Evolution of TDF-associated tubular dysfunction after switching to tenofovir alafenamide (TAF) in people living with HIV

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Introduction

Tenofovir alafenamide (TAF) is a tenofovir prodrug with improved renal safety compared with TDF-containing therapies.

Objective

We report the evolution of tubular and renal function in people living with HIV (PLH) who had tubular dysfunction during TDF treatment, and who were switched to a TAF-containing regimen.

Methods

We evaluated virologically suppressed PLH who were enrolled and followed in a study about TDF-associated renal toxicity during 2014-16. After discontinuation of TDF, independently of the cause, patients were followed with renal and tubular parameters evaluation.

For the purpose of this analysis, we analyzed those with previous diagnosis of tubular dysfunction (≥2 alterations in tubular parameters: proteinuria, glycosuria, hyperuricosuria, phosphaturia) who received a TAF-containing regimen during follow-up. The primary endpoint was the change in estimated glomerular filtration rate (eGFR) by using CKD-epi formulae and the changes in the parameters of tubular dysfunction.

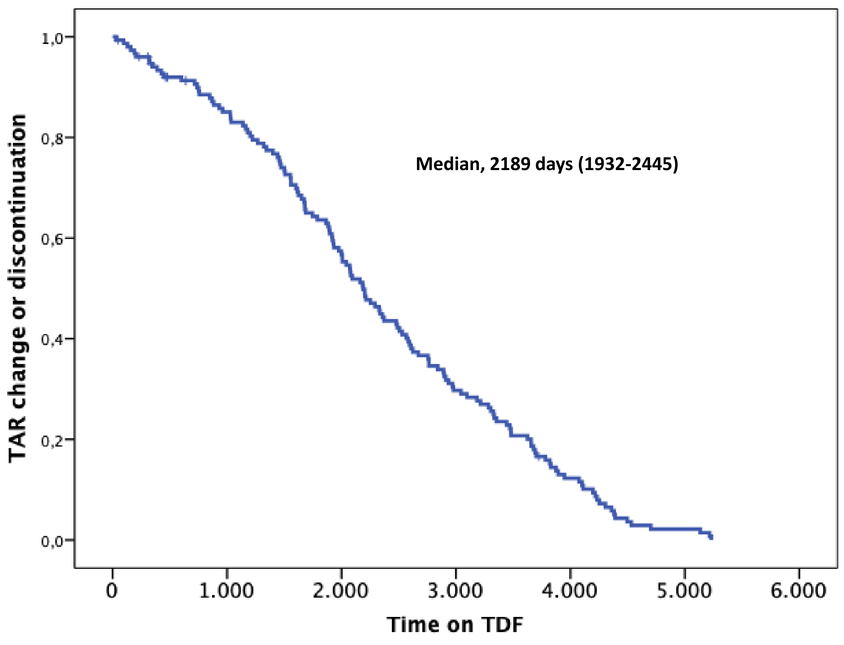
Baseline characteristics (n=198)

Table 1. Baseline characteristics of the 198 patients included

Variable	N= 198
Mean age (yrs, range)	49.1 (24-78)
Female sex	31(16%)
Mean BMI (kg/ m², IQR)	23.8 (21.9-25.5)
Former IDU MSM	41 (21%) 102 (52%)
HTA	28 (14%)
HCV coinfection	32 (16%)
Time of HIV infection (months, IQR)	157.8 (75.5-298.8)
Nadir CD4+ count (cells/mcL)	270 (157-380)
Current CD4+ count (cells/mcL)	567 (398-733)
Time on TDF (months, IQR)	51.4 (15-77)
Renal function	
Mean serum creatinine (mg/dL, range)	0.91 (0.61-1.78)
Mean eGFR-scr (ml/min/1.73 m², range)	98.1 (41-129)
Mean eGFR-cysC (ml/min/1.73 m2, range)	97.7 (52-143)
Serum phosphate (mg/dl, range) Hypophosphatemia (< 2.6 mg/dl)	3.2 (1.6-4.5) 28 (14%)
Tubular parameters	
uPCR, mg/gr, range uPCR≥ 100 mg/gr	84.4 (62.3-109.9) 73 (37%)
Mean albumin to creatinine ratio (uACR,mg/gr, range)	5.6 (4.2-9.2)
FE of phosphate (%, range) % of patients with FE phosphate ≥ 20%	18 (14-24.8) 79 (40%)
FE of uric acid (%, range) % of patients with FE uric acid ≥10%	6.7 (4.7-9.1) 30 (15%)
Glycosuria (>100 mg/dl)	14 (7%)
Complete Fanconi syndrome	3 (2%)
Tubular dysfunction criteria	32 (16%)

Data as expressed as median, interquartile range, unless otherwise specified.
BMI, body mass index; IDU, intravenous drug users; MSM, men having sex with men; HTA, hypertension arterial; HCV, hepatitis C virus; eGFR-scr, estimated glomerular filtration rate-serum creatinine; eGFR-cysC, estimated glomerular filtration rate-cystatin C; uPCR, urinary protein to creatinine ratio; uACR, urinary albumin to creatinine ratio; FE, fractional excretion.

Time on TDF until change of TAR (TDF discontinuation)



Conclusion

In PLH with tubular dysfunction who switched to TAF, there was an overall improvement in tubular parameters.

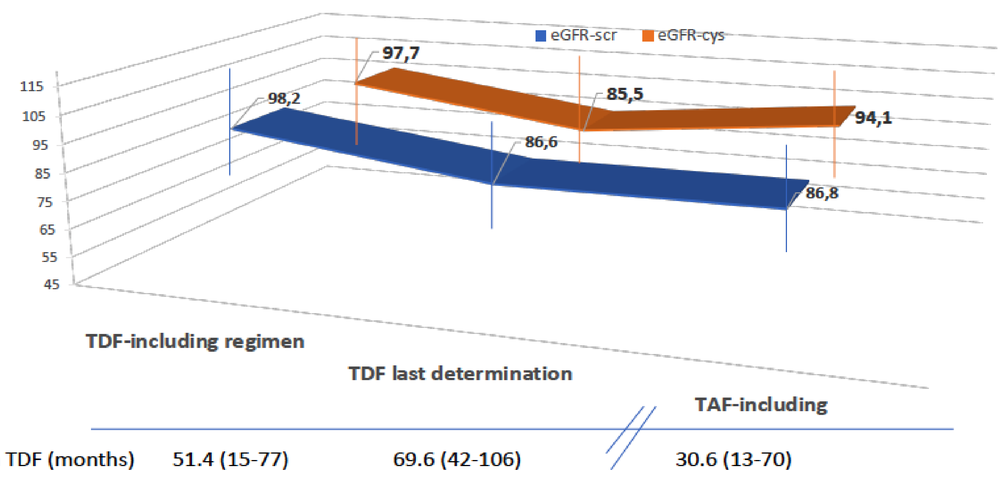
However, even after several years, there was no or mild benefit in those PLH changing with longer history of TDF treatment and/or with advanced renal and tubular impairment.

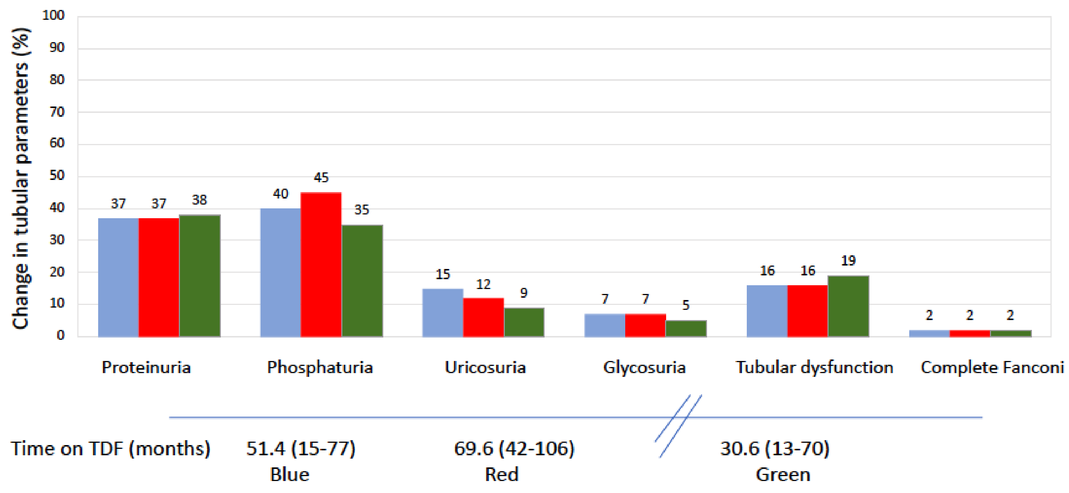
32 PLH (16%) had a diagnosis of tubular dysfunction, including 3 (2%) cases of Fanconi syndrome. PLH with tubular dysfunction were significantly older, had a worse eGFR and lower levels of phosphatemia compared to those without tubular dysfunction, leading to early TDF discontinuation (after 9.7 vs 30.1 months; p<0.01)

Variable	TD (32)	No TD (166)	P value
Mean age (yrs, range)	54.8 (38-75)	49.2 (25-78)	0.007
Female sex	7 (22%)	24 (16%)	0.43
Mean BMI (kg/ m², IQR)	24.4 (22.1-25.7)	23.7 (22-26)	0.3
Former IDU MSM	10 (33%) 11 (37%)	31 (19%) 91 (55%)	0.08
HTA	11 (34%)	17 (10%)	0.1
HCV coinfection	17 (53%)	15 (9%)	0.05
Time of HIV infection (months, IQR)	293 (161-360)	153 (77-278)	0.001
Nadir CD4+ count (cells/mcL)	208 (111-368)	270 (160-387)	0.426
Current CD4+ count (cells/mcL)	601 (447-736)	555 (387-750)	0.785
Time on TDF (months, IQR)	62.5 (38-89-77)	52 (14-77)	0.054
Renal function			
Mean serum creatinine (mg/dL, range)	0.99 (0.63-1.78)	0.9 (0.61-1.45)	0.021
Mean eGFR-scr (ml/min/1.73 m², range)	88.4 (41-115)	99.2 (57-130)	0.002
Mean eGFR-cysC (ml/min/1.73 m2, range)	87.8 (57-125)	100.1 (51-143.5)	0.014
Serum phosphate (mg/dl, range) Hypophosphatemia (< 2.6 mg/dl)	2.7 (2.1-4.3) 12 (29%)	3.26 (2.9-4.6) 16 (10%)	0.002
Tubular parameters			
uPCR, mg/gr, range uPCR≥ 100 mg/gr	126.2 (107-147) 29 (90%)	78.6 (59-101) 44 (27%)	0.002
Mean albumin to creatinine ratio (uACR,mg/gr, range)	9.5 (6.1-23.5)	5.2 (4-7.3)	0.02
FE of phosphate (%, range) % of patients with FE phosphate ≥ 20%	26 (23-33) 31 (97%)	16.2 (13-22) 48 (29%)	<0.001
FE of uric acid (%, range) % of patients with FE uric acid ≥10%	6.7 (4.7-7.1) 0	6.6 (4.7-8.8) 30 (18%)	0.086
Glycosuria (>100 mg/dl)	10 (31%)	4 (2%)	<0.001
Complete Fanconi syndrome	3 (10%)	0	

After a median of 25.5 months, all the individuals were switched to a TAF-containing regimen and received it for 30.6 months (IQR, 13-70).

Tubular dysfunction persisted in 19% of individuals, associated with age (57.6 vs 50.8 years, p<0.001), previous tubular dysfunction (relative risk, RR, 3.03; 95%CI, 1.62-5.66), longer time on TDF (95 vs 76.2 months; p=0.036), presence of hypertension-diabetes (RR 2.4; 95%CI, 1.2-7.1), and a worse renal and tubular status at the time of TDF switch (eGFR, 75.6 vs 94.3ml/min; p=0.003; FE of phosphate 72% vs 79.1%, p=0.003; proteinuria 166.7 vs 92.3 mg/gr; p=0.009; albuminuria 59.1 vs 15.6 mg/gr; p=0.003)





Proteinuria: uPCR, urinary protein to creatinine ratio; Phosphaturia, % with FE phosphate >20%; Uricosuria, % of patients with FE of uric acid >10%; Glycosuria, >100 mg/dL; Tubular dysfunction, two or more altered tubular parameters; Complete Fancony syndrome, presence of >3 tubular alterations + hypophosphatemia

During TAF-containing regimens, tubular parameters improved (proteinuria –11.4 mg/gr, FE of phosphate -0.66%, FE of uric acid -0.92) but not the eGFR (-6.5 ml/min) due to the inhibition of creatinine secretion by concomitant antiretrovirals. However, we observed an improvement in eGFR-cysC after changing to TAF-including regimens.

In a Cox multivariate analysis, the presence of tubular dysfunction during a TAF-including regimen, after adjusting by age, sex, nadir CD4 count, eGFR-scr at baseline and eGFR-scr at discontinuation, proteinuria, and hypertension/diabetes was associated with

- **Age HR 1.061 (95%CI, 1.014-1.109), p=0.010 per year**
- **Time on TDF HR 1.001 (95% CI, 1.001-1.006) p=0.012 per month on therapy**

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