Comparison of Telomere Length Changes Over 48 Weeks in SALSA Study: DTG/3TC vs CAR

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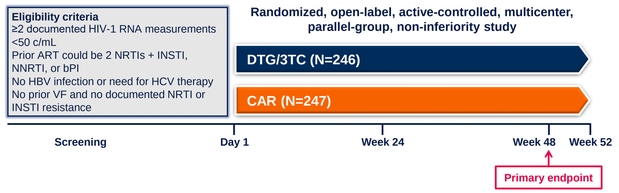
Introduction

- Telomere length (TL) shortens with biological age, and decreased TL is associated with disorders such as cardiovascular disease, stroke, and diabetes. For people living with HIV-1 (PWH) without treatment, TL shortening is seen,[1] and has been associated with immune activation and lower immunological response.
- ARVs and regimen received can impact TL; tenofovir has been shown to inhibit telomerase activity in vitro,[2] and in the clinic may be associated with shorter TL.[3]
- The SALSA study (Figure 1) in virologically suppressed adults showed switching to DTG/3TC fixed-dose combination (FDC) was non-inferior to continuing current antiretroviral regimen (CAR) at Week 48[4] for HIV-1 RNA ≥50 c/mL (Snapshot) at Week 48.
  - ITT-E population, 1/246 (0.4%) vs 3/247 (1.2%); adjusted difference, −0.8%; 95% CI, −2.4% to 0.8%
- No participants met CVW criteria in the DTG/3TC or CAR groups through 48 weeks.
- This analysis assesses TL at baseline (BL) and change from baseline (CFB) through 48 weeks.

Figure 1. SALSA Phase 3 Study Design



Methods

- Adults with VL <50 c/mL for ≥6 months were randomized to DTG/3TC FDC or continued CAR, with 81% (200/247) in the CAR group receiving TAF or TDF.
- qPCR using genomic DNA extracted from whole blood samples was performed to generate ratios of telomere TTAGGG repeats to a single-copy gene (T/S ratios) reflecting average TL of the total cell population.
- The adjusted mean difference in TL at Week 48 between treatment groups (DTG/3TC vs CAR) was calculated using an ANCOVA model including the following pre-specified covariates (Figure 2): CD4+ cell count, age, sex, race, depression or anxiety, BMI, smoking status, vitamin use, statin use, BL TL, time since first prior ART, and BL third agent class (PI, INSTI, or NNRTI).

Sensitivity Analysis for TAF and TDF Effect on TL

- ANCOVA sensitivity analysis included 1 additional variable, prior ART (TAF/TDF) vs other ART, to assess the impact of TAF or TDF on TL.

Participant Demographics

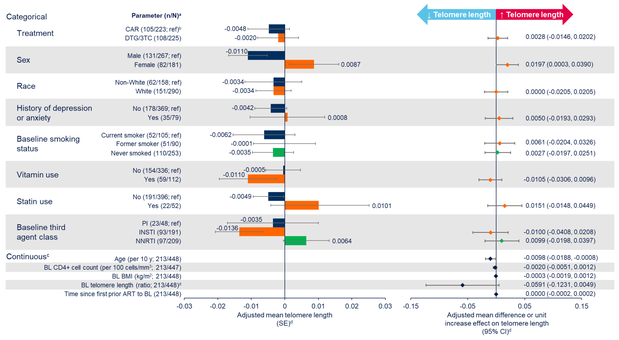
- In the ITT-E participant population,[4] 39% were female (DTG/3TC group = 44% vs CAR group = 34%) with other characteristics well balanced; at baseline, 39% were ≥50 years; 19% were African American or of African heritage; across all participants, 50% had NNRTI for third agent class, 40% had INSTI, and 10% had PI; third agents most commonly taken were efavirenz (EFV; 31%) and DTG (17%); the most commonly used NRTIs at screening were FTC (62%), TDF (43%), 3TC (38%), and TAF (35%).

No telomere length (TL) difference was observed over 48 weeks between treatment groups in participants who switched to the 2-drug regimen DTG/3TC vs those who continued current antiretroviral regimen (CAR), including when 3-drug CAR contained a tenofovir prodrug

Results

- As shown in Figure 2, adjusted mean CFB in TL in the DTG/3TC and CAR groups were similar, −0.0020 vs −0.0048, respectively (treatment difference, 0.0028; 95% CI, −0.0146, 0.0202; *P*=0.751).
- Baseline factors associated with TL included age and sex (women had longer TL).
- TL decreased with increasing age and trended toward shorter length at Week 48 with baseline TL.

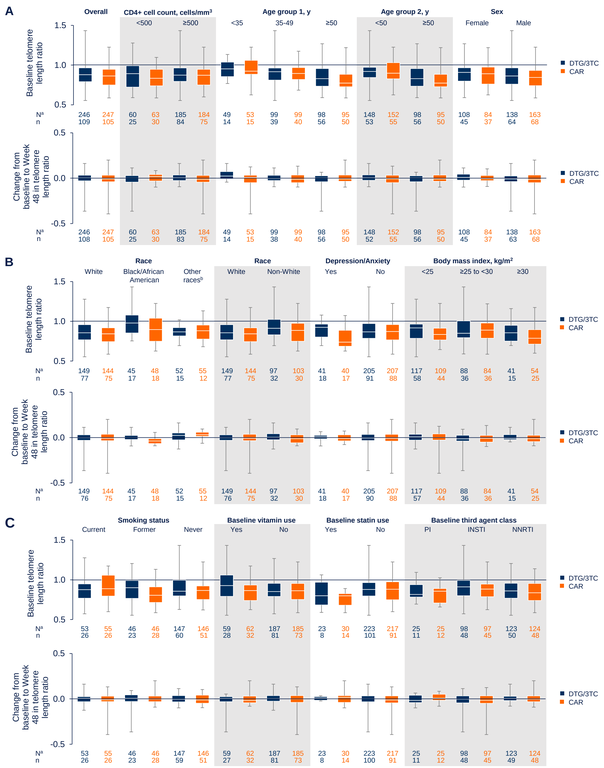
Figure 2. Forest Plot View of Telomere Length Change From Baseline (CFB) at Week 48 by Covariate and Treatment Group



BL, baseline; Ref, reference. [a]N represents the number of participants with non-missing baseline covariate data, and n represents the number of participants with at least one telomere length data at either baseline or Week 48. [b]Reference for adjusted mean difference. [c]Reported as increase (>0) or decrease (<0) in adjusted mean change in telomere length. [d]Telomere length is measured as a ratio of telomere to single-copy gene.

- A trend to shorter TL with increasing age at BL was observed (both Age group 1 and Age group 2 categories), and also perhaps by statin use (Figure 3).
- Variable TL at BL by group (eg, Depression/Anxiety + Yes, and others), as well as low numbers (N and/or n) for covariates, suggest caution in extrapolation.
- CFB values were near zero in all subgroups, consistent with both treatment groups suppressing viral replication associated with telomere shortening.

Figure 3. BL and CFB TL Ratios by Subgroup: Unadjusted Data

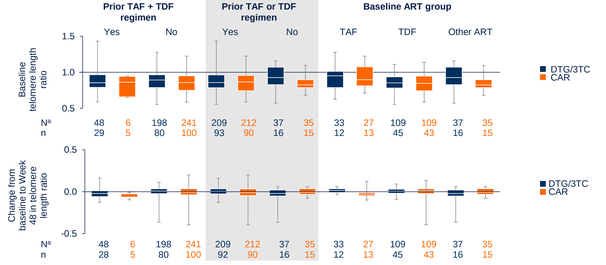


[a]N represents the number of participants with non-missing baseline covariate data, and n represents the number of participants with at least one telomere length data at either baseline or Week 48. [b]Includes American Indian or Alaska Native, Asian, or individuals of multiple races.

TAF/TDF Sensitivity Analysis Results

- Following the TAF/TDF sensitivity ANCOVA analysis, the direction of prior estimates in Figure 2 remained the same.
  - The TL associations with age and sex remained consistent with the main model after adjusting for TAF/TDF, and TAF/TDF was not differentially associated with TL.
- TL ratio BL and CFB at Week 48 for tenofovir categories are provided in Figure 4.

Figure 4. TL Ratios at BL and for CFB by Tenofovir Group



[a]Groups plotted included Prior TAF or TDF (can have received TAF or TDF), TAF category (excludes prior TDF), TDF category (excludes prior TAF), Other ART (excludes participants with prior TAF or TDF), Prior TAF + TDF (previously have received both TAF and TDF). N represents the number of participants with non-missing baseline covariate data, and n represents the number of participants with at least one telomere length data at either baseline or Week 48 (the latter for CFB).

- Median BL TL ratios for subgroups ranged between ~0.8 and 1.0, showing TL variability when measured prior to changing regimen.
- CFB values at Week 48 were close to zero for all subgroups.

Discussion

- Overall, these results show no significant impact on TL between the 2 study groups. TL changes very gradually and at variable rates; for example, one study reported that mean human TL decreases by 42 base pairs annually.[5] TL in humans is variable in the literature, but one review[6] noted a median ~10k base pairs in healthy newborns and ~5 to 6k base pairs in adults aged >60 years. TL measurements can be dependent on cell type; for example, CD8+ cells showed the greatest negative effect of receiving a tenofovir-containing regimen compared with a non-tenofovir regimen in total peripheral blood mononuclear cells (PBMCs) or CD4+ cells in long-term aviremic PWH.[7] Overall, while shortened telomeres in PWH can be restored under effective ART, confounders, including treatment duration and masking of cell types (eg, CD8+ subsets within PBMC populations), may limit the ability to distinguish slow rates of TL change.

Conclusions

- In the SALSA study, we show that age and sex significantly influenced TL as expected.
  - Continuing TAF or TDF in the CAR group did not appear to have an impact, though limitations include that 19% of participants in the CAR group did not receive a tenofovir prodrug.
- Of note, there was no impact on TL when switching to DTG/3TC over 48 weeks.
- These data, alongside non-inferior efficacy and minimal impact across inflammatory markers seen with DTG/3TC, challenge the value of a second NRTI in a virologically suppressed switch population.
- Additional and longer-term data and analyses are needed to understand how TL (as a marker of inflammation or immune state) may be maintained, or recover, via ART in PWH.

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References: 1. Raffenberg et al. *J Infect Dis.* 2021;224:1775-1784. **2.** Stella-Ascariz et al. *J Acquir Immune Defic Syndr.* 2017;74:91-94. **3.** Upal et al. CROI 2022; Virtual. Poster 625. **4.** Llibre et al. *Clin Infect Dis.* 2022 [Epub ahead of print]. **5.** Farzaneh-Far et al. *PLoS One.* 2010;5:e8612. **6.** Vaiserman and Krasnienkov. *Front Genet.* 2021;11:630186. **7.** Rodríguez-Centeno et al. *J Antimicrob Chemother.* 2022;77:1125-1132.

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