# Chronic HIV Infection Exacerbates Cellular Aging Markers in Isolated T cell Subsets

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## Background

- Combination antiretroviral therapy (cART) helps extend the lifespan of people living with HIV, but treated people are still at a higher risk for age-related comorbidities
  - This is suggestive of accelerated aging in this population
- These diseases include cardiovascular disease, osteoporosis, non-AIDS-related cancers, liver disease, and frailty among others
  - These may be driven by early immunosenescence, a known HIV pathology
- Previous studies have linked HIV infection status with persistent age-related immunologic abnormalities such as
  - an expanded senescent CD8$^+$ T cell compartment
  - shorter telomere in senescent CD8$^+$ T cells in untreated individuals
  - a decreased CD4/CD8 cell count ratio
  - shorter leukocyte telomere length
- It is unknown whether
  - the association between HIV infection and skewed cellular aging markers that are indicative of immunosenescence would remain in a larger well-balanced cohort
  - in HIV-relevant immune subsets, clinical factors known to impact cellular age including viral coinfections, HIV viral load, cART, and time since HIV diagnosis, are associated with aging markers such as telomere length and mitochondrial DNA oxidative damage

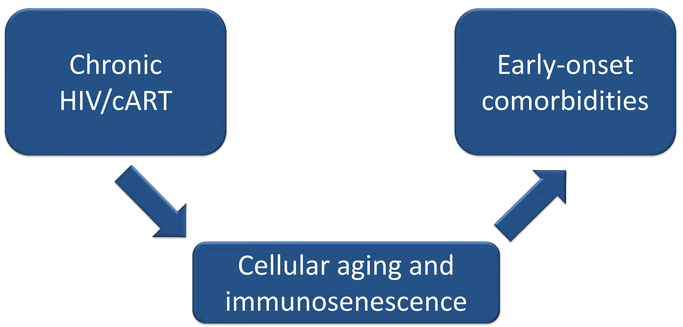



**Figure 1.** A putative model for HIV/cART modulating age-related comorbidities

## Pilot Study Objectives

- Study an initial sample (n=43, ages 6-70) consisting of HIV$^+$ (n=33) and HIV$^-$ (n=10) participants to investigate the cellular processes that may lead to early onset comorbidities in people living with HIV
- Characterize cellular aging in sorted CD4$^+$ and CD8$^+$ T cell subsets and explore potential subset-specific associations with clinical parameters
- Investigate the possible role of HIV and/or cART on immune aging

## Methods and Materials

1. Collect whole blood
2. Isolate peripheral blood mononuclear cells
3. Sort cell subsets by FACS
4. Assay cellular markers by qPCR:
   - Telomere length
   - Mitochondrial DNA (mtDNA) oxidative damage
5. Perform Mann-Whitney tests, Spearman's rank correlations, and analyses of covariance
   - Each analysis included only samples with available relevant clinical data
   - Experimental data were included in accordance with quality control protocol

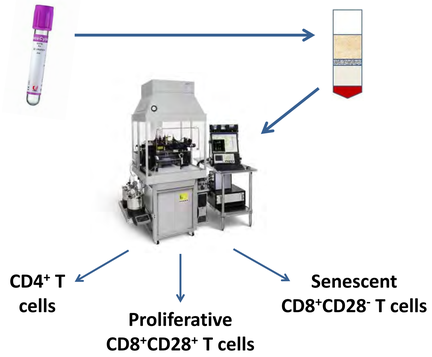



**Figure 2.** Schematic of methodology

## Results

- Telomere lengths are negatively correlated with age in CD4$^+$ T cells (n=26) and proliferative CD8$^+$CD28$^+$ T cells (n=27). This was not seen in senescent CD8$^+$CD28$^-$ T cells.

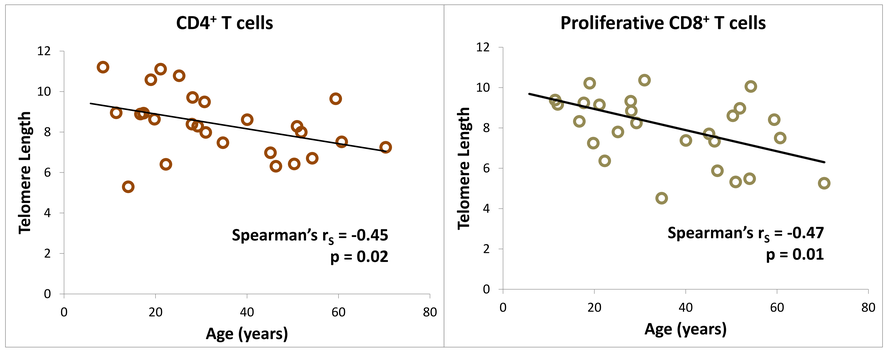



**Figure 3.** Relationship between telomere length and age in CD4$^+$ and proliferative CD8$^+$CD28$^+$ T cells

- Mitochondrial DNA oxidative damage is negatively correlated with lifetime cART duration in both proliferative (n=22) and senescent (n=22) CD8$^+$ T cells. This was not seen in CD4$^+$ T cells.

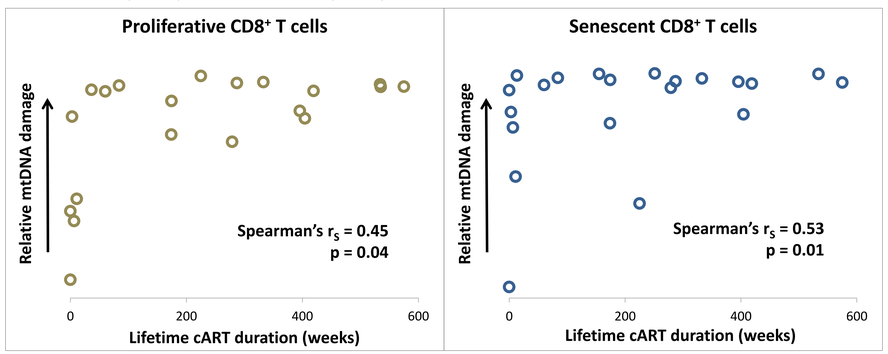



**Figure 4.** Relationship between relative mtDNA damage and lifetime cART duration in proliferative CD8$^+$CD28$^+$ and senescent CD8$^+$CD28$^-$ T cells

**Table 1: Relationship of HIV Seropositivity with Clinical Parameters**

| Clinical Parameters | n | Direction for HIV$^+$ vs HIV$^-$ | p value |
|---|---|---|---|
| CD4:CD8 T cell ratio | 43 | ↓ | **<0.01** |
| Senescent CD8$^+$ count (per total T cells) | 43 | ↑ | **0.02** |
| Proliferative CD8$^+$ Telomere Length (age-adjusted) | 27 | ↓ | **0.02** |
| Senescent CD8$^+$ Telomere Length (age-adjusted) | 29 | — | 0.56 |
| CD4$^+$ T cell Telomere Length (age-adjusted) | 26 | — | 0.53 |

## Conclusions

- This pilot study reveals a potential relationship between HIV infection and shorter telomere length in proliferative CD8$^+$ T cells
- This suggests a need for further investigation of proliferative CD8$^+$ T cells and their role in HIV immune cell aging
- MtDNA oxidative damage may be related to lifetime cART duration, suggesting that cumulative exposure may contribute to lymphocyte mitochondrial aging
- As shown in small previous studies, HIV seropositivity is associated with abnormal lymphocyte distributions consistent with immunosenescence

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