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Impact of antiretroviral treatment containing tenofovir difumarate on the telomere length of aviremic HIV-infected patients

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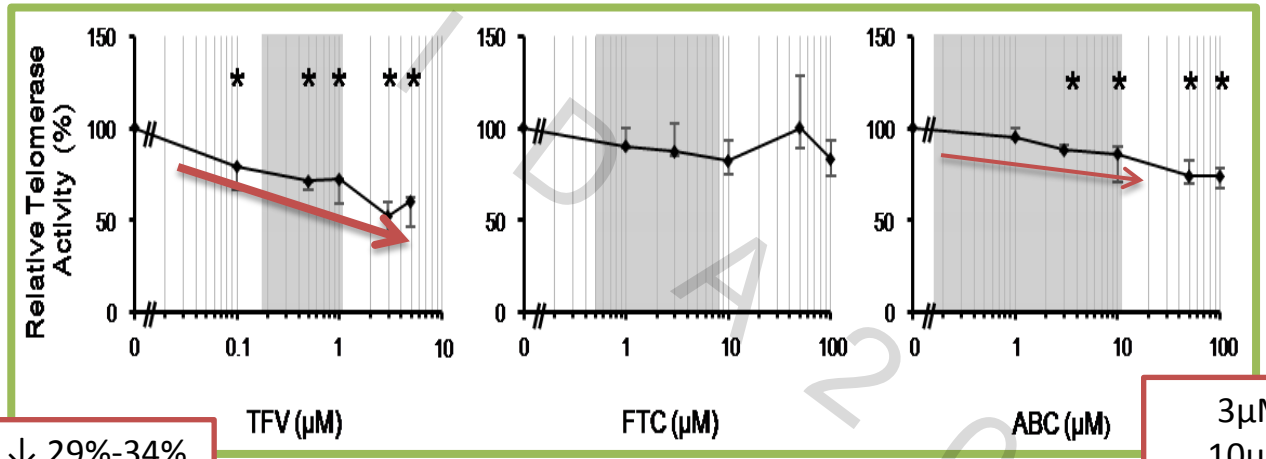
Background

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

► Two prior studies have shown that tenofovir (TFV), abacavir (ABC), lamivudine (3TC) and emtricitabine (FTC) can inhibit telomerase activity in vitro in activated peripheral blood mononuclear cells (PBMCs). (1,2)



► Of the currently recommended Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (N(t)RTIs), TFV is a more potent inhibitor of telomerase than ABC, 3TC or FTC.

► Our research hypothesis was that exposure to TDF would be associated with shorter telomere length (TL).

(1) J Infect Dis. 2013; 207(7):1157–65.
(2) J Acquir Immune Defic Syndr. 2017 Jan 1;74(1):91-94.

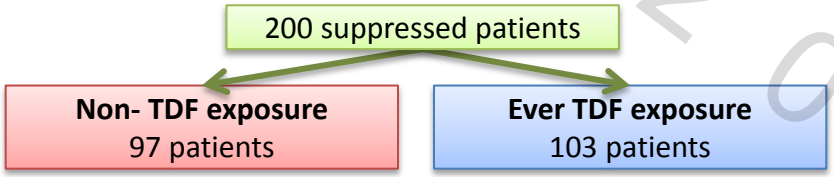
Objectives

- To evaluate the in vivo relevance of the inhibitory effect of TFV upon telomerase activity observed in vitro.
- To compared TL in a group of virologically suppressed HIV-infected patients who were receiving antiretroviral regimens including and not including TDF.
- To evaluate the association of independent factors with TL.

Methods

- We designed a cross sectional study of HIV-1 infected patients with suppressed virological replication

- Inclusion criteria: stable ART and plasma HIV RNA <50 copies/mL for ≥1 year prior to enrollment.



- TL was measured in whole blood by monochrome quantitative multiplex PCR assay.

- All samples were run in triplicate.

- Multivariate analysis to elucidate factors associated with TL and also evaluated the association between TL and the use of TDF adjusted by significant confounders.

Baseline Characteristics

	Non-TDF group N (%)	TDF group N (%)	p-value
N	97 (48.5)	103 (51.5)	
Sex, Men	74 (76.3)	70 (68.0)	0.190
Age*	49 [45-55]	49 [46-54]	0.993
<45 years	24 (24.7)	18 (17.5)	0.279
45-50 years	27 (27.8)	38 (36.9)	
≥ 50 years	46 (47.4)	47 (45.6)	
Paternal age at birth †	32.2 (7.4)	32.0 (6.1)	0.898
Maternal age at birth †	29.7 (6.4)	29.3 (0.56)	0.710
Race, Caucasian	89 (91.8)	100 (97.1)	0.098
Income			
Lower (≤12000 €/year)	45 (46.4)	50 (48.5)	0.761
Higher (>12000 €/year)	52 (53.6)	53 (41.5)	
Education			
Primary	41 (42.3)	45 (43.7)	0.323
Secondary	26 (26.8)	35 (34.0)	
University	30 (30.9)	23 (22.3)	
Alcohol , Y/N	32 (33)	59 (58.3)	0.001
Smoking ,Y/N	47 (48.5)	59 (57.3)	0.211
Ever IDU	24 (24.7)	37 (35.9)	0.086

*Median [IQR], † Mean (SD)

Telomere length (T/S)†	0.749, 0.797 [0.685-0.861]	0.772, 0.768 [0.664-0.863]	0.962

† Median, Mean [IQR]

	Non-TDF group N (%)	TDF group N (%)	p-value
N	97 (48.5)	103 (51.5)	
HIV transmission route			
Sexual	65 (67.0)	59 (57.3)	0.167
Parenteral	28 (28.9)	42 (40.8)	
Unknown	4 (4.1)	2 (1.9)	
Time HIV infection (years)*	16.9 [11.98-21.94]	19.39 [15.72-23.59]	0.007
<10 years	15 (15.5)	8 (7.8)	0.070
10-20 years	51 (51.6)	48 (46.6)	
≥20 years	31 (32.0)	47 (45.6)	
CD4 count, (cells/µL)*	801 [575-1080]	733 [519-1005]	0.21
Previous AIDS stage	51 (52.6)	55 (53.4)	0.907
Time on ART (years)*	14.34 [10.02-17.12]	15.0 [11.08-18.52]	0.09
<10 years	22 (22.7)	18 (17.5)	0.206
10-20 years	68 (70.1)	70 (68.0)	
≥20 years	7 (7.2)	15 (14.6)	
Current ART regimen			
Triple therapy	69 (71.3)	59 (57.28)	<0.001
Boosted PI monotherapy	21 (21.25)	44 (42.7)	
NRTI-sparing regimen	7 (7.22)	-	

*Median [IQR]

MULTIVARIANT ANALYSIS

Variable	ALL	
	exp (coef.) [CI (95%)]	p-value
Age (Ref. <45 years)		
≥45/50 years	0.95 [0.87-1,03]	0.216
≥50 years	0.90 [0.83-0.97]	**0.008**
Father's age at birth (per year)	1.005 [1.000-1.009]	**0.038**
Race (Ref. Caucasic) -Other	1.13 [1.00-1.28]	**0.048**
Education (Ref. Primary)		
Secondary	-	
University	-	
Income (Ref. Low) - High		
Time with HIV infection (Ref. <10 years)		
≥ 10-20 years	0.87 [0.79-0.95]	**0.003**
≥ 20 years	0.91 [0.82-1.00]	0.056
Time on ART (Ref. <10 years)		
≥ 10-20 years	-	
≥ 20 years	-	

Conclusions

- Our data do not suggest that telomerase activity inhibition caused by TDF in vitro, leads to telomere shortening in peripheral blood of HIV infected patients.

- Significant predictors of shorter telomere length were age, paternal age at birth and Caucasian race.

- Longer time of HIV infection was associated with shorter telomere length.

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Poster #062- Impact of Antiretroviral Treatment Containing Tenofovir Difumarate on Telomere Length Attrition in a Prospective Cohort of Aviremic HIV-Infected Participants

Aknowledgments

Patients & Study Team

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