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Simplification with Fixed-Dose Tenofovir-Emtricitabine or Abacavir-Lamivudine in Treatment Experienced, Virologically Suppressed Adults with Hiv Infection: Combined Analysis of Two Randomised, Non-Inferiority Trials Bicombo and Steal

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Abstract

Background: There is uncertainty about the comparative safety and efficacy of the fixed-dose-combination tablets tenofovir 300mg+emtricitabine 200mg (TDF/FTC); and abacavir 600mg+lamivudine 300mg (ABC/3TC).

Methods: We used random effects meta-analysis to compare 96 week data for ABC/3TC and TDF/FTC randomised arms from the BICOMBO (n=333) and STEAL (n=357) treatment experienced and virologically suppressed switch studies. Endpoints included: virological failure (VF, repeat plasma HIV RNA >400 copies/mL); mean change to week 96 in CD4 and metabolic parameters; proportion with serious non-AIDS events (SNAEs, retrospectively collected in BICOMBO). We used exact statistics for relative difference in proportions (RD), and ANOVA for differences between means. Difference was for ABC/3TC minus TDF/FTC.

Results: There was no significant difference between arms in VF (RD% 0.7 95%CI -3.4, 4.8). Change from baseline in CD4 was of marginal significance (ITT 0.16 cells/mL 95%CI 0.0, 0.32). Mean change in HDL, LDL, total cholesterol triglycerides were significantly greater in the ABC/3TC arm (p <0.01 for all), there was no difference in total cholesterol:HDL ratio (0.11 95%CI -0.16, 0.29). There was a greater proportion of SNAEs in the ABC/3TC arm (relative difference 3.8%, 95%CI 0.1, 7.6) primarily arising from the STEAL study.

Conclusions: In a switch study setting ABC/3TC based therapy was virologically non-inferior over 96 weeks to TDF/FTC based therapy. Lipid markers were generally elevated in the ABC/3TC arm.

Introduction

In 2004 fixed dose combination (FDC) tablets containing abacavir (ABC)+lamivudine (3TC) (Kivexa®) and tenofovir (TDF) + emtricitabine (FTC) (Truvada®) were licensed. The long term safety and efficacy profile of these drugs in once-daily, FDC formulations is not known. In recent years particular attention has been drawn to the effect of antiretroviral (ARV) therapies on the incidence of serious non-AIDS events (SNAEs), including cardiovascular disease (CVD), end-stage renal disease, liver failure and fractures.[1-3]Of particular interest is the effect of individual ARVs or ARV classes on these events. There has been some indication, though not consistent, of an association between ABC and CVD.[4-6] There are also some data to suggest TDF exposure may be associated with renal toxicity, at least during early exposure, and bone loss.[7-11]

Two very similar randomised clinical trials investigating the safety and efficacy of switching to ABC+3TC or TDF+FTC FDC combinations in ARV therapy experienced HIV infected stable and virologically suppressed populations were commenced in 2005 in Spain (BICOMBO) and Australia (STEAL). [12,13] Both trials completed 96 week follow up in 2008. The availability of data from these trials provides an opportunity to investigate consistency and generalisability of study outcomes.

Methods

Source data were extracted for the trials by the statisticians responsible for each trial. End points for each trial were analysed using a pre-specified analysis plan to ensure that all analyses were conducted in the same manner. Analyses were conducted for data collected up to week 96. The primary endpoint was proportion with virological failure [VF] (repeat plasma HIV RNA >400 copies/mL; intention-to-treat, missing=failure [ITTM=F] analysis). Secondary endpoints were VF missing/switch =failure [ITTS=F], VF (per protocol [PP]), mean change from baseline to week 96 in CD4 (ITT last observation carried forward and PP), metabolic parameters (per protocol [PP]) and proportions with serious non-AIDS events (SNAE).

In STEAL, SNAE endpoints were defined and collected in February 2006, after the study commenced but before the database was un-blinded and analysed in August, 2008 [13]. SNAE data were retrospectively collected in BICOMBO in 2009 by blinded review of clinical records by two site physicians for events as defined in the STEAL study. In brief SNAEs were defined as cardiovascular events (myocardial infarction, ischaemic stroke, peripheral vascular disease, cardiac revascularisation procedure), non-AIDS defining cancer, end-stage liver disease, non-traumatic fractures of long torso-bones.

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Formal analysis of comparison of the number of events by randomised arm was conducted only for individual SNAE events where greater than ten events were reported.

For binary endpoints, we used exact statistics to determine the relative differences in proportions (RD), and ANOVA based methods for differences between means. Difference was for ABC/3TC minus TDF/FTC. Data were summarised across trials using random effects meta-analysis methods to maintain the integrity of each trial. Heterogeneity was assessed using I^2 [14]. In all comparisons two sided tests were used with $\alpha<0.05$ considered as significant. Sensitivity of findings regarding continuous outcomes was assessed by stratification of baseline use of PI and baseline use of ABC, TDF or other NRTI. Due to the small number of eligible studies, no formal analysis of publication bias was undertaken. All analyses were conducted using STATA™ 10 using the metan function.

Results

Study Characteristics

Eligibility criteria for BICOMBO and STEAL have been published elsewhere [12,13]. In both trials participants were required to have baseline exposure to two nucleoside reverse transcriptase inhibitors (NRTIS) and either a non-NRTI or protease inhibitor, and be virologically suppressed (HIV RNA < 200 and <50 copies /mL plasma respectively). In summary the main differences in eligibility criteria between trials were: STEAL alone required participants to be HLA-B*5701 negative or have had prior exposure to ABC and eGFR≥70mL/min/1.73m^2; BICOMBO participants were excluded if plasma creatinine was >2mg/dL. Both trials required written informed consent prior to randomisation. Recruitment for BICOMBO and STEAL were exclusively from Spain and Australia respectively.

Baseline Data

Baseline and follow-up characteristics, which were measured in both trials, by randomised arm are shown in (Table 1). Loss to follow-up differed between trials, and within BICOMBO by study arm, with the BICOMBO TDF/FTC having the greatest loss to follow up (16%). Within each trial all other baseline characteristics were balanced across randomized arms. BICOMBO in comparison to STEAL had a lower proportion of participants who were male (77% vs 98%), exposed to ABC at baseline (9% vs 20%) and with HIV transmission via male homosexual contact (31% vs 89%) and a higher proportion who had prior AIDS (38% vs 16%). Biochemical parameters were similar between trials except eGRF was lower in BICOMBO (mean 75 vs 98 ml/min/1.73m^2)

Outcomes

In terms of virological and immunological findings, results were similar between trials (Figure 1 and Figure 2). Pooled analysis showed no difference between arms for virologic failure, regardless of whether analysis was by ITTM=F (relative difference 0.7 %, 95%CI-3.4, 4.8), ITTS=F (relative difference 2.8%, 95%CI -2.6, 8.2), or PP (relative difference 0.8%, 95%CI -0.8, 2.4). There were no differences between randomised arms in change from baseline to week 96 in log10 HIV RNA copies/mL (SMD ITT 0.08 95%CI -0.08, 0.23; PP -0.02 95%CI -0.22, 0.18). Change in CD4+Tcell count/μL was significantly greater in the ABC/3TC arm in the ITT population but there was no significant difference in the PP population (SMD, ITT 0.16 95%CI, 0.00, 0.32; PP 0.15 95%CI -0.03, 0.34) (Table 2). There was no significant difference in cessation of randomised therapy by treatment arm (relative difference 1.5%, 95%CI -3.9, 6.8).

The following lipid parameters (Figure 2) were significantly higher in the ABC+3TC arm compared to the TDF+FTC arm in pooled analysis: triglycerides mmol/L (SMD 0.25 95%CI 0.08, 0.42); total cholesterol (SMD 0.62 95%CI 0.45, 0.80);HDL cholesterol (SMD 0.30 95%CI 0.13, 0.48); LDL cholesterol (SMD 0.33 95%CI 0.14, 0.51). There were no significant difference in total cholesterol: HDL ratio (SMD 0.11 95%CI -0.06, 0.29).

There were no significant differences between arms in pooled analysis of weight (SMD 0.02 95%CI -0.45, 0.49), kidney function (SMD CrCl -0.08 95%CI-0.51, 0.36; GFR -0.01 95%CI-0.18, 0.16) nor liver function (SMD ALT -0.06 95%CI -0.47, 0.34; AST 0.00 95%CI -0.40, 0.40) (Figure 2). These variables showed the greatest between trial heterogeneity, significantly so for aminotransferases (ALT I^2=82%, p=0.018; AST I^2=80.7% p=0.023). There were no clinically relevant

	BICOMBO				STEAL			
	ABC/3TC		TDF/FTC		ABC/3TC		TDF/FTC	
	n=167		n=166		n=178		n=179	
Lost to follow up (%)	13	7.8	27	16.3	4	2.2	2	1.1
Baseline ABC (%)	12	7.2	18	10.8	36	20.2	37	20.7
Baseline TDF (%)	44	26.3	56	33.7	54	30.3	53	29.6
Baseline PI (%)	17	10.2	16	9.6	42	23.6	41	22.9
NRTI exposure [years(sd)]	4.4	2.9	4.1	2.9	5.7	3.4	5.9	3.8
Male (%)	130	77.8	127	76.5	176	98.9	173	96.6
Male homosexual transmission (%)*	55	35.0	51	32.1	157	88.2	159	88.8
Prior AIDS (%)	63	37.7	65	39.2	31	17.4	28	15.6
Age [years(sd)]	43	9	45	10	46	9	44	8
CD4 count [cells/mm^3(sd)]	533	292	554	299	627	306	599	257
Creatinine clearance [ml/min(sd)]	105	25.2	100	27	112	26.3	114	27.4
eGFR [ml/min/1.73m^2 (sd)]	75.7	31.6	73.3	34	98.2	22.4	98.4	17
Triglycerided[mmol/L(sd)]	1.8	1.1	2	1.4	2.2	2.7	2.3	3
Total:HDL ratio	4	1.3	4.2	1.4	4.3	1.6	4.4	1.4
Total cholesterol[mmol/L(sd)]	5.2	1	5.4	1	5.2	1	5.4	1.3
HDL cholesterol[mmol/L(sd)]	1.4	0.4	1.4	0.5	1.3	0.4	1.3	0.4
LDL cholesterol[mmol/L(sd)]	3.1	0.8	3.1	0.9	3.1	0.9	3.1	0.9
ALT > ULN**	48	31.4	54	34.8	40	22.4	36	20.2
AST >ULN†	23	15.6	36	24.8	36	20.1	31	17.4

*Transmisssion information was available only for 157 and 159 participants in ABC/3TC and TDF/FTC BICOMBO arms respectively
**ALT data available only for 153, 155, 178,178 participants on ABC/3TC and TDF/FTC in BICOMBO and STEAL respectively
†AST data available only for 147 and 145 participants on ABC/3TC and TDF/FTC in BICOMBO
ALT-alanine aminotransferase
AST-aspartate aminotransferase
ULN- upper limit of normal

Table I: Baseline characteristics by trial and randomised arm.

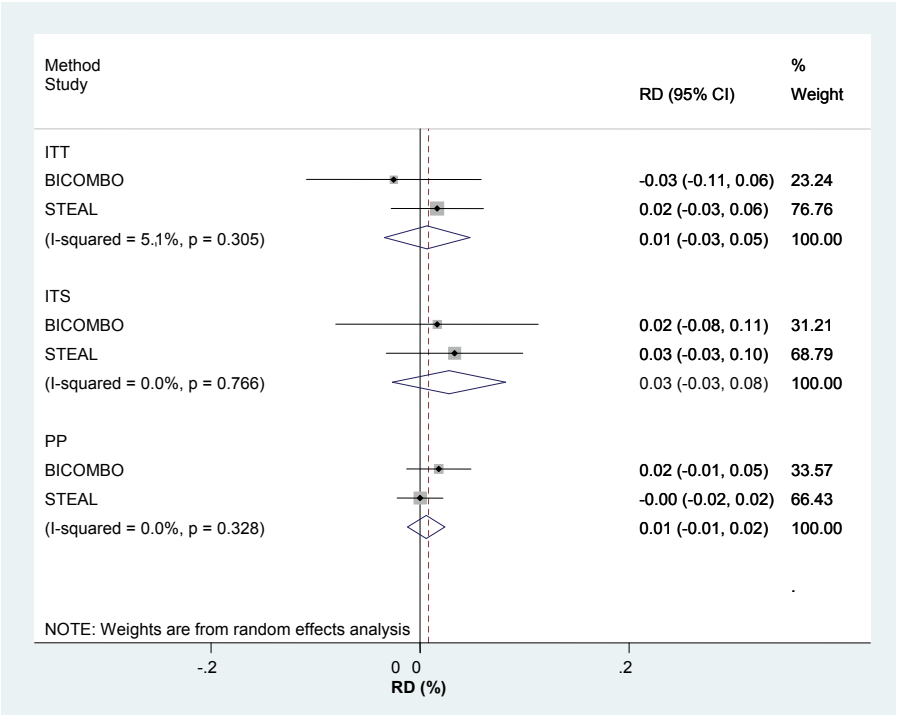
differences in outcomes after stratification for baseline PI or NRTI use (data not shown).

A total of 37 SNAEs were reported across both trials (Table 2). A significantly greater proportion of SNAEs were reported in the ABC+3TC arm (relative difference 3.8% 95%CI 0.1, 7.6 p=0.044; I^2=19.5% p heterogeneity=0.265). Across trials the most frequently reported events, of all SNAEs, were cancer (17/37, 46%) and cardiovascular disease (CVD) (12/37, 32%). There were no significant differences between arms in pooled data for either of these events (relative difference 1.5% 95%CI -0.8, 3.7 p=0.197 and RD 2.1 95%CI -1.6, 5.7 p=0.267 respectively). The following cancers were reported: four Hodgkin's lymphoma, three cervical, two lung and one of kidney, prostate, liver, larynx, vulvar, testicular, an unknown primary and one metastatic melanoma. The following CVD events were reported: 6 myocardial infarctions, two peripheral arterial disease [one with angioplasty], one coronary artery by-pass surgery, two ischaemic stroke, and one deep venous thrombosis. The majority of CVD events were reported in the STEAL ABC+3TC arm (8/12, 67%), and variation in relative difference that was attributable to between trial heterogeneity was 73% (I^2) which was of borderline significance (p=0.055).

	BICOMBO				STEAL			
	ABC/3TC		TDF/FTC		ABC/3TC		TDF/FTC	
	n=167		n=166		n=178		n=179	
	n	%	n	%	n	%	n	%
Deaths	0	-	2	1.2	2	1.1	2	1.1
AIDS events	1	0.6	0	-	0	-	0	-
Serious non-AIDS								
Cardio vascular	2	1.2	1	0.6	8	4.5	1	0.6
Study RD [%(95% CI]	0.6 (-1.4,2.6)				3.9 (0.7, 7.1)			
RD[% (95%CI)]	2.1 (-1.6, 5.7)p=0.267, heterogeneity $I^2$72.9 p=0.055							
Cancer	6	3.6	4	2.4	5	2.8	2	1.1
Study RD [%(95% CI]	1.2(-2.5, 4.8)				1.7 (-1.2, 4.5)			
RD[% (95%CI)]	1.5 (-0.8, 3.7) p=0.197, heterogeneity $I^2$0.0% p=0.834							
Fracture	3	1.8	2	1.2	0	0.0	1	0.6
Renal disease	0	0.0	1	0.6	0	0.0	0	0.0
Liver disease	0	0.0	0	0.0	1	0.6	0	0.0
Total	11	6.6	8	4.8	14	7.9	4	2.2
Study RD [% (95%CI)]	1.8	(-3.2, 6.7)			5.6	(1.1, 10.1)		
RD[% (95%CI)]	3.8 (0.1, 7.6) p=0.044, heterogeneity I^2=19.5% p=0.265							

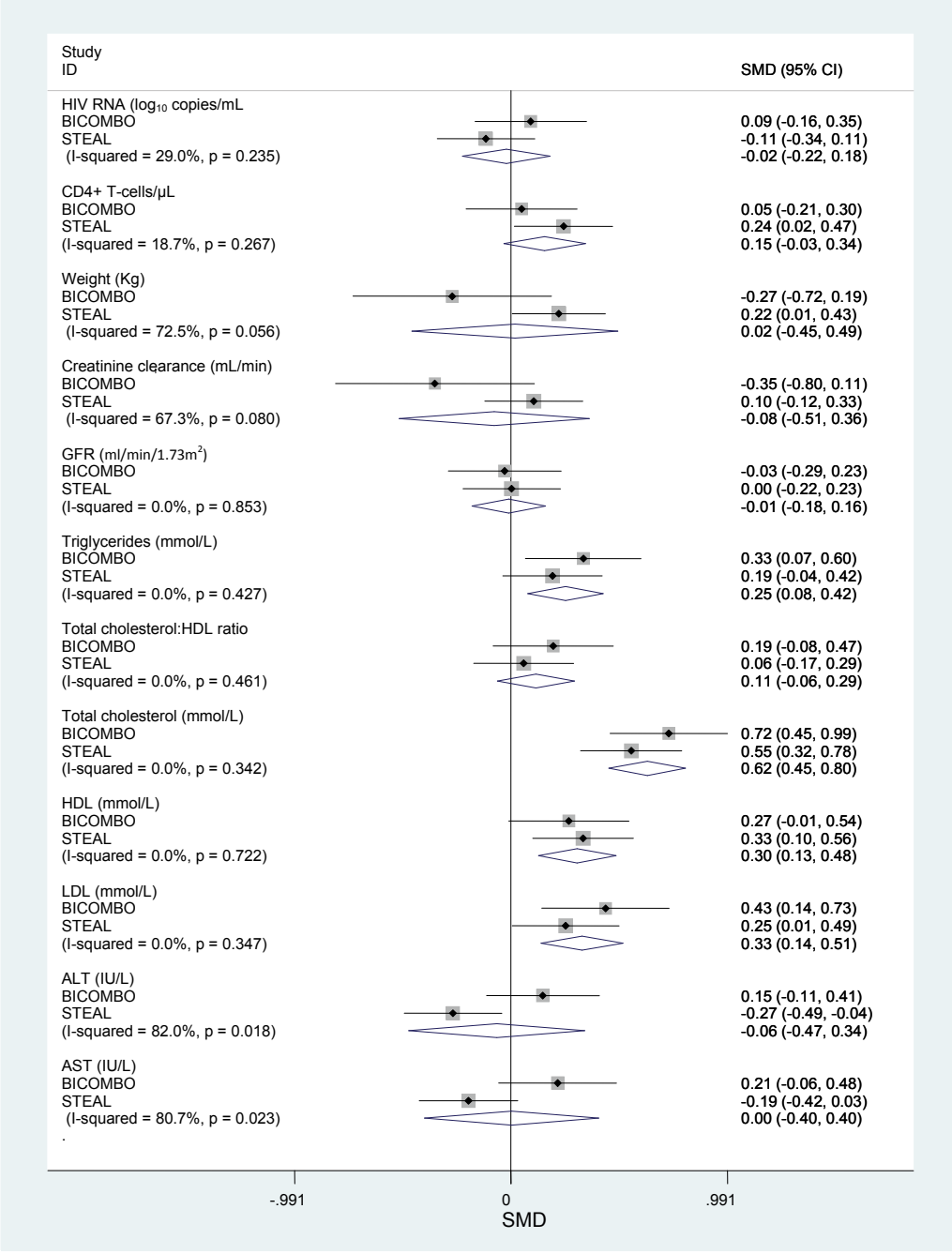
*Only grade 3/4 adverse events that resulted in treatment cessation
RD= Difference in proportions, (ABC+3TC) minus (TDF+FTC)

Table 2: Serious non -AIDS events by randomised arm and trial.



RD Difference in proportions, (ABC/3TC) minus (TDF/FTC)
ITT Intention to treat missing=failure
ITS Intention to treat missing/switch=failure
PP Per protocol

Figure 1: Difference between treatment arms in proportion (RD) with virologic failure by method of analysis.



SMD= Difference in mean change from baseline, (ABC/3TC) minus (TDF/FTC)
Weights are from random effects analysis: % weight range BIOCOMBO 40.04-48.70; STEAL 51.30-58.78

Figure 2: Standardised mean difference (SMD) between randomised arms in change from baseline to week 96 in the per protocol population.

There were six deaths in the trials, two in BICOMBO on TDF+FTC (one acute myocardial infarction, one cerebral hemorrhage) and four in STEAL (all cancers). There was one new AIDS event (*Cryptosporidium parvum* enteritis), which occurred in the in ABC+3TC arm of BICOMBO.

Discussion

This meta-analysis showed an overall consistency in efficacy in response to randomization to ABC/3TC or TDF/FTC across the BICOMBO and STEAL trials. Over 96 weeks, ABC/3TC was found to be non-inferior to TDF/FTC in terms of ability to maintain virologic suppression and with regards to CD4+ T-cell response. ABC/3TC was associated with greater increases in lipid levels and a greater frequency of SNAEs. The greatest imbalance in SNAEs was for CVD events, the majority of which were reported in the STEAL study.

Greater lipid increases in the ABC/3TC were evident across a range of measures including total cholesterol, triglycerides, LDL. These findings may lend support to potential cardiac risk following exposure to ABC, however HDL was significantly greater in the ABC/3TC arm and there was no significant difference in total cholesterol:HDL ratio.

Our findings regarding SNAEs are of interest however should be interpreted cautiously. Firstly, the higher proportion of SNAEs in the ABC arm was of borderline significance (p 0.044) and appears driven by the distribution of CVD events in STEAL. The pooled result for CVD was not statistically significant and between study heterogeneity for this event approached statistical significance (p=0.055). The numbers of CVD events in BICOMBO were much lower than in STEAL (3 vs 9). Secondly, underlying differences in cardiac risk in the Spanish and Australian populations may explain some of the difference in this finding between BICOMBO and STEAL. The STEAL population consisted of more men than the BICOMBO population, an important risk factor for CVD.[15] Thirdly, bias in assignment of SNAEs in the BICOMBO study cannot be discounted as endpoints were identified by retrospectives case record review. Fourthly, the higher rate of loss to follow up in BICOMBO may have resulted in the omission of some longer term outcomes (such as CVD). Finally, while our findings lend some support to the association of ABC use and myocardial infarction observed in observational studies,[4,5,16] our definition of CVD includes other cardiac events, such as stroke and peripheral vascular disease, which may have different underling aetiology and have resulted in misclassification error.

Across the studies there was no evidence of difference by randomised arm in renal function as determined by change in GFR, creatinine clearance or serious renal events. Liver function (as assessed by ALT and AST results) similarly showed no difference overall, however there was significant heterogeneity between trials, perhaps indicating differing underlying risk for this variable. Baseline ALT and AST were higher in BICOMBO than STEAL. Hepatitis B and C co-infection, which contribute to ALT and AST elevation, were not ascertained in STEAL. However, the estimated prevalence of these co-infections in the Spanish HIV population (37% and 20-50% respectively) is greater than in the Australian (6% and 13% respectively). [17-19]

The primary limitation of BICOMBO and STEAL, and therefore this combined analysis, was the inclusion of participants who were not naïve to TDF and ABC. However stratification by baseline NRTI showed no significant interaction between baseline exposure to ABC/TDF and randomised treatment for any outcome. Further, as week 96 analysis was not protocol mandated in BICOMBO, no BICOMBO DEXA data are available for this time point, as such no combined analysis of body composition nor bone mineral density could be undertaken. Further, it is unknown how the higher rate of loss to follow up in BICOMBO may have affected trial outcomes.

The primary strength of this analysis is that raw data were available for both trials. Therefore we were able to ensure that all endpoints were analysed in the same way prior to pooling. Another strength is that by encompassing both the BICOMBO and STEAL study populations, the findings are generalisable to a more diverse population. This was possible because there was very little evidence of heterogeneity for the majority of endpoints across the trial, indicating that the response to ABC/3TC and TDF/FTC is not trial specific.

In summary, our data demonstrate that over 96 weeks, switching to ABC/3TC is virologically non-inferior to switching to TDF/FTC in ART experienced virologically suppressed HIV infected populations. SNAEs and some lipids were however elevated in the ABC/3TC arm. Our analysis lends support to the suggestion that SNAEs should be routinely collected in switch trials.

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Disclosures

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