Surrogate markers of cardiovascular risk: a summary and what it all means

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Competing interests disclosure

- I have received grants for research funding from Gilead Sciences Ltd
Platelet Biology Group

- Cardiovascular Pharmacology
- Themes:
  - Cardio-protection
  - Mechanisms of pollution-driven cardiovascular risk
  - Mechanisms of HIV-associated cardiovascular risk
- Scientific approaches
  - Cell and animal models
  - Collaborative clinical studies
HIV and Cardiovascular Risk

- Cardiovascular risk is associated with:
  - Pollution
  - HIV

Potential drivers of pollution-associated cardiovascular risk
- Gases
- Particulate matter
- Urban living

Potential drivers of HIV-associated cardiovascular risk
- ARVs
- HIV
- Lifestyle
Platelets and Myocardial Infarction (MI)

- MI is a platelet activation event and build up
- Underlying endothelial dysfunction
- Platelets are a major target in treatment and prevention of MI (aspirin)
Platelets and endothelium: A question of balance

**Platelet activation**
- Collagen
- ADP/adrenaline

**Inhibition of activation**
- Nitric oxide
- Prostacyclin

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**Health**
- Low cardiovascular risk

**Endothelial dysfunction**
- Increased platelet activation

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**Cardio-protective processes**

**Mechanisms of cardiovascular risk**

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**Heart attack**
- High cardiovascular risk
Platelet aggregometry assay

- Human blood
- HIV-
- Platelet rich plasma
- Platelet aggregation = light transmission
- Plate based approach
Nitric oxide: the good stuff
Abacavir: proposed mechanism
Abacavir: exploring a mechanism

- Abacavir blocks the inhibitory (cardio-protective) effects of NO upon platelet activation

![Graphs showing platelet inhibition](chart.png)
Comparative ARV effects *in vivo*

**A)** WT

**B)** WT

[Diagram showing comparative effects of different ARV treatments on platelet aggregation and time course of aggregation.]
What does it all mean?

- ARVs induce platelet activation to different extents
- Are our studies relevant to PLWH?
  - Relevance of dosing
  - Relevance of individual ARVs
Why platelets as surrogates?

- Studies are potentially **predictive**
- Cardiovascular effects conclusively linked with **individual** ARVs
- Purely basic studies require confirmation in clinical studies
Endothelial cells

ARVs impact endothelial pro-coagulant properties

Factor X → Prothrombin → Thrombin → Blood Clot

Tissue Factor → Blood Clot

Factor Xa

ARVs impact endothelial anti-thrombotic properties

ATP/ADP → AMP → Adenosine

CD39 → CD73

How do ARVs impact platelet-endothelial crosstalk?

Poster: P022

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

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Summary

- Evidence of differential impacts of ARVs upon platelet and endothelial function
- Platelets have potential value as **predictive** indicators of cardiovascular risk
- Assays are established, sensitive and reliable
- Assay of choice varies with proposed mechanism
- Surrogate approaches allow mechanistic links with ARVs to be established
- Caveat is relevance to PLWH therefore conduct in association with clinical studies
- Collaboration is key
Pharmacological impact of antiretroviral therapy on platelet function to investigate human immunodeficiency virus-associated cardiovascular risk

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Background and purpose: Some clinical studies have reported increased myocardial infarction in people living with human immunodeficiency virus (HIV) taking the antiretroviral abacavir sulphate (ABC). Given that clinical studies contain confounding...
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