Inflammatory Biomarkers During Treatment with *Dovato*

Inflammation in PLHIV

Persistent inflammation and immune activation have been linked to the increased frequency of age-related conditions in PLHIV.[1] Clinical significance of residual immune activation/inflammation is unknown.

There are a number of lifestyle factors (smoking, alcohol, obesity and other comorbidities) that may cause inflammation in PLHIV in addition to HIV and ART.[1–6]

ART reduces systemic inflammation and immune activation caused by HIV-infection, but cytokine levels remain elevated compared to those measured in HIV-uninfected populations.[1–3]

Viral particles[a] released from viral reservoirs and sanctuary sites, and low-level viremia drive the immune response, leading to persistent immune activation and inflammation.[1–3]

Evidence from the large, randomized, Phase 3 TANGO and SALSA trials showed a comparable impact on inflammatory markers for DTG/3TC and various 3-DRs.[7-16]

There were no differences in very low-level viremia (TND), viral load blips, virological control in sanctuary sites or virologic failures in DTG/3TC when compared to 3-DR.[8,17-23]

[a]In addition to progeny viruses released by replication-competent viruses, viral reservoirs can release viral mRNA and viral proteins from populations within the viral reservoir that are not replication competent.[24]

Use of Biomarkers in the Detection of Immune Activation in HIV

No individual stable, reliable and reproducible biomarker or group of biomarkers have been identified to have predictive utility in the detection of immune activation seen in HIV.[25–28]

Although the clinical significance of inflammatory biomarkers is currently unclear, these measures did not worsen with DTG/3TC versus 3-DRs. [7,9-13,15-18,23,29,33]

The DHHS guidelines do not currently recommend clinical monitoring with immune activation or inflammatory markers (AII).[28]

Inflammatory Biomarkers Evaluated as Exploratory Endpoint in HIV-1 Treatment-Naive Patients in Two Phase 3 Clinical Trials Evaluating DTG/3TC vs 3-DR

GEMINI-1 and -2: IL-6 and CRP[9-11]

- Minimal or no changes from Baseline to Week 144 in IL-6 (median [IQR] for both groups: 0.0 [0.0, 0.0] ng/L) and high-sensitivity CRP [median [IQR]: DTG+3TC, 0.0 [−0.9, 0.8] mg/L; DTG+TDF/FTC, −0.2 [−0.9, 0.5] mg/L]. Results were similar at Week 48 and 96.[9-11]

There were no differences between groups or consistent patterns of change from Baseline to Week 144 in surrogate biomarkers for inflammation in these studies.[9-11]

Impact on Inflammatory Biomarkers in HIV-1 Treatment Experienced Patients After Switch to DTG/3TC vs 3- or 4-DRs

DTG/3TC and 3- or 4-DRs have a similar and small impact on inflammatory mediators, with no clinically relevant differences. [7,8,13,15]

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	247		↑ 1.010	↑ 1.061	↑ 1.142	↓ 0.970	
	48	DTG/3TC	246		↓ 0.904	↑ 1.001	↓ 0.836	↑ 1.045	
		CAR	247		↑ 1.036	↑ 1.038	↓ 0.935	↑ 1.030	
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
	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 = 0.006 (Serum IL-6); *P* = 0.048 (Serum sCD14); *P* = 0.002 (Serum sCD163); *P* = 0.039 (Serum IL-6); *P* = 0.044 (Serum sCD14)

↓ Improved ↑ Worsened

Note: *P*-value are for treatment comparison. *P*-value were not reported for SALSA 24-week data for TANGO CD4+/CD8+ ratio data. Other *P*-values that are not shown were not significant. [a] Ratio is the estimated adjusted ration 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

Viral Suppression with DTG/3TC vs 3-DRs

Parameter	Treatment-Naïve: GEMINI-1 and -2 DTG + 3TC (N = 716) vs DTG + TDF/FTC (N = 717)	Virologically Suppressed: TANGO DTG/3TC (N = 369) vs TAF-based regimens (N = 372)	Virologically Suppressed: SALSA DTG/3TC (N = 246) vs CAR (N = 247)
Primary efficacy endpoint	**Non-inferior** at Week 48[30]	**Non-inferior** at Week 48[7]	**Non-inferior** at Week 48[32]
Durable efficacy	**Non-inferior** through **144 weeks**[31]	**Non-inferior** through **144 weeks**[14]	NR
Blips	**Similar** through **144 weeks**[23]	**Similar** through **144 weeks**[19]	NR
TD/TND	**Similar from Week 4** through **144 weeks**[23]	**Similar** through **144 weeks**[13]	**Similar** through **48 weeks**[20]

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Abbreviations: ARV = antiretroviral; ART = antiretroviral therapy; BL = baseline; BMI = body mass index; CAR = current antiretroviral regimen; CD = cluster of differentiation; CRP = c-reactive protein; DHHS = Department of Health and Human Services; DR = drug regimen; DTG = dolutegravir; ES = early switch; FTC = emtricitabine; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs = high-sensitivity; IL = interleukin; IQR = interquartile range; LS = late switch; mRNA = messenger RNA; NR = not reported; PLHIV = people living with HIV; s = soluble; TAF = tenofovir alafenamide; TBR = tenofovir alafenamide–based regimen; 3TC = lamivudine; TD = target detected; TDF = tenofovir disoproxil fumarate; TND = target not detected; VL = viral load

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