Blood Telomere Length in ART-Naïve PLWH Starting DTG+3TC vs Triple Regimen with Two Nucleosides

820

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BACKGROUND

- People living with HIV (PLWH) are characterized by a marked shortening of blood telomere length (BTL).
- The pronounced telomere attrition is a hallmark of accelerated/accentuated aging and immunosenescence, a distinctive status observed in PLWH that can persist over time despite effective antiretroviral therapy (ART).
- BTL substantially shortens early after HIV seroconversion. This can be caused by HIV proteins that inhibit the telomerase and/or chronic antigen stimulation that leads to a shift of T-cell subtypes towards more differentiated phenotypes with shorter telomeres.
- By means of initial control of HIV replication, antiretroviral therapy (ART) in treatment-naïve PLWH determines an increase in naive and central memory cells that have longer telomeres, leading to an overall BTL increase [1,2].
- However, it has been observed that at therapeutic concentration tenofovir (TFV) and abacavir (ABC), two commonly recommended NRTIs in ART, are potent inhibitors of human telomerase activity in vitro and might negatively affect the BTL increase.

AIM

- Our aim was to investigate the effect on BTL over 96 weeks in treatment-naïve PLWH who started either a standard triple therapy (**TT**) with an anchor drug plus two NRTIs, one of which was TFV (TDF/TAF) or ABC, or a dual therapy (DT) with dolutegravir (DTG) plus lamivudine (3TC).

METHODS

- Prospective longitudinal study.
- From 2018 to 2023 we enrolled 71 treatment-naïve PLWH with the following inclusion criteria: adults (≥18 years of age) and with no current AIDS event who had started TT (n=41) or DT (n=30).
- BTL was measured on genomic DNA isolated from whole blood samples collected at different time-points:

1) **BL** (Baseline, the time of ART initiation),
2) **VS** (Virological success, defined as achievement of HIV-RNA<50cps/mL)
3) **W48** (48 weeks after starting ART)
4) **W96** (96 weeks after starting ART)

- BLT was assessed with a monochrome multiplex quantitative PCR method (qMMPCR) and expressed as the telomere to albumin single copy gene ratio (T/S) [3].
- We used an adjusted mixed model (GLM) to evaluate the effects of both between- and within-subject factors over time. Linear regressions were performed to identify the variables associated with BL BTL and BTL changes over W96.

Treatment-naïve PLWH starting ART regardless of triple or dual regimen, showed a significant increase of BTL after 96 weeks

RESULTS

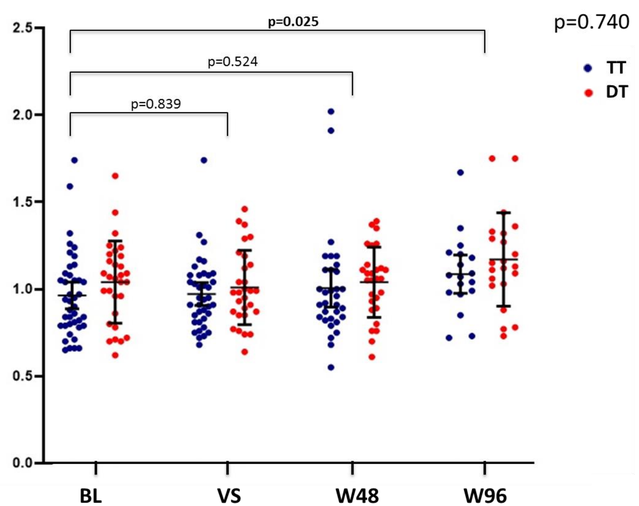
Baseline characteristics of study participants

	Whole population n=71	TT n=41	DT n=30	p
Gender, n (%)				0.311
Male	55 (77.5)	30 (73.2)	25 (83.3)	
Female	16 (22.5)	11 (26.8)	5 (16.7)	
Age, median (IQR), years	38 (32-52)	44 (36-54)	35 (25-50)	**0.008**
Caucasian, n(%)				
Risk factor				0.961
MSM	42 (59.2)	24 (58.5)	18 (60.0)	
Heterosexual	27 (38.0)	16 (39.0)	11 (36.7)	
PWID	2 (2.8)	1 (2.4)	1 (3.3)	
BMI, median (IQR), Kg/m^2	23 (22-25)	23 (22-25)	24 (23-25)	0.208
Smokers, n (%)[a]	29 (40.8)	15 (36.6)	14 (46.7)	0.393
Alcohol habit, n (%)[b]	25 (35.2)	12 (29.3)	13 (43.3)	0.220
HIV Subtype				0.056
B	15 (21.1)	8 (19.5)	7 (21.1)	
non-B	11 (15.5)	3 (7.3)	8 (26.7)	
Unknown	37 (63.4)	30 (73.2)	15 (50.0)	
CD4 count, median (IQR), cells/µL	290 (171-508)	225 (76-481)	382 (261-598)	**0.002**
HIV-RNA, median (IQR), Log$_{10}$ copies/mL	4.77 (4.15-5.50)	5.27 (4.11-5.92)	4.67 (4.19-5.07)	0.110
HIV-DNA, median (IQR), Log$_{10}$ copies/10^{6}CD4	4.18 (3.55-4.59)	4.30 (3.62-4.92)	4.08 (3.55-4.28)	0.071
Starting ART within two months from HIV diagnosis, n (%)	67 (94.4)	40 (97.6)	27 (90.0)	0.172
Time to virological success, median (IQR), days	58 (26-117)	68 (26-121)	48 (25-121)	0.601

Abbreviations: MSM: Men who have sex with men; PWID: People who inject drugs; BMI: Body mass Index; [a] >10 cigarettes per day; [b] ≥2 alcoholic units/day

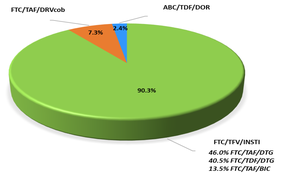
- All PLWH reached VS.
- N= 36 and N=28 PLWH in TT and DT group, respectively, reached W48.
- N= 21 and N=22 PLWH in TT and DT group, respectively, reached W96.
- Three single blips in TT and 1 in DT and no virological failure occurred at W48.
- No blips and 1 virological failure in each group occurred at W96.

BTL trend over time according to the study group



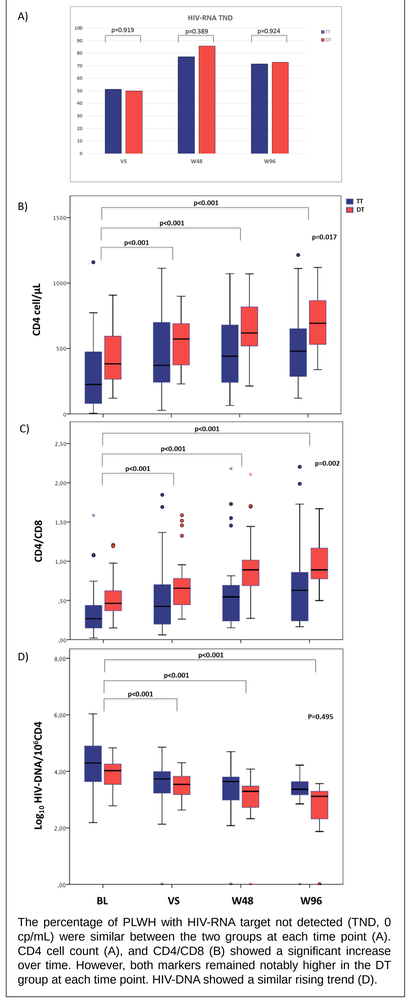
- At BL, the medians (IQR) of BTL were similar in the TT and DT groups: 0.93 (0.79-1.09) and 1.06 (0.84-1.19) (p=0.103).
- We observed an overall increase of BTL over time, which showed a similar trend in both groups (p=0.740).
- However, we observed no statistically significant variation up to VS (+0.004, p=0.839) and W48 (+0.021, p=0.524), but observed a statistically significant mean gain at W96 **(+0.103, p=0.025)**.

Baseline triple standard regimen (n=41)



The majority of PLWH who started triple regimen were on FTC/TFV/INSTI

Viro-immunological profile over time



The percentage of PLWH with HIV-RNA target not detected (TND, 0 cp/mL) were similar between the two groups at each time point (A). CD4 cell count (A), and CD4/CD8 (B) showed a significant increase over time. However, both markers remained notably higher in the DT group at each time point. HIV-DNA showed a similar rising trend (D).

Factors associated with BL BTL

Linear regression analysis showed that only younger age was associated with BL BTL. (-0.043 per 10 yr. increase; -0.109/-0.022; p=0.004)

Factors associated with BTL change over 96 weeks

	UNIVARIATE			MULTIVARIATE		
Dependent variable: BTL change (w96)	B	95% CI	p	B	95% CI	p
Group						
TT	0					
DT	0.067	-0.165/0.299	0.562			
Gender						
Male						
Female	-0.043	-0.348/0.262	0.779			
Age/10years	0.018	-0.068/0.105	**0.673**			
Caucasian	-0.289	-0.600/0.022	0.068			
Risk factor						
MSM	-0.06	-0.313/0.192	0.631			
Heterosexual	-0.06	-0.192/0.313	0.631			
BMI (Kg/m2)	0.044	-0.005/0.093	0.101			
Smokers	-0.111	-0.341/0.120	0.336			
Alcohol habit	0.102	-0.021/0.425	0.111			
HIV Subtype						
non -B	0			0		
B	300	0.059/0.540	0.016	0.155	-0.0828402	0.094
CD4/10, cells/µL	0.000	-0.005/0.005	0.954			
HIV-RNA, Log$_{10}$ copies/mL	-0.081	-0.207/0.045	0.203			
HIV-DNA, Log$_{10}$ copies/10^{6}CD4	-0.010	-0.173/0.154	0.907			
BL BTL	**-0.939**	**-1.236/-0.642**	**<0.001**	**-0.869**	**-1.170/-0.568**	**<0.001**
Starting ART within two months from HIV diagnosis	-0.308	-0.500/0.033	0.085			

Linear regression analysis showed that higher BTL change was associated with shorter BL BTL (-0.869; -1.170/-0.568; p<0.001).

CONCLUSIONS

In this setting, treatment-naïve PLWH who initiated either TT or DT showed a similar evolution of BTL over time. Any significant change in BTL was observed at VS and after the 1-year follow-up. However, a statistically significant gain was observed at W96.

These data suggest that starting ART, with either a triple or a dual regimen, mainly determines the effective control of viral replication with a beneficial impact on BTL in the long term.

ADDITIONAL KEY INFORMATION

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Ethics: The study was approved by the Ethics Committee of Fondazione Policlinico Universitario A. Gemelli. IRCCS (Rome, Italy) [ID4968]. Written informed consent was obtained from all participants.

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