Background: Current and recent use of the nucleaside reverse transcriptase inhibitor, abacavir (ABC) has been associated with increased risk of myocardial infarction, with both endothelial dysfunction and altered platelet reactivity with ABC use implicated.
Methodology: Changes in markers of platelet function were examined in a sub-study of the SWIFT trial, a prospective, randomised, 48-week trial of virally suppressed, protease-inhibitor-treated, HIV-1 positive subjects randomised to switch abacavir/ lamivudine (ABC/3TC) to tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) or remain on ABC/3TC. Soluble glycoprotein VI (sGPVI), a marker of collagen-mediated platelet activation, and soluble P-selectin (sP-sel), involved in platelet-leukocyte interactions, were measured by enzyme-linked immunosorbent assays (Meso Scale Discovery, Rockville, MD) in stored plasma samples collected at weeks 0, 4, 12, 24, 36 and 48. Changes in platelet markers over time were assessed using mixed effect models. Data are mean [SD] unless specified.
Results: Of 312 patients (age 46 [9.3] years, 85% male, 65% Caucasian), 156 switched to TDF/FTC. Groups were well matched for baseline demographic and laboratory data including CD4+ T-cell count (TDF/TFC versus ABC/3TC, 548 [257], 582 [287] /µl respectively), platelet count (244 [58], 253 [72] x10^3/µl), total cholesterol (5.4 [1.2], 5.3 [1.0] mmol/L), LDL (3.1 [1.0], 3.1 [0.8] mmol/L) and HDL (1.29 [0.38], 1.31 [0.42] mmol/L) cholesterol and history of dyslipidaemia or hypertension. There were no between-group differences in baseline sGPVI (mean (SEM) 3.75 [0.25] ng/ml versus 3.61 [0.22] ng/ml, p=0.68) or sP-sel (65.0 [2.2] ng/ml versus 69.2 [2.9], p=0.25) and no between-group differences in change in sP-sel from baseline to 48 weeks (p=0.37, figure 1b). However, relative to the ABC/3TC group, sGPVI increased to week 48 in those who switched to TDF/FTC (effect size +0.012 (95%CI 0.0041, 0.02), between group p=0.002, figure 1a). This effect persisted when corrected for age, ethnicity, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and change from baseline to week 48 in creatinine, LDL, HDL, CD4+ T-cell and platelet count.
Conclusions: The observed increases in sGPVI point to changes in intrinsic platelet function with a switch away from ABC/3TC to TDF/FTC. Further mechanistic research is required to determine the relevance of these changes to overall platelet reactivity and cardiovascular disease.

Effect of Switch from Abacavir to Tenofovir DF on Platelet Function Markers: a SWIFT Trial Sub-study

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Introduction

•Current and recent use of the nucleoside reverse transcriptase inhibitor, abacavir (ABC) has been associated with increased risk of myocardial infarction (MI) [1-3]. To date, no such association has been found with tenofovir disoproxil fumarate (TDF) in these studies.

•This association has not been observed consistently however, raising doubts over the robustness of the observation[4, 5].

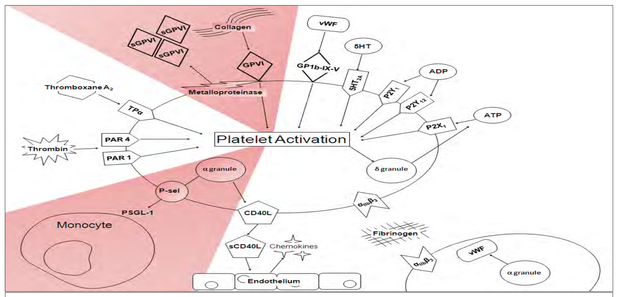
•Several potential underlying mechanisms, such as changes in vascular endothelial function[6] and platelet activation[7], have been proposed.

• Glycoprotein VI (GPVI) is a platelet membrane glycoprotein receptor that plays a pivotal role in collagen-mediated platelet activation and aggregation[8].

•GPVI, present on the platelet surface, is cleaved in response to GPVI ligands such as collagen and shed from the platelet surface in a metalloproteinase-dependent manner, resulting in soluble GPVI.

•P-selectin (P-sel) is a cell adhesion molecule that mediates interactions of leukocytes and platelets with the endothelium[9].

•P-sel is stored in its inactivated form in both platelets and endothelial cells and upon activation is rapidly transported to the cell surface.



Pathways of platelet activation. PAR 1, Proteinase- activated receptor 1; PAR 4, proteinase- activated receptor 4; TP_α, thromboxane protanoid receptor alpha; GP, glycoprotein; sGPVI, soluble glycoprotein VI; vWF, von Willebrand factor; 5HT, serotonin; $5HT_{2a}$, serotonin receptor 2A; ADP, adenosine diphosphate; $P2Y_1$, P2Y purinoreceptor 1; $P2Y_{12}$, P2Y purinoreceptor 12; ATP, adenosine triphosphate; $P2X_1$, P2X purinoreceptor 1; sCD40L, soluble CD40 ligand; P- sel, P-selectin; PSGL-1, P-selectin glycoprotein ligand-1.

Objective

To examine changes in markers of platelet function in a sub study of the SWIFT trial, a prospective, randomised, 48-week trial of virally suppressed, protease-inhibitor-treated, HIV-1 positive subjects randomised to switch abacavir/ lamivudine (ABC/3TC) to tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) or remain on ABC/3TC.

Methods

•Markers of platelet activation were measured using enzyme-linked immunosorbent assays on stored plasma samples collected at weeks 0, 4, 12, 24, 36 and 48.
•Changes in platelet markers over time were assessed using mixed effect models corrected for age, ethnicity, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and change from baseline to week 48 in creatinine, LDL, HDL, CD4+ T-cell and platelet count.
•The study team was blinded to subject randomization until data analysis was complete.

Results

Of 312 subjects, 156 were randomised to switch to TDF/FTC. Groups were well matched for baseline demographic and laboratory parameters (Table 1). There was no between group difference at baseline for sGPVI or sP-selectin (Figure 1). There was no between-group difference in change in sP-selectin from baseline to 48 weeks using mixed effects models (p=0.37).

Table 1. Baseline demographics and laboratory parameters

Characteristic	TDF/FTC n=156	ABC/3TC n=156
Age (years)	46.0 (9)	46.7 (9.7)
Male [N (%)]	130 (83.3)	134 (85.9)
Caucasian ethnicity [N (%)]	97 (62.2)	106 (67.9)
History of dyslipidaemia [N (%)]	88 (56.4)	102 (65.4)
History of hypertension [N %]	49 (31.4)	50 (32.1)
CD4+ T cell count (/ul)	548 (257)	582 (287)
Platelets (x 10^3/ul)	244 (58)	253 (72)
Cholesterol (mmol/L)	5.44 (1.19)	5.32 (1.02)
LDL- cholesterol (mmol/L)	3.13 (0.99)	3.05 (0.83)
HDL- cholesterol (mmol/L)	1.29 (0.38)	1.31 (0.42)

Data are mean (SD) unless otherwise indicated. LDL = low density lipoprotein. HDL = high density lipoprotein.

Figure 1. sGPVI and sP- selectin at baseline

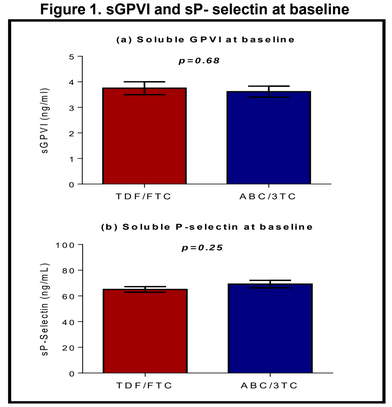
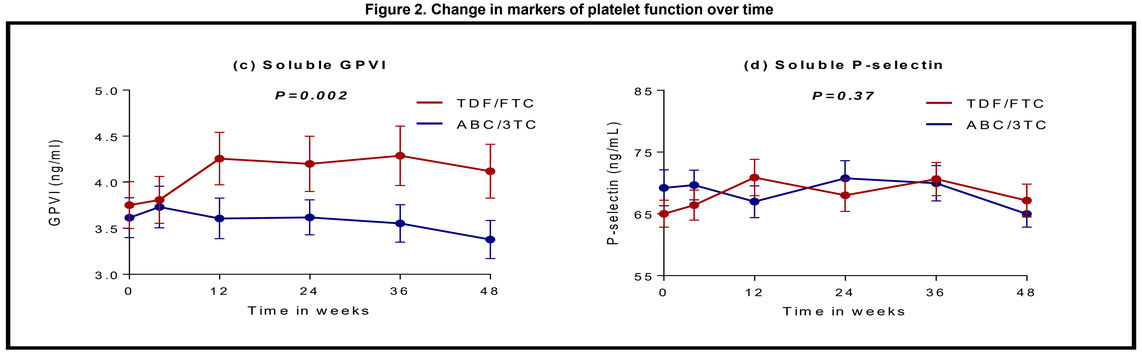


Figure 2. Change in markers of platelet function over time



Soluble GPVI increased from baseline to week 48 in those who switched from ABC/3TC to TDF/FTC, (effect size +0.012 (95%CI 0.0041, 0.02), between group p=0.002, figure 2a).

This effect persisted when corrected for age, ethnicity, history of dyslipidaemia or hypertension, baseline CD4+ T-cell and platelet count and change from baseline to week 48 in creatinine, LDL, HDL, CD4+ T-cell and platelet count.

Conclusions

The observed increases in sGPVI point to changes in intrinsic platelet function with a switch away from ABC/3TC to TDF/FTC.

Regarding the changes observed in sGPVI, possible interpretations include:

1. **Increased GPVI receptor expression on the platelet surface leading to increased cleavage.**

   ABC decreases availability of GPVI on the platelet surface and a switch to TDF results in increased GPVI receptor availability for cleavage and therefore increased measurable sGPVI levels.

2. **Alteration in metalloproteinase dependant cleavage of GPVI receptor from the platelet surface.**

   Decreased metalloproteinase function in the presence of ABC is reversed on switching to TDF resulting in increased cleavage and increased measurable sGPVI.

These mechanisms are consistent with ABC induced platelet dysfunction and are in keeping with other studies showing an association with ABC, platelet dysfunction and MI.

3. **Change in the availability of factors, such as collagen, that stimulate receptor engagement and result in cleavage of GPVI.**

   Switching to TDF results in increased availability of collagen, leading to increased GPVI receptor engagement.

However, there is currently no data to support an association between platelet dysfunction and TDF or increased MI risk with TDF use.

Further mechanistic research is required to determine the relevance of these changes to overall platelet reactivity and to cardiovascular disease

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