Immune Regulation and T Cell Activation in HIV Disease

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Learning Objectives

- To appraise:
  - Role of immune activation in HIV pathogenesis
  - Persistence of immune activation despite ART-mediated viral suppression
  - Relationship between immune activation and non-AIDS-associated co-morbidities
  - Potential therapeutic strategies / targets in this setting.
- To review the biology of immune reconstitution inflammatory syndromes during ART

Off Label Disclosure

This presentation will not discuss any non-FDA-approved or investigational uses of any products/devices.

Why is systemic immune activation bad for you in HIV infection?

An Important Clue from Nature

Sooty Mangabey

- Infect with SIV
- High Levels of Viral Replication
- **No AIDS, normal lifespan**
- ***Minimal* Immune Activation**

Rhesus Macaque

- Infect with SIV
- High Levels of Viral Replication
- **AIDS and death**
- ***Massive* Immune Activation**

Silvestri, Immunity, 2003

What do we know about immune activation in HIV-infected people?

The NEW ENGLAND JOURNAL of MEDICINE Dec 10, 1981

Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency

MS Gottlieb, R Schroff, HM Schanker, JD Weisman, PT Fan, RA Wolf, and A Saxon

An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction

H Masur, MA Michelis, JB Greene, I Onorato, RA Stouwe, RS Holzman, G Wormser, L Brettman, M Lange, HW Murray, and S Cunningham-Rundles

Table 3. Characterization of T-Lymphocyte Subsets.

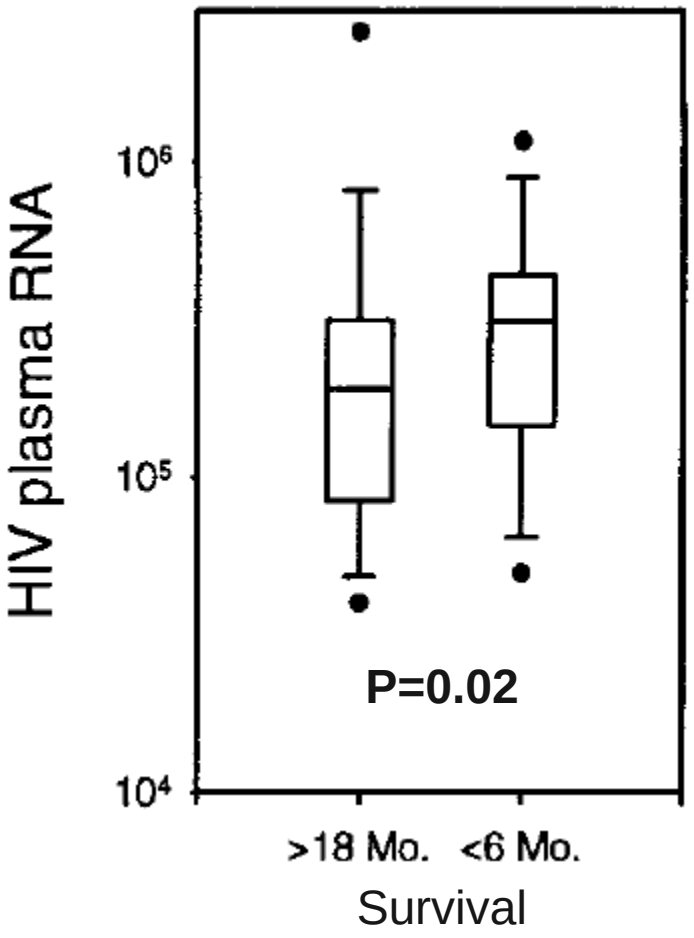
Group	Lymphocyte Subset				Leu 3/ Leu 2 Ratio
	Leu 1	Leu 2	Leu 3	T10	
	per cent lymphocytes reactive with monoclonal antibodies				
Patients					
1	45	57	0	59	0
2	47	52	0	59	0
3	49	57	10	79	0.18
4	67	47	2	81	0.04
Mean ±S.D.	52 * ±10.1	53.3 † ±4.7	3.0 † ±4.76	69.5 † ±12.1	0.05 ±0.08 *
Normal subjects (n = 16 [mean ±S.D.])	71.0 ±10.0	28.0 ±8.0	46.0 ±12.0	15.0 ±6.6	1.6 ±0.74

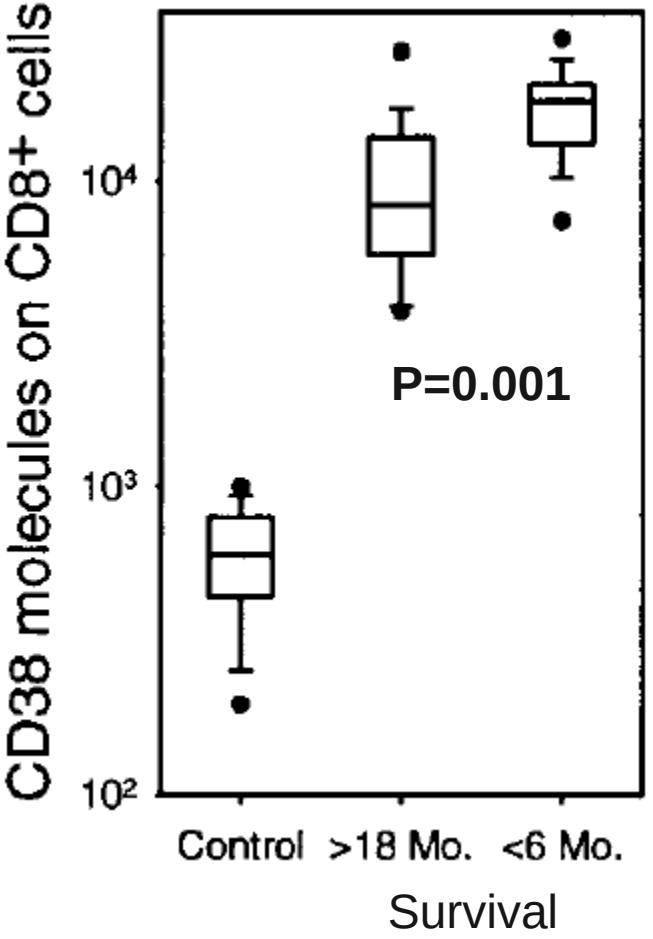
Leu3=CD4

T10=CD38

Immune activation predicts HIV disease progression better than VL

in patients with AIDS (CD4<200)



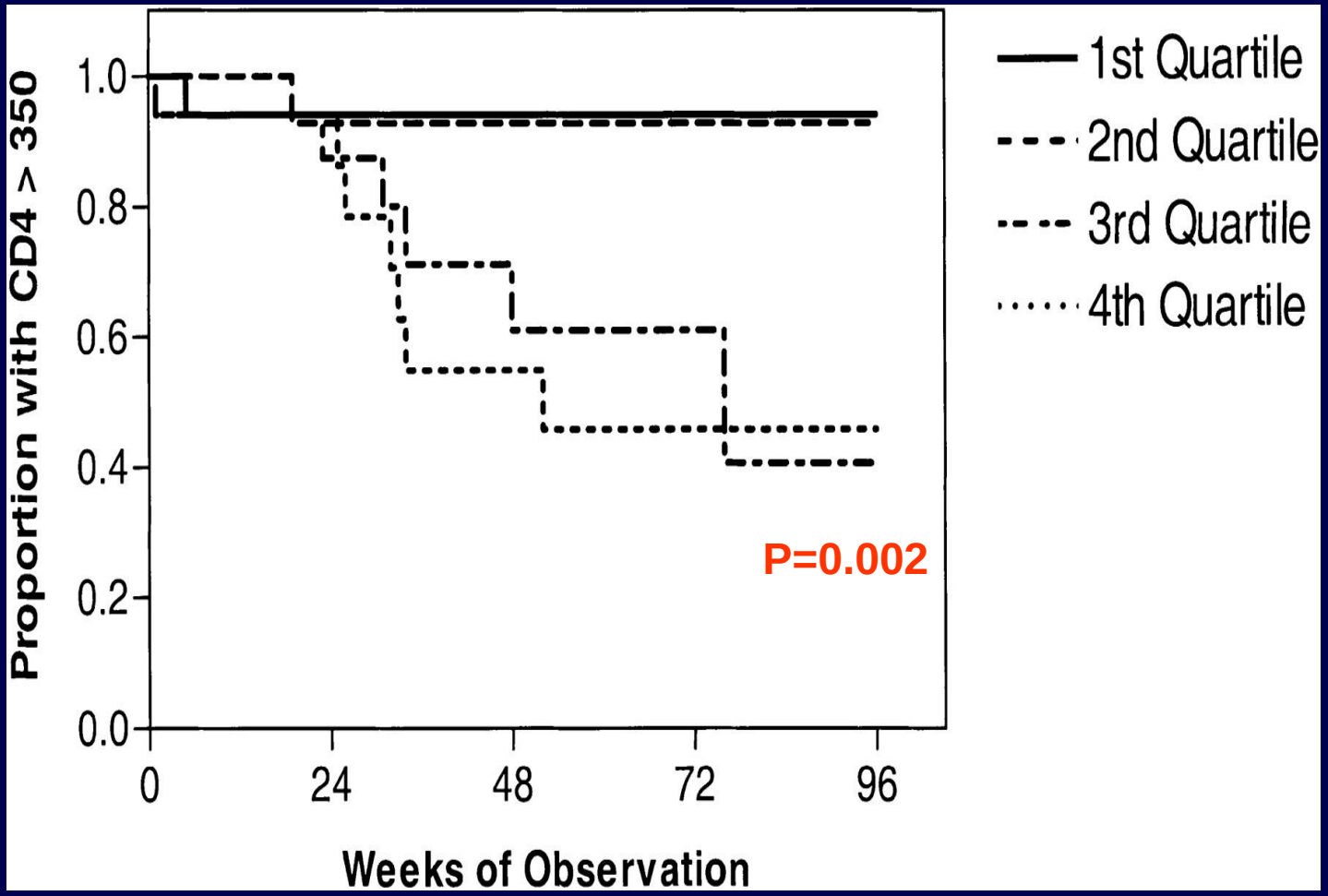


Janice Giorgi

Giorgi, JID, 1999 (see also: Giorgi, JAIDS, 2002)

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

How Might Activation Lead To CD4+ T cell Depletion and AIDS?

- May cause depletion of long-lived naïve and central memory T cells by activation-induced apoptosis
  (Zvi Grossman, others)

- May result in lymph node fibrosis, impairing naïve and resting memory T cell homeostasis.
  (Tim Schacker, Ashley Haase, others)

- May induce CCR5 expression in naïve and central memory T cells, facilitating direct viral infection.
  (Guido Silvestri, others)

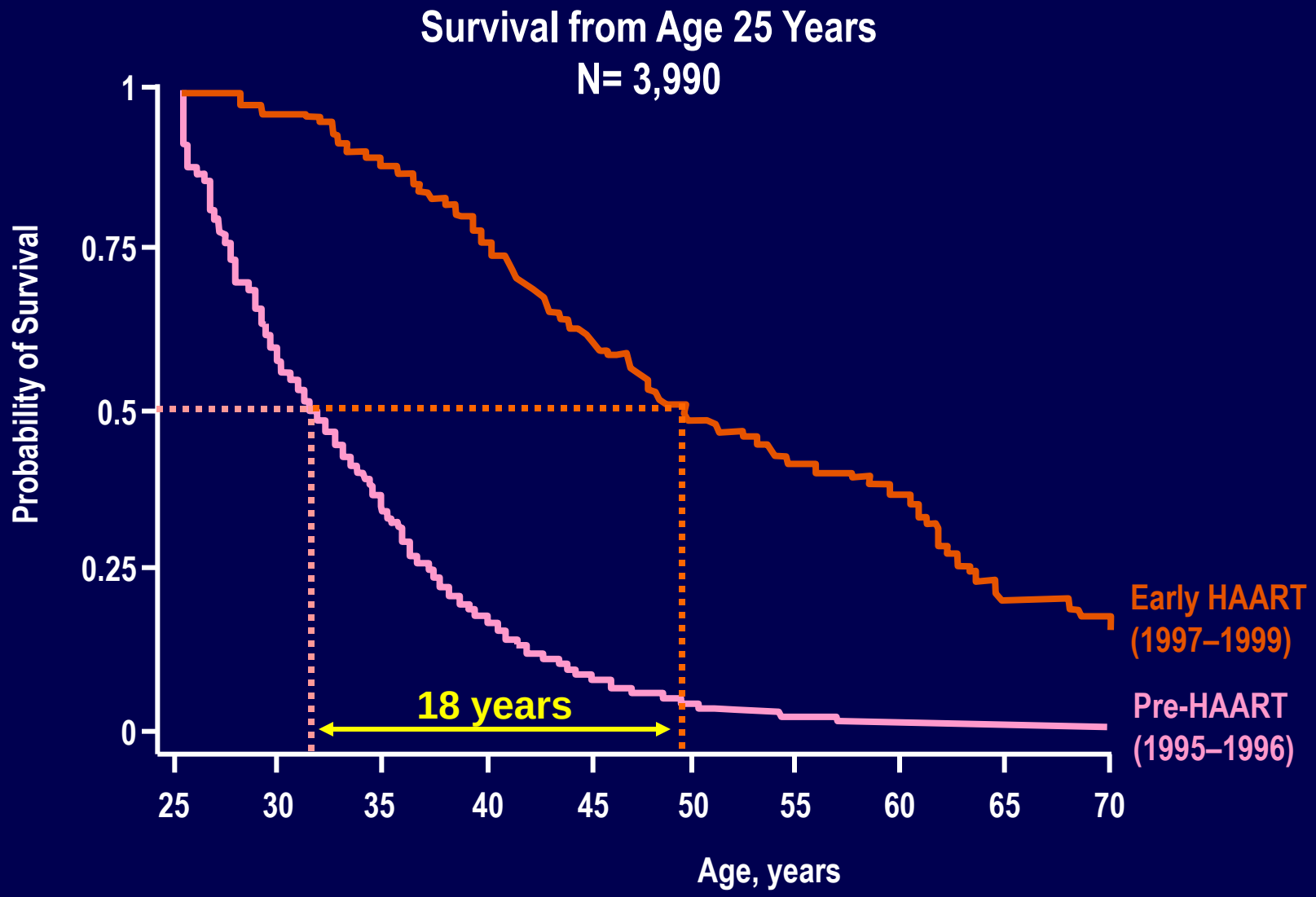
Systemic Immune Activation in HIV/SIV is Not Just a Problem For CD4+ T Cells

- Most cells of the immune system are activated
  - CD8+ T cells
  - B cells (polyclonal gammopathy)
  - Monocytes
  - NK cells
  - Dendritic cells
- Once cells are activated, they become exhausted and less capable of responding

What is the relevance of immune activation in 2010?

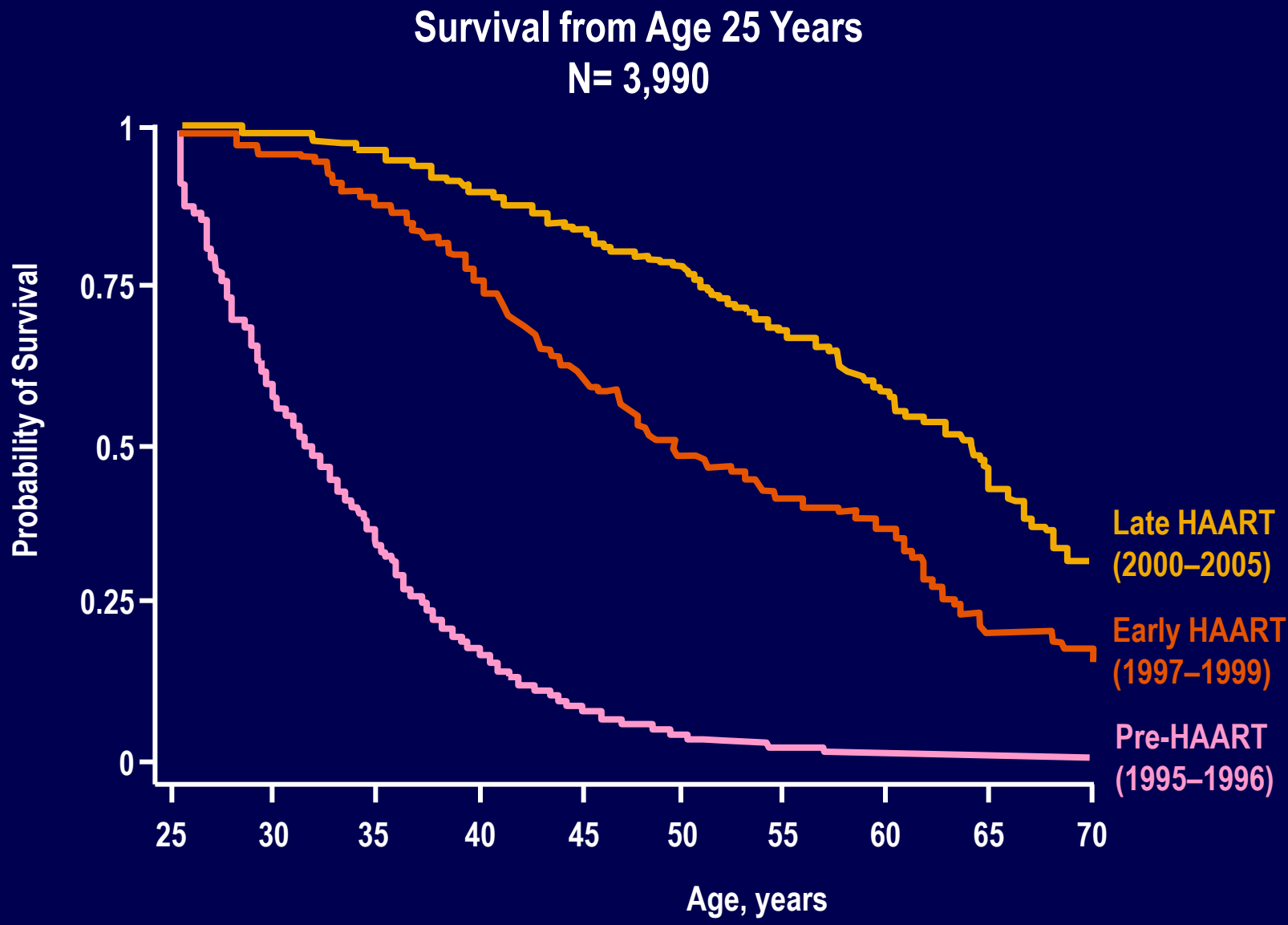
Vast majority of patients able to achieve and maintain VL suppression.

Dramatically Improved Life Expectancy in Early HAART Era



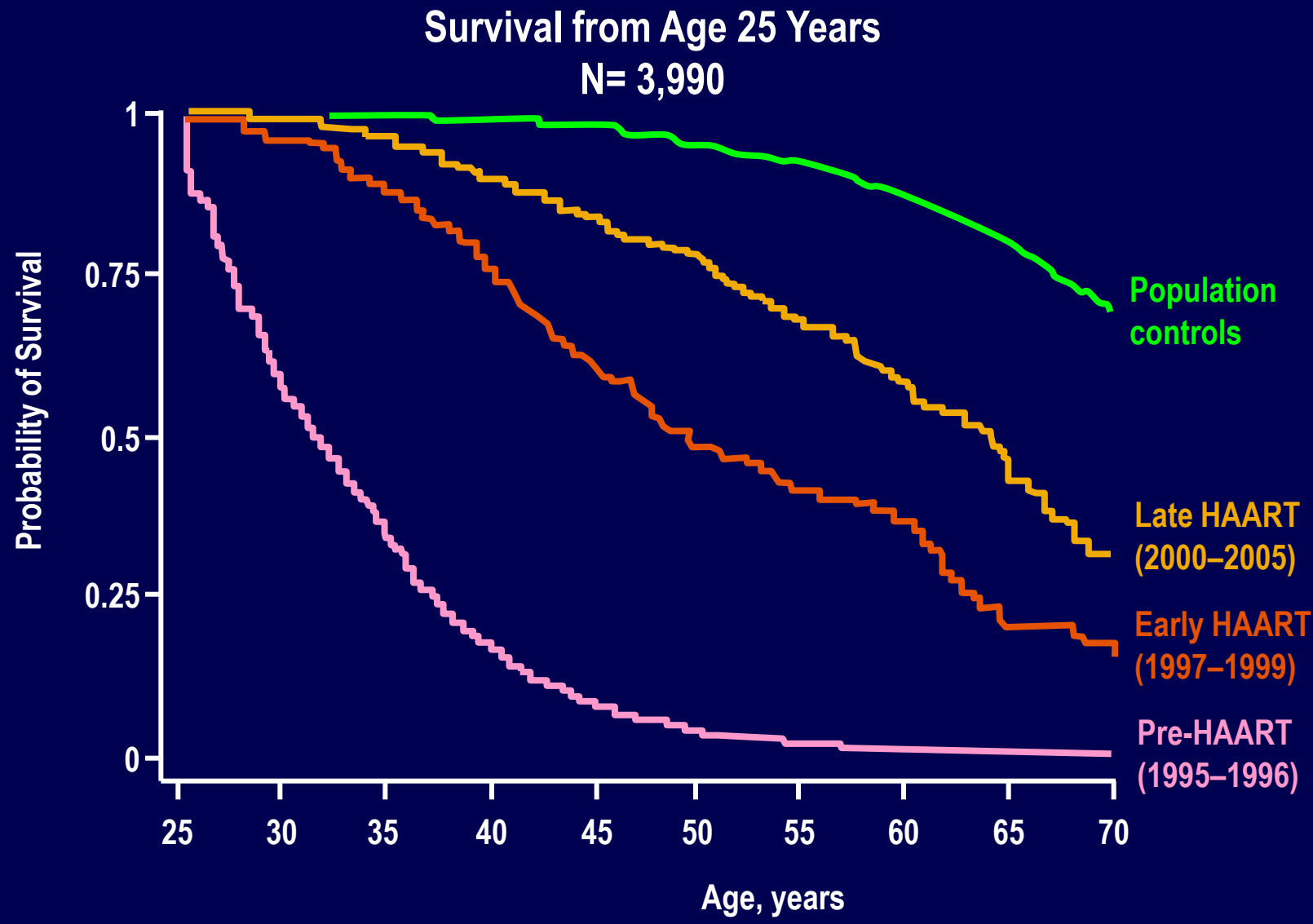
Adapted from Lohse N, et al. Ann Intern Med 2007;146:87–95

Late HAART Era Extended Life Expectency Even Further



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

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

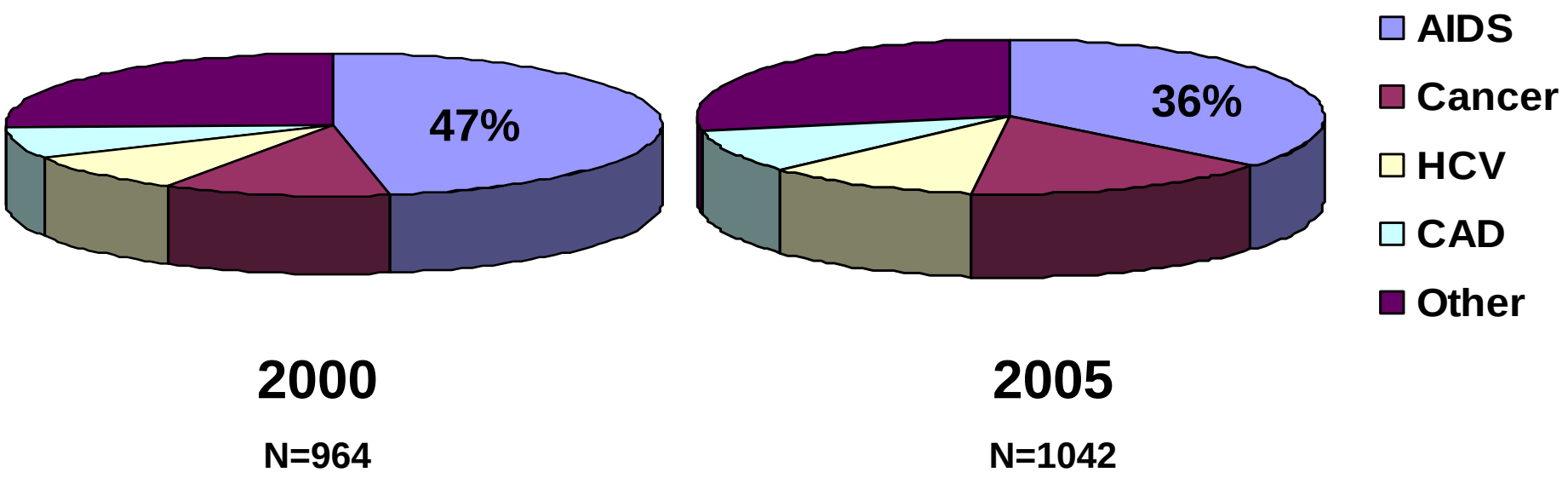


Adapted from Lohse N, et al. Ann Intern Med 2007;146:87–95

(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

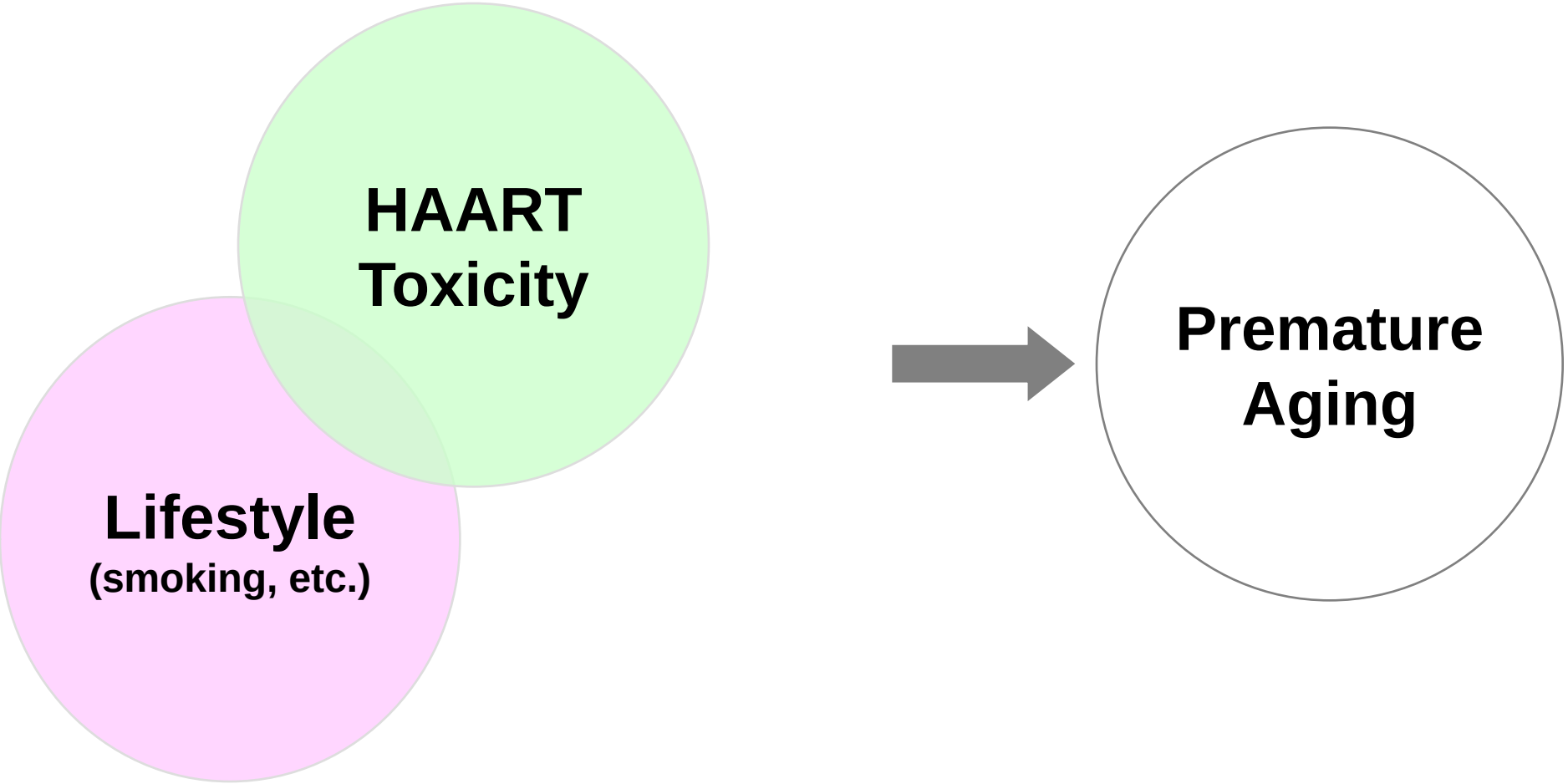
Many morbidities associated with aging also appear to be increased in treated HIV disease

- **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

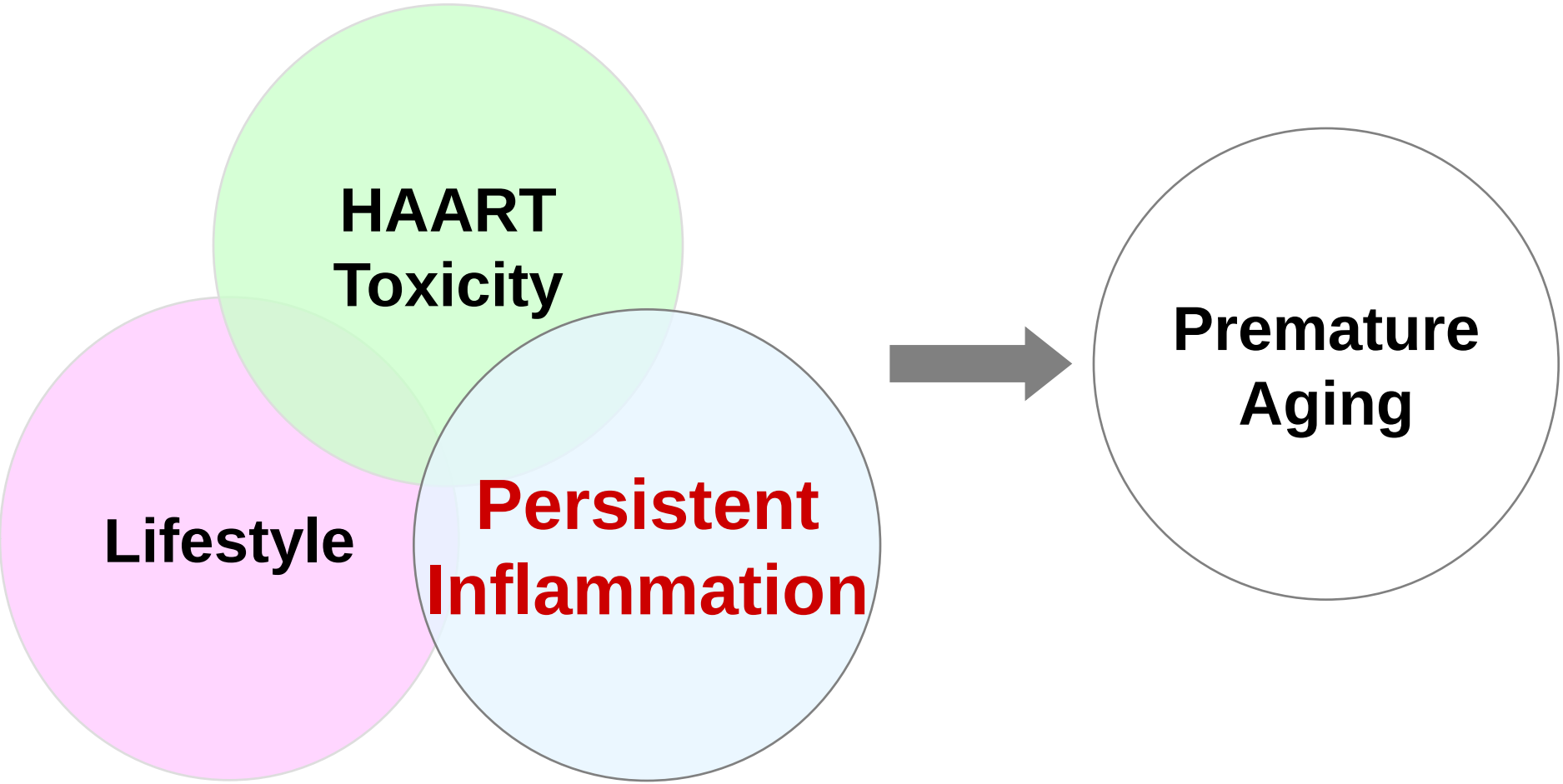
Why are HIV-infected Patients at Increased Risk for Diseases Associated with Aging?

Non-AIDS Events May Be Partially Driven By Lifestyle Factors and HAART Toxicity



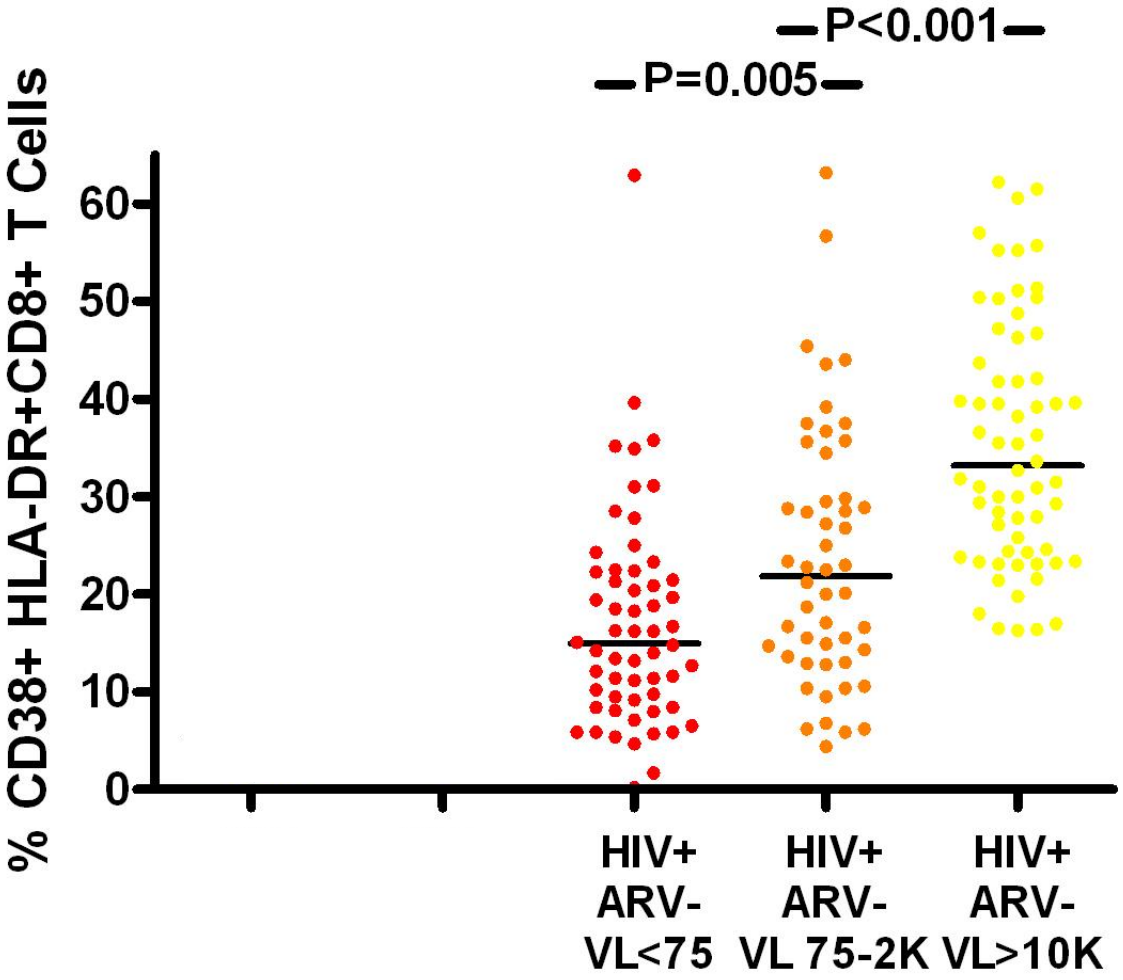
Deeks and Phillips, BMJ, 2009

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



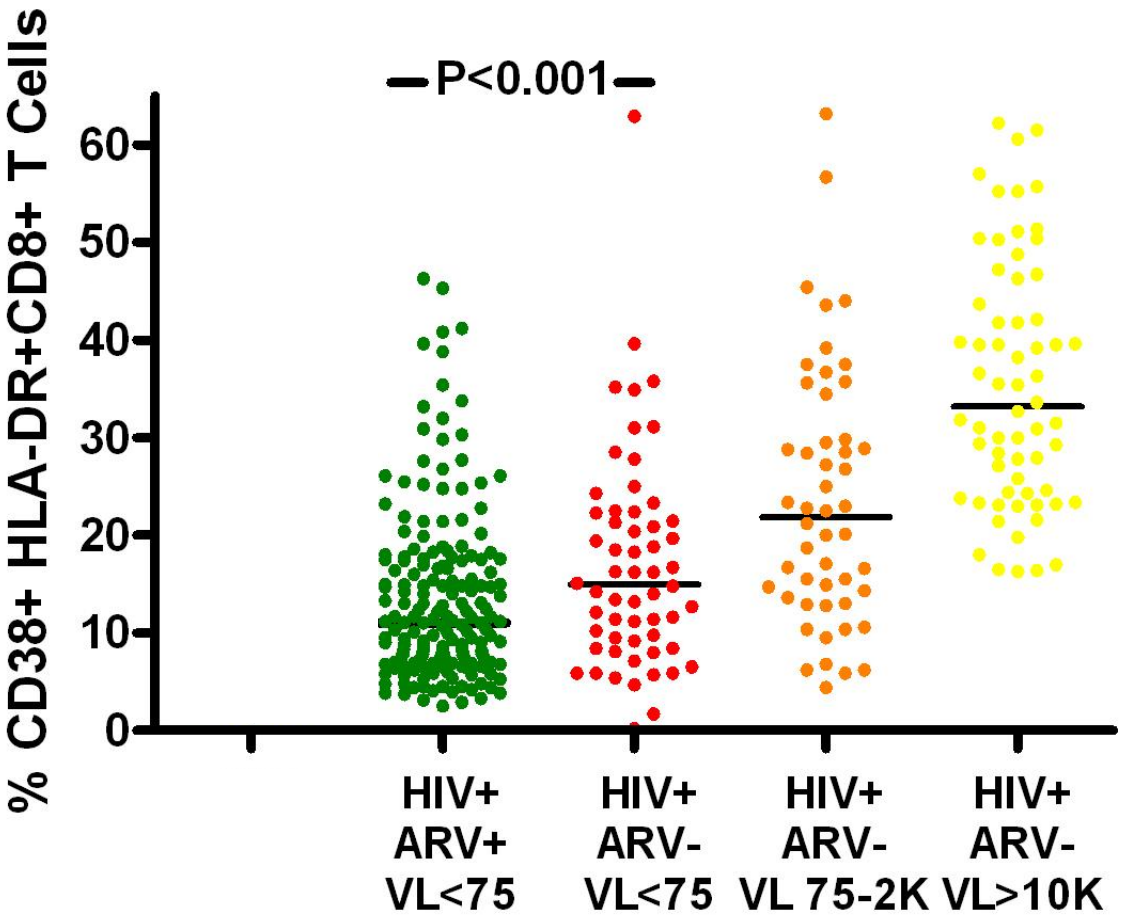
Deeks and Phillips, BMJ, 2009

T Cell Activation Declines with Lower Levels of Viral Replication



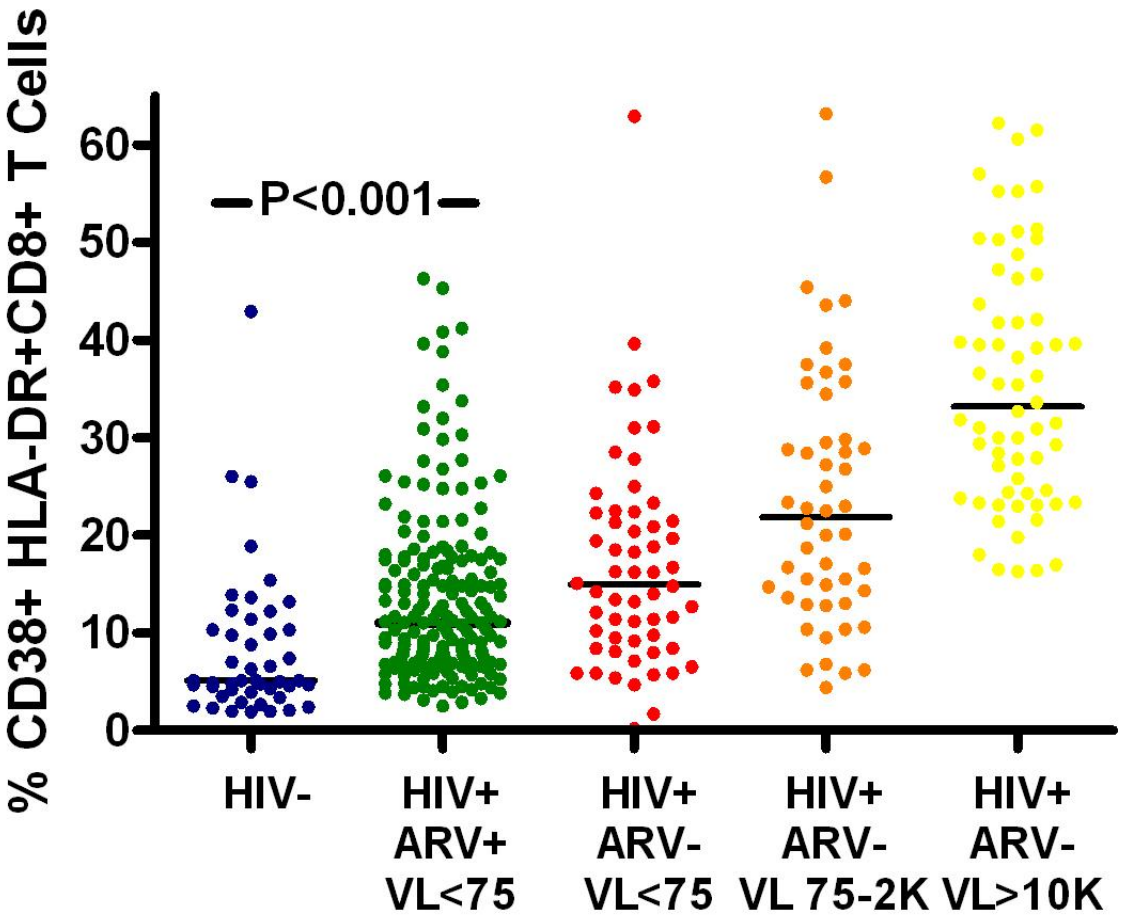
Hunt et al, JID, 2003 and 2008

T Cell Activation Declines Further During ART-mediated VL Suppression



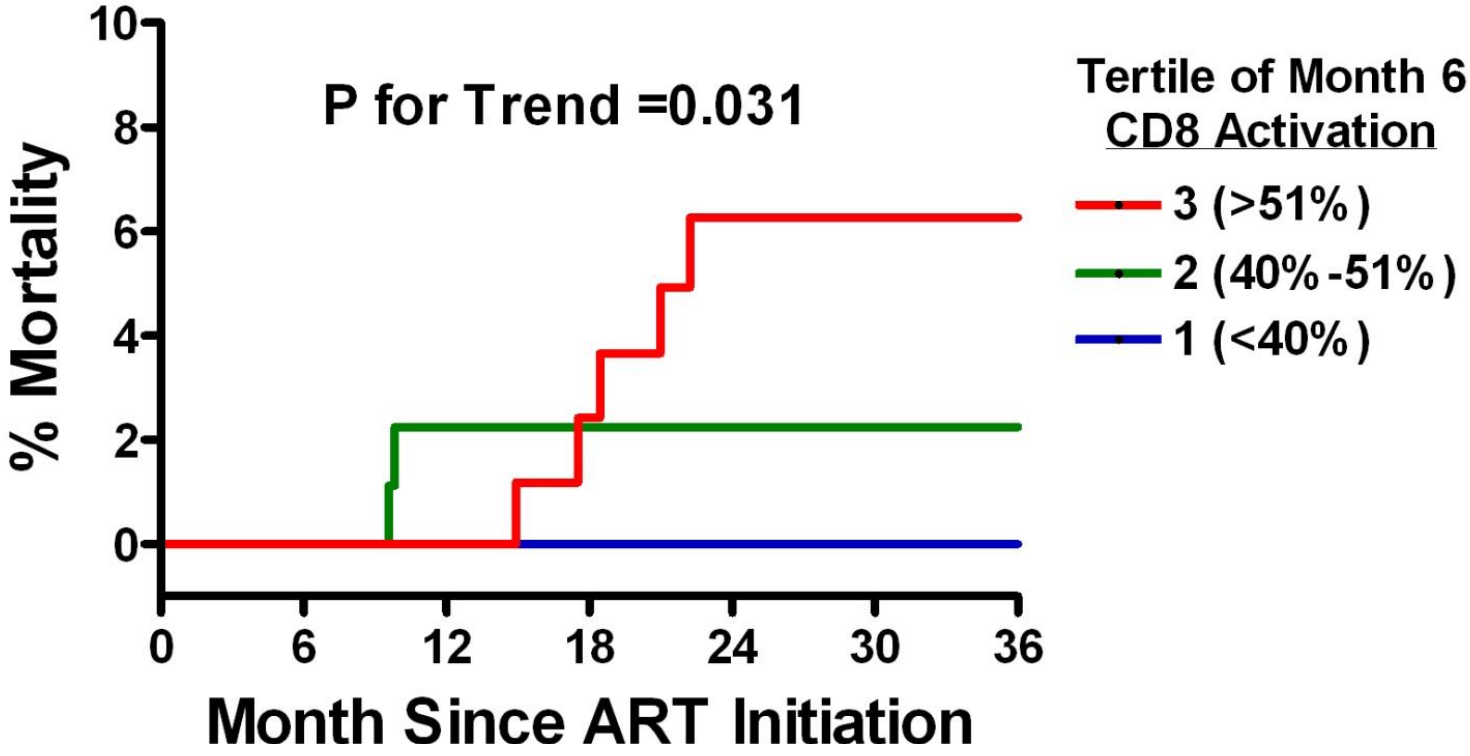
Hunt et al, JID, 2003 and 2008

…but ART-suppressed Patients Have Persistently Abnormal T Cell Activation



Hunt et al, JID, 2003 and 2008

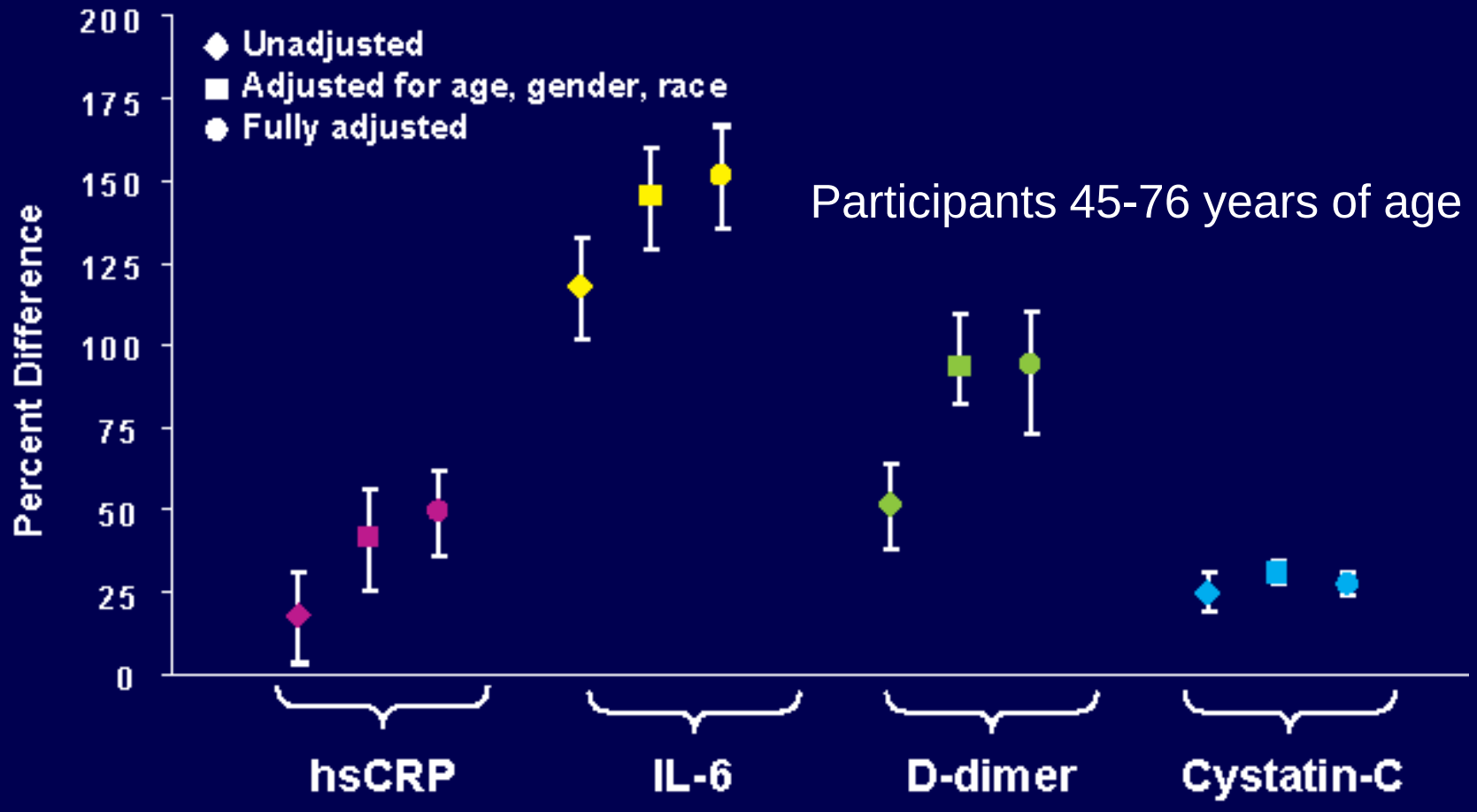
UARTO: High CD8+ T Cell Activation at Month 6 of ART Predicts Subsequent Mortality in Ugandans with VL<400



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, CROI 2010, Poster #306

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



Participants 45-76 years of age

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

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

Kuller L *et al.* CROI 2008, Abs 139.

Immune activation and inflammation persist during suppressive ART, which may increase risk of AIDS- and non-AIDS-associated morbidities.

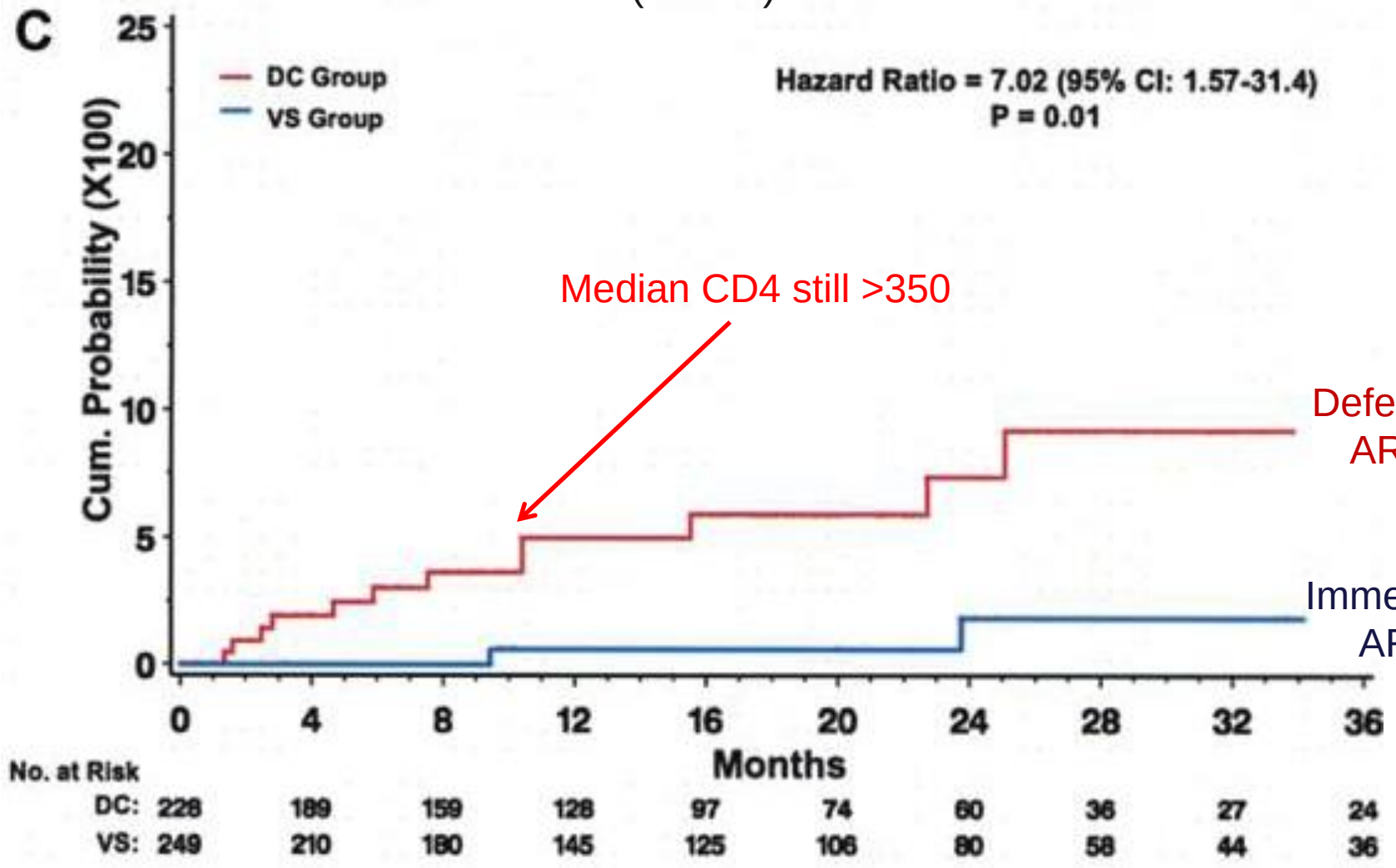
Might this be a reason to start ART earlier in the course of HIV infection?

An Immunologic Cost of Delaying ART?

- Higher T cell activation during suppressive ART associated with lower pre-treatment CD4+ T cell nadirs (Hunt, JID, 2003)
- Poor T cell function (vaccine responses) during suppressive ART associated with lower pre-treatment CD4+ cell nadirs (Lange, AIDS, 2003)

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

What about patients who present late in the course of HIV infection?

Are there any interventions that might decrease persistent immune activation during ART?

Short Answer:
Not yet, but many of us are working on it…

Potential Determinants of Inflammation During ART

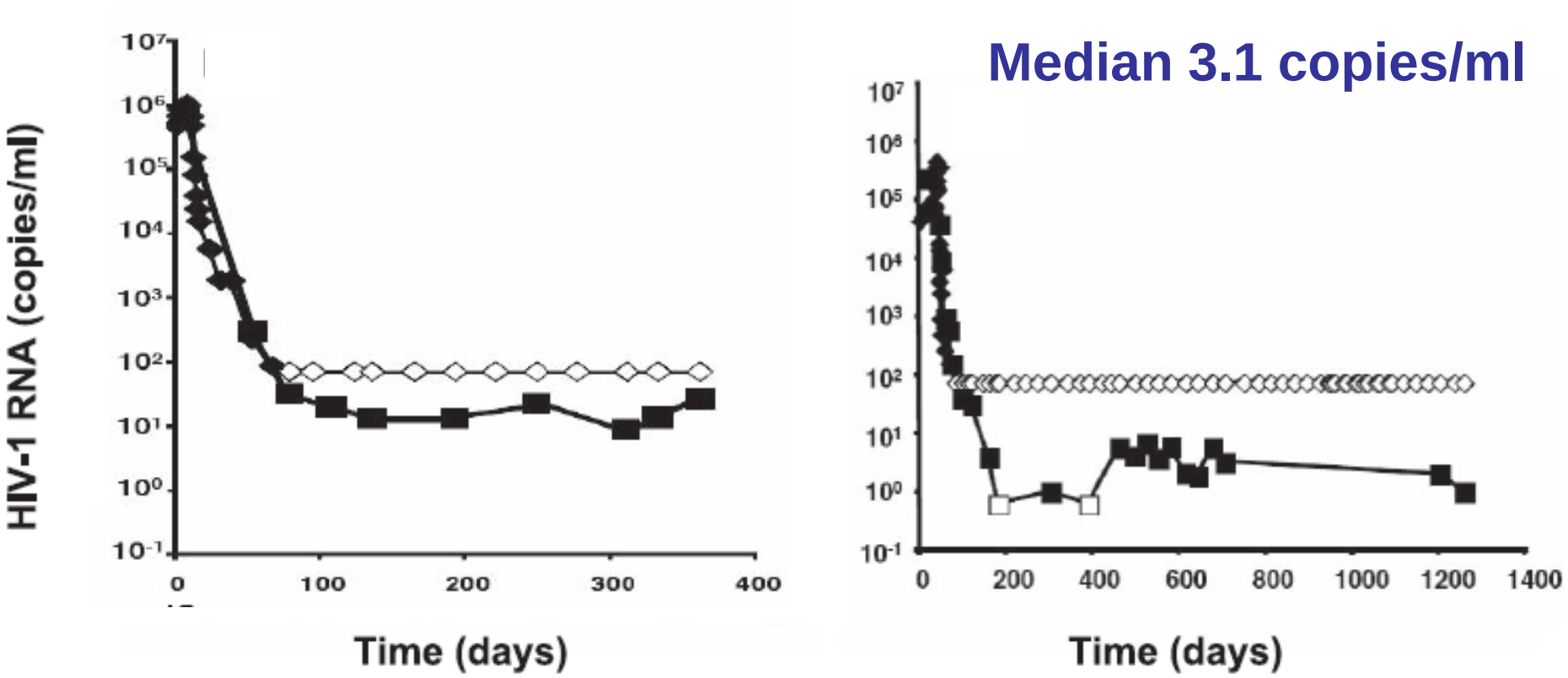
- HIV itself (passive release vs productive replication)
- Microbial Translocation
- Other co-infections

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

N=130

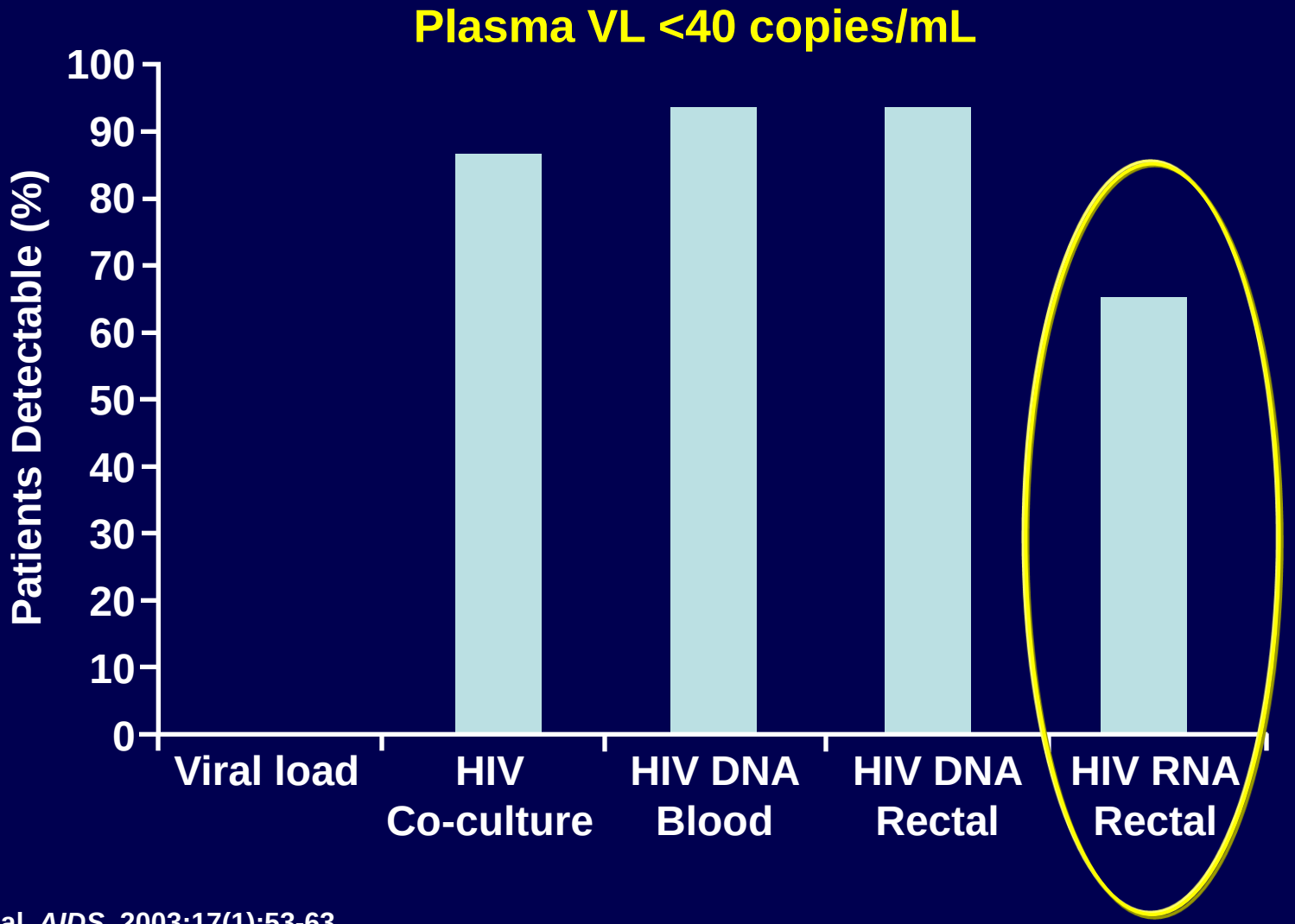
80% Patients had detectable viremia

Median 3.1 copies/ml



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

HIV RNA Is Also Readily Detectable in Rectal Tissue During "Suppressive" HAART



N=40.

Anton PA et al. *AIDS.* 2003;17(1):53-63.

Is this residual low-level virus in plasma and tissues the result of ongoing *productive* rounds of viral replication or just release from latent reservoir?

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

HIV as a cause of persistent immune activation during suppressive ART?

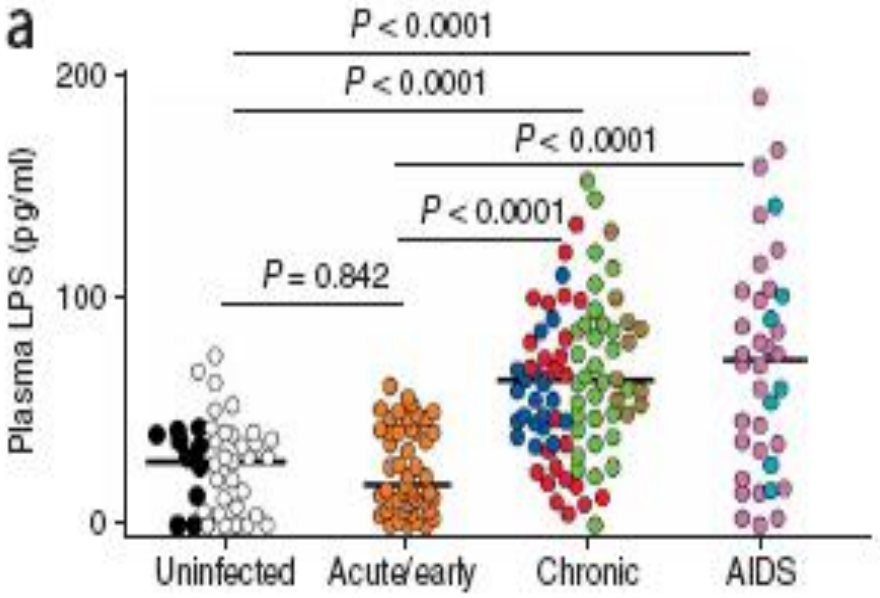
- Productive virus replication unlikely to be a major cause of systemic immune activation in this setting.
- Even release of HIV from latently infected cells may be enough to drive immune activation.
  - Would not be impacted by ART intensification
  - Need new interventions to block downstream inflammation from HIV release.
    - Statins?
    - TLR antagonists?
    - CCR5 inhibitors?

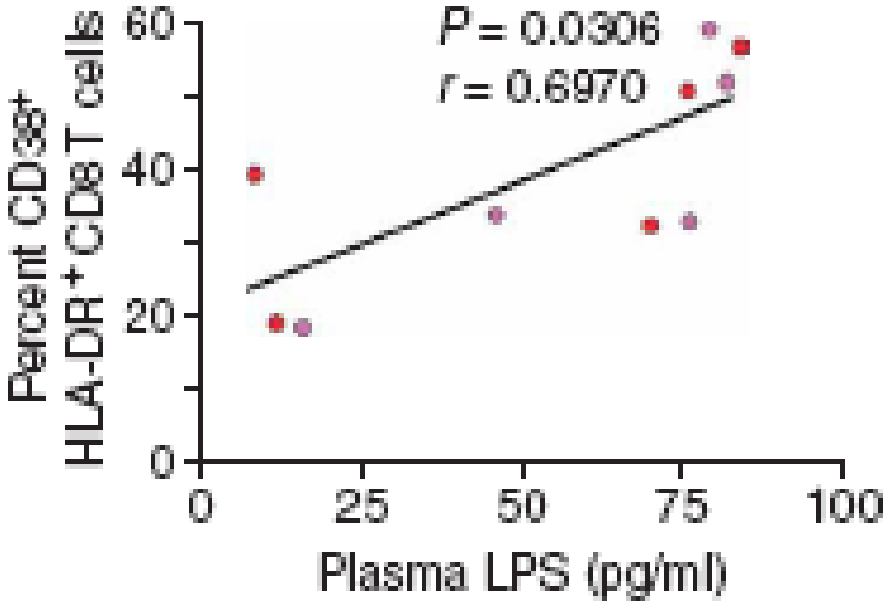
Potential Determinants of Inflammation During ART

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

Mucosal Translocation of Bacterial Products

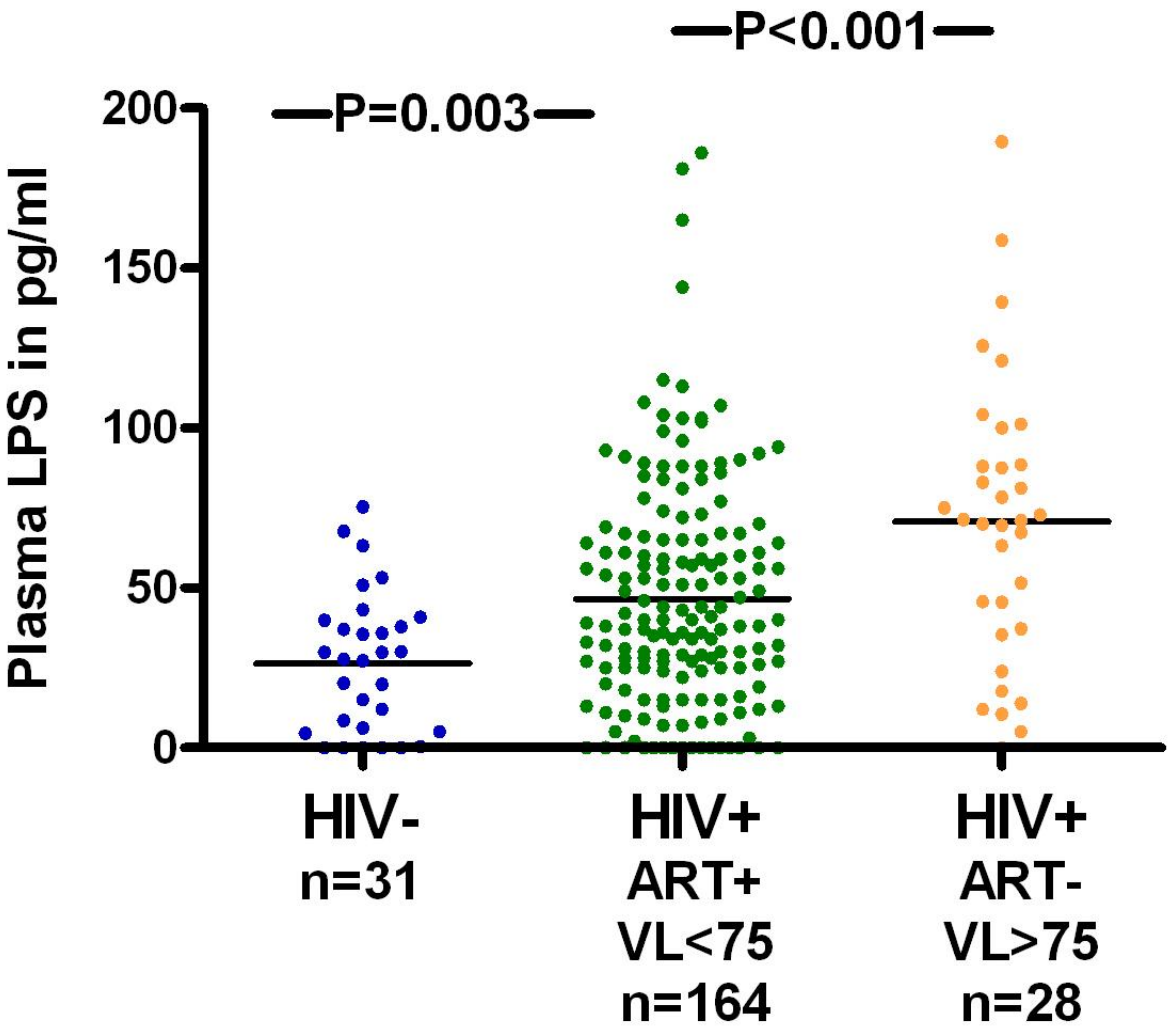
A potential cause of T cell activation in HIV





Brenchley et al, Nat Med, 2006

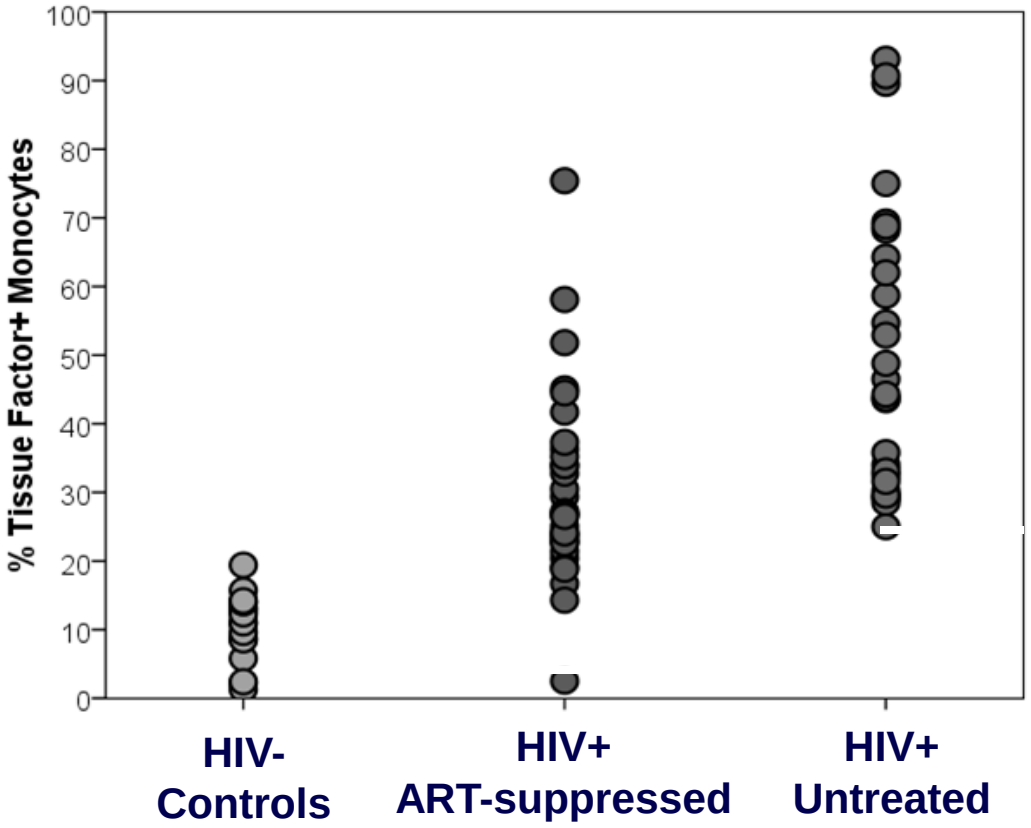
Microbial Translocation Decreases with Suppressive ART but Persists for Years



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

Funderburg, Blood, 2009

Interventions to decrease microbial translocation?

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

- Randomized, placebo controlled trial of NR100157 (n=340 untreated patients with early disease)
  - Bovine colostrum, oligosccharides, 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*

Other ACTG Trials:

Chloroquine (TLR antagonist)

Rifaximin (luminal antibiotic)

UCSF

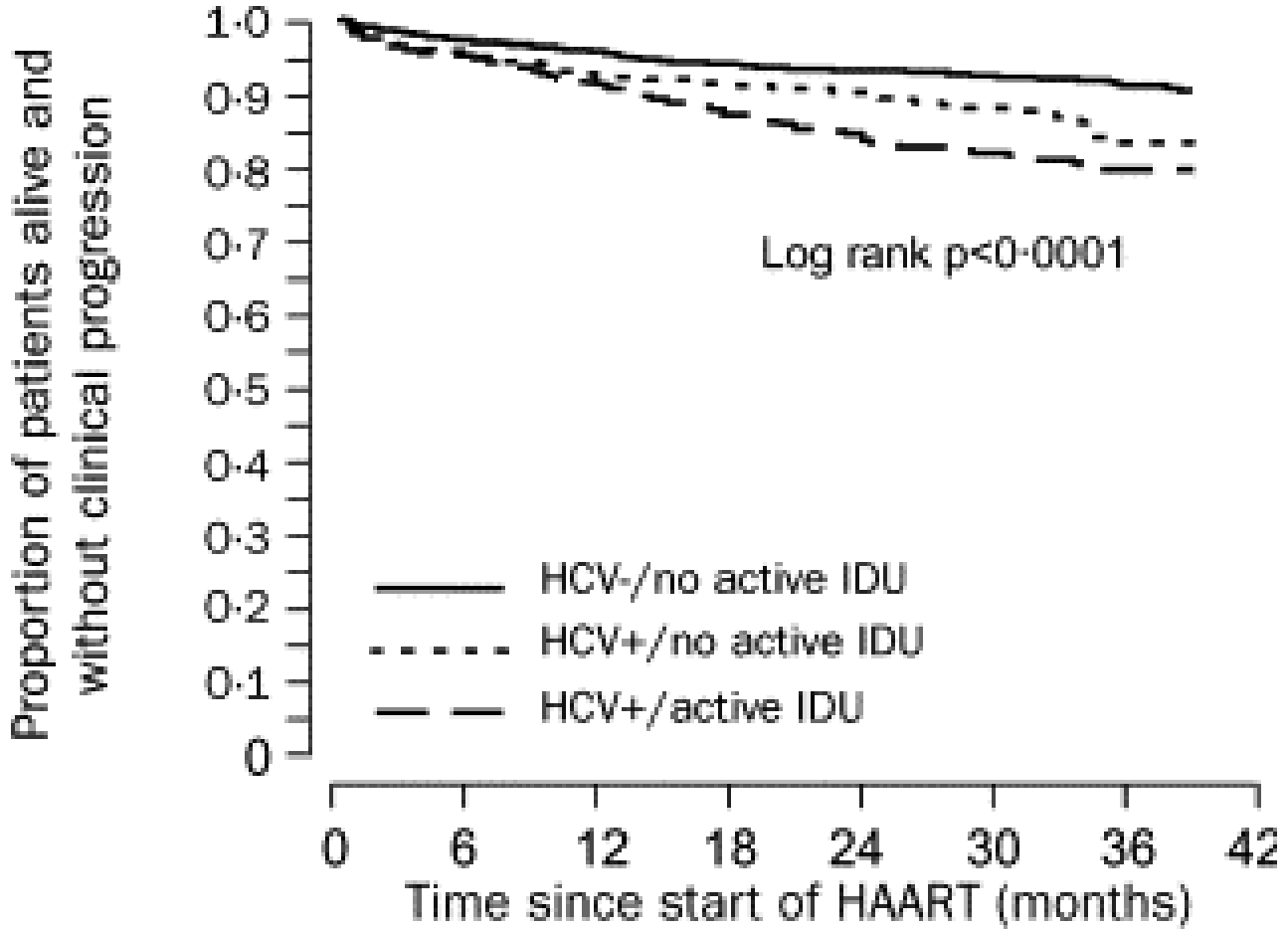
Mesalamine
(luminal anti-inflammatory)

Lange J, et al. 49th ICAAC; 2009

Potential Determinants of Inflammation During ART?

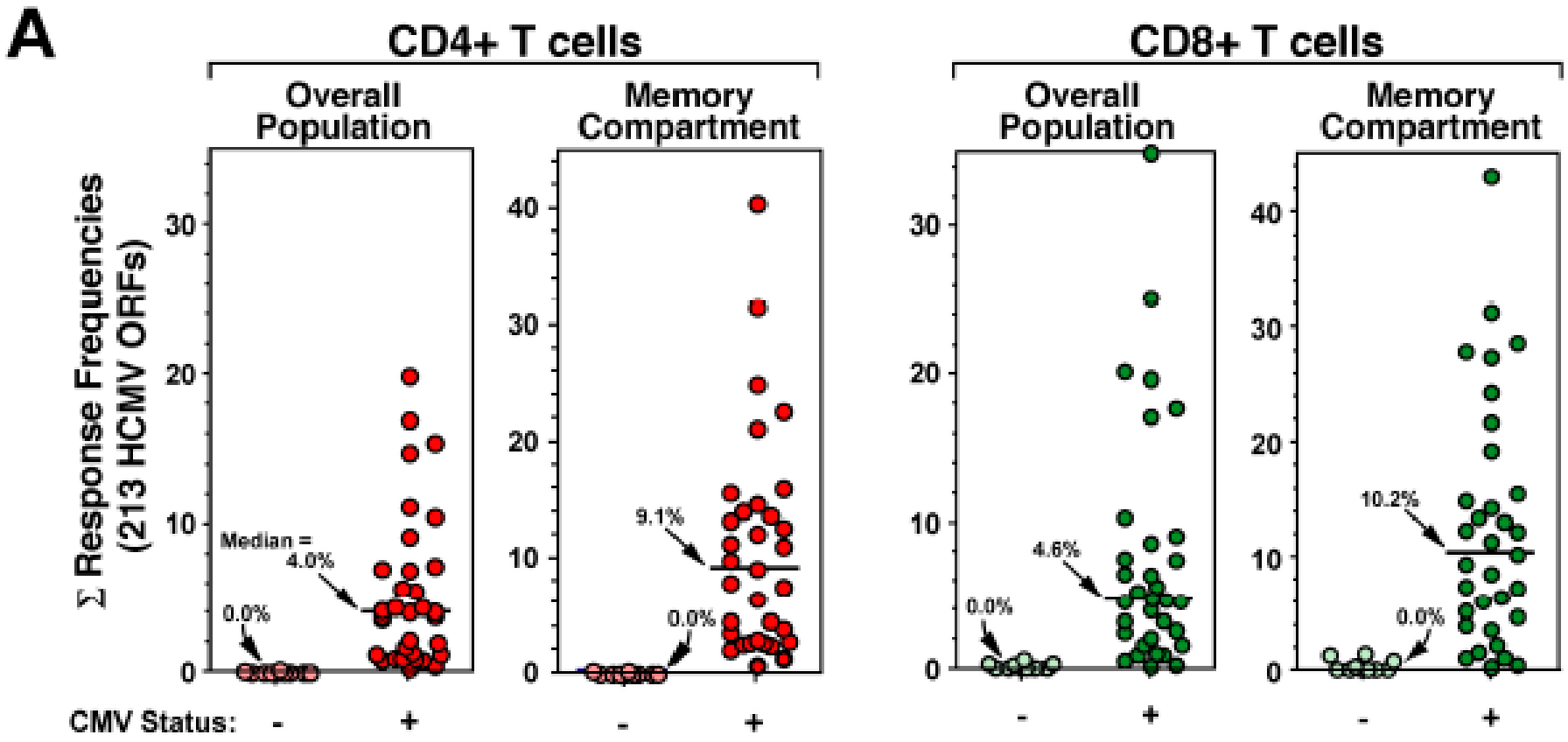
- HIV itself (passive release vs productive replication)
- Microbial Translocation
- Other co-infections
- Accumulation of senescent cells

HCV Associated with Progression to AIDS/Death During HAART



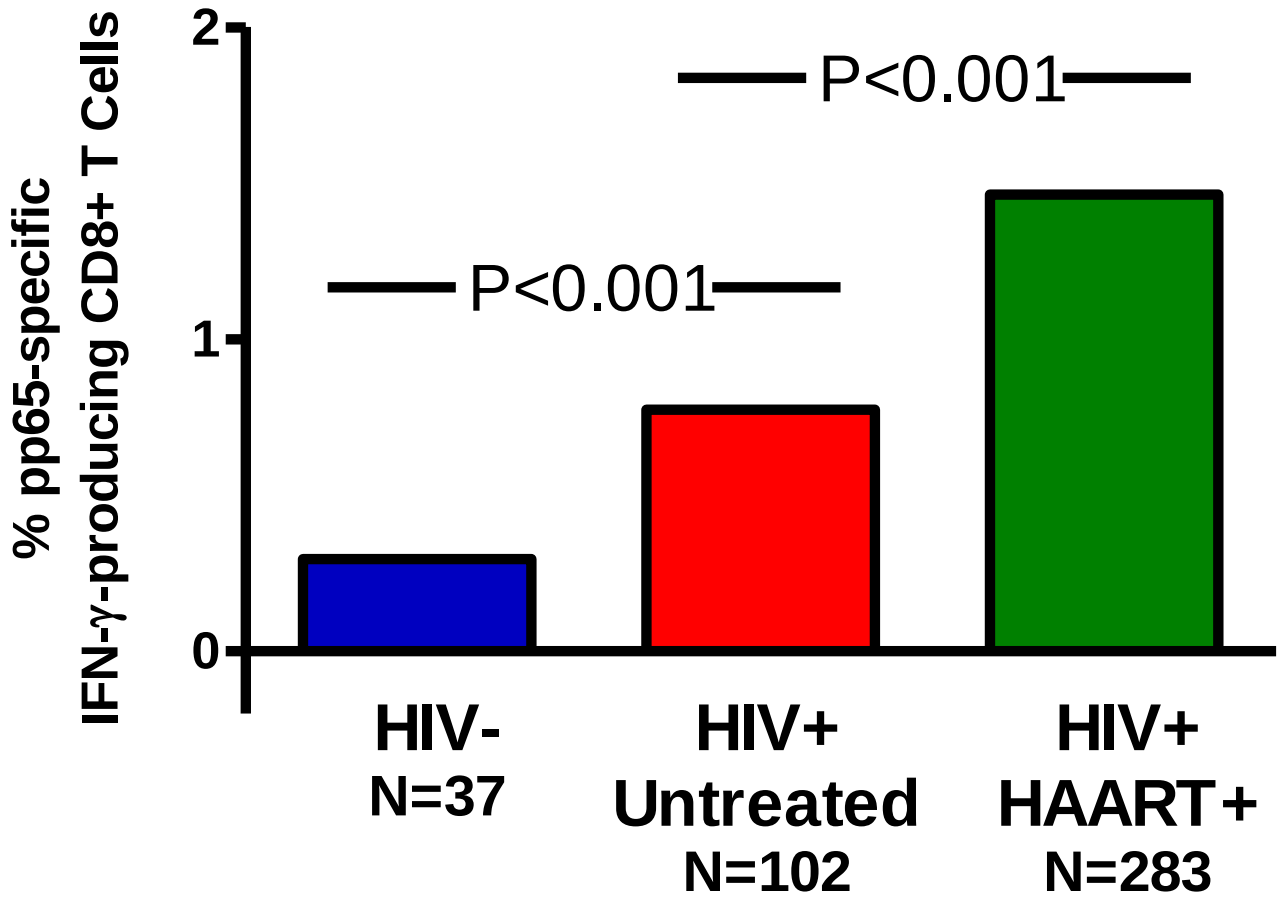
Greub, Lancet, 2000 (see also Kovacs, JID, 2010)

CMV elicits massive immune responses even in asymptomatic HIV- individuals



Sylwester/Picker, JEM, 2005

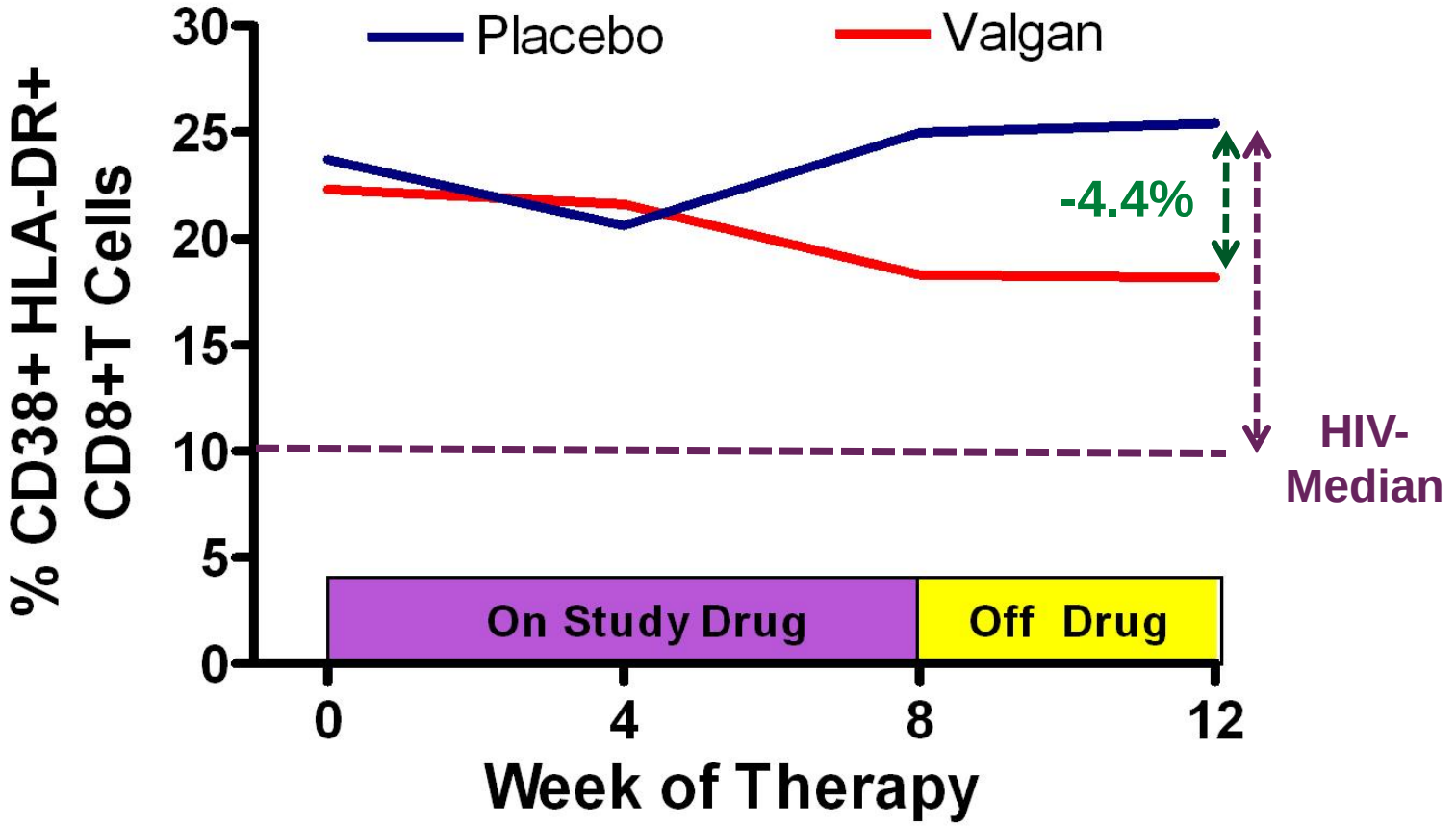
CMV-specific T Cell Responses are Higher in HIV-infected Patients



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

Summary 1

- Immune activation is an important determinant of HIV pathogenesis
- Abnormal immune activation persists during “suppressive” HAART and may contribute to morbidity/mortality.
- Starting ART earlier in the course of HIV infection *likely* decreases this risk. (Level C)
- Novel interventions being studied to decrease immune activation from HIV, microbial translocation, and co-infections.

Immune Reconstitution Inflammatory Syndromes

- Inflammatory response leading to clinical deterioration after the initiation of antiretroviral therapy (ART)
- “Unmasking” of a subclinical infection or a worsening inflammatory response to a treated infection or self antigen.
- Incidence ranges from 3-25% [1,2,3]
- Commonly associated with CD4 nadir <100[3,4]

[1]Rodriquez-Rosado, AT, 1998 [2,] Michelet, AIDS, 1998, [3]French, HIV Med, 2000, [4]Manabe, JAIDS, 2007

Many Pathogens and Syndromes

Mycobacteria

- M. avium
- M. tuberculosis

Fungal

- Cryptococcus
- Pneumocystis
- Histoplasmosis

Viruses

- CMV
- HSV/VZV
- Hepatitis B and C
- PML (JC virus)
- HIV (encephalopathy)

Other Bacteria

- Chlamydia trachomatis
- Bartonella

Infection-related Malignancies

- Kaposis sarcoma

Autoimmune/Inflammatory Disease

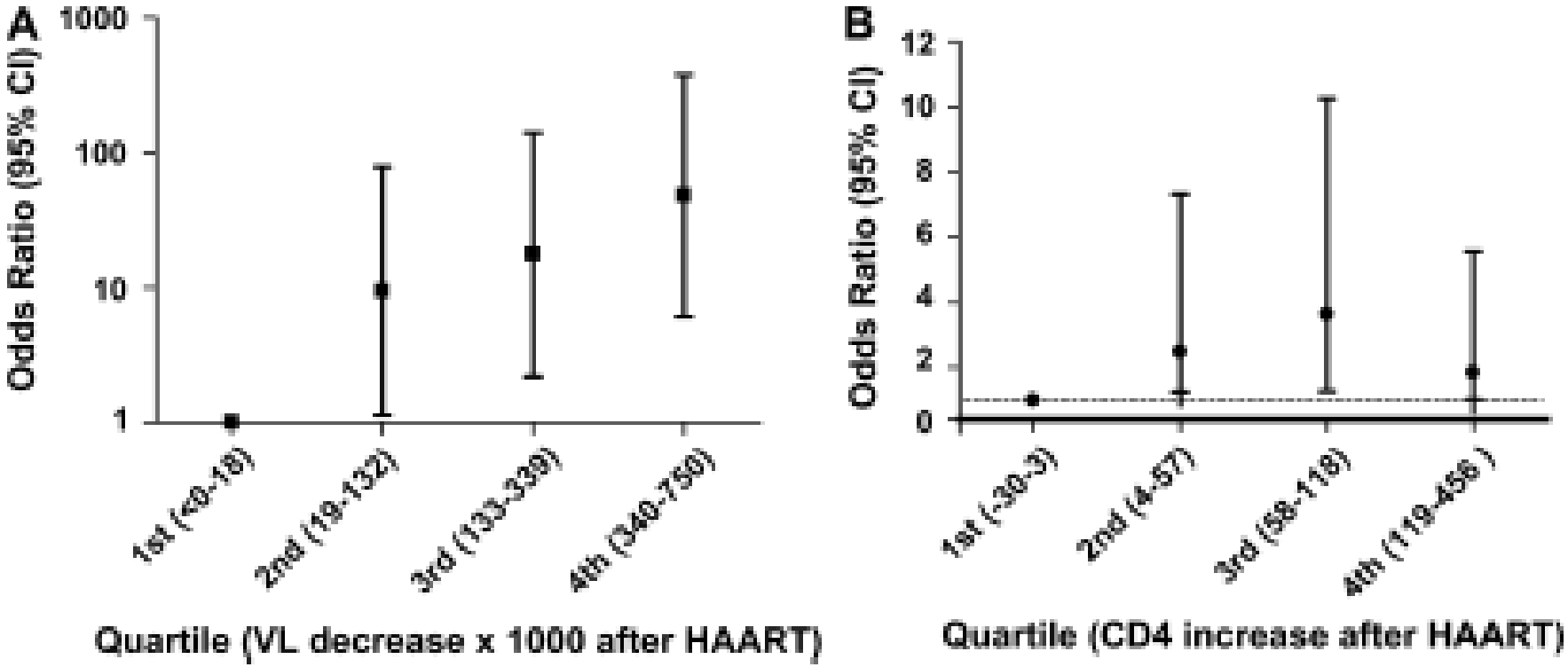
- Sarcoidosis
- Graves disease
- Guillain Barre

What Characterizes IRIS vs. a Typical OI?

- Timing: usually first 4-8 weeks of ART (but as early as 1 week and as long as 2 years)
- Marked inflammatory response
  - Fever
  - Edema
  - High WBC count
- Small pathogen load
  - Cultures are often negative
  - Declining antigen titers

(reviewed by French, CID, 2009)

VL Reduction (*But Not CD4 Increase*) Associated with IRIS



Manabe, JAIDS, 2007 (See Also: Shelburne, AIDS, 2005)

Many "Exhausted" Cell Types in Untreated HIV May Have Restored Function During ART

- CD4+ and CD8+ T cells
- B cells
- Monocytes
- NK cells
- Dendritic cells
- This may explain why multiple types of inflammation characterize IRIS (T cells, granulomas, Autoimmune diseases)

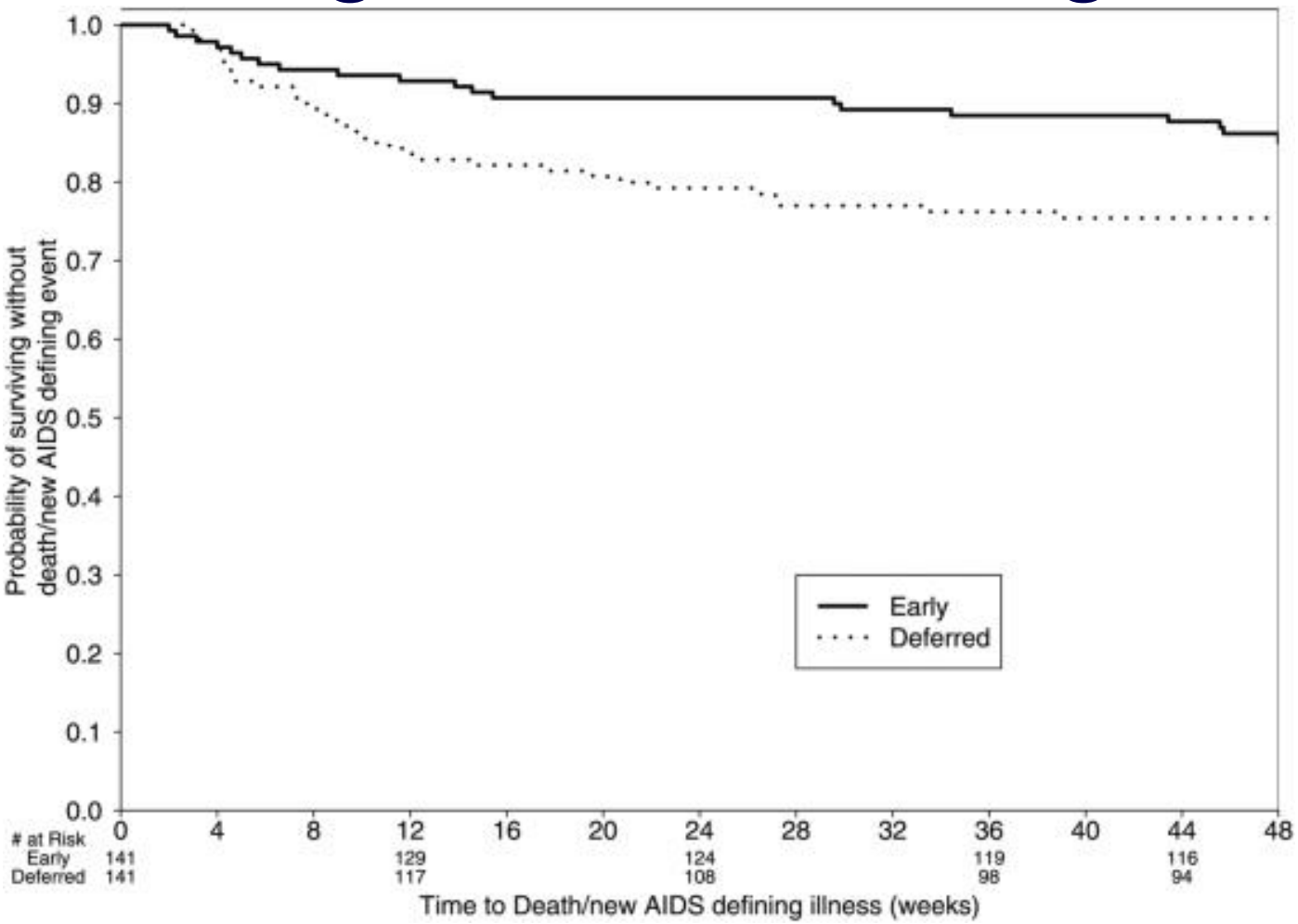
(reviewed by French, CID, 2009)

Treatment of IRIS to Infections

- Key is treating the underlying infection to decrease antigen load
- Continue ART in all cases
- Most cases are self-limited
- However, CNS IRIS (crypto and PML) can be lethal and may require intensive management of ICP and/or steroids
- Steroids can be used, but should be reserved for severe cases as they may result in reactivation of other infections.

(reviewed by French, CID, 2009) (Level C)

Increased Mortality When Deferring ART in Setting of OI



(Zolopa, PLoS One, 2009)

Summary 2

- IRIS is common during early ART, particularly in patients with low CD4 nadir
- Caused by a restoration of immune function – not just CD4 cells
- Usually self-limited, but may require steroids in life-threatening cases
- Treatment against the underlying pathogen and ART should be continued.

Acknowledgements

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ARS Questions