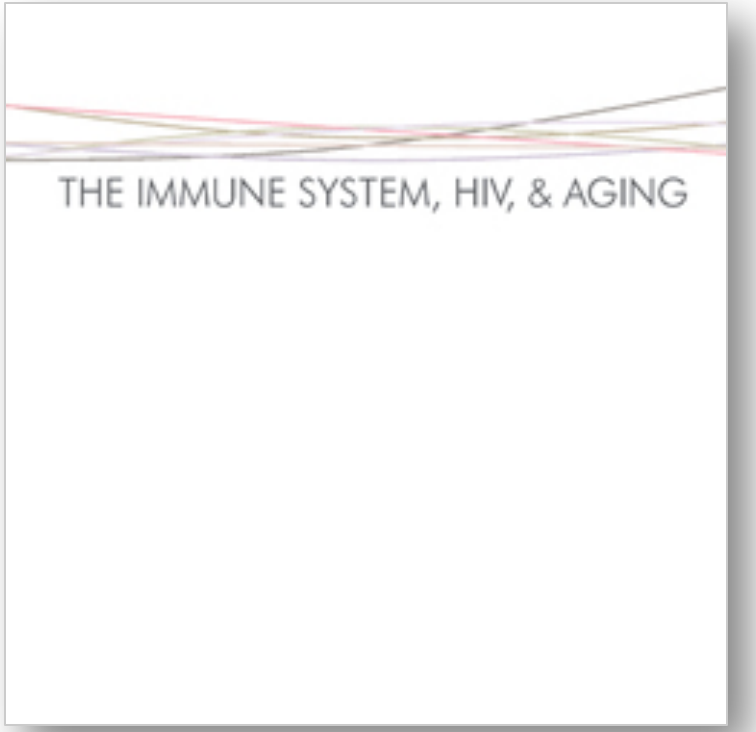
TAG

PART II
IMMUNE SENESCENCE



IMMUNE SENESCENCE RESEARCH IN HIV

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Background

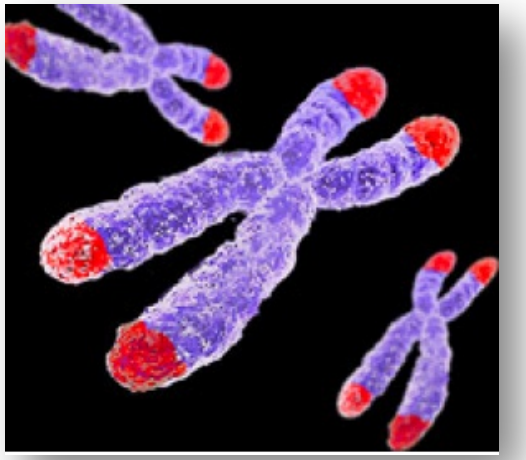
- Senescence: the state of being old or the process or aging
- Immune senescence: the immune system profile seen in the elderly
- Does immune senescence occur earlier in PLWHIV?
  - A topic of research for many years

Replicative Senescence

- Cells that have divided so many times that they can divide no more
- CD8+ T cells can reach a state of replicative senescence in PLWHIV
  - CD8+ cells (aka “killer T cells”) unable to look for, and eliminate, cells infected with disease-causing microorganisms

Evidence of CD8+ T-Cell Senescence

- Telomeres cap the end of chromosomes to protect DNA when cells divide
- The more cells divide, the shorter telomeres become



- CD8+ T-cell telomere lengths in PLWHIV similar to those in very old HIV-negative people (pre–modern ARV era)
- Associated with loss of CD28 marker on CD8+ T cells

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Loss of “Naive” Cells

- Naive cells: CD4 cells, CD8 cells, and antibody-producing B cells waiting to encounter new disease-causing pathogens
- Naturally decline with age
- Greater decline in HIV-positive people compared with age-matched HIV-negative people
- May be even better indicator of immune system aging in HIV than CD8+ T-cell senescence

Loss of “Naive” Cells

- Several possible mechanisms:
  - HIV damage to stem cells responsible for producing new immune-system cells
  - HIV hastens natural loss of thymus-gland function, which helps produce T cells
  - Chronic inflammation (caused by HIV) can lead to scarring of lymph tissues needed to maintain naive T cells
  - Ongoing HIV replication activates these naive cells and, as a result, turns them into “memory” T cells

Summary

- HIV worsens natural immune-system aging (senescence)
  - Helps explain link between HIV and age-related health problems
- Older people start with an immune system that has eroded over time
  - HIV compounds the aging-associated deficits that are already present

IMMUNE SENESCENCE IN ERA OF EFFECTIVE HIV TREATMENT

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Background

- ARV therapy to suppress viral load:
  - Rapidly reduces immune activation
  - Improves CD4+ T-cell counts
  - Reconstitutes immune-system responses to disease-causing pathogens
  - Greatly reduces risk of AIDS-related illnesses
  - Substantially improves likelihood of survival

Background

- Immune senescence can persist
  - Recovery of naive T cells is slow
  - Senescent CD8 cells decline slowly
  - Senescent CD4 cells, though low in number, decline even slower
  - Inflammation decreases, but remains above levels seen in HIV-negative individuals
  - CD28-negative CD4 and CD8 cells decreased in treated PLWHIV cohort, but elevated vs. HIV-negative individuals

Immunologic Nonresponders (INRs)

- INRs: Poor CD4+ T-cell recovery, despite ARV treatment and viral-load suppression
  - *Indirect* link between senescence and health outcomes
- Approximately 5–10% of PLWHIV initiating ART characterized as INRs
  - Usually based on minimal CD4+ T-cell increase or failure to reach a threshold (e.g., 350 cells/mm^3) after several years of viral suppression
- CD4+ T-cell count that remains below 500/mm^3 correlates with increased risk of death

Senescence and Older Age

- Slow CD4+ T-cell recovery more common among PLWHIV >50 years of age
- As a result, U.S. guidelines* now recommend HIV treatment for all PLWHIV >50 years old, regardless of CD4+ T-cell count
  - Based on expert opinion
  - Strategic Timing of Antiretroviral Therapy (START) study to confirm benefit of immediate ARV treatment in PLWHIV >50 years old

*U.S. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

CD28-CD8+ T Cells

- More direct link between senescence and health outcomes
- Higher proportion of CD28-negative CD8+ T cells is associated with:
  - More rapid disease progression in HIV-positive men (MACS)
  - Arterial disease in HIV-positive women (WIHS)
  - Increased risk of benign Kaposi's sarcoma

Summary

- Immune senescence persists in PLWHIV, even if HIV is undetectable
- Can contribute to poor immune system recovery following treatment
  - Immunologic nonresponders (INRs)
- More common in PLWHIV >50 years old
- CD28-CD8+ T cells more direct link between senescence and health outcomes
  - Linked to HIV disease progression; arterial disease