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
- Sequelae 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
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

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, PO₄, Mg, CD4 cell count, viral load
- eGFR calculated using CKD-epi
Methods

Fanconi syndrome case definition:

= normoglycaemic glycosuria
+ proterinura
+ one of:
  • Hypophosphataemia (<0.75mmol/L)
  • Metabolic acidosis
  • eGFR fall by >30ml/min/1.73m² or to <60ml/min/1.73m²
  • Renal biopsy proven tubulopathy
  • Phosphaturia

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)
Results

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

<table>
<thead>
<tr>
<th></th>
<th>All ART</th>
<th>Non-TDF ART</th>
<th>TDF only</th>
<th>TDF and ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1537</td>
<td>807</td>
<td>1044</td>
<td>398</td>
</tr>
<tr>
<td>Age in years (± SD)*</td>
<td>37.7 (± 10.3)</td>
<td>36.9 (± 10.5)</td>
<td>38.4 (± 11.0)</td>
<td>40.8 (± 10.7)</td>
</tr>
<tr>
<td>Male % (n)</td>
<td>89.9% (1392)</td>
<td>88.4% (713)</td>
<td>90.1% (941)</td>
<td>87.2% (347)</td>
</tr>
<tr>
<td>MSM % (n)</td>
<td>78.3% (965)</td>
<td>74.9% (453)</td>
<td>78.3% (704)</td>
<td>74.5% (239)</td>
</tr>
<tr>
<td>Born Australia % (n)</td>
<td>55.8% (820)</td>
<td>57.3% (441)</td>
<td>56.3% (564)</td>
<td>58.8% (222)</td>
</tr>
<tr>
<td>Diabetes % (n)%</td>
<td>2.9% (45)</td>
<td>3.8% (31)</td>
<td>3.4% (33)</td>
<td>4.3% (17)</td>
</tr>
<tr>
<td>Hypertension% (n)</td>
<td>10.0% (154)</td>
<td>13.5% (112)</td>
<td>10.1% (105)</td>
<td>11.6% (46)</td>
</tr>
<tr>
<td>Hyperlipidaemia% (n)</td>
<td>5.8% (89)</td>
<td>7.7% (62)</td>
<td>5.9% (62)</td>
<td>8.3% (33)</td>
</tr>
<tr>
<td>Hepatitis B % (n)**</td>
<td>3.2% (49)</td>
<td>4.1% (33)</td>
<td>3.5% (37)</td>
<td>3.8% (15)</td>
</tr>
<tr>
<td>Hepatitis C % (n)**</td>
<td>6.8% (104)</td>
<td>6.6% (53)</td>
<td>6.5% (68)</td>
<td>8.3% (33)</td>
</tr>
<tr>
<td>Suppression % (n)**</td>
<td>98.3% (1511)</td>
<td>97.3% (785)</td>
<td>99.4% (1038)</td>
<td>98.5% (392)</td>
</tr>
<tr>
<td>CD4 nadir mean (± SD)</td>
<td>314 (± 195)</td>
<td>314 (± 207)</td>
<td>355 (± 192)</td>
<td>315 (± 203)</td>
</tr>
<tr>
<td>Total exposure (PY)</td>
<td>10500</td>
<td>5063</td>
<td>2779</td>
<td>1637</td>
</tr>
<tr>
<td>Mean exposure months (± SD)</td>
<td>8.10 (± 74.1)</td>
<td>75.3 (± 69.8)</td>
<td>42.3 (± 35.6)</td>
<td>49.4 (± 36.8)</td>
</tr>
<tr>
<td>Baseline eGFR mean (± SD)</td>
<td>103.5 (± 19.6) (1332)</td>
<td>107.1 (± 19.2) (325)</td>
<td>105.9 (± 17.0) (820)</td>
<td>102.3 (± 18.4) (287)</td>
</tr>
<tr>
<td>% with eGFR &lt; 50 (n)**</td>
<td>5.1% (78/1537)</td>
<td>4.3% (24/558)</td>
<td>2.5% (48/944)</td>
<td>1.6% (6/379)</td>
</tr>
</tbody>
</table>

Characteristics of 1357 HIV-positive patients stratified by antiretroviral exposure

Results

Characteristics of 13 cases of Fanconi Syndrome
Results

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

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

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
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