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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**

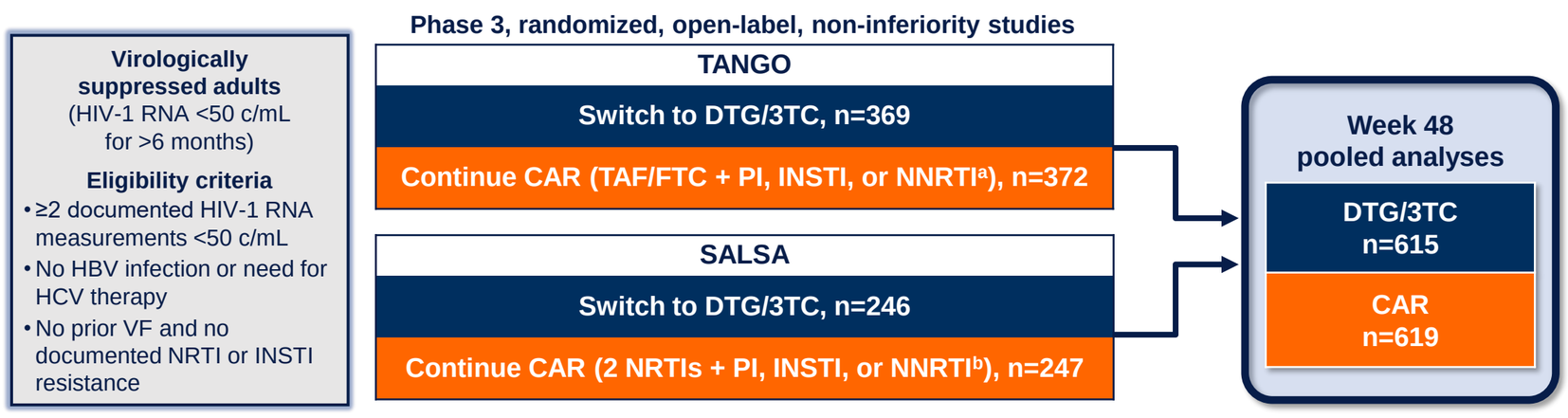
Introduction

- Persistent inflammation is associated with increased risk of age-related diseases[1]
- 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[1]
- ART-induced HIV suppression reduces some measures of HIV-related inflammation and immune activation but not necessarily to levels observed in people without HIV[2-4]
- 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[5,6]
- 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)[7,8]
- 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[7,8]
- 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[6]

Figure 1. Study Design



Randomization (1:1) in both studies was stratified by baseline third agent class (PI, INSTI, or NNRTI). [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]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[a]	30 (5)	28 (5)	58 (5)
BMI, n (%)[b]			
Underweight/Normal (<25 kg/m^2)	292 (47)	266 (43)	558 (45)
Overweight (25 to <30 kg/m^2)	219 (36)	221 (36)	440 (36)
Obesity (≥30 kg/m^2)	104 (17)	131 (21)	235 (19)
CD4+ cell count, median (range), cells/mm^3	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 (%)[c]			
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)

[a]Included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, mixed White race, and individuals of multiple races. [b]For CAR, N=618; for overall, N=1233. [c]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, × 10^6 ng/L	Baseline	1.58 (1.56-1.61)	1.53 (1.51-1.56)
	Week 48 (adjusted)[a]	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)[a]	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)[a]	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)[a]	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)[a]	1.00 (0.96-1.03)	1.01 (0.97-1.05)

[a]Adjusted mean at Week 48 calculated using an ANCOVA model on $\log_e$-transformed data adjusted for treatment, sex, race, baseline BMI, baseline CDC category, baseline smoking status, HCV co-infection, age, baseline CD4+/CD8+ ratio, $\log_e$-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)

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

[a]Number of participants with non-missing biomarker data at Week 48. [b]Included American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, mixed White race, and individuals of multiple races. [c]Adjusted geometric mean and ratio calculated using an ANCOVA model on $\log_e$-transformed data adjusting for treatment, sex, race, baseline BMI, baseline CDC category, baseline smoking status, HCV co-infection, age, baseline CD4+/CD8+ ratio, $\log_e$-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. **[d]Lower limit for the estimated treatment ratio is 0.9985.**

- 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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