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Switching from abacavir to tenofovir disoproxil fumarate is associated with rises in soluble glycoprotein VI (sGPVI), suggesting changes in platelet collagen interactions.

Running head: Platelet biomarkers in treated HIV infection

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Abstract

Objectives

Altered platelet function has been proposed as an underlying mechanism to explain increased risk of MI in people living with HIV (PLWH) associated with use of the nucleoside reverse transcriptase inhibitor abacavir (ABC). We aimed to examine changes in platelet biomarkers in PLWH switching from ABC.

Methods

In a prospective, 48-week sub-study, of virally suppressed, HIV-1 positive subjects randomised to remain on ABC/lamivudine (ABC/3TC) or switch to tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), we measured soluble glycoprotein VI (sGPVI), soluble P-selectin (sP-sel), soluble CD40 ligand (sCD40L) and von Willebrand factor (vWF) in plasma collected overtime and assessed differences using mixed effect models.

Results

Of 312 randomised, 310 were included in the analysis. Mean [SD] age 46.4 [9.3] years, 262 (85%) male and 201 (65%) white. At baseline there was no significant between-group difference in sGPVI (TDF/FTC 3.75 [0.25] versus ABC/3TC 3.61 [0.22] ng/ml, $p=0.69$). Greater increases in sGPVI from baseline to week 48 occurred in those switched from ABC/3TC (effect size +0.57 ng/ml, 95% CI; 0.2- 0.94, $p=0.003$). There was no significant baseline difference or change overtime in sP-sel, sCD40L or vWF between groups.

Conclusions

The significant increases in sGPVI that occur with a switch from ABC/3TC are consistent with changes in platelet function centred on platelet/collagen interactions as an underlying mechanism to explain increased risk of MI with ABC.

Keywords: Abacavir, Cardiovascular Disease, HIV, Platelet Function, Glycoprotein VI

Introduction

People living with HIV (PLWH) are at higher risk of cardiovascular disease (CVD) and myocardial infarction (MI), with increased prevalence of traditional CVD risk factors, HIV infection itself and exposure to antiretroviral therapy (ART) all implicated. The Data collection on Adverse events of Anti-HIV Drugs (D:A:D) study, a large, international, prospective, observational cohort study designed to ascertain associations between exposure to ART and MI in PLWH^[1] identified an unexpected, reversible association with current or recent use of the nucleoside reverse transcriptase inhibitor, abacavir (ABC)^[2]. Although the association between MI and ABC exposure has been reported in a number of studies, it has not been consistently observed^[3, 4]. However, an updated analysis of the D:A:D cohort, examining data from the five years since the initial ABC observation, upheld the finding despite a channelling bias away from ABC use in the intervening period in those with high underlying CVD risk^[5].

Several potential mechanisms have been proposed to explain the association between ABC exposure and MI including altered endothelial function, increased inflammation, and platelet activation, all of which can modify CVD risk^[6-8]. Given the reversible character of the observation between ABC and MI observed in D:A:D (strongest association in subjects with current or recent ABC use) altered platelet activation has been proposed as an underlying mechanism, with increased platelet activation assessed by aggregometry observed in PLWH on ABC in cross-sectional studies^[7, 8], but no differences observed when a limited number of circulating biomarkers of platelet function were examined in a randomised study of virally-suppressed, ART-treated subjects switching to ABC^[9].

To further investigate the role of ABC on platelet function we aimed to examine the effect of switching from ABC-containing ART on an expanded set of circulating platelet function biomarkers in a prospective, randomized, controlled trial.

Methods

We conducted a platelet biomarker sub-study on stored samples taken from the 'Study to Evaluate Efficacy and Safety of Switching to Emtricitabine/Tenofovir from Lamivudine/Abacavir in Virologically Suppressed HIV-1 Infected Patients on a Boosted Protease Inhibitor Containing Antiretroviral Regimen' or SWIFT study, which was a prospective, randomised, open-label, multicentre, 48 week study to evaluate the safety and efficacy of switching from fixed dose combination (FDC) abacavir/ lamivudine (ABC/3TC) to FDC tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC) in virologically-suppressed, HIV-1 infected subjects on protease inhibitor-containing ART (Clinical trials.gov identifier, NCT00724711)^[10]. The study recruited adults (>18 years) on ABC/3TC with HIV-1 RNA <200 copies/ml for three months. Detailed descriptions of the study design and virological endpoints have been described elsewhere^[10]. The study was approved by local regulatory authorities and subjects provided written informed consent.

Study visits were performed at baseline, 4, 12, 24, 36 and 48 weeks. Routine laboratory parameters were measured at each visit and plasma samples stored at -80°C for subsequent analysis. The platelet biomarker sub-study included all subjects for whom stored plasma was available at one or more time points.

The following circulating platelet biomarkers were measured batched, in duplicate, with the operators blinded to randomised treatment allocation and results subject to a pre-specified analysis plan:

Soluble P-selectin (sP-sel), measured by electrochemiluminescence using commercially available kits (Human P-Selectin Kit, Meso Scale Discovery, Rockville, USA), with a mean intra- and inter-assay co-efficient of variation (CV) of 4.7% and 8.8% respectively.

Soluble glycoprotein VI (sGPVI) and soluble CD40 ligand (sCD40L), measured using electrochemiluminescence assays developed in conjunction with Meso Scale Discovery (MSD), Rockville, USA, with mean intra- and inter-assay CV for sGPVI of 3.4% and 11.5% and sCD40L of 3.2% and 9.7% respectively.

Von Willebrand factor (vWF), measured by enzyme-linked immunosorbent assay, (Von Willebrand Factor BioassayTM ELISA Kit, US Biological, Massachusetts, USA), with mean intra- and inter-assay CV of 6.4% and 20.4% respectively. To reduce the impact of inter-assay variability, samples from all time points for an individual were run on a single 96-well plate for each marker.

The primary aim of the platelet biology sub-study was to examine change in platelet biomarkers over time. Continuous and categorical clinical parameters were expressed as mean [standard deviation (SD)] and percentages respectively. Platelet markers were expressed as mean and standard error of mean [SEM]. Between-group differences in platelet markers at baseline were compared using two-sample independent student *t* test. The difference in absolute change in platelet markers over time between groups was assessed using mixed effects regression models with adjustment for potential influential baseline covariates. *P* values of <0.05 were considered statistically significant. Analyses were performed using STATA 12.1 (College Station, Texas) and Graph Pad Prism 6.0 (GraphPad Software Inc, San Diego, USA).

Results:

Of 312 participants from the original SWIFT study, stored samples were available for 310 subjects who received at least one dose of study drug. Average age was 46.4 [9.3] years, 262 (85%) were male, 201 (65%) were white and 80 (26%) were smokers. At baseline, the average CD4+ T-cell count was 564 [273] cells/mm³, 284 (92%) subjects had HIV RNA <50 copies/ml with 56 (18%) subjects reporting a previous AIDS diagnosis. Both treatment arms were well matched at baseline for demographics and laboratory parameters (table 1). 138 subjects in the

TDF/FTC arm and 139 in the ABC/3TC arm completed 48 weeks of the study. There was no significant change in platelet count in either group from baseline to 48 weeks.

At baseline there was no significant between-group difference in sGPVI (TDF/FTC 3.75 [0.25] versus ABC/3TC 3.61 [0.22] ng/ml, $p=0.69$) and this remained unchanged to week 4. However, by week 12 sGPVI had increased in those switched away from ABC/3TC and persisted at all timepoints out to week 48, with significant between-group differences in change in sGPVI occurring in those who switched away from ABC/3TC to TDF/FTC compared to those who remained on ABC/3TC (unadjusted effect size +0.57 ng/ml, 95% CI; 0.2 to 0.94, $p=0.003$, figure 1a), an effect that persisted when corrected for age, gender, ethnicity, smoking status, history of hypertension, lipid lowering agents use, non-steroidal anti-inflammatory agents use including aspirin, creatinine, baseline CD4+ T cell and platelet counts (adjusted effect size +0.59 ng/ml, 95% CI; 0.2 to 0.98, $p=0.003$). Further adjustment for changes in creatinine or changes in total cholesterol, LDL or HDL did not alter the findings (adjusted effect size +0.58 ng/ml, 95% CI; 0.2 to 0.96, $p=0.006$).

In contrast no between-group differences in baseline or change over 48 weeks in sP-sel, sCD40L or vWF were observed (figure 1b-d, all $P>0.2$).

Discussion

This is the first prospective, randomised study to demonstrate a significant change in sGPVI with a switch away from ABC/3TC to TDF/FTC, offering insights into a potential pathogenesis linking ABC to increased risk of MI. The differences in sGPVI observed in this study suggest an effect mediated through collagen-platelet interactions, which are involved in altering platelet reactivity, and are consistent with previous studies demonstrating enhanced platelet reactivity in response to collagen in those exposed to ABC^[7].

Several studies have examined platelet biomarkers prospectively in PLWH on ABC, but none have examined sGPVI. In one, small, case-control study, patients initiating ABC-containing ART had significantly higher levels of platelet function markers sP-sel, soluble glycoprotein V (sGPV) and secretory phospholipase A2 (sPLA2) but not sCD40L at follow-up compared with those commenced on TDF-based ART^[11]. In contrast, a platelet biomarker sub study of the STEAL study, which randomised virally-suppressed HIV-positive subjects on stable ART containing an NRTI, to switch to either TDF/FTC or ABC/3TC, did not observe any significant between-group difference in sP-sel, a biomarker linked to platelet activation pathways driven by inflammation and platelet leucocyte interactions, at 12 weeks after switch^[9]. Similar findings were seen in a sub-study from the BICOMBO study which also randomised subjects to switch their NRTI backbone to ABC/3TC or TDF/FTC^[12]. Consistent with these studies, we did not observe a significant difference in sP-sel, suggesting that any impact on platelet function by ABC is not mediated through pathways that initiate inflammation or platelet leucocyte interactions.^[13]

GPVI is solely expressed on the surface of platelets and megakaryocyte precursors and is the principal platelet receptor for collagen^[14]. Under resting conditions, the majority of GPVI remains intact on the platelet surface. Metalloproteinase-dependant cleavage of the 55 KD ectodomain of GPVI, results in the formation of sGPVI^[15] with shedding increased in response to collagen exposure, binding of other ligands such as factor Xa or by high shear flow within blood vessels^[16, 17]. Under physiological conditions, regulation of proteolytic cleavage of GPVI represents an important homeostatic mechanism by controlling platelet surface GPVI levels and subsequent downstream platelet activation^[18].

The exact function of cleaved, circulating sGPVI has not yet been fully elucidated. However, imbalances between platelet bound and soluble GPVI have been observed in studies of non-HIV populations with MI and stroke^[19-21]. In one large study of 2,438 subjects with symptomatic CVD, decreased levels of sGPVI and increased levels of platelet-bound GPVI were observed in patients with ST elevation and non-ST elevation MI compared to subjects with stable angina pectoris (SAP)^[21]. In this study the percentage difference for sGPVI between SAP and non-ST elevation MI was 13% and for ST- elevation MI 15.3%, in keeping with the percentage change of 17.5% observed between groups at 48 weeks in our study suggesting clinical significance differences.^[22]

Although reduced sGPVI observed in those who remained on ABC/3TC in our study, coupled with previous studies of increased platelet reactivity with ABC, are consistent with disturbed platelet-collagen interactions associated with ABC, further research examining the effect of ABC exposure on platelet-bound GPVI is needed to further explore this hypothesis.

This study has limitations. Although randomised, the study design prevents definitive attribution of the changes in sGPVI to the removal of ABC/3TC versus addition of TDF/FTC, however use of TDF/FTC has not been associated with either altered platelet reactivity or increased MI risk, having been associated with decreased CVD risk in a recent study^[23]. As stored samples were used, we were limited to examining circulating markers and were unable to measure platelet-bound GPVI. As with the majority of ART switch studies, we did not ascertain clinical cardiovascular endpoints. Although sGPVI was the only marker of platelet function to demonstrate between-group differences, that the observed changes were consistently seen over several consecutive timepoints in a randomised study suggests this observation did not arise by chance. In addition, that sGPVI alone is altered with switch away from ABC/3TC arguably strengthens the hypothesis that changes in platelet function, focused on platelet-collagen interactions explains the clinical observations of increased MI risk with use of ABC.

In conclusion, in subjects randomised to switch from ABC/3TC to TDF/FTC we observed significant increases in sGPVI. These data coupled with studies showing increased platelet reactivity with ABC exposure build a consistent mechanistic picture of altered platelet function centered on platelet-collagen interactions to explain increased MI rates in ABC-treated patients.

Acknowledgements

PWG Mallon & D Kenny designed the study; JA O'Halloran, E Dunne and S Denieffe performed research; JA O'Halloran, E Dunne, W Tinago, S Denieffe, D Kenny and PWG Mallon analysed and interpreted the data; JA O'Halloran, PWG Mallon wrote the manuscript.

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ACCEPTED

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Table 1. Baseline characteristics by allocated treatment group

	Switch TDF/FTC		Continue ABC/3TC	
Age (years)	46.0	9	46.7	9.7
Male Gender (N%)	129	83.2%	133	85.8%
Non-Hispanic Ethnicity (N%)	117	75.5%	120	76.9%
Race				
White	96	61.9%	105	67.7%
Black	43	27.7%	44	28.4%
Asian	4	2.6%	3	1.9%
Other	12	7.7%	3	1.9%
AIDS (N%)	33	21.2%	23	14.7%
Protease inhibitor at baseline (N%)				
LPV/r	47	30.3%	52	33.5%
ATV/r	62	40.0%	61	39.4%
FPV/r	34	30.0%	30	19.4%
Other	12	7.7%	12	7.7%
Concomitant medication (N%)				
Aspirin	20	12.9%	23	14.7%
NSAIDS	24	15.5%	17	10.9%
Anti-hypertensive agents	41	26.5%	44	28.2%
Lipid lowering agents	97	62.6%	107	69.0%
Current smokers (N%)	38	24.5%	42	26.9%
Medical history (N%)				
Ischaemic heart disease	11	7.1%	7	4.5%
Hypertension	49	31.6%	50	32.1%
Dyslipidaemia	87	56.1%	102	65.4%
Diabetes mellitus	15	9.7%	15	9.6%
Lipodystrophy	17	11.0%	15	9.6%
Hepatitis B	1	0.6%	2	1.3%
Hepatitis C	6	3.9%	3	1.9%
Baseline observation				
Weight (kg)	81.9	16.9	82.3	15.6
Body mass index (kg/m ²)	27.2	5.8	27.2	5.0
Systolic BP (mm Hg)	124	14	125	15
Diastolic BP (mm Hg)	77	10	78	11
Laboratory data				
CD4 T cell count (cells/cm ³)	546	256	581	288
CD4 T cell count % (N%)	29	10	29	9.6
HIV RNA (copies/ml)	14	53	8	29

Cholesterol (mg/dL)	5.42	1.18	5.32	1.03
HDL (mg/dL)	1.30	0.39	1.32	0.42
LDL (mg/dL)	3.12	0.97	3.07	0.85
Triglycerides(mg/dL)	2.61	2.09	2.55	2.23
Glucose (mg/dL)	5.5	1.4	5.4	1.0
Creatinine Clearance (ml/min)	1.9	0.6	1.9	0.5
Creatinine ($\mu\text{mol/L}$)	83	17	84	18
Platelets ($10^9\mu\text{L}$)	244	58	253	72

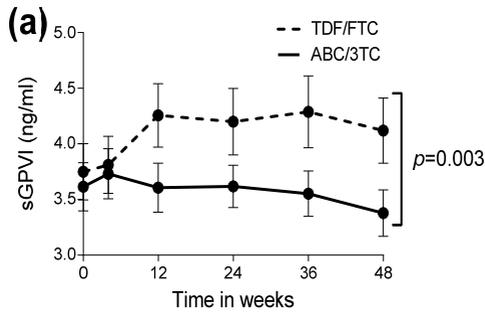
Values represent mean (SD) unless otherwise stated. TDF/FTC= tenofovir disoproxil

fumerate/ emtricitabine; ABC/3TC= abacavir/ lamivudine; LPV/r = lopinavir/ritonavir;

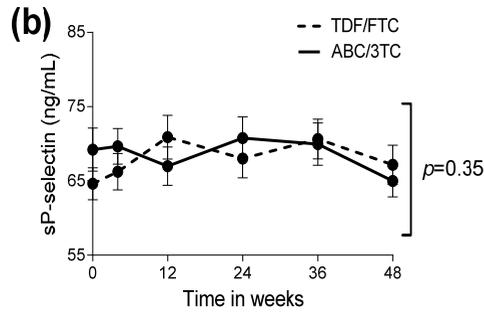
ATV/r= atazanavir/ ritonavir; FPV/r= fosamprenavir/ ritonavir; Kg = kilogram; BP= blood

pressure; HDL= high- density lipoprotein; LDL= low- density lipoprotein.

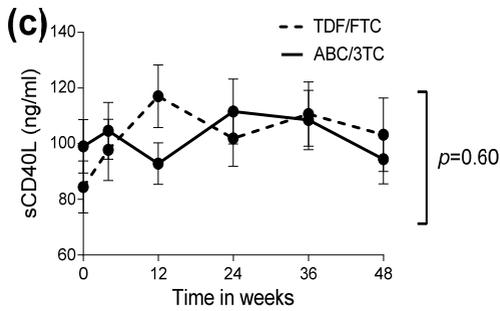
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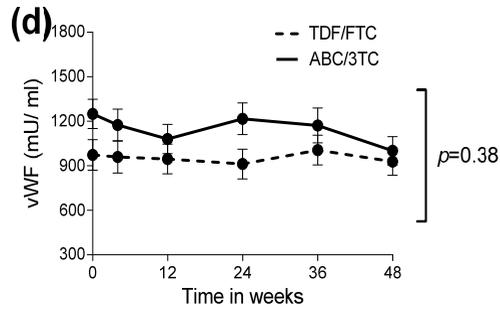
Week	0	4	12	24	36	48
TDF/FTC	155	155	148	145	139	138
ABC/3TC	154	153	152	147	142	138



Week	0	4	12	24	36	48
TDF/FTC	155	155	148	145	139	139
ABC/3TC	154	153	152	147	142	137



Week	0	4	12	24	36	48
TDF/FTC	154	155	148	144	139	135
ABC/3TC	154	153	150	147	141	135



Week	0	4	12	24	36	48
TDF/FTC	154	155	147	141	138	134
ABC/3TC	154	153	148	146	140	133

Figure 1. Platelet marker values over 48 weeks, (a) sGPVI, (b) sP-sel, (c) sCD40L and (d) vWF. Data are presented as mean and standard error of mean. *P*-value represents between- group differences in sGPVI, sP-sel, sCD40L and vWF as determined by mixed effects model. *P*value of <0.05 considered significant