The Impact of HIV and its Treatment on Healthy Aging

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Most of the clinical focus over the past 25 years has been on inhibiting HIV replication and preventing AIDS.
Although ART prevents AIDS and improves health, the risk for developing many morbidities remains higher than expected (~1.5 to 2.0 fold)

• Cardiovascular disease [1-3]
• Cancer (notable exceptions include prostrate and breast CA) [4]
• Bone fractures / osteoporosis [5,6]
• Liver disease [7]
• Kidney disease [8]
• Cognitive decline (controversial) [9]
• Frailty (rare but 80% more common) [10]

Impact of HIV on risk in some studies comparable to traditional risk factors including HTN, DM and hyperlipidemia
Risk of many - but not all - cancers is increased in patients with HIV/AIDS

Strikingly similar pattern of cancer risk in RA and psoriasis (Smitten, Arth Res 08)

Adjusted for age, gender, race, calendar year, and cancer registry.

Shiels, Annals Int Med, 2010 (see also: Silverberg, AIDS, 2009)
There is even a concern in the popular press that HIV “accelerates” aging

59 year old man less “robust” than father

HIV associated with multiple morbidities of aging


Integrative nature of geriatric syndromes ("aging")

- **General medicine**: focus on specific diseases (CVD, cancer) with linear pathways

- **Geriatric medicine**: focus on functional status
  - Loss of **redundancy** (or **physiologic reserve**) that arises as a consequence of multiple **deficits** that accumulate (often exponentially) with age
  - Frailty, incontinence, immobility, falls

- **Biology**: mitochondrial toxicity, chronic inflammation, telomerase/telomere dysfunction, cell senescence, stem cell dysfunction, excess nutrients (insulin resistance)

- **HIV**: Kidney/hepatic dysfunction, neuropathy, sarcopenia, metabolic syndrome, obesity, mitochondrial DNA damage
Frailty-like syndrome occurs earlier in HIV disease (predicted by CD4 nadir, duration of infection)

Prevalence among those receiving modern treatment regimens unknown
Role of chronic inflammation in health
Multiple factors cause persistent inflammation during ART

Deeks, Lewin, Havlir; Lancet 2013
After adjusting for traditional risk factors, inflammatory biomarkers remain elevated during long-term ART, and strongly predictive of disease progression.
Microbial Translocation Predicts Mortality during ART-mediated Viral Suppression
After adjusting for traditional risk factors, inflammatory biomarkers remain elevated during long-term ART, and strongly predictive of disease progression.
Can harmful inflammation and/or immune dysfunction be monitored in the clinic?
Among individuals with a high CD4+ T cell count (>500 cells/mm3), a low ratio is associated with markers of immune dysfunction (n=67)
It may be easier to prevent age-associated complications than reverse them
Rosuvastatin Decreases Both Monocyte and T Cell Activation during Suppressive ART

SATURN Trial (n=147)

**sCD14**

Week 0 and Week 48

- Placebo: Decrease in sCD14
- Rosuvastatin: Significant decrease in sCD14

**CD8 Activation**

Week 0 and Week 48

- Placebo: Decrease in CD8+CD38+DR+
- Rosuvastatin: Significant decrease in CD8+CD38+DR+

*Funderburg, CROI 2014, Abstract #335 (see also: Funderburg, Clin Infect Dis, 2014)*
Several rigorous high-profile studies aimed at reducing microbial translocation failed

- Sevelamer: blocks LPS absorption
  - Single arm study (n=40) of chronic untreated HIV disease
- Mesalimine: local anti-inflammatory in GALT
  - RCT cross-over study (n=30)
- Rifaximin: non-absorbed antibiotic, decreases LPS and hepatic encephalopathy in cirrhosis
  - RCT (immunologic non-responders)

*No effect on LPS, sCD14 or measures of inflammation*

*Destruction to mucosa barriers may be irreversible*
Concerns regarding microbial translocation (not dysbiosis) have led to number of pilot studies of probiotics/prebiotics, with most reporting a modest but inconsistent immune benefit.
Moderate exercise (brisk walking/strength training 3 times/week) decreases inflammation during ART (n=49)

Longo, CROI 2014, Abstract #763
Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study

Chi Pang Wen*, Jackson Pui Man Wai*, Min Kuang Tsai, Yi Chen Yang, Ting Yuan David Cheng, Meng-Chih Lee, Hui Ting Chan, Chwen Keng Tsao, Shan Pou Tsai, Xifeng Wu

Over a mean duration of 8 years, higher intensity activity predicted reduced morbidity/mortality (N=416,175)

Every additional 15 minutes of daily exercise reduced all-cause mortality by 4% (95% CI 2.5–7.0)
Healthy aging requires aggressive risk factor management, exercise and diet
Early ART is associated with less inflammation during ART
*Will this result in benefit?*

**ART-naïve with CD4+ count > 500 cells/mm³**

**Early ART Group**
- Initiate ART immediately
- N=2,300

**Deferred ART Group**
- Defer ART until the CD4+ count declines to < 350 cells/mm³
- N=2,300
Many HIV-associated factors could affect healthy aging

**INITIATORS OF INFLAMMATION**
- HIV replication/production
- Co-pathogen excess (CMV, HCV)
- Microbial translocation
- Loss of regulatory responses
- Obesity
- Lipodystrophy
- Metabolic syndrome
- Substance abuse

**OTHER RISK FACTORS**
- Antiretroviral/HIV toxicity
  - Mitochondrial toxicity
  - Telomerase/telomere dysfunction
  - Metabolic abnormalities
  - Kidney dysfunction
  - Neuropathy
  - Sarcopenia
  - Osteopenia
  - Immunosenescence
- Substance abuse
- Social isolation
- Polypharmacy

**MICROBIAL TRANSLOCATION**
- Loss of CD4+ T cells
- Loss of epithelial cells
- Altered bowel flora
- Loss of Th17 cells
- Local inflammation (IFN-α, IDO)

**INNATE IMMUNITY**
- Activated monocytes and macrophages

**LIVER FIBROSIS OR DYSFUNCTION**
- Microbial translocation
- HIV infection of liver cells
- Inflammation
- ARV toxicity
- HCV
- HBV
- Alcohol

**Tissue factor expression**

**CARDIOVASCULAR DISEASE**
- Atherosclerosis
- Plaque Rupture
- Vascular dysfunction

**HYPERCOAGULATION**
- Microclotting
- VTE, MI, CVA

**AGE ASSOCIATED DISEASES**

*Deeks, Tracy, Douek. Immunity 2013*
Conclusions

• HIV may or may not “accelerate” aging, depending on how one defines aging
• HIV infection and its treatment affects biology of aging (inflammation, cellular senescence, telomerase/telomeres, mitochondria disease)
• HIV infection and its treatment causes multi-morbidity (neuropathy, sarcopenia, vascular disease, metabolic syndrome, osteopenia)
• HIV disease associated with many known socioeconomic risk factors for aging (isolation, poverty)
• Healthy aging requires interventions early in life