683 Clinical risk factors for severe tenofovir (TDF) associated renal tubulopathy

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Background

- The use of tenofovir (TDF) is infrequently associated with treatment limiting renal tubular disease, which may range from acute tubular injury (ATI) to severe proximal tubulopathy (PT) [1-3]
- The clinical spectrum of and risk factors for TDF-induced treatment-limiting nephrotoxicity remain poorly defined

Aim

- To determine the risk factors for developing TDF associated severe renal tubulopathy (RT)

Methods

Study population

- Cases of TDF-associated treatment-limiting RT were retrospectively identified using clinical databases and physician recall, and included in the analyses if they had at least 2 markers of PT and/or ATI on kidney biopsy which was not explained by other aetiologies
- Markers used to define PT [3]
  - **Normoglycaemic glycosuria**
  - **Hypophosphataemia (serum phosphate [PO_4] <0.64 mmol/l [<1.98 mg/dl])**
  - **Proteinuria (urinary protein-creatinine ratio [PCR] >30 mg/mmol [>26.5 g/g])**
  - **Hypokalaemia (serum potassium [K^+] <0.3 mmol/l [<0.3 mEq/l])**
  - **Metabolic acidosis (serum bicarbonate [HCO_3] <19 mmol/l [<19 mEq/l])**
- All people included in this analyses contributed data to the UK Collaborative HIV Cohort (UK CHIC) [4]
- Comparator subjects within UK CHIC were patients from the same seven clinics as the RT cases who received TDF for >4 weeks and who were not diagnosed with RT
- Follow up was from the date of starting TDF to either the date of stopping TDF or the last visit (up to 31/12/2013) if TDF was continued

Variables

- Baseline variables including CD4 cell count, HIV viral load (VL, $\log_{10}$), CKD-Epi calculated estimated glomerular filtration rate (eGFR), hepatitis B sAg and hepatitis C antibody positivity were defined as the most recent measurement prior to starting TDF

Statistical analysis

- Incidence and baseline characteristics of all cases of TDF-associated RT and the comparator group were described
- Multivariable Poisson regression was used to investigate factors associated with RT, including baseline demographics and time updated covariates such as hepatitis B or C status, CD4 cell count and VL

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Characteristics at TDF start

- 15983 subjects received TDF for >4 weeks between October 2002 and July 2013
- Between 1st July 2002 and 3rd June 2013, 69 were diagnosed with TDF-associated RT
  - 48 were clinically diagnosed with TDF-associated RT and had ≥2 markers of PT
  - 12 had ATI on biopsy (4 with ≥2 markers of PT)
  - 9 clinical cases had <2 markers of PT and were excluded from this analysis
- Clinically diagnosed PT and ATI cases had similar characteristics at TDF start

Table 1: Baseline characteristics at TDF start

		Clinically diagnosed PT (n=48)	Acute tubular injury (n=12)	All RT cases (N=60)	Controls (N=15,914)
Age - years	Mean (SD)	45.8 (10.0)	44.6 (11.0)	45.6 (9.5)	40.7 (9.5)
Male	N (%)	44 (92)	11 (92)	55 (92)	12,689 (80)
Ethnicity - White/Other	N (%)	45 (94)	11 (92)	56 (93)	11,739 (74)
Exposure - MSM	N (%)	37 (77)	9 (75)	46 (79)	9,819 (62)
Calendar year at TDF start					
1996-2003	N (%)	16 (33)	3 (18)	17 (28)	1,178 (7)
2004-2007	N (%)	20 (42)	7 (41)	28 (47)	5,022 (32)
2008-2010	N (%)	6 (13)	7 (41)	9 (15)	5,014 (32)
2011-2014	N (%)	6 (13)	0 (0)	6 (10)	4,700 (30)
Years on ART	Median (IQR)	3.9 (0.0, 9.3)	4.7 (1.6, 6.5)	4.2 (0.0, 7.5)	0.0 (0.0, 5.5)
Previous AIDS event	N (%)	19 (40)	5 (41)	24 (40)	4,091 (26)
HBV positive	N (%)	3 (10)	0 (0)	3 (8)	639 (4)
HCV positive	N (%)	1 (3)	0 (0)	1 (3)	1,033 (6)
Nadir CD4 cell count	Median (IQR)	110 (25, 185)	156 (75, 242)	119 (28.5, 184.5)	190 (91, 284)
CD4 cell count	Median (IQR)	317 (169, 459)	470 (335, 635)	360.5 (197.5, 470)	364 (237, 528)
Viral Load ($\log_{10}$copies)	Median (IQR)	2.5 (1.7, 3.6)	1.7 (1.7, 2.4)	2.2 (1.70, 3.4)	2.2 (1.7, 3.1)
eGFR (ml/min/1.73m²)	Mean (SD)	93.1 (17.2)	94.9 (16.5)	93.6 (16.9)	96.2 (16.4)

Characteristics at presentation

- RT was diagnosed after a median (IQR) of 44.1 (20.4, 64.4) months on TDF, and 83% of cases had co-administration of a ritonavir-boosted PI (44% lopinavir, 35% atazanavir, 16% darunavir, 5% other)
- Only 4 patients with ATI had sufficient data to assess the presence of PT. However duration of TDF exposure (44.1 vs. 43.4 months, p=0.39) and proportion with PI co-administration (60.4% vs. 66.7%, p=0.69) were similar for all PT and all ATI cases respectively

Table 2: Presentation of RT

	Summary statistic	N	All RT cases (n=60)
eGFR (mL/min/1.73m²) at presentation	Median (IQR)	57	52.7 (44.5, 71.5)
>25% drop eGFR	N(%)	57	34 (60)
Normoglycaemic glycosuria	N(%)	54	37 (62)
Hypophosphataemia	N(%)	55	41 (68)
Proteinuria	N(%)	55	55 (92)
Hypokalaemia	N(%)	44	3 (5)
Metabolic acidosis	N(%)	22	7 (12)
Raised alkaline phosphatase	N(%)	59	33 (55)

Risk factors for renal tubulopathy

- RT was associated with older age, white ethnicity, lower CD4 cell count and PI based therapy

Table 3: Univariate and multivariate analyses of factors associated with RT (N=60)

	Univariate			Multivariate$		
	RR	**95% CI**	**P**	**RR**	**95% CI**	**P**
Age at baseline	**1.30**	**(1.15, 1.47)**	**<0.0001**	**1.31**	**(1.15, 1.49)**	**<0.0001**
Sex						
Male	1					
Female	**0.38**	**(0.15, 0.94)**	**0.037**	0.81	(0.30, 2.18)	0.674
Ethnicity N (%)						
White/Other	1			1		
Black	**0.21**	**(0.08, 0.57)**	**0.002**	**0.22**	**(0.07, 0.65)**	**0.006**
Calendar year at TDF start						
1996-2003	1			1		
2004-2007	**0.46**	**(0.26, 0.81)**	**0.007**	0.57	(0.31, 1.04)	0.068
2008-2010	**0.31**	**(0.15, 0.63)**	**0.001**	**0.34**	**(0.15, 0.78)**	**0.011**
2011-2014	**0.39**	**(0.15, 0.97)**	**0.043**	0.58	(0.22, 1.53)	0.272
Time on TDF (per year increase)*	1.08	(0.98, 1.19)	0.125			
Years on antiretrovirals at TDF start	**1.06**	**(1.00,1.12)**	**0.034**	1.00	(0.94, 1.06)	0.990
Antiretroviral regime*						
NNRTI	1			1		
PI based	**4.43**	**(2.55, 7.69)**	**<0.0001**	**4.17**	**(2.38, 7.32)**	**<0.0001**
Previous AIDS event	1.48	(0.88, 2.48)	0.137			
Hepatitis B status*						
Negative	1					
Positive	1.27	(0.46, 3.53)	0.647			
Hepatitis C status*						
Negative	1					
Positive	0.37	(0.09, 1.52)	0.167			
Nadir CD4 cell count (per 50 cell ↑)*	0.89	(0.80, 1.00)	0.049			
CD4 cell count (per 50 cell increase)*	**0.91**	**(0.85, 0.96)**	**0.001**	**0.91**	**(0.86, 0.97)**	**0.002**
HIV Viral load (per 1 log increase)*	0.74	(0.44, 1.23)	0.241			
Baseline eGFR (per 10ml/min ↓)	0.90	(0.76, 1.08)	0.256			

*Time updated

$ adjusted for fixed covariates: age, ethnicity, calendar year of TDF start, years on ARVs prior to TDF start, time updated covariates: ARV regime, time on TDF and CD4 cell count

- Analysis restricted to the 52 cases with ≥2 markers of PT gave similar results

Conclusions

- Severe TDF-associated renal tubulopathy was uncommon in the UK CHIC study
- Not all patients had proteinuria, glycosuria and hypophosphataemia, and approximately half had no or relatively minor reductions in eGFR suggesting that these biomarkers in isolation are insufficient to monitor patients on TDF for the development of severe PT or ATI
- Hypophosphataemia and raised alkaline phosphatase suggest RT may have been accompanied by osteomalacia in approximately 60% of cases
- Age and PI co-administration were important risk factor for the development of RT; black ethnicity and higher CD4 cell count were protective
- Baseline eGFR did not identify subjects at increased risk of developing RT

References *(1) Woodward et al. HIV Med 2009 (2) Gupta et al. Pharmacogenet Genomics 2015 (3) Hamzah et al. AIDS 2015 (4) UK Collaborative HIV Steering Committee HIV Med 2004*

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