IMPACT ON INFLAMMATORY AND ATHEROGENESIS BIOMARKERS WITH THE 2-DRUG REGIMEN DOLUTEGRAVIR PLUS LAMIVUDINE IN TREATMENT-EXPERIENCED PEOPLE WITH HIV-1: A SYSTEMATIC LITERATURE REVIEW

Josep M. Llibre,[1] Pedro E. Cahn,[2] Janet Lo,[3] Tristan J. Barber,[4,5] Cristina Mussini,[6] Berend J. van Welzen,[7] Beatriz Hernandez,[8] Cynthia Donovan,[9] Michelle Kisare,[10] Myooran Sithamparanathan,[11] Jean van Wyk[11]

[1]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [2]Fundación Huésped, Buenos Aires, Argentina; [3]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [4]Royal Free London NHS Foundation Trust, London, UK; [5]University College London, London, UK; [6]AOU Policlinico, University of Modena and Reggio Emilia, Modena, Italy; [7]University Medical Centre Utrecht, Utrecht, The Netherlands; [8]ViiV Healthcare, Madrid, Spain; [9]ViiV Healthcare, Research Triangle Park, NC, USA; [10]GlaxoSmithKline, Nairobi, Kenya; [11]ViiV Healthcare, Brentford, UK

P053

Introduction

- Even in the setting of maintained ART-mediated virologic suppression, HIV may be associated with persistent inflammation, contributing to an increased risk of non–AIDS-related comorbidities[1-3]
- Several biomarkers of inflammation (C-reactive protein [CRP], interleukin-6 [IL-6]), monocyte and macrophage activation (eg, soluble CD14 [sCD14], soluble CD163 [sCD163]), and atherogenesis and hypercoagulation (eg, D-dimer) have been linked to increased risk of morbidity and mortality in people living with HIV-1 (PLHIV), although correlations of each biomarker with specific clinical events are largely unknown[1]
- Persistently low CD4+/CD8+ ratio (≤0.4) has been associated with systemic inflammation in ART-treated PLHIV, which may be linked to increased morbidity and mortality[4,5]
- The 2-drug regimen (2DR) dolutegravir/lamivudine (DTG/3TC) has demonstrated rapid and sustained virologic suppression vs 3-/4-drug regimens (3/4DRs) in phase III trials[6-10]
  - More stringent analyses of residual viremia (target not detected) and viral blips have demonstrated no difference between DTG/3TC and comparator 3/4DRs[11,12]
  - Studies have shown no differences in virologic suppression in compartments and sanctuary sites or viral escape from reservoirs with DTG/3TC vs 3/4DRs[13,14]
- This systematic literature review summarizes clinical trial and real-world evidence (RWE) evaluating the impact of DTG/3TC on biomarkers of inflammation and atherogenesis in PLHIV

Methods

Search Strategy

- Randomized controlled trials (RCTs): Embase® and PubMed were used to source articles and congress abstracts published from January 1, 2013, to July 7, 2021, describing RCTs
  - Search terms were "dolutegravir or DTG" and "lamivudine or 3TC"
- RWE: A previously published systematic literature review was updated through July 14, 2021[15]
  - Ovid MEDLINE®, Embase, PubMed, and Cochrane library databases and conference proceedings were searched for studies of RWE evaluating the effectiveness and safety of DTG/3TC
- Additional searches were performed for both RCTs and RWE to identify any relevant data from conference proceedings through October 3, 2021

Inclusion/Exclusion Criteria

- Eligible studies included observational cohort studies (prospective or retrospective), case-control studies, cross-sectional studies, database studies, and clinical trials of DTG/3TC in treatment-experienced, virologically suppressed PLHIV aged ≥18 years that included data on CD4+/CD8+ ratio or inflammatory biomarkers CRP, sCD14, IL-6, sCD163, D-dimer, fatty acid binding protein-2, or soluble vascular cell adhesion molecule-1
- Studies that did not report clinical trial data on DTG/3TC were excluded
- Eligibility was independently assessed by 2 reviewers

Data Extraction

- Data extracted from eligible studies included (1) number of PLHIV receiving DTG/3TC, (2) baseline demographic characteristics, (3) prior ART duration, (4) prior duration of virologic suppression, and (5) inflammatory and atherogenesis biomarker outcomes

Results

Search Results

RCTs

- Of the records identified through initial database search and in the additional search of proceedings through October 3, 2021, 4 records corresponding to 2 clinical trials (TANGO and SALSA) met the inclusion criteria[8,10,11,16]
  - TANGO and SALSA were phase III, open-label trials in which virologically suppressed PLHIV (HIV-1 RNA <50 c/mL for >6 months) were randomized to remain on current antiretroviral regimen (CAR; TAF-based 3/4DR or a variety of 3/4DRs, respectively) or switch to DTG/3TC
  - Switching to DTG/3TC demonstrated non-inferior virologic efficacy to CAR (through Week 144 for TANGO and Week 48 for SALSA)

RWE

- Of the records previously identified and published in a systematic literature review, 13 met the inclusion criteria[15]
  - In the update to this search conducted on July 14, 2021, and in the search of congress proceedings through October 3, 2021, 3 additional records were identified
  - After excluding duplicate cohorts and studies not reporting data specifically for DTG/3TC, 6 studies remained for inclusion in this analysis: 1 case-crossover study[17] and 5 observational cohort studies,[18-22] with all studies evaluating CD4+/CD8+ ratio and 1 assessing inflammatory and atherogenesis biomarkers

Demographics and Baseline Characteristics

RCTs

- Across both RCTs, most participants who switched to DTG/3TC were male (TANGO: 93%, SALSA: 56%) and White (TANGO: 80%, SALSA: 61%; Table 1)[8,10]
- Switching to DTG/3TC was non-inferior to continuing TAF-based regimens (TANGO) or CAR (SALSA) for the maintenance of virologic suppression[7-10,16]
  - Proportions of participants with HIV-1 RNA ≥50 c/mL were similar in the DTG/3TC vs TAF-based regimen groups (0.3% vs 0.5% at Week 48; <1% vs 1% at Week 96; 0.3% vs 1.3% at Week 144, respectively) and in the DTG/3TC vs CAR groups (<1% vs 1% at Week 48, respectively)[7-9]
  - In TANGO, proportions of participants with HIV-1 RNA target not detected were also similar with DTG/3TC vs TAF-based regimens (73% vs 69% at Week 96; 76% vs 72% at Week 144, respectively)[11,16]
  - Occurrence of blips (viral load 50-200 c/mL with adjacent values <50 c/mL) was infrequent and similar between the DTG/3TC and TAF-based regimen groups (4% vs 6%, respectively) through Week 96[11]

Table 1. Demographics and Baseline Characteristics for PLHIV Receiving DTG/3TC vs Comparator in Randomized Controlled Trials

Characteristic	TANGO[8]		SALSA[10]	
	DTG/3TC (N=369)	TAF-based regimen (N=372)	DTG/3TC (N=246)	CAR (N=247)
Age				
Median (range), y	40 (20-74)	39 (18-73)	45 (22-74)	45 (23-83)
Age ≥50 y, n (%)	79 (21)	92 (25)	98 (40)	95 (38)
Female, n (%)	25 (7)	33 (9)	108 (44)	84 (34)
Race, n (%)				
African American/African heritage	50 (14)	58 (16)	45 (18)	48 (19)
Asian	13 (4)	13 (3)	31 (13)	39 (16)
White	297 (80)	289 (78)	149 (61)	144 (58)
CD4+ cell count, median (range), cells/mm^3	682 (133-1904)	720 (119-1810)	675 (154-2089)	668 (94-1954)
Duration of ART before Day 1, median (range), mo	34 (7-201)	35 (7-161)	63 (4-240)	71 (12-253)
Baseline third agent class, n (%)				
INSTI	289 (78)	296 (80)	98 (40)	98 (40)
NNRTI	51 (14)	48 (13)	123 (50)	124 (50)
PI	29 (8)	28 (8)	25 (10)	25 (10)

RWE

- Most studies included high proportions of male participants (70%-77%), and median duration of ART ranged from 10.2 to 17.9 years (Table 2)[17-22]

Table 2. Demographics and Baseline Characteristics for RWE Studies

			Demographics and baseline characteristics					
Study	N	Time point	Age, y	Female, n (%)	Race, n (%)	Nadir CD4+ cell count, cells/mm^3	Time on ART, median (IQR)	BL regimen used in ≥5% of participants, n (%)
Lombardi 2019[17]	67	48 wk	Median (IQR), 49.4 (41.2-54.9)	18 (27)[a]	White, 67 (100)	Median (IQR), 237 (64-306)	10.9 (4.8-16.4) y	DRV/r, 43 (64); ATV/r, 18 (27); LPV/r, 6 (9)
Hidalgo-Tenorio 2019[18]	177	48 wk	Mean (SD), 48.5 (14.2)	40 (23)[a]	NR	Mean (SD), 252.2 (494.2)	13 (4-18) y	DRV/r or COBI, 27 (15); ATV/r + 3TC, 12 (7)[b]
Taramasso 2019[19]	22	12 mo	NR	NR	NR	NR	NR	NR
Baldin 2019[20]	556	144 wk	Median (IQR), 51.7 (45.3-57.4)	165 (30)	NR	Median (IQR), 230 (98-328)	11.5 (6.1-18.3) y	FTC/TDF-containing, 231 (42); 3TC + PI-containing, 171 (31); DTG-containing, 52 (9)
Reynes 2020[21]	27	48 mo	Median, 59	NR (26)[a,c]	White (100)[c]	Median (range), 167 (8-450)	215 (22-329) mo	PI/r-containing, 22 (81); TDF-containing, 13 (48); RAL-containing, 7 (26)
Maggiolo 2021[22]	218	60 mo	Median (IQR), 52 (12)	NR (25)[c]	NR	Median (IQR), 669 (446)[d]	10.2 (13) y	NR

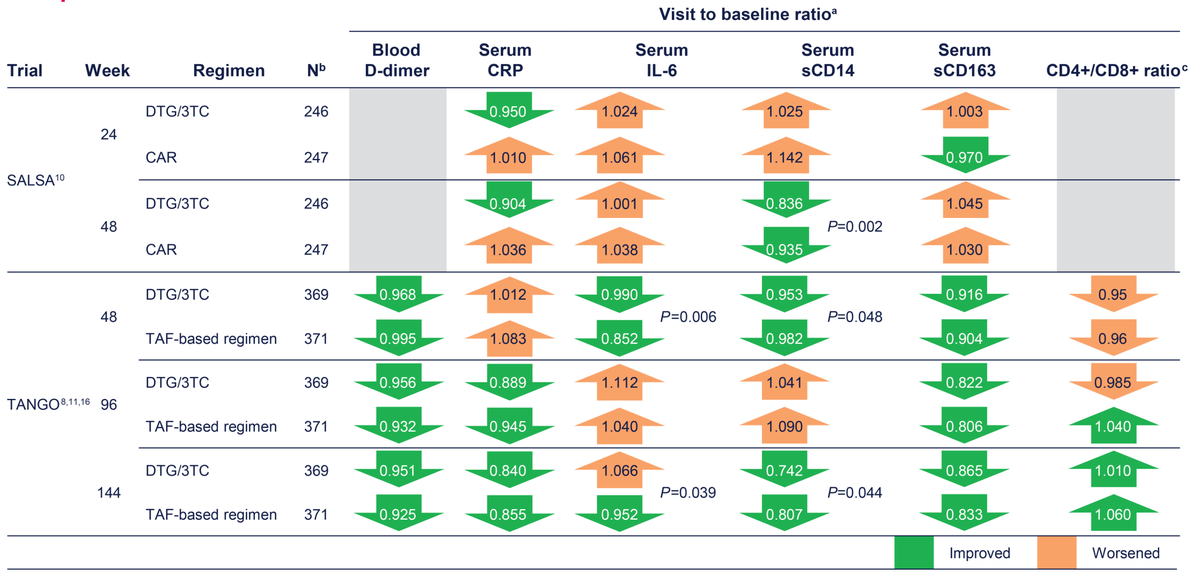
[a]Number of female participants calculated by subtracting originally reported data for male participants from total population. [b]Triple therapy was used by 66% of participants, but regimens were not specified; values listed in table reflect dual or monotherapies used by ≥5% of total participants. [c]Source only reported percentage (not n). [d]Source does not specify value as nadir CD4+ cell count.

Biomarkers of Inflammation and Atherogenesis

RCTs

- Changes in inflammatory and atherogenesis biomarkers after switch to DTG/3TC were small, with no consistent reproducible pattern (Figure 1)[8,10,11,16]
  - Significant differences in sCD14 favoring DTG/3TC in TANGO at Weeks 48 and 144 and SALSA at Week 48 were reported
  - Significant differences in IL-6 favoring TAF-based regimens were reported in TANGO at Weeks 48 and 144, but no differences between DTG/3TC and CAR were reported in SALSA at Week 48
  - There were no significant differences in CRP or sCD163 after switching to DTG/3TC in TANGO or SALSA
  - There was no significant difference in D-dimer after switching to DTG/3TC in TANGO; analysis of D-dimer could not be performed in SALSA as the vast majority of participants had levels below the limit of quantification
- No significant change in CD4+/CD8+ ratio was reported in virologically suppressed participants switching from a 3/4DR to DTG/3TC (Figure 1)[8,10,16]

Figure 1. Reported Inflammatory and Atherogenesis Outcomes in PLHIV Receiving DTG/3TC vs Comparator in RCTs



P values are for treatment comparison. *P* values were not reported for SALSA 24-week data or for TANGO CD4+/CD8+ ratio data. Other *P* values that are not shown were not significant. [a]Ratio is the estimated adjusted ratio in each group calculated using mixed-models repeated measures applied to change from baseline in $\log_e$-transformed data adjusting for treatment, visit, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, BMI (continuous), smoking status, HCV co-infection status, $\log_e$-transformed baseline biomarker value (continuous), treatment-by-visit interaction, and baseline value-by-visit interaction, with visit as the repeated factor. [b]Participant numbers for individual inflammatory biomarkers vary. [c]Median value at specified time point.

RWE

- Increases in CD4+/CD8+ ratios were observed in all 6 RWE studies after switch to DTG/3TC over different follow-up periods (Figure 2)[17-22]
  - Statistically significant changes were seen in 4 of 6 studies
- In the only real-world study evaluating changes in inflammatory biomarkers, median sCD14 significantly decreased from baseline post-switch to Week 48 (6.04 vs 5.95 $\log_{10}$ pg/mL; *P*<0.001), while other biomarkers remained stable[17]

Figure 2. Change From Baseline in CD4+/CD8+ Ratio in PLHIV Receiving DTG/3TC in RWE Studies

Study	N	Time point	CD4+/CD8+ ratio	
Lombardi 2019[17]	67	48 weeks	0.03[a]	NS
Hidalgo-Tenorio 2019[18]	177	48 weeks	0.06[b]	*P*=0.023
Taramasso 2019[19]	22	12 months	0.26[b]	*P*<0.05
Baldin 2019[20]	556	144 weeks	0.10[a]	*P*=0.002
Reynes 2020[21]	27	48 months	0.14[a]	NR
Maggiolo 2021[22]	218	60 months	0.21[a]	*P*<0.0001
				Improved

NR, not reported; NS, not significant. [a]Median. [b]Mean.

Conclusions

- Switching to the 2DR DTG/3TC was not associated with consistent changes in inflammatory or atherogenesis biomarkers in 2 large, randomized, phase III trials (TANGO, n=369; SALSA, n=246) or in 1 real-world study (N=67) with 1 to 3 years of follow-up, suggesting a lack of impact of the number of drugs in an ART regimen on inflammation as long as virologic suppression is maintained
- Biomarker changes are in concordance with virologic efficacy results from clinical trials, demonstrating no significant difference in rates of virologic suppression, residual viremia, viral blips, or virologic control in sanctuary sites and reservoirs with DTG/3TC vs comparator 3/4DRs
- Consistent increases in CD4+/CD8+ ratios were observed in real-world studies after switch to DTG/3TC, and CD4+/CD8+ ratios were similar between DTG/3TC vs comparator post-switch in RCTs
- HIV-associated inflammation is multifactorial, with comorbidities, lifestyle factors, co-infections, long-term immune damage, and persistent HIV-driven immune activation all contributing to the inflammatory landscape

Acknowledgments: This research was funded by ViiV Healthcare. 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. Independent article review and data extraction were conducted by MedThink SciCom. Data included in this poster have previously been presented in part at the 23rd International Workshop on Long-term Complications of HIV and SARS-CoV-2; December 6-9, 2021; Virtual; Poster ADRLH-24.

References: 1. del Mar Gutierrez et al. *Expert Rev Clin Pharmacol*. 2019;12:389-396. **2.** Deeks et al. *Immunity*. 2013;39:633-645. **3.** van Welzen et al. *Front Immunol*. 2021;12:637910. **4.** Hunt et al. *J Infect Dis*. 2016;214(suppl 2):S44-S50. **5.** Serrano-Villar et al. *PLoS Pathog*. 2014;10:e1004078. **6.** Cahn et al. *AIDS*. 2022;36:39-48. **7.** van Wyk et al. IAS 2021; Virtual. Poster PEB164. **8.** van Wyk et al. *Clin Infect Dis*. 2020;71:1920-1929. **9.** van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441. **10.** Llibre et al. IAS 2021; Virtual. Slides OALB0303. **11.** Wang et al. IAS 2021; Virtual. Slides OAB0301. **12.** Underwood et al. IAS 2021; Virtual. Poster PEB163. **13.** Charpentier et al. *J Antimicrob Chemother*. 2020;75:1611-1617. **14.** Tiraboschi et al. *J Infect Dis*. 2021;223:1928-1933. **15.** Patel et al. *Infect Dis Ther*. 2021;10:2051-2070. **16.** Osiyemi et al. IDWeek 2021; Virtual. Poster 900. **17.** Lombardi et al. *HIV Res Clin Pract*. 2019;20:92-98. **18.** Hidalgo-Tenorio et al. *Medicine (Baltimore)*. 2019;98:e16813. **19.** Taramasso et al. ICAR 2019; Milan, Italy. Poster PD50. **20.** Baldin et al. *Int J Antimicrob Agents*. 2019;54:728-734. **21.** Reynes et al. AIDS 2020; Virtual. Poster PEB0241. **22.** Maggiolo et al. IAS 2021; Virtual. Poster PEB179.

Presenting Author: Myooran Sithamparanathan; myooran.x.sithamparanathan@viivhealthcare.com