# PLATELET FUNCTION AFTER DOLUTEGRAVIR AND/OR DARUNAVIR/COBISCISTAT IN HEALTHY SUBJECTS

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## Background

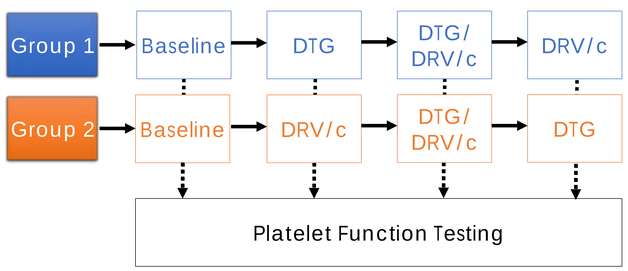
- Platelets are central to thrombotic disease (i.e. myocardial infarction)
- People living with HIV (PLWH) have increased CV risk[1,2]
- The effect of antiretroviral (ARV) combinations on cardiovascular health remains unclear
- We recently demonstrated differential effects of NRTIs on platelet function *in vitro*[3]
- The impact of third agents on platelet function remains unclear
- Both dolutegravir (DTG) and darunavir/cobicistat (DRV/c) are effective third agents recommended by International HIV Treatment Guidelines

## Aim

To evaluate the impact of clinically-relevant concentrations of third agents on platelet function to understand cardiovascular risk in PLWH

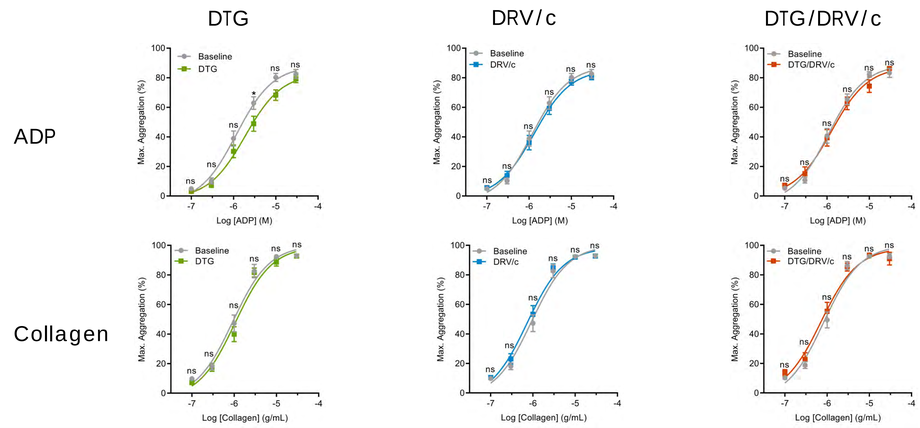
## Methods

- Platelets were isolated from two populations of HIV-negative volunteers:
  1. Subjects that were not taking any medication and exposed to ARVs *in vitro*
  2. 21 subjects enrolled on a Phase I clinical trial (NCT03094507) who were randomised into two groups and received DTG (50mg, QD), DTG plus DRV/c (800/150mg, QD) and DRV/c for 7d with a 14d wash-out period between drugs



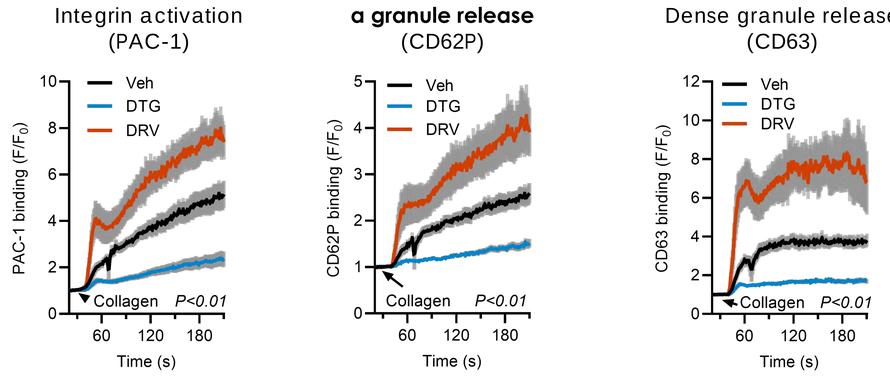

- Platelet function was assessed using plate-based aggregation and real-time flow cytometric expression of platelet activation markers

## Reduced platelet aggregation in the presence of DTG




- Platelets isolated following steady-state for each ARV
- Aggregation responses to increasing concentrations of ADP (upper panel) and collagen (lower panel)
- Summary data compare responses after DTG, DRV/c or DTG/DRV/c with baseline responses
- Platelet aggregation to ADP was significantly lower in subjects receiving daily DTG
- No effects were observed for the other ARV combinations

## Differential effects of DTG and DRV on platelet activation markers




- *In vitro* studies were conducted using plasma $C_{max}$ derived from the clinical trial (DTG; 3.67µg $mL^{-1}$ and DRV; 4.99µg $mL^{-1}$)
- Collagen-evoked platelet activation was monitored by real-time flow cytometry
- Exposure to DRV enhanced platelet integrin activation and granule release, whilst DTG reduced platelet activation responses

## Conclusions

- Reduced platelet activation in the presence of DTG may be explained by altered platelet granule release, that potentially confers a cardioprotective phenotype
- Enhanced granule release following DRV exposure may be important when considering protease inhibitor-related cardiovascular risk
- Further studies should consolidate basic science and clinical approaches to understand the impact of ARVs on CV health in PLWH
- Our data suggest that the choice of third agent may be an important consideration for managing CV risk in PLWH

## References

1. Islam *et al.*, (2012), *HIV Med.* 8: 453-68. 2. D:A:D study group (2008), *Lancet,* 371: 1417-26. 3. Taylor *et al.,* (2019), Br. J. Pharmacol.

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