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Imperial College London

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

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25th Annual Conference of the British HIV Association Bournemouth 2019

P|B|G
Platelet Biology Group

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Competing interests disclosure

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

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- 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

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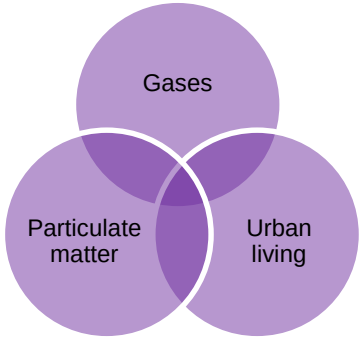
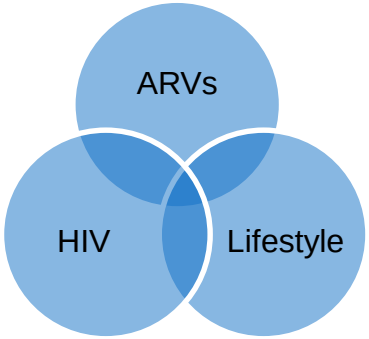
HIV and Cardiovascular Risk

- Cardiovascular risk is associated with:
  - Pollution
  - HIV

Potential drivers of pollution-associated cardiovascular risk



Potential drivers of HIV-associated cardiovascular risk



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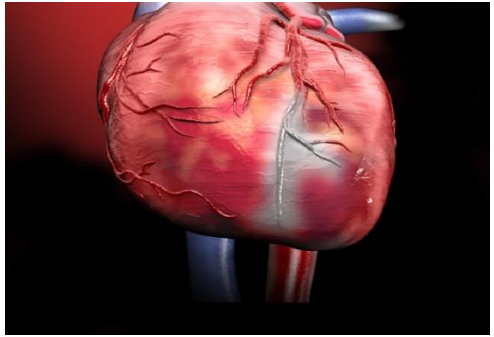
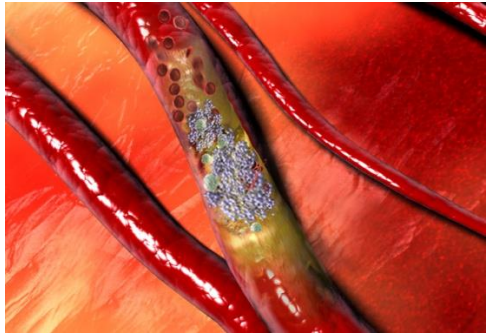
Platelets and Myocardial Infarction (MI)

Occluded coronary artery



Platelet-rich thrombus



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

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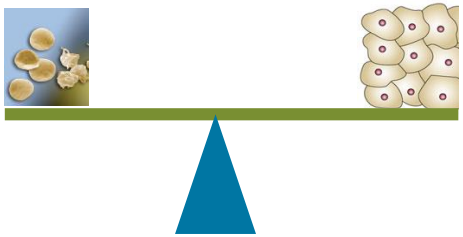
Platelets and endothelium: A question of balance

Platelet activation
- Collagen
- ADP/adrenaline

Inhibition of activation
- Nitric oxide
- Prostacyclin



Health

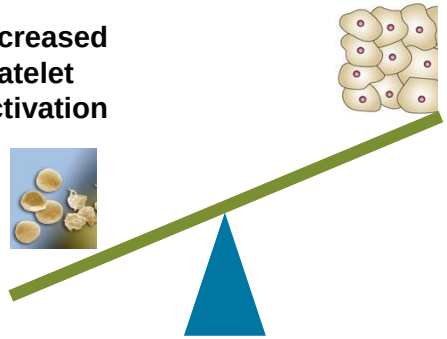
Low cardiovascular risk

Cardio-protective processes

Mechanisms of cardiovascular risk

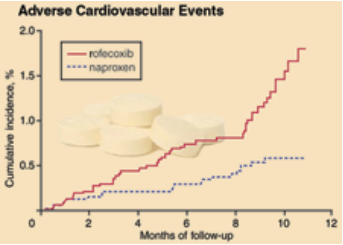
Endothelial dysfunction

Increased platelet activation



Heart attack

High cardiovascular risk



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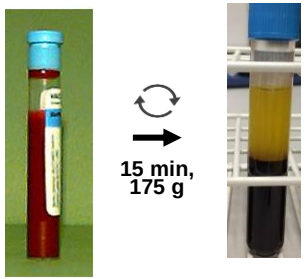
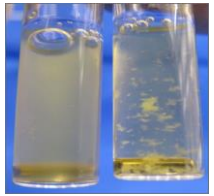
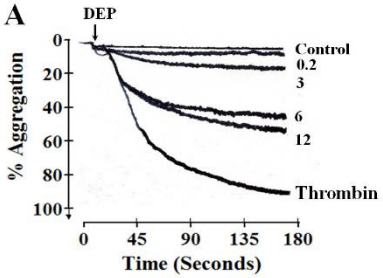
Platelet aggregometry assay

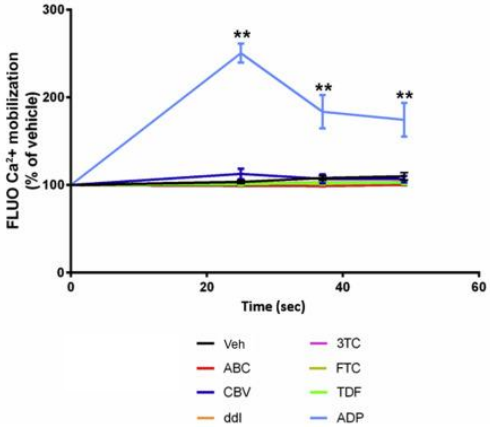


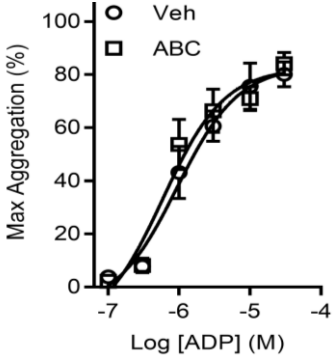
- Human blood
- HIV-
- Platelet rich plasma

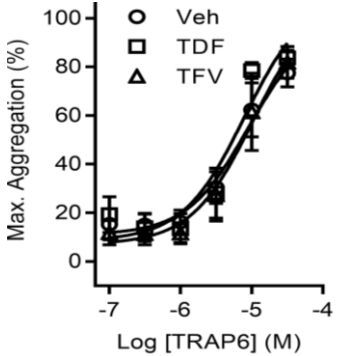


- Platelet aggregation = light transmission
- Plate based approach









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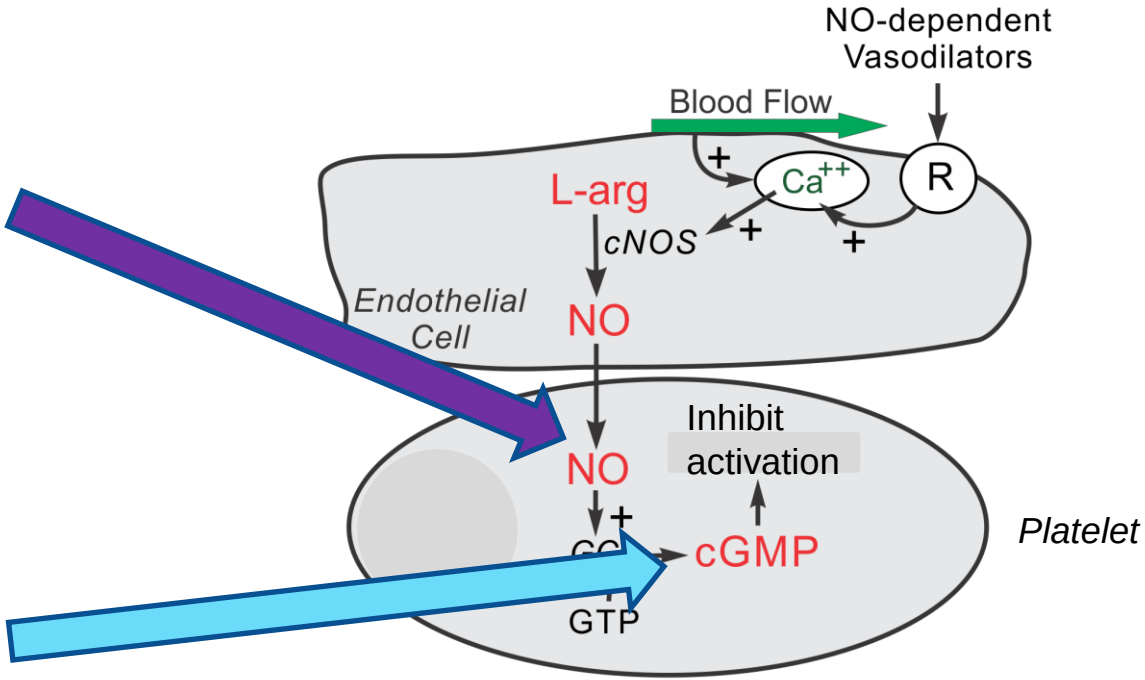
Nitric oxide: the good stuff



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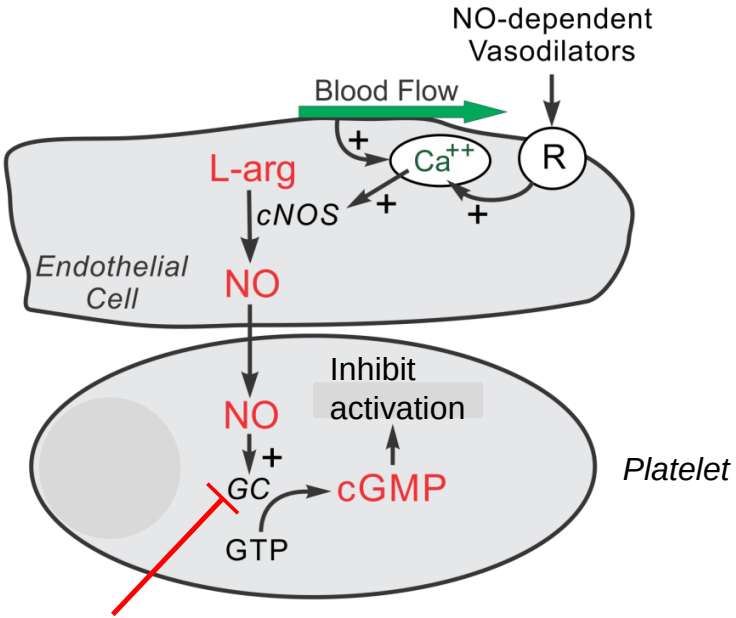
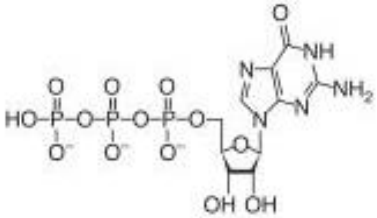
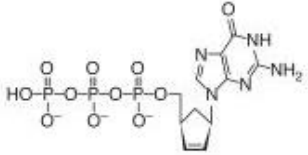
Abacavir: proposed mechanism

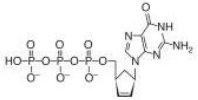




GTP



CTP



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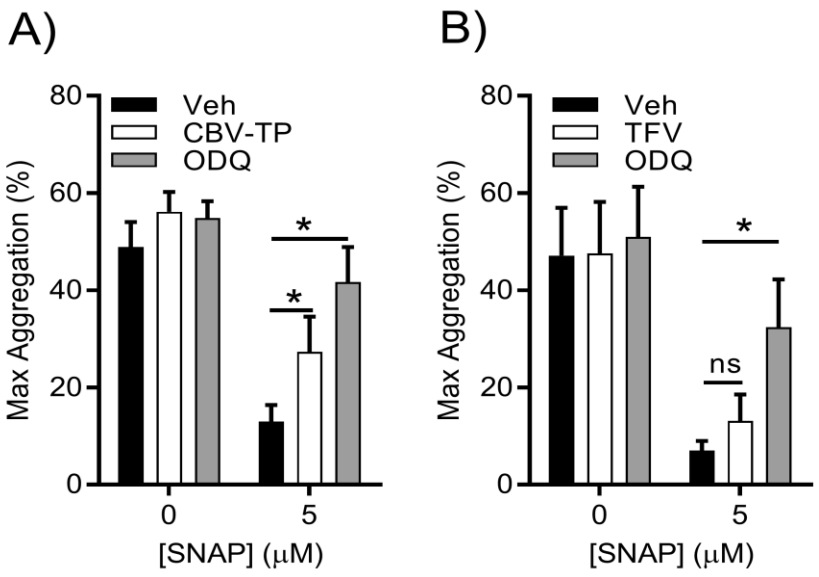
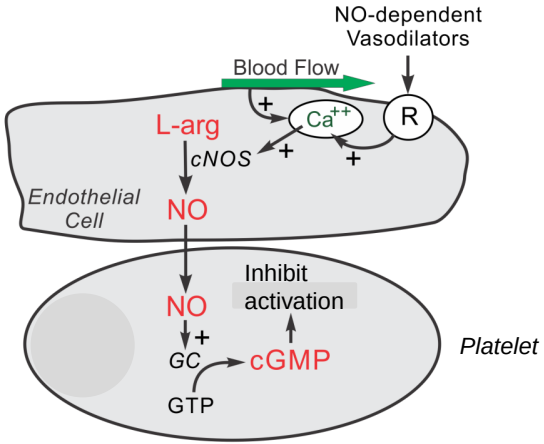
Abacavir: exploring a mechanism





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

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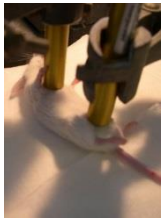
Comparative ARV effects *in vivo*



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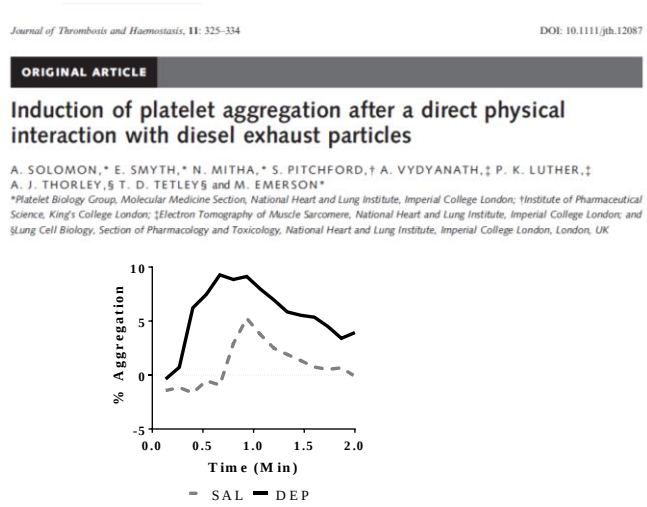
CONCORDAT ON OPENNESS ON ANIMAL RESEARCH IN THE UK



Journal of Thrombosis and Haemostasis, **11**: 325–334 DOI: 10.1111/jth.12087

ORIGINAL ARTICLE

Induction of platelet aggregation after a direct physical interaction with diesel exhaust particles

A. SOLOMON,* E. SMYTH,* N. MITHA,* S. PITCHFORD,† A. VYDYANATH,‡ P. K. LUTHER,‡ A. J. THORLEY,§ T. D. TETLEY§ and M. EMERSON*

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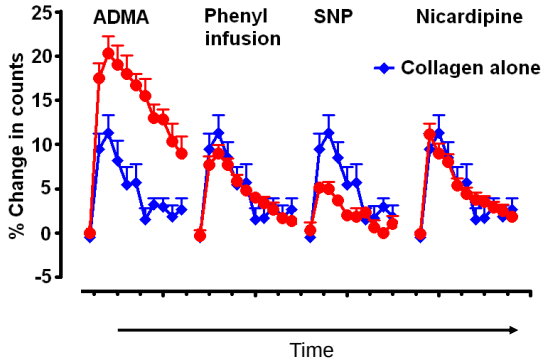

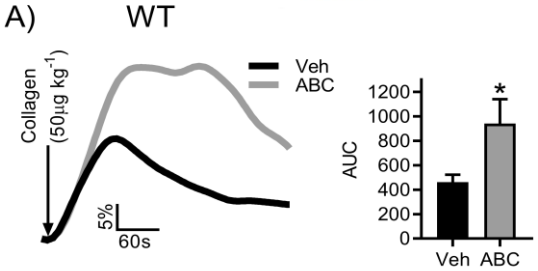

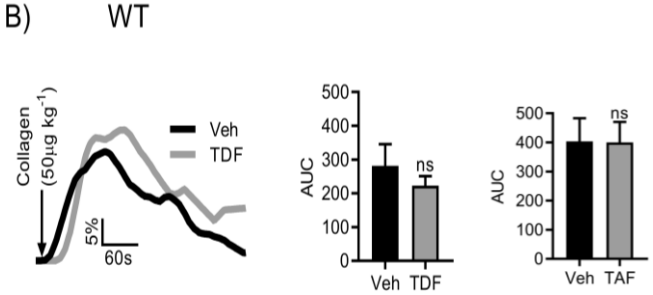

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What does it all mean?

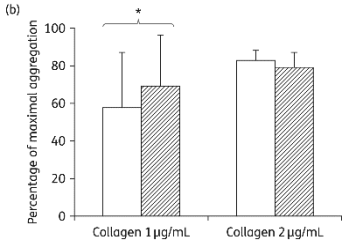
- ARVs induce platelet activation to different extents
- Are our studies relevant to PLWH?
  - *Relevance of dosing*
  - *Relevance of individual ARVs*

J Antimicrob Chemother 2016; **71**: 3506–3509
doi:10.1093/jac/dkw303 Advance Access publication 11 August 2016

Journal of Antimicrobial Chemotherapy

Abacavir has no prothrombotic effect on platelets *in vitro*

Yacouba L. Diallo[1], Véronique Ollivier[1], Véronique Joly[2,3], Dorothée Faille[1,3,4], Giovanna Catalano[2,3], Martine Jandrot-Perrus[1,3,4], Antoine Rauch[5], Patrick Yeni[2,3] and Nadine Ajzenberg[1,3,4]*



Increased Platelet Reactivity in HIV-1–Infected Patients Receiving Abacavir-Containing Antiretroviral Therapy

Claudette S. Satchell,[1] Jane A. O'Halloran,[2] Aoife G. Cotter,[2] Aaron J. Peace,[3] Eileen F. O'Connor,[2] Anthony F. Tedesco,[3] Eoin R. Feeney,[1] John S. Lambert,[2] Gerard J. Sheehan,[2] Dermot Kenny,[3] and Patrick W. G. Mallon[1,2]

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Why platelets as surrogates?

- Studies are potentially **predictive**

- Cardiovascular effects conclusively linked with **individual** ARVs
- Purely basic studies require confirmation in clinical studies

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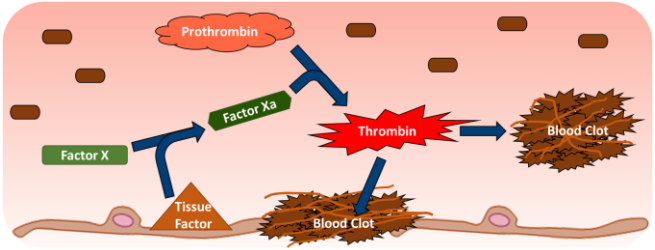
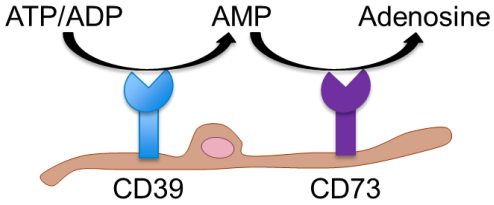
Endothelial cells

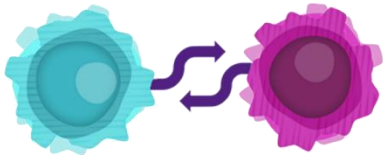
ARVs impact endothelial pro-coagulant properties



ARVs impact endothelial anti-thrombotic properties



How do ARVs impact platelet-endothelial crosstalk?



Poster: P022

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]

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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

Further details…..

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DOI: 10.1111/bph.14589

RESEARCH PAPER

BJP BRITISH PHARMACOLOGICAL SOCIETY

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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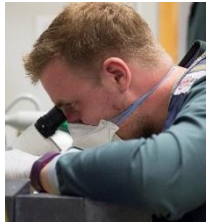
- Antonia Solomon
- Chris Moore
- Sarah Jones
- David Sanz-Rosa
- Lisa-Marie Holbrook

Collaborators:

- Marta Boffito (Imperial, Chelsea and Westminster)
- Brian Gazzard (SSAT)
- Myra McClure (Imperial)
- Xinzhu Wang (Imperial)
- Terry Tetley (Imperial)
- Alan Winston (Imperial, St Mary's)
- Mark Nelson (Imperial, Chelsea and Westminster)



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