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Association of HIV Viral Load and Shorter Telomere Length

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Background

- Telomeres are DNA sequences on the ends of chromosomes that protect genomic integrity and shorten as cells age. Telomerase is an enzyme that counteracts telomere shortening and prevents cellular aging.
- Telomerase may be inhibited by reverse transcriptase inhibitors and telomeres in T cells may be shortened by excess HIV-associated proliferation.
- Given the association of HIV with cardiovascular disease and other aging-associated conditions, we evaluated telomere length (TL), telomerase activity (TA), and vascular function in a diverse cohort of HIV-infected and uninfected adults.

Methods

- PBMC samples were obtained from a cohort of 65 HIV-infected and 24 uninfected controls in an effort to measure TL, TA, and endothelial function. Study participants were recruited at San Francisco General Hospital.
- TL was measured from DNA by a quantitative PCR assay that compares mean telomere repeat sequence abundance (T) to a reference single copy gene number (S) in each sample and validated by comparison with Southern blot terminal restriction fragment (TRF) analysis. Lab personnel that performed the assay received de-identified samples and were blind to all demographic and clinical data.
- TA was assessed using a telomere repeat amplification protocol assay on a polyacrylamide gel (Gel-TRAP), with telomerase used to elongate the oligonucleotide primer. Signals from product ladders on the gels were normalized against the signal from the internal control band to obtain the product/internal control value.
- Endothelial function was measured using flow-mediated vasodilation of the brachial artery (FMD). Brachial artery diameter was measured at baseline and during reactive hyperemia following 5 minutes of induced forearm ischemia. Maximal diameter increase was captured after 1 minute of reactive hyperemia. FMD was measured as a percentage of increase from baseline. Vascular response and dilation was measured by change in baseline resting brachial diameter and velocity following 0.4mg sublingual nitroglycerin administration. Maximal brachial artery dilation was measured 3 minutes post nitroglycerin administration.
- We compared levels and distributions of TL and TA by disease category, grouping participants by HIV status, ART use, and presence of detectable viremia. We then used multivariable generalized linear regression with a log link to identify factors associated with levels of TL and TA. Candidate covariates included HIV viral load, sCD163, IL-6, D-dimer, CRP, and sCD14.

Results

Median TL was 0.95 in treated and virally suppressed patients and 0.93 in untreated and non-suppressed, compared with 1.07 in uninfected controls (p=0.046). Median TL was 1.02 in untreated, virally suppressed patients (p=0.72 vs. controls).

TL remained 12% shorter (p=0.004) in untreated individuals with detectable viremia compared with controls after adjustment for age, gender and race.

Correlations with FMD were weak for both TL (r=0.12, p=0.34) and TA (r=0.11, p=0.46). Variations in TA were not statistically significant between groups. Analysis of TL/TA ratios among groups did not demonstrate statistical significance.

Table 2

Among HIV+ participants	
HAART use	36.9%
NRTI use	36.9%
NNRTI use	20.0%
PI use	21.5%
Mean CD4 (cells/μL)	689 (100-2004)
Nadir CD4 (cells/μL)	417 (3-1190)
Median HAART duration in years (IQR)	0.00 (0.00-3.61)

Table 1

	HIV+ (n=65)	HIV- (n=24)	P value
Median Age (IQR)	47.0 (42.0-53.0)	44.5 (33.0-55.0)	0.649
Female	3.1%	4.2%	0.647
Known CAD	4.6%	0.0%	0.392
Diabetes	4.6%	0.0%	0.560
Hypertension	21.5%	8.3%	0.217
Hepatitis C	18.5%	4.2%	0.172
Race			0.859
Caucasian	55.4%	58.3%	
African-American	27.7%	20.8%	
Latino	6.2%	4.2%	

Subject demographics and clinical characteristics are displayed in Table 1. Antiretroviral use and serum CD4 markers can be seen in Table 2. Table 3 describes factors independently associated with shorter TL in HIV+ patients.

In a separate demographics-adjusted model of HIV+ individuals, higher sCD163 was associated with a decrease in TL (p=0.016).

Figure 1

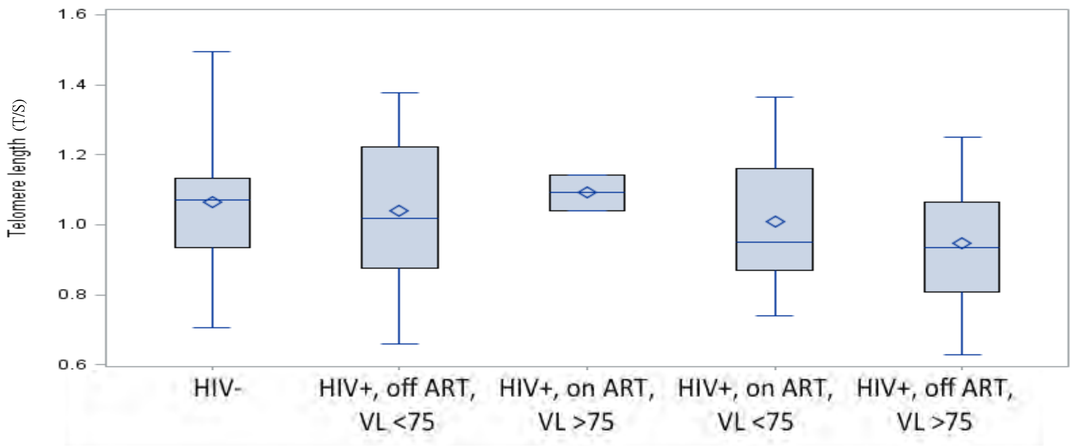


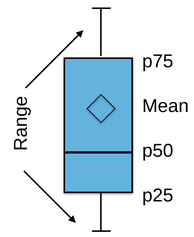
Table 3

Age	10% shorter per decade (-13%, -6%)	p<0.001
Viral load >10,000	21% shorter than VL <2,000 (-30%, -11%)	p<0.001

Conclusions

- Treated, virally suppressed HIV+ individuals and untreated non-suppressed HIV+ individuals have shorter TL compared to controls, a finding that appears to be driven by HIV replication.
- Having an HIV RNA level >10,000 copies/ml was associated with a larger reduction in TL than a decade of aging.
- Higher sCD163, a marker of monocyte/macrophage activation, was also associated with shortened TL.
- These data support the concept that HIV infection compromises telomere maintenance.
- Further studies may address the possibility of antiretroviral therapy leading to partial reversal of telomere shortening.
- TL may also be influenced by monocyte/macrophage activation and other processes; larger studies are necessary to define the role of TL and telomerase in HIV+ persons.

Figure Legend



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