

Metabolic-related outcomes after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in adults living with HIV: a multicentre prospective cohort study

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Background and Objective

- Tenofovir alafenamide (TAF) is widely used to avoid the bone and kidney toxicity associated with tenofovir disoproxil fumarate (TDF) ¹⁻². However, concerns remain about potential metabolic complications of TAF ³⁻⁴.
- We aimed to evaluate changes in weight, laboratory markers, and metabolic-related clinical events after replacing TDF with TAF.

Methods

- Multicentre prospective cohort study in the Spanish CoRIS cohort.
- We included virologically suppressed adults with HIV receiving TDF for more than 12 months who either switched to TAF or maintained TDF, with no changes in the core agent.
- The index date of each participant was established after 1:1 matching by time from ART initiation. Then participants were matched by propensity score. Covariates included age, sex, mode of HIV transmission, educational level, ethnic group, AIDS diagnosis, baseline weight, use of corticosteroids or psychotropic drugs, baseline T-CD4+ cell count, and third ART drug.
- We fitted GEE models to assess changes in weight, blood lipids, and hepatic steatosis index (HSI). We compared the incidence of diabetes, hypertension, and lipid-lowering drug use after 144 weeks.

Results

A cohort of 1950 participants who switched to TAF met the inclusion criteria, with a follow-up of at least 144 weeks. They were matched 1:1 with participants who maintained TDF, according to time since ART initiation. Of these 3900 selected participants, 2892 were matched 1:1 after calculating the propensity score (1446 in each group). **Table 1** shows the baseline characteristics of the participants before and after propensity score matching. Almost all of the unmatched participants in the TAF group were on integrase strand transfer inhibitor (INSTI)-based regimens, as the percentage of INSTI was lower in the TDF cohort. The cohort included in the analyses is representative of a middle-aged population (median age 38 years), with a higher representation of men (85%) from Western Europe (75%). Only 3% were of black ethnicity. Sixty-nine percent received an NNRTI-based regimen.

Table 1. Baseline characteristics of the study population

	Cohort matched by follow-up time since ART initiation		Propensity-score matched cohort	
	Continued TDF (n=1955)	Switched to TAF (n=1955)	Continued TDF (n=1446)	Switched to TAF (n=1446)
Age *	39 (33, 47)	38 (32, 46)	38 (32, 46)	38 (31, 46)
Male sex, n (%)	1605 (82)	1672 (86)	1225 (85)	1233 (85)
Mode of transmission, n (%)				
MSM	1078 (55)	1215 (62)	878 (61)	883 (61)
Heterosexual	652 (33)	546 (28)	428 (30)	397 (28)
IDU	171 (9)	121 (6)	96 (7)	99 (7)
Origin, n (%)				
Western Europe	1476 (75)	1505 (77)	1090 (75)	1121 (78)
Eastern Europe	36 (2)	34 (2)	27 (2)	30 (2)
Sub-Saharan Africa	85 (4)	61 (3)	59 (4)	43 (3)
Northern Africa	14 (1)	23 (1)	7 (1)	14 (1)
Latin America	335 (17)	308 (15)	256 (18)	219 (15)
Ethnicity, n (%)				
Black	64 (3)	45 (2)	45 (3)	32 (2)
Other	1891 (97)	1910 (98)	1401 (97)	1414 (98)
Education level, n (%)				
No studies / Primary	286 (15)	267 (13)	204 (14)	184 (13)
Secondary	373 (19)	317 (16)	244 (17)	220 (15)
University	1017 (52)	1040 (53)	767 (53)	760 (53)
ART regimen, n (%)				
NNRTI	1382 (71)	990 (51)	1007 (70)	989 (68)
PI	417 (21)	284 (15)	287 (20)	282 (20)
INSTI	156 (8)	681 (35)	152 (11)	175 (12)
AIDS diagnosis, n (%)	428 (22)	318 (16)	256 (18)	220 (15)
Time from ART initiation to index date, months *	55 (31, 82)	55 (31, 82)	55 (32, 82)	60 (39, 86)
Baseline CD4+ count (cells/ μ L)*	641 (455, 855)	681 (496, 892)	662 (476, 877)	688 (503, 883)
Weight (kg) *	73 (66, 82)	73 (67, 81)	73 (67, 81)	73 (66, 80)
BMI (kg/m ²) *	24.8 (22.6, 27.4)	24.5 (22.5, 27.2)	24.6 (22.4, 27.1)	24.5 (22.3, 27.1)
Use of corticosteroids or psychotropic drugs, n (%)	110 (6)	100 (5)	73 (5)	70 (5)
Diabetes, n (%)	75 (4)	65 (3)	50 (3)	43 (3)
Hypertension, n (%)	443 (23)	396 (20)	330 (22)	288 (20)
Lipid-lowering therapy, n (%)	107 (5)	114 (6)	67 (5)	83 (6)
Total cholesterol, mg/dL *	183 (159, 210)	176 (153, 204)	183 (158, 208)	175 (151, 201)
HDL cholesterol, mg/dL *	47 (39, 57)	45 (37, 53)	47 (39, 56)	45 (37, 54)
Triglycerides, mg/dL *	110 (78, 159)	106 (76, 149)	108 (77, 155)	103 (74, 145)
Total cholesterol-HDL ratio *	3.8 (3.1, 4.7)	3.9 (3.2, 4.8)	3.8 (3.1, 4.7)	3.9 (3.1, 4.7)
Hepatic Steatosis Index *	33.7 (30.5, 37.5)	32.9 (30.1, 36.6)	33.7 (30.2, 37.4)	32.7 (30.0, 37.1)

* Median (IQR)

Table 2. Incidence of metabolic events during follow-up

	TDF (n = 1446)	TAF (n = 1446)	OR (95% CI)	p
Diabetes, n (%)	20 (1.4)	20 (1.4)	1.00 (0.53, 1.86)	1.000
Hypertension, n (%)	69 (4.8)	51 (3.5)	0.78 (0.54, 1.13)	0.193
Use of lipid-lowering therapy, n (%)	63 (4.4)	61 (4.2)	0.97 (0.67, 1.38)	0.854
NAFLD, n (%)	84 (5.8)	76 (5.2)	0.90 (0.65, 1.24)	0.515

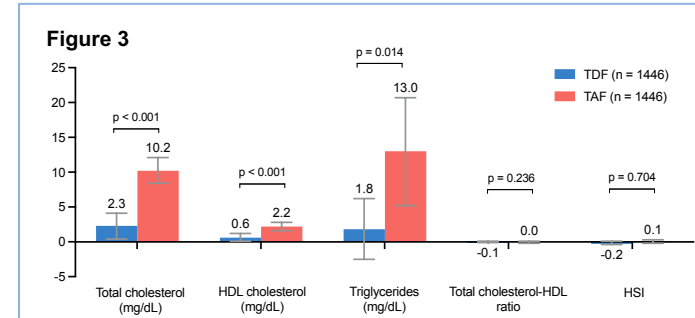
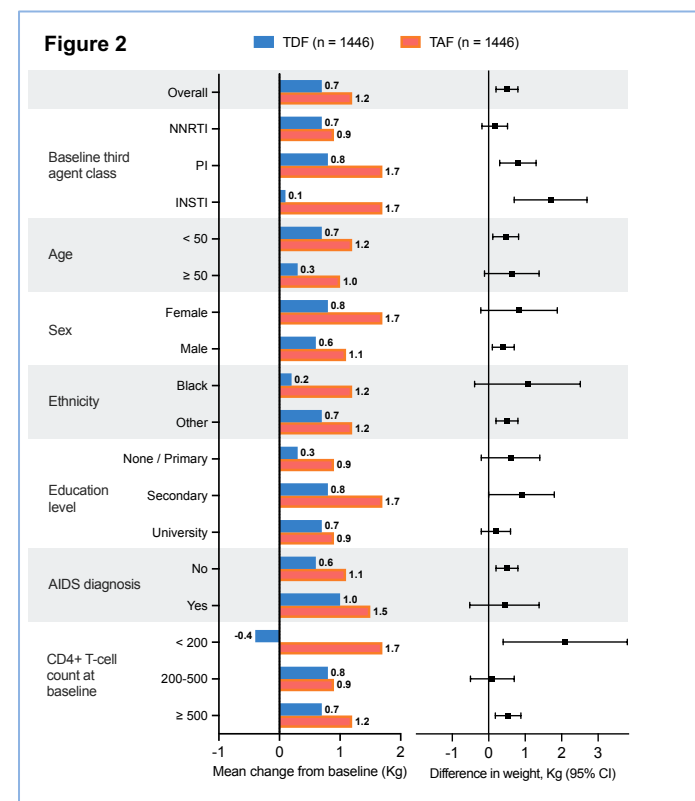
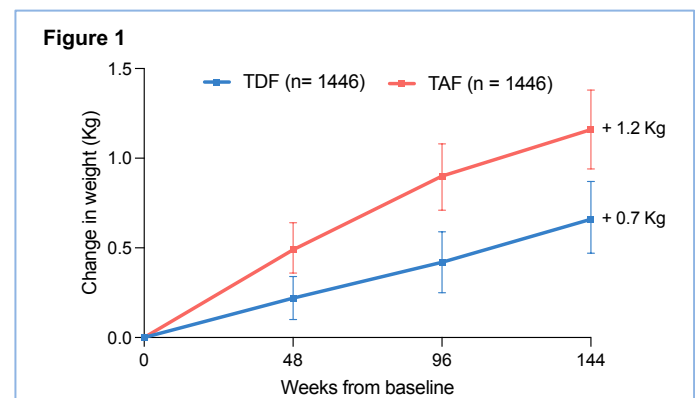
Participants who switched to TAF had a mean weight increase of +0.5 (95% CI: 0.2, 0.8, $p < 0.001$) kg at 144 weeks over those who maintained TDF. The differences were observed from week 48 (**Figure 1**).

Figure 2 shows the subgroup analysis for mean weight gain at 144 weeks, with consistent results. Between-group weight differences of TAF compared with TDF were larger among participants receiving INSTI, women, black ethnicity, and those with CD4+ count < 200 cells/ μ L.

We did not observe differences in the prevalence of overweight over time, which increased by 3.0% in the TAF group versus 2.3% in the TDF group ($p = 0.217$), or in the prevalence of obesity, which increased by 1.8% in the TAF group versus 1.8% in the TDF group ($p = 0.871$).

Participants who switched to TAF had a significantly higher increase in total cholesterol (+7.9 mg/dL), HDL-cholesterol (+1.7 mg/dL), LDL-cholesterol (+4.1 mg/dL), and triglycerides (+11.2 mg/dL) at 144 weeks. There were no differences in total cholesterol-HDL ratio or hepatic steatosis index (**Figure 3**).

During follow-up, 20 individuals (1.4%) who switched to TAF were diagnosed with diabetes mellitus, 51 (3.5%) with hypertension, 76 (5.2%) started a new lipid-lowering agent, and 76 (5.2%) met non-alcoholic fatty liver disease (NAFLD) criteria. No significant differences were observed with participants who continued on TDF (**Table 2**).



Conclusions Switching from TDF to TAF is associated with modest weight gain and an increase in total cholesterol, triglycerides, LDL and HDL cholesterol, with no differences in total cholesterol-HDL ratio. However, this is not associated with an increased incidence of overweight or obesity or metabolic clinical events.

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