Dettaglio abstract

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Title: Liver enzymes levels, metabolic and renal profile modifications after switching from TDF to TAF-based regimens among ART experienced PLWH in ICONA cohort

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Metabolic issues in effective HAART

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Abstract
Background: Liver enzymes elevation during treatment with Tenofovir Disoproxil Fumarate (TDF) and reduction in Alanine aminotransferase (ALT) values after TDF replacement with Tenofovir Alafenamide (TAF) have been described among ART-experienced PLWH. However, the rate of change of liver enzymes concomitantly with that of other markers after a switch to TAF have been seldom investigated and the possible role of the anchor drug used on markers trajectories remains unclear.
Materials and Methods: The analysis includes >18 years, ART-experienced PLWH enrolled in the ICONA Foundation Study cohort who at any time were switched from a TDF-based to a TAF-based regimen while they had a VL≤50 copies/mL. PLWH had to have ≥2 values of the markers while receiving TDF and TAF to be included. Pearson rho was used to evaluate baseline correlations. Mean changes in liver enzymes (AST, ALT, GGT, ALP), metabolic profile (Glucose, Triglycerides, Total, LDL and Total/HDL Cholesterol) and serum creatinine/eGFR using pair of values measured before and after the switch were compared using a paired t-test. Mixed models with random intercept and slope were used to evaluate the trajectories of the markers. A step-linear model with a change in slope at 1 year after switch was used for all markers. A quadratic model with interactions was used to assess the effect of the anchor drug class (NNRTI, PI, INSTI) used in the TAF regimen on ALT changes.
Results: 2,911 PLWH, mainly males (81%), median age 45 (37-53) years, after having received TDF for a median (IQR) of 31 (19-47) months, were switched to a regimen containing TAF in combination with a NNRTI (N=1337), PI/r (N=489) or INSTI (N=1105). At baseline, 347 subjects (12%) presented with chronic viral hepatitis, while only 44 (2%) had liver enzyme elevation. At baseline, weak correlations were found between ALT and HDL Cholesterol, Triglycerides and Glucose (ρ=-.07, p<0.0001; ρ=.13, p<.001; ρ=.08, p<.001, respectively).
We noticed differences in the changes of some of the parameters when comparing the periods while participants were on TDF vs. TAF, although none of these were clinically significant (Table 1). Over a median of 42 (34-47) months follow-up after switch, for liver enzymes we observed a moderate reduction over the 1st year followed by a slight increase; the opposite trend was observed for the metabolic and renal profiles, although again within the normal limit range (Table 2). U-shape trajectories for ALT after the switch was confirmed when we fitted a quadratic model, suggesting a difference in the evolution of ALT according to the anchor drug class (interaction p-value=0.04, Figure 1).
Conclusions: In our cohort of PLWH who were switched from TDF to TAF-based regimens with a VL≤50 copies/mL, no clinically significant changes in markers over a median of 42 months after the switch were observed. The class of the anchor drug used appeared to have an effect on the shape of ALT changes.

Table 1. Comparison between metabolic, hepatic and renal profiles measured during TDF and after switch to TAF using pairs of values.

	Pairs												
	T[-2]-T[0] (while on TDF)							T[0]-T[2] (while on TAF)					
Biomarker	**N**	**Mean1**	**SD1**	**Mean2**	**SD2**	**Difference**	**p-value**	**N**	**Mean1**	**SD1**	**Mean2**	**SD2**	**Difference**	**p-value**
Metabolic profile														
LDL Chol	1737	109.7	31.0	111.9	31.9	2.2	*<.01*	839		31.1	124.2	33.7	10.0	*<.01*
T-Chol	2666	176.4	38.0	179.0	37.4	2.5	*<.01*	2666	180.7	38.0	179.0	37.4	12.9	*<.01*
Triglycerides	2650	125.0	83.7	124.3	86.2	-0.6	*0.71*	2650	124.2	83.7	124.3	86.2	8.4	*<.01*
T-Chol/HDL ratio	2199	4.11	1.40	4.06	1.95	-0.05	*0.20*	2199	4.02	1.40	4.06	1.95	-0.01	*0.76*
Glucose	2847	89.98	20.31	89.26	19.77	-0.72	*0.03*	2847	89.22	20.31	89.26	19.77	1.83	*<.01*
Hepatic profile														
ALT	2921	37.06	49.74	35.66	99.15	-1.39	*0.48*	2921	34.28	49.74	35.66	99.15	-6.66	*<.01*
AST	2833	30.69	35.30	29.30	55.54	-1.38	*0.25*	2833	28.32	35.30	29.30	55.54	-2.54	*0.02*
GGT	2155	41.66	59.58	37.83	52.66	-3.83	*<.01*	2155	39.95	59.58	37.83	52.66	-5.20	*0.02*
ALP	2041	86.8	43.4	86.4	43.1	-0.4	*0.66*	2041	81.7	43.4	86.4	43.1	-11.3	*<.01*
Renal profile														
Creatinine	2933	1.0	3.1	0.9	0.2	-0.1	*0.26*	2933	1.0	3.1	0.9	0.2	0.0	*0.03*
Egfr	2924	93.46	17.99	88.86	17.02	-4.61	*<.01*	2924	88.07	17.99	88.86	17.02	-1.61	*<.01*

T[-2] = from 2 years to 1 month prior to T0

T[0] = date of switch to TAF

T[2] = from 1 month prior to 2 years after T0

LDL Col: Low-density Lipoprotein Cholesterol; *T-Chol:* Total Cholesterol; *ALT:* Alanine aminotransferase; *AST:* Aspartate transaminase; *GGT:* Gamma Glutamil Transpeptidase; *ALP*: Alcaline Phosphatase; *egfr:* esteemed glomelural filtration rate; *TDF:* Tenofovir Disoproxil Fumarate; *TAF:* Tenofovir Alafenamide
P-values from a paired t-test

Table 2. Slopes from fitting a step-linear mixed model with change at 1 year after the switch.

	Slopes/year by window periods					
Laboratory parameter	**Pre-switch**		**0-1 year after switch**		**>1 year after switch**	
	Mean	**p-value***	**Mean**	**p-value***	**Mean**	**p-value***
Metabolic profile						
LDL Chol	3.5 (2.7, 4.2)	*<.001*	7.8 (6.1, 9.5)	*<.001*	-16.2 (-18.9, -13.4)	*<.001*
T-Chol	4.2 (3.6, 4.9)	*<.001*	10.2 (8.7, 11.8)	*<.001*	-21.1 (-23.6, -18.5)	*<.001*
Triglicerydes	1.4 (-0.6, 3.3)	*0.163*	10.5 (5.7, 15.3)	*<.001*	-14.3 (-22.1, -6.6)	*<.001*
T-Chol/HDL ratio	-0.0 (-0.1, 0.0)	*0.080*	0.1 (0.0, 0.2)	*0.020*	-0.2 (-0.3, -0.1)	*0.006*
Glucose	-0.3 (-0.6, 0.1)	*0.176*	2.5 (1.6, 3.4)	*<.001*	-2.5 (-3.9, -1.0)	*<.001*
Hepatic profile						
ALT	3.1 (-0.0, 6.1)	*0.051*	-24.4 (-32.5, -16.3)	*<.001*	30.3 (17.3, 43.4)	*<.001*
AST	1.5 (-0.5, 3.4)	*0.146*	-12.7 (-17.9, -7.5)	*<.001*	17.2 (8.8, 25.7)	*<.001*
GGT	-1.3 (-2.7, 0.1)	*0.070*	-4.6 (-8.0, -1.2)	*0.008*	5.9 (0.4, 11.4)	*0.035*
ALP	-2.6 (-3.7, -1.4)	*<.001*	-13.6 (-16.3, -10.9)	*<.001*	22.9 (18.4, 27.4)	*<.001*
Renal profile						
Creatinine	-0.0 (-0.1, 0.0)	*0.101*	0.1 (-0.0, 0.1)	*0.172*	-0.1 (-0.2, 0.0)	*0.185*
eGFR	-2.6 (-2.8, -2.4)	*<.001*	2.3 (1.7, 2.8)	*<.001*	-1.5 (-2.4, -0.6)	*<.001*

*Wald test

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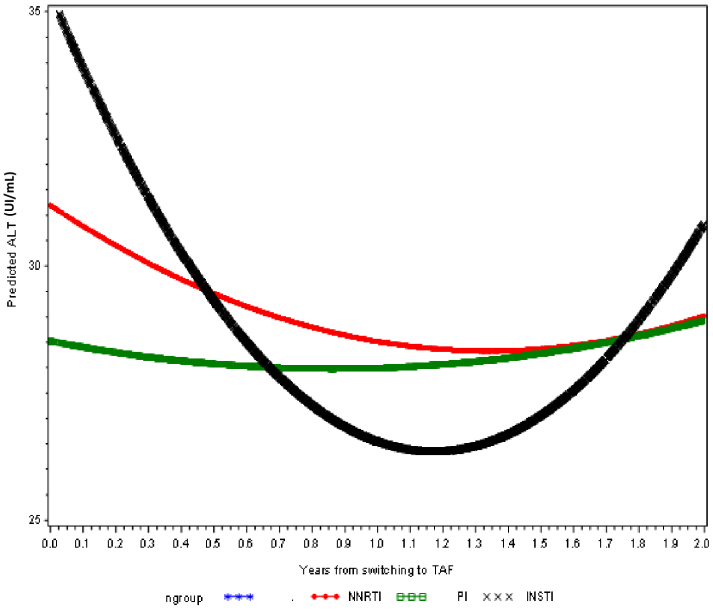
Figure 1. Predictions of ALT changes after switch to TAF from fitting a quadratic mixed model, stratified by class of anchor drug used in the TAF-based regimen.



NNRTI: Non Nucleosidic Reverse Trascriptase Inibhitors; *PI:* Protease Inibhitors; *INSTI*: Integrase Strand Transfer Inhibitors
P-value for interaction drug class* time =0.04