

# Changes in proximal tubular function after early discontinuation of Tenofovir Disoproxil Fumarate (TDF) in HIV patients with TDF induced renal dysfunction



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## Abstract

**Background:** Tenofovir (TDF) is the first line nucleoside reverse transcriptase inhibitors (NRTIs) for treatment of HIV-1 infection in Thailand. TDF causes a decline in renal function and proximal tubular dysfunction. The Thai guideline recommends stopping TDF in patients with eGFR decline greater than 25% from the baseline. Early discontinuation of TDF might preserve long-term renal function.

**Methods:** A prospective, controlled study was carried out in HIV-1 infected patients at King Chulalongkorn Memorial Hospital, Bangkok, Thailand from 1 September 2017 to 31 March 2018. Patients with TDF-induced nephropathy were switched the regimen to either to abacavir, lamivudine and efavirenz (ABC+3TC+EFV) or lopinavir/ritonavir plus lamivudine (LPV/r +3TC). Early discontinuation was applied in patients with proximal renal tubular dysfunction (PRTD) that was defined as the presence of  $\geq 2$  abnormalities in renal proximal tubular function; phosphaturia, non-diabetic glycosuria, hyperuricosuria, proteinuria and/or increased urinary beta-2 microglobulin or a decline in eGFR of 10-25% from baseline. The other group was made up of patients that continued TDF until eGFR declined to greater than 25% (standard treatment arm). The changes in proximal tubular function between these two arms were compared.

**Results:** A total of 26 patients were included in this study. Fifteen patients were in the early discontinuation arm and 11 patients were in the standard treatment arm (four patients were in the standard discontinuation and seven patients were in the continuation group). Thirteen patients were switched to ABC+3TC+EFV and six patients were switched to LPV/r +3TC. The median durations of TDF treatment were 73.46 ( $\pm 23.14$ ) months in the early discontinuation arm and 85.27 ( $\pm 37.01$ ) months in the standard treatment arm. At 12 weeks after TDF discontinuation, the percentage of change (% change) in rate of fractional excretion (FE) of phosphate was improved 31.3 (IQR: -4.4, 65.3) in the early discontinuation arm but worsening -17.4 (IQR: 39, 34.7) in the standard treatment arm ( $p=0.052$ ). The changes in fractional excretion (FE) of uric, urine protein to creatinine ratio and urine  $\beta 2$  microglobulin were also improved at 12 weeks after TDF withdrawal. The eGFR was stable (% Change 0 (IQR: -8.8, 6)) in the early discontinuation arm at 12 weeks after TDF withdrawal but was worsening -1.8 (IQR: -2.7, 9) ( $p=0.678$ ) in the standard treatment arm.

**Conclusions:** Early detection in TDF induced nephropathy leads to early withdrawal and may result in a better outcome of renal function.

**Table 1: Baseline characteristics**

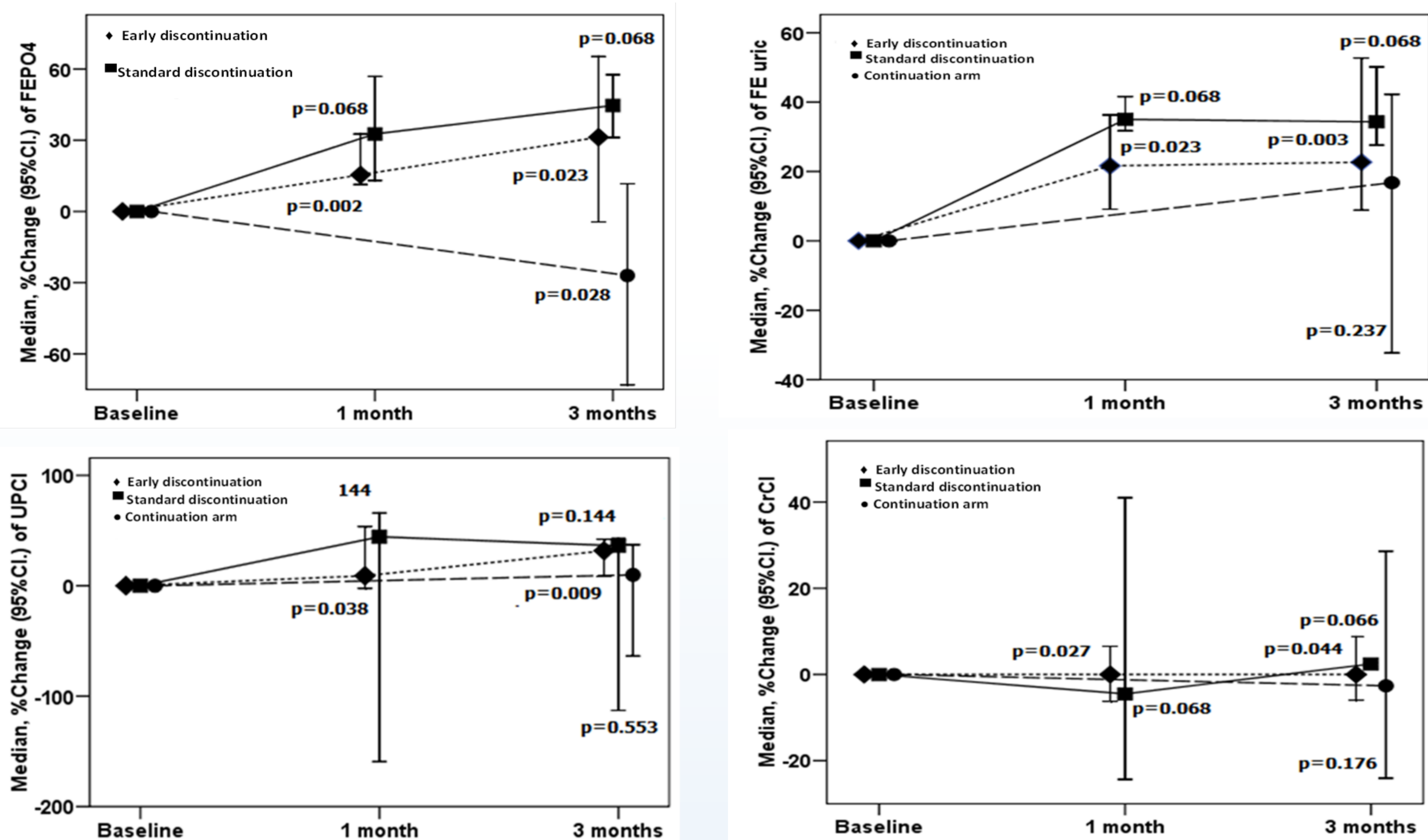
	Early discontinuation (n=15)	Standard treatment (n=11)	p-value
Mean Age (SD) (yrs)	52.33 ( $\pm 12.01$ )	44.45 ( $\pm 9.02$ )	0.08
male, n (%)	11 (73.3)	7 (63.6)	0.59
Mean $\pm$ SD Body weight (Kg)	64.33 ( $\pm 12.79$ )	64 ( $\pm 11.01$ )	0.94
Underlying disease			0.61
- HT	2 (13.3)	0	
- DM	2 (13.3)	2 (18.2)	
- HCV	1 (6.6)	0	
Median (IQR) Baseline CD4 (cells/mL)	74 (4%) (13-143 (2-10%))	175 (11%) (57-599 (6-18%))	0.02
Median (IQR) CD4 at inclusion (cells/mL)	485 (21%) (266-749 (18-23%))	591 (25%) (266-749 (20-30%))	0.58
HIV VL <40 at inclusion	15 (100)	11 (100)	
Antiretroviral regimen			0.36
- TDF+3TC+EFV	14 (93.3)	9 (81.8)	
- TDF+3TC+NVP	1 (6.7)	2 (18.2)	
Switch antiretroviral regimen			0.001
- ABC+3TC+EFV	9 (60%)	4 (36.4)	
- 3TC+LPV/r	6 (40%)	0	
Mean $\pm$ SD of Times on TDF (months)	73.46 ( $\pm 23.14$ )	85.27 ( $\pm 37.01$ )	0.32
Mean $\pm$ SD Cr at baseline	0.88 ( $\pm 0.23$ )	0.88 ( $\pm 0.18$ )	0.98
Mean $\pm$ SD eGFR at baseline, mL.min <sup>-1</sup> .1.73m <sup>2</sup>	93.86 ( $\pm 17.45$ )	98.45 ( $\pm 21.92$ )	0.55
Mean $\pm$ SD Cr at inclusion	1.07 ( $\pm 0.23$ )	1.14 ( $\pm 0.40$ )	0.56
Mean $\pm$ SD eGFR at inclusion, mL.min <sup>-1</sup> .1.73m <sup>2</sup>	77.73 ( $\pm 14.57$ )	76.72 ( $\pm 23.61$ )	0.95
Median (IQR) FE of phosphate	16.5 (11.8-18.92)	10.85 (9.23-39.63)	0.37
Median (IQR) TmP/GFR	2.88 (2.31-3.35)	2.63 (1.57-3.45)	0.51
Median (IQR) FE of uric	12.07 (10.07-15.10)	10.09 (8.50-40.70)	0.45
Median (IQR) UPCI	269.4 (120-530)	155.97 (108-790)	0.83
Urine glucose (positive)	3 (20)	4 (36.36)	0.35
Median (IQR) Urine $\beta 2$ microglobulin ( $\mu$ g/L)	1400 (360-7590)	3240 (250-21700)	0.85

## Background

- Tenofovir (TDF) is the first line nucleoside reverse transcriptase inhibitors (NRTIs) for treatment of HIV-1 infection in Thailand.
- TDF causes a decline in renal function and proximal tubular dysfunction.
- Most of the guidelines recommend stopping TDF if there is a significant decline in renal function. The Thai guideline recommends stopping TDF in patients with eGFR decline greater than 25% from the baseline.
- Early discontinuation of TDF might preserve long-term renal function.

## Methods

- A prospective, controlled study was carried out in HIV-1 infected patients at King Chulalongkorn Memorial Hospital, Bangkok, Thailand from 1 September 2017 to 31 March 2018.
- Patients with TDF-induced nephropathy were switched the regimen to either to abacavir, lamivudine and efavirenz (ABC+3TC+EFV) or lopinavir/ritonavir plus lamivudine (LPV/r +3TC).
- Early discontinuation was applied in patients with proximal renal tubular dysfunction (PRTD) that was defined as the presence of  $\geq 2$  abnormalities in renal proximal tubular function; phosphaturia, non-diabetic glycosuria, hyperuricosuria, proteinuria and/or increased urinary beta-2 microglobulin or a decline in eGFR of 10-25% from baseline. The other group was made up of patients that continued TDF until eGFR declined to greater than 25% (standard treatment arm).
- The changes in proximal tubular function between these two arms were compared.



Change	Early discontinuation		Standard discontinuation		Continuation		Total		p-value		
	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	n	Median (IQR)	E vs. S	E vs. C	S vs. C
<b>FEPO4</b>											
1 month	15	15.42 (11.37, 32.61)	4	32.67 (18.42, 49.2)	0	-	19	19.42 (12.37, 38.16)			
p-value		0.002*		0.068		NA		<0.001*			
3 months	15	31.29 (-4.4, 65.3)	4	44.64 (32.89, 56.12)	7	-26.98 (-61.53, -17.44)	26	16.17 (-17.44, 46.81)	0.530	0.001*	0.006*
p-value		0.023*		0.068		0.028*		0.032*			
<b>TmP/GFR</b>											
1 month	15	-8.9 (-22.92, 9.31)	4	-71.35 (-92.62, -43.14)	0	-	19	-14.93 (-28.9, 6.73)	0.006*		
p-value		0.334		0.068		NA		0.064			
3 months	15	0.44 (-12.66, 12.33)	4	-64.77 (-77.26, -44.25)	7	4.64 (-5.08, 19.09)	26	-3.24 (-16.02, 12.01)	0.006*	0.407	0.006*
p-value		0.910		0.068		0.237		0.568			
<b>FE uric</b>											
1 month	15	21.64 (9.15, 36.29)	4	35.02 (32.74, 38.97)	0	-	19	26.22 (14.17, 36.33)	0.152		
p-value		0.023*		0.068		NA		0.003*			
3 months	15	22.68 (8.87, 52.7)	4	34.31 (28.31, 44.89)	7	16.79 (-21.49, 39.12)	26	25.17 (11.69, 39.62)	0.185	0.490	0.109
p-value		0.003*		0.068		0.237		<0.001*			
<b>UPCI</b>											
1 month	15	9.03 (-2.44, 53.65)	4	44.34 (-63.81, 61.45)	0	-	19	31.65 (-2.44, 57.04)	0.810		
p-value		0.038*		0.144		NA		0.013*			
3 months	15	31.71 (8.4, 42.11)	4	36.17 (-40.03, 41.06)	7	9.84 (-22.22, 21.21)	26	20.81 (6.04, 37.17)	0.961	0.162	0.315
p-value		0.009*		0.144		0.553		0.004*			
<b>eGFR</b>											
1 month	15	0 (-6.25, 6.52)	4	-4.5 (-20.3, 24.15)	0	-	19	0 (-7.45, 7.27)	1.000		
p-value		0.027*		0.068		NA		0.003*			
3 months	15	0 (-5.97, 8.79)	4	2.44 (2.07, 2.63)	7	-2.63 (-9.71, 4.81)	26	0.91 (-5.97, 4.81)	0.885	0.490	0.315
p-value		0.044*		0.066		0.176		0.002*			
<b>UB2M</b>											
1 month	14	-0.9 (-40.04, 98.8)	4	3.24 (-37.72, 27.14)	0	-	18	-0.9 (-40.04, 70.2)	0.721		
p-value		0.374		0.109		NA		0.109			
3 months	14	31.22 (0, 56.52)	3	16.18 (0, 93.59)	7	-20 (-58.64, 2.02)	24	9.1 (-26, 51.88)	0.859	0.172	0.183
p-value		0.347		0.180		0.498		0.170			

**Table 2: Percentage of change in rate of renal tubular function and eGFR**

## Conclusion

- Improvement in proximal tubular function after TDF cessation is incomplete.
- Particularly in patients with a more gradual decline in change of proximal tubular function especially fractional excretion (FE) of phosphate in TDF withdrawal patients.
- The changes in the eGFR were also better in the early discontinuation arm.
- Early detection in TDF induced nephropathy leads to early withdrawal and may result in a better outcome of renal function.

## References:

Casado JL, Del Rey JM, Banon S, Santiuste C, Rodriguez M, Moreno A, et al. Changes in Kidney Function and in the Rate of Tubular Dysfunction After Tenofovir Withdrawal or Continuation in HIV-Infected Patients. J Acquir Immune Defic Syndr. 2016;72(4):416-22.

**Figure 1: Flow of recruitment**

