

Tenofovir tubulopathy: sorting the horses from the zebras

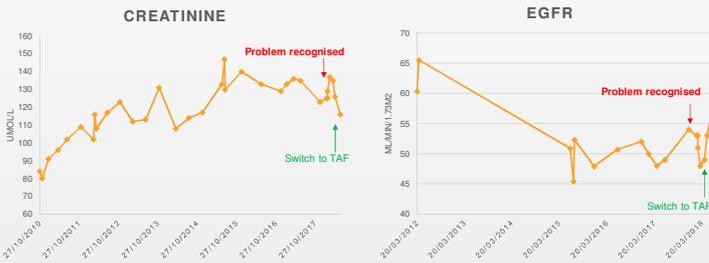
Clinical lesson

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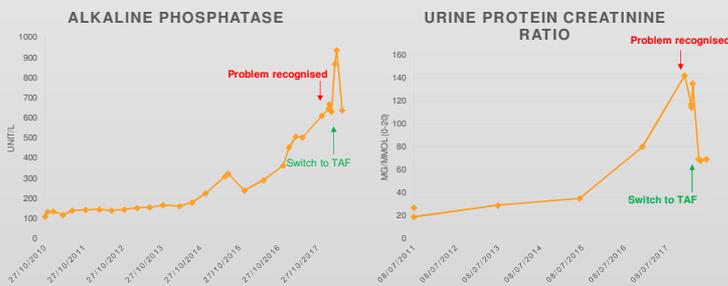
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Introduction

A 65-year-old male with HIV diagnosed over 20 years ago was found to have progressive derangement in his renal and bone biochemistry profiles. His adherence to antiretroviral medication was excellent, with sustained viral suppression for many years and CD4 counts consistently greater than 700. His medical history included pancreatic insufficiency, lumbar osteoarthritis, facet joint injections for chronic spinal pain, renal colic and recurrent bacteriuria, hypercholesterolaemia, and plantar fasciitis with navicular avascular necrosis. His HIV medication since October 2010 was Tenofovir Disproxil Fumarate (TDF) / Emtricitibine (FTC) / Efavirenz (EFZ) in a fixed-dose once daily combination.



There had been a modest decline in his renal function over the past 5 years, now with an estimated glomerular filtration rate (eGFR) of 51. In addition, the Alkaline Phosphatase (AlkP) was high (646iu/L), serum phosphate low (0.5mmol/L) and urine protein/creatinine ratio was markedly raised (135). He presented with symptoms of loin pain and thigh pain. The biochemical abnormalities in the context of long-term TDF therapy prompted a tubulopathy screen. There were also concerns that the new biochemical abnormalities were indicative of CKD-Mineral Bone Disease (CKD-MBD).



Methodology

Clinical examination revealed bilateral loin discomfort but was otherwise unremarkable, with no hypertension and a normal ECG. Renal ultrasound did not reveal any acute or focal pathology. The tubulopathy screen found glycosuria on dipstick test, a raised urine retinol binding protein (129mg/L), raised urine phosphate/creatinine ratio (3.5), low serum urate (119umol/L) and low vitamin D (20nmol/L), all confirming tubulopathy.

TDF was switched to Tenofovir Alafenamide (TAF) and high-dose Vitamin D replacement was commenced. After these changes, creatinine improved to 126umol/L, eGFR improved to 58 and urine protein/creatinine ratio fell from 142 to 68. The loin and muscle pains improved rapidly, although the patient now complained of focal pain and tenderness in the ribs posteriorly. His AlkP continued to rise, reaching a peak of 935iu/L. The remainder of the liver profile remained normal. Parathyroid hormone (PTH) was slightly raised at 9.8pmol/L. A renal specialist advised that the AlkP was too high to be explained by CKD-MBD and that an alternative cause needed to be considered, including primary bone pathology such as myeloma, sarcoma or Paget's Disease. DEXA bone densitometry was within normal limits for age and sex; serum free light chains were not markedly elevated; an isotope bone scan revealed multiple bilateral posterior rib fractures in a roughly linear conformation (Figure 1). On further questioning the patient gave a corroborative history of an episode of trauma while on the top deck of a bus in early 2018.

Risk factors for CKD¹

Traditional risk factors

- Increasing age
- Diabetes mellitus
- Hypertension
- Cardiovascular disease
- Previous AKI

Additional risk factors in HIV

- Low CD4
- High viral load
- Intravenous drug use
- Co-infection with Hepatitis C
- Combination antiretroviral therapy

TDF-related renal injury

Mechanisms¹

Intracellular accumulation
Direct toxicity in proximal tubules
Mitochondrial depletion

Consequences²

Vitamin D deficiency
Metabolic bone disease

- Hypophosphataemia
- Bone pain
- Osteomalacia
- Decreased bone mineralisation
- Bone fractures

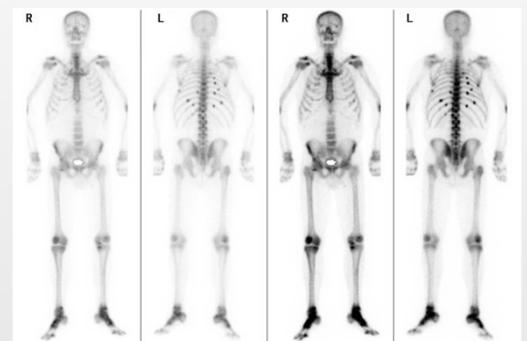


Figure 1. Isotope bone scan of our patient showing multiple bilateral rib fractures.

Discussion

TDF is one of the most commonly prescribed antiretrovirals and renal toxicity through tubulopathy has come to be a well-known problem, including the potential to develop Fanconi Syndrome. Tubular dysfunction secondary to TDF therapy may reverse on stopping the drug. The newer preparation of TAF is marketed on its lower renal toxicity compared to TDF and we have shown in this case that TDF-related renal function can significantly improve after switching to TAF. Our patient's biochemical profile was further complicated by the markedly raised AlkP, out of keeping with CKD-MBD and calling into question whether instead a primary bone problem such as malignancy or Paget's disease were at play (Zebras). However, the additional history of rib fractures (Horse) explained the disproportionately raised AlkP. Given the unusual presentation, it may also be that a degree of underlying CKD-MBD was a contributory factor to fracture vulnerability.



Conclusion

This was a case of renal tubulopathy from Tenofovir Disproxil Fumarate with disproportionately raised alkaline phosphatase.

The clinical lesson is that while it is important to be vigilant for the clinical manifestations of renal disease in HIV-infected patients on treatment, and to consider rarer diagnoses, Occam's Razor may be blunted by Hickam's Dictum when teasing apart the causes of biochemical abnormalities.

References

1. Pedro Campos, Alberto Ortiz, Karina Soto; HIV and kidney diseases: 35 years of history and consequences. *Clinical Kidney Journal*. Volume 9, Issue 6, 1 December 2016, Pages 772–781
2. Tourret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword?. *J Am Soc Nephrol*. 2013;24(10):1519-27.