

# Changes in Inflammatory Biomarkers and Baseline Variables After Switching to Dolutegravir/Lamivudine (DTG/3TC) in 2 Randomized Clinical Trials of Virologically Suppressed Adults: 48-Week Pooled Analysis

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## Key Takeaways

- In a pooled analysis of virologically suppressed adults in the TANGO and SALSA studies, inflammatory biomarker levels at Week 48 were low and comparable overall between the 2-drug regimen DTG/3TC and a broad range of 3- and 4-drug antiretroviral regimens

- These data are reflective of the non-inferior virologic efficacy of DTG/3TC vs 3- or 4-drug antiretroviral regimens observed in clinical trials, including similar rates of blips and target not detected

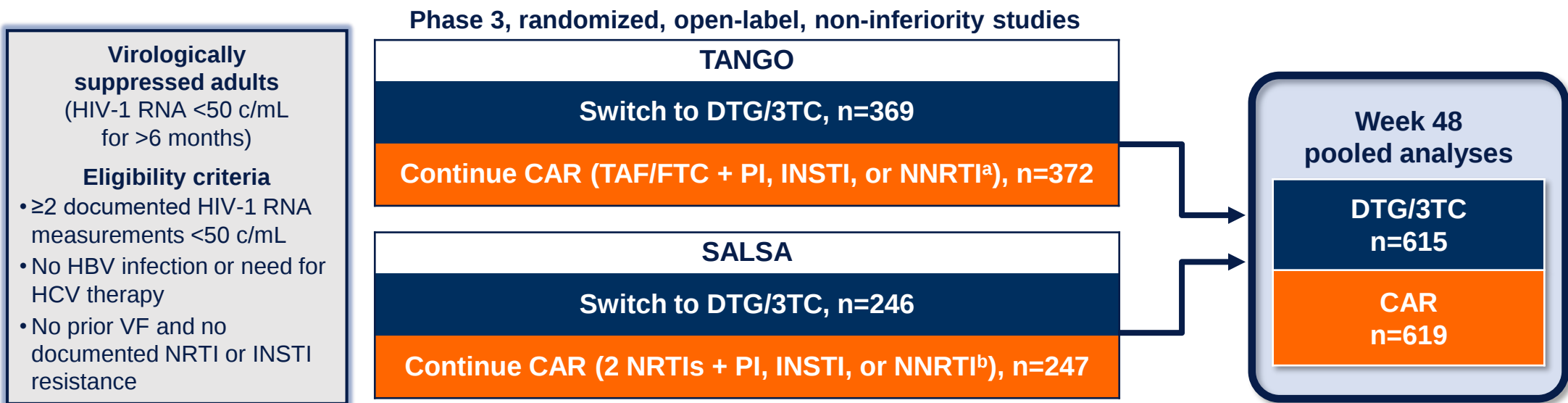
## Introduction

- Persistent inflammation is associated with increased risk of age-related diseases<sup>1</sup>
- People living with HIV have multiple etiologies of both acute and chronic inflammation, which have been linked to increased risk of non-AIDS-related comorbidities<sup>1</sup>
- ART-induced HIV suppression reduces some measures of HIV-related inflammation and immune activation but not necessarily to levels observed in people without HIV<sup>2-4</sup>
- The phase 3 TANGO and SALSA studies demonstrated non-inferior virologic efficacy of switching to DTG/3TC vs continuing 3- or 4-drug TAF-based regimens at 144 weeks or various current antiretroviral regimens (CAR) at 48 weeks, respectively, in virologically suppressed adults<sup>5,6</sup>
- High and similar proportions of participants in both DTG/3TC groups and groups that continued their current regimen had HIV-1 RNA <40 c/mL and target not detected (TND)<sup>7,8</sup>
- In this analysis, we present the adjusted comparison of Week 48 inflammatory biomarker levels between treatment groups and associated baseline variables in the pooled TANGO and SALSA studies

## Methods

- This analysis included 48-week pooled data from the phase 3 TANGO and SALSA trials of adults with HIV-1 RNA <50 c/mL randomized to switch to once-daily DTG/3TC fixed-dose combination or continue their CAR (Figure 1)
- Detailed methods have previously been published<sup>7,8</sup>

Figure 1. Study Design



Randomization (1:1) in both studies was stratified by baseline third agent class (PI, INSTI, or NNRTI). <sup>a</sup>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. <sup>b</sup>Participants were on uninterrupted ART regimen for ≥3 months.

## Results

### Population

- Demographics and baseline characteristics were balanced between the DTG/3TC and CAR groups in the pooled TANGO and SALSA ITT-E population (N=1234; Table 1)

Table 1. Demographics and Baseline Characteristics: TANGO and SALSA Pooled ITT-E Population

| Parameter                                              | DTG/3TC (N=615) | CAR (N=619)   | Overall (N=1234) |
|--------------------------------------------------------|-----------------|---------------|------------------|
| Age, median (range), years                             | 42 (20-74)      | 42 (18-83)    | 42 (18-83)       |
| ≥50, n (%)                                             | 177 (29)        | 187 (30)      | 364 (29)         |
| Female, n (%)                                          | 133 (22)        | 117 (19)      | 250 (20)         |
| Race, n (%)                                            |                 |               |                  |
| White                                                  | 445 (72)        | 433 (70)      | 878 (71)         |
| Black                                                  | 96 (16)         | 106 (17)      | 202 (16)         |
| Asian                                                  | 44 (7)          | 52 (8)        | 96 (8)           |
| Other races <sup>a</sup>                               | 30 (5)          | 28 (5)        | 58 (5)           |
| BMI, n (%) <sup>b</sup>                                |                 |               |                  |
| Underweight/Normal (<25 kg/m <sup>2</sup> )            | 292 (47)        | 266 (43)      | 558 (45)         |
| Overweight (25 to <30 kg/m <sup>2</sup> )              | 219 (36)        | 221 (36)      | 440 (36)         |
| Obesity (≥30 kg/m <sup>2</sup> )                       | 104 (17)        | 131 (21)      | 235 (19)         |
| CD4+ cell count, median (range), cells/mm <sup>3</sup> | 680 (133-2089)  | 684 (94-1954) | 681 (94-2089)    |
| CD4+/CD8+ ratio, mean (SD)                             | 1.1 (0.54)      | 1.1 (0.50)    | 1.1 (0.52)       |
| Duration of ART before Day 1, median (range), months   | 41.2 (4-240)    | 45.0 (7-253)  | 43.4 (4-253)     |
| Baseline third agent class, n (%)                      |                 |               |                  |
| INSTI                                                  | 387 (63)        | 394 (64)      | 781 (63)         |
| NNRTI                                                  | 174 (28)        | 172 (28)      | 346 (28)         |
| PI                                                     | 54 (9)          | 53 (9)        | 107 (9)          |
| Baseline backbone NRTI, n (%) <sup>c</sup>             |                 |               |                  |
| TAF                                                    | 451 (73)        | 462 (75)      | 913 (74)         |
| TDF                                                    | 109 (18)        | 110 (18)      | 219 (18)         |
| ABC                                                    | 45 (7)          | 34 (5)        | 79 (6)           |
| ≥1 Baseline co-morbidity, n (%)                        | 457 (74)        | 474 (77)      | 931 (75)         |

<sup>a</sup>Included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, mixed White race, and individuals of multiple races. <sup>b</sup>For CAR, N=618; for overall, N=1233. <sup>c</sup>For DTG/3TC, N=605; for CAR, N=606; for overall, N=1211.

### Inflammatory Biomarker Outcomes

- Inflammatory biomarker geometric means (95% CI) at baseline vs adjusted geometric means (95% CI) at Week 48 for the DTG/3TC and CAR groups are shown in Table 2

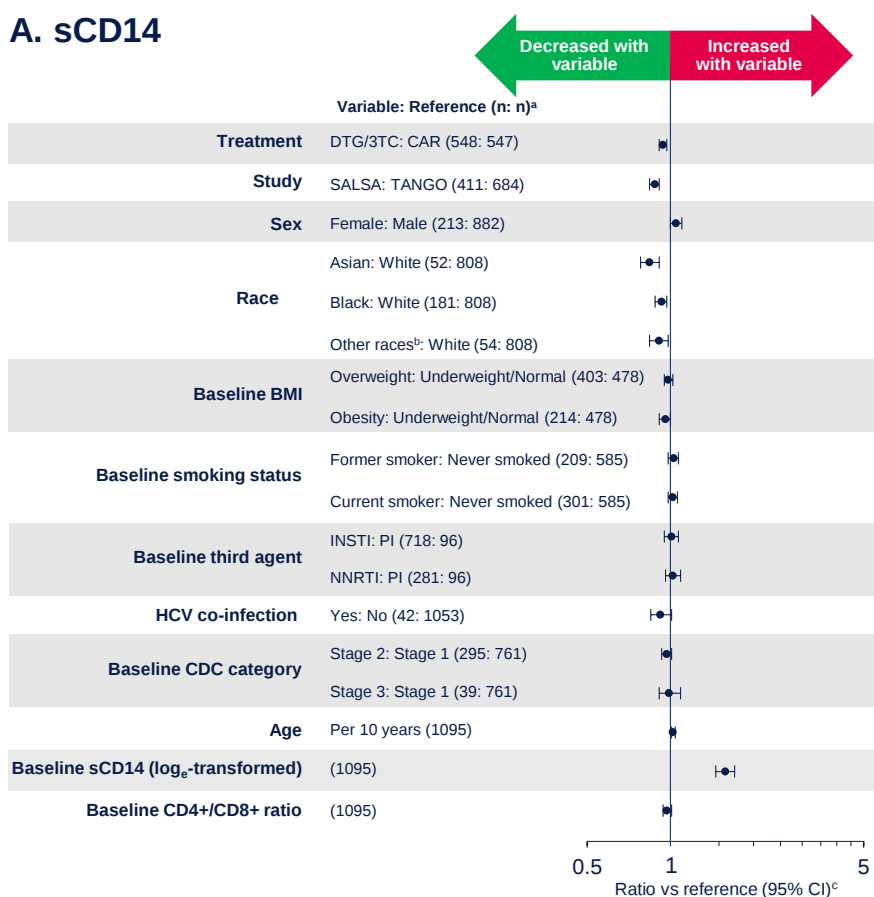
Table 2. Baseline and Week 48 Geometric Means (95% CI) for Inflammatory Biomarkers and CD4+/CD8+ Ratio

| Parameter, geometric mean (95% CI) |                                 | DTG/3TC                | CAR                    |
|------------------------------------|---------------------------------|------------------------|------------------------|
| sCD14, × 10 <sup>6</sup> ng/L      | Baseline                        | 1.58 (1.56-1.61)       | 1.53 (1.51-1.56)       |
|                                    | Week 48 (adjusted) <sup>a</sup> | 1.27 (1.19-1.35)       | 1.35 (1.27-1.43)       |
| sCD163, ng/L                       | Baseline                        | 611.08 (589.99-632.92) | 602.08 (582.52-622.30) |
|                                    | Week 48 (adjusted) <sup>a</sup> | 570.49 (540.06-602.63) | 561.02 (530.89-592.85) |
| IL-6, ng/L                         | Baseline                        | 1.67 (1.58-1.78)       | 1.67 (1.57-1.78)       |
|                                    | Week 48 (adjusted) <sup>a</sup> | 1.63 (1.40-1.90)       | 1.51 (1.29-1.76)       |
| hs-CRP, mg/L                       | Baseline                        | 1.36 (1.25-1.49)       | 1.29 (1.18-1.41)       |
|                                    | Week 48 (adjusted) <sup>a</sup> | 1.13 (0.90-1.42)       | 1.30 (1.03-1.63)       |
| CD4+/CD8+ ratio                    | Baseline                        | 0.94 (0.90-0.98)       | 0.95 (0.91-0.99)       |
|                                    | Week 48 (adjusted) <sup>a</sup> | 1.00 (0.96-1.03)       | 1.01 (0.97-1.05)       |

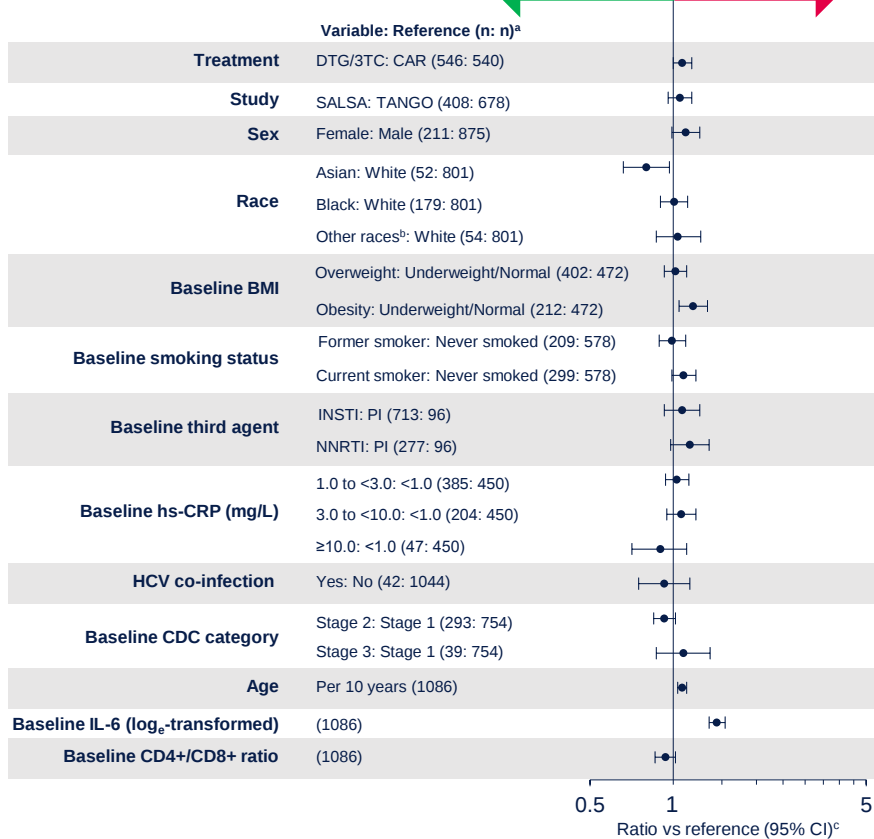
<sup>a</sup>Adjusted mean at Week 48 calculated using an ANCOVA model on log<sub>e</sub>-transformed data adjusted for treatment, sex, race, baseline BMI, baseline CDC category, baseline smoking status, HCV co-infection, age, baseline CD4+/CD8+ ratio, log<sub>e</sub>-transformed baseline biomarker value, study, and baseline third agent class. Analyses for IL-6 and CD4+/CD8+ ratio also adjusted for baseline hs-CRP. Analysis for hs-CRP also adjusted for baseline triglycerides, baseline lipid-modifying agent use, baseline total cholesterol, baseline LDL-C, and baseline HDL-C. Please refer to Figure 2 for statistical comparisons.

- Week 48 levels of soluble CD14 (sCD14) and high-sensitivity C-reactive protein (hs-CRP) were lower in the DTG/3TC vs CAR group based on 95% CIs, and for sCD163, IL-6, and CD4+/CD8+ ratio, Week 48 values were similar between groups (Figure 2)

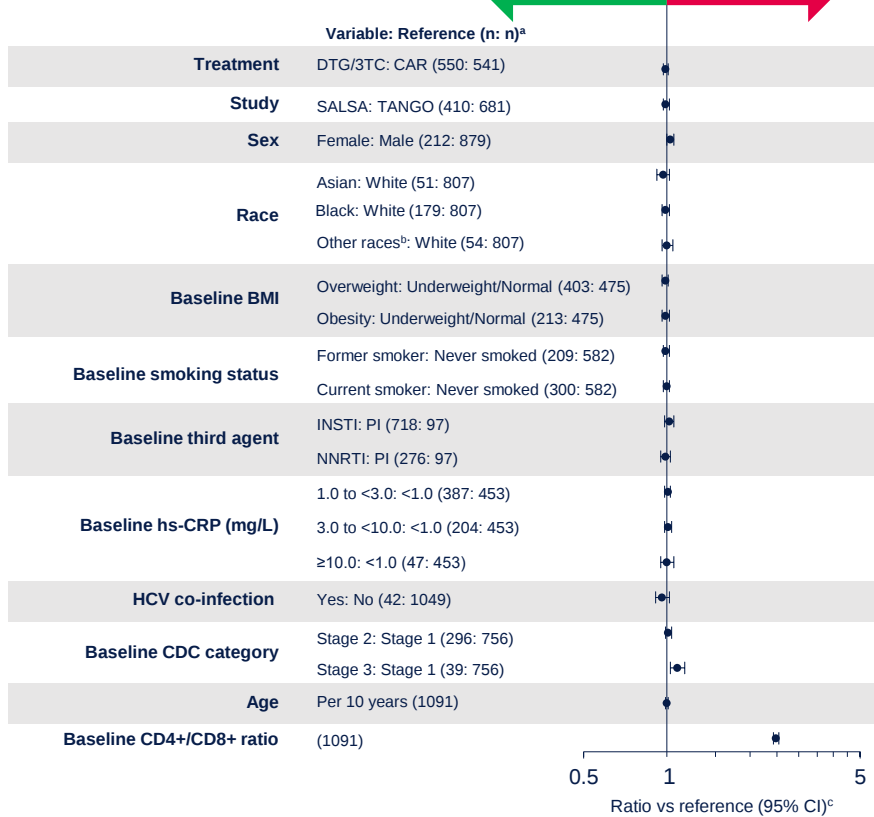
### A. sCD14



### C. IL-6



### E. CD4+/CD8+ ratio

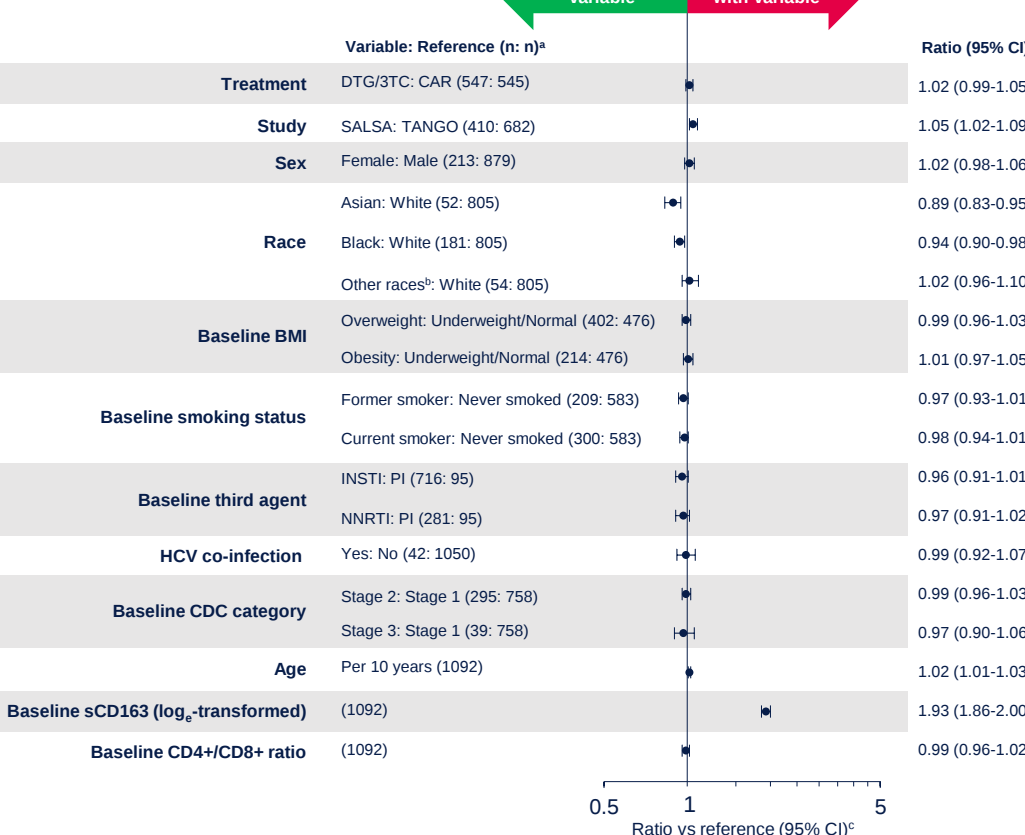


<sup>a</sup>Number of participants with non-missing biomarker data at Week 48. <sup>b</sup>Included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, mixed White race, and individuals of multiple races. <sup>c</sup>Adjusted geometric mean and ratio calculated using an ANCOVA model on log<sub>e</sub>-transformed data adjusting for treatment, sex, race, baseline BMI, baseline CDC category, baseline smoking status, HCV co-infection, age, baseline CD4+/CD8+ ratio, log<sub>e</sub>-transformed baseline biomarker value, study, and baseline third agent class. Analyses for IL-6 and CD4+/CD8+ ratio also adjusted for baseline hs-CRP. Analysis for hs-CRP also adjusted for baseline triglycerides, baseline lipid-modifying agent use, baseline total cholesterol, baseline LDL-C, and baseline HDL-C. <sup>d</sup>Lower limit for the estimated treatment ratio is 0.9985.

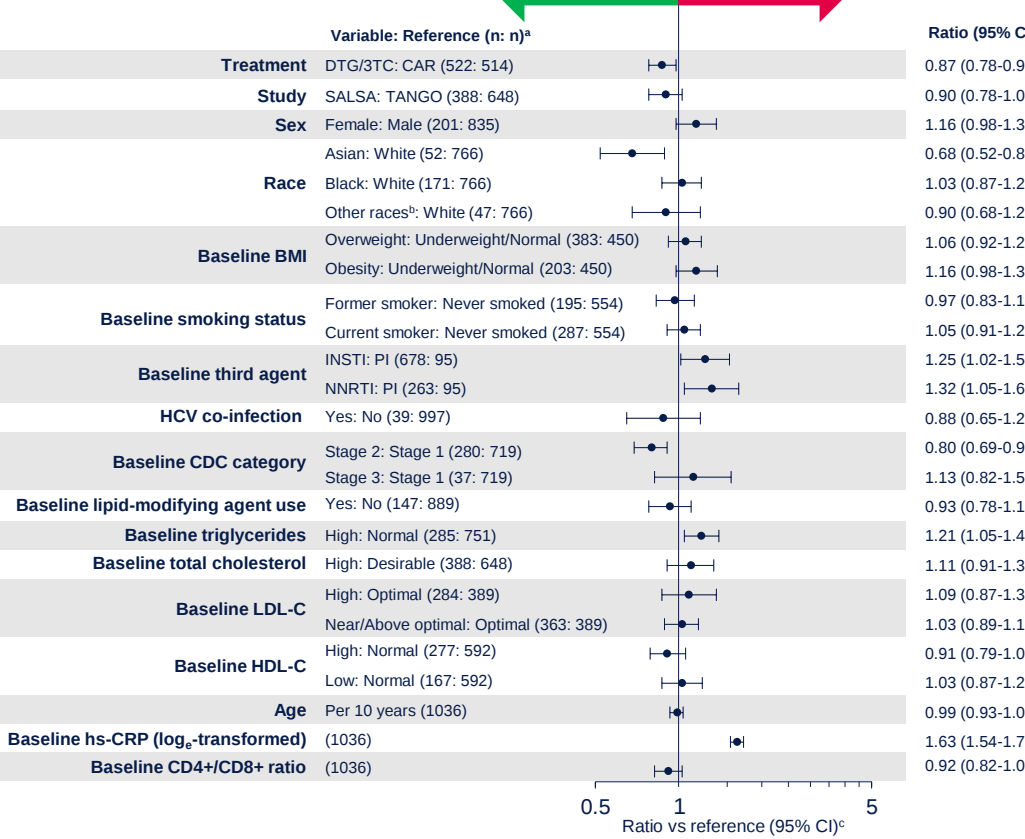
- Using multivariate ANCOVA models adjusting for relevant baseline variables, log-transformed Week 48 serum inflammatory biomarker levels and CD4+/CD8+ ratios were compared between treatment groups and associations with baseline variables were evaluated as fixed effects
- Although D-dimer was measured in TANGO and SALSA, it was excluded from this pooled analysis because MMRM analysis was not performed in SALSA due to the high proportion of participants with D-dimer < LLQ in both treatment groups<sup>6</sup>

Figure 2. Demographic and Baseline Characteristics Associated With Inflammatory Biomarker Levels at Week 48 (TANGO and SALSA Pooled ITT-E Population): (A) sCD14, (B) sCD163, (C) IL-6, (D) hs-CRP, and (E) CD4+/CD8+ Ratio

### B. sCD163



### D. hs-CRP



- All Week 48 biomarker levels were strongly associated with higher baseline biomarker values based on 95% CIs
- Increasing age was associated with higher Week 48 sCD14, sCD163, and IL-6 levels based on 95% CIs
- Asian participants had lower Week 48 levels compared with White participants across all inflammatory biomarkers based on 95% CIs, although sample sizes were small
- Other baseline factors showed some associations with Week 48 biomarker levels:
  - Female participants had higher Week 48 levels of all inflammatory biomarkers compared with male participants and had higher CD4+/CD8+ ratios vs male participants
  - Participants with obesity at baseline had higher IL-6 levels at Week 48
- Sample sizes were small for some baseline factor categories, which should be considered when interpreting the results

## Conclusions

- In conclusion, switching to the 2-drug regimen DTG/3TC vs continuing 3- or 4-drug regimens led to low and comparable Week 48 inflammatory biomarker levels with no consistent directionality between groups
- Multiple demographic and baseline factors besides ART were independently associated with inflammatory biomarker levels, highlighting the multifactorial aspect of the inflammatory response
- These results continue to support the absence of increased inflammation after switching to DTG/3TC vs continuing current antiretroviral regimen

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