



TELOMERE LENGTH, TELOMERASE ACTIVITY, AND AGE-RELATED DISEASE: ACTG NWCS 422

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Background

- Telomeres are nucleoproteins with TTAGGG repeats on chromosomes
- Shorten with cell division until critical length of senescence and dysfunction
- Telomere length (TL) maintained by telomerase -- ribonucleoprotein enzyme complex with reverse transcriptase (TERT)
- *In vitro* -- all NRTIs inhibit TERT: TFV>FTC>AZT>ABC
- *Ex vivo* -- TL shorter and TERT less active with NRTIs
- Short TL associated with death, CVD, Alzheimer's, ESRD and cancer in HIV-negative
- Which factors are associated with shorter TL or reduced telomerase activity?
- Are telomere length or telomerase activity associated with age-related disease among HIV-infected individuals on ART?

Methods

- Design: nested case-control study
- Data and banked PBMCs from ACTG Longitudinal Linked Randomized Trials (ALLRT) participants with sustained HIV RNA suppression to <200 copies/mL within 24 weeks of ART initiation without rebound for at least 96 weeks

Methods (cont.)

- Cases: non-accidental death or confirmed diagnosis of cancer, cardiovascular, liver, renal, neurocognitive, or pulmonary disease, osteoporosis/bone fractures, or diabetes mellitus; and banked PBMCs samples pre-ART and prior to event (closest within 6 months)
- Controls: 2 to 1 matched for sex, age, NRTI duration, and timing of PBMC samples without events listed above
- TL: qPCR with relative TL measured by quantifying a telomere repeat copy (T) versus single copy reference gene (S) ratio
- Telomerase activity: real-time quantitative telomeric repeat amplification protocol (RQ-TRAP)
- Multivariable logistic regression for matched case-control

Results

- Analyzed 351 ALLRT participants (117 cases and 234 controls) 117 Cases on ART for median of 4.3 years (Table 1): 14 (35%) diabetes, 33 (28%) renal disease, 18 (15%) cancer, 14 (12%) CVD, 7 (6%) death, and 4 (4%) bone fractures
- Short pre-ART TL (<0.4 T/S ratio) associated with pre-ART VL >10⁵ copies/mL (OR=1.9; 95% CI 1.2-3.0) and pre-ART TA in the lowest quartile (OR 1.8; 95% CI 1.0-3.2)
- Short pre-event TL (or matching time point) (<0.4 T/S ratio) associated with female sex (OR=2.8 ; 95% CI 1.5-4.9), non-white race (OR=1.8; 95% CI 1.2-2.8), ART with TDF (OR 1.6; 95% CI 1.0-2.5), and entry year (OR 1.1; 95% CI 1.03-1.14)
- Factors associated with age-related disease were earlier calendar study entry year, pre-ART CD4<200 cells/μl, higher pre-ART VL, initial ART regimen without TDF, lower CD4/CD8 ratio after 96 weeks on ART and smoking (Tables 1 and 2)
- TL and TA (pre-ART, pre-event and delta) were not associated with age-related disease in univariable or multivariable analyses (Table 1 and 2 and Figures)

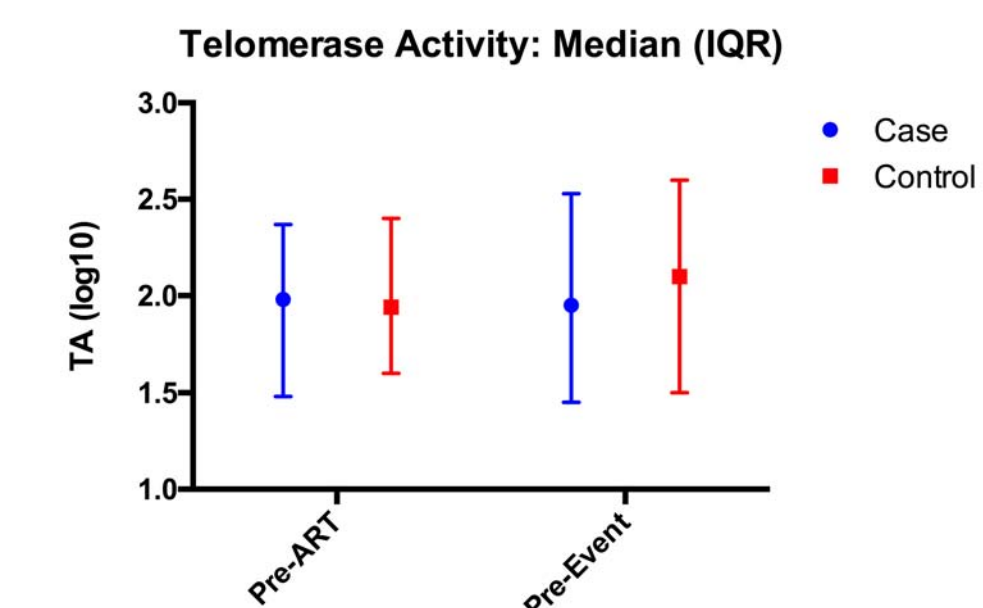
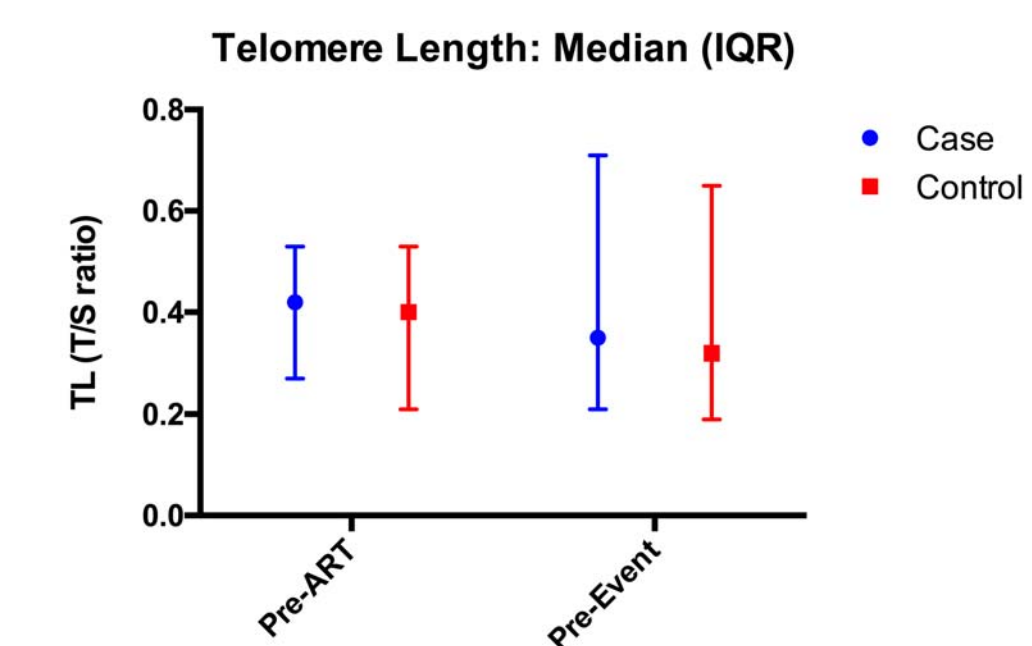
Table 1. Participant characteristics and comparison between cases and controls

Characteristic	Case (n=117)	Control (n=234)	p-value*
Age	43 (38, 50)	42 (36, 49)	0.15
Female sex	27 (23%)	54 (23%)	1.0
White race	54 (46%)	110 (47%)	0.88
Smoking (ever)	76 (65%)	119 (51%)	0.01
Smoking (pack-yrs)	7.5 (0, 22.5)	0.13 (0, 10.6)	<0.001
IDU	14 (12%)	15 (6%)	0.07
ART with TDF	28 (24%)	119 (51%)	<0.001
Entry Year	2002 (1999, 2003)	2004 (2002, 2010)	<0.001
Time to event (years)	4.3 (2.7, 7.6)	--	--
<i>Pre-ART</i>			
CD4 (cells/μl)	204 (77, 393)	254 (89, 397)	0.70
<200	58 (50%)	90 (38%)	0.05
CD8 (cells/μl)	857 (545, 1156)	752 (551, 1128)	0.38
CD4/CD8	0.23 (0.11, 0.41)	0.33 (0.14, 0.45)	0.29
HIV RNA (log₁₀)	4.9 (4.5, 5.5)	4.7 (4.3, 5.3)	0.01
TL (T/S ratio)	0.42 (0.27, 0.53)	0.40 (0.21, 0.53)	0.19
TA (log ₁₀)	1.98 (1.48, 2.37)	1.94 (1.60, 2.40)	0.67
<i>Pre-Event**</i>			
TL (T/S ratio)	0.35 (0.21, 0.71)	0.32 (0.19, 0.65)	0.30
TA (log ₁₀)	1.95 (1.45, 2.53)	2.1 (1.5, 2.6)	0.34
<i>Delta***</i>			
TL (T/S ratio)	+0.0006 (-0.22, +0.37)	-0.01 (-0.26, +0.28)	0.44
TA (log ₁₀)	+0.07 (-0.53, +0.69)	+0.02 (-0.55, +0.76)	0.86
CD4/CD8 96 weeks	0.59 (0.37, 0.89)	0.72 (0.46, 1.0)	0.02

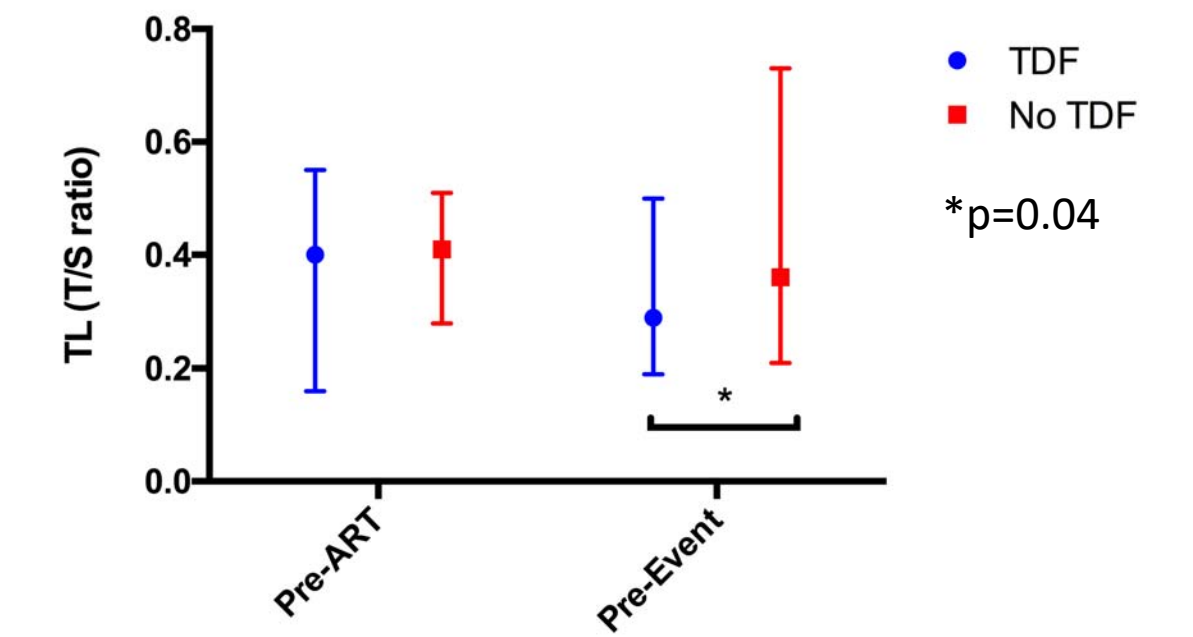
N (%) or median (IQR); *Comparison between cases and controls by Fischer exact test or Wilcoxon rank test; **For controls at matching time point; ***Change from pre-ART to pre-event or matching time point

Table 2. Multivariable case-control logistic regression

	OR	95% CI
<i>Pre-Event TL (T/S ratio)</i>		
<0.19	1.0	0.50, 2.0
0.19 – 0.33	0.97	0.49, 1.9
0.34 – 0.65	0.93	0.47, 1.83
>0.65	1.0	--
Smoking (ever)	2.2	1.4, 3.7
ART with TDF	0.54	0.19, 1.56
Entry Year	0.95	0.84, 1.1
Pre-ART CD4<200	1.1	0.61, 2.0
Pre-ART HIV RNA per log copies/mL	1.34	0.94, 1.9
CD4/CD8 ratio 96 weeks	0.93	0.47, 1.83



Telomere Length: Median (IQR) by initial ART with TDF



Conclusions

- Prior to ART, telomeres were significantly shorter among participants with higher HIV RNA and lower telomerase activity
- After median of 4 years on ART, telomeres declined (non-significant) and were significantly shorter among women, non-white race and those on ART with TDF
- TA did not change over time on ART
- We found no associations between TL, TA or changes in these biomarkers on ART, and age-related diseases
- The only independent factor associated with age-related disease in this study was smoking

Future Directions:

- Longer term follow-up (>10 years on ART) in older populations (>60 years) with more events and time points (ACTG HAILO)
- TL of CD8+CD28- T cells expressing CD57
- TL/TA after TAF switch -- intracellular TFV 7-10x higher