Inflammatory profile of B/F/TAF, DTG/ABC/3TC, and DTG+F/TAF over 5-years and effects of viral blips

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ABSTRACT

Background
Elevated levels of inflammatory markers are linked to increased morbidity/mortality in people with HIV (PWH) and often remain elevated after suppression of HIV-1 replication below the limit of detection by antiretroviral therapy (ART). As new combinations of ART become available, an evaluation of their effects on biomarkers of inflammation are needed. Additionally, it remains unknown whether transient elevations of viral load ("blips") during ART are associated with increases in inflammatory biomarkers. This study analyzed the effect of ART on selected biomarkers of inflammation and immune activation.

Methods
We utilized cryopreserved samples from a convenience sampling of treatment-naïve PWH enrolled in two Phase 3 clinical studies investigating the efficacy and safety of B/F/TAF, DTG/ABC/3TC and DTG+F/TAF over a 5-year window (GS-US-380-1489/1490). At wk144, participants were switched to open label B/F/TAF. We measured levels of interleukin-6 (IL-6), C-reactive protein (hsCRP), D-Dimer, soluble CD14 (sCD14), and tumor necrosis factor-α receptor 1 (TNFR1) by ELISA from select baseline and selected time points; (B/F/TAF, N=123; DTG/ABC/3TC, N=62; DTG+F/TAF, N=58). A subset of samples from PWH who experienced a viral blip (n=44, defined as single VL>50c/mL) were also analyzed and paired with the most recent suppressed sample. Longitudinal biomarker changes were assessed using a constrained mixed-effects linear regression model (LMEM) adjusting for covariates (sex and baseline viral load). Associations between inflammation biomarkers and viral load were tested with LMEM adjusting for treatment arm and time.

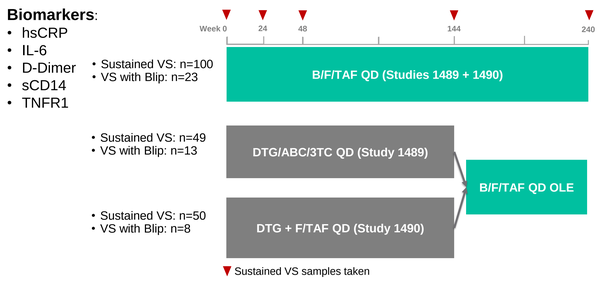
CONCLUSIONS

- The decrease in inflammatory biomarkers was more pronounced in groups with elevated baseline inflammatory marker values or higher pre-ART viral loads (data not shown).
- Significant decreases in three of the five biomarkers were measured after ART (sCD14, D-Dimer, TNFR1). Changes were similar with B/F/TAF vs DTG with either TAF/FTC or ABC/3TC.
- Levels of hsCRP were stable over time in all arms; levels of IL-6 were stable over time in the B/F/TAF arm.
- In the subgroup with viral blips, we observed a significant positive association (p=0.02) between increasing viral load and sCD14.
- D-dimer levels increased during viral blips (p=0.04) in the B/F/TAF arm.
- Virologic blips may be a cause or consequence of intermittent immune activation and further studies are warranted.

This work was funded by Gilead Sciences.

RESULTS

Figure 1. GS-US-380-1489/90 Clinical Study Design and Plan for Retrospective Biomarker Analysis.



Inclusion Criteria:

1. Samples from baseline, week 24, 48, 144, and 240 (Wk 96 OLE) from participants who had consistently suppressed viremia (**Figure 1**) and those who experienced a viral blip (Figure 3).
2. Samples from participants with baseline viral loads (VL) > 100,000 cp/mL were over selected.

Exclusion Criteria:

1. Participants who failed to complete the trial to week 240 (Wk 96 OLE).
2. Participants who had or developed an underlying comorbid condition that may complicate their inflammatory profiles.
3. Participants who had co-infection with HCV.

- hsCRP, high-sensitive C-reactive protein; IL-6, Interleukin-6; TNFR1, Tumor necrosis factor receptor; VS, virologically suppressed; OLE, open label extension. Blip, single viral load >50 c/mL preceded and followed by <50 c/mL

Figure 2. Several Inflammatory Markers Decreased Significantly in All Study Arms.

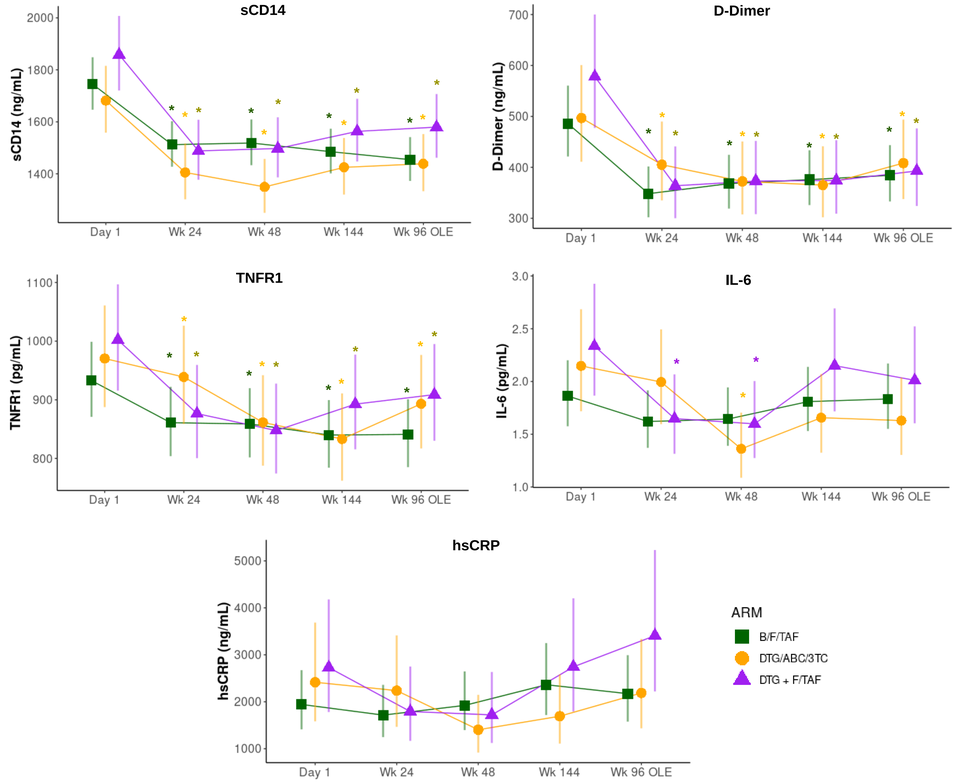


Figure 2. Longitudinal Changes in Serum Biomarkers Associated with Inflammation (least-squares means±confidence intervals). Asterisks denote significance difference from baseline at a false discovery rate (FDR) < 0.05.

Figure 3. Transient Viral Elevations (Blips) were Associated with Increases in sCD14 and D-dimer levels.

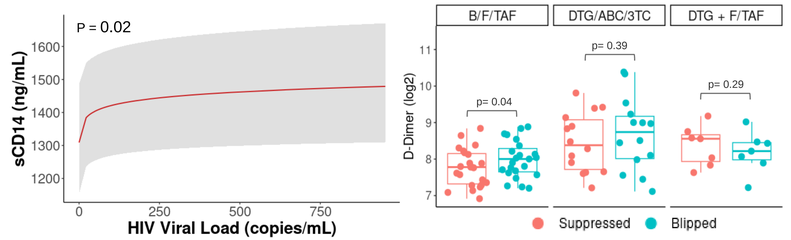


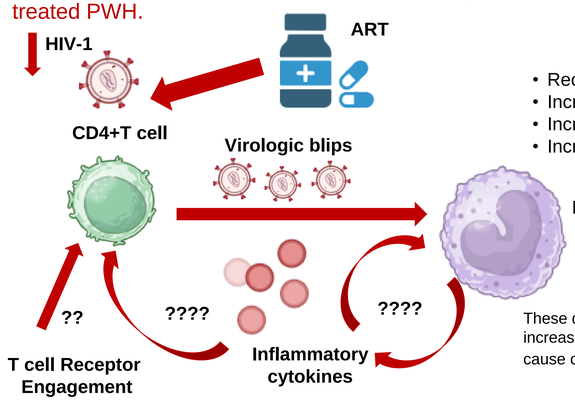
Figure 3. Association of Biomarker Changes with Transient Viral Elevations (Blips). Least-squares means and confidence intervals shown for sCD14 and median (IQR) shown for D-Dimer, with p-values tested by Wilcoxon Signed Rank Test.

Table 1. Baseline Biomarker Levels were Higher in Participants with High Baseline Viral Load.

Marker	VL > 100,000 cp/mL (n=64)	VL ≤ 100, 000 cp/mL (n=132)	Units	padj
hsCRP	1516 (615-4670)	1352 (642-3767)	ng/mL	0.57
IL-6	2 (1.2-3)	1.5 (0.9-3)	pg/mL	0.03
D-Dimer	423 (304-792)	356 (249-571)	ng/mL	0.03
sCD14	1947 (1557-2340)	1688 (1411-1918)	ng/mL	<0.01
TNFR1	1032 (823-1287)	877 (750-1057)	pg/mL	<0.01

Median (IQR); Wilcoxon Rank Test – two sided.

Figure 4. Transient Viral Elevations (Blips) may contribute to inflammation in ART-treated PWH.



- Recognition of viral products
- Increased sCD14
- Increased tissue factor (?)
- Increased D Dimer

These data cannot determine whether increased immune activation was a cause or consequence of virologic blips.

Figure 4. Proposed model for study findings. Treatment with combination ART reduces HIV-1 replication and improves CD4+ T cell counts. Viral blips were associated with increased monocyte activation (sCD14). Based on previous work, monocytes can respond to HIV-1 by increasing expression of tissue factor (TF), which can activate the extrinsic coagulation pathway, increasing D-dimer levels (Funderburg *Blood* 2012). There are potentially multiple causes of viral blips, including activation of CD4+ T cells through T cell receptor engagement or by exposure to inflammatory cytokines. These cytokines could also induce monocyte activation and TF expression. Images generated on BioRender.