

Immune Activation and Inflammation: Role in Co- morbidity in HIV Disease

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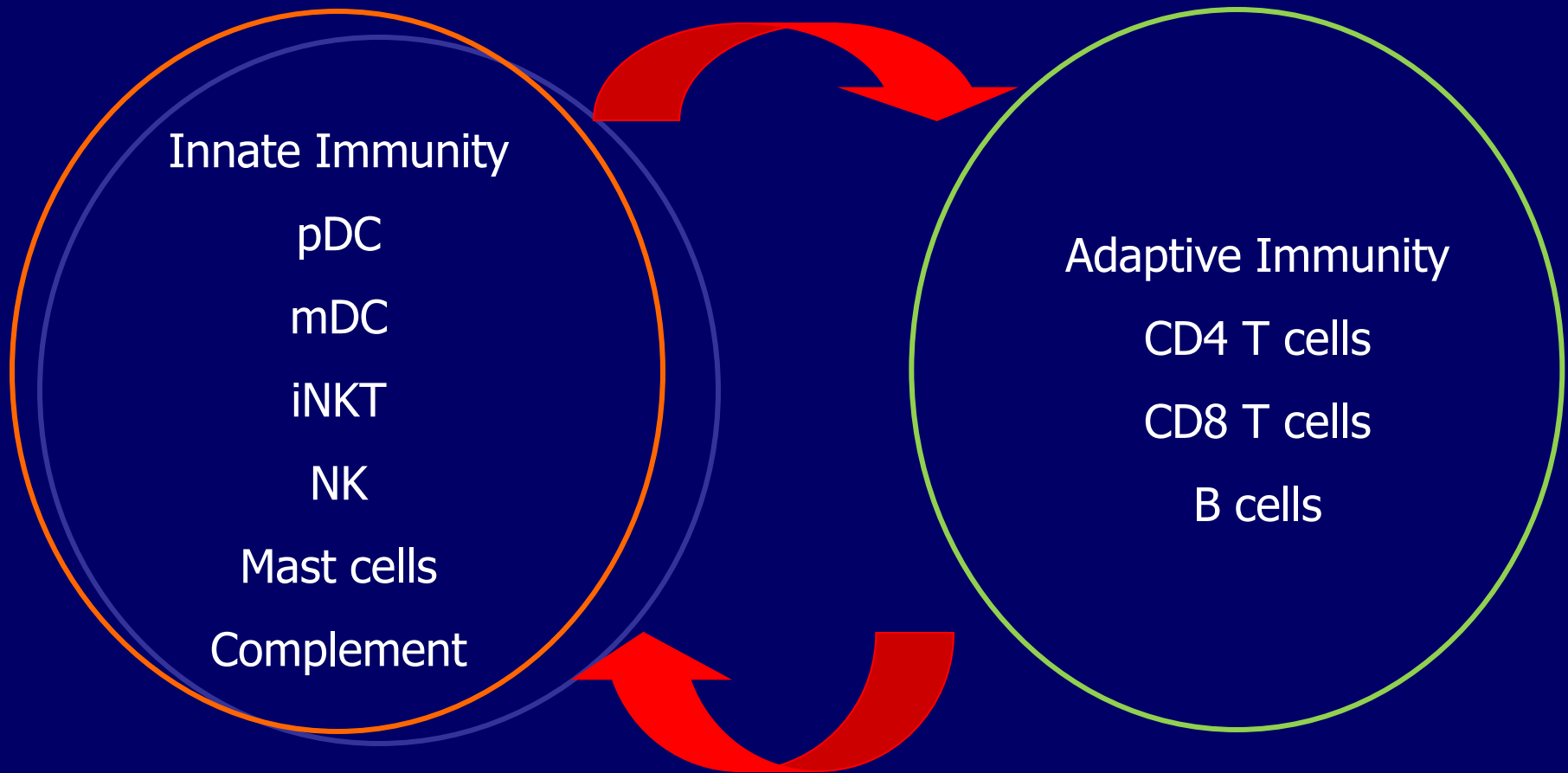
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Learning Objectives:

At the conclusion of this presentation, learners should be better able to:

- Describe the relationship of immune activation inflammation and how they can impact non HIV co-morbidities
- Discuss the potential pathways such a microbial translocation that can contribute to immune activation/inflammation in HIV subjects

Human Immune System





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	
	<i>per cent lymphocytes reactive with monoclonal antibodies</i>				
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

T10=CD38

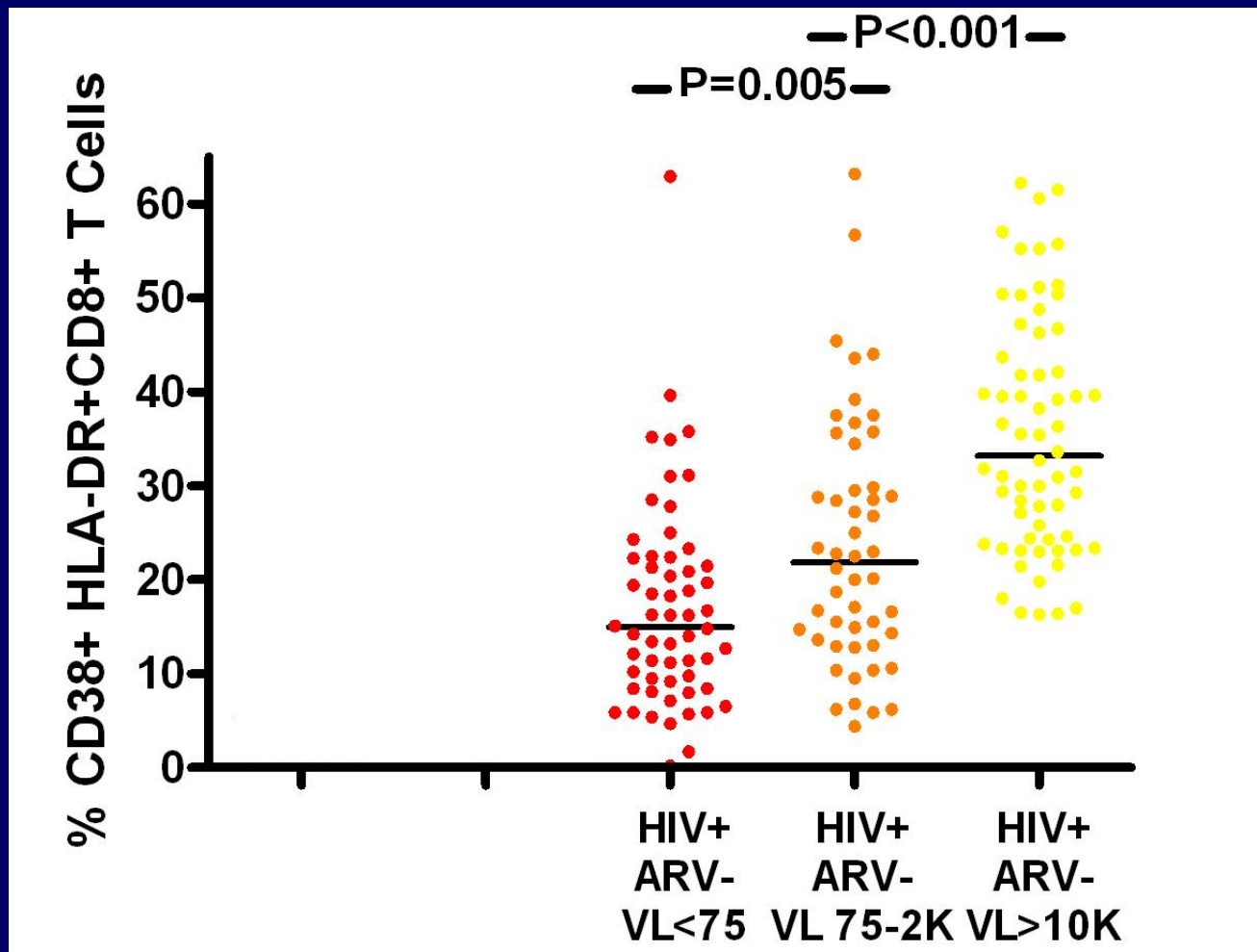
What is meant by “immune activation”?

- Activated cells express “activation markers”
- Activated cells make more stuff
 - B cells make Immunoglobulins
 - T cells, NK cells, monocytes and other APC make cytokines
- Activated cells also may enter cell cycle with an “intent” to divide
 - T cells enter cell cycle when their T cell receptors encounter antigen
 - T cells can also be induced to enter cell cycle by “bystander” mechanisms, e.g. via exposure to certain cytokines

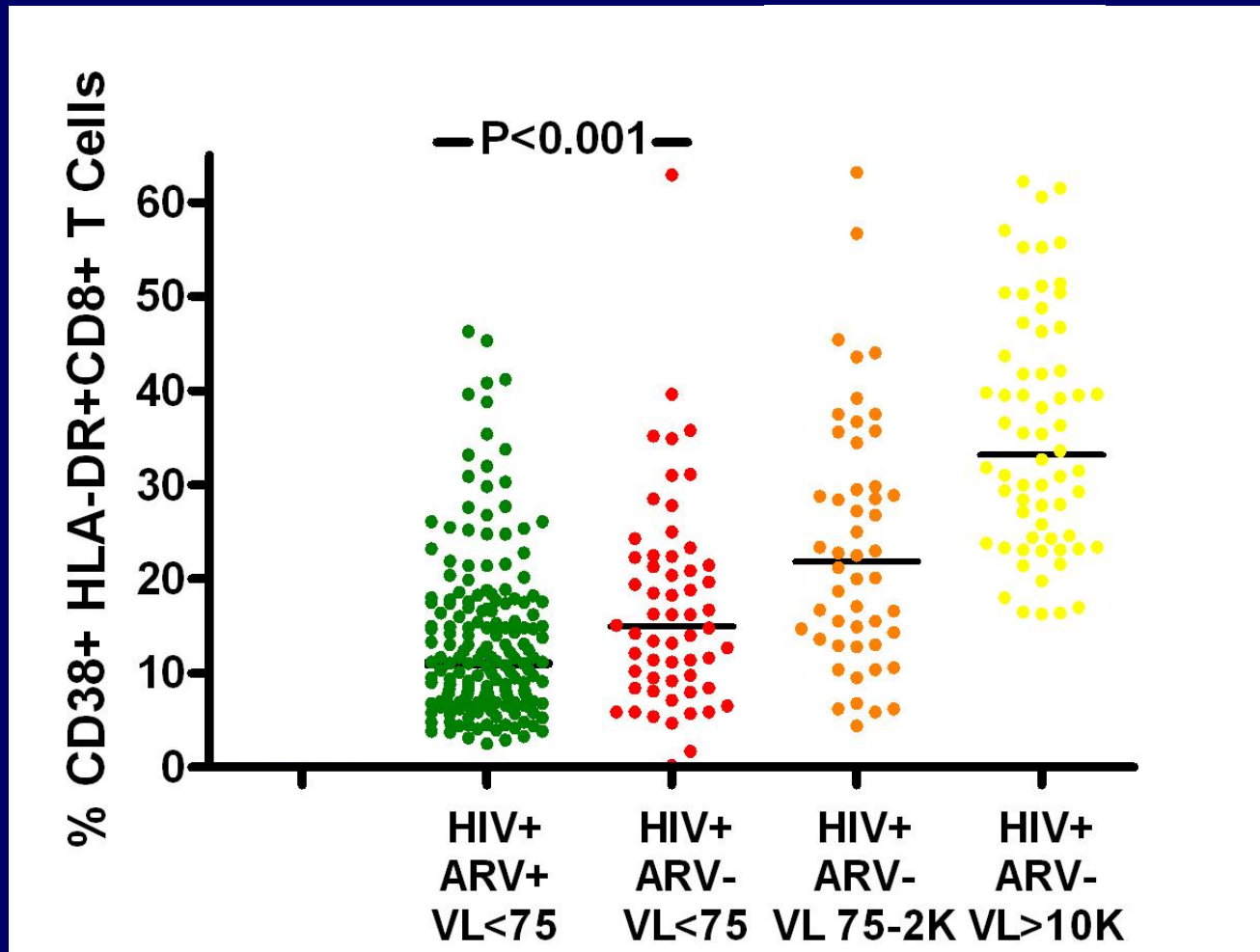
Why Do We Still Care About Inflammation and Immune Activation in HIV?

- Most HIV-infected patients now achieve and maintain viral suppression on ART
- Abnormal immune activation and inflammation persist despite VL<75
- Inflammatory markers predict CAD and death during ART
- Strategies to decrease inflammation and immune activation are urgently needed.

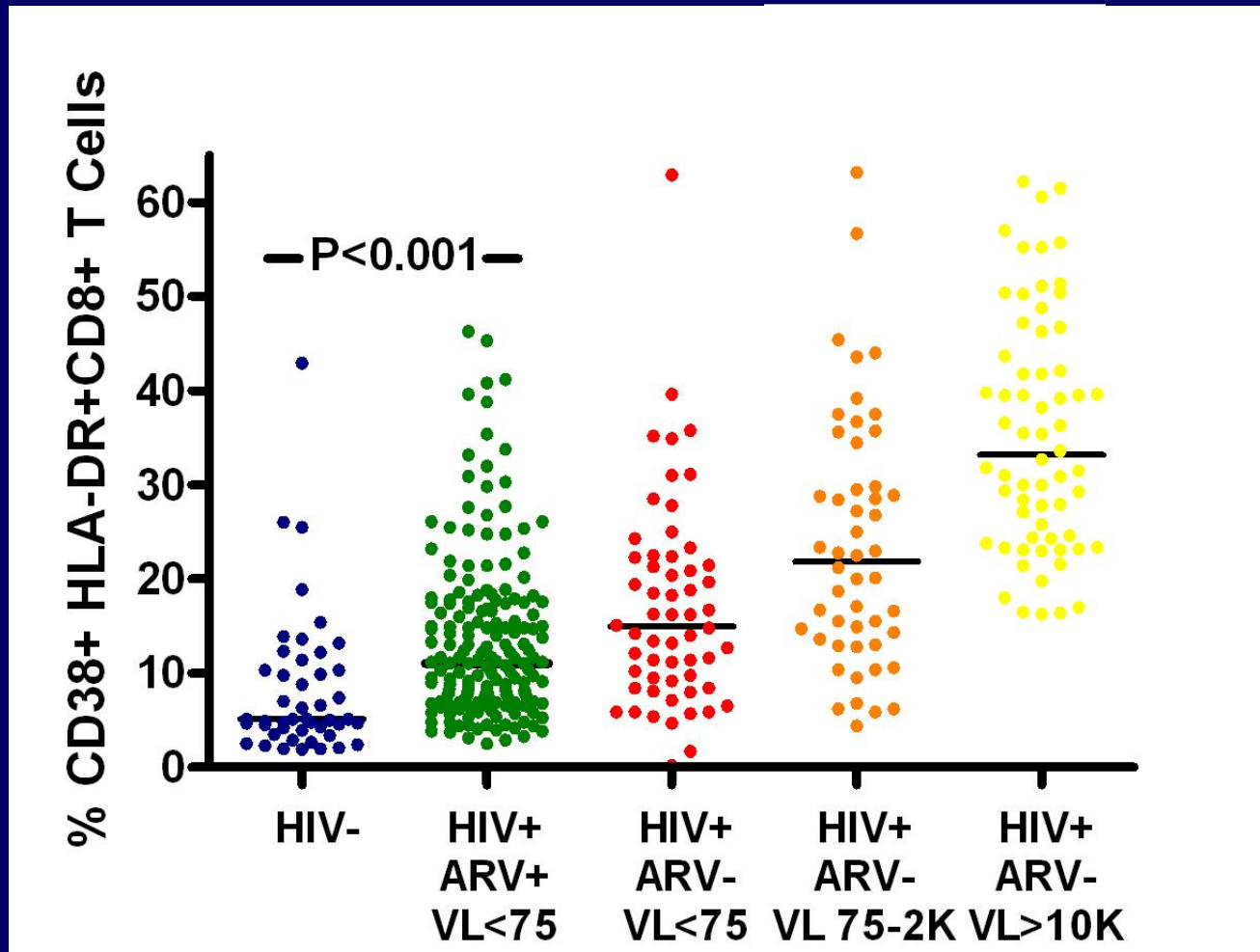
T Cell Activation Declines with Lower Levels of Viral Replication



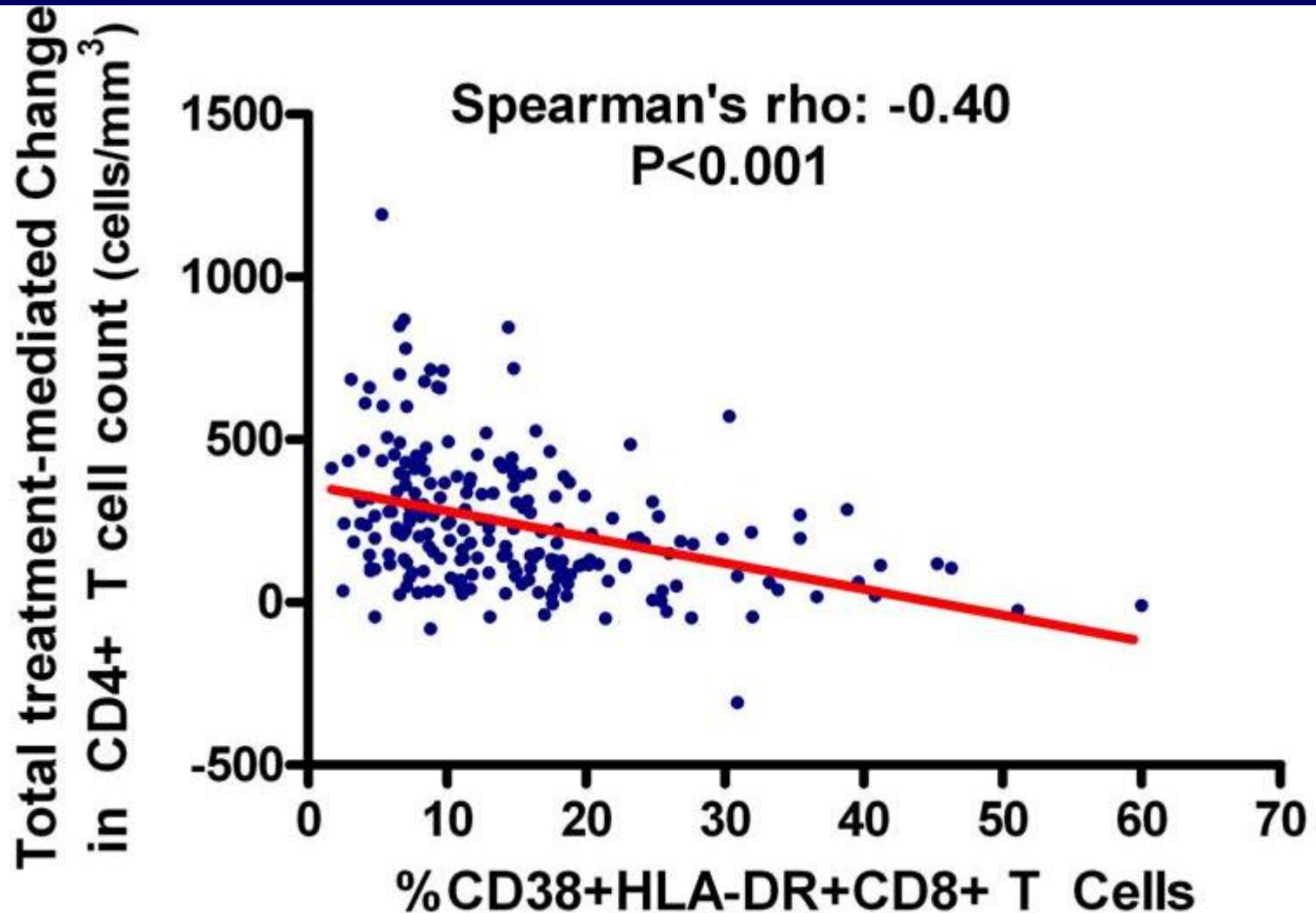
T Cell Activation Declines Further During ART-mediated VL Suppression



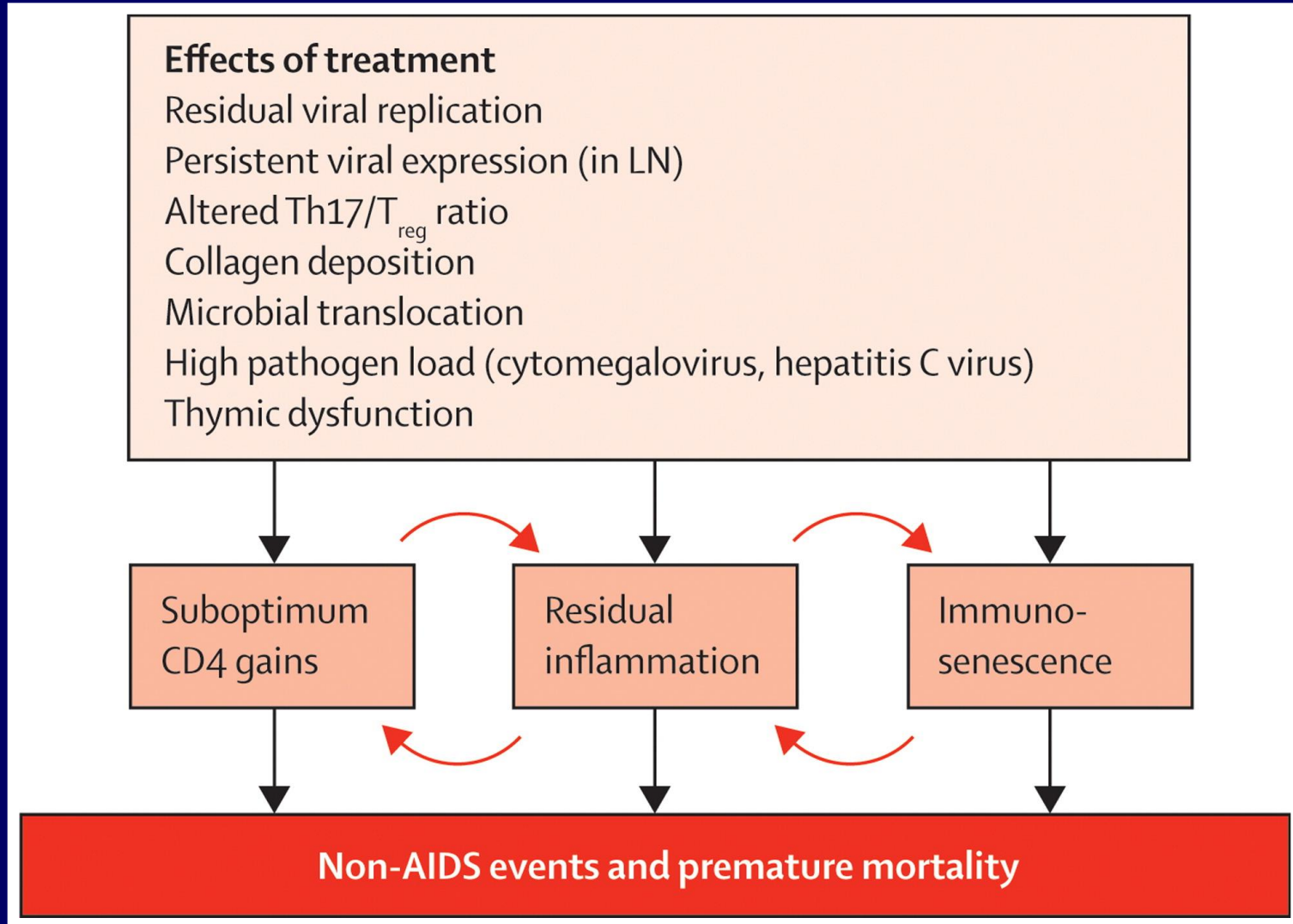
...but ART-suppressed Patients Have Persistently Abnormal T Cell Activation



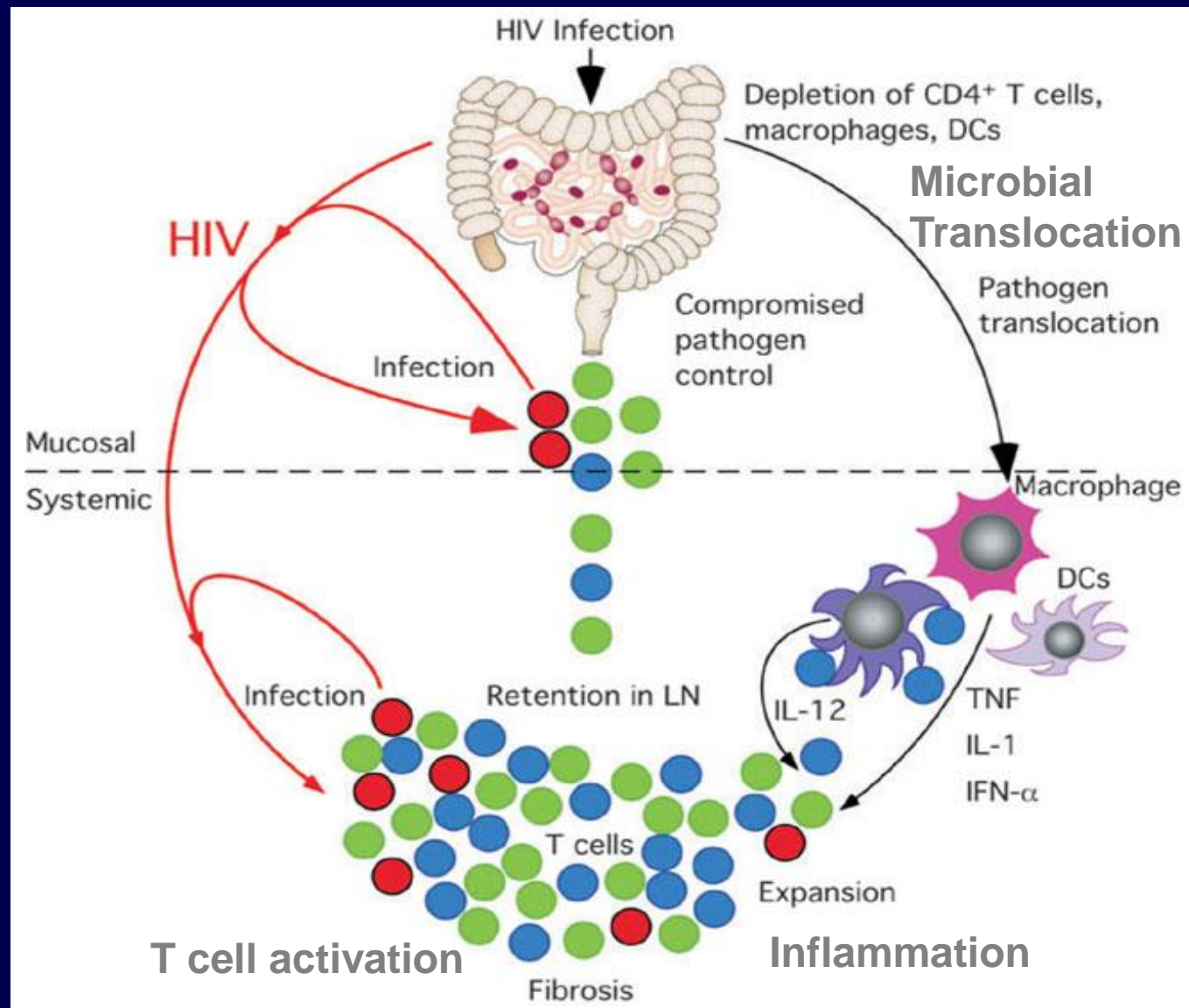
High T Cell Activation Associated with Blunted CD4 Recovery



Determinants of Accelerated Aging in HIV Infection



Implications of Mucosal CD4 T Cell Depletion, Barrier Defect, and Inflammation



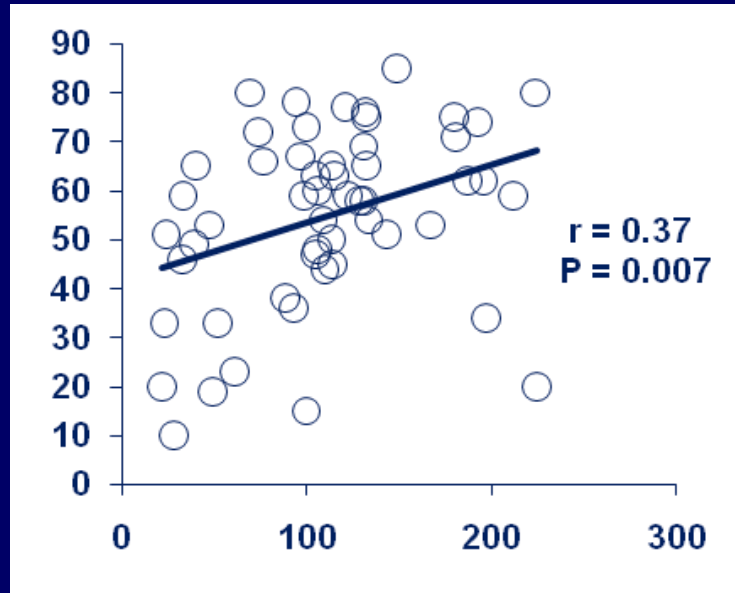
Markers of Microbial Translocation

- LPS – Lipopolysaccharide
- LBP - LPS binding protein
- Soluble CD14
- IFN- α

Microbial Translocation Correlates With Immune Activation and Inversely With Immune Reconstitution

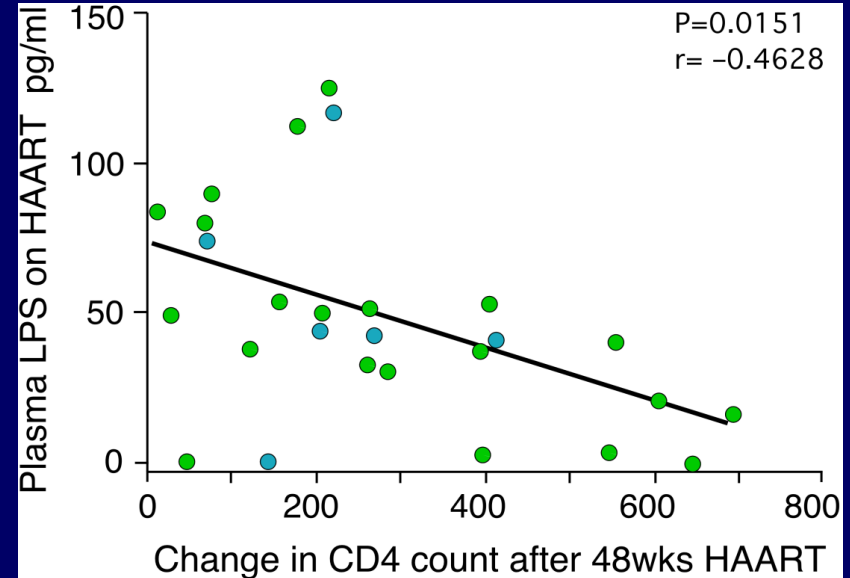
A

%CD8⁺CD38⁺DR⁺

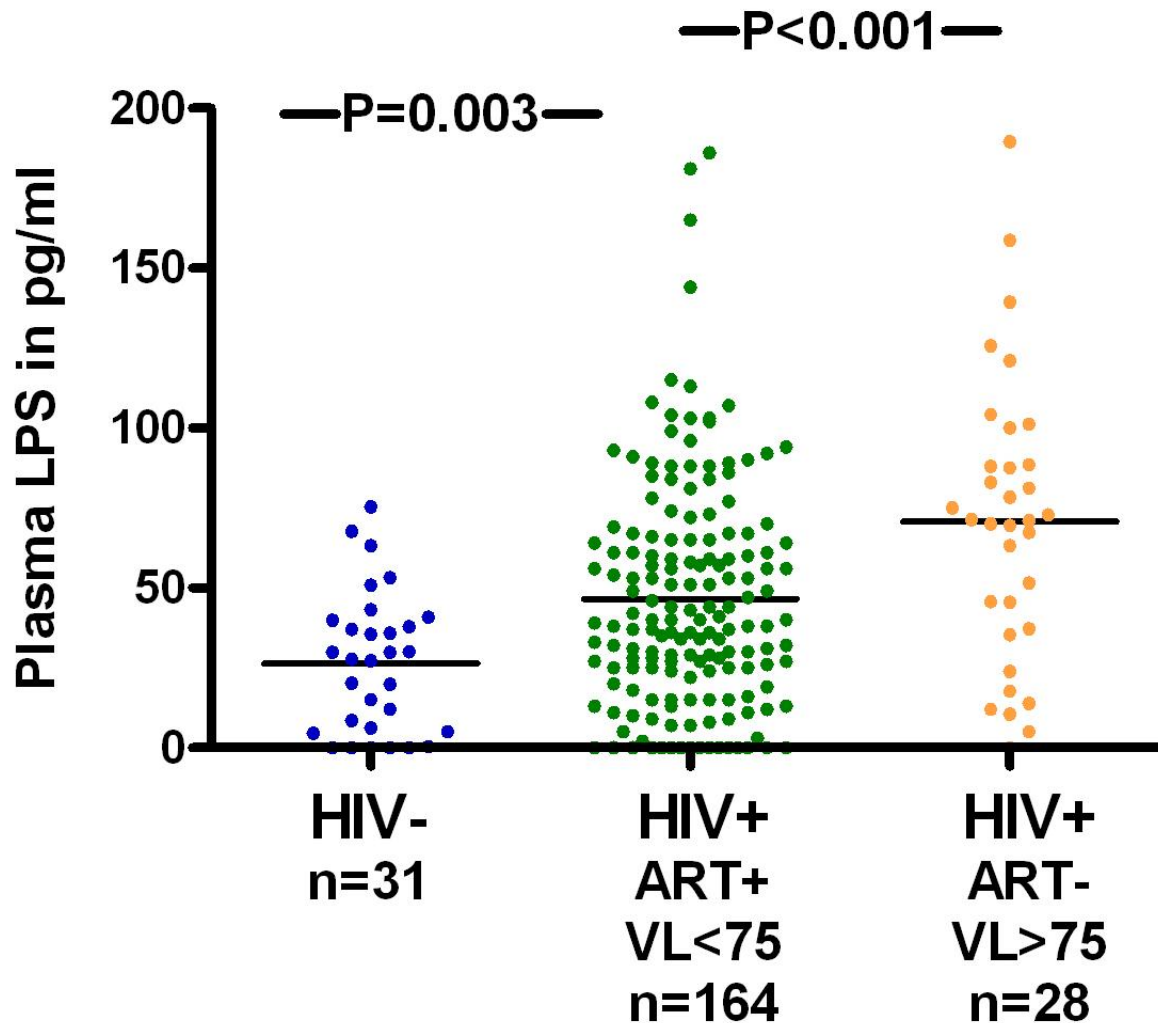


Plasma 16S rDNA (copies/μl)

B



Microbial Translocation Decreases with HAART but Persists for Years



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

Consequences of Microbial Translocation

Inflammation
Chronic Immune Activation
Altered Microbiome



HIV disease progression
Non AIDS defining Co-morbidities
Early Aging

Unresolved Questions Around Persistent HIV-associated Inflammation

- Any interventions that actually improve clinical outcomes?
- How much non-AIDS morbidity is due to ongoing inflammation vs. irreversible damage accumulated prior to HAART?
- Does HIV cause irreversible aging of the immune system?

Aging With HIV Disease

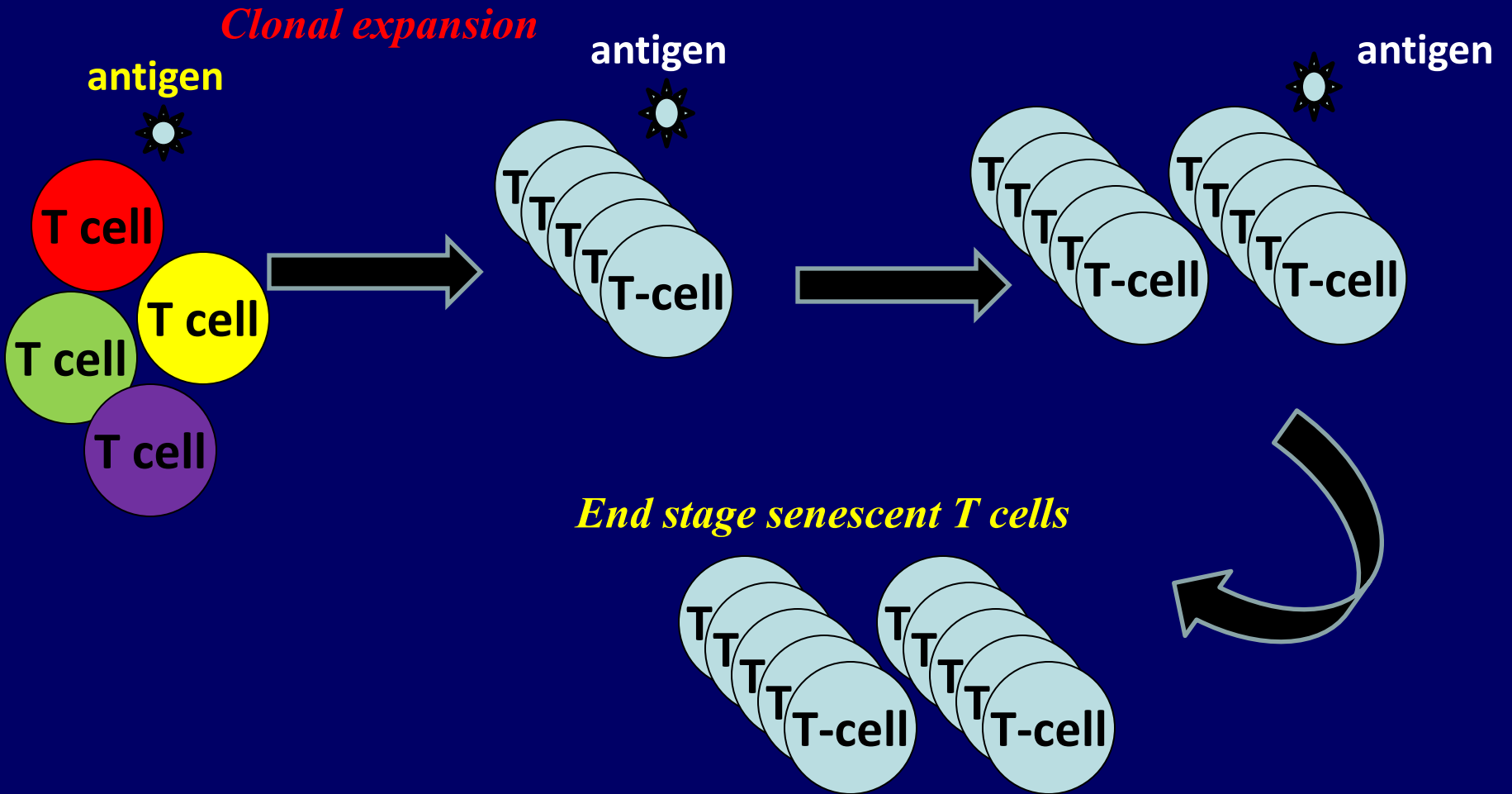
- At 25 years into the HIV epidemic many HIV-infected patients have survived to older ages.....by 2015, > 50% of the HIV-infected population will be > 50 years of age^[1]
- Late HAART Era Patients Have an Extended Life Expectancy though still Have a 10y Shorter Life Expectancy than HIV-Negative Controls^[2]
- Results from the SMART study showed that non-AIDS defining co-morbidities occur despite HAART^[3]
- Several immunological alterations such as activation/inflammation that characterize HIV-1 infection are similar to those associated with normal aging
- Thus, immunological and physiological alterations along with co-morbidities suggests that advanced aging occurs in HIV disease

1. Effros RB, et al. *Clin Inf Dis*. 2008;47:542-553. 2. Lohse N, et al. *Ann Intern Med* 2007;146:87-95. 3. El Sadr W, et al. *N Engl J Med*. 2006;355:2283-2296.
4. Desai et al, *Current HIV AIDS Rep* 2010; 7:4-10.

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

Mechanism Leading To End Stage Senescence



Senescent T cells affect organ Function

Immune system

- ↓ Proliferation, killing
- ↑ Pro-inflammatory cytokines function as suppressor cells
- Correlate with poor vaccine response

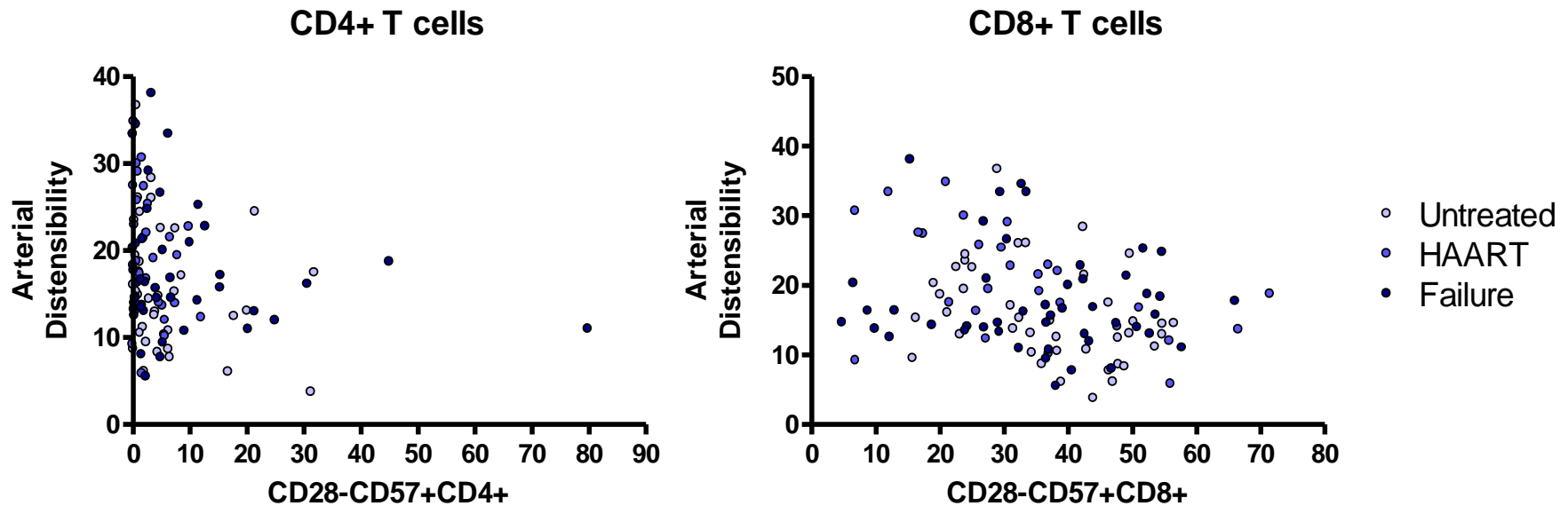
Neurocognitive (Alzheimer's disease)

Telomere length correlates with disease status

Bone

Correlate with osteoporotic fractures
IL-6, TNF- α correlates with bone loss

A higher frequency of senescent T cells is associated with lower arterial distensibility (WIHS)



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)

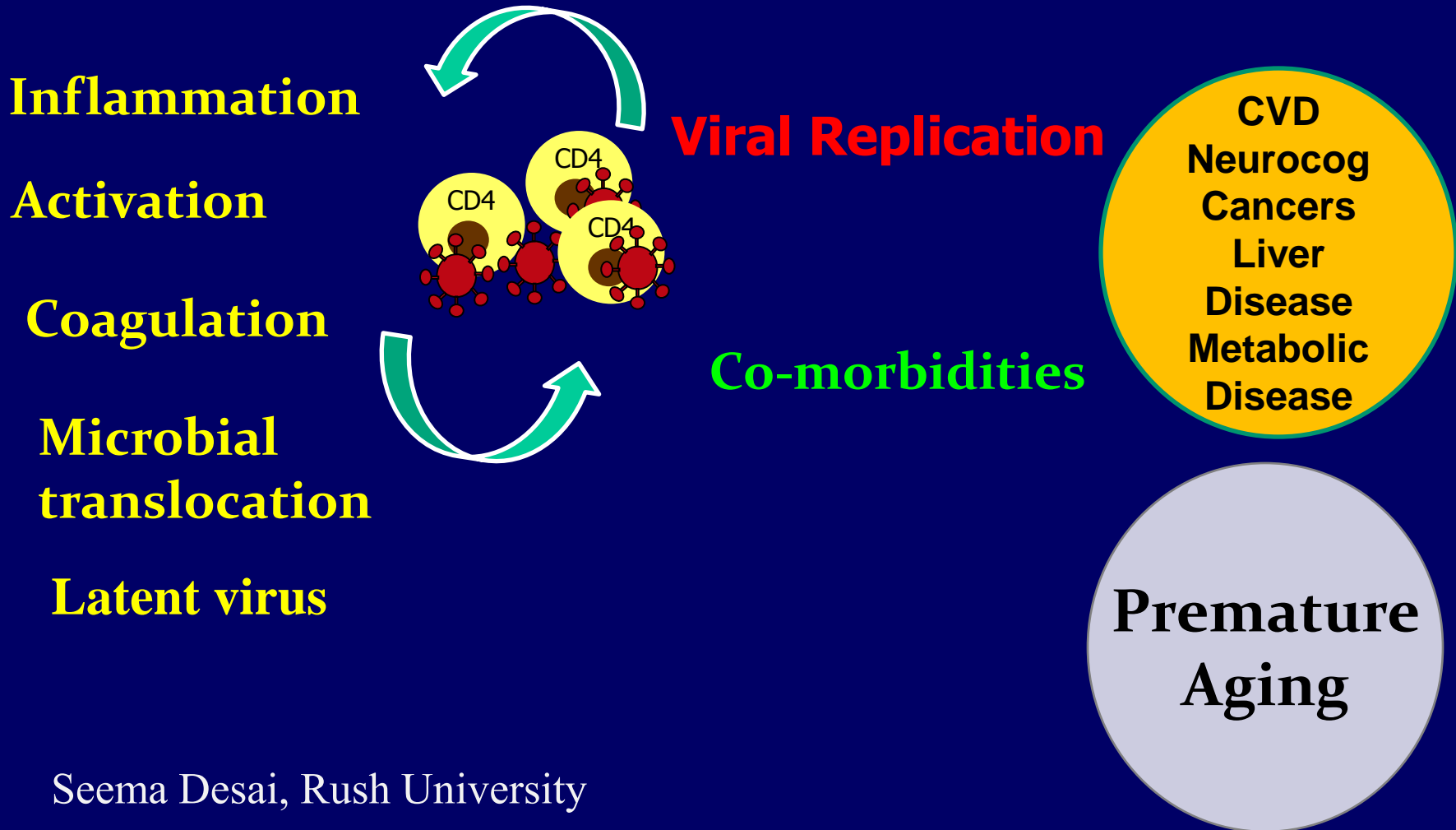
T-cell activation and carotid lesions

Multivariate analyses, HIV+ patients

	<i>Prevalence</i>		
	<i>Ratio_{SD}</i>	<i>95% Conf</i>	
	<i>Lesions</i>	<i>Interval</i>	<i>p</i>
CD4+ T-cell activation	1.6	1.1, 2.2	0.02
CD8+ T-cell activation	2.0	1.2, 3.3	<0.01
C-reactive protein	1.0	0.6, 1.4	0.84

Adjusted for HIV medication use, age, race, education, income level, family history of MI, smoking, alcohol consumption, opiate use, injection drug use, study site, lipids, glucose, BMI

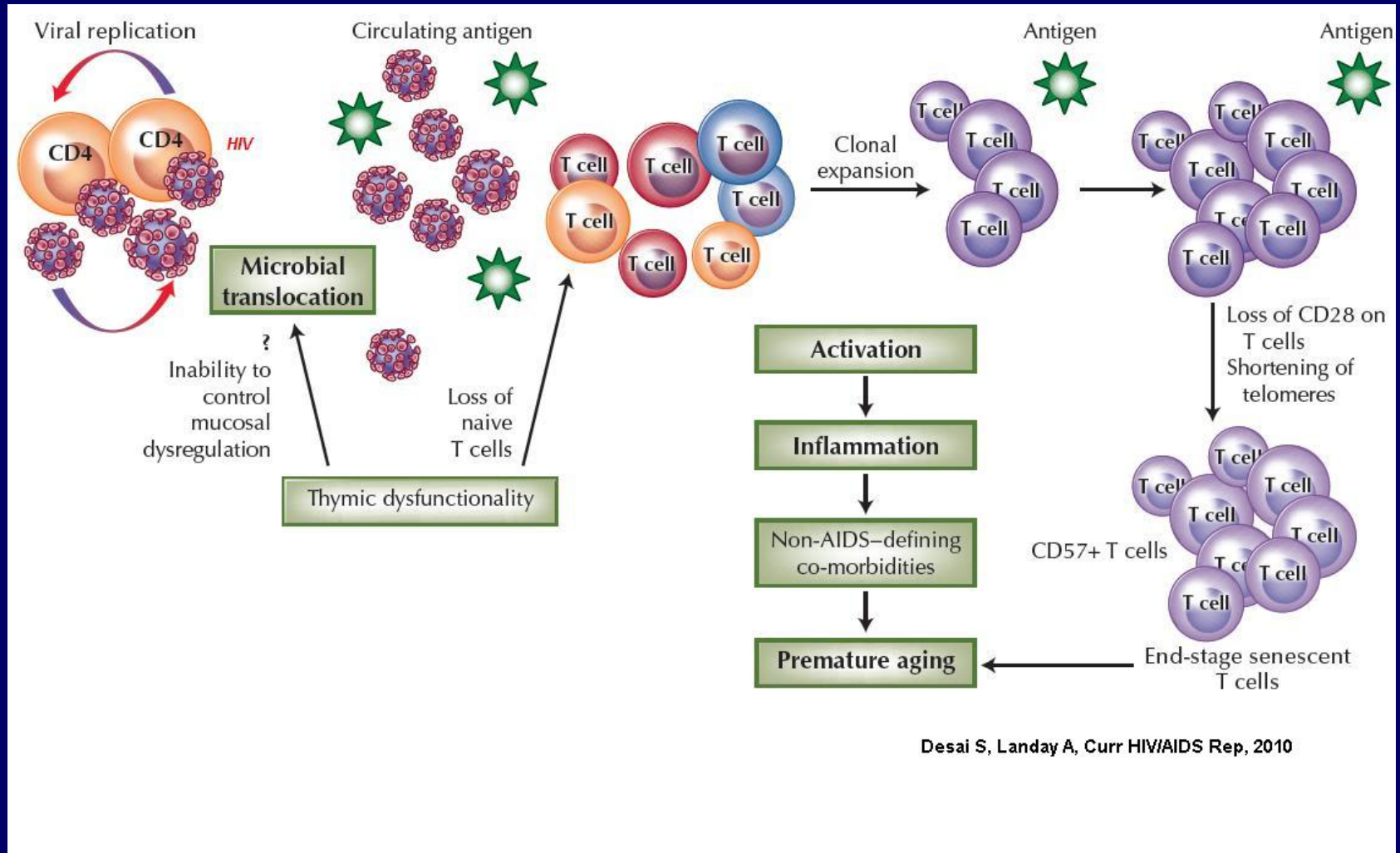
Causes & Consequences of Co-morbidities In HAART Treated HIV Infected Patients



Modalities of De-accelerating Senescence

- HAART: reduces naive T-cell consumption and helps to restore their numbers, although sub-optimally
- Inhibitors of pro-inflammatory cytokines (eg, anti-IL-1 β , anti-IL-6, or anti-TNF- α)
- Controlling translocation: Antagonists of TLR-4, antibiotic (Rifaximin) to restore gut flora and prebiotic sugar to select good bacteria. Sevelamer to block endotoxin.
- Adjuvant therapies such as r-hIL-7 to stimulate recent thymic emigrant and increase the naïve pool.
- Telomerase-based approaches such as TAT2 (cycloastragenol) that activate telomerase could slow telomere loss
- Others targeting immune exhaustion need to be explored.

Immune Aging Model



Desai S, Landay A, Curr HIV/AIDS Rep, 2010

**What have we learned,
a quiz**

Which of the Following Can Contribute to Immune Activation/Inflammation in HIV+

1. Low level viral replication
2. Microbial translocation
3. Co-infections
4. All of the above

Chronic Immune Activation- quiz

1. Improves the clinical response to antiretroviral therapy
2. Is not important as long as patients are adherent to their medications
3. Associated with early aging
4. Effectively increases CD4 counts

Early Aging in HIV+ Patients

1. Associated with a normal immune response to vaccines
2. Characterized by development of non-AIDS co-morbidities, i.e. cardiovascular disease
3. Improves with antiretroviral intensification
4. Does not impact life expectancy of HIV+ patients