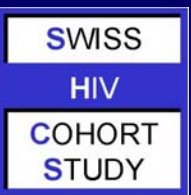


Tenofovir and Protease Inhibitor Use Are Associated with an Increased Prevalence of Proximal Renal Tubular Dysfunction in the Swiss HIV Cohort Study (SHCS)

CROI 2009
Poster 743



Christoph A. Fux¹, M Opravil², M Cavassin³, A Calmy⁴, B Spycher⁵, M Flepp⁶, B Hasse², P Schmid⁷, M Stöckle⁸, V Gurtner-De la Fuente⁹, A Rauch¹, H Furrer¹ and the Swiss HIV Cohort Study

¹ University Clinic for Infectious Diseases and University of Bern; ² University Hospital Zürich; ³ Centre Universitaire Hospitalier Vaudois, Lausanne; ⁴ Geneva University Hospital; ⁵ Institute for Social and Preventive Medicine, University of Bern; ⁶ Klinik im Park, Zürich; ⁷ Kantonsspital St. Gallen; ⁸ University Hospital Basel; ⁹ Ospedale Civico Lugano; Switzerland

Christoph A. Fux, MD
christoph.fux@insel.ch

Background

Tenofovir (TDF)-use has been associated with proximal renal tubulopathy (PRT). Excessive renal phosphate losses are of particular concern, as they may stimulate compensatory bone resorption and result in reduced bone mineral density over time.

Aims

To analyze the prevalence of PRT in general and excessive renal phosphate losses in particular and identify associated risk factors in HIV-positive patients.

Patients and Methods

We performed a cross-sectional analysis in 1202 unselected patients treated within the SHCS. Four parameters with the following thresholds for pathology were measured in fasting state:

- 1) the fractional excretion of phosphate (FE_p) >20% / >10% if hypophosphatemic
p/creat(urine) / p/creat(serum)
- 2) the fractional excretion of uric acid >10%
UA/creat(urine) / UA/creat(serum)
- 3) the urine protein/creatinine ratio >0.1
- 4) euglycemic glucosuria >0.8 mmol/L

PRT was defined as ≥3/4 pathological parameters.

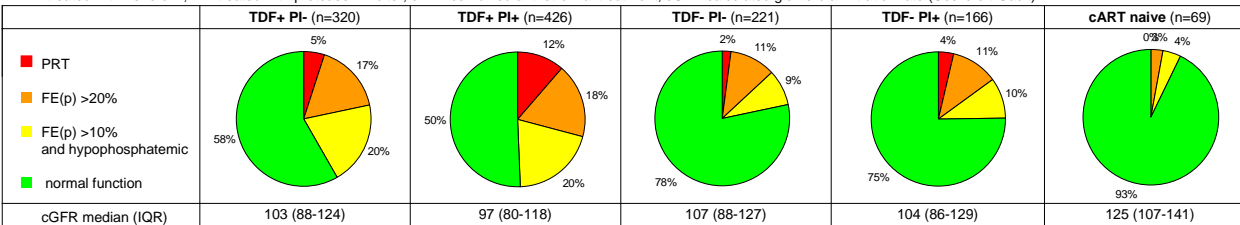
Logistic regression analyses were performed to identify associated risk factors. 174 patients with pathologic findings and 41 controls were re-tested to examine the reproducibility of our findings. Furthermore, we tried to overcome the lack of a gold standard for PRT with statistical modeling using latent class analysis, multiple imputation and factor analysis.

Results I: Cross-sectional analysis

Rates of PRT and pathological FE_p differed significantly between treatment groups (p=0.006 for PRT, p<0.001 for FE_p), being highest in patients treated with TDF and a PI (Table 1, Figure 1).

treatment	OR (95% CI) for PRT	p-value	OR (95% CI) for path FE _p	p-value
TDF- / PI-	1		1	
TDF+ / PI-	2.9 (0.9-8.7)	0.06	2.4 (1.6-3.6)	<0.001
TDF- / PI+	2.0 (0.6-7.3)	0.3	1.3 (0.8-2.2)	0.3
TDF+ / PI+	7.1 (2.5-19.8)	<0.001	3.4 (2.3-5.1)	<0.001

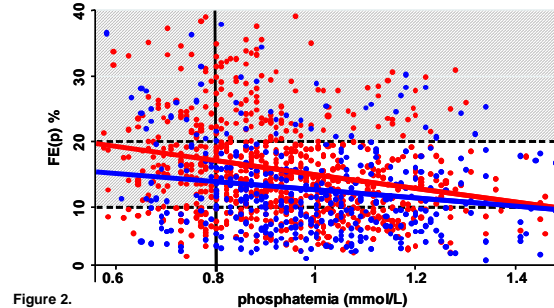
Figure 1. Rates of PRT (red; ≥3/4 pathological parameters) and pathological FE_p (orange: >20% & yellow: >10% and hypophosphatemic) by treatment group. TDF+ treated with Tenofovir; PI+ treated with protease inhibitor; cART combined antiretroviral treatment; cGFR calculated glomerular filtration rate (Cockcroft-Gault)



Logistic regression analyses identified TDF- and PI-use as the only HIV-related parameters associated with PRT (Table 2) and pathological FE_p (data not shown; adjusted OR of 2.6 [1.9-3.6] for TDF and 1.5 [1.1-2.0] for PI-use).

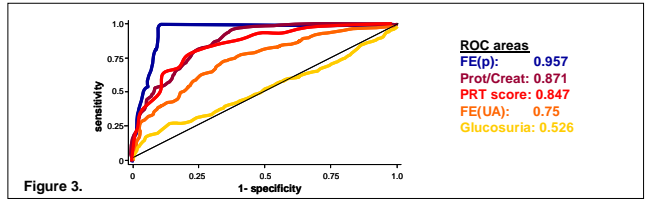
	Univariable analysis		Multivariable analysis	
	OR	p-value	Adjusted OR	p-value
female sex	1.5 (0.9-2.5)	0.1	1.5 (0.8-2.8)	0.2
age (by 10 years)	1.3 (1.1-1.7)	0.006	1.6 (1.2-2.1)	0.001
BMI (kg/m ²)	0.9 (0.8-0.9)	<0.001	0.9 (0.8-0.9)	0.001
IDU	2.0 (1.2-3.5)	0.01	1.6 (0.8-3.2)	0.2
HIV RNA (log10)	0.8 (0.6-1.1)	0.1	0.8 (0.5-1.2)	0.3
CD4 (by 100 cells/μl)	0.9 (0.8-1.0)	0.01	0.9 (0.8-1.1)	0.3
AIDS	1.8 (1.1-2.9)	0.02	1.4 (0.8-2.4)	0.3
Duration HIV (by year)	1.1 (1.0-1.1)	0.001	1.0 (0.9-1.1)	1.0
Duration cART (by year)	1.1 (1.1-1.2)	<0.001	1.1 (0.9-1.2)	0.4
TDF-use	3.6 (1.8-7.1)	<0.001	3.3 (1.6-7.0)	0.001
PI-use	2.7 (1.6-4.5)	<0.001	1.8 (1.0-3.3)	0.05

As excessive renal phosphate losses can be compensated by extrarenal factors, we used the fractional excretion of phosphate instead of hypophosphatemia as an endpoint. The correlation between phosphatemia and FE_p is shown in Figure 2 comparing patients treated with TDF (red dots) or a TDF-sparing regimen (blue dots). The linear prediction plots illustrate the higher phosphate losses in hypophosphatemic patients, suggesting a causal relationship.



Results II: statistical modeling – latent class analysis

Statistical modeling allowed us to construct a virtual pathology indicator from our data and calculate ROC curves for the performance of the four measured parameters and the cumulative PRT score. Figure 3 documents the outstanding performance of FE_p for the modeled gold standard of PRT.



Results III: Confirmatory testing

Confirmatory testing was performed after a median of 10 months (IQR 9-12). Some 75% of patients with PRT and 50% of patients with a pathological FE_p showed persistent anomalies, while new pathologies were very rare in negative controls (Figure 4).

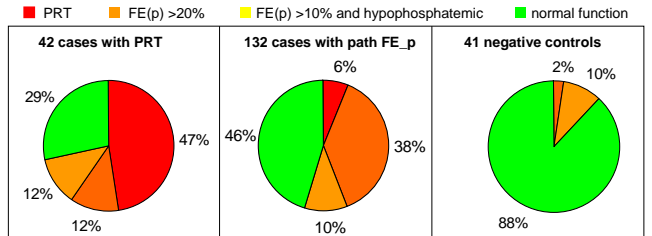


Figure 4.

Conclusions

- Proximal renal tubulopathy was documented in 22% to 50% of cART-treated patients depending on the regimen used
- The prevalence was increased under TDF and PI, especially when combined
- FE_p is most accurate to document proximal tubular dysfunction
- Confirmatory testing is necessary, as pathological findings only persist in 50-75%
- The clinical impact of excessive renal phosphate losses, particularly for the bone, have to be addressed in further studies