Change in Soluble Glycoprotein VI When Switching From ABC/3TC to TAF/FTC

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Introduction

People living with HIV (PLWH) are at higher risk of cardiovascular disease (CVD) and myocardial infarction¹

Glycoprotein VI

Collagen

- Multifactorial etiology: traditional CVD risk factors, HIV infection, and antiretroviral therapy²
- ◆ Abacavir (ABC) has been associated with increased risk of cardiovascular events^{3,4}
- Altered platelet function implicated⁵
- Glycoprotein VI (GPVI)
- Platelet membrane receptor
- Regulates platelet activation in response to collagen exposure⁶
- Activity mediated through cleavage from the platelet surface by metalloproteinase, resulting in soluble GPVI (sGPVI), which can be measured in blood⁷
- Lower sGPVI levels observed in PLWH prior to onset of coronary artery disease events⁸
- In PLWH who are virologically suppressed, we demonstrated the following:
- On switching from ABC to tenofovir disoproxil fumarate, increases in sGPVI⁹
- On switching from ABC to tenofovir alafenamide (TAF), decrease in platelet reactivity in response to collagen and increases in GPVI expression on platelets¹⁰
- Changes in sGPVI on switching from ABC to TAF have not yet been determined

Objective

◆ To determine changes in sGPVI in PLWH who are virologically suppressed on switching from ABC/3TC to TAF/FTC vs continuing ABC/3TC after 48 weeks of follow-up

Methods

Study Design: Phase 3, Randomized, Double-blind, Double-Dummy, Active-Controlled Study in USA and EU (GS-US-311-1717)¹¹ n=280 TAF/FTC QD ABC/3TC + 3rd Agent **Continue 3rd Agent** HIV-1 RNA <50 copies/mL for ≥6 mo - N=556 (1:1) - No CD4 criteria Estimated CrCl ≥50 mL/min ABC/3TC QD No single-tablet regimen allowed n=276 Continue 3rd Agent Week 0 1° Endpoin 2° Endpoint **Platelet Substudy** n=545 Aggregation assay (Mallon P, et al. CROI 2018, oral 258810) Surface markers *From sites in Dublin and London. CrCl, creatinine clearance

sGPVI measurement:

- Conducted in the whole study population
- Plasma derived from ethylenediaminetretraacetic acid-treated blood and stored
- Measured in platelet poor plasma
- Quantified by electrochemiluminescence (Meso Scale Discovery): mean intra- and interassay coefficients of variation (CV) of 3.4% and 11.5%, respectively

Statistical analysis:

Data are median (interquartile range [IQR]) unless otherwise specified.

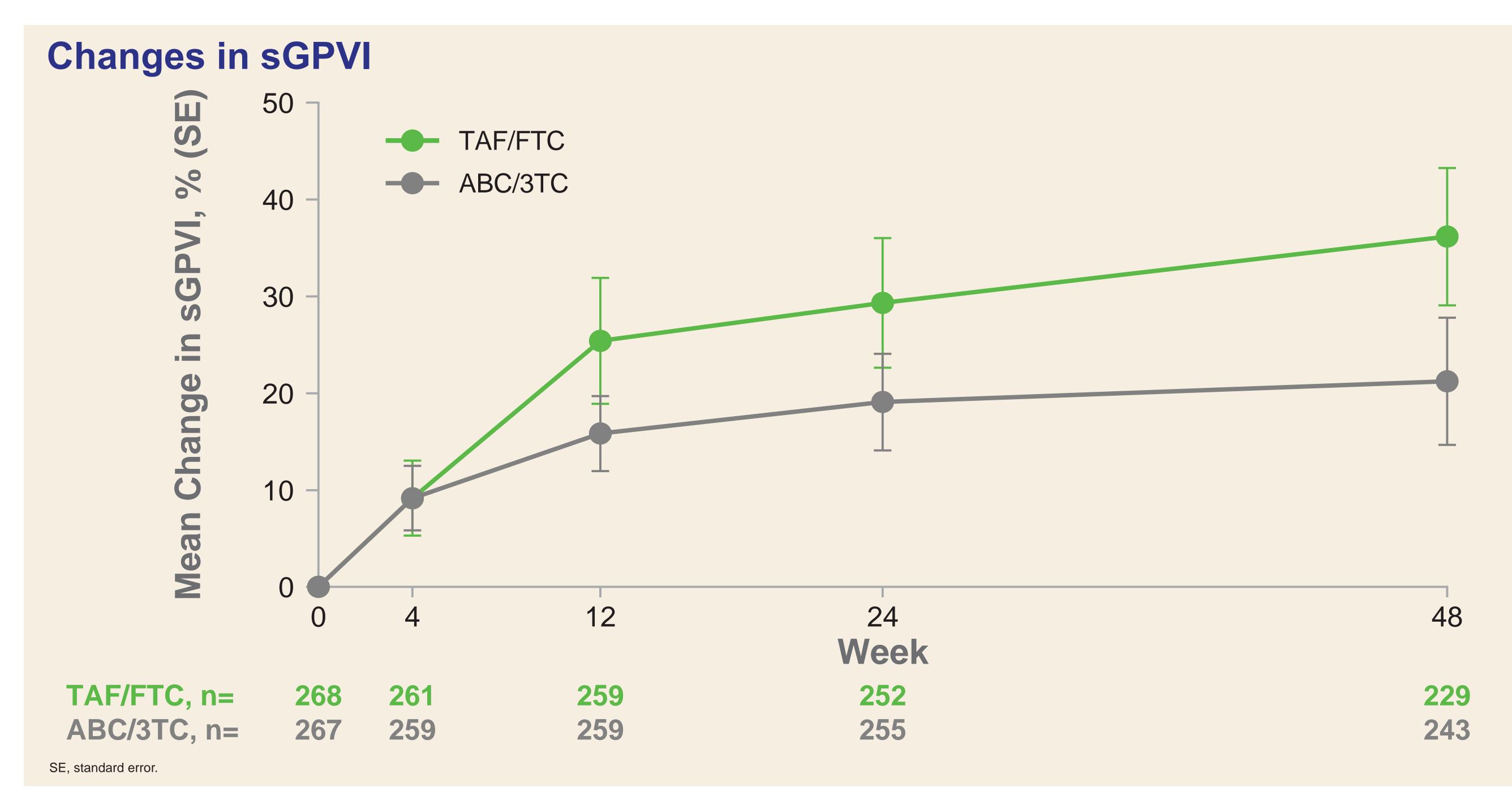
Primary endpoint: between-group difference in the change in sGPVI over 48 weeks
Longitudinal differences analyzed using linear mixed models

Results

aseline Characteristics			
	TAF/FTC, n=273	ABC/3TC, n=272	
Age, years	52 (46, 57)	52 (45, 57)	
Male, n (%)	233 (85)	212 (78)	
White race, n (%)	198 (73)	196 (72)	
Body mass index, kg/m ²	25.7 (23.3, 28.9)	26.4 (23.9, 29.5)	
Duration of ABC use, years	8 (3, 11)	8 (4, 11)	
Smoking status, n (%)			
Current smoker	73 (27)	62 (23)	
Former smoker	66 (24)	72 (27)	
Never smoker	134 (49)	138 (51)	
Hyperlipidemia, n (%)	128 (47)	137 (50)	
Hypertension, n (%)	106 (39)	108 (40)	
Diabetes, n (%)	32 (12)	36 (13)	
Aspirin use, n (%)	35 (13)	21 (8)	
Statin use, n (%)	86 (32)	85 (31)	

- ◆ Of 556 patients enrolled in the study, 545 (98%) had samples available for analysis
- Baseline demographic and laboratory characteristics of the participants were balanced across the study groups

Baseline Laboratory Parameters			
Dascinic Laboratory i aranictors	TAF/FTC, n=273	ABC/3TC, n=272	
HIV-1 RNA <50 copies/mL (SD)	271 (99.3)	269 (98.9)	
CD4 cell count, /mm³	644 (487, 841)	700 (550, 891)	
Platelet count, x10 ⁹ /μL	220 (182, 254)	218 (181, 259)	
Total cholesterol, mg/dL	198 (170, 229)	201 (176, 226)	
HDL cholesterol	56 (45, 69)	52 (43, 66)	
LDL cholesterol	122 (99, 147)	124 (103, 146)	
Data are median (IQR) unless otherwise specified. HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.			



- At baseline, sGPVI levels were similar between groups:
- TAF/FTC median (IQR) 0.736 (0.520, 1.274) ng/mL vs ABC/3TC 0.846 (0.527, 1.451) ng/mL (p=0.18)
- ◆ The TAF/FTC group had a significantly greater increase in sGPVI to Week 48
- Difference in changes over 48 weeks (vs ABC/3TC): +14.7 % (95% confidence interval: 4.1, 26.3;
 p=0.005 by mixed-effects model)

Conclusions

- ◆ In PLWH who were virologically suppressed, switching from ABC/3TC to TAF/FTC led to significantly greater increases in sGPVI levels through Week 48 compared with continuing ABC/3TC
- Our findings are in agreement with previous results from randomized trials of platelet function in PLWH who switched from ABC⁹
- ◆ These results, in combination with the demonstrated decrease in platelet reactivity and increased GPVI receptor expression on platelets in PLWH switching from ABC/3TC to TAF/FTC,¹⁰ suggest a reversible, inherent platelet dysfunction with ABC/3TC centered on GPVI function, which may contribute to increased risk of cardiovascular events observed in PLWH exposed to ABC
- Further research is required to determine the relevance of the observed changes in platelet function to cardiovascular outcomes

References

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