CD4/CD8 T-Cell Telomere Length at 96 Weeks in the PASO-DOBLE Trial Comparing BIC/FTC/TAF vs DTG/3TC

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BACKGROUND

Telomere length (TL) attrition is a surrogate biomarker of immunosenescence and aging. HIV-1 infection leads to shortening of blood cells TL, which is partially recovered after ART initiation. However, some nucleos(t)ide reverse transcriptase inhibitors (NRTIs), such as tenofovir (TFV), have been suggested to inhibit telomerase activity, potentially limiting telomere maintenance and contributing to accelerated cellular aging despite effective ART.

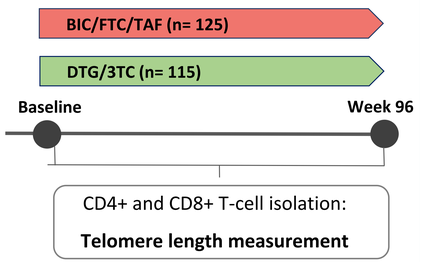
Objective: Here, we aimed to compare CD4 and CD8 T-cell TL dynamics after 96 weeks of exposure to a TFV-containing regimen (BIC/FTC/TAF) versus a non-TFV regimen (DTG/3TC), among participants enrolled in the senescence sub-study of the PASO-DOBLE trial (EUDRACT 2020-003686-18), a randomized, multicenter, open-label, non-inferiority trial.

METHODS

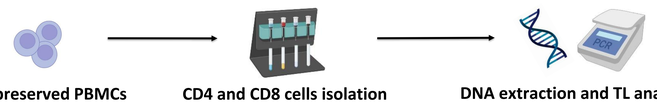
The senescence sub-study of PASO-DOBLE was offered to the participants before trial randomization. Design and participants (n=240):

Inclusion criteria:
- Consent to participate in the senescence sub-study.
- ≥ 18 years old.
- Viral load < 50 copies/ml for at least 24 weeks prior to screening.
- Current ART containing >1 pill/day or single dose with COBI, EFV or TDF.

Exclusion criteria:
- No prior virological failure.
- Resistance mutations to study drugs.
- Pregnancy, chronic hepatitis B, untreated hepatitis C.



CD4+ and CD8+ T-cells were isolated from cryopreserved PBMCs by magnetic immunoseparation. Relative TL was measured using a monochrome multiplex quantitative PCR (MMqPCR) protocol and expressed as the telomere-to-single copy gene (T/S) ratio.



We evaluated the adjusted mean change in TL from baseline to week 96 between groups using linear regression models adjusted for age, sex, ethnicity, baseline TL, baseline CD4 or CD8 counts, prior TFV exposure, duration of viral suppression and study center.

RESULTS

A total of 240 participants were included in this sub-study and completed follow-up. Adequate samples for TL assessment, based on DNA quantity and quality criteria, were available in 190, with 96 receiving BIC/FTC/TAF (50.5%) and 94 DTG/3TC (49.5%). The main sociodemographic and clinical characteristics of the participants are shown in **Table 1**. The groups were well balanced. In both CD4+ and CD8+ T-cells, we observed a moderate inverse correlation between TL and chronological age (**Figure 1**). At study entry, TL in CD4+ and CD8+ T-cells did not differ between the two treatment arms (**Figure 2**).

Over 96 weeks, participants receiving BIC/FTC/TAF experienced more CD8+ telomere shortening than those on DTG/3TC, suggesting a potential influence of tenofovir-containing therapy on telomere dynamics

Table 1. Baseline characteristics of the participants.

	BIC/FTC/TAF (n= 96)	DTG/3TC (n= 94)
Age, years	49 (± 11.1)	48.9 (± 11.6)
Female sex	24 (25%)	24 (25.5%)
White ethnicity	71 (74%)	68 (72.3%)
Time since HIV diagnosis, years	15.7 (± 8.2)	15.3 (± 8.6)
Duration of viral suppression, years	9.4 (± 6.1)	9.9 (± 6.4)
Prior exposure to TFV	60 (62.5%)	53 (56.4%)
CD4 counts, cells/µl	737 (± 289)	727 (± 248)
CD8 counts, cells/µl	662 (± 261)	697 (± 298)

Data presented as n (%) or mean with standard deviation

Figure 1. Correlation between chronological age and CD4+ T-cell TL (A) and CD8+ T-cell TL (B) at baseline. Analysis was determined by Pearson correlation.

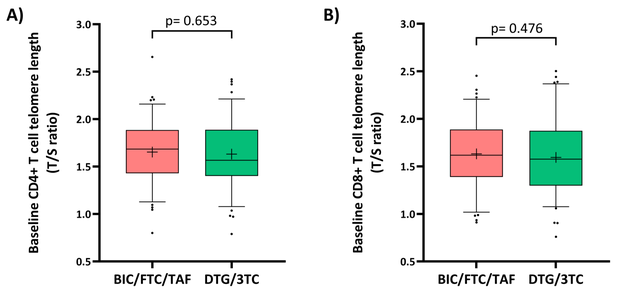


Figure 2. Comparison of CD4+ (A) and CD8+ (B) T-cell TL at baseline between groups. Comparisons were assessed using the t-test. Boxes show medians and whiskers represent the 95th percentiles; the "+" symbol denotes the mean.

Across the overall study population, a reduction in TL over the 96-weeks follow-up was observed in both CD4+ T-cells (mean T/S change: –0.086) and CD8+ T-cells (mean T/S change: –0.057). We subsequently evaluated differences in TL dynamics by treatment group. In CD4+ T-cells, no significant differences were observed, with similar TL evolution in both treatment arms (mean T/S change: –0.086 and –0.085, respectively; p= 0.976) (**Figure 3A**). In CD8+ T-cells, numerically greater TL shortening was observed in participants exposed to BIC/FTC/TAF compared with those receiving DTG/3TC (mean T/S change: –0.078 and –0.035, respectively; p= 0.104). (**Figure 3B**).

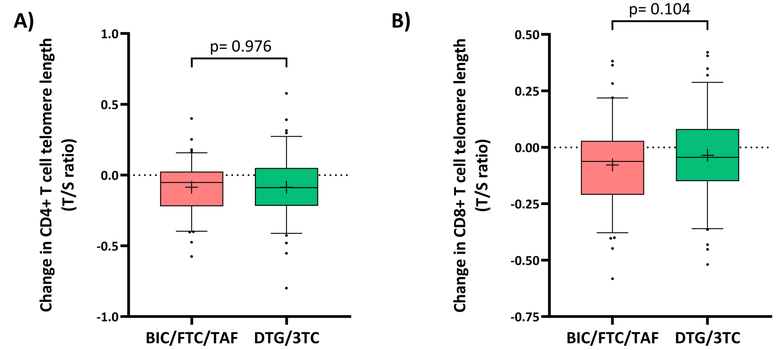


Figure 3. Unadjusted comparison of TL change in CD4+ (A) and CD8+ (B) T-cells between treatment arms after 96 weeks. Comparisons were assessed using the t-test. Boxes show medians and whiskers represent the 95th percentiles; the "+" symbol denotes the mean.

After adjusting for potential confounders, participants receiving BIC/FTC/TAF showed significant TL shortening in CD8+ T-cells compared with those receiving DTG/3TC (β coefficient: –0.056; p= 0.029). Adjusted models showed no significant differences in TL change in CD4+ T-cells.

CONCLUSIONS

Over 96 weeks, TL dynamics in CD4+ T-cells did not differ between the BIC/FTC/TAF and DTG/3TC regimens. In CD8+ T-cells, greater TL shortening was observed in the BIC/FTC/TAF arm after adjustment for covariates, suggesting a possible effect of TFV-containing regimens on CD8+ TL trajectories that warrants further investigation.

ACKNOWLEDGEMENTS

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PLAIN LANGUAGE SUMMARY

Over two years, people taking tenofovir-based treatments showed faster cellular aging in one type of immune cell, suggesting this therapy may affect long-term immune health and deserves further study.

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