DOLUTEGRAVIR EXPOSURE, BUT NOT BICTEGRAVIR, INCREASES *IN VITRO* PLATELET AGGREGATION

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Background

- People living with HIV (PLWH) have 60% greater risk of developing cardiovascular disease (CVD) than HIV-negative individuals, and PLWH on antiretroviral therapy (ART) have double the risk than ART-naïve people (1).
- Abacavir (ABC) exhibits a pro-thrombotic phenotype in endothelial cells and platelets, whereas tenofovir alafenamide (TAF) showed a more cardio-protective effect (2,3).
- Dolutegravir (DTG) and bictegravir (BIC), two integrase inhibitors with similar structures used with ABC and TAF in regimens, have an unclear effect on the vasculature and platelets.
- We aimed to define the effects of DTG and BIC on platelets to better understand their cardiovascular side-effects.

DTG/ ABC/ 3TC

BIC/ TAF/ FTC

Dolutegravir enhances *in vitro* platelet aggregation

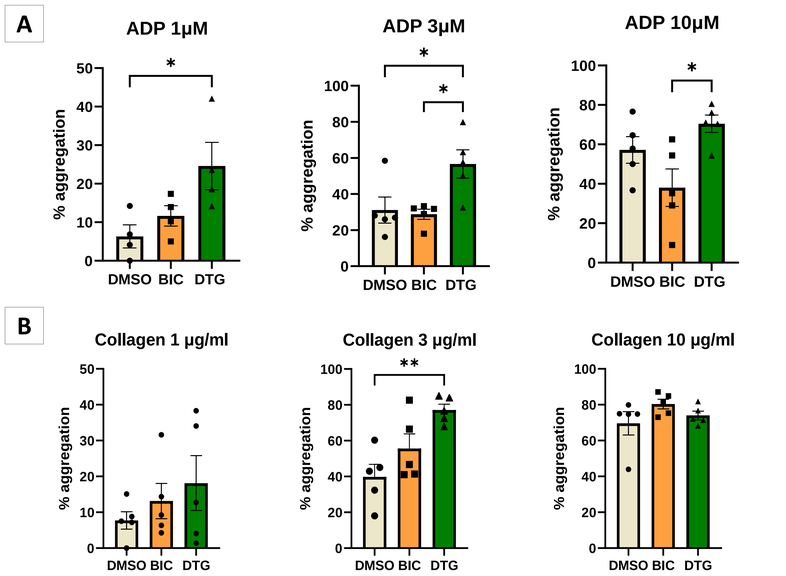


Figure 1. Aggregation responses upon drug treatment. Graphs in [A] show ADP-induced platelet aggregation at different agonist concentrations upon exposure to vehicle (control), BIC or DTG, whereas ones in [B] show collagen-evoked platelet aggregation at various concentrations.

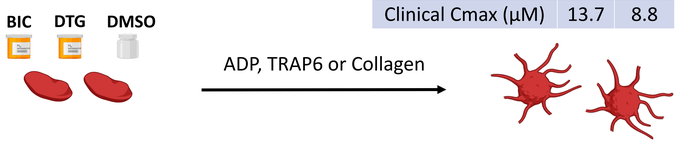
Conclusions

- Some antiretrovirals have been shown to have effects on endothelial cells and platelets, which may contribute to cardiovascular events.
- We demonstrated that integrase inhibitors with overlapping chemical structures behave differently in the context of platelet activation.
- Dolutegravir-exposed platelets aggregate more than bictegravir-exposed as shown in **Figure 1**, suggesting a possible pro-thrombotic phenotype.
- This was also confirmed in the heightened alpha-granule release in DTG-treated platelets illustrated in **Figure 2**, indicating a potential activation mechanism.
- Our results suggest that BIC/TAF/FTC might be a better regimen to DTG and/or ABC containing regimens (e.g. DTG/ABC/3TC) in the context of cardiovascular side effects.
- Future studies will include more physiologically relevant flow assays, observations of effects of drug combinations and patient studies to understand the links between the observed effects and CVD in PLWH.
- Ultimately our study will improve understanding of the side-effects of anti-retrovirals on the cardiovascular system.

Materials & Methods

- Platelet-rich plasma (PRP) from HIV-negative donors (60% men, aged 25+/-3yrs) was exposed to BIC, DTG or DMSO (control) *in vitro* for 30min, prior to adding a range of agonists; ADP & Thrombin Receptor Activator for Peptide-6 (TRAP-6) [1-30µM] or collagen [1-30µg/ml].
- Platelet aggregation was measured using microplate-based aggregometry and activation markers by real-time Flow Cytometry.

	BIC	DTG
Clinical Cmax (µM)	13.7	8.8



Alpha-granule release heightened upon dolutegravir exposure

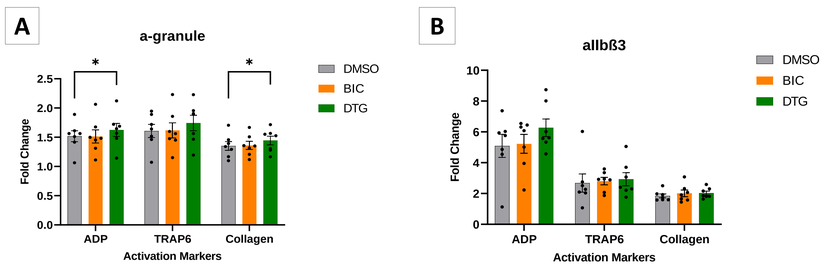


Figure 2. Activation markers upon drug treatment. Graphs in [A] show platelet degranulation upon various agonist stimulations, indicating a higher α-granule release in platelets exposed to dolutegravir compared to vehicle control. A trend of higher αιιbβ3 integrin activation was observed in dolutegravir-exposed platelets upon ADP activation as shown in graph [B] compared to the rest of the groups.

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References

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