The impact of abacavir sulphate and tenofovir on platelet function *in vitro* and *in vivo*

Smyth E[1], Nelson M[2], Emerson M[1]

[1] Platelet Biology Group and [2] Chelsea and Westminster NHS trust, National Heart and Lung Institute, Imperial College London, London, UK.

Background

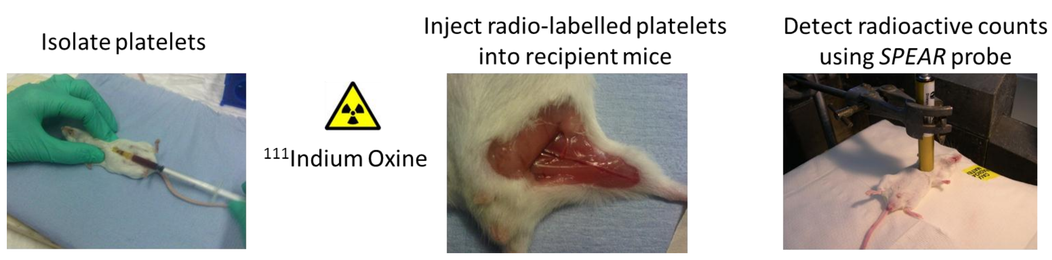
- Highly active antiretroviral therapy (HAART) has considerably improved the life expectancy of HIV-infected individuals.
- Nucleoside reverse transcriptase inhibitor (NRTI) abacavir sulphate, may also be associated with increased risk of cardiovascular complications such as myocardial infarction (MI).
- Platelet aggregation underlies thrombotic events such as MIs.

Aims

- To assess the potential impact of two NRTIs, abacavir sulphate and tenofovir on cardiovascular risk by assessing their impact on the function of healthy platelets *in vitro* and *in vivo.*

Methods

- Platelet aggregation was investigated *in vitro* by measuring changes in light transmission in isolated human platelets.
- Platelet aggregation was measured *in vivo* in anaesthetised C57bl/6 mice by measuring radiolabelled platelet thromboembolism in the pulmonary vasculature.



Results

- Tenofovir significantly inhibited collagen (A) and thrombin (B) induced platelet aggregation *in vitro.*
- Abacavir sulphate had no effect on agonist-induced platelet aggregation *in vitro.*

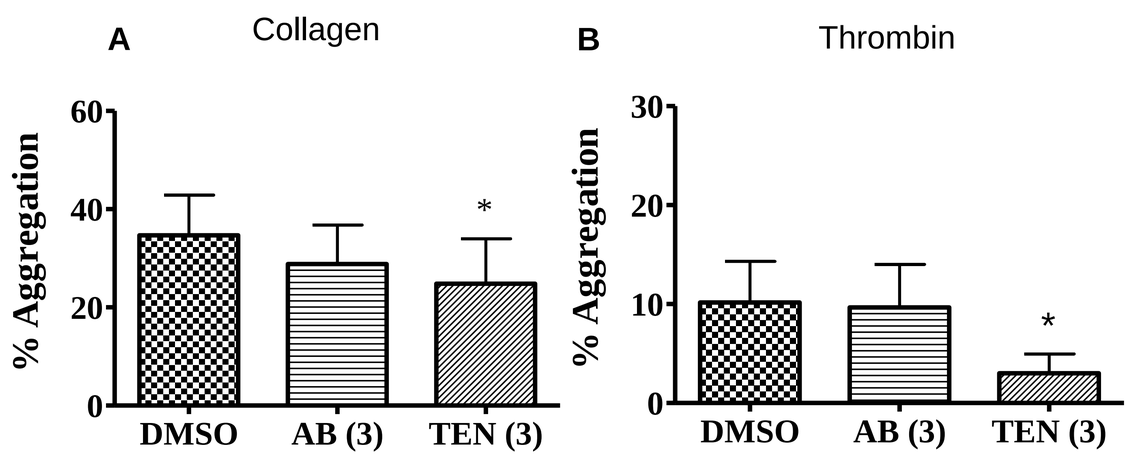


Figure 1. The effect of abacavir sulphate and tenofovir on thrombin and collagen - induced platelet aggregation *in vitro*.
Isolated human platelets were incubated with abacavir sulphate (AB) (3 µg/ml), tenofovir (TEN) (3 µg/ml) or vehicle (DMSO 0.2 %) for 10 minutes and then stimulated with EC50 concentrations of thrombin (0.06 U/ml) (B) or collagen (0.3 µg/ml) (A) . Platelet aggregation was detected as changes in light transmission and reported as maximum percentage change in light transmission. Data is presented as mean±SEM percentage platelet aggregation. * = P < 0.05 compared to DMSO using a one-way repeated measures ANOVA with bonferroni post hoc analysis. N = 6.

Results

- Acute administration of abacavir sulphate (30 minutes) enhanced collagen-induced platelet aggregation *in vivo* but tenofovir had no effect.

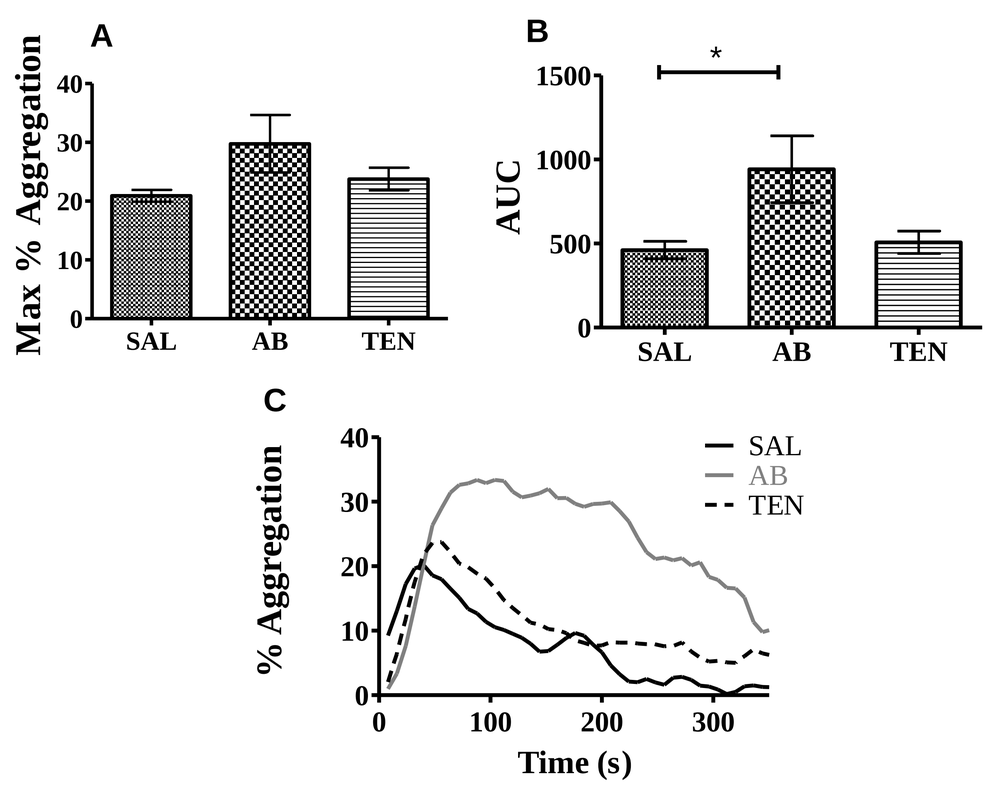


Figure 2. The acute effect of abacavir sulphate and tenofovir on platelet aggregation *in vivo*.
Anaesthetised C57bl/6 mice (urethane 25 % w/v) were intraperitoneal (*i.p.*) administered with abacavir sulphate (AB) (30 µg/ml), tenfovir (TEN) (30 µg/ml) or saline (SAL) (0.9 %) 30 minutes prior to being intravenously administered (*i.v.*) with collagen (50 µg/kg). Changes in the maximum percentage increase in platelet aggregation (A) and area under the curve (AUC) were measured (B). Data is presented as mean±SEM (A-B) or representative traces (C), *P < 0.05 compared using a one-way test ANOVA with bonferroni post hoc analysis. N = 7-8.

- Neither abacavir sulphate nor tenofovir had any effect on collagen-induced platelet aggregation *in vivo* following a chronic exposure (3-4 hours).

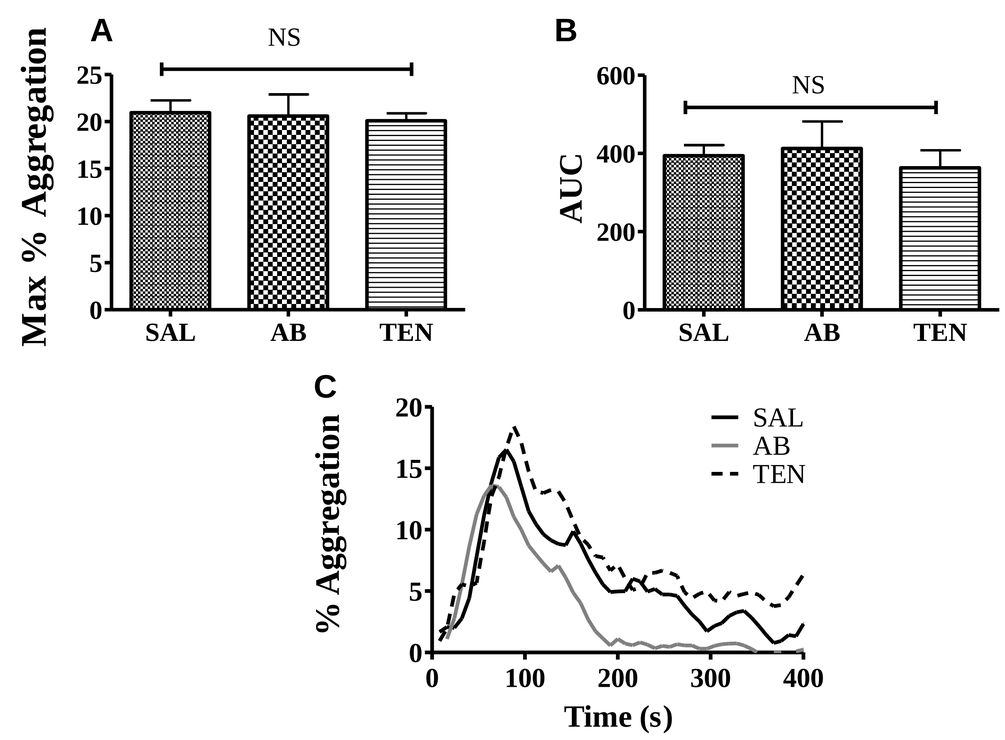


Figure 3. The chronic effect of abacavir sulphate and tenofovir on platelet aggregation *in vivo*.
C57bl/6 mice were intraperitoneal (*i.p.)* administered with abacavir sulphate (AB) (30 µg/ml), tenfovir (TEN) (30 µg/ml) or saline (SAL) (0.9 %) and following 3-4 hours were anaesthetised (urethane 25 % w/v) and intravenously administered (*i.v.*) with collagen (50 µg/kg). Changes in the maximum percentage increase in platelet aggregation (A) and area under the curve (AUC) were measured (B). Data is presented as mean±SEM (A-B) or representative traces (C), *P < 0.05 compared using a one-way test ANOVA with bonferroni post hoc analysis. N = 6.

Conclusions

- Tenofovir may offer protection against platelet-driven thrombotic events *via* a direct action on the platelet.
- Abacavir sulphate has no direct effect on platelets but when administered systemically may enhance the risk of MI by an indirect effect on platelets.

Administration of abacavir sulphate to patients may increase the risk of MI by indirectly affecting platelets