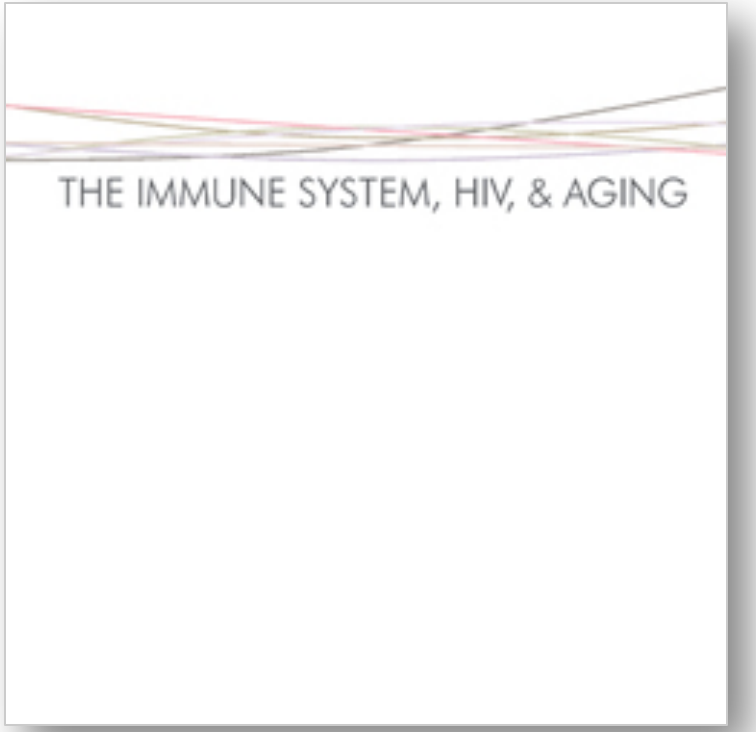

TAG

PART V
ANTIRETROVIRALS & AGING

Background

- Potential effects of ART toxicity on aging process cannot be discounted
- ARV toxicity must be considered in context of immuno-aging effects of HIV
- The question isn't whether it is HIV or ART that is associated with aging, but rather how they both contribute

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- NRTIs can be toxic to the DNA in mitochondria, the energy powerhouses of cells
- Known consequences in PLWHIV
  - Peripheral neuropathy
  - Pancreatitis
  - Lactic acidosis
  - Lipoatrophy

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Also linked to muscle fibers deficient in the essential COX enzyme required for energy production
  - COX deficiency typically seen in the elderly
- Newcastle University study
  - HIV– and HIV+ not on ART had normal muscle fibers
  - NRTI-treated PLWHIV had increased frequency of COX-deficient muscle fibers

Payne B, Wilson I, Hateley C, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. Nat Genet. 2011 Jun 26;43(8):806–10.

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

- Mitochondrial DNA dysfunction also linked to increased oxidative stress
  - Zidovudine and stavudine led to slowing of cell division, similar to aging
- Tenofovir can inhibit telomerase activity
  - Unclear if this results in more rapid shortening of telomere length or has any consequences on aging

Caron M, Auclairt M, Vissian A, Vigouroux C, Capeau J. Contribution of mitochondrial dysfunction and oxidative stress to cellular premature senescence induced by antiretroviral thymidine analogues. Antivir Ther. 2008;13(1):27–38.

Leensyah E, Cameron P, Solomon A, et al. Inhibition of telomerase activity by HIV nucleos(t)ide reverse transcriptase inhibitors: a potential factor contributing to HIV-associated accelerated ageing. J Infect Dis. 2013 Apr;207(7):1157–65.

Protease Inhibitors

- Ritonavir and ritonavir/lopinavir increased senescence markers, oxidative stress, and inflammation in artery cells in test tubes
- Senescence also increased in blood cells from PLWHV receiving PI-based regimens
  - Linked, in one study, to accumulation of prelamin A, which can cause genetic instability in cells
  - Second study did not confirm findings

Lefèvre C, Auclair M, Boccara F, et al. Premature senescence of vascular cells is induced by HIV protease inhibitors: implication of prelamin A and reversion by statin. Arterioscler Thromb Vasc Biol. 2010 Dec;30(12):2611–20.
Perrin S, Cremer J, Faucher O, et al. HIV protease inhibitors do not cause the accumulation of prelamin A in PBMCs from patients receiving first line therapy: the ANRS EP45 “aging” study. PLoS One. 2012;7(12):e53035.

Summary

- Though ART might have some aging-related effects, there is no evidence that these increase the risk of death
- Potential for less robust CD4+ T-cell increases, in response to treatment, as PLWHIV age
- Drug interactions may become increasingly complex as other medications are prescribed for age-related diseases