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

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Background and Methods

- 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 and atherogenesis have been investigated in HIV and linked to increased risk of morbidity and mortality; however, correlations of each marker with specific clinical events are largely unknown[1]
- The 2-drug regimen dolutegravir plus lamivudine (DTG/3TC) has demonstrated rapid and sustained virologic suppression vs 3-/4-drug regimens (3/4DRs) in phase III trials.[4-8] More stringent analyses of residual viremia (target not detected) and viral blips have demonstrated no difference between DTG/3TC and comparator 3/4DRs[9,10]
- 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 people with HIV-1 (PWH)
- Using records from Ovid MEDLINE®, Embase®, PubMed, and Cochrane library databases published from January 1, 2013, to July 14, 2021, and conference proceedings through October 3, 2021, we searched for studies reporting changes in inflammatory and atherogenesis biomarkers with DTG/3TC in treatment-experienced, virologically suppressed PWH aged ≥18 years
- 4 records representing 2 randomized controlled trials (RCTs)[6,8,9,11] and 6 records of RWE met eligibility criteria[12-17]
  - All RWE studies evaluated CD4+/CD8+ ratio, while only 1 assessed inflammatory and atherogenesis biomarkers

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.** Cahn et al. *AIDS.* 2022;36:39-48. **5.** van Wyk et al. IAS 2021; Virtual. Poster PEB164. **6.** van Wyk et al. *Clin Infect Dis.* 2020;71:1920-1929. **7.** van Wyk et al. HIV Glasgow 2020; Virtual. Slides O441. **8.** Llibre et al. IAS 2021; Virtual. Slides OALB0303. **9.** Wang et al. IAS 2021; Virtual. Slides OAB0301. **10.** Underwood et al. IAS 2021; Virtual. Poster PEB163. **11.** Osiyemi et al. IDWeek 2021; Virtual. Poster 900. **12.** Lombardi et al. *HIV Res Clin Pract.* 2019;20:92-98. **13.** Hidalgo-Tenorio et al. *Medicine (Baltimore).* 2019;98:e16813. **14.** Taramasso et al. ICAR 2019; Milan, Italy. Poster PD50. **15.** Baldin et al. *Int J Antimicrob Agents*. 2019;54:728-734. **16.** Reynes et al. AIDS 2020; Virtual. Poster PEB0241. **17.** Maggiolo et al. IAS 2021; Virtual. Poster PEB179.

Comparable Impact on Inflammatory Markers After Switch to DTG/3TC Versus 3- or 4-Drug Regimens

Inflammatory and atherogenesis outcomes in PWH receiving DTG/3TC vs comparator[1-4]

Trial	Week	Regimen	N[b]	Visit to baseline ratio[a]: Blood D-dimer	Serum CRP	Serum IL-6	Serum sCD14	Serum sCD163	CD4+/CD8+ ratio[c]
SALSA	24	DTG/3TC	246		0.950	1.024	1.025	1.003	
		CAR[d]	247		1.010	1.061	1.142	0.970	
	48	DTG/3TC	246		0.904	1.001	0.836	1.045	
		CAR[d]	247		1.036	1.038	0.935	1.030	
							P=0.002		
TANGO	48	DTG/3TC	369	0.968	1.012	0.990	0.953	0.916	0.95
		TAF-based regimen	371	0.995	1.083	0.852	0.982	0.904	0.96
						P=0.006	*P*=0.048		
	96	DTG/3TC	369	0.956	0.889	1.112	1.041	0.822	0.985
		TAF-based regimen	371	0.932	0.945	1.040	1.090	0.806	1.040
	144	DTG/3TC	369	0.951	0.840	1.066	0.742	0.865	1.010
		TAF-based regimen	371	0.925	0.855	0.952	0.807	0.833	1.060
						P=0.039	*P*=0.044		

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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-model 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. [d]3- or 4-drug current antiretroviral regimen.

- No consistent overall pattern of change in inflammatory markers was reported after switch to DTG/3TC[1-5]
  - There were significant changes in sCD14 favoring DTG/3TC in TANGO at Weeks 48 and 144 and SALSA at Week 48[1-3]
  - There were significant changes in IL-6 favoring TAF-based regimens in TANGO at Weeks 48 and 144 but not in SALSA at Week 48[1-3]
  - In the only RWE study evaluating inflammatory biomarkers, median sCD14 significantly decreased from baseline (6.04 $\log_{10}$ pg/mL) post-switch to Week 48 (5.95 $\log_{10}$ pg/mL; $P<0.001$), while other biomarkers remained stable[5]
- No significant change in CD4+/CD8+ ratio was observed in virologically suppressed participants switching from a 3DR to DTG/3TC in RCTs[1-3]

1. van Wyk et al. *Clin Infect Dis.* 2020;71:1920-1929. **2.** Osiyemi et al. IDWeek 2021; Virtual. Poster 900. **3.** Llibre et al. IAS 2021; Virtual. Slides OALB0303. **4.** Wang et al. IAS 2021; Virtual. Slides OAB0301. **5.** Lombardi et al. *HIV Res Clin Pract.* 2019;20:92-98.

Increased CD4+/CD8+ Ratios After Switch to DTG/3TC in Real-world Studies

- Increases in CD4+/CD8+ ratios were observed in all 6 RWE studies (statistically significant in 4/6) after switch to DTG/3TC over different follow-up periods[1-6]

Study	N	Time point	CD4+/CD8+ ratio	
Lombardi 2019[1]	67	48 weeks	0.03[a]	NS
Hidalgo-Tenorio 2019[2]	177	48 weeks	0.06[b]	*P*=0.023
Taramasso 2019[3]	22	12 months	0.26[b]	*P*<0.05
Baldin 2019[4]	556	144 weeks	0.10[a]	*P*=0.002
Reynes 2020[5]	27	48 months	0.14[a]	NR
Maggiolo 2021[6]	218	60 months	0.21[a]	*P*<0.0001
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NR, not reported; NS, not significant.
[a]Median. [b]Mean.

1. Lombardi et al. *HIV Res Clin Pract*. 2019;20:92-98. **2.** Hidalgo-Tenorio et al. *Medicine (Baltimore)*. 2019;98:e16813. **3.** Taramasso et al. ICAR 2019; Milan, Italy. Poster PD50. **4.** Baldin et al. *Int J Antimicrob Agents*. 2019;54:728-734. **5.** Reynes et al. AIDS 2020; Virtual. Poster PEB0241. **6.** Maggiolo et al. IAS 2021; Virtual. Poster PEB179.

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 (SALSA, n=246; TANGO, n=369) or in 1 real-world study (N=67) with 1 to 3 years of follow-up
- 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
- Overall, changes in CD4+/CD8+ ratio were similar between DTG/3TC vs comparator post-switch in randomized controlled trials
  - Consistent increases in CD4+/CD8+ ratios were observed in real-world studies after switch to DTG/3TC
- 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

The data suggest a lack of impact of the number of drugs in an ART regimen on inflammation as long as virologic suppression is maintained

Data included in this presentation have previously been presented in full at 23rd International Workshop on Long-term Complications of HIV and SARS-CoV-2; December 6-9, 2021; Virtual; Poster ADRLH-24.