

# Aging gracefully with HIV: how did we get here and where are we going?

Julian Falutz MD, FRCPC

Immunodeficiency Treatment Center

Division of Geriatrics

McGill University Health Center

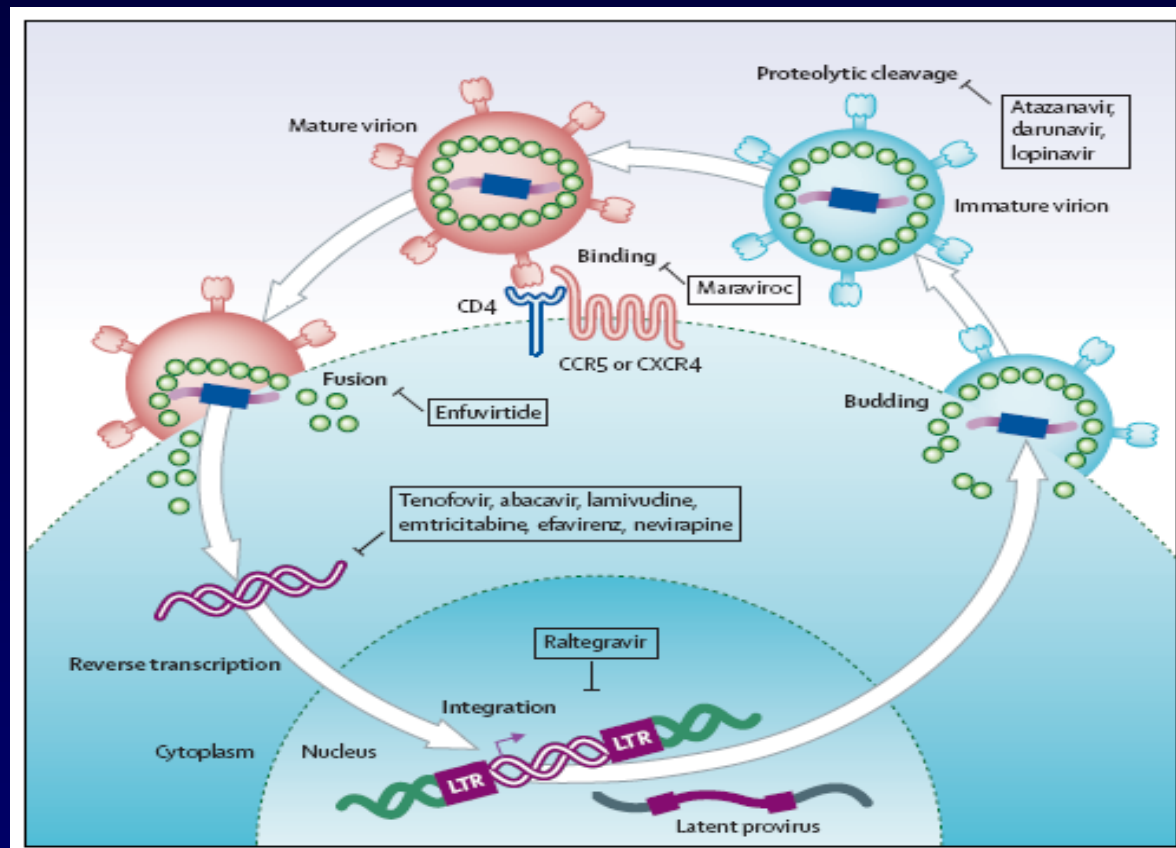
# Financial Disclosure

- Consulting: Theratechnologies
- Advisory Boards: Abbott, BMS, Tibotec
- Speaker Bureaus: BMS, Abbott, GSK,  
Serono EMD, ViiV

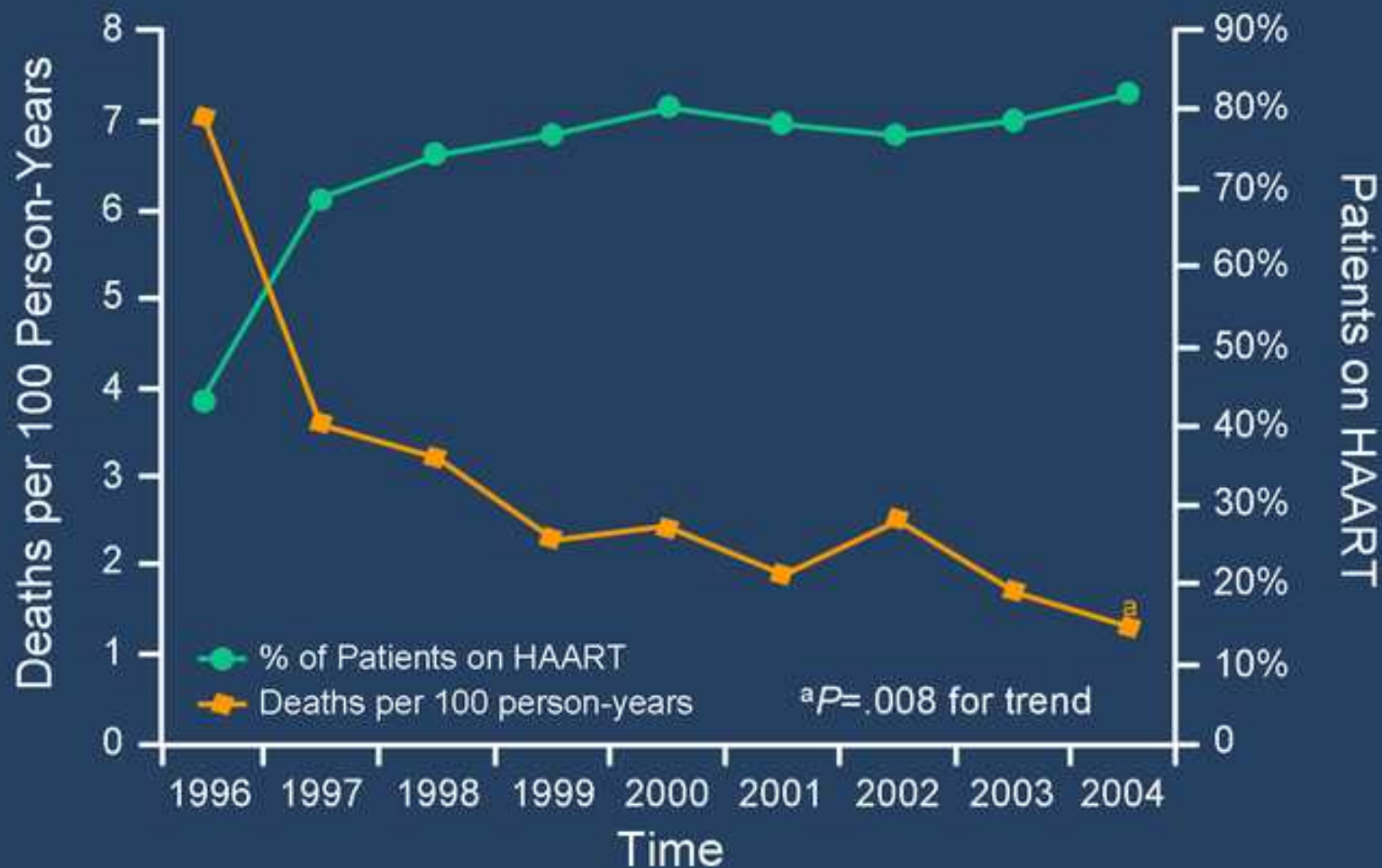
# Goals

- Discuss changing epidemiology and demographics of HIV in older persons
- Discuss evolving spectrum of clinical conditions and possible pathophysiologic contributors

# HIV life cycle and drug targets



# Mortality and HAART Over Time



HAART, highly active antiretroviral therapy. Palella FJ et al. *J Acquir Immune Defic Syndr*. 2006;43:27-34.

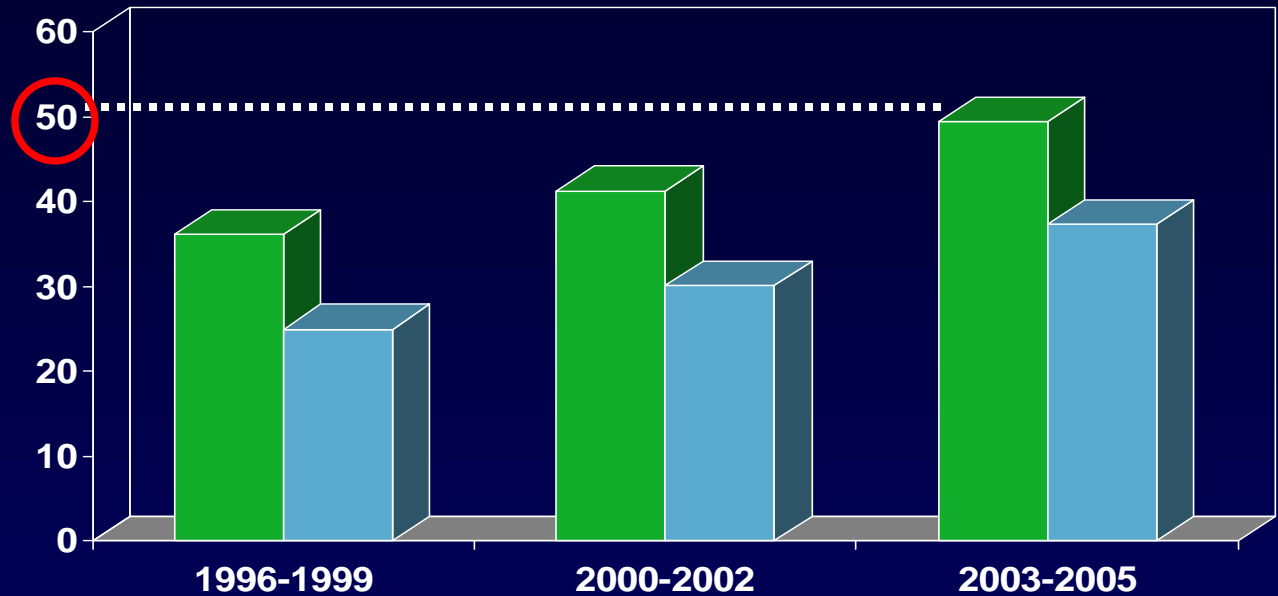
# Survival of treated HIV patients

Stratified by  
treatment period

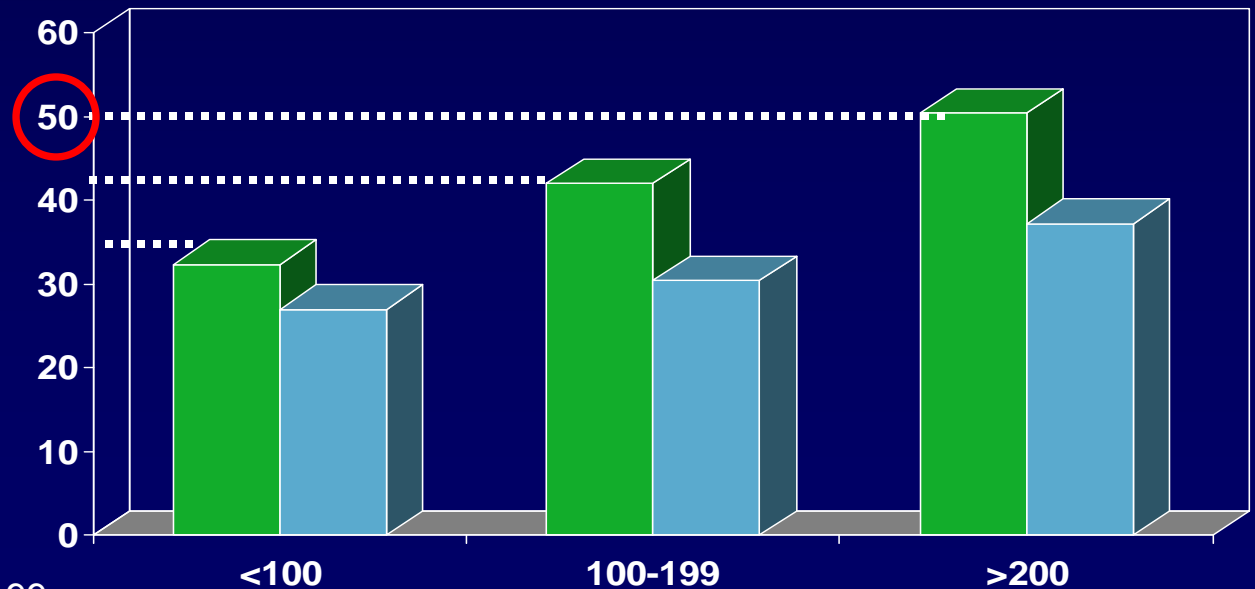
Age at diagnosis

Age 20 ■

Age 35 ■

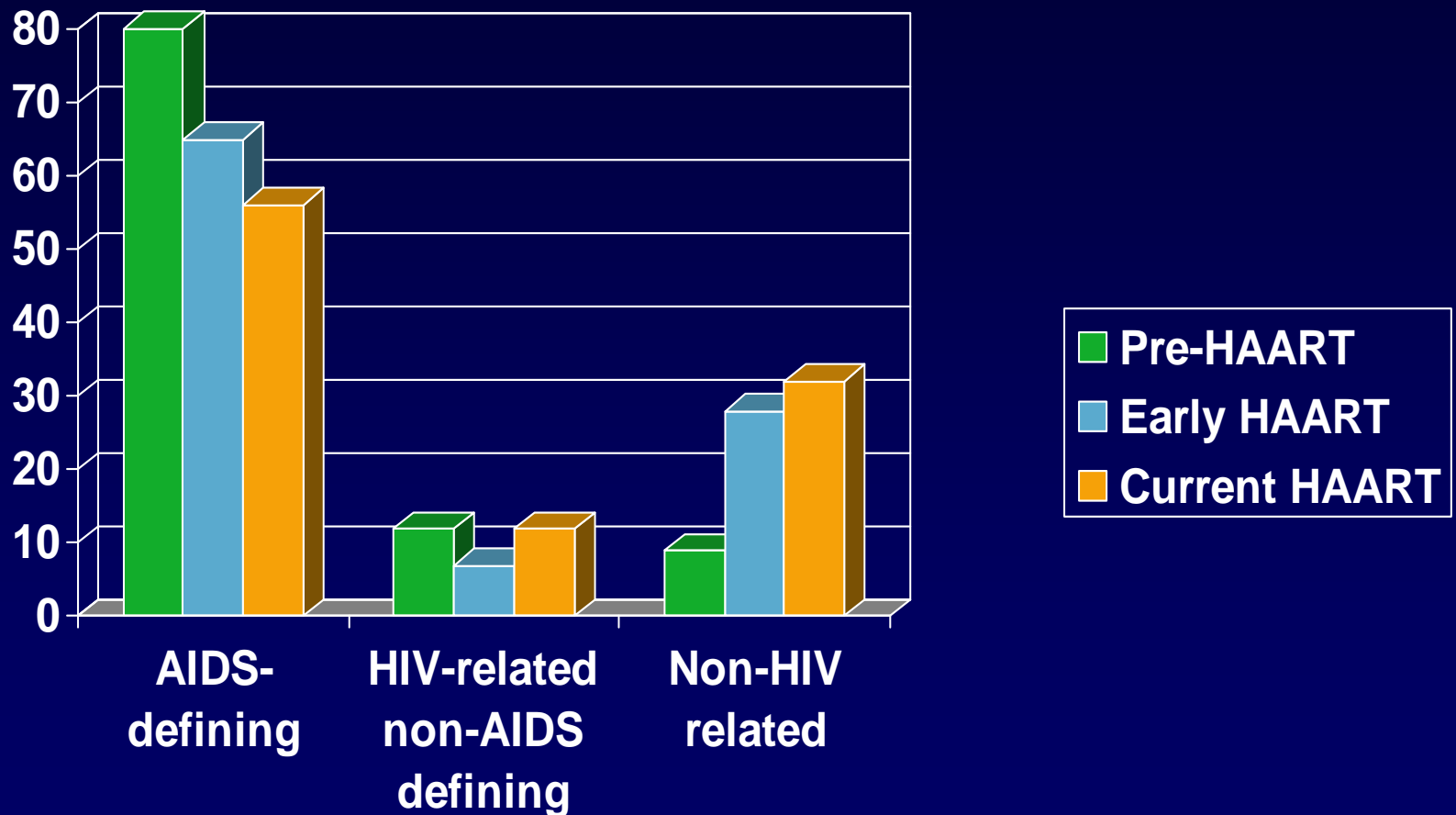


Stratified by  
baseline CD4



**But, “success”  
comes at the price  
of “unexpected”  
consequences...**

# Changing causes of mortality: decrease in AIDS-related but increase in serious non-AIDS-related events (*SNARE*)



# Complications in HAART-responding HIV pts consist of Serious Non-AIDS Related Events (*SNARE*): associated with low nadir or most recent post-HAART CD4+ cell count <500

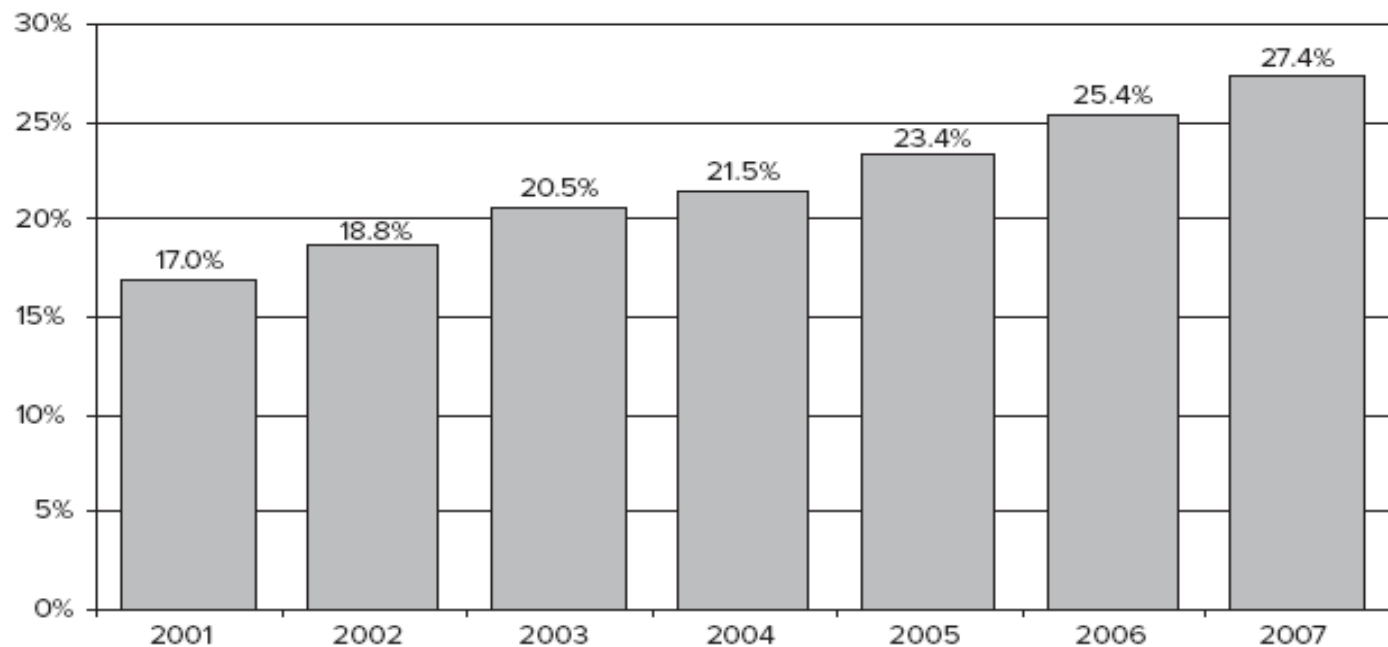
- Non-AIDS malignancies [1]
- Liver disease [1]
- Non-AIDS infections [1]
- Bone demineralization [2]
- Myocardial infarctions [3]
- HIV-associated dementia and non-dementia cognitive dysfunction [4]

1. Marin B et al. AIDS. 2009;23(13):1743-53
2. Dutronc H et al. CROI 2010. Abstract 762
3. Lichtenstein K et al. CID 2010;51:435-47
4. Wright EJ. Curr Opin HIV/AIDS. 2009;4:447-52

# Changing Demographics

# Prevalence of HIV+ persons > 50 y.o. is increasing: *50% predicted by 2015*

**Estimated percentage of persons living with HIV/AIDS who are 50+  
by year, 2001–2007**

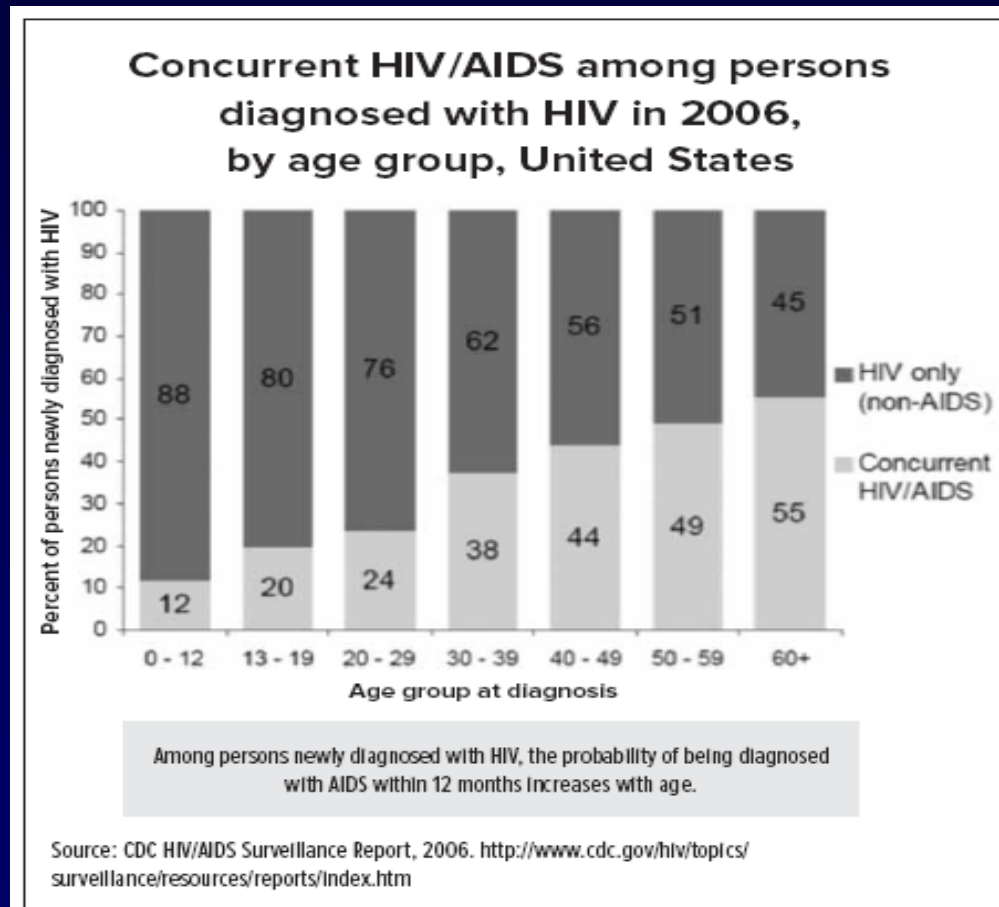


For years 2001-2003, data is based on 33 states and U.S. dependent areas with confidential name-based HIV infection reporting, *Centers for Disease Control: HIV/AIDS Surveillance Report, 2005*. For years 2004-2007, data is based on 34 states and 5 U.S. dependent areas with confidential name-based HIV infection reporting, *Centers for Disease Control: HIV/AIDS Surveillance Report, 2007*.

# Older HIV Patients

- Successfully treated *chronically infected* patients
- *New seroconverters*

# Older persons are often diagnosed with HIV concurrently with their first diagnosis of an AIDS-defining illness: **delayed Dx**



# Prevalence of modes of HIV transmission differ by age and gender

Males

Females

15-49 yo: MSM > ? > Hetero = IDU

Hetero > ? > IDU

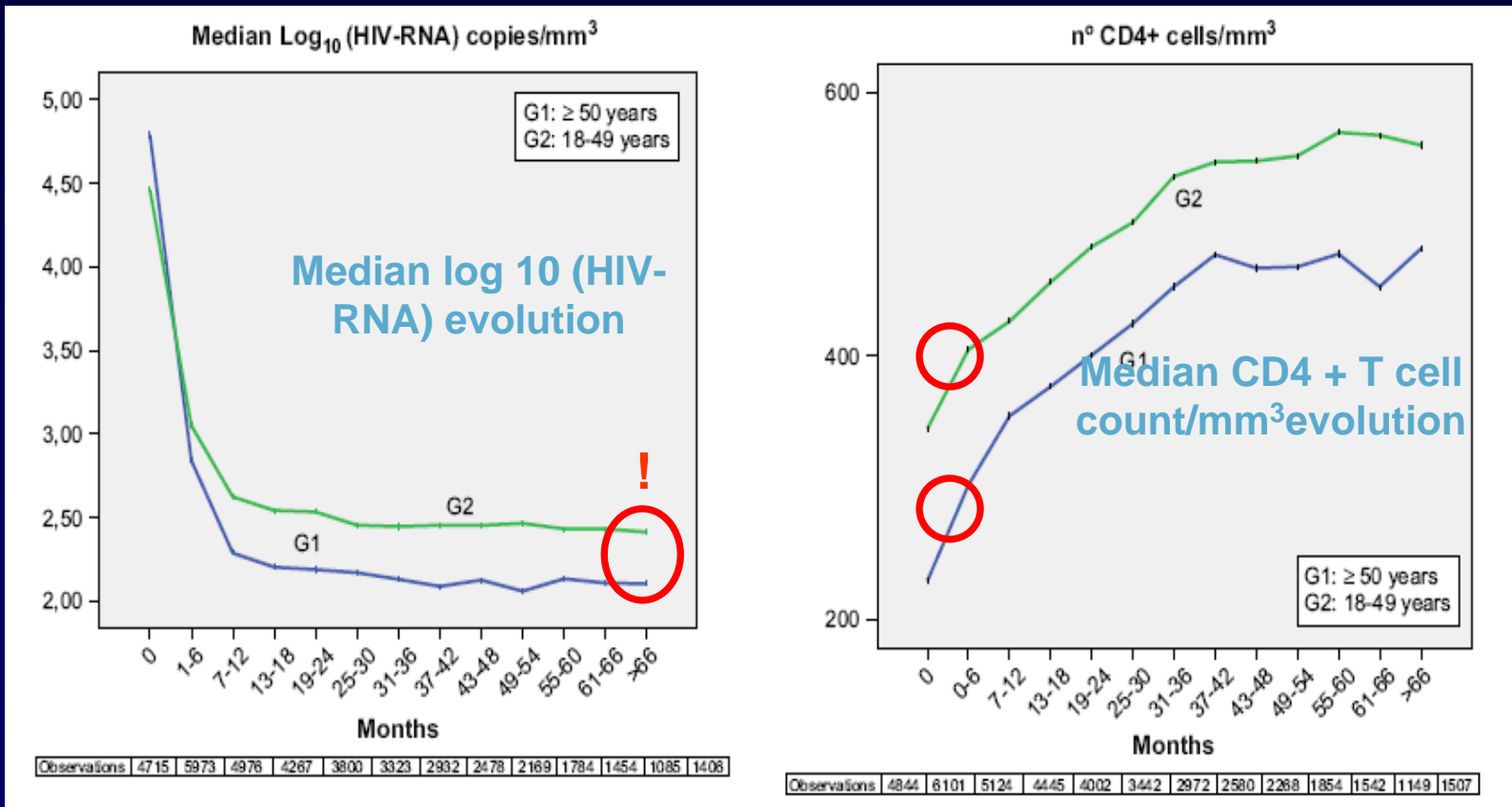
>50 yo: ? > Hetero > MSM = IDU

Hetero > ? > IDU

? = unknown

# **Age-related treatment response characteristics**

# Similar HIV RNA but **lower CD4 cells** at baseline after HAART in patients <50 yrs old>



Nogueras M et al. BMC Inf Dis 2006;6:159

**Link between HIV  
and *SNAREs*:  
Inflammation**

**PIRE**

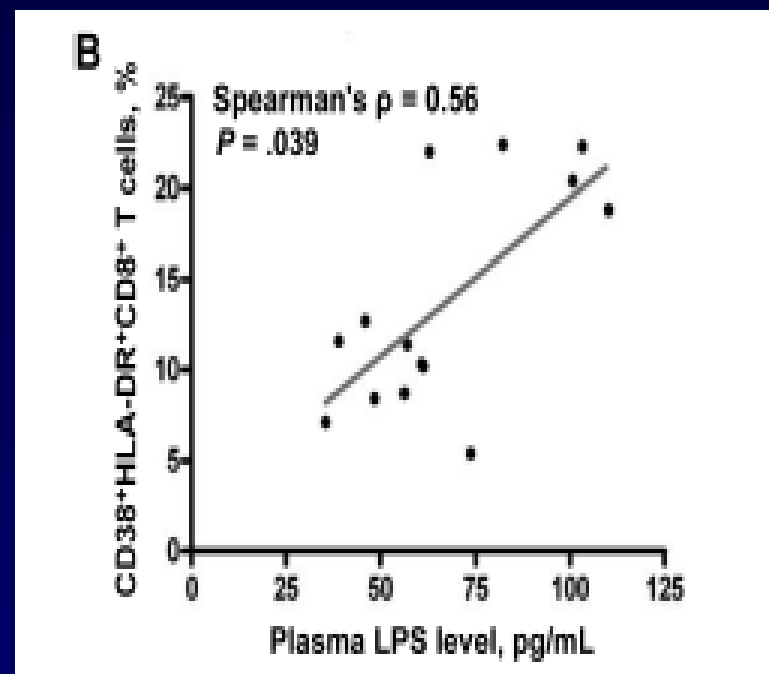
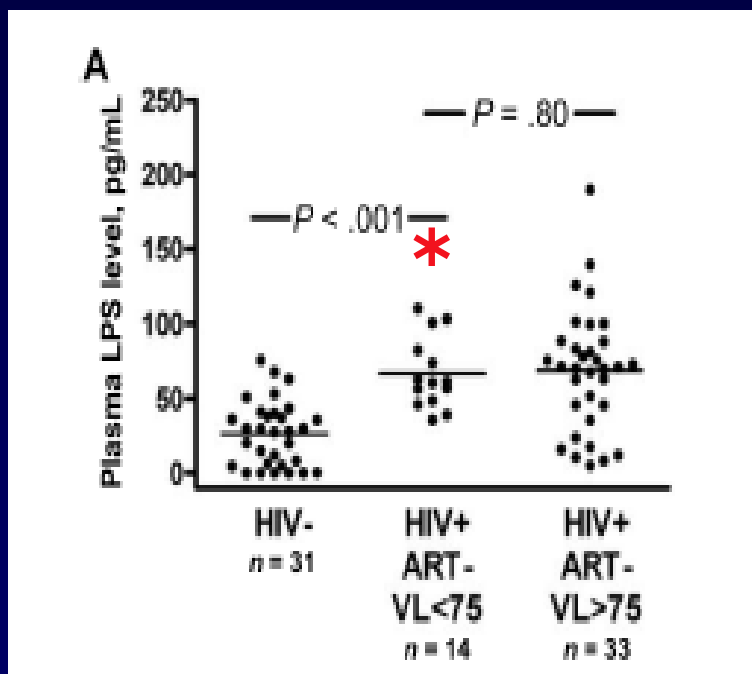
**Ongoing, *low-level*, HIV  
replication is associated with  
increased inflammatory markers**

# Chronic inflammation in treated HIV

## Association with immune activation

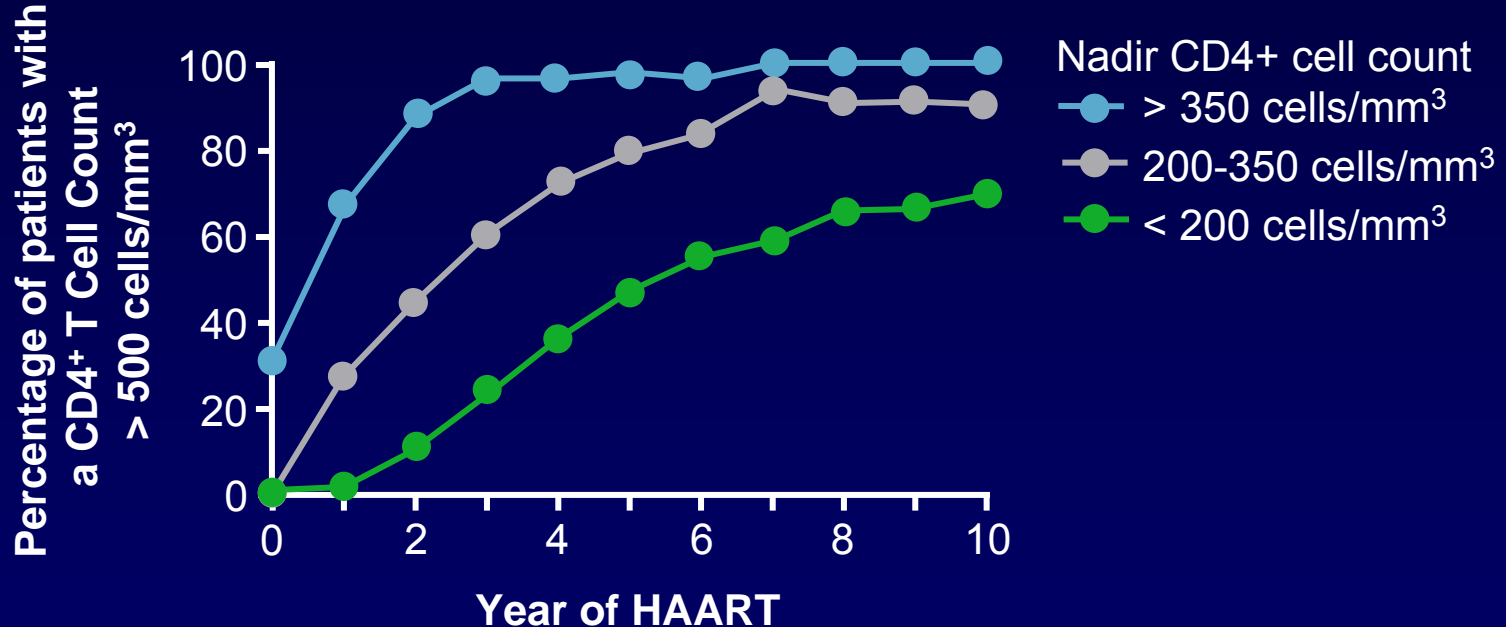
- Ongoing low-level HIV replication
- Microbial translocation
- Co-infection with HBV, HCV
- Accelerated immunosenescence

# LPS levels (marker of microbial translocation) are elevated in HIV pts *regardless of Rx* and correlate with T-cell activation markers



NB: GIT is "leaky" in normal aging

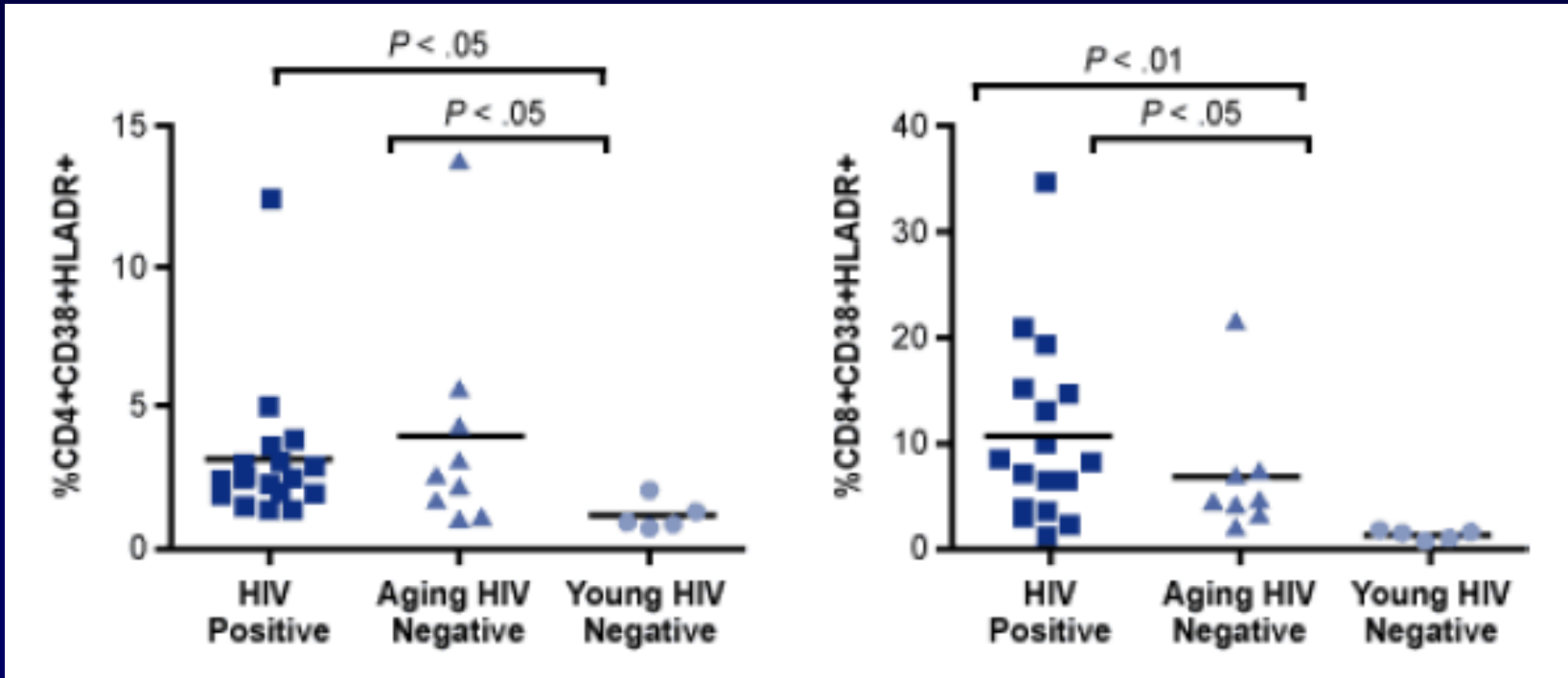
# Several factors predict poor immune recovery (ie CD4 increase to >500) on HAART: nadir CD4s, age



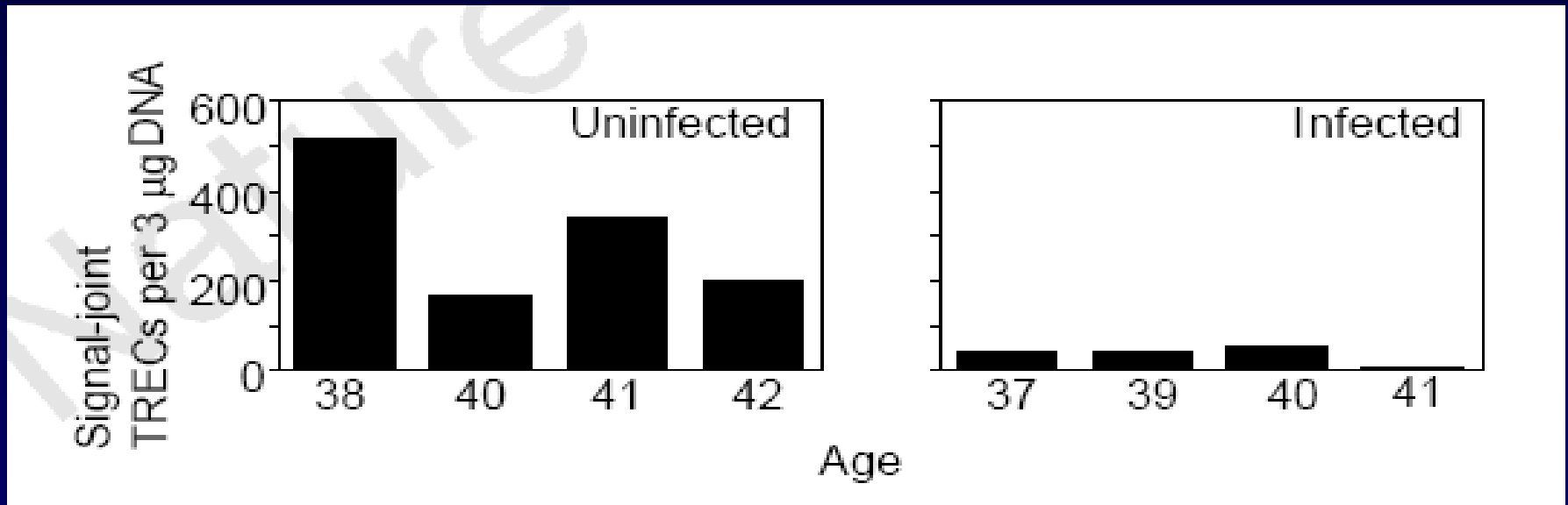
# **Immunosenescence (aging immune system)**

**HIV infection induces accelerated aging and  
homeostatic changes in the  
naïve CD4+ T-cell compartment**

# Immune activation levels in HIV-1 infected patients are *similar* to older HIV-neg subjects

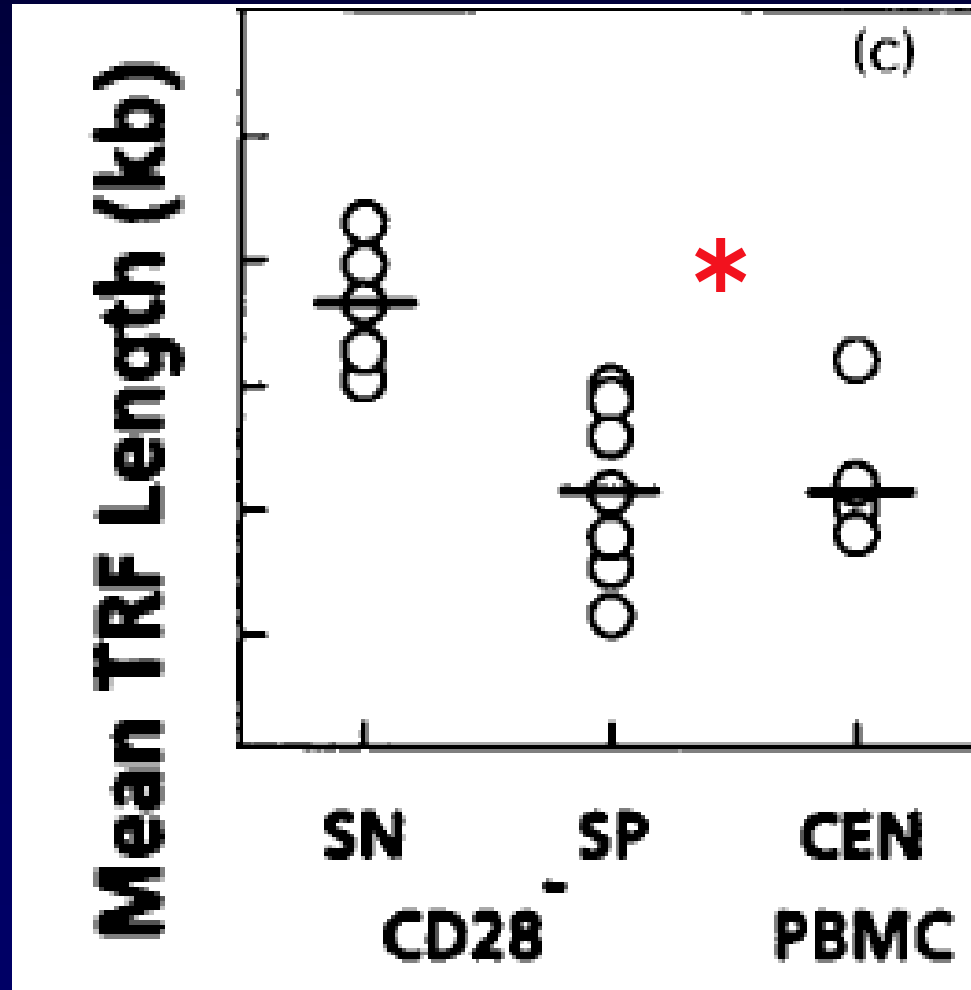


# Markers of thymic output (TREC\*) are significantly reduced in HIV pts c/w healthy controls



\* TREC – T cell receptor Rearrangement Excision Circles:  
marker for recent thymic emigrants

# Similar telomere length in HIV+ vs healthy 100 y.o.'s implicate immunosenescence in HIV pathogenesis

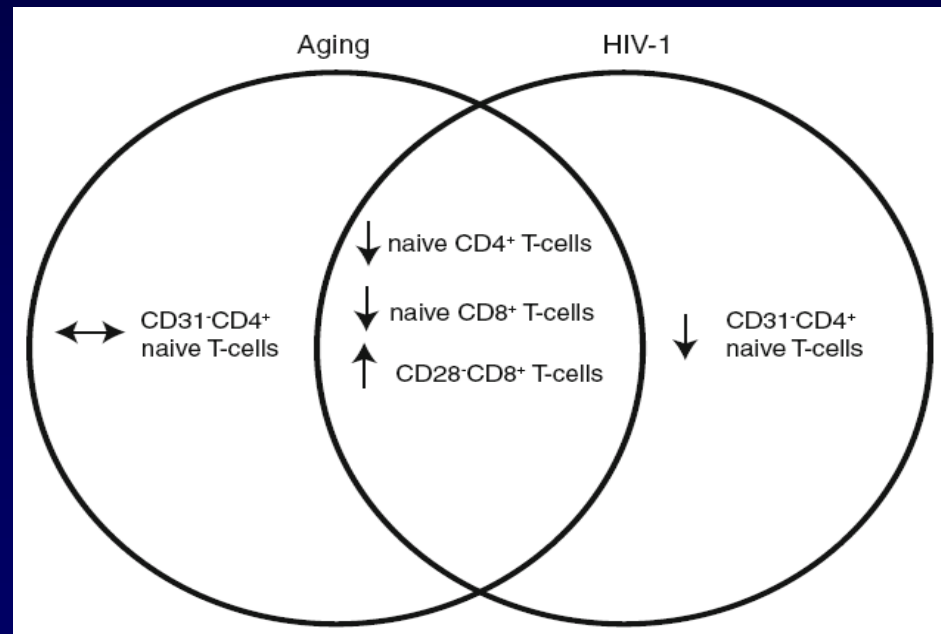


SN= seronegative

SP= seropositive

CEN= centenarian

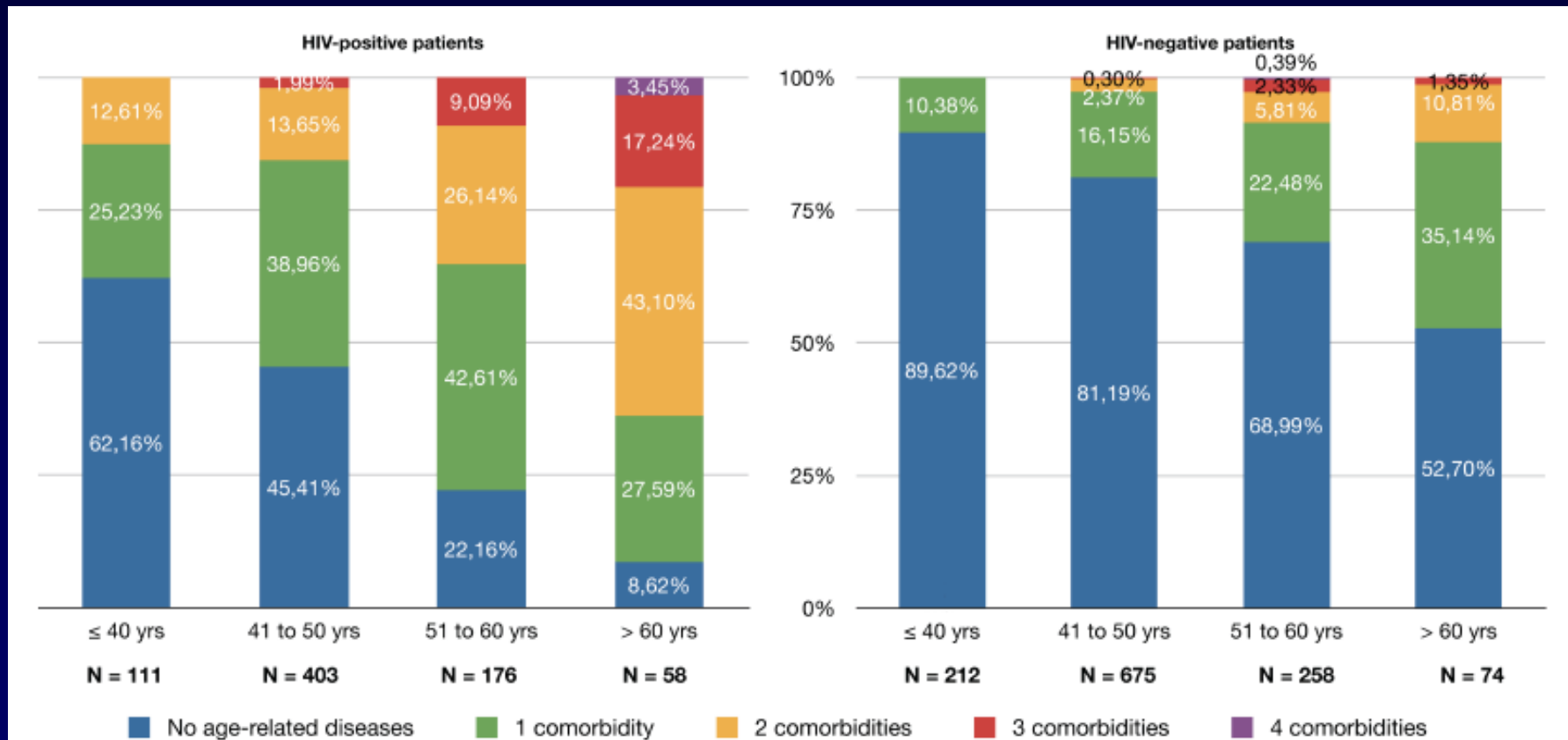
**HIV (both treated and untreated) and aging are associated with *decreased* naïve T-cells which become *hyporesponsive* to stimuli, exhibit *decreased proliferative capacity* and reach *replicative senescence***



# Clinical conditions in “aging” HIV patients characteristic of “old” age

- Bone demineralization
- Accelerated atherosclerosis
- Cognitive decline
- Frailty

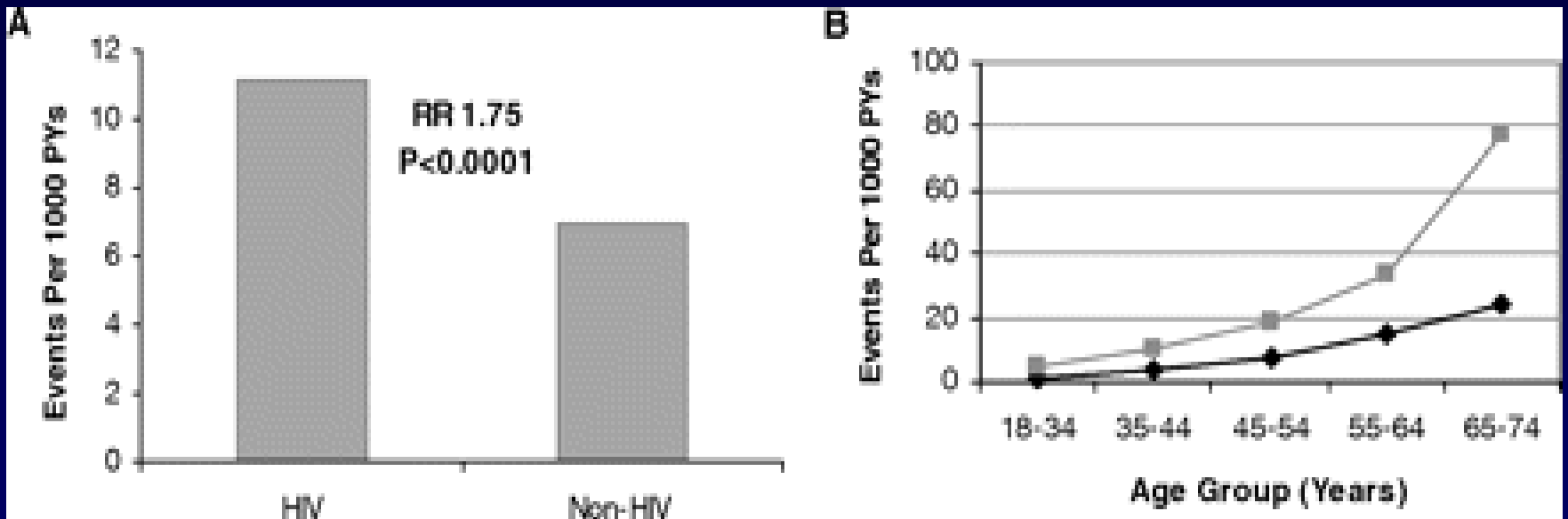
# Co-morbidities are increased in older HIV+ vs HIV-negative subjects



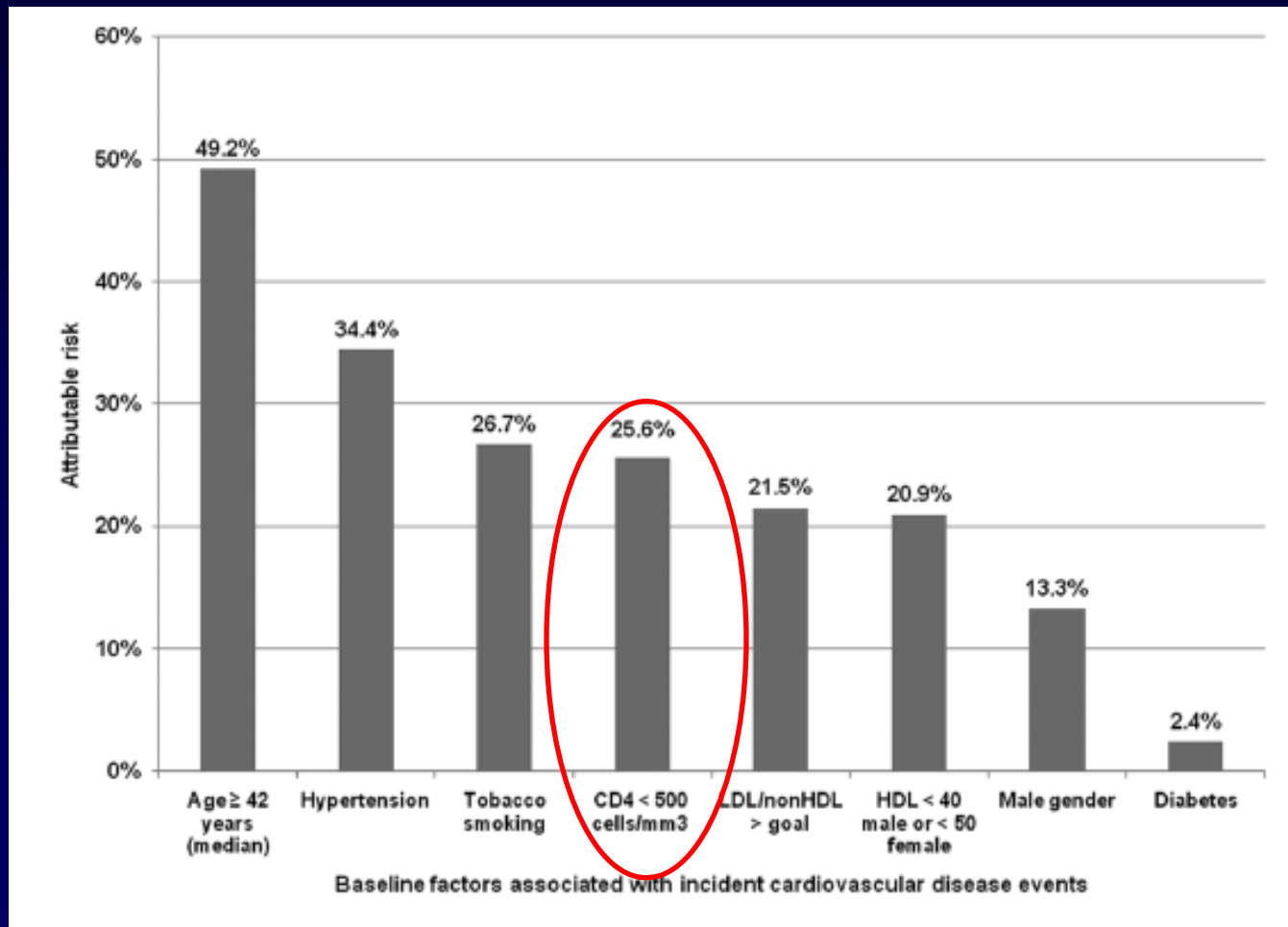
The following co-morbidities were analysed: Hypertension, Type 2 Diabetes, Cardiovascular Disease and Osteoporosis.

# **HIV, Aging & CVD Risks**

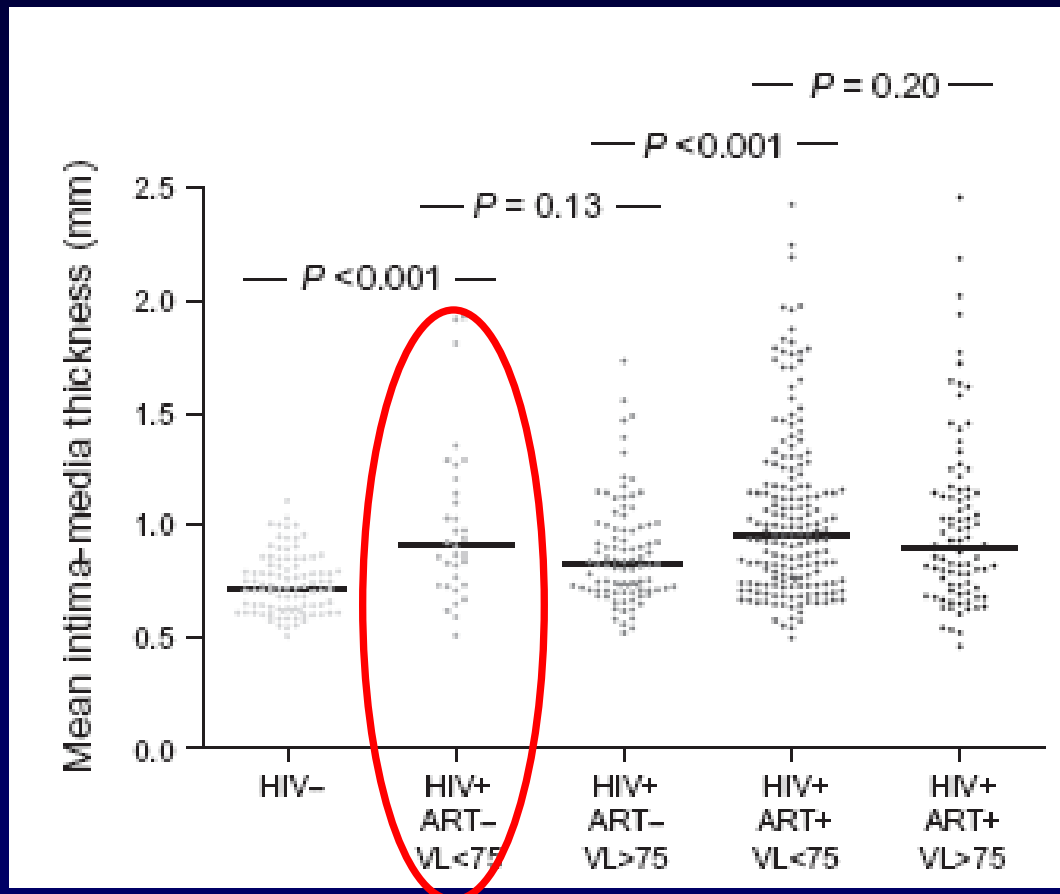
# Increased rates of acute MI and CV risks among HIV+ patients



# HOPS Study: Baseline factors associated with incident CVD



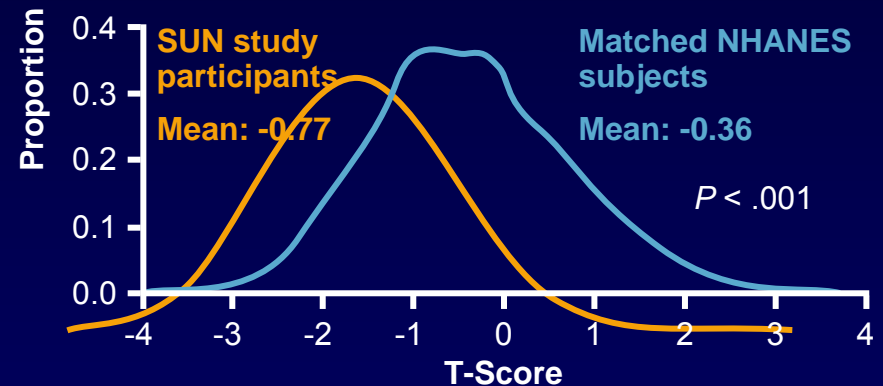
# Effects of chronic inflammation on c IMT: comparison between HIV-neg and HIV+ individuals, including “elite controllers”



# **HIV, Aging & Bone**

# SUN Study: increased prevalence of osteopenia (10X)/osteoporosis(2-3X) in HIV-infected patients

Comparison of Femoral Neck T-Scores Among SUN Study Participants and Matched Controls



## Multivariate Analysis: Factors Related to Osteoporosis

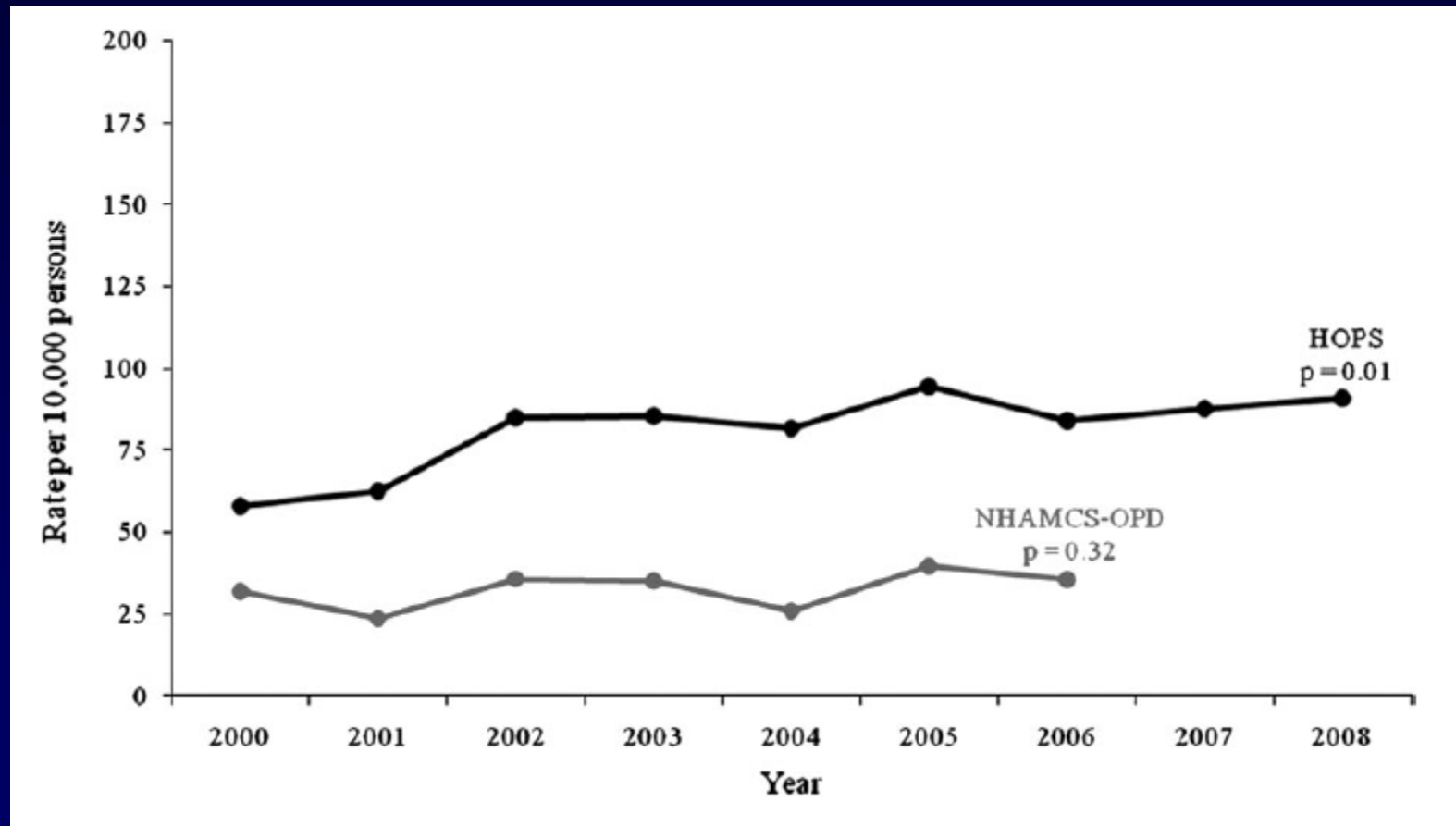
Factor	OR (95% CI)	P Value
BMI < 22.5 kg/m <sup>2</sup>	3.01 (2.24-5.69)	<.001
Age > 45 years	2.35 (1.33-4.15)	.003
BL CD4+ < 300	2.10 (1.16-3.78)	.013
HIV > 97.7 mos	1.56 (1.09-3.55)	.023

# Factors associated with osteopenia and osteoporosis in HIV+ women, compared to normal BMD: ANRS CO3 Aquitaine Cohort

	Osteopenia or Osteoporosis (n=79)	
	OR (95% CI)	<i>p</i> -value
Age (by 10 years)	1.69 (1.10;2.59)	0.02
CD4+ count nadir (/mL)	0.70 (0.54;0.91)	0.0001

OR: Odds ratio; CI: Confidence Interval

# Increased bone fracture rates among HIV pts compared to US population: HOPS Study

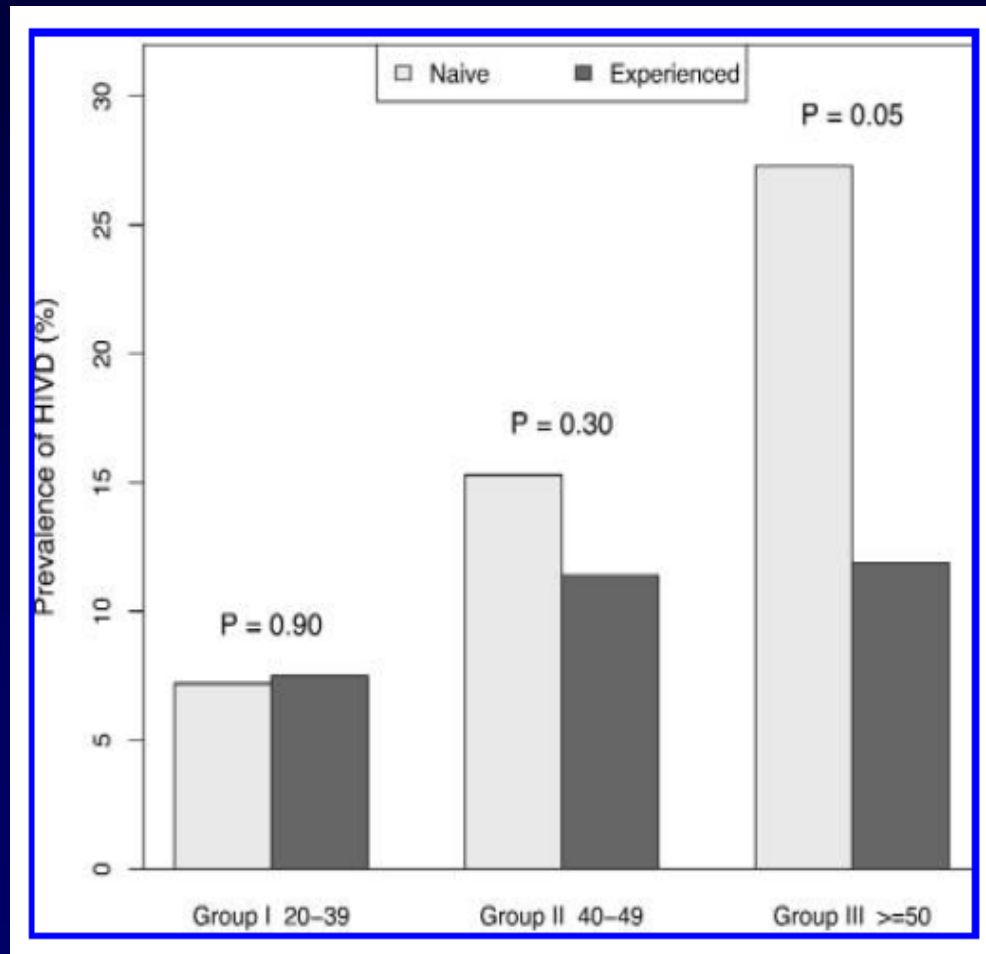


# **HIV, Aging & Cognition**

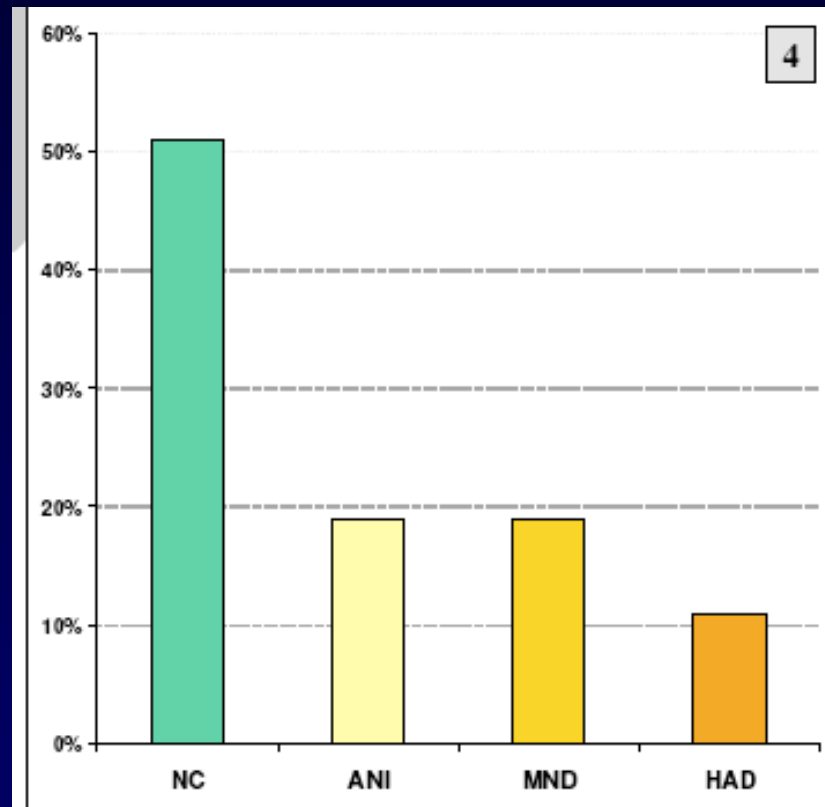
# Spectrum of neurocognitive disorders in HIV infection

- Normal
- Asymptomatic neurocognitive impairment (ANI)
- Mild neurocognitive decline (MND)
- HIV-associated dementia (HAD)

# Decreased prevalence of HIV-associated dementia (HAD) primarily in older treated HIV+ subjects

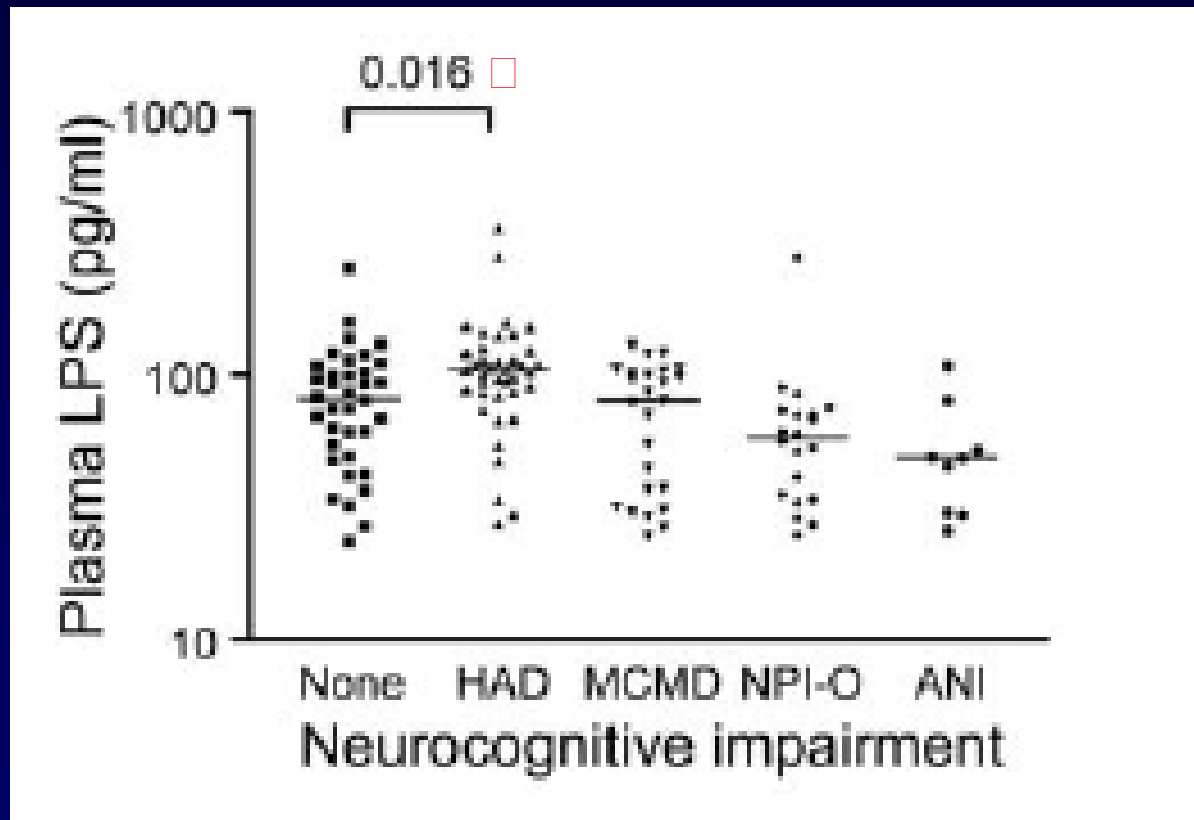


# Proportion of HIV pts with neurocognitive impairment according to HAND criteria



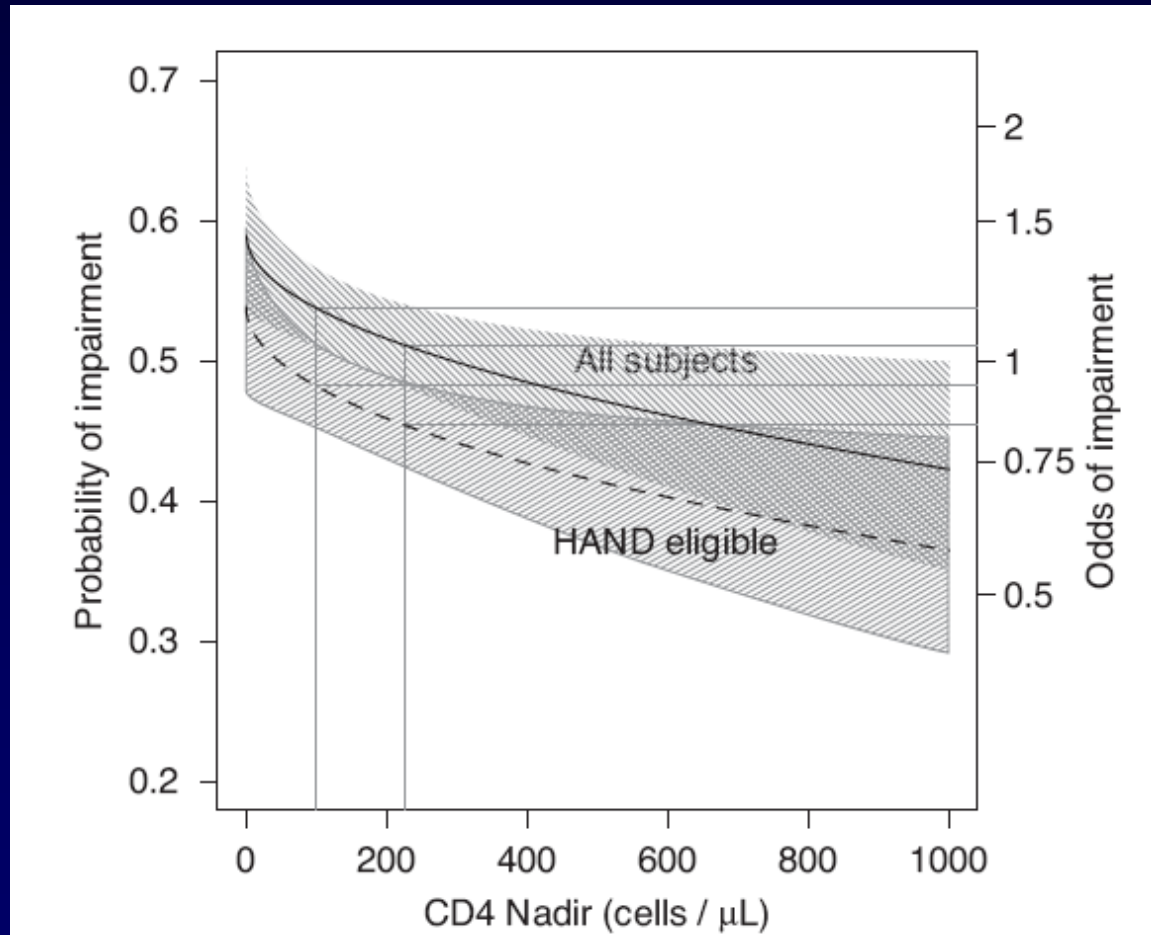
**Figure 4.** Proportion of patients with neurocognitive impairment according to HAND criteria (NC = normal cognition, ANI = asymptomatic neurocognitive impairment; MND = mild neurocognitive disorder; HAD = HIV-associated dementia).

# LPS (assoc with microbial translocation and immune activation) is increased in HAD



Ancuta P et al. PLoS ONE 2008

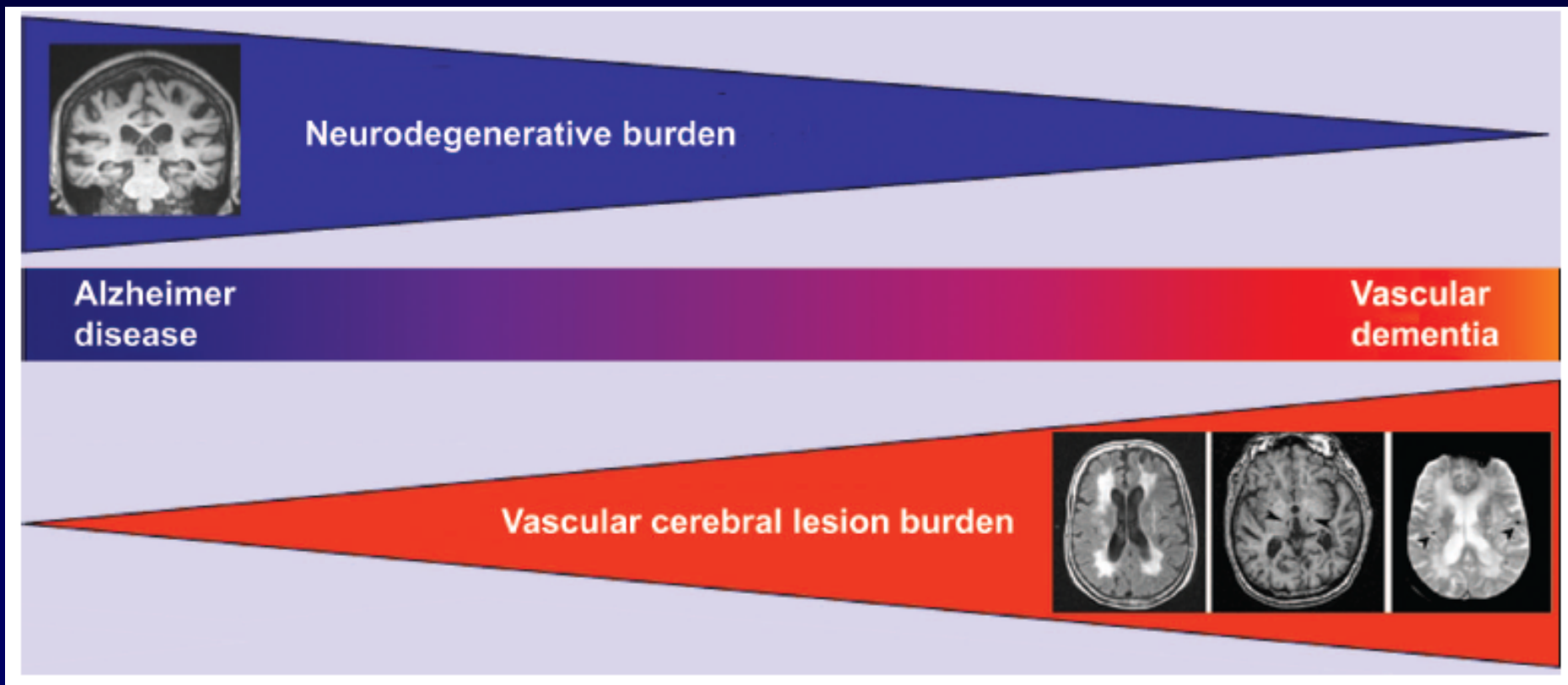
# CHARTER Study: Higher CD4 nadirs associated with lower risk of neuropsychological impairment



# Systemic inflammation leads to neuro-inflammation and contributes to Alzheimer disease

- **Increased LPS** leads to peripheral inflammation and increase in cytokine release from activated cells
- **LPS** and activated monocytes alter the BBB resulting in increased influx and decreased efflux of amyloid beta protein in the brain
- **LPS** increases production of LRP which increases the processing of APP to amyloid beta

# Alternative classification of dementia: Alzheimer disease (AD) and vascular dementia (VaD) fall on a continuous spectrum of disease



EDITORIAL COMMENT

# **HIV-associated neurocognitive disorders: is there a hidden epidemic?**

**Justin C. McArthur<sup>a</sup> and Bruce J. Brew<sup>b</sup>**

*AIDS* 2010, **24**:1367–1370

**Keywords:** HIV, neurological disorders, HIV Dementia Scale

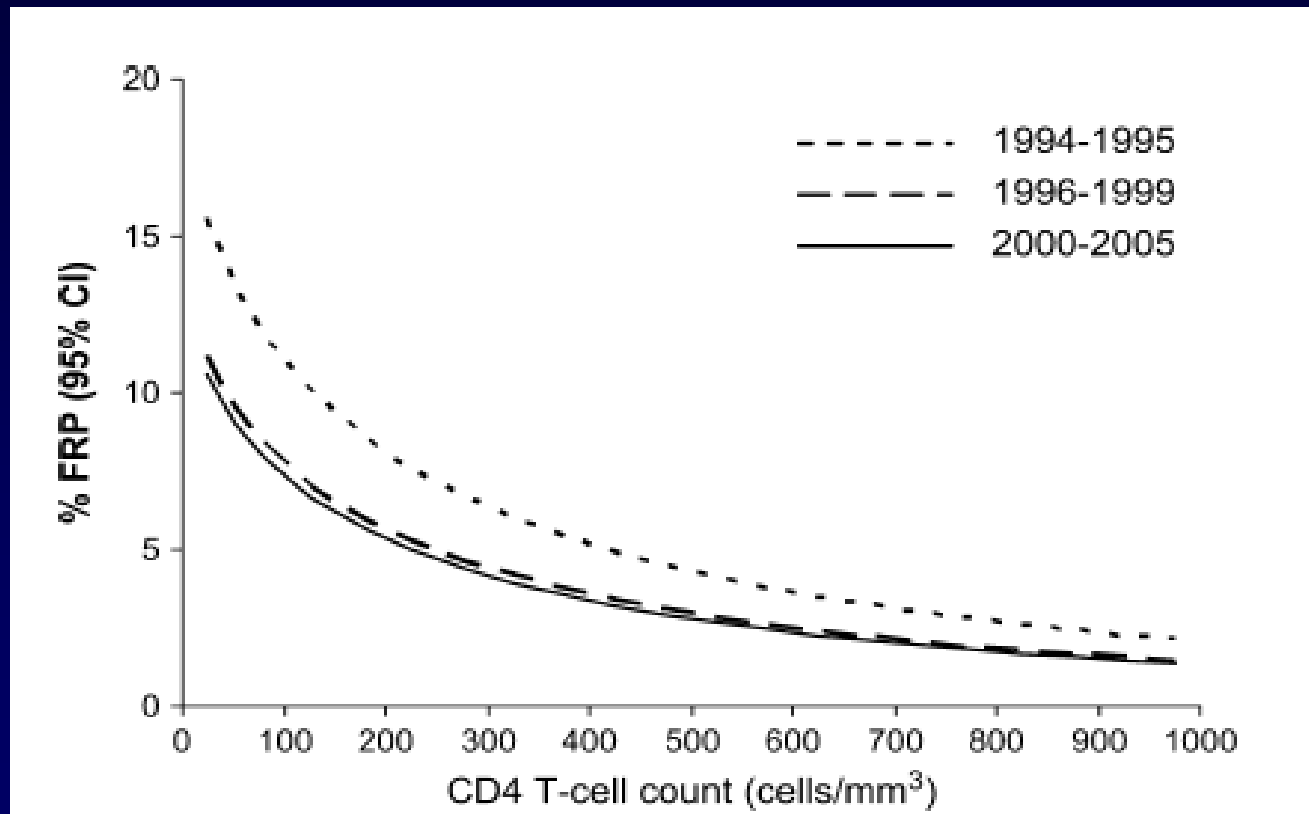
# **HIV, Aging & Frailty**

# HIV-1 is associated with an earlier occurrence of the Frailty Related Phenotype (FRP)

OR for HIV+ vs HIV- men to manifest each of the 4 components of the FRP and the overall FRP

	Frailty Component				Overall FRP
	Physical shrinking	Exhaustion	Slowness	Low physical activity level	
	OR	OR	OR	OR	OR
PV* analyzed	12.8	3.0	3.9	3.4	10.9
PV without weight loss	-	2.2	2.8	2.5	4.4
*PV = patient visits					

# Low CD4s are associated with increased risk of a FRP



# **HIV and Aging**

**Are the 50's the new 70's?**

**Thank You**