

# HIV and Accelerated Aging: *Epidemiology Mechanisms Treatment*

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*The International AIDS Society—USA*

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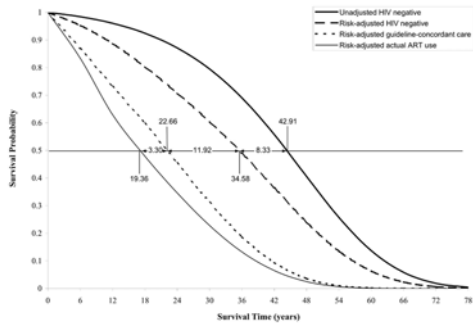
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Even with optimal care, current cohort and modeling data suggest that treating HIV disease does not fully restore full life expectancy



*Losina et al CID 2009*

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## HIV and the Aging Research Agenda

- HIV-infected persons are living longer
  - HIV infection and its treatment may affect the presentation and management of common age-associated complications
  - Poly-pharmacy, drug interactions
- Growing number of individuals who are acquiring HIV at an advanced age
  - Natural history of HIV infection may be unique
- HIV is associated with accelerated aging
  - Premature onset of age associated complications
  - Clearly shown for immune system

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**Many Age-associated Diseases Are More Common in Treated HIV Disease Than In Age-matched Uninfected Persons**

- Cardiovascular disease
- Cancer (non-AIDS)
- Bone fractures/osteopenia
- Left ventricular dysfunction
- Liver failure
- Kidney failure
- Cognitive decline
- Frailty

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**Independent Effect of HIV on Non-AIDS Morbidity?**

Non-AIDS Disease	Effect of Lifestyle Factors?	Effect of ARVs?	Effect of HIV itself?
Cardiovascular Disease	YES	YES: Pls Possible: ABC, ddi	YES
Non-AIDS Cancer	YES	Possibly	Probably
Neurocognitive Dysfunction	YES	Possibly (CNS Penetration)	Probably
Osteoporosis	YES	YES (TDF, ?EFV-VitD?)	Probably
HBV/HCV Cirrhosis	YES	YES	YES
Renal Disease	YES	YES (TDF)	Probably

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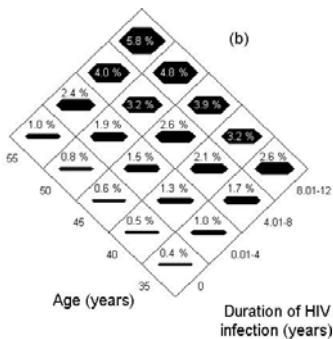
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**HIV+ Adults with High Risk of Frailty (MACS)**



Frailty risk in HIV+ patients similar to that observed in HIV-'s 10 years older.

Excludes data within 6 months prior to AIDS diagnosis Desquilbet, J of Gerontology, 2007

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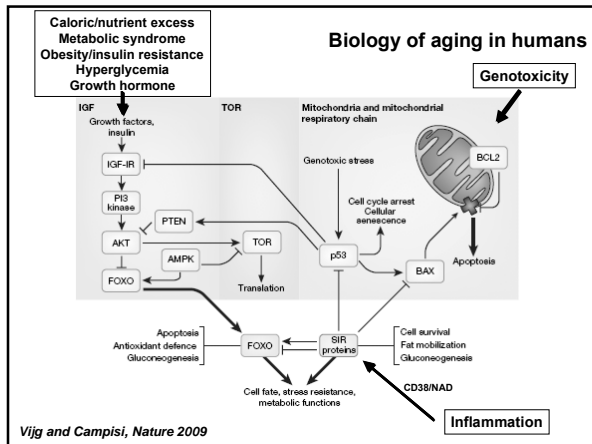
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- Questions**
- What impact does (treated) HIV infection have on immunologic factors known or thought to be involved in aging in general, or cardiovascular disease in particular?
  - Do these factors predict non-HIV morbidity in treated HIV infection?
  - Can these immunologic perturbations be prevented or reversed?
    - Association ≠ causation
    - Pilot data for larger therapeutic studies

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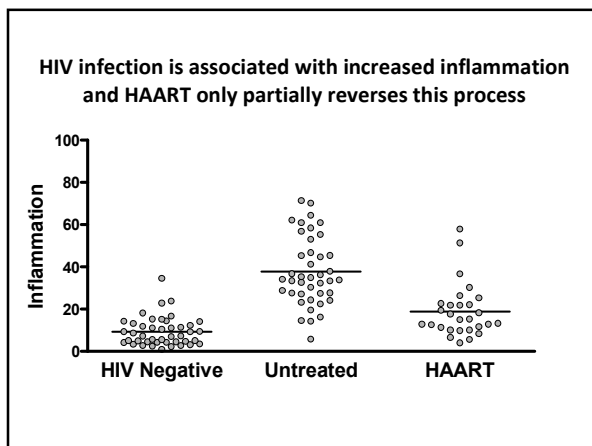
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**“Immunosenescence”: T Cell Characteristics In The Very Old That Predict Morbidity/Mortality**

- Reduced regenerative capacity (stem cells, thymus)
- Low naïve/memory T cell ratios
- Low CD4/CD8 ratio
- Increased T cell activation
- Increased in general inflammatory markers (IL6, CRP)
- Clonal expansion of CD28-CD57+ T cells
- Expanded CMV specific T cell responses
- Reduced T cell proliferation

Weng N. *Immunity*. 2006; 24:495-499. Linton PJ, Dorshkind K. *Nat Immunol*. 2004 ;2:133-139.

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**T Cell “Activation”**

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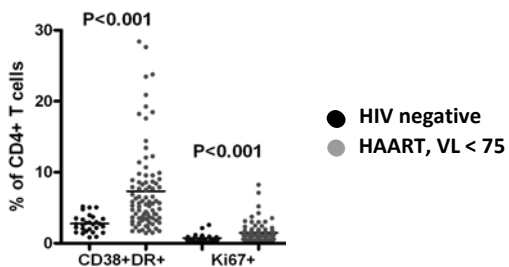
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**HAART-Suppressed Patients Have Persistently High Levels of CD4+ T Cells Expressing “Activation” and Cell Cycle Markers**



Hunt et al (CROI 2010)

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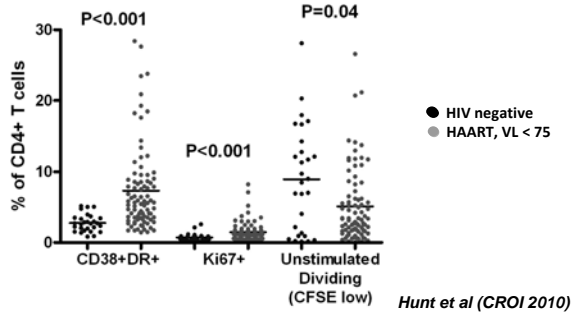
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**SCOPE: Despite Higher "Activation" and Ki67 Expression, Fewer CD4+ T Cells Are Actually Dividing *in vivo***




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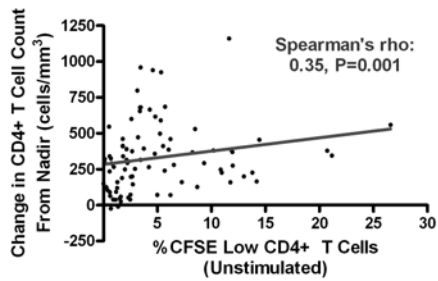
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**Lower CD4 Proliferation is Associated with Lower CD4 Recovery**



Significant even after adjustment for age, % naïve and % activated CD4+ T cells (P=0.019)

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**T Cell Senescence**

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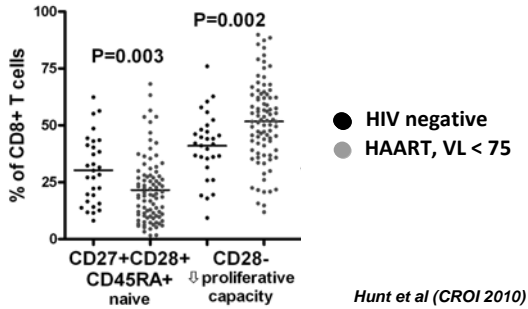
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**HAART-suppressed Patients Have Fewer Naïve CD8+ T Cell and More CD8+CD28- T Cells Than Age Matched HIV Negatives**




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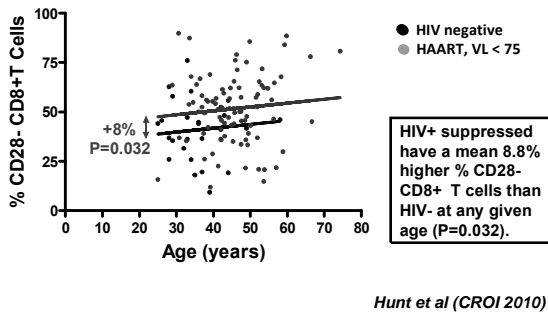
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**Despite long term HAART, HIV-infected persons have higher frequencies of immunosenescent CD8+ T cells than age matched controls**




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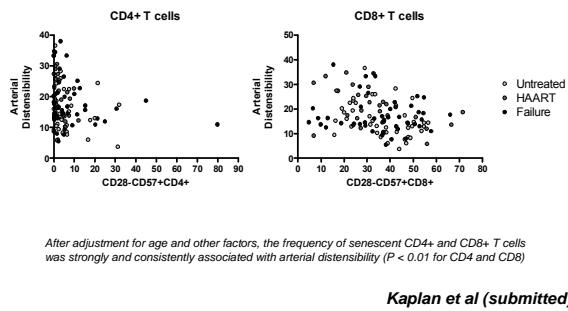
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**WIHS: A Higher Frequency of CD28-CD57+ Senescent T Cells Is Associated With Lower Arterial Distensibility**




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## CMV-specific T Cells

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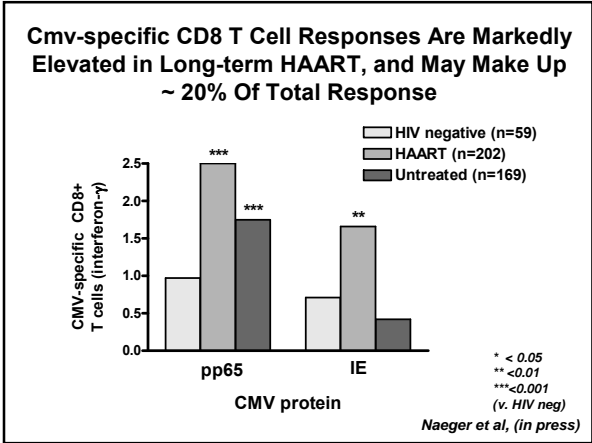
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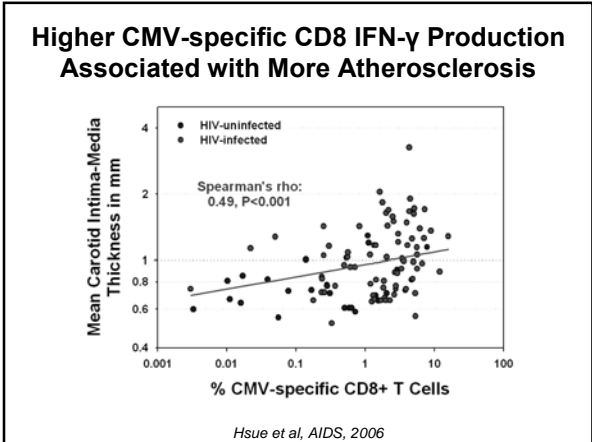
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## Biomarkers of Aging Predict Disease In HAART-treated Patients

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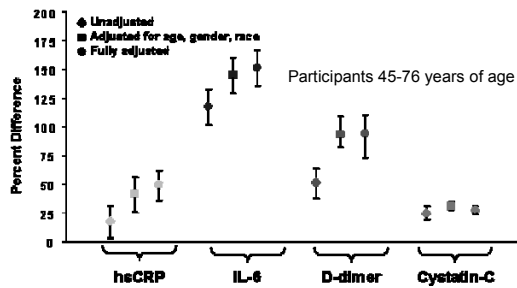
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### Slide #26

## Inflammatory Markers Are Higher In Treated HIV Disease Compared with HIV Seronegatives, Adjusted for Demographics and CV Risk Factors



Neuhaus J, et al. CROI 2009. Abstract O-140.

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## 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. PLoS Medicine 2008

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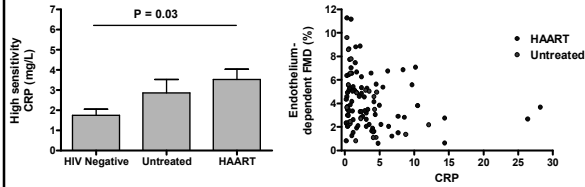
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**SCOPE: CRP—an Aging Biomarker—are High in Treated HIV Infection, and Strongly Associated with Endothelial Dysfunction**



Hsue et al (CROI 2010)

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**T Cell Immunosenescence in Advanced Age Versus Long-term HAART**

Biologic Parameter	Aging (> 70 years)	Long-term treated HIV infection
Low CD4/CD8 ratio	Yes	Yes*
Low naïve T cell %	Yes	Yes*
Low T cell proliferation	Yes	Yes*
Increased T cell activation	Yes	Yes*
Expansion of CMV-specific T cells	Yes	Yes*
Reduced T cell repertoire	Yes	Probably
Reduced T cell telomeres/telomerase	Yes	Unknown
Reduced regenerative potential (HSM, thymus)	Yes	Probably

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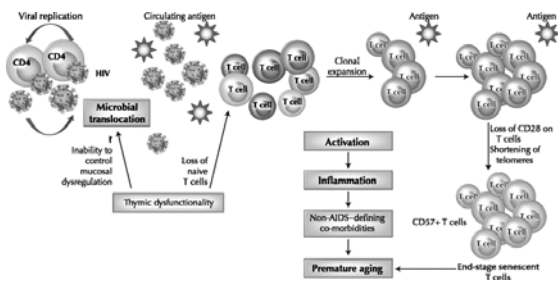
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**HIV infection may result in accelerated immunologic aging**



Desai and Landay, Current HIV/AIDS Reports 2010

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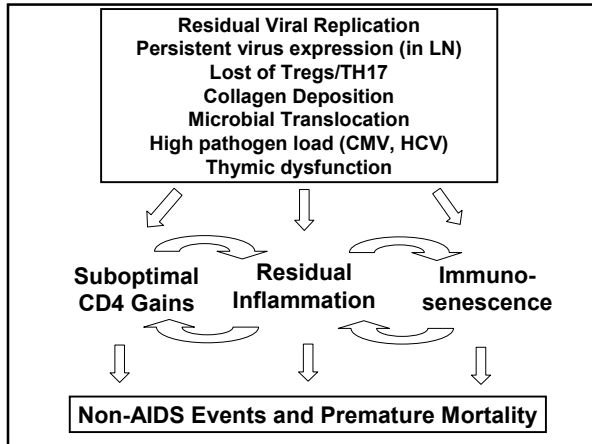
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- Inflammation and aging: Novel therapeutic strategies**
- Reduce inflammation
    - Prednisone, hydroxyurea, cyclosporin, mycophenolic acid
    - Chronic/persistent co-infections (HCV, CMV)
    - Residual HIV replication (HAART intensification)
    - Microbial translocation (sevelamer, colostrum)
    - CCR5 inhibitors
    - Chloroquine (reduced PDC mediated IFN $\alpha$ )
    - NSAIDs (COX-2 inhibitors)
  - Enhance T cell renewal: GH, IL-2, IL-7, stem cell transplant, perfenidone, lupron
  - Anti-aging interventions: Caloric restriction, sirtuin activators, telomerase activators, vitamin D, omega-3 fatty acids, rapamycin (TOR)

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### The Vitamin D and Omega-3 Trial (VITAL)

- 20,000 U.S. men and women over the age of 60 (men) or 65 (women) who have not had significant CAD or cancer
- Randomized one of four arms
  - Placebo
  - Vitamin D (~2000 IU)
  - Omega-3 fatty acids (1 gram)
  - Vitamin D plus omega-2 fatty acids
- Outcomes: CAD, stroke, cancer
- Study initiation: January 2010
- Duration of FU: 5-7 years

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### A mechanistic rationale for starting therapy as early as possible

- Untreated HIV disease is associated with increased T cell activation/inflammation and these markers predict disease
- Treatment dramatically reduces but does not normalize levels inflammation
  - Inflammation on HAART predicts disease
- The degree of residual inflammation during HAART is determined in part by CD4 nadir (strong effect < 200, less clear effect > 350)

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### When to Begin Treatment for asymptomatic patients - U.S. guidelines (December 1, 2009)

Therapy should be started in all patients with a CD4 <350, or AIDS-defining condition

Therapy is also indicated for pregnancy, HIVAN, HBV

Therapy is recommended for all patients with CD4 350-500 (55% voted for strong recommendation and 45% voted for moderate recommendation)

For patients with CD4 counts > 500, 50% favor starting antiretroviral therapy at this stage of HIV disease and 50% view initiating therapy at this stage as optional

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### **HIV, Inflammation and Aging**

- **HAART does not fully restore life expectancy**
- **Many age-associated complications appear to occur at a younger age in antiretroviral-treated patients than well matched uninfected controls**
  - CAD, cancer, ESRD, liver failure, bone
- **Inflammatory markers are higher in those with HIV than well matched controls**
  - May be biomarkers of aging
- **Inflammatory biomarkers predict non-AIDS morbidity**

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