EVALUATING THE RELATIONSHIP BETWEEN INFLAMMATION BIOMARKER INTERLEUKIN-6 (IL-6) LEVELS AND RESIDUAL, LOW-LEVEL VIREMIA IN HIV-1 SUPPRESSED PARTICIPANTS IN THE TANGO STUDY AT WEEK 96

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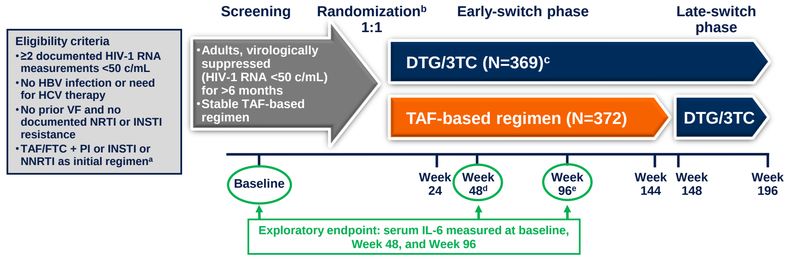
Introduction

- Interleukin-6 (IL-6) is an inflammation biomarker that has been positively associated with viral load (VL) in both viremic and virologically suppressed people living with HIV (PLWH)[1-4]
- Multiple factors independently impact IL-6 levels in PLWH, including older age, higher BMI, smoking status, and comorbid conditions such as intercurrent co-infections[1]
  - IL-6 levels also fluctuate in individuals without HIV and are similarly affected by a variety of factors[5,6]
- The purpose of this post hoc analysis was to investigate factors associated with serum IL-6 and to evaluate the relationship between IL-6 levels and VL in participants from the TANGO study

Methods

- TANGO is a phase III, randomized, open-label, active-controlled, multicenter, non-inferiority study to assess the efficacy and safety of switching to the 2-drug regimen DTG/3TC compared with continuing 3- or 4-drug TAF-based regimens in virologically suppressed adults on a stable antiretroviral regimen (Figure 1)
- An exploratory endpoint of TANGO was assessment of inflammation biomarkers, including IL-6
  - VL and serum IL-6 testing were conducted at Q^2 Solutions (Valencia, CA, and Edinburgh, UK)
  - IL-6 was measured at baseline, Week 48, and Week 96 using MSD Multi-Spot Assay System for Proinflammatory Panel 1, with a verified detection range of 0.633 to 488 ng/L
  - A multivariate analysis of covariance (ANCOVA) model was used to assess association between baseline variables and log$_e$-transformed Week 96 IL-6 levels
  - Change from baseline in IL-6 at Week 96 was compared between treatment groups using mixed-model repeated-measures analysis
  - Week 96 IL-6 levels were summarized by post-baseline VL categories over time and by treatment group

Figure 1. TANGO Study Design and IL-6 Measurements

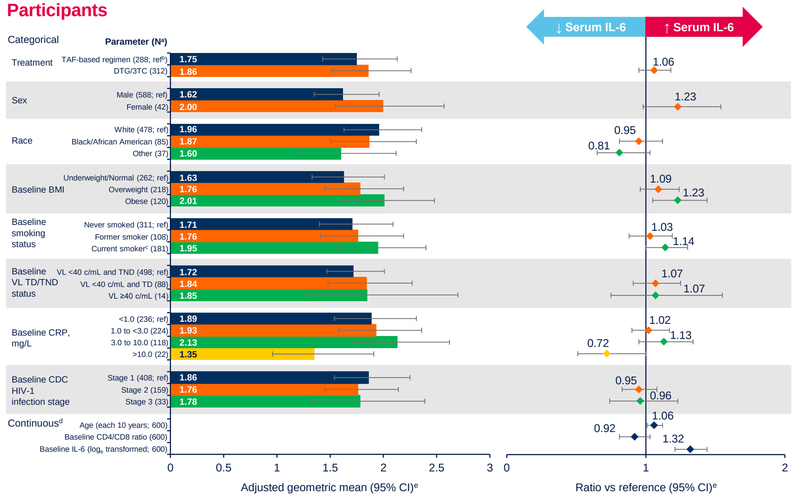


[a]Participants with initial TDF treatment who switched to TAF ≥3 months before screening, with no changes to other drugs in their regimen, were also eligible. [b]Stratified by baseline third agent class (PI, INSTI, or NNRTI). [c]2 participants excluded who were randomized but not exposed to study drug. [d]Primary endpoint was proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot) with a 4% non-inferiority margin. [e]Analysis of participants with non-missing IL-6 data at Week 96.

Results

- DTG/3TC was non-inferior to continuing TAF-based regimens for maintaining virologic suppression (HIV-1 RNA <50 c/mL, FDA Snapshot, ITT-E population) at Week 96 (DTG/3TC, 85.9%; TAF-based regimen, 79.0%; adjusted treatment difference, 6.8%; 95% CI, 1.4-12.3)
  - Results for HIV-1 RNA <40 c/mL and target not detected (TND; Snapshot, ITT-E) at Week 96 were similar (DTG/3TC, 73.4%; TAF-based regimen, 68.5%; adjusted treatment difference, 4.9%; 95% CI, −1.7 to 11.4)
- No difference was observed in Week 96 adjusted geometric mean of log-transformed serum IL-6 between DTG/3TC and TAF-based regimen (treatment ratio, 1.06; 95% CI, 0.95-1.18; *P*=0.282)
- Baseline obese BMI (*P*=0.009), smoking status (*P*=0.008; sensitivity analysis excluding participants with CRP >10 mg/L at Week 96), older age at baseline (*P*=0.020), and elevated baseline IL-6 (*P*<0.001) were associated with higher serum IL-6 at Week 96 (Figure 2)

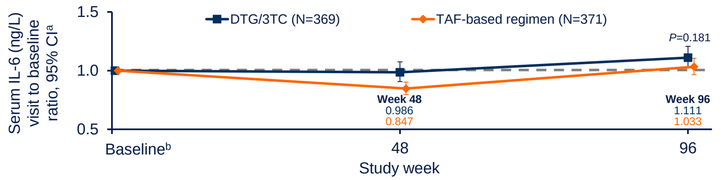
Figure 2. Parameters Associated With Serum IL-6 Levels at Week 96 in TANGO Study Participants



Ref, reference. [a]N is the number of participants with non-missing IL-6 data at Week 96. [b]Reference for ratio comparison. [c]CRP >10 mg/L is suggestive of acute inflammation according to the American Heart Association[4,7]; therefore, a sensitivity analysis excluding participants with CRP >10 mg/L at Week 96 was also performed, which showed that smokers had an adjusted geometric mean of 1.92 (95% CI, 1.57-2.35) and a ratio vs never smoked of 1.18 (95% CI, 1.05-1.34; *P*=0.008). [d]Reported as an increase (>1) or decrease (<1) in ratio for a unit increase in that parameter (unless otherwise specified). [e]Adjusted geometric mean at Week 96 using ANCOVA model on log$_e$-transformed IL-6 adjusting for variables shown in Figure 2.

- At Week 96, change from baseline in IL-6 was generally minimal and comparable between treatment groups (Figure 3)

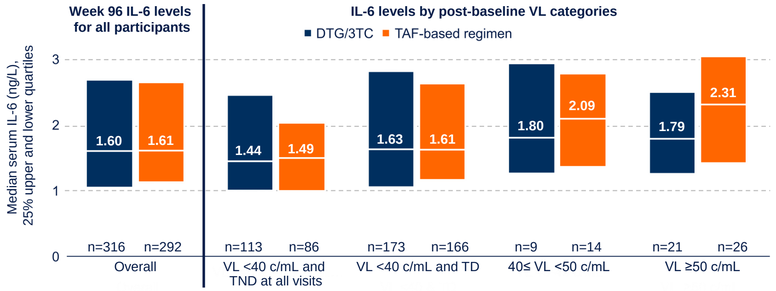
Figure 3. Change in Serum IL-6 From Baseline to Week 96



[a]Estimated geometric mean ratios and 95% CIs calculated from a repeated-measures model applied to change from baseline in log$_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count, age, sex, race, BMI, smoking status, HCV co-infection status, log$_e$-transformed baseline biomarker value, treatment-by-visit interaction, and baseline value-by-visit interaction. [b]Baseline median IL-6 values: DTG/3TC, 1.56 ng/L; TAF-based regimen, 1.61 ng/L.

- Across both groups, Week 96 IL-6 levels generally increased with increasing levels of post-baseline viremia, and the lowest Week 96 IL-6 levels were observed in participants with post-baseline VL <40 c/mL and TND at all visits (Figure 4)
- Median serum IL-6 at Week 96 was similar between groups with 1.60 ng/L (range, 0.29-79.04) and 1.61 ng/L (0.45-20.93) observed in the DTG/3TC and TAF-based regimen groups, respectively (Figure 4)
  - In both groups, IL-6 level was comparable to a ≤1.8-ng/L reference value reported in the general population[8] and within the normal range of IL-6 reported from commercially sourced serum samples from the general population (median, 0.47 ng/L; range, 0.16-27.2; percent detected, 37%)[9]

Figure 4. Serum IL-6 at Week 96 and by Post-Baseline VL Categories



White line on each bar represents median value. n is the number of participants in the specific post-baseline VL category with IL-6 value at Week 96. Post-baseline VL categories are defined as (1) VL <40 c/mL and TND at all visits through Week 96, (2) VL <40 c/mL and TD for at least one visit and no VL ≥40 c/mL after baseline through Week 96, (3) 40≤ VL <50 c/mL for at least one visit and no VL ≥50 c/mL after baseline through Week 96, and (4) VL ≥50 c/mL for at least one visit after baseline through Week 96.

Discussion

- Although DHHS guidelines[10] do not recommend clinical monitoring of inflammatory markers and state the focus of care should be on maintaining ART-mediated virologic suppression, the findings demonstrate minimal impact on inflammation after switching to DTG/3TC vs continuing TAF-based regimens over 96 weeks

Conclusions

- Serum IL-6 levels and small changes from baseline at Week 96 were comparable between groups
- Across both groups, older age at baseline, elevated baseline IL-6, baseline obese BMI, and smoking were associated with higher serum IL-6 at Week 96, supporting previous findings[1]
- Although IL-6 levels are impacted by multiple factors (including pre-ART VL set point),[1] this analysis suggests an association between lower IL-6 levels in participants with VL <40 c/mL and TND at all visits vs participants in higher VL categories

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