

Switching from Tenofovir disoproxil fumarate (TDF) to Tenofovir alafenamide (TAF) and hepatic safety: a new paradigm?

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Background

A switch from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) was associated with a better renal and bone profile. Some studies reported liver toxicity due to TDF [1, 2]. We aimed at investigating the effect of switching TDF to TAF on lipid, renal and hepatic safety profile.

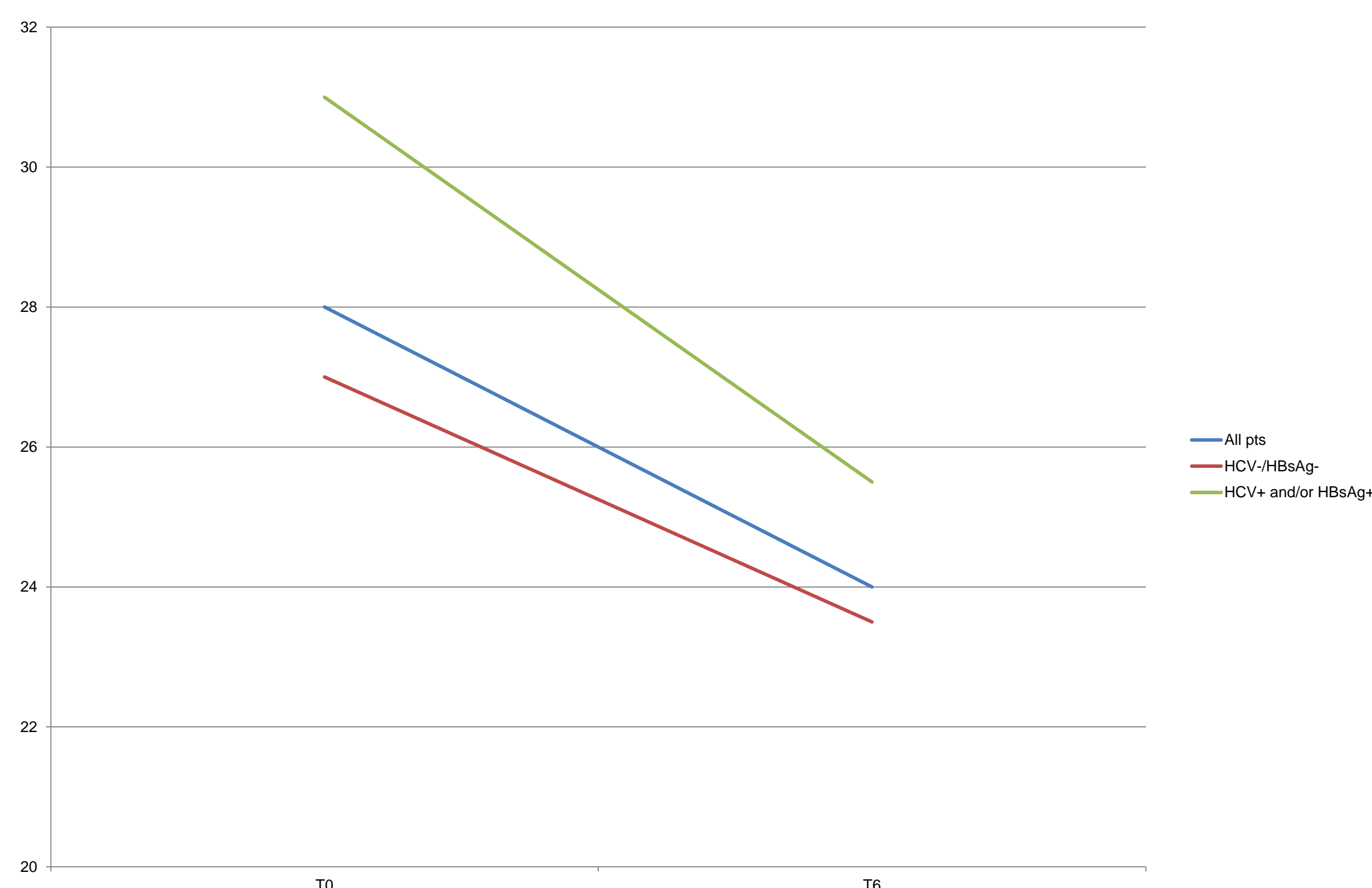
Methods

Consecutive HIV patients enrolled in Surveillance Cohort Long-term Toxicity Antiretrovirals/Antivirals (SCOLTA) project switching from TDF/FTC/EVG/COBI to TAF/FTC/EVG/COBI for any reasons were included. Changes from baseline (T0) to 6-month follow-up (T1) were evaluated using paired t-test if differences were normally distributed (blood lipids, estimated glomerular filtration rate - eGFR), and using signed rank test if not (liver enzymes).

Table 2. AST and ALT median changes from T0 to T6

	N	Median, IQR	P§
AST (IU/L)	83	-1, -2 to 5	0.02
HCV -	67	-1, -5 to 2	0.049
HCV +	16	-1, -5.5 to 2	0.26
HbsAg -	76	-1.5, -5 to 2	0.009
HbsAg +	7	1, -5 to 14	0.56
HCV - / HbsAg -	62	-1, -5 to 2	0.022
HCV+ e/o HbsAg +	21	0, -5 to 2	0.50
BL AST > 40 (IU/L)	4	-20.5, -29 to -11.5	0.12
ALT (IU/L)	86	-2, -7 to 2	0.009
HCV -	70	-2, -7 to 2	0.037
HCV +	16	-2.5, -10.5 to 3	0.16
HbsAg -	77	-3, -7 to 1	0.005
HbsAg +	9	1, -4 to 13	0.89
HCV - / HbsAg -	63	-2, -7 to 2	0.033
HCV+ e/o HbsAg +	23	-2, -14 to 4	0.18
BL ALT > 40 (IU/L)	16	-23.5, -38.5 to -13.5	<0.0001

Figure 1. ALT median changes from T0 to T6



Conclusions

Switching from TDF/FTC/EVG/COBI to TAF/FTC/EVG/COBI in a real life setting was associated with an improvement in eGFR, with increased TC and LDL, and stable HDL, TC/HDL ratio and TG. A significant reduction of ALT and AST, especially in pts without HBV and/or HCV infection, was observed. Further studies are needed to confirm a possible better profile of TAF vs TDF on liver toxicity.

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Table 1 : Patients switching from TDF to TAF

	All N=188	6-month follow-up N=100
	N (%) or mean ± SD or median (IQR)	N (%) or mean ± SD or median (IQR)
Males	147 (78.2)	79 (79.0)
Risk factor IVDU	20 (10.6)	12 (12.0)
CDC Stage C	39 (20.7)	24 (24.0)
HCV coinfection (6 missing)	28 (15.4)	16 (16.3)
Second-line ART	61 (32.4)	36 (36.0)
Undetectable HIV-RNA at switch	181 (96.2)	97 (97.0)
Age (years)	44.9 ± 11.0	45.1 ± 10.6
BMI (Kg/m ²)	24.8 ± 3.6	24.5 ± 3.3
CD4+ (cells/ml)	651 (480-900)	716 (513-914)
ART duration (years)	5.6 (2.9-13.3)	5.6 (2.0-12.2)
Total cholesterol (mg/dL)	193 ± 41	193 ± 37
HDL cholesterol (mg/dL)	51 ± 31	54 ± 40
Triglycerides (mg/dL)	112 (82-158)	112 (77-156)
Blood glucose (mg/dL)	89 ± 18	90 ± 20
AST (IU/L)	23 (19-31)	23 (19-30)
ALT (IU/L)	27 (19-39)	24 (18-33)
Creatinine (mg/dL)	1.0 ± 0.2	1.0 ± 0.2
eGFR	89 ± 24	88 ± 18

Results

188 patients (pts) switched from TDF/FTC/EVG/COBI to TAF/FTC/EVG/COBI, and 100 had at least one 6-month follow-up. Patients' characteristics are depicted in Table 1.

Sixteen pts were positive for HCV-Ab and ten pts for HbsAg. TDF/FTC/EVG/COBI duration before switch was 827 days (range 41-1610). Mean changes (Mean ± SD) from switch (T0) to six months follow up were: 13 ± 26 mg/dl for total cholesterol (p<0.0001), 2 ± 13 mg/dl for HDL cholesterol (p =0.07), 0.07 ± 1.04 for total cholesterol/HDL ratio (p=0.58), 8 ± 28 mg/dl for LDL-Cholesterol (p <0.05), 10 ± 82 mg/dl for Triglycerides (p=0.28), 2 ± 16 mg/dl for glucose (p=0.12), 2.6 ± 13.0 ml/min for eGFR (p=0.05).

At T1, both ALT (median -1, IQR -7 to 2 IU/L, p=0.009) and AST (median -1, IQR -2 to 5 IU/L, p=0.02) were significantly reduced. AST and ALT reduction remained significant in HCV-/HbsAg- patients. Median changes splitted according to positivity for HCV-Ab and HbsAg are showed in Table 2.

ALT median changes are depicted in Figure 1.

At T1, eGFR showed a slight increase (+2.6 ± 13.0 ml/min, p=0.05)

Discussion

Our data, obtained from an observational cohort, demonstrated a significant decrease in liver enzymes (ALT and AST) in patients switching from TDF vs TAF.

Liver toxicity of TDF has been demonstrated in animal models and it was reported as mild/moderate and consisting in collagen deposition and cytomegaly and appeared to be reversible after stopping TDF [3,4].

A study on pre-exposure prophylaxis (PREP) in African women demonstrated an increase in AST/ALT levels in patients randomized to TDF/FTC arm vs placebo especially in patients with previous exposure to HBV [1]. Data collection on Adverse Events of anti-HIV Drugs (DAD) study showed an increased probability to have liver enzyme elevation in patients on TDF mostly when associated with Efavirenz [2].

Studies on switching from TDF to TAF in HBV infection demonstrated a high probability to normalize ALT levels in patients on TAF therapy vs TDF therapy [5]. Our results showed a better impact of switch to TAF on liver enzymes in patients without HBV and HCV infection suggesting that a mechanism not linked to viral co-infections.

We can argue that TAF could have a better liver toxicity profile that might be probably due to a direct drug effect on liver or on a possible best impact on progression of liver steatosis.