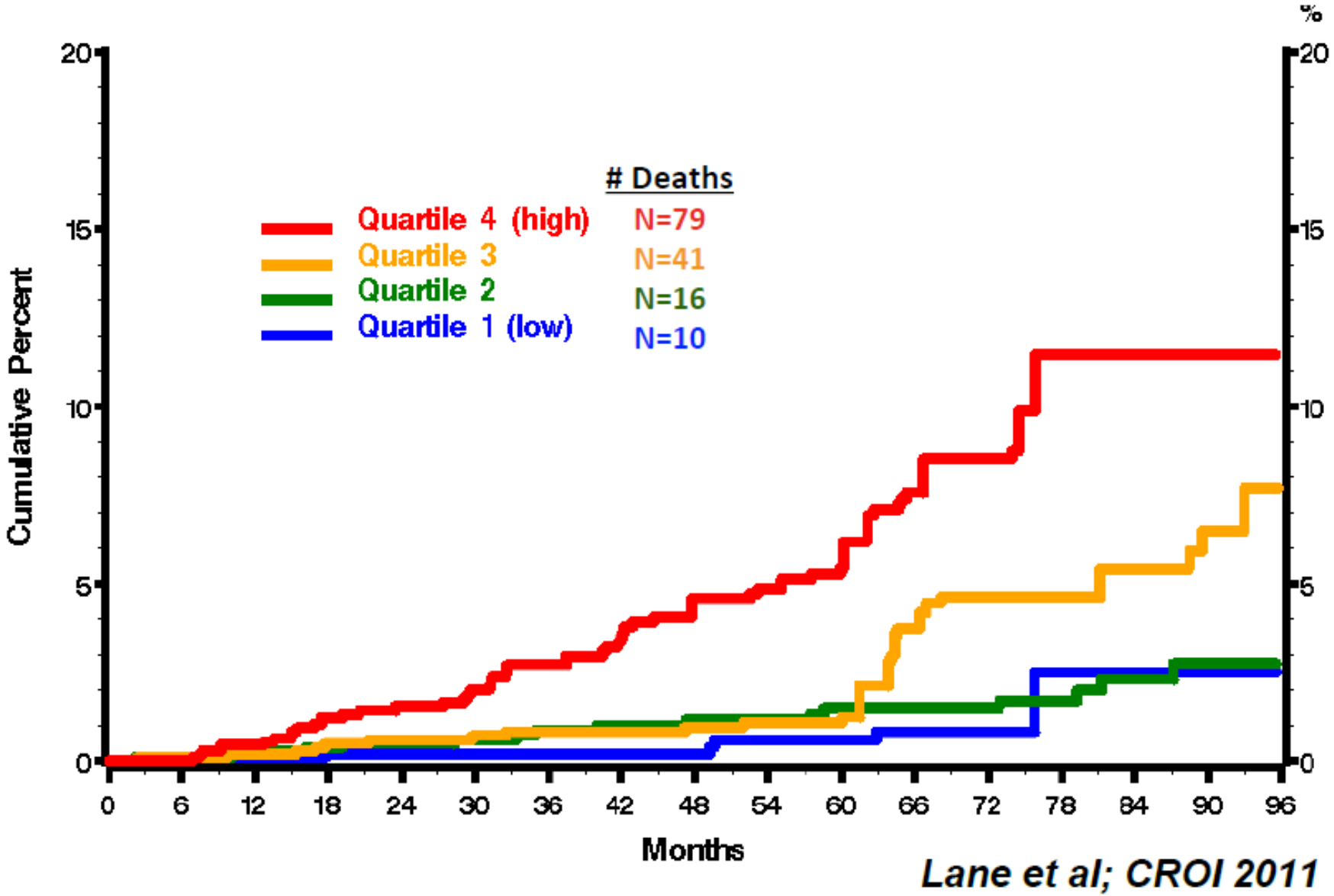
A single measurement of D-dimers predicts mortality through 8 years of observation, whereas effect wanes in 2-3 years in general population (SMART/ESPRIT; n=3227)



Lane et al; CROI 2011

Cumulative Deaths Over Time by IL-6 Quartile

SMART/ESPRIT control arms with HIV RNA <500 at entry (n=3227)



Lane et al; CROI 2011

Potential Determinants of Inflammation During ART

- HIV itself (passive release vs productive replication)
- Microbial Translocation
- Other co-infections

Differential Effects of HIV Type 1 Clade B and Clade C Tat Protein on Expression of Proinflammatory and Antiinflammatory Cytokines by Primary Monocytes

Gandhi et al., AIDS Res Hum Retroviruses. 2009 Jul;25(7):691-9

- Estimates suggest that of a total of about 46 million people infected with HIV-1, more than 56% of the infection is with clade C.

- Clade B and C exert differential effects on primary monocytes leading to differential gene expression and production of proinflammatory and antiinflammatory cytokines associated with neuropathogenesis.

- Tat B was more potent than Tat C in stimulating gene expression of proinflammatory cytokines TNF-a and IL-6 in a time- and dose-dependent manner by primary human monocyte cultures. (Clade B: Nord America, Europa, Medio Oriente, Asia dell'Est, America Latina, Clade C: Sud Africa, Asia del Sud, Etiopia)

- Antiinflammatory cytokine (IL-4 and IL-10) expression was upregulated by Tat C compared to Tat B.

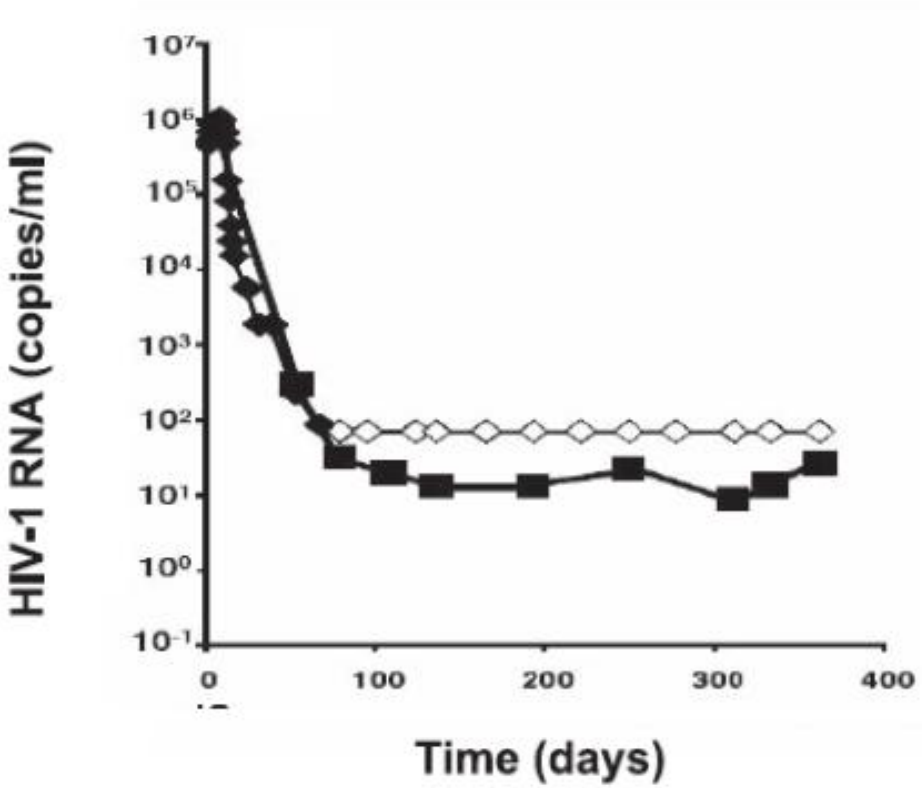
Gandhi et al., AIDS Res Hum Retroviruses. 2009 Jul;25(7):691-9

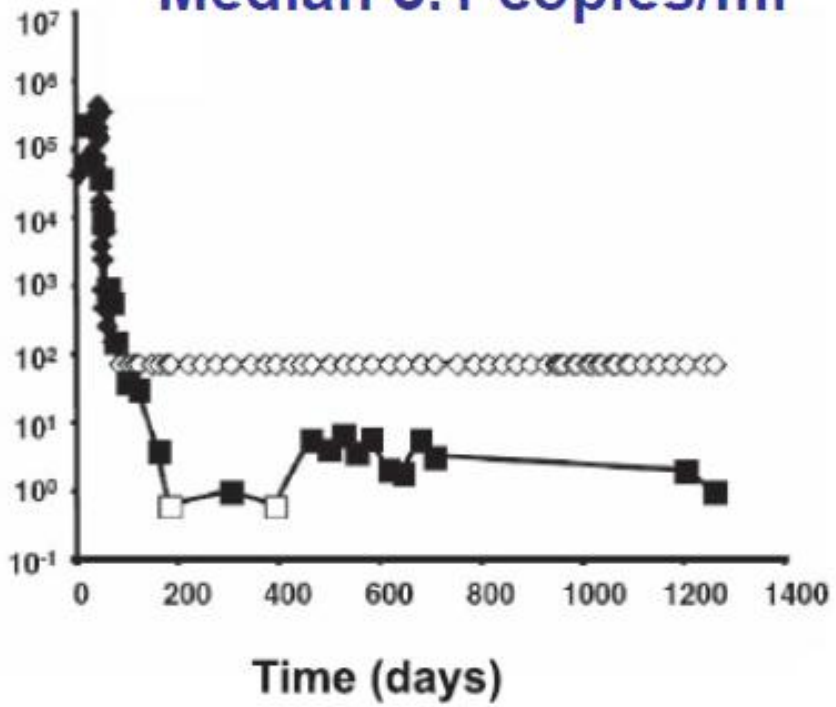
Low-level Viremia <75 copies/ml is Common During Apparent Viral Suppression on HAART

N=130

80% Patients had detectable viremia

Median 3.1 copies/ml





Maldarelli F. *et al., PLOS Path*, 2007; Palmer S. et al, *PNAS*, 2008.

Passive HIV release from infected cells?
or
Productive HIV Replication?

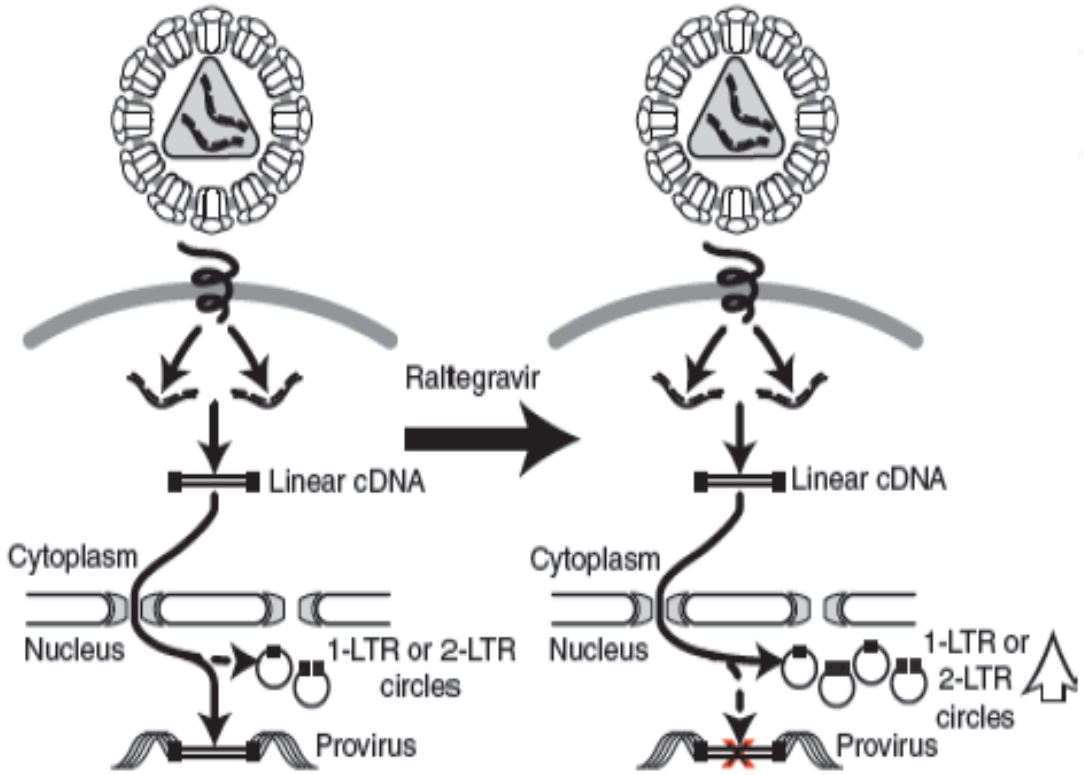
Intensifying ART with an additional agent might block the latter, but not the former.

Most ART intensification trials have NOT reduced low-level viremia or activation

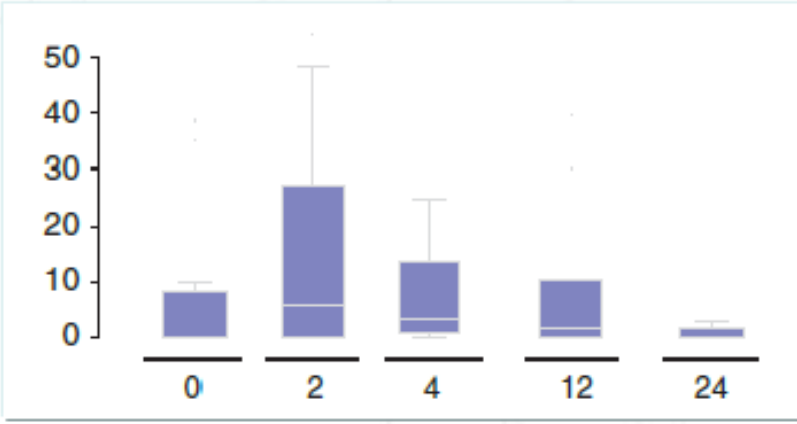
- LPV/r vs. EFV intensification (Dinoso, PNAS, 2009)
  - No decrease in extent of low-level viremia
- T20 intensification (Gandhi, CROI, 2009, Ab. 424)
  - No decrease in cell-associated HIV DNA levels
- RGV intensification (Maldarelli, CROI, 2009, Ab. 423b; Gandhi, 5th IAS, 2009, Ab. WELBB104; Hatano, CROI, 2010, Ab. 101)
  - No decrease in extent of low-level viremia or T cell activation
- RGV intensification (Buzon, Nature Medicine, 2010)
  - Transient increase in episomal HIV DNA in 1/3 patients with RGV
  - Decreased CD8 activation with intensification in this subgroup

Integrase Inhibitor Intensification Unmasks Low-level HIV Replication

RGV May Transiently ↑2-LTR Circles



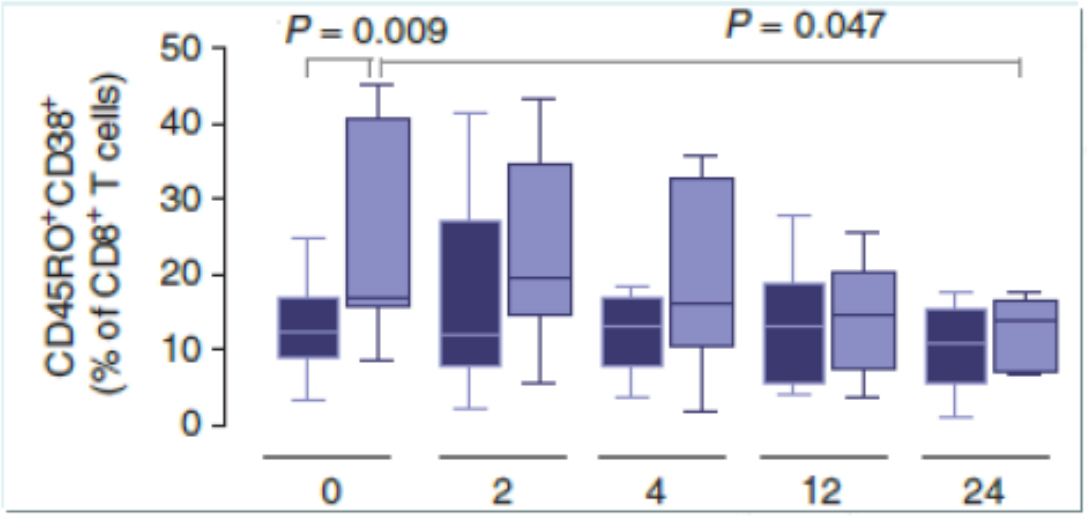
2-LTR circles during RGV Intensification



[1]Buzon M, et al. *Nature Medicine*. 2010; 16(4): 460-465; [2]Llibre J. *Antiviral Therapy, 2011;*

Integrase Inhibitor Intensification Unmasks Low-level HIV Replication

Wk24 Δ CD8 Activation

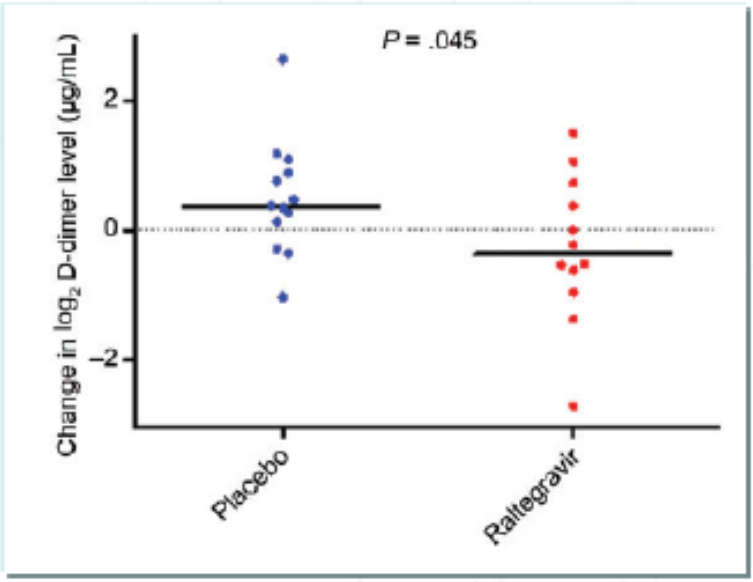


Week of RGV intensification

Light blue: +2-LTR circle increase

Dark blue: No 2-LTR circle increase

Wk24 Δ D-dimer



[1]Buzon M, et al. *Nature Medicine*. 2010; 16(4): 460-46 [3]Hatano H, et al. JID, 2013

HAART can halt ongoing replication, memory CD4 T cells harboring replication-competent HIV-1 provirus can still produce progeny virus after reactivation. Thus, the latent reservoir likely contributes to the residual viremia in patients on HAART.

That a major part of free plasma virus may be derived from some as of yet unidentified cellular source has several important clinical implications with respect to HAART regimen management, virologic failure, rebound viremia associated with treatment interruption, and strategies aimed at eradication

Brennan P.T., J.Vir, 2009

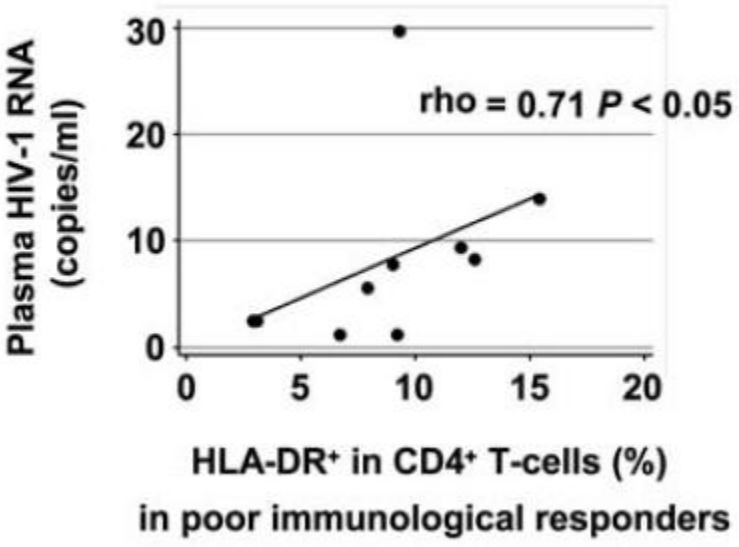
OPEN ACCESS Freely available online

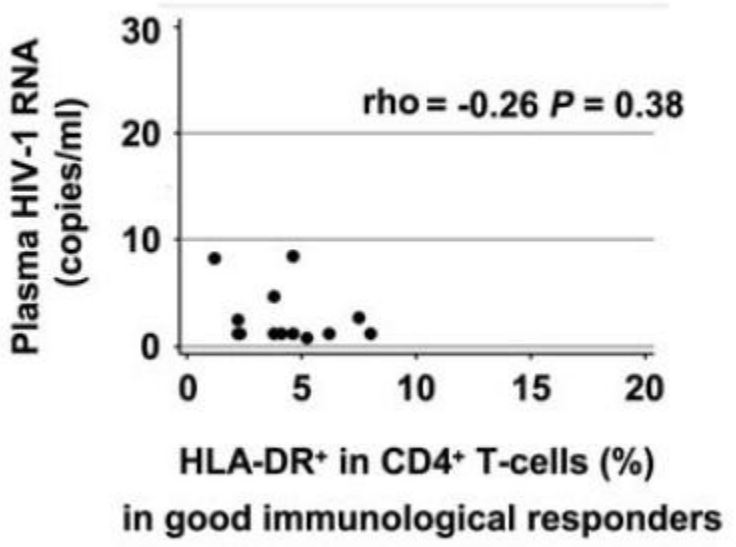
PLoS one

HIV-1 Residual Viremia Correlates with Persistent T-Cell Activation in Poor Immunological Responders to Combination Antiretroviral Therapy

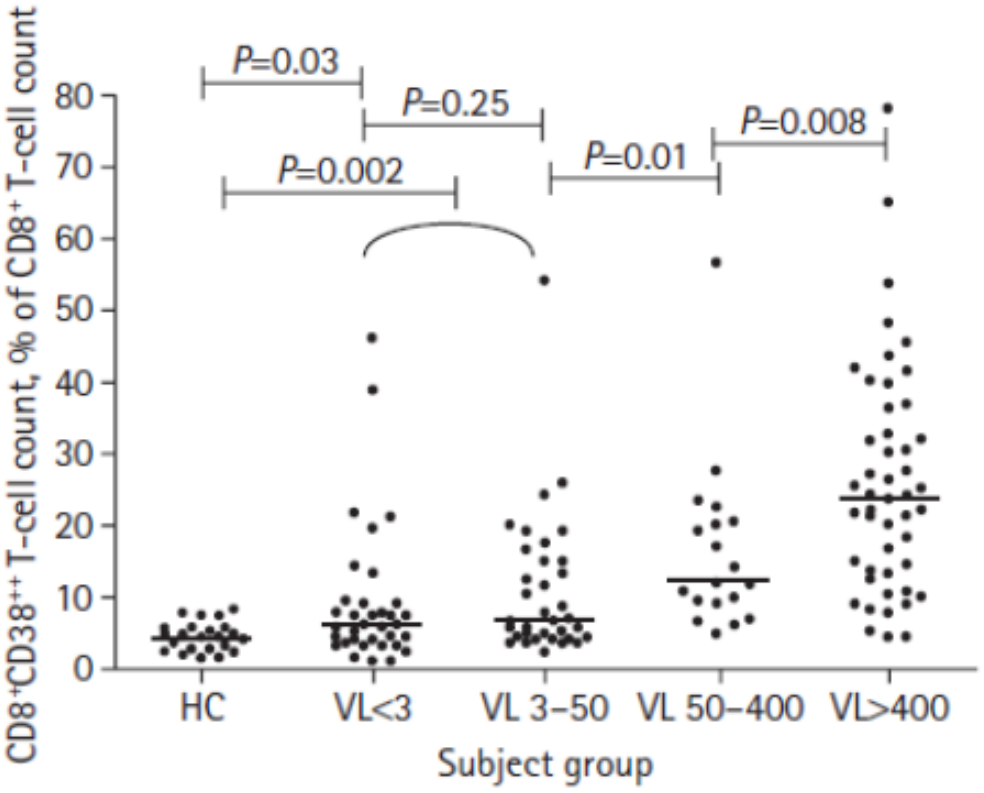
Maud Mavigner[1], Pierre Delobel[1,2,3], Michelle Cazabat[1,4], Martine Dubois[1,4], Fatima-Ezzahra L'Faqihi-Olive[1], Stéphanie Raymond[1,2,4], Christophe Pasquier[1,2,4], Bruno Marchou[2,3], Patrice Massip[2,3], Jacques Izopet[1,2,4]*

1 INSERM, U563, Toulouse, France, **2** Université Toulouse III Paul-Sabatier, Centre de Physiopathologie de Toulouse Purpan, Toulouse, France, **3** CHU Toulouse, Hôpital Purpan, Service des Maladies Infectieuses et Tropicales, Toulouse, France, **4** CHU Toulouse, Hôpital Purpan, Laboratoire de Virologie, Toulouse, France





Extent of Low-level Viremia Not a Strong Predictor of T cell Activaton



Low-level viremia may be associated with ↑

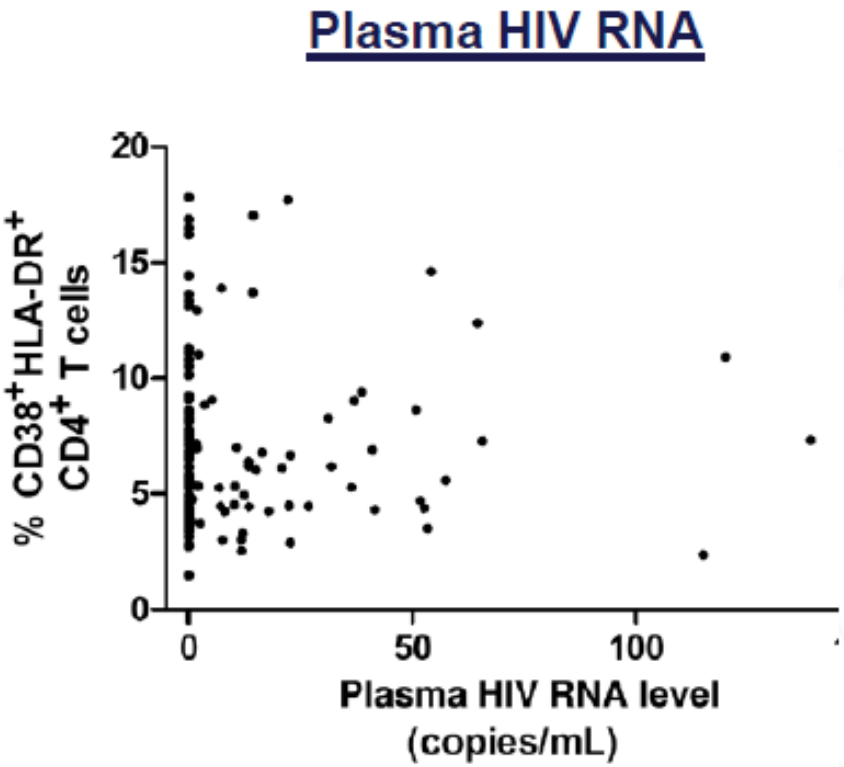
- sTNF-RII
- B2 microglobulin

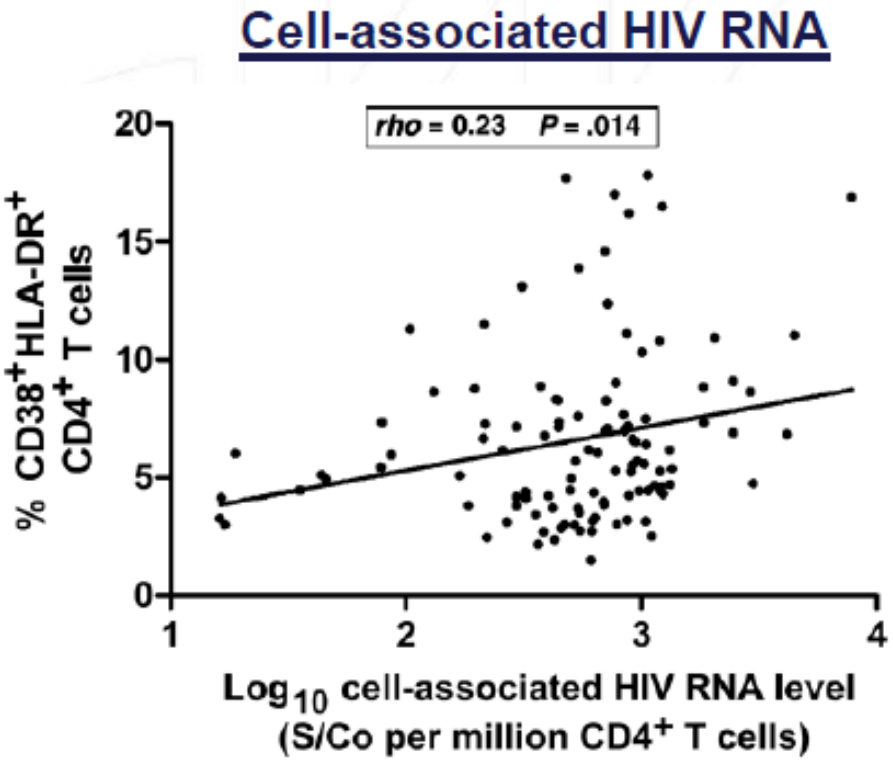
(*Ostrowski, Scand J Imm, 2008)

*small N…

Steel/Kelleher, Antiviral Ther, 2007

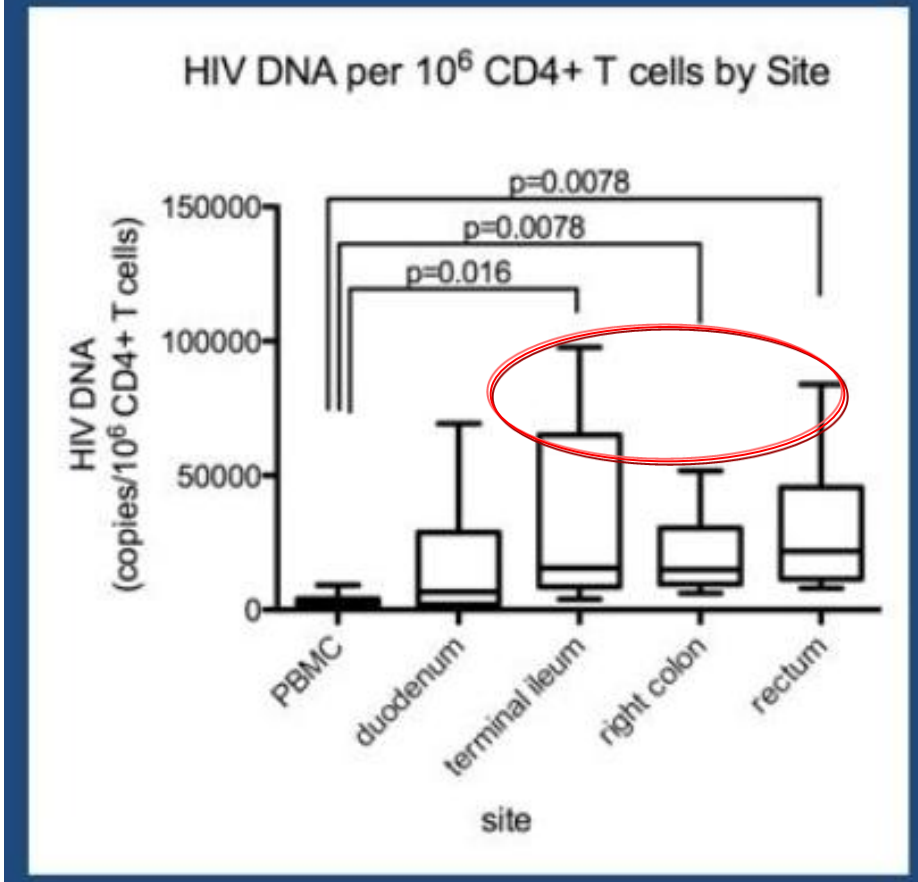
Cell-associated Measures of HIV Persistence More Strongly Correlated with Immune Activation





Hatano, JID, 2013

The frequency of infected cells (DNA, unspliced RNA) is higher in gut than in blood



HIV DNA is 3 to 9 times higher in the gut

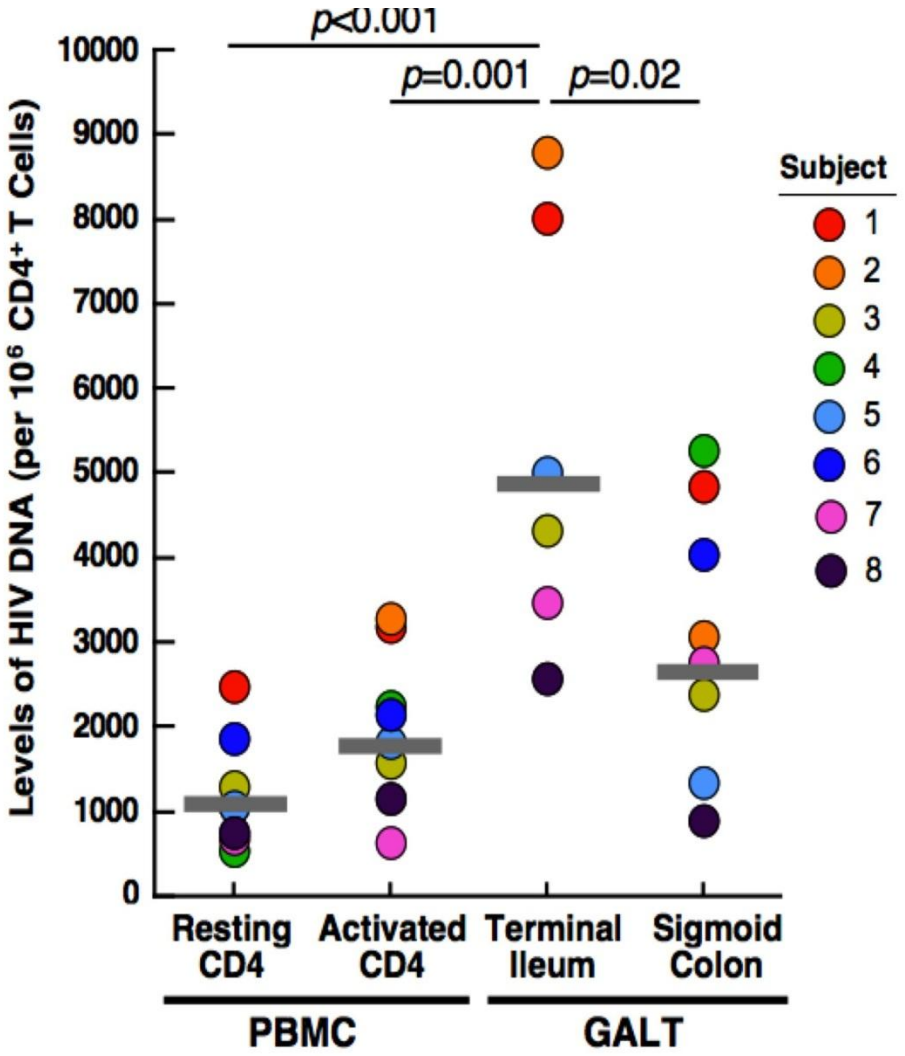
Estimates of gut HIV reservoir:

83 to >95% of all infected cells in body

1 x 10^9 infected CD4+ T cells

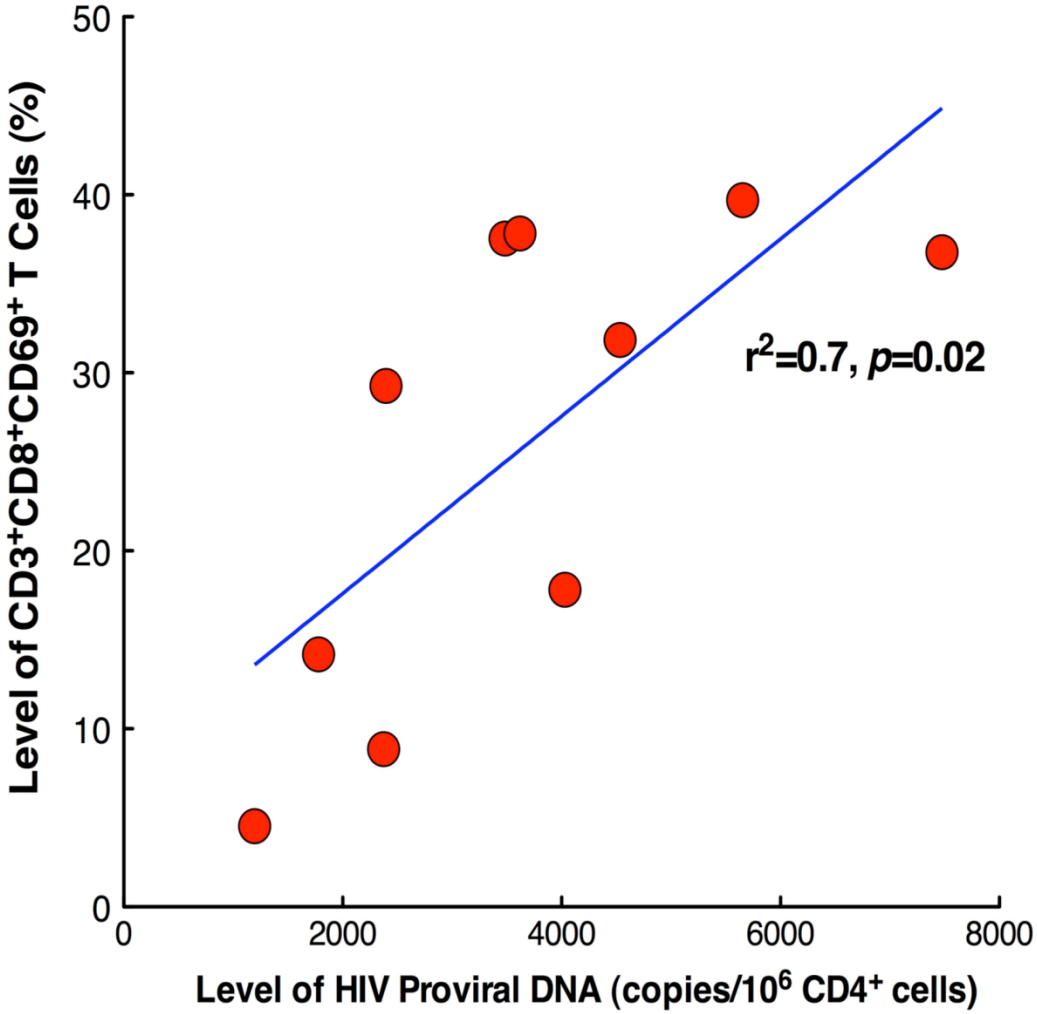
Yukl et al, JID 2010

HIV during HAART is preferentially found in activated cells within the gut, particularly ileum



Chun et al., J Infect Dis.,197:714-20, 2008

The Size of HIV Reservoir is Predicted by the Level of Activated CD8+ T cells (in Sigmoid Colon)

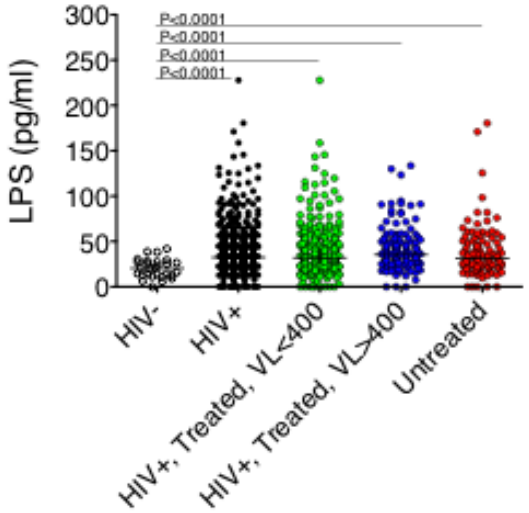


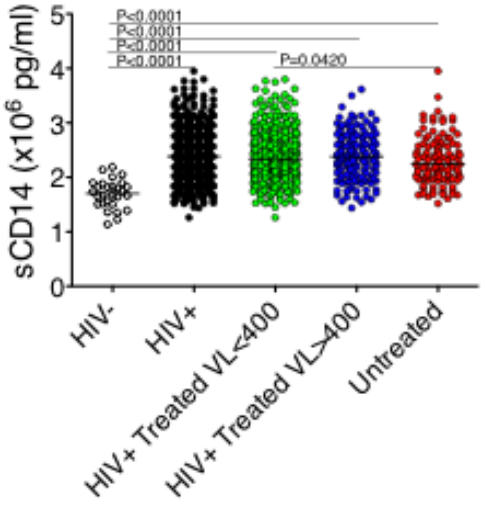
Sheth et al., *Mucosal* Immunology, 1: 382–388, 2008

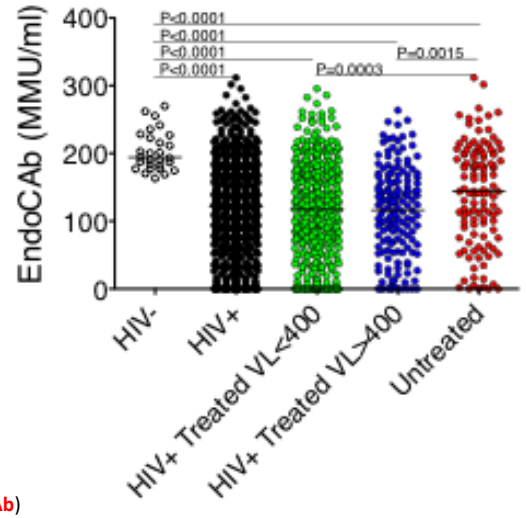
Potential Determinants of Inflammation During ART

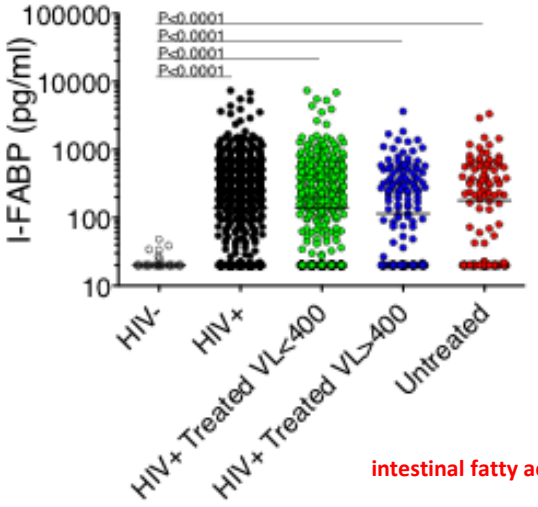
- HIV itself (passive release vs productive replication)
- Microbial Translocation
- Other co-infections

Microbial Translocation and Enterocyte Damage









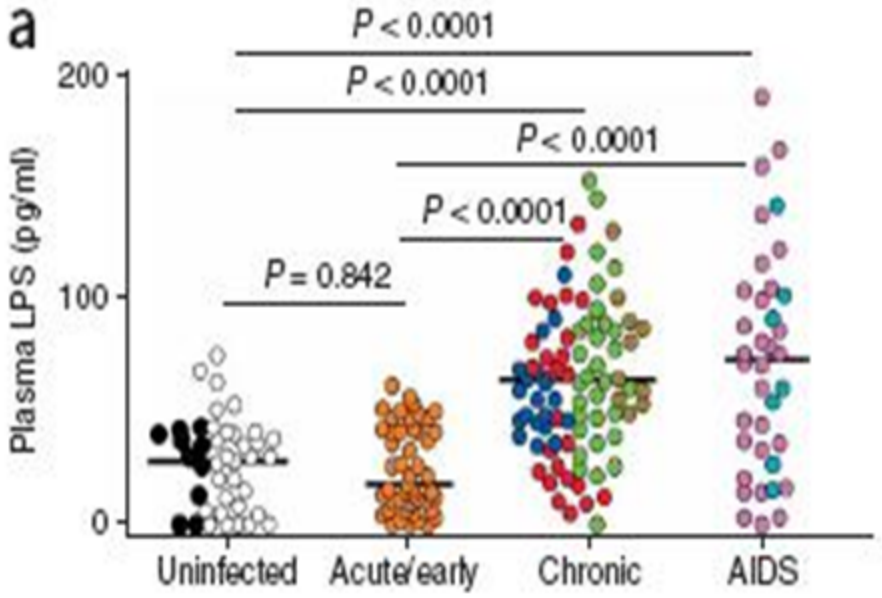
ENDOTOXIN-CORE ANTIBODY (EndoCAb)

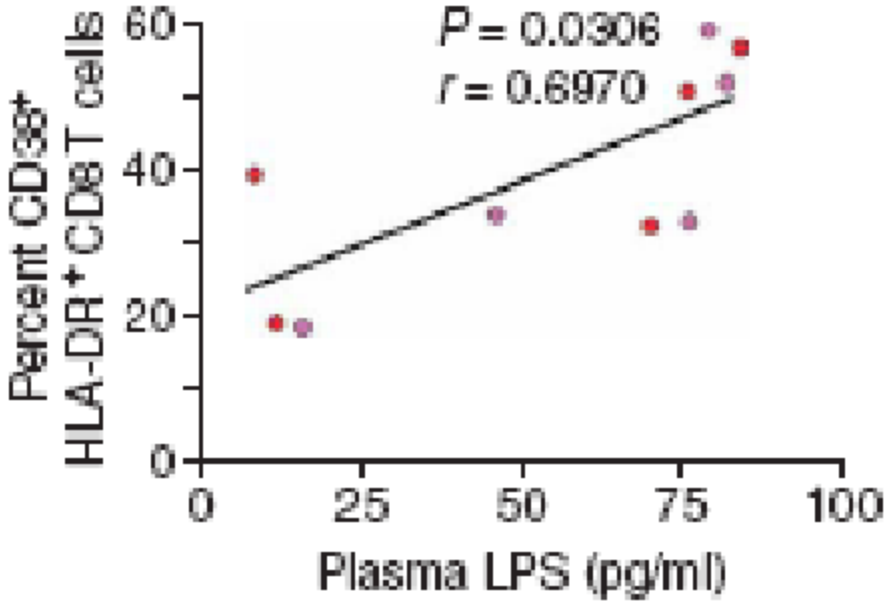
intestinal fatty acid binding protein (I-FABP)

Biomarkers indicate microbial translocation, LPS bioactivity and enterocyte damage in treated and untreated subjects

Mucosal Translocation of Bacterial Products

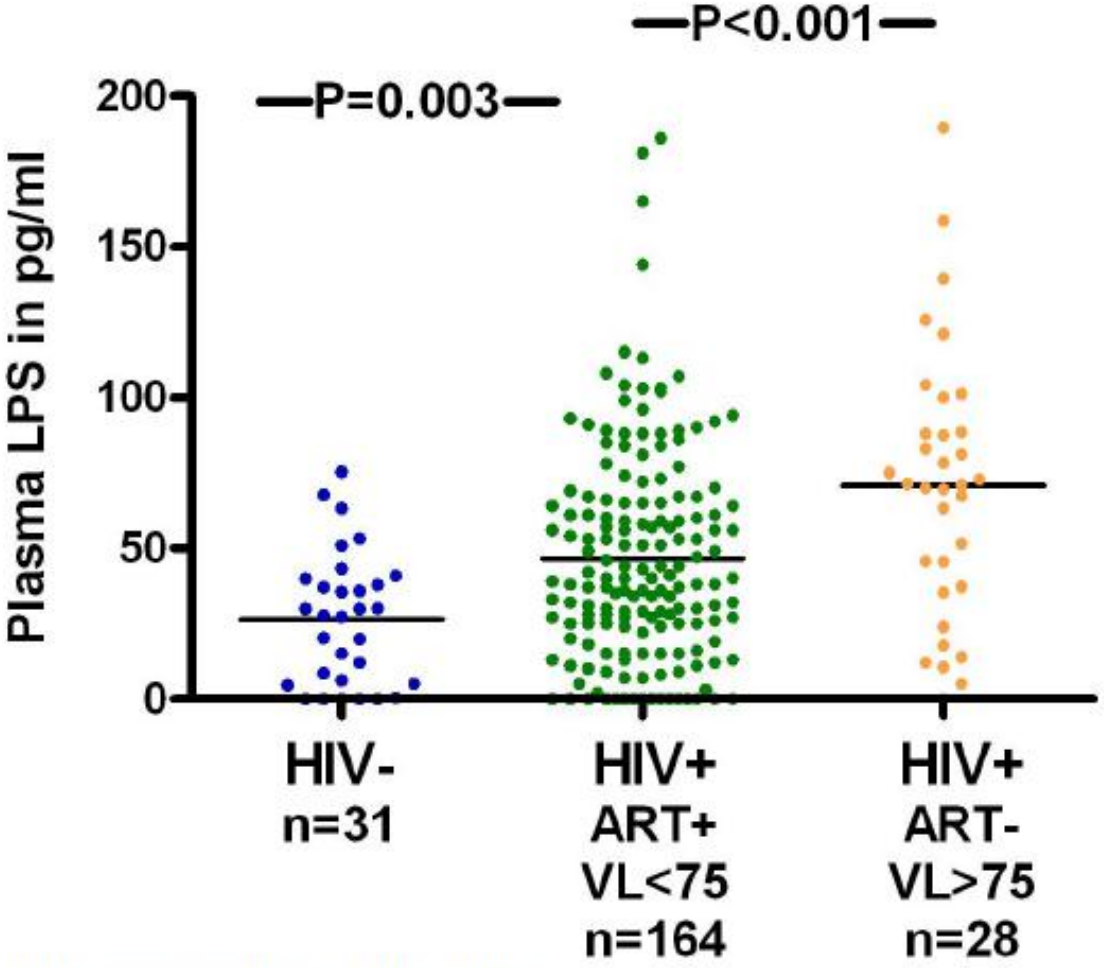
A potential cause of T cell activation in HIV





Brenchley et al, Nat Med, 2006

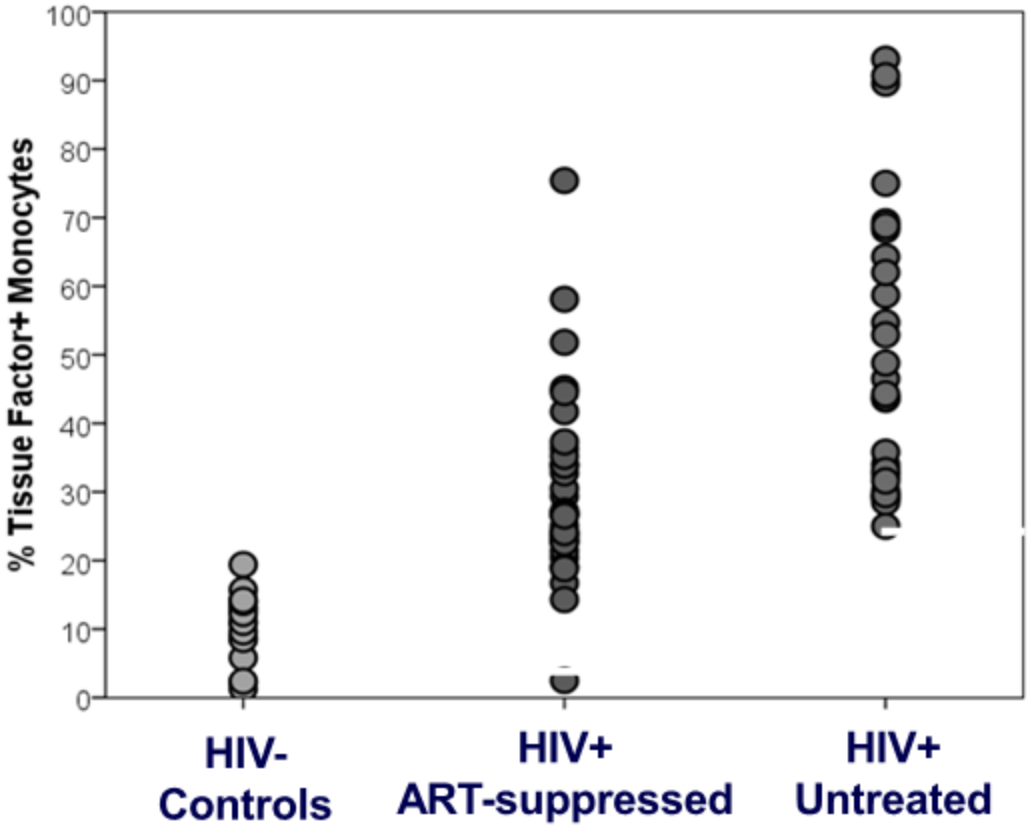
Microbial Translocation Decreases with Suppressive ART but Persists for Years



Jiang et al, JID, 2009 (also Marchetti, AIDS, 2008)

Microbial Translocation May Drive Tissue Factor Expression in HIV

Potential Mechanism for CAD Risk



- Tissue Factor expression induced by LPS *in vitro*
- *In vivo*, associated with:
  - sCD14 (marker of microbial translocation)
  - % activated CD8+ T cells
  - D-Dimer levels

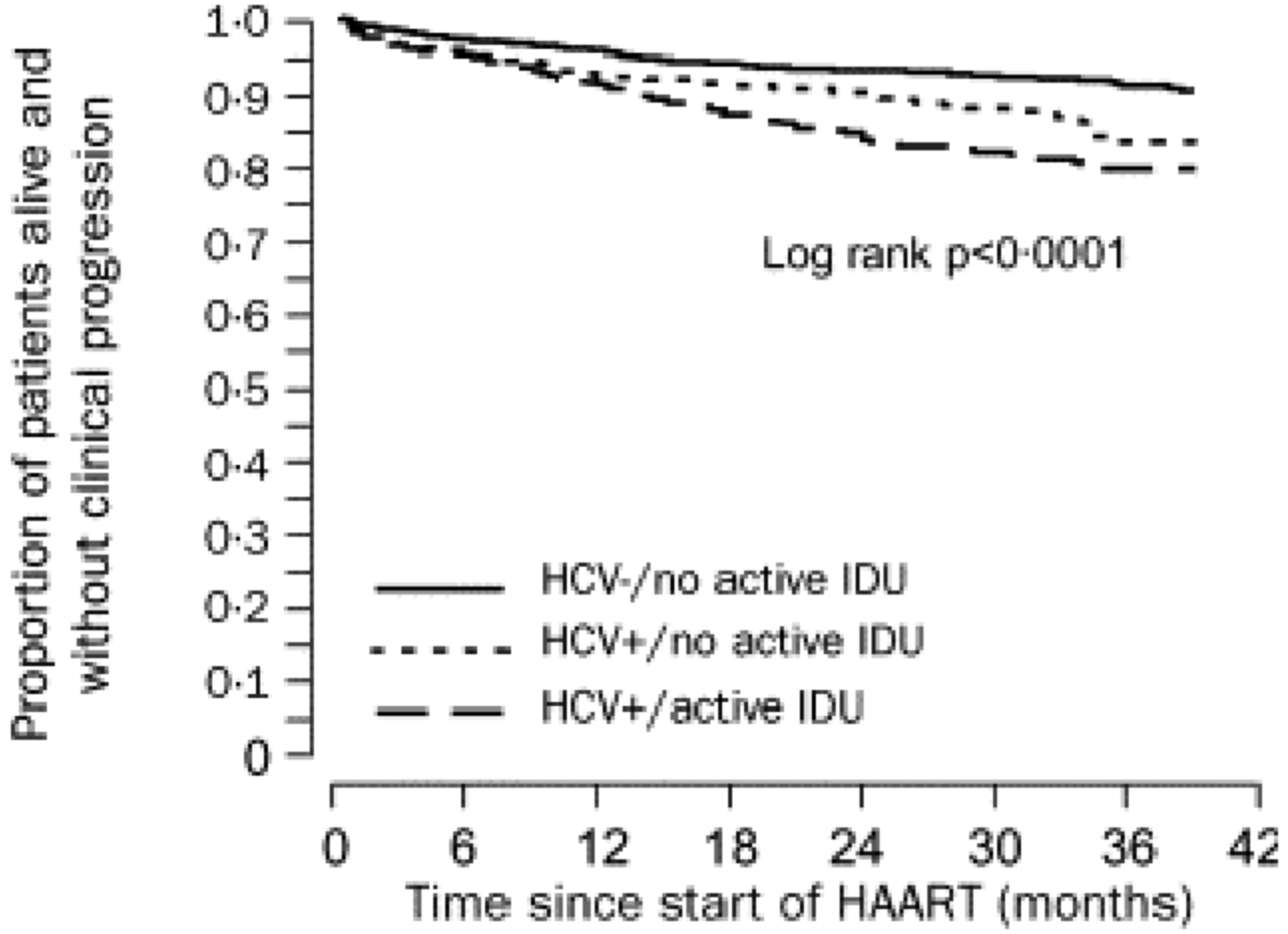
monocytes expressing cell surface tissue factor

Funderburg, Blood, 2009

Potential Determinants of Inflammation During ART?

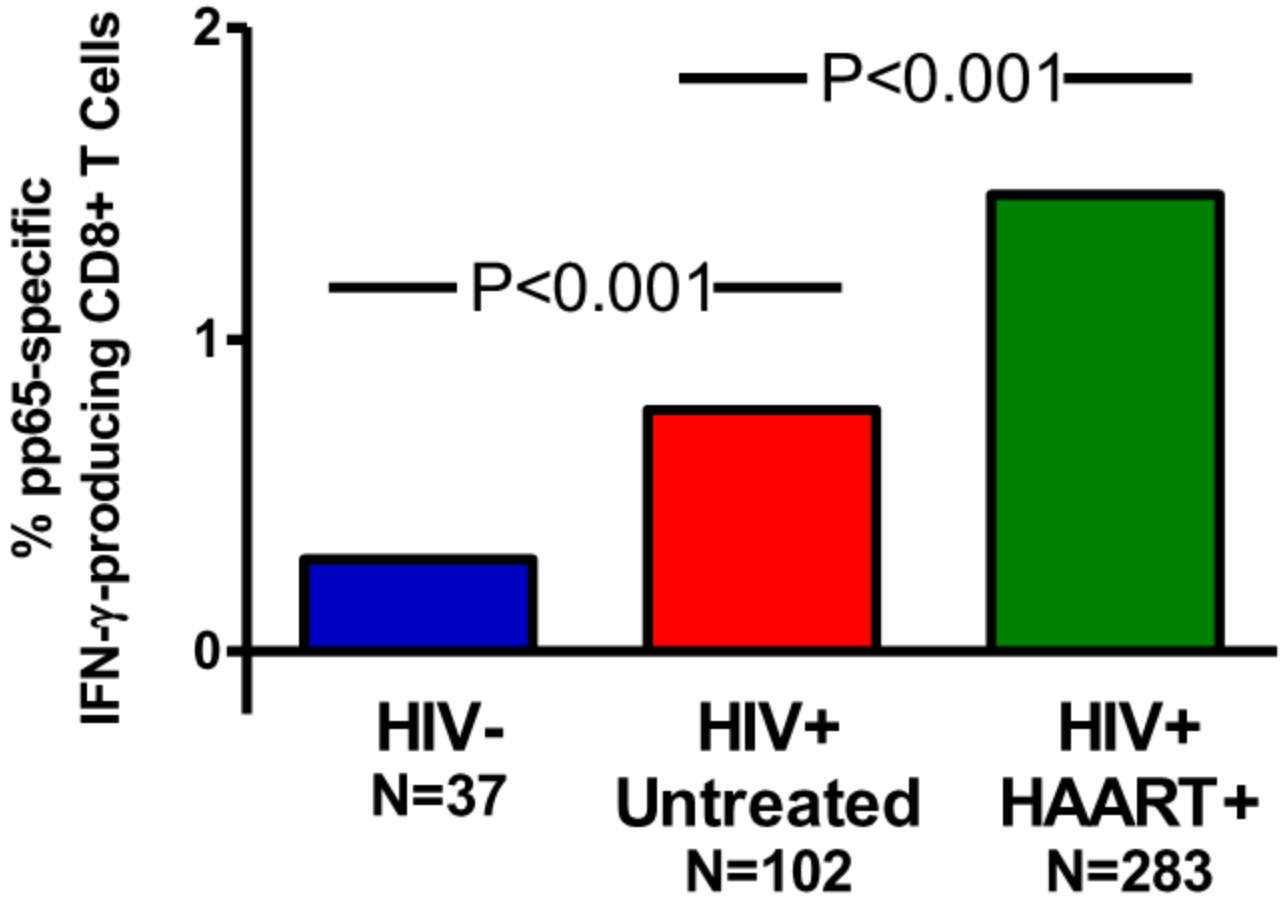
- HIV itself (passive release vs productive replication)
- Microbial Translocation
- Other co-infections
- Accumulation of senescent cells

HCV Associated with Progression to AIDS/Death During HAART



Greub, Lancet, 2000 (see also Kovacs, JID, 2010)

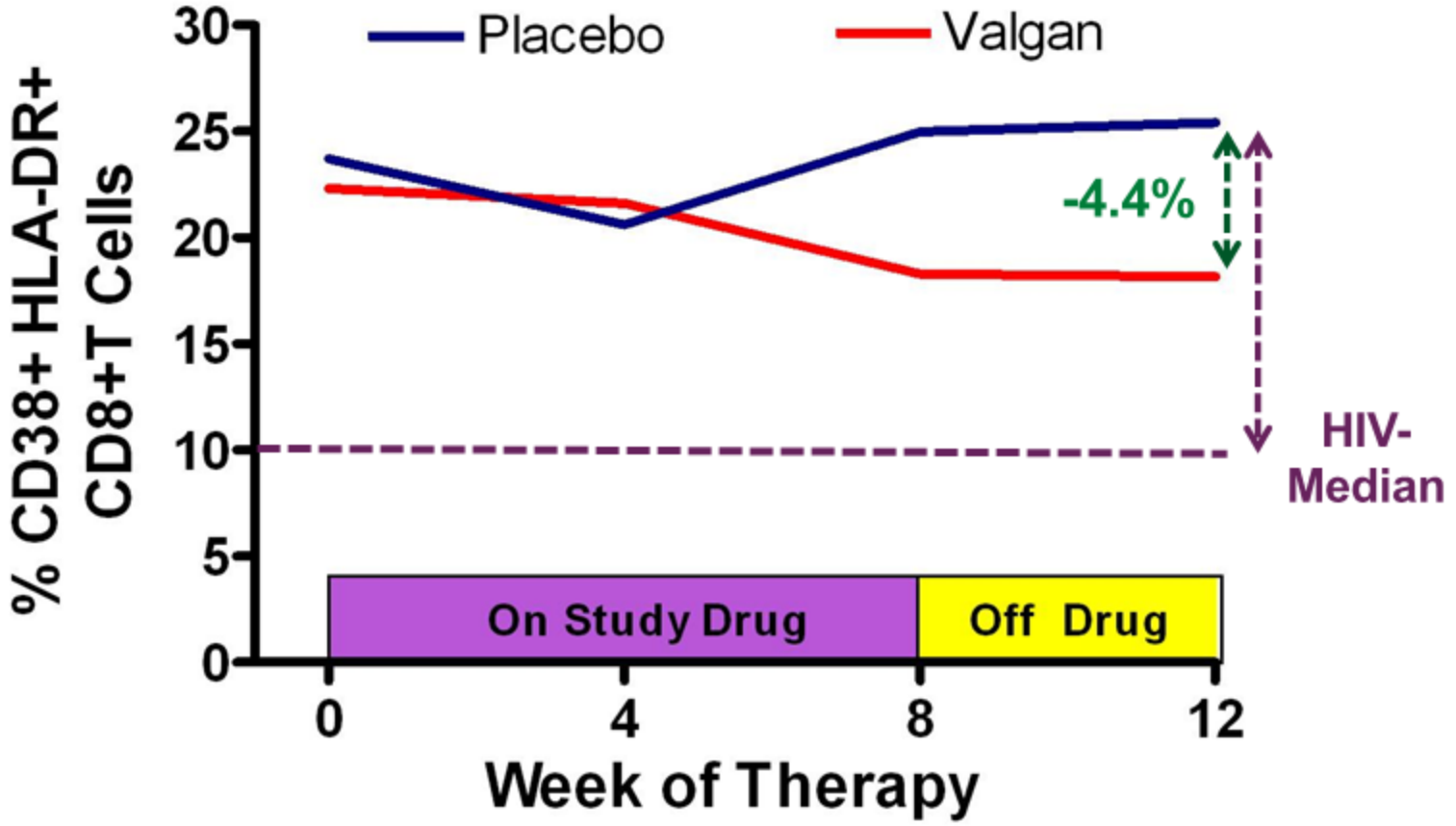
CMV-specific T Cell Responses are Higher in HIV-infected Patients



Naeger et al, PLoS One 2010

Decreasing Asymptomatic CMV Replication with Valganciclovir Decreases Immune Activation

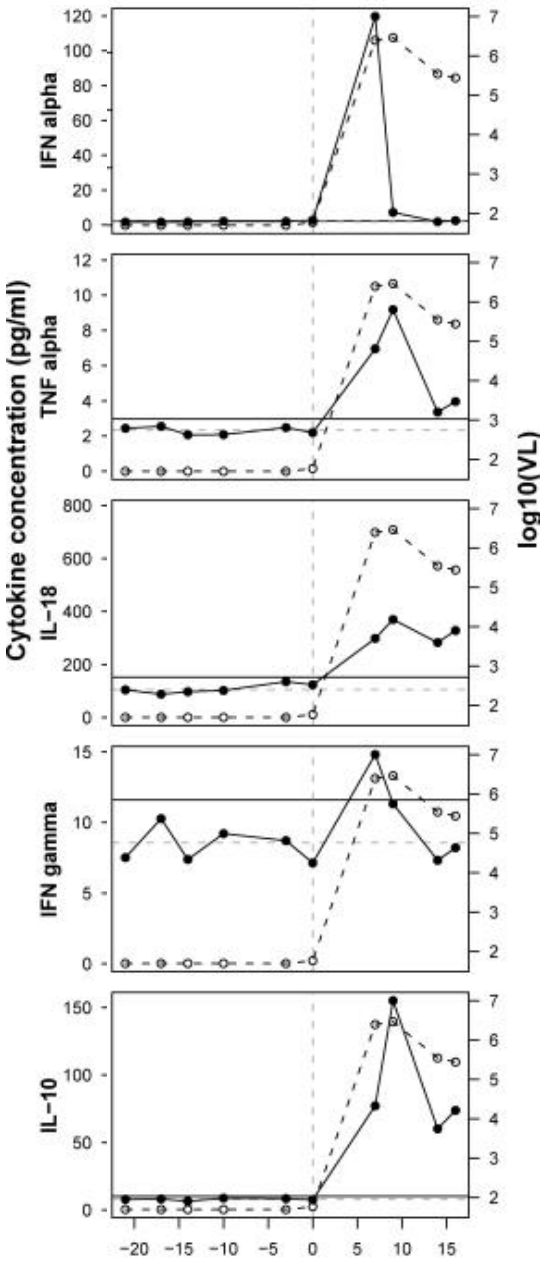
in HIV+ Patients with CD4<350 despite ART



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

Hunt et al, CROI, 2010

Immune Activation Occurs Very Early



○ Virus load

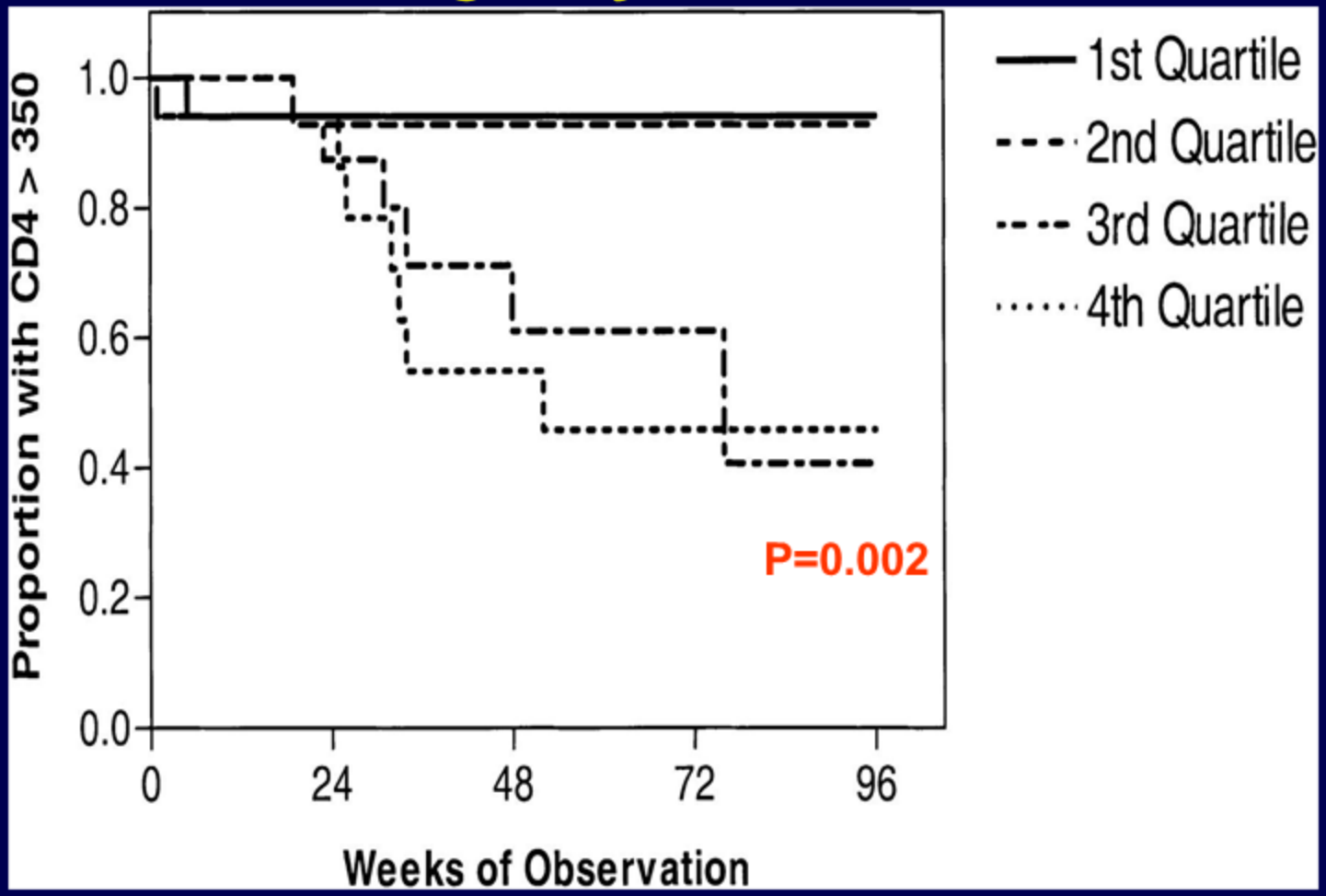
● Cytokine

A.R. Stacey et al JV 2009

‘Normal’ innate response to viral infection in the acute phase of the infection

High CD8+ T cell Activation Set-point Associated with Rapid CD4 Decline

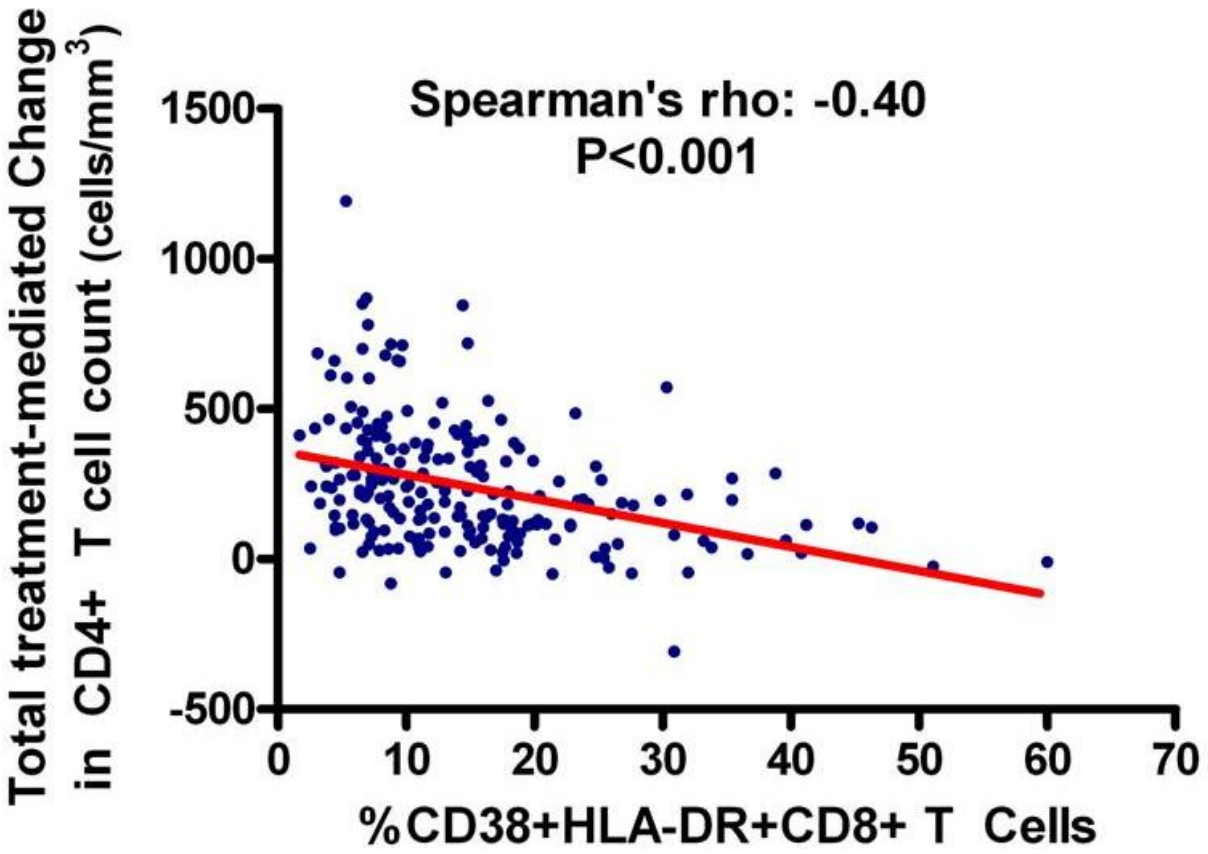
During Early HIV Infection



Independent of plasma HIV RNA Levels

Deeks, Blood, 2004

ART, Immune Activation and CD4 T Cell Recovery

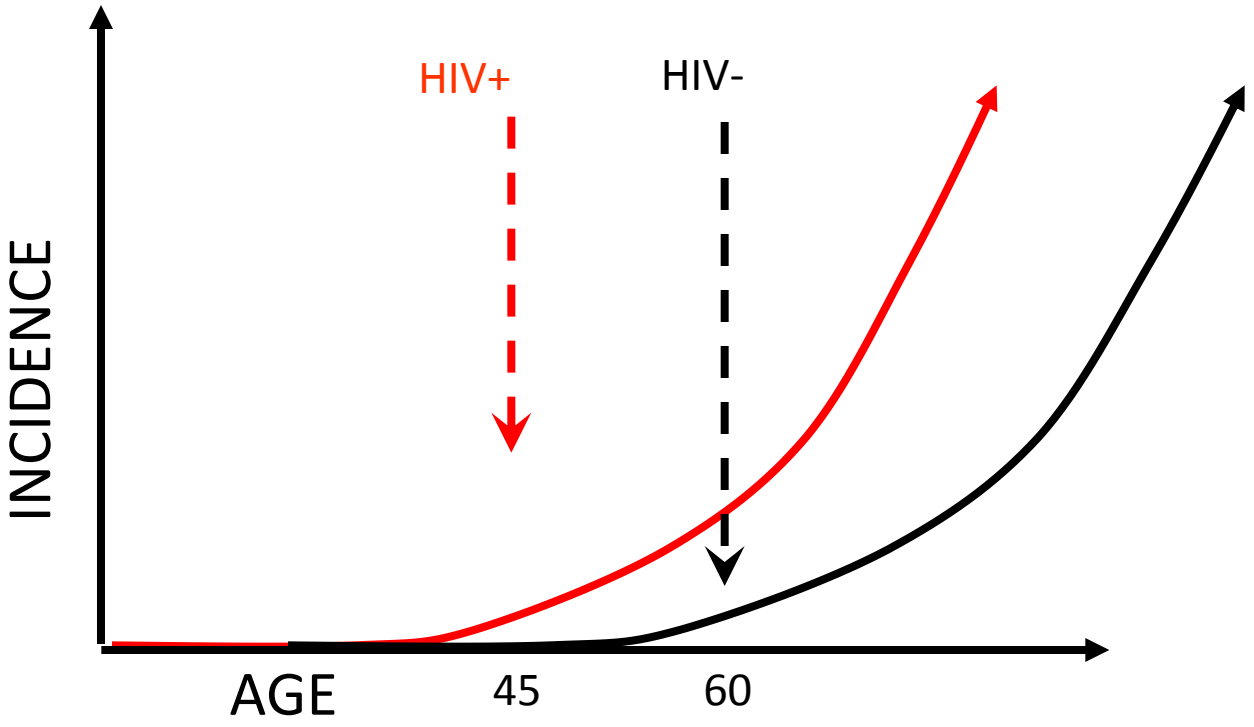


Hunt, et al. J Infect Dis. 2003 and unpublished observations

Reduced CD4 T cell recovery associated with immune activation

- **Ongoing immune activation and inflammation due to constant stimulation by HIV or other chronic infections accelerates the process of T-cell exhaustion that occurs during the normal course of aging. T-cell homeostasis—the balance between cell production and cell death—may also be disrupted by changes in cytokine levels and premature CD4 and CD8 cell apoptosis.**
- Middle-aged people with HIV show evidence of immunosenescence resembling that of HIV negative individuals two decades older. This includes low naive-to-memory cell ratio, reversal of the normal CD4-to-CD8 cell ratio, reduced T-cell proliferation, more cells with apoptosis markers, and more exhausted immune cells expressing CD57 without CD28. Once it occurs, T-cell senescence fails to normalize even with suppressive ART.

- In the age of HAART, now that we can fully suppress virus, morbidity and mortality from 'inflammatory diseases' may be the greatest impediment to achieving full health
- Inflammatory disease can accelerate the ageing process in HIV

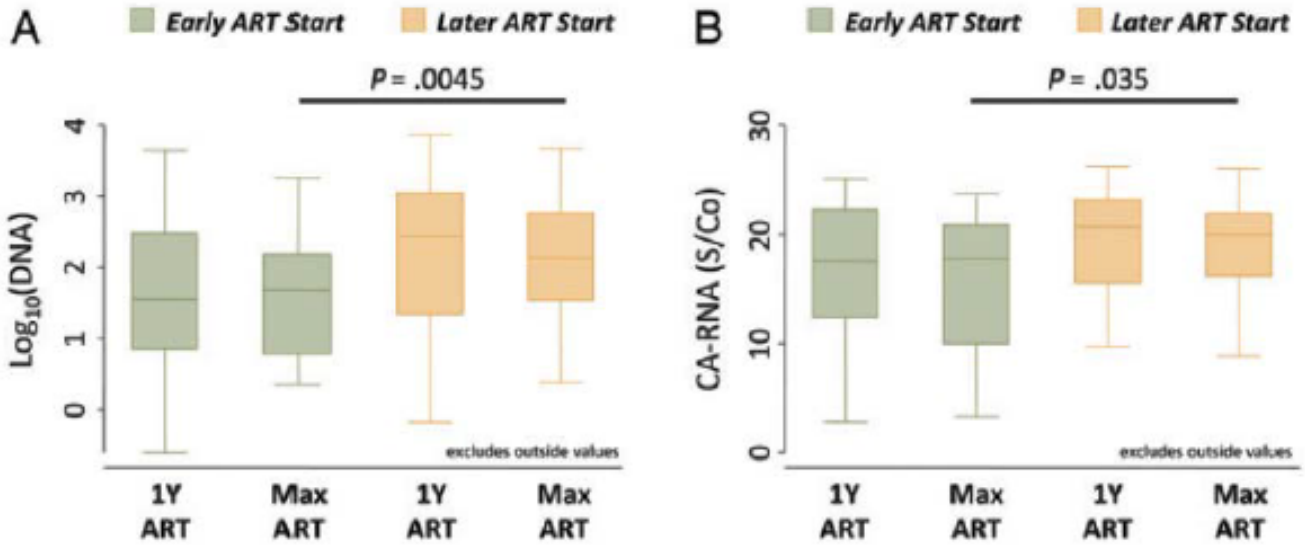


Antiretroviral Therapy Initiated Within 6 Months of HIV Infection Is Associated With Lower T-Cell Activation and Smaller HIV Reservoir Size

2013:208 (15 October) 1202-11

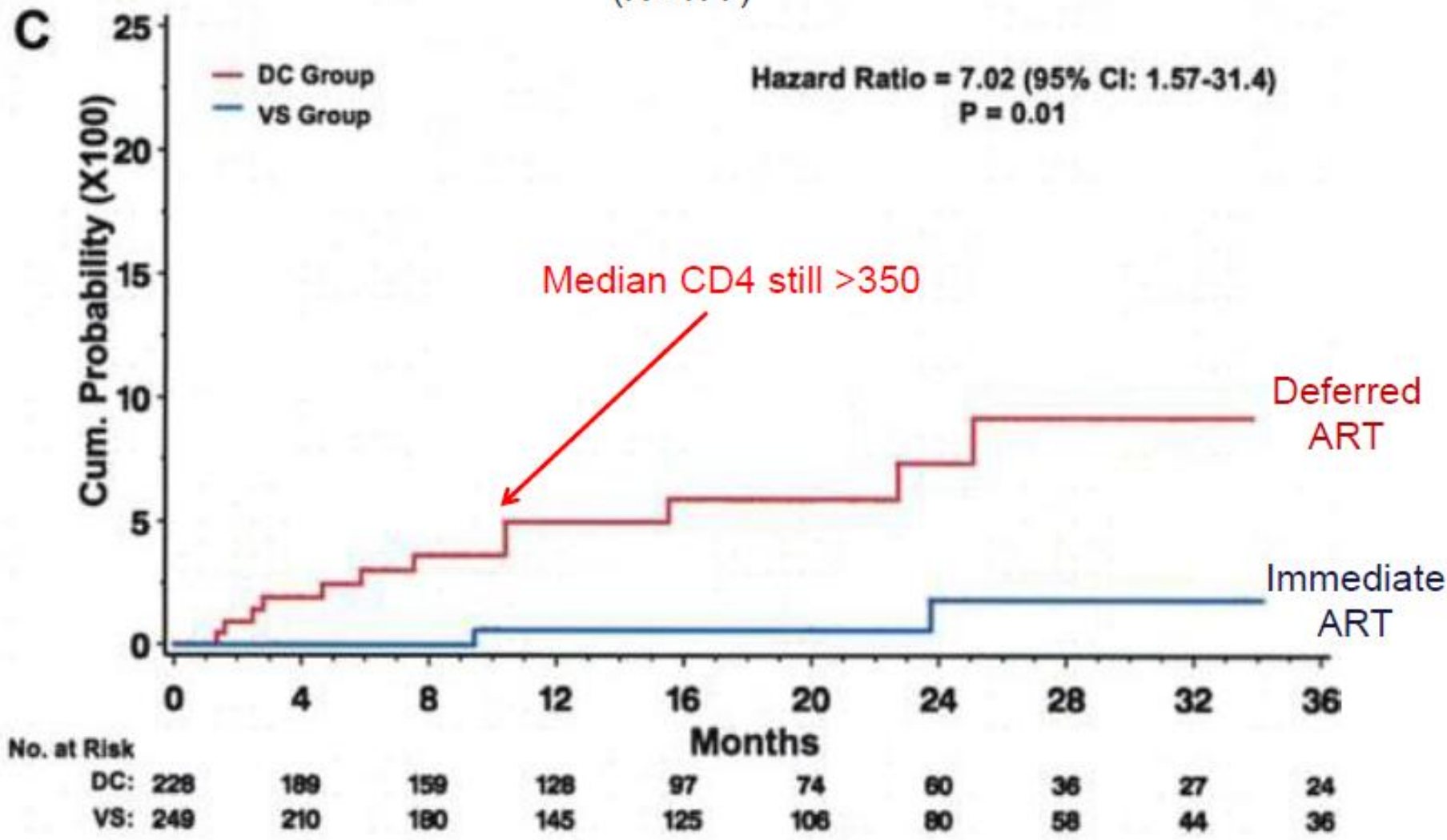
Vivek Jain,[1] Wendy Hartogensis,[1] Peter Bacchetti,[2] Peter W. Hunt,[1] Hiroyu Hatano,[1] Elizabeth Sinclair,[3] Lorrie Epling,[3] Tzong-Hae Lee,[4] Michael P. Busch,[4] Joseph M. McCune,[3] Christopher D. Pilcher,[1] Frederick M. Hecht,[1] and Steven G. Deeks[1]

ART initiation <6 months after infection is associated with lower levels HIV-DNA and cell-associated RNA levels



Higher Risk of Serious non-AIDS events and Death with Deferring ART to CD4 <350 in SMART

(N=477)



(See also: Kitahata, NEJM, 2009; Sterne, Lancet, 2009)

Emery, JID, 2008

Summary

- Inflammation and immune activation are important determinant of HIV pathogenesis
- Abnormal inflammation and immune activation persist during “suppressive” HAART and may contribute to morbidity/mortality also with immunosenescence.
- Starting ART earlier in the course of HIV infection *likely decreases this risk.*
- Novel interventions being studied to decrease immune activation from HIV, microbial translocation, and co-infections.