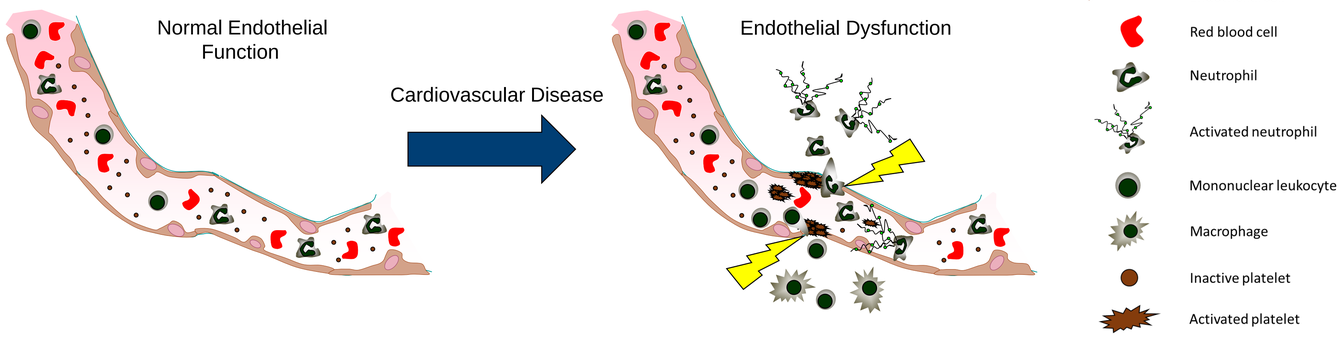
Abacavir Sulphate and Tenofovir Disoproxil Fumarate or Tenofovir Alafenamide Differentially Regulate Endothelial Dysfunction

Akif A. Khawaja[1*], Kirk A. Taylor[1], Mark Nelson[2,3], Brian Gazzard[2,3], Marta Boffito[2,3] and Michael Emerson[1]

[1]National Heart and Lung Institute, Imperial College London, London, UK
[2]Department of Medicine, Imperial College London, London, UK
[3]Chelsea and Westminster NHS Trust, London, UK
*Contact email: akif.khawaja10@imperial.ac.uk

Background

- For reasons that remain unclear, people living with HIV (PLWH) are twice as likely to develop cardiovascular disease (CVD)[1].
- Certain classes of antiretroviral drugs (ARVs) (e.g. abacavir sulphate (ABC) and protease inhibitors) may contribute to increased cardiovascular risk[2,3].
- Endothelial dysfunction has a well established role in atherosclerosis and CVD[4]
- Endothelial dysfunction can involve cellular activation, pro-coagulant effects and increased cellular crosstalk.



Aim

To investigate the effects of different ARVs upon endothelial activation in order to better understand enhanced cardiovascular risk in PLWH.

Methods

Cell Culture

- Human umbilical cord vein endothelial cells (HUVEC) were treated with plasma C_{max} concentrations of ABC, tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide (TAF) over 2 days prior to experimentation (90 minutes/day).

Flow Cytometry

- Adhesion molecule expression (cellular activation)
- Ectonucleotidase expression (anti-thrombotic effects)
- Tissue factor (TF) expression (pro-coagulant effects)
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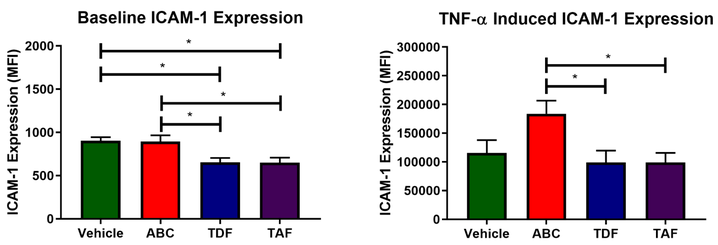
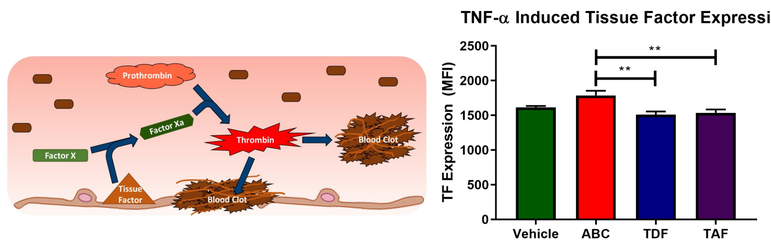
- Endothelial microparticle characterisation (cellular activation and cell crosstalk)

ABC Increases Vascular Endothelial Cell Activation



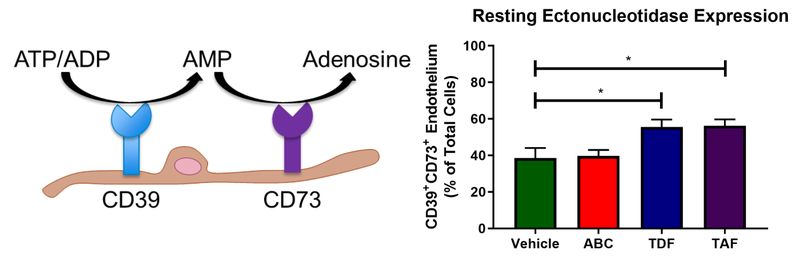
Endothelial cells interact with circulating blood cells via numerous adhesion molecules, including ICAM-1. We measured ICAM-1 expression to assess the effects of ARVs on endothelial activation. n=5, *= p<0.05

ABC Enhances Endothelial Pro-Coagulant Properties



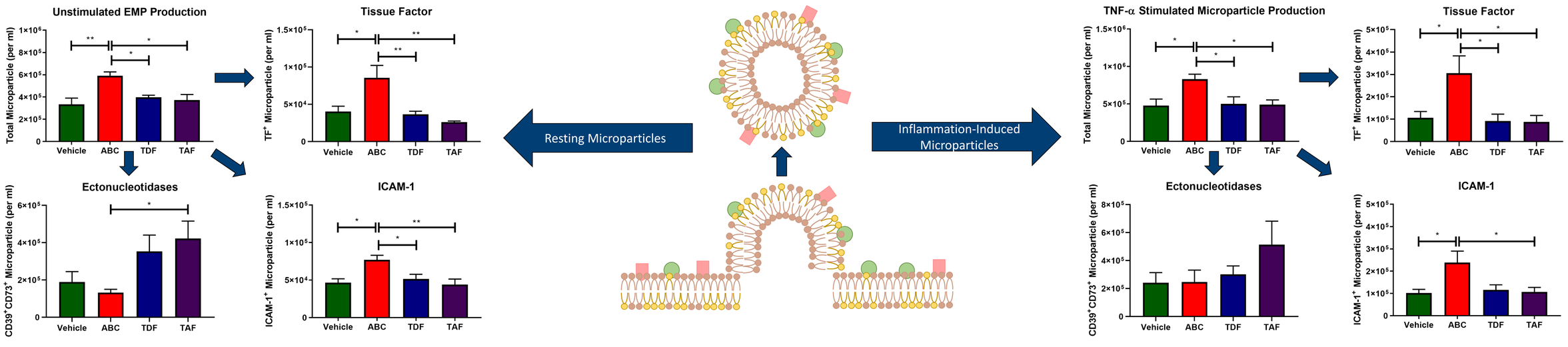
The vascular endothelium influences coagulation through expression of TF, which can initiate thrombosis. We examined inflammation-induced TF expression to determine any changes in pro-coagulant properties. n=5, *= p<0.05

TAF Increases Endothelial Anti-Thrombotic Properties



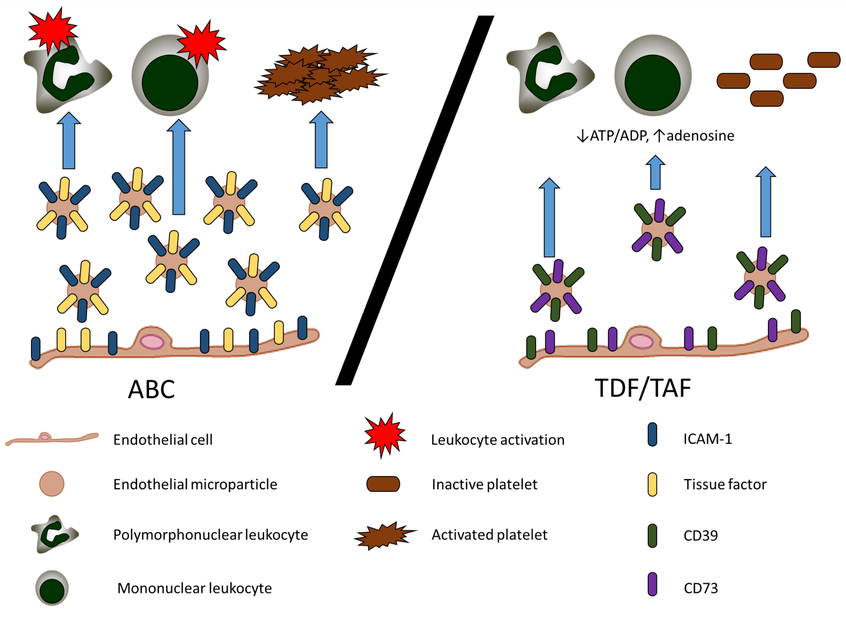
CD39 and CD73 degrade cell-free ADP, a platelet agonist that drives granule release, platelet aggregation and thrombus formation. We examined CD39 and CD73 expression to assess differences in anti-thrombotic effects. n=5, *= p<0.05

ABC Increases Microparticle Production and Promotes a 'Pro-Thrombotic' Microparticle Phenotype



Microparticles are small vesicles (0.1-1μm in size) that are produced by all cells. When activated, cells release more microparticles. Aberrant microparticle production has been implicated in various inflammatory diseases. We quantified endothelial microparticles and examined adhesion molecule (inflammatory), TF (pro-coagulant) and ectonucleotidase (CD39 and CD73) (anti-thrombotic) levels to determine any modulatory effects of ARVs upon potential platelet crosstalk. n=5, *= p<0.05, **= p<0.01

Proposed Mechanism



Summary and Conclusions

In summary, we found:

- ABC-treated cells had higher levels of endothelial activation and pro-coagulant properties.
- TAF increased endothelial anti-thrombotic properties
- ABC enhanced pro-thrombotic endothelial microparticle production.
- TAF increased basal anti-thrombotic endothelial microparticle production.

In conclusion, differential impacts of ARVs on endothelial activation may provide potential mechanisms underlying CV risk in PLWH. Patient studies are required to validate our findings within a clinical setting and determine the potential of endothelial dysfunction markers to act as predictive biomarkers of cardiovascular risk and/or therapeutic targets in PLWH.

[1]Shah et al. *Circulation*. 2018; **138**, 1100-1112. [2]Hsue et al. *AIDS*. 2009; **23(15)**, 2021-2027. [3]D:A:D study group. *Lancet*. 2008; **371(9622)**, 1417-1426. [4]Cai and Harrison. *Circ Res.* 2000; **87(10)**, 840-844.