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Blood Telomere Length changes after DRV/R + either RAL or TDF/FTC as first line ART

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Background

► Telomere attrition is one of the hallmarks of aging. However, it is unknown if this mechanism contributes to accelerated aging in HIV infected patients.

► Tenofovir is a potent inhibitor of human telomerase in vitro (1, 2).

► The in vivo relevance of this inhibition is unknown.

Hypothesis

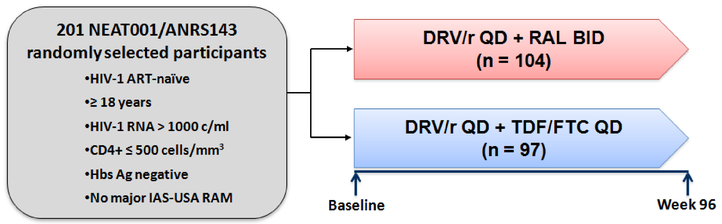
► Exposure to tenofovir would have a negative impact on blood telomere length (TL) changes.

Objectives

► To evaluate the impact of TDF on blood TL changes in naïve patients who start ART.

Methods

► 201 NEAT001/ANRS143 participants were randomly selected among those from whom stored blood samples were available (baseline and 96 weeks).



► Telomere length, expressed as ratio of telomere (T) to single-copy gene (S), was determined by monochrome quantitative multiplex PCR assay (3).

- Baseline and follow-up samples were analyzed together in the same run.
- All samples were run in triplicate and those with a coefficient of variation (CV) > 10% were retested.
- Intra and inter-assay CV were 4.7% and 5.7%, respectively.

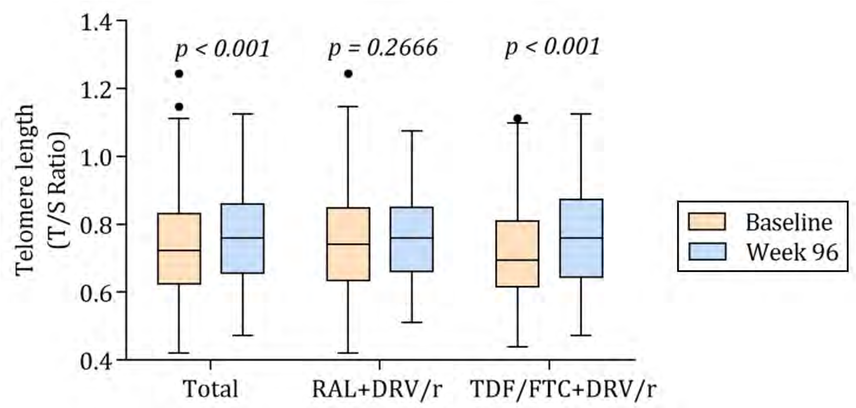
► Statistics: Multivariable estimative analysis and predictive linear regression for TL change (week 96 minus baseline). All models were adjusted by baseline TL.

Participants Characteristics

	RAL + DRV/r N=104	TDF/FTC + DRV/r N=97	p-value
Age, (yr) *	38.7 (10.4)	38.6 (10.8)	0.961
Female, n(%)	11 (10.6)	11 (11.3)	0.862
Smoking (Currently), n(%)	35 (33.7)	39 (40.2)	0.417
Alcohol use (Currently), n(%)	4 (3.8)	10 (10.3)	0.197
Time since HIV diagnosis (yr)*	2.2 (3.3)	2.0 (2.8)	0.699
Baseline HIV-1 RNA (log_{10} cp/mL)*	4.7 (0.7)	4.7 (0.6)	0.729
HIV RNA < 50 copies/mL at week 96, n(%)	99 (95.2)	89 (91.8)	0.322
Median time to HIV RNA < 50 copies/mL, weeks (IQR)	8 (4-12.6)	18 (9.4-24.1)	<0.001
CD4 Baseline (cells/mm^3)*	332.6 ± 133.3	315.3 ± 122.2	0.339
CD4 Change (cells/mm^3)*	265.52 ± 159.6	253.40 ± 167.4	0.602
CD8 Baseline (cells/mm^3)*	948.2 ± 442.7	924.6 ± 500.2	0.507
CD8 Change (cells/mm^3)*	-123.9 ± 442.2	-124.9.6 ± 350.4	0.987
CD4/CD8 Baseline*	0.5 ± 0.8	0.4 ± 0.2	0.536
CD4/CD8 Change*	0.4 ± 0.8	0.4 ± 0.3	0.403
CD4/CD8 >0.4 at week 96, n(%)	94 (90.4)	83 (85.6)	0.558
CD4/CD8 >1 at week 96, n(%)	35 (33.7)	30 (30.9)	0.918

*Mean ± Standard deviation. Change was calculated as week 96 minus baseline.

Telomere Length Change

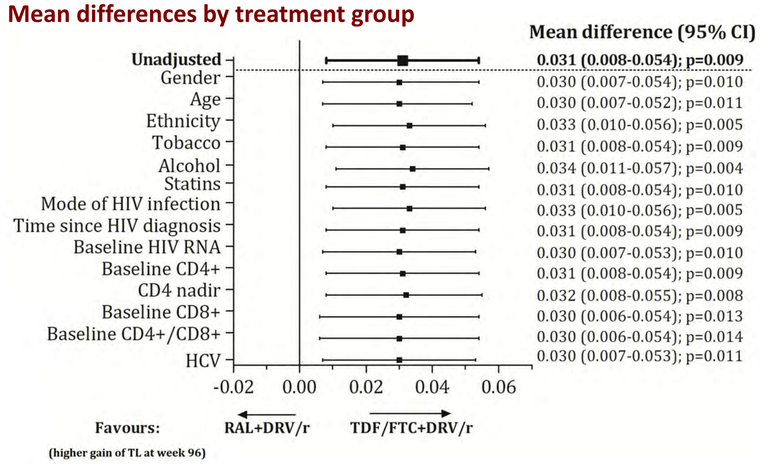


	TOTAL N=201	RAL + DRV/r N=104	TDF/FTC + DRV/r N=97	p-value
Baseline Mean TL (SD)	0.738 (0.152)	0.750 (0.154)	0.724 (0.149)	0.221
Week 96 Mean TL (SD)	0.766 (0.136)	0.760 (0.133)	0.772 (0.140)	
Mean Change TL (95% CI)	0.028 (0.015; 0.041)	0.009 (-0.007; 0.026)	0.048 (0.028; 0.067)	0.009*
Participants with TL gain at week 96 (%)	128 (63.68)	59 (56.73)	69 (71.13)	0.034
Participants with TL gain >1 SD at week 96 (%)	47 (23.38)	21 (20.19)	26 (26.80)	0.268

*Adjusted by baseline telomere length

Telomere Length Change at week 96

Mean differences by treatment group



All differences adjusted by baseline telomere length

Independent predictors of change in TL

	Mean Difference (95%CI)	p-value *
TDF/FTC vs RAL	0.033 (0.010; 0.056)	0.005
Younger age	0.001 (0.000; 0.002)	0.097
No current drinker	0.052 (0.006; 0.094)	0.026

*Adjusted by baseline telomere length

Discussion

► The observed gain in blood TL probably represent shifts in CD8 lymphocytes subpopulations towards less mature phenotypes with longer TL.

► Our current hypothesis is that differences in TL are due to a higher efficacy of TDF/FTC to decrease viral replication in lymph nodes. Two recent studies have reported that compared to TDF and FTC, both DRV and RAL have lower drug levels in lymph node tissue (4, 5).

Conclusions

► This is the first comparative clinical trial evaluating blood TL changes in naïve HIV participants starting ART.

► After 96 weeks participants receiving TDF/FTC + DRV/r had a significant higher gain in blood TL than those receiving RAL + DRV/r.

► The cause and clinical relevance of these differences between ART regimens are unknown and require further research.

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