# 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

Phase 3, randomized, open-label, non-inferiority studies Virologically TANGO suppressed adults (HIV-1 RNA <50 c/mL Switch to DTG/3TC, n=369 **Week 48** for >6 months) pooled analyses Continue CAR (TAF/FTC + PI, INSTI, or NNRTI<sup>a</sup>), n=372 **Eligibility criteria**  ≥2 documented HIV-1 RNA DTG/3TC measurements <50 c/mL n=615 SALSA No HBV infection or need for HCV therapy Switch to DTG/3TC, n=246 CAR • No prior VF and no n=619 documented NRTI or INSTI Continue CAR (2 NRTIs + PI, INSTI, or NNRTI<sup>b</sup>), n=247 resistance

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:

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. sCD14

**B. sCD163** 



**EPB165** 

- 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>

## **TANGO and SALSA Pooled ITT-E Population**

Parameter	DTG/3TC (N=615)	CAR (N=619)	Overall (N=1234)
Age, median (range), years ≥50, n (%)	42 (20-74) 177 (29)	42 (18-83) 187 (30)	42 (18-83) 364 (29)
Female, n (%)	133 (22)	117 (19)	250 (20)
Race, n (%) White Black Asian Other races <sup>a</sup>	445 (72) 96 (16) 44 (7) 30 (5)	433 (70) 106 (17) 52 (8) 28 (5)	878 (71) 202 (16) 96 (8) 58 (5)
BMI, n (%) <sup>b</sup> Underweight/Normal (<25 kg/m²) Overweight (25 to <30 kg/m²) Obesity (≥30 kg/m²)	292 (47) 219 (36) 104 (17)	266 (43) 221 (36) 131 (21)	558 (45) 440 (36) 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 NNRTI PI	387 (63) 174 (28) 54 (9)	394 (64) 172 (28) 53 (9)	781 (63) 346 (28) 107 (9)
Baseline backbone NRTI, n (%) <sup>c</sup> TAF TDF ABC	451 (73) 109 (18) 45 (7)	462 (75) 110 (18) 34 (5)	913 (74) 219 (18) 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. bFor CAR, N=618; for overall, N=1233. °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, geome (95% CI)	tric mean	DTG/3TC	CAR
sCD14, × 10 <sup>6</sup> ng/L	Baseline Week 48 (adjusted) <sup>a</sup>	1.58 (1.56-1.61) 1.27 (1.19-1.35)	1.53 (1.51-1.56) 1.35 (1.27-1.43)
sCD163, ng/L	Baseline Week 48 (adjusted) <sup>a</sup>	611.08 (589.99-632.92) 570.49 (540.06-602.63)	602.08 (582.52-622.30) 561.02 (530.89-592.85)
IL-6, ng/L	Baseline Week 48 (adjusted) <sup>a</sup>	1.67 (1.58-1.78) 1.63 (1.40-1.90)	1.67 (1.57-1.78) 1.51 (1.29-1.76)
hs-CRP, mg/L	Baseline Week 48 (adjusted) <sup>a</sup>	1.36 (1.25-1.49) 1.13 (0.90-1.42)	1.29 (1.18-1.41) 1.30 (1.03-1.63)
CD4+/CD8+ ratio	Baseline Week 48 (adjusted) <sup>a</sup>	0.94 (0.90-0.98) 1.00 (0.96-1.03)	0.95 (0.91-0.99) 1.01 (0.97-1.05)

	Vallable. Reference (II. II)-			Katio
Treatment	DTG/3TC: CAR (548: 547)	Ħ		0.94 (
Study	SALSA: TANGO (411: 684)			0.88 (
Sex	Female: Male (213: 882)	•		1.05 (
	Asian: White (52: 808)	н		0.84 (
Race	Black: White (181: 808)	H		0.93 (
	Other races <sup>b</sup> : White (54: 808)	H		0.91 (
Baseline BMI	Overweight: Underweight/Normal (403: 478	3) 🙀		0.98 (
	Obesity: Underweight/Normal (214: 478)	H		0.96 (
Baseline smoking status	Former smoker: Never smoked (209: 585)	-		1.03 (
	Current smoker: Never smoked (301: 585)	•		1.02 (
Pacalina third agant	INSTI: PI (718: 96)	H		1.01 (
Buschne third agent	NNRTI: PI (281: 96)	Hel .		1.02 (
HCV co-infection	Yes: No (42: 1053)	<b>⊢●</b>		0.92 (
Baseline CDC category	Stage 2: Stage 1 (295: 761)	•		0.97 (
	Stage 3: Stage 1 (39: 761)	H		0.99 (
Age	Per 10 years (1095)	+		1.02 (
Baseline sCD14 (log <sub>e</sub> -transformed)	(1095)		┝●┥	1.58 (
Baseline CD4+/CD8+ ratio	(1095)	•		0.97 (
	0.5	. 1	5	
	Ra	atio vs re	eterence (95% CI) <sup>c</sup>	

C. IL-6	-	ecreased with variable	Increased with variable	
	Variable: Reference (n: n) <sup>a</sup>		•	Ratio (95% CI)
Treatment	DTG/3TC: CAR (546: 540)	•	н	1.08 (1.00-1.17)
Study	SALSA: TANGO (408: 678)	⊦•	Н	1.06 (0.96-1.17)
Sex	Female: Male (211: 875)	+•	H	1.11 (0.99-1.25)
Race	Asian: White (52: 801) Black: White (179: 801) Other races <sup>b</sup> : White (54: 801)			0.80 (0.66-0.97) 1.01 (0.90-1.13) 1.04 (0.87-1.26)
Baseline BMI	Overweight: Underweight/Norm Obesity: Underweight/Normal (	nal (402: 472)	+ ●-	1.02 (0.93-1.12) 1.18 (1.05-1.33)
Baseline smoking status	Former smoker: Never smoked	I (209: 578)	l ⊨l	0.99 (0.89-1.11) 1.09 (0.99-1.21)
Baseline third agent	INSTI: PI (713: 96) NNRTI: PI (277: 96)	++  -	⊢ ←	1.08 (0.93-1.25) 1.15 (0.98-1.35)
Baseline hs-CRP (mg/L)	1.0 to <3.0: <1.0 (385: 450) 3.0 to <10.0: <1.0 (204: 450) ≥10.0: <1.0 (47: 450)	⊢●┤ ┝─●┤	+ ⊷  +	1.03 (0.94-1.14) 1.07 (0.95-1.21) 0.90 (0.71-1.12)
HCV co-infection	Yes: No (42: 1044)	<b>⊢</b> ●	4	0.93 (0.75-1.15)
Baseline CDC category	Stage 2: Stage 1 (293: 754) Stage 3: Stage 1 (39: 754)	<b> </b> ●   ●	►I	0.93 (0.85-1.02) 1.09 (0.87-1.36)
Age	Per 10 years (1086)		•	1.08 (1.04-1.12)
Baseline IL-6 (log <sub>e</sub> -transformed)	(1086)		H	1.44 (1.35-1.54)
Baseline CD4+/CD8+ ratio	(1086)	H		0.94 (0.86-1.02)
		0.5 1 Ratio vs	reference (95% CI) <sup>c</sup>	

E. CD4+/CD8+ ratio	O Decreased with variable	Increased with variable	
	Variable: Reference (n: n) <sup>a</sup>		Ratio (95% CI)
Treatment	DTG/3TC: CAR (550: 541)	+	0.99 (0.97-1.01)
Study	SALSA: TANGO (410: 681)	•	0.99 (0.97-1.02)
Sex	Female: Male (212: 879)	•	1.03 (1.00-1.06)
	Asian: White (51: 807)	•	0.97 (0.92-1.02)
Race	Black: White (179: 807)	+	0.99 (0.96-1.02)
	Other races <sup>b</sup> : White (54: 807)	<b>H</b>	1.00 (0.96-1.05)
Baseline BMI	Overweight: Underweight/Normal (403: 475)	•	0.99 (0.96-1.01)
Dasenne Dmi	Obesity: Underweight/Normal (213: 475)	+	0.99 (0.96-1.02)
De l'activité de la constante	Former smoker: Never smoked (209: 582)	*	0.99 (0.97-1.02)
Baseline smoking status	Current smoker: Never smoked (300: 582)	+	1.00 (0.97-1.02)
Baseline third agent	INSTI: PI (718: 97)	•	1.02 (0.98-1.06)
baseine tina agent	NNRTI: PI (276: 97)	•	0.99 (0.95-1.03)
	1.0 to <3.0: <1.0 (387: 453)	+	1.01 (0.98-1.03)
Baseline hs-CRP (mg/L)	3.0 to <10.0: <1.0 (204: 453)	•	1.01 (0.98-1.04)

55% CI)		variable: Reference (n. n).		Ratio (95% Ci
91-0.97)	Treatment	DTG/3TC: CAR (547: 545)	•	1.02 (0.99-1.05
84-0.91)	Study	SALSA: TANGO (410: 682)	el .	1.05 (1.02-1.09
00-1.10)	Sex	Female: Male (213: 879)	•	1.02 (0.98-1.06
78-0.91)		Asian: White (52: 805)	<b> ● </b>	0.89 (0.83-0.95
88-0.97)	Race	Black: White (181: 805)		0.94 (0.90-0.98
84-0.98)		Other races <sup>b</sup> : White (54: 805)	H <b>e</b> -I	1.02 (0.96-1.10
95-1.02)	Baseline BMI	Overweight: Underweight/Normal (402: 476)	+	0.99 (0.96-1.03
91-1.00)	Buddhild Bill	Obesity: Underweight/Normal (214: 476)	(e)	1.01 (0.97-1.05
98-1.07)	Baseline smoking status	Former smoker: Never smoked (209: 583)	-	0.97 (0.93-1.01
98-1.06)	Dasenne smoking status	Current smoker: Never smoked (300: 583)	-	0.98 (0.94-1.01
95-1.07)	Deceline third event	INSTI: PI (716: 95)	•	0.96 (0.91-1.01
96-1.09)	Baseline third agent	NNRTI: PI (281: 95)	H	0.97 (0.91-1.02
85-1.01)	HCV co-infection	Yes: No (42: 1050)	H <del>e</del> I	0.99 (0.92-1.07
93-1.01)	Baseline CDC category	Stage 2: Stage 1 (295: 758)	+	0.99 (0.96-1.03
91-1.09)	Dubbinio OD o bulogory	Stage 3: Stage 1 (39: 758)	He-I	0.97 (0.90-1.06
01-1.04)	Age	Per 10 years (1092)	•	1.02 (1.01-1.03
46-1.71)	Baseline sCD163 (log <sub>e</sub> -transformed)	(1092)	(e)	1.93 (1.86-2.00
94-1.01)	Baseline CD4+/CD8+ ratio	(1092)	H	0.99 (0.96-1.02

0.5 1 Ratio vs reference (95% CI)c

#### D. hs-CRP

	Variable: Reference (n: n) <sup>a</sup>		Ratio (95% CI)
Treatment	DTG/3TC: CAR (522: 514)	⊢●┥	0.87 (0.78-0.98)
Study	SALSA: TANGO (388: 648)	⊢∙−	0.90 (0.78-1.03)
Sex	Female: Male (201: 835)	┡━━┥	1.16 (0.98-1.37)
	Asian: White (52: 766)	•	0.68 (0.52-0.89)
Race	Black: White (171: 766)	<b>⊢</b> •-1	1.03 (0.87-1.21)
	Other races <sup>b</sup> : White (47: 766)		0.90 (0.68-1.20)
Pasolino PM	Overweight: Underweight/Normal (383: 45	0) [	1.06 (0.92-1.21)
Baseline Divi	Obesity: Underweight/Normal (203: 450)	┝━─┤	1.16 (0.98-1.38)
	Former smoker: Never smoked (195: 554)	⊢∎ <mark>-</mark> -1	0.97 (0.83-1.14)
Baseline smoking status	Current smoker: Never smoked (287: 554)	⊢●−1	1.05 (0.91-1.20)
<b>Baseline third agent</b>	INSTI: PI (678: 95)	<b>⊢</b> ●	1.25 (1.02-1.53)
Baseline third agent	NNRTI: PI (263: 95)	<b>⊢</b> −●−−1	1.32 (1.05-1.65)
HCV co-infection	Yes: No (39: 997)		0.88 (0.65-1.20)
Baseline CDC category	Stage 2: Stage 1 (280: 719)	⊢●┥	0.80 (0.69-0.91)
Baseline CDC category	Stage 3: Stage 1 (37: 719)		1.13 (0.82-1.55)
Baseline lipid-modifying agent use	Yes: No (147: 889)		0.93 (0.78-1.11)
Baseline triglycerides	High: Normal (285: 751)		1.21 (1.05-1.40)
Baseline total cholesterol	High: Desirable (388: 648)	⊢+●1	1.11 (0.91-1.34)
Pasolino I DL-C	High: Optimal (284: 389)		1.09 (0.87-1.37)
Baseline LDL-C	Near/Above optimal: Optimal (363: 389)	<b>⊢</b> ∎-1	1.03 (0.89-1.18)
Baseline HDI -C	High: Normal (277: 592)	<b>⊢</b> ● <u> </u>	0.91 (0.79-1.06)
Baseline HDL-G	Low: Normal (167: 592)	<b>⊢</b> ∎-1	1.03 (0.87-1.22)
Age	Per 10 years (1036)	H	0.99 (0.93-1.04)
Baseline hs-CRP (log <sub>e</sub> -transformed)	(1036)		1.63 (1.54-1.72)
Baseline CD4+/CD8+ ratio	(1036)		0.92 (0.82-1.03)
	0.5	1 5	

Ratio vs reference (95% CI)<sup>a</sup>

- 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

<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)

	≥10.0: <1.0 (47: 453)	I <del>e</del> l	1.00 (0.95-1.06
HCV co-infection	Yes: No (42: 1049)	i•i	0.96 (0.91-1.02
Receive CDC esterony	Stage 2: Stage 1 (296: 756)	•	1.01 (0.99-1.04
Baseline CDC category	Stage 3: Stage 1 (39: 756)	H	1.09 (1.03-1.16
Age	Per 10 years (1091)	•	1.00 (0.99-1.01
Baseline CD4+/CD8+ ratio	(1091)		2.48 (2.43-2.54
		0.5 1	5
		Ratio vs reference (95% CI) <sup>c</sup>	

<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. cAdjusted geometric mean and ratio calculated using an ANCOVA model on log,-transformed data adjusting for treatment, sex, race, baseline BMI, baseline CDC category, baseline smoking status, HCV co-infection, age, baseline CD4+/CD8+ ratio, logetransformed 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. dLower limit for the estimated treatment ratio is 0.9985.

# 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

Acknowledgments: These studies were funded by ViiV Healthcare. The authors thank the study participants and their families and caregivers; the investigators and site staff who participated in the TANGO and SALSA studies; and the ViiV Healthcare and GSK study team members. Editorial assistance and graphic design support for this poster were provided under the direction of the authors by MedThink SciCom and funded by ViiV Healthcare.

References: 1. Gabuzda et al. Pathog Immun. 2020;5:143-174. 2. Wada et al. AIDS. 2015;29:463-471. 3. Hattab et al. HIV Med. 2015;16:553-562. 4. Borges et al. J Infect Dis. 2015;212:585-595. 5. Osiyemi et al. Clin Infect Dis. 2022 [Epub ahead of print]. 6. Llibre et al. Clin Infect Dis. 2022 [Epub ahead of print]. 7. Wang et al. CROI 2022; Virtual. Poster 484. 8. Underwood et al. CROI 2022; Virtual. Poster 481.

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