

Immune Senescence in HIV Disease

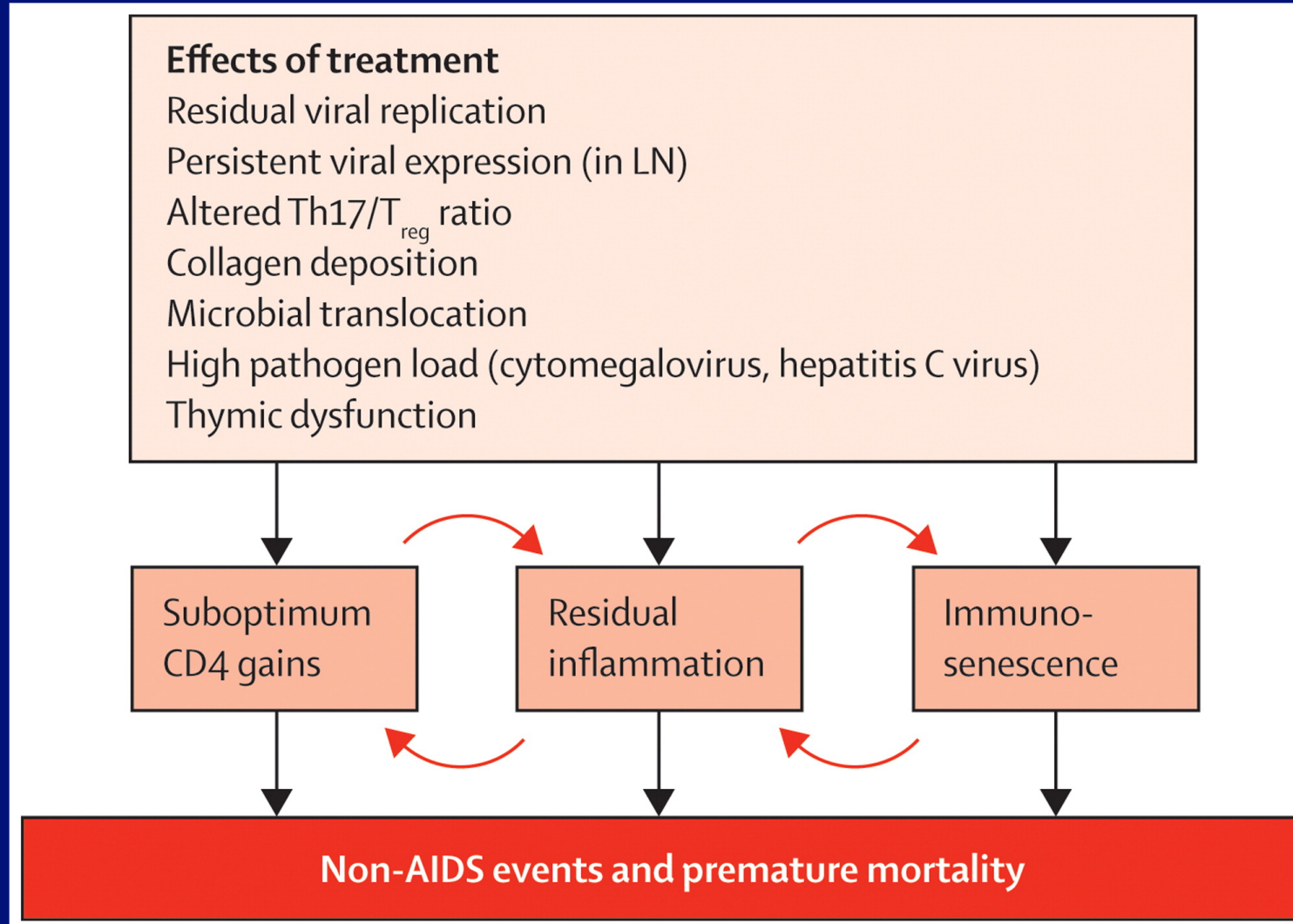
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Dept of Immunology/Microbiology

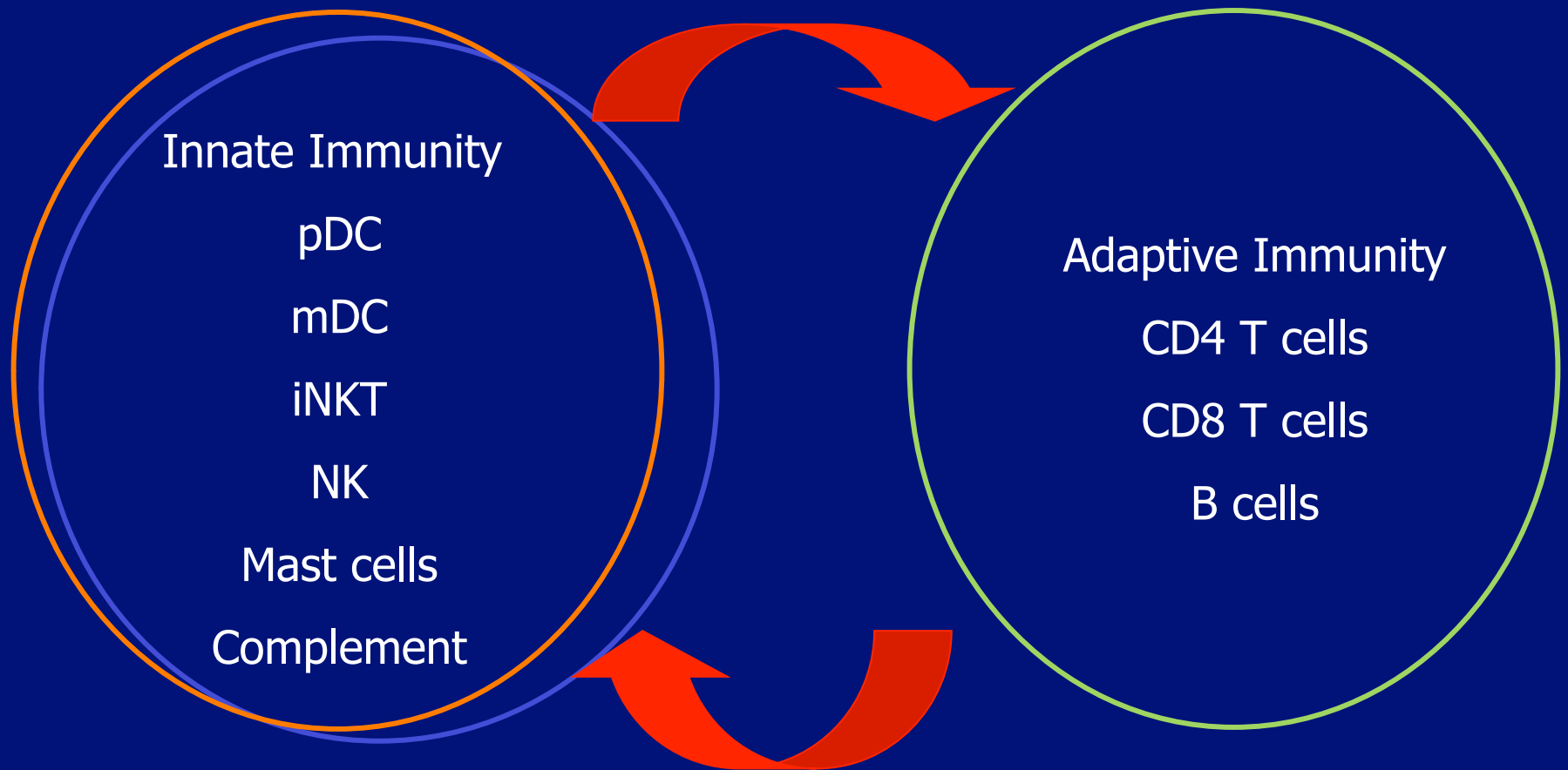
Rush University Medical Center

Chicago, IL

Determinants of Accelerated Aging in HIV Infection

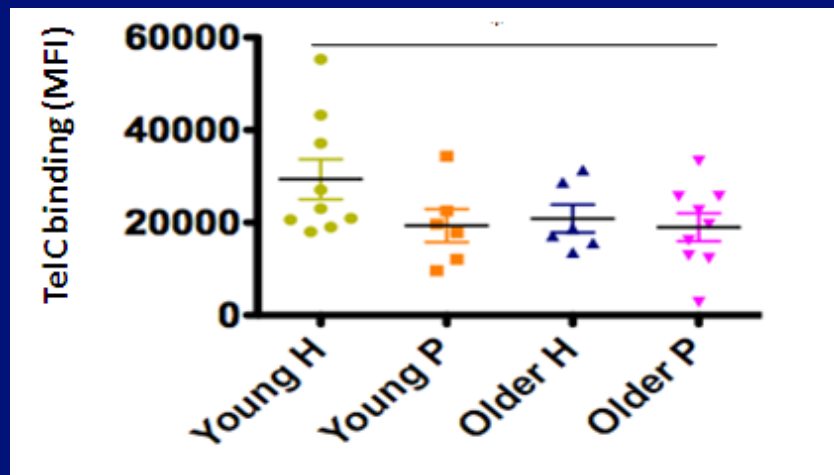
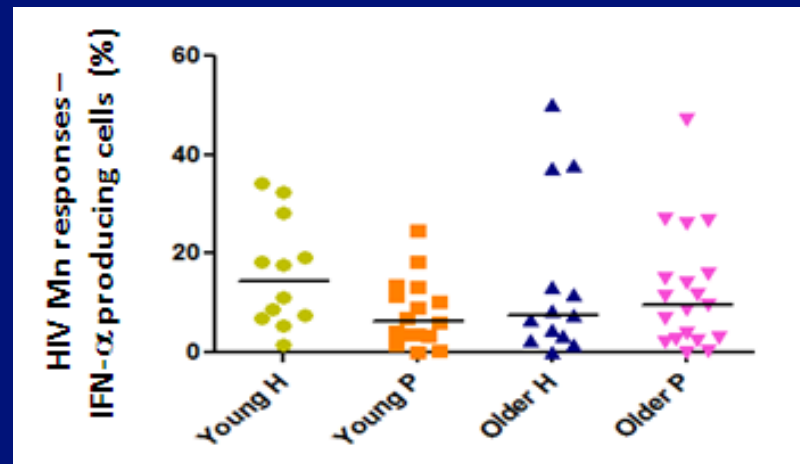
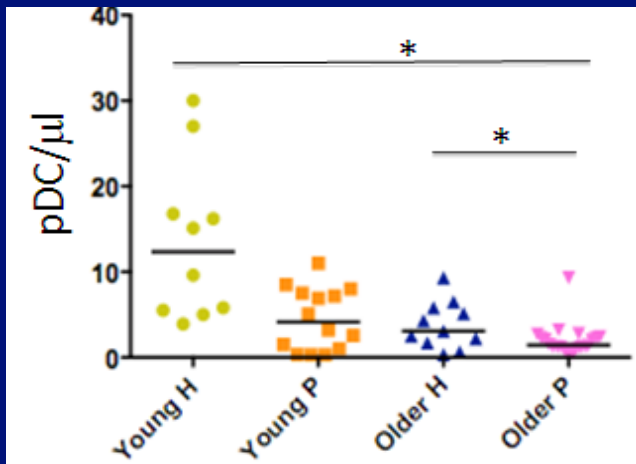


Human Immune System



Innate Immune Aging

Senescent first line of defense: replicative senescence in pDC impaired frequency, function and telomere length



Adaptive Immune Aging

Aging and the Immune System

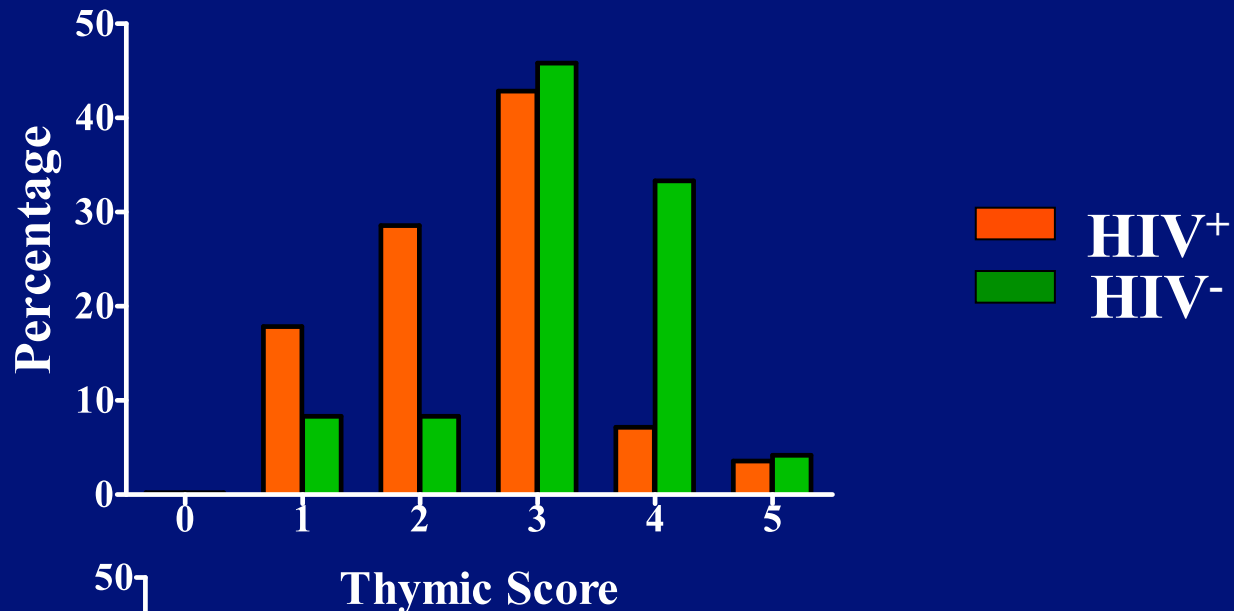
T Cell Compartment

- Thymic Involution
- Decreased Naïve T Cells
- Increase in Memory T Cells
- Increase T Cell Activation
- T Cell Clonal Expansion with Loss in T Cell Repertoire (ie CMV)
- Inversion CD4/CD8 Ratio
- Reduced TCR Signalling and IL2 Production
- Telomere Shortening

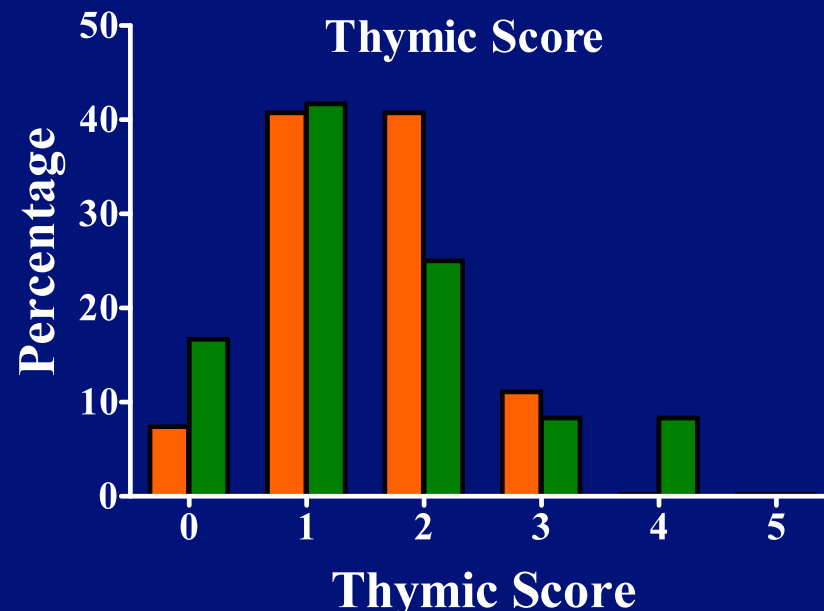
Imprints of accelerated aging on the thymus:

Impact of HIV on thymic volumes is more pronounced in younger HIV- infected individuals and is not altered differentially at older age

“Younger”
18-30 y

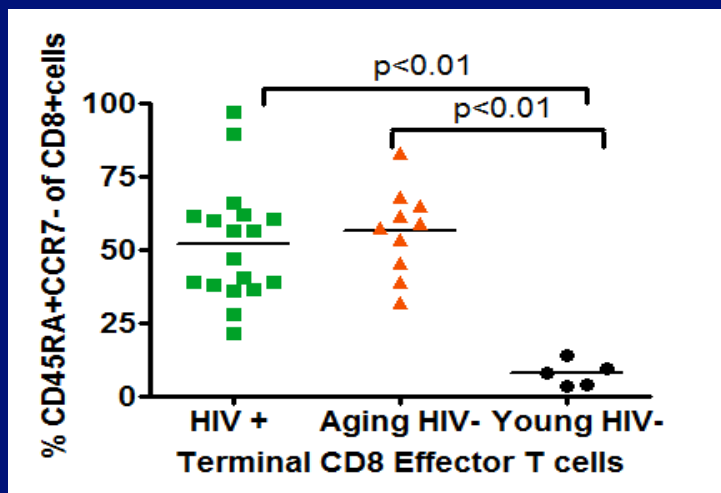
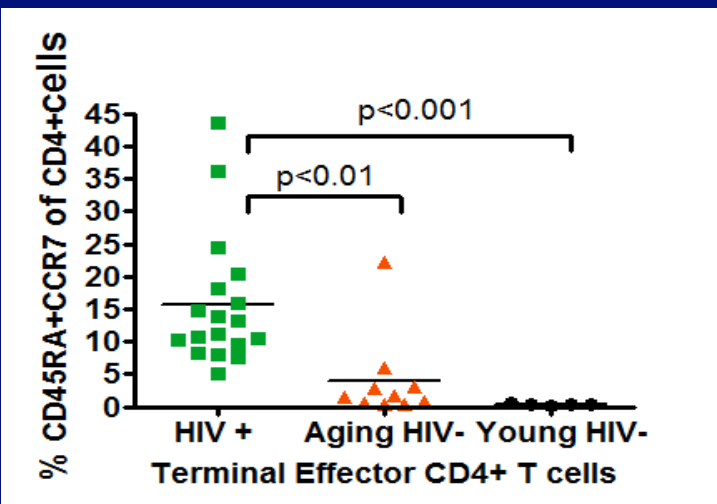
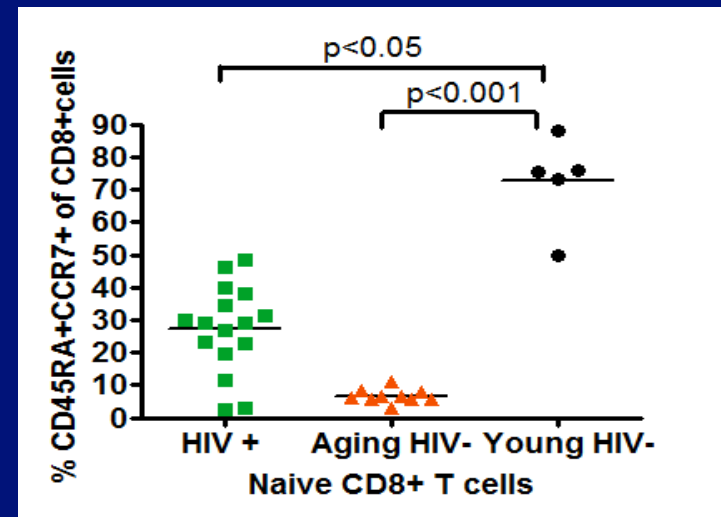
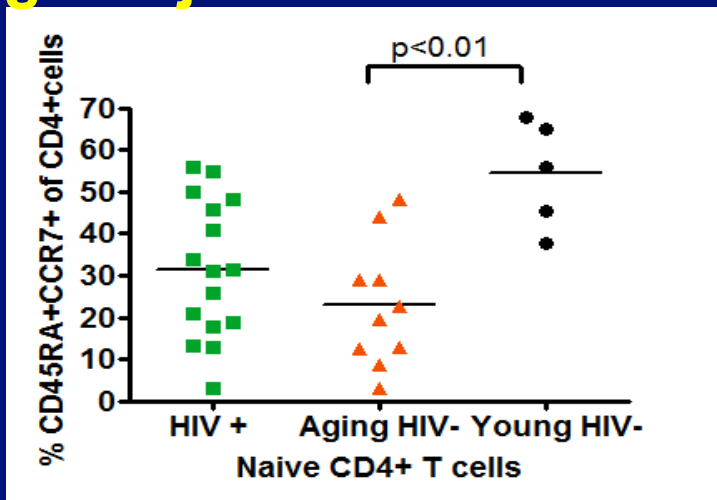


“Older”
≥ 45 y



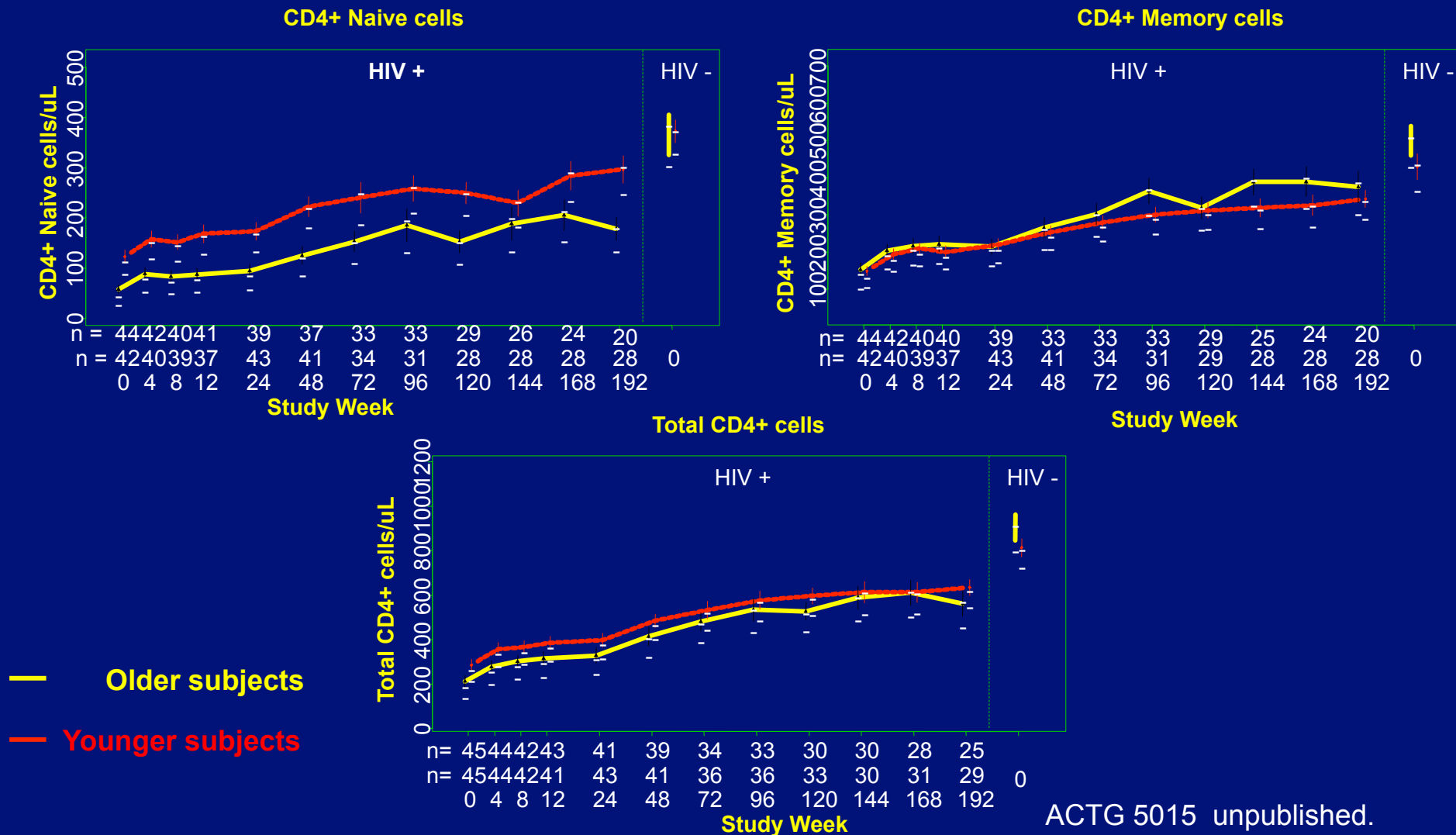
Kalayjian R, et al. J Infect Dis. 2005;192:1577-1587.

Impaired T cell Homeostasis: Depletion of Naïve CD4 Cells and Accumulation of Terminal Effectors In HIV-Infected and Aging Subjects



Desai, S et al. CROI 2009. Abstract 381.

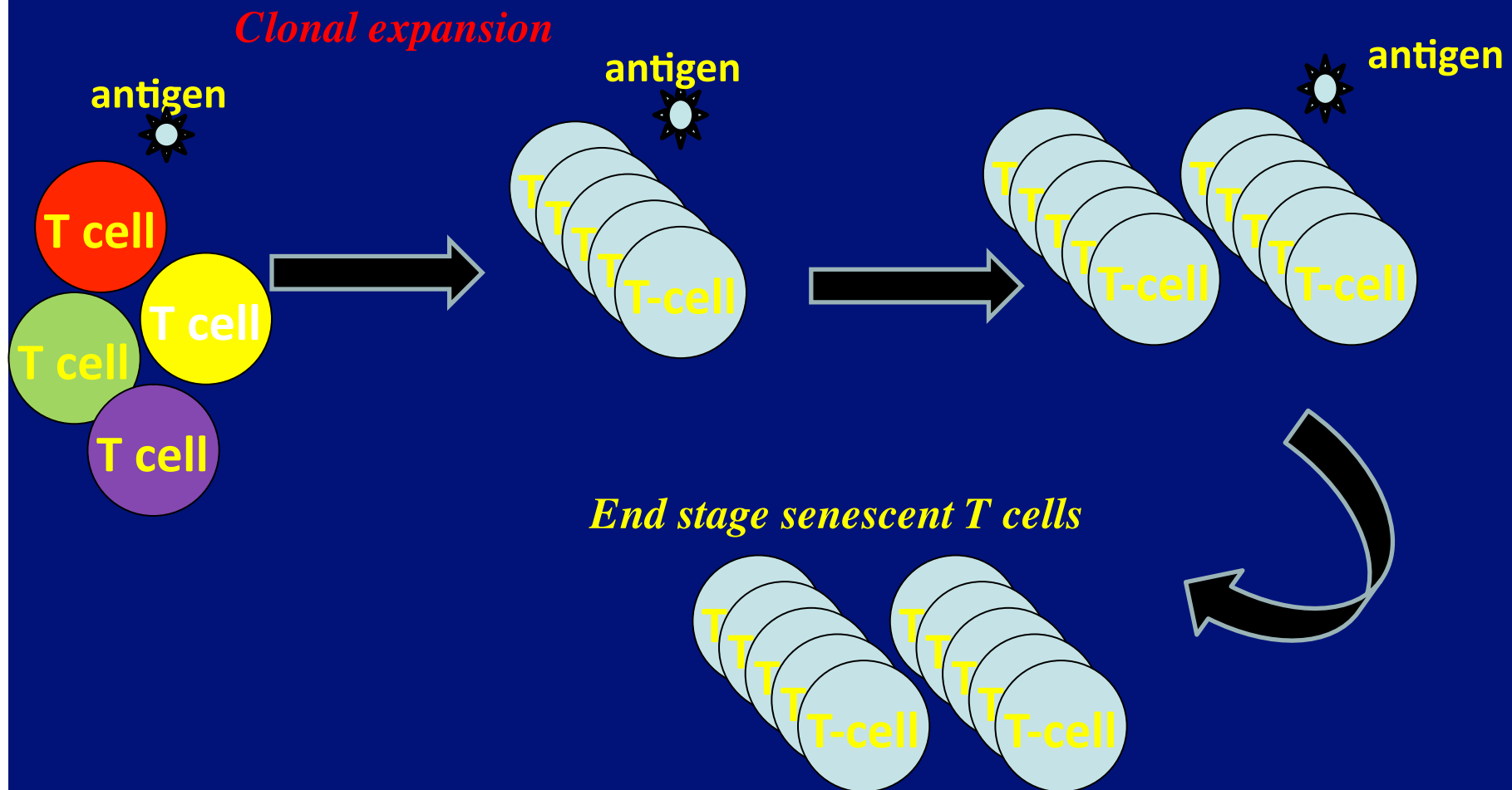
Dysfunctional thymus in HIV-infected patients: Naive T cell counts do not reconstitute to the same degree as memory or total CD4+T cells



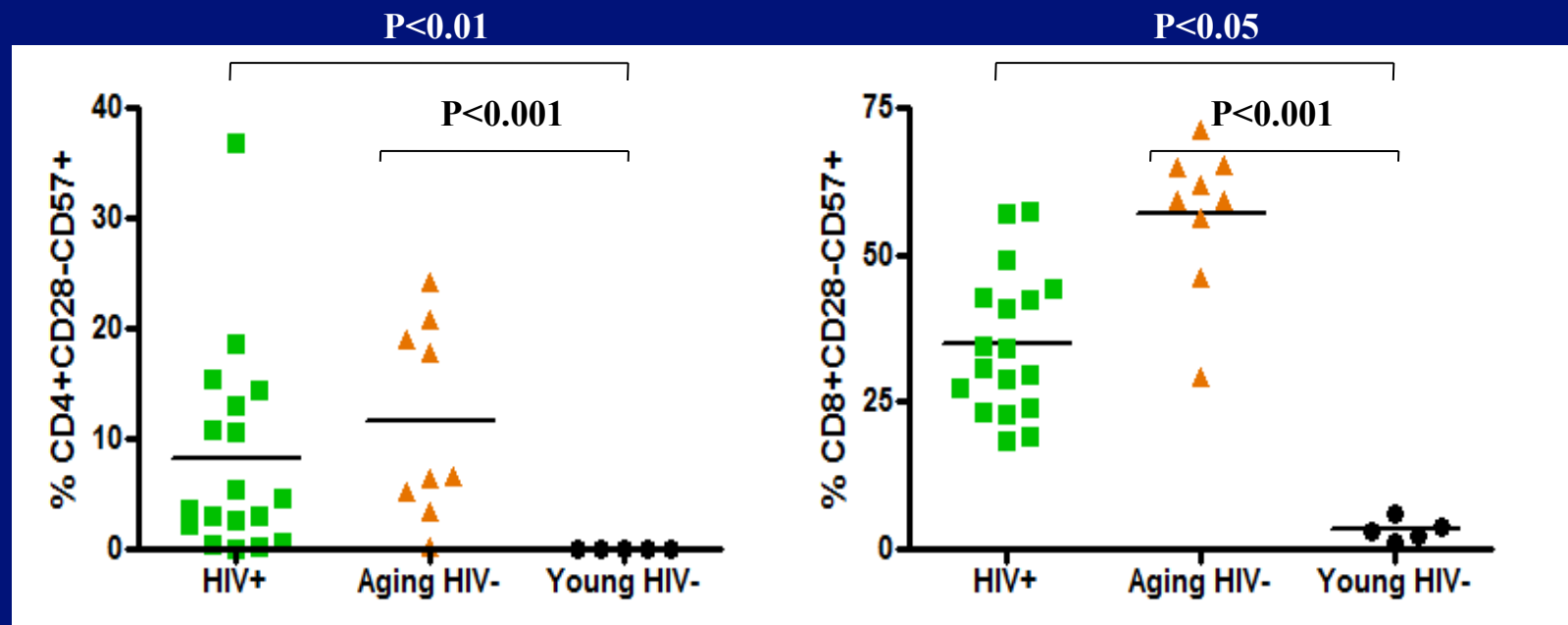
ACTG 5015 unpublished.

What is immune aging?

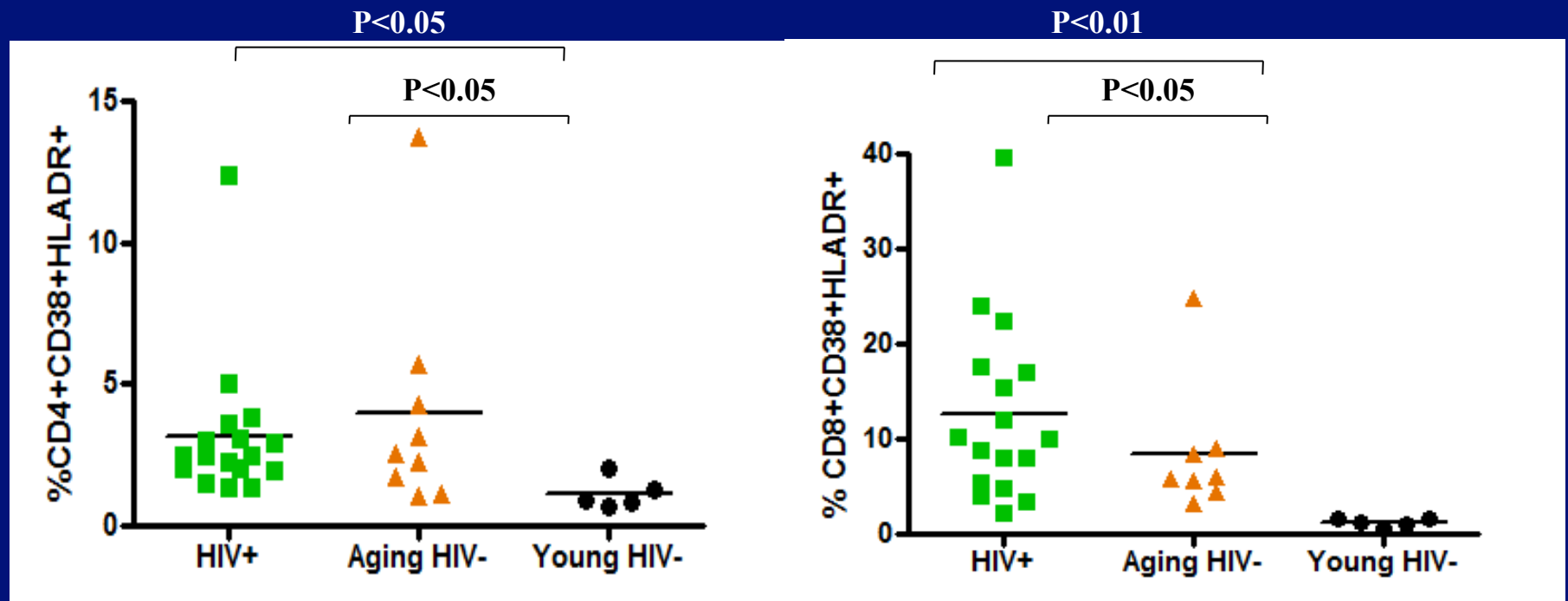
Mechanism Leading To End Stage Senescence



Replicative Senescence in HIV-1-Infected Patients Is Comparable to Older HIV-Negative Subjects



Immune Activation Levels in HIV-1 Infected Patients Are Similar to Older HIV-Negative Subjects



Conclusion

HIV-induced activation leads to early senescence

Inflammageing

- Enhanced Pro-inflammatory Mediator (IL6, IL1, TNF- α)
- Reduced Anti Inflammatory Mediator (IL10)

Senescent T cells Affect Organ Function

Cardiovascular Disease

Correlates with increased levels of TNF RII, IL-6, TNF- α , acute phase marker CRP and coagulation marker 2D-dimer

Neurocognitive (Alzheimer's disease)

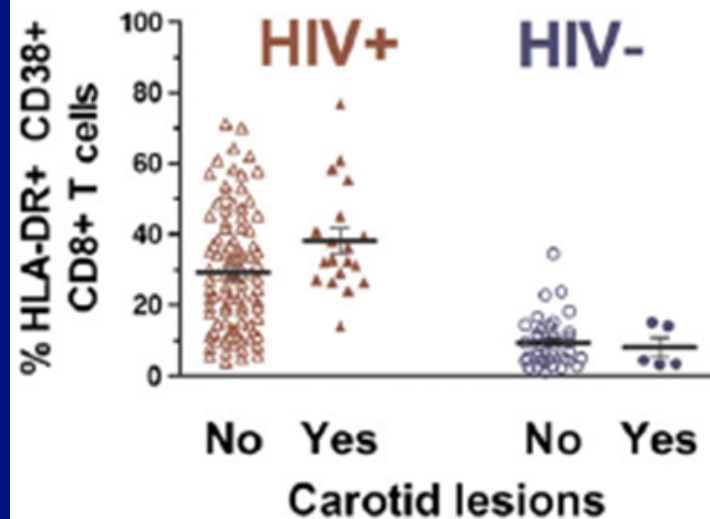
Telomere length correlates with disease status

Bone

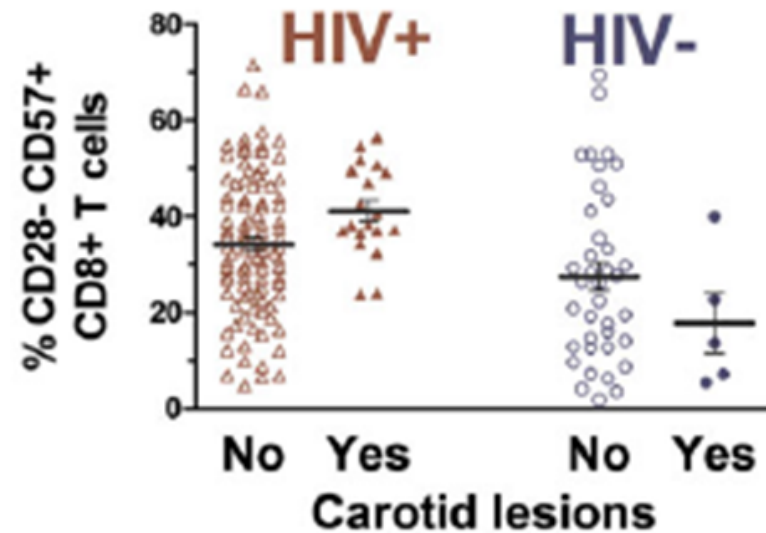
Correlate with osteoporotic fractures
IL-6, TNF- α correlates with bone loss

T Cell Activation, Senescence, and Atherosclerosis

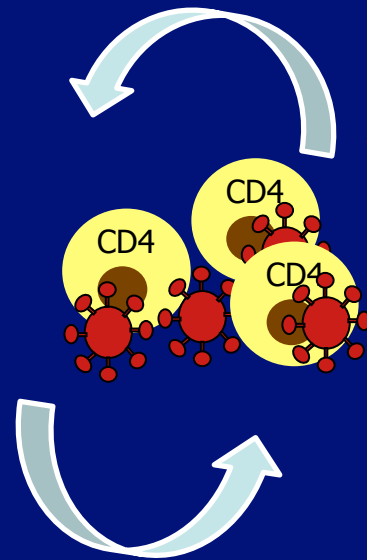
CD8 Activation



CD8 Senescence



Inflammation
Activation
Coagulation
**Microbial
translocation**



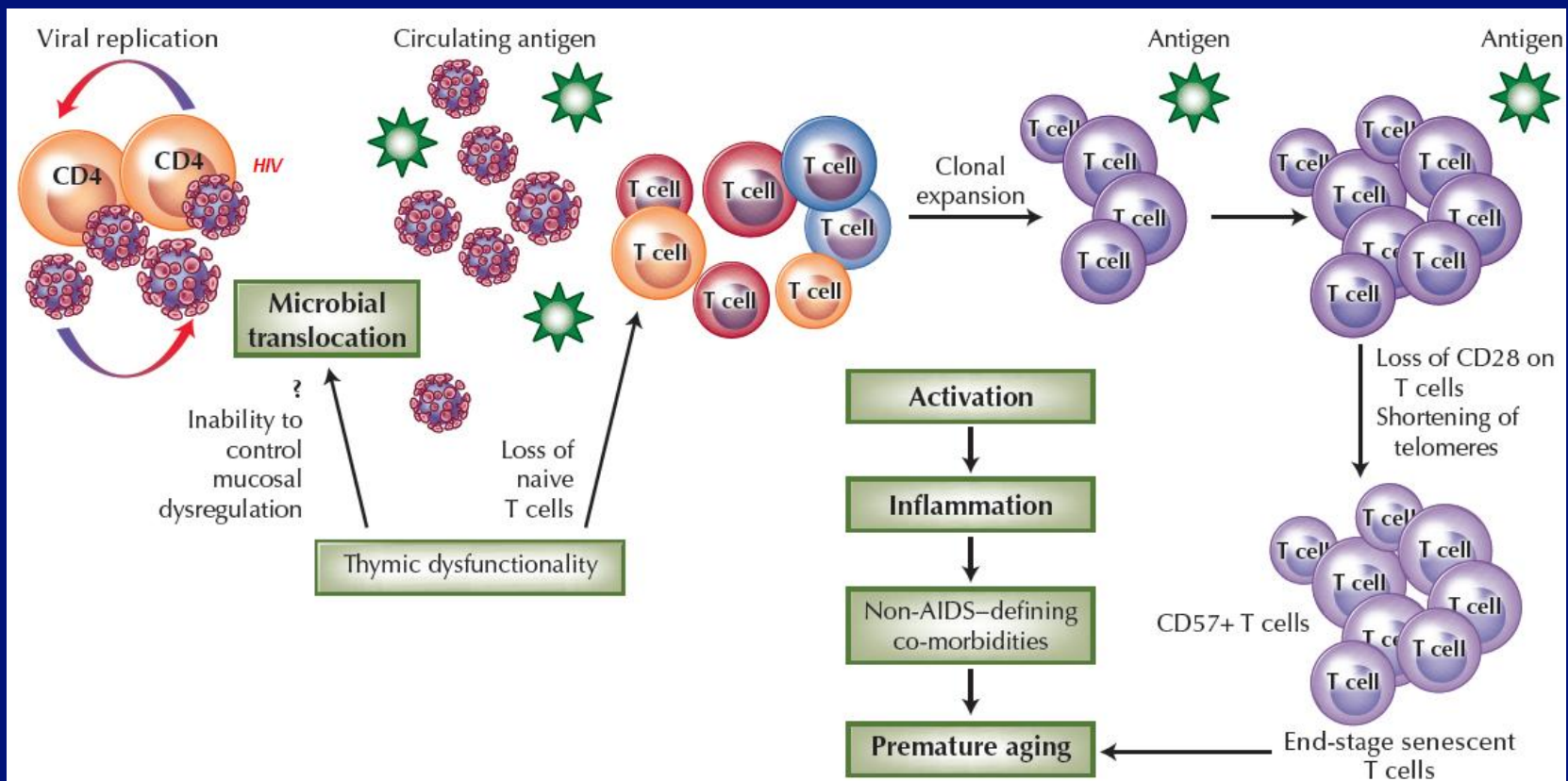
Viral Replication

Co-morbidities

CVD
Neurocog
Cancers
Liver
Disease
Metabolic
Disease

Premature
Aging

Aging with HIV -Model



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

Desai S, Landay A. Curr HIV AIDS Rep 2010;7: 4-10.

Gaps in Our Knowledge of HIV and Immune Senescence

Big Questions.....

- ☐ Inflammation leads to Immune activation or vice versa
- ☐ Does Immune senescence lead to end organ senescence
- ☐ Does early senescence lead to early onset of Co-morbidities

What is the mechanism leading to immune senescence –
implication for interventional strategy