Incidence of renal Fanconi Syndrome in patients taking antiretroviral therapy including tenofovir disoproxil fumarate.

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Background

Renal Fanconi Syndrome (FS):

- Linked to use of tenofovir disoproxil fumarate (TDF) since early use of the drug
- Leakage from impaired proximal tubule into the urine of substances normally absorbed back:
  - glucose, amino acids, phosphate, bicarbonate
  - diagnosed through the higher than normal levels of those substances in urine or lower than normal levels of those substances on plasma
- Sequeallae include acute kidney injury, chronic bone calcium loss
- Relationship with TDF poorly studied despite 15 years of use and more than 10 million patients
  - No working case definition
  - Not detected in early RCTs

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Aims:

Determine the incidence of Fanconi syndrome:

- In routine clinical practice
- Using routinely available renal monitoring

Determine if it is associated with risk factors for chronic kidney disease or other patient or treatment factors

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Methods

Retrospective cohort of all patients taking ART attending MSHC from 2002 to 2016

Extracted from electronic record:

- ART history, diagnoses of diabetes, hypertension, hyperlipidemia, HBV, HCV, age, gender, country of birth
- Urinalysis results (qualitative)

Extracted from laboratory:

- serum creatinine, Ca, PO_4, Mg, CD4 cell count, viral load
- eGFR calculated using CKD-epi

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Methods

Fanconi syndrome case definition:

= normoglycaemic glycosuria

+ proterinura

+ one of:

- Hypophosphataemia (<0.75mmmol/L)
- Metabolic acidosis
- eGFR fall by >30ml/min/1.73m^2 or to <60ml/min/1.73m^2
- Renal biopsy proven tubulopathy
- Phosphaturia

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Methods

Examined each period of ART exposure.

Time from initiation of ART to:

- end of study (censor),
- Change ART for reason other than Fanconi syndrome (censor) or
- Meet FS case definition (event)

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Results

Table 1. Demographic characteristics and clinical information among 1537 HIV-positive patients at MSHC, stratified by antiretroviral exposure.

	All ART	Non-TDF ART	TDF only	TDF and ritonavir
Number of patients	1537	807	1044	398
Age in years mean (±SD)[a]	37.7 (±10.3)	36.9 (±10.5)	38.4 (±11.0)	40.8 (±10.7)
Male % (n)	89.9% (1382)	88.4% (713)	90.1% (941)	87.2% (347)
MSM % (n)	78.3% (965)	74.9% (453)	78.5% (704)	74.5% (239)
Born Australia % (n)	55.8% (820)	57.3% (441)	56.3% (564)	58.4% (222)
Diabetes % (n)[b]	2.9% (45)	3.8% (31)	3.4% (35)	4.3% (17)
Hypertension[b] % (n)	10.0% (154)	13.9% (112)	10.1% (105)	11.6% (46)
Hyperlipidaemia[b] % (n)	5.8% (89)	7.7% (62)	5.9% (62)	8.3% (33)
Hepatitis B % (n)[c]	3.2% (49)	4.1% (33)	3.5% (37)	3.8% (15)
Hepatitis C % (n)[c]	6.8% (104)	6.6% (53)	6.5% (68)	8.3% (33)
Suppression % (n)[d]	98.3% (1511)	97.3% (785)	99.4% (1038)	98.5% (392)
CD4 nadir mean (±SD)	314 (±195)	343 (±207)	355 (±192)	315 (±203)
Total exposure (PY)	10501	5063	3779	1637
Mean exposure months (±SD)	81.0 (±74.1)	75.3 (±69.8)	42.3 (±35.6)	49.4 (±36.8)
Baseline eGFR mean (±SD) (n)[e]	103.5 (±19.6) (1132)	107.1 (±19.2) (325)	105.9 (±17.0) (820)	102.3 (±18.4) (287)
% with eGFR < 50 (n)[f]	5.1% (78/1537)	4.3% (24/558)	2.5% (48/844)	1.6% (6/379)

Characteristics of 1537 HIV-positive patients stratified by antiretroviral exposure

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Results

Case	Age[a]	Gender	Risk	Country of birth	CD4 min[b]	Co-morbidities[c]	Current ART[d]	Months TDF[e]	Months TDF + rit[f]	Viral load
1	39.9	M	MSM	Australia	243	Hyperlipidaemia, Hepatitis C	TDF ABC ATV LPV/r	98	98	BLD[g]
2	43.7	M	MSM	Australia	132	–	TDF ABC 3TC EFV LPV/r	70	70	BLD[g]
3	56.4	M	MSM	Australia	627	Hepatitis B	TDF FTC EFV	73	–	BLD[g]
4	48.2	M	MSM	Australia	421	–	TDF FTC ATV/r	34	34	BLD[g]
5	51.7	M	MSM	Australia	265	–	TDF FTC RPV	53	–	BLD[g]
6	34.1	M	MSM	Australia	400	Hyperlipidaemia	TDF FTC ATV/r	40	40	BLD[g]
7	33.4	M	MSM	Australia	507	–	TDF FTC LPV/r	12	12	BLD[g]
8	48.6	M	MSM	Australia	335	–	TDF FTC ATV/r	40	40	BLD[g]
9	37.0	M	MSM	UK	558	Hypertension, hyperlipidaemia	TDF FTC ATV/r	16	16	BLD[g]
10	54.6	M	MSM	UK	338	–	TDF FTC RPV	29	–	BLD[g]
11	29.6	M	HPC	Ethiopia	25	–	TDF FTC ATV LPV/r	85	85	BLD[g]
12	46.2	M	HPC	Australia	154	–	TDF FTC EFV	74	–	BLD[g]
13	47.7	M	Unknown	Australia	314		TDF FTC LPV/r	91	91	BLD[g]

Characteristics of 13 cases of Fanconi Syndrome

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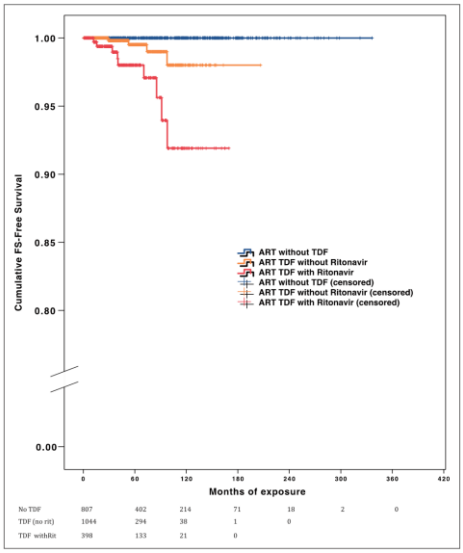
Results



Cumulative FS-free survival (months) after exposure to ART)

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Results

	n[a]	Cases[b]	Person Years	Incidence/1000PY (95%CI)	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)[c]	p-value
TDF+RIT								
Yes[d]	398	9	1637	5.50[e] (3.66–7.33)	4.87 (1.50–15.82)	.008	4.71 (1.37–16.14)	.014
No	1044	4	3679	1.09[e] (0.54–1.63)	Ref		Ref	
Age[f]	1442	13	–	–	1.021 (0.98–1.07)	.414		
Baseline eGFR	1107	11	–	–	0.97 (0.94–1.01)	.089	0.97 (0.94–1.00)	.074
CD4 Nadir[g]	1142	13	–	–	1.00 (0.76–1.32)	.985		
Diabetes[h]								
Yes	52	0	253	–	–	.572		
No	1390	13	5064	2.57 (1.86–3.28)	–			
Hypertension[h]								
Yes	151	1	803	1.24 (0.00–2.49)	0.37 (0.05–2.87)	.341		
No	1291	12	4513	2.66 (1.89–3.43)	Ref			
Hyperlipidaemia[h]								
Yes	95	3	513	5.84 (2.47–9.22)	2.28 (0.62–8.38)	.215		
No	1347	10	4803	2.08 (1.42–2.74)	Ref			
Hepatitis B[i]								
Yes	52	1	242	4.13 (0.00–8.27)	1.46 (0.19–11.29)	.720		
No	1390	12	5075	2.36 (1.68–3.05)	Ref			
Hepatitis C[i]								
Yes	101	1	392	2.55 (0.00–5.10)	1.00 (0.13–7.72)	.998		
No	1341	12	4924	2.44 (1.73–3.14)	Ref			
Male								
No[j]	154	0	538	–	–	.448		
Yes	1288	13	4778	2.72 (1.97–3.48)	–			
Born in Australia								
No[j]	596	3	2040	1.47 (0.62–2.32)	0.48 (0.13–1.76)	.268		
Yes	786	10	3075	3.25 (2.22–4.28)	Ref			
MSM								
No[j]	275	3	1121	2.68 (1.13–4.22)	0.96 (0.26–3.49)	.958		
Yes	942	10	3668	2.73 (1.86–3.59)	Ref			

Results of Cox Regression Analysis: crude and adjusted hazard ratio of time to development of FS after initiation of ART

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Results

13 cases of FS

- Mean TDF exposure 55 months
- Incidence:
  - 1.09/1000 PY (0.54-1.63) TDF without ritonavir
  - 5.50/1000PYs (3.66-7.33) TDY with ritonavir (p=0.0057).
- aHR (time to FS) for ritonavir co-administration 4.71 (1.37-16.14, p=0.014).
- age, sex, co-morbidities (hypertension, hyperlipidaemia, diabetes, viral hepatitis), CD4 cell count nadir and baseline eGFR not associated

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Discussion

Limitations:

- Retrospective cohort using routine laboratory parameters (but prospective cohorts using advanced laboratory investigations are not unfeasible)
- Patients may have change treatment due to renal disease and not met criteria of FS
- Likely under-estimate incidence of proximal tubular disease

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Conclusion

- Fanconi syndrome occurs late
  - Explains why not detected in RCTs
- Uncommon but not rare
- Ritonavir administration increases the incidence approximately 5 times
- Frequent monitoring is required, including in very long term patients who do not appear to be at increased risk

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