A HOLIDAY TO REMEMBER

Tenofovir-induced osteomalacia

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1. INTRODUCTION

Tenofovir (TDF), a nucleotide reverse transcriptase inhibitor, is widely used in the backbone of combined HIV antiretroviral therapy. Fanconi's syndrome is a defect in proximal tubule function causing hypophosphatemia and osteomalacia, which can be caused by tenofovir therapy. We report a rare case of this complication.

2. CASE RECORD

A 48 year old Zimbabwean woman, visiting her daughter in Perth WA, presented wheelchair-bound with incapacitating pelvic and lower limb pain.

Past Medical History (figure 2):

1. HIV infection – diagnosed 2000, managed in Zimbabwe
   Drug resistance with extensive anitretroviral treatment (ART) history (Figure 2)
   Recent CD4 287 (16%) with virological suppression and 100% compliance
2. Uncharacterised biliopathy with portal hypertension: normal liver USS (2015)
   New onset jaundice (2016)

3. HISTORY OF PRESENTING COMPLAINT

The patient reported a 12 month history of gradually progressive pain in her pelvis, proximal limbs, lower back and ribs that had become severely disabling, such that she was largely bed-bound and wheelchair dependent.
Following a normal MRI spine, a provisional diagnosis of "peripheral neuropathy" had been made in Zimbabwe.

Examination:

- Cognitive slowing; reduced BMI
- Jaundice; no peripheral signs of chronic liver disease
- Generalized bony tenderness; mild quadriceps muscle wasting
- Reduced proximal power due to severe pain
- Preserved reflexes, coordination and sensation
- Moderate splenomegaly; systems exam otherwise unremarkable

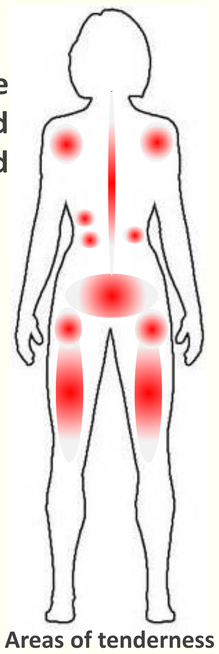
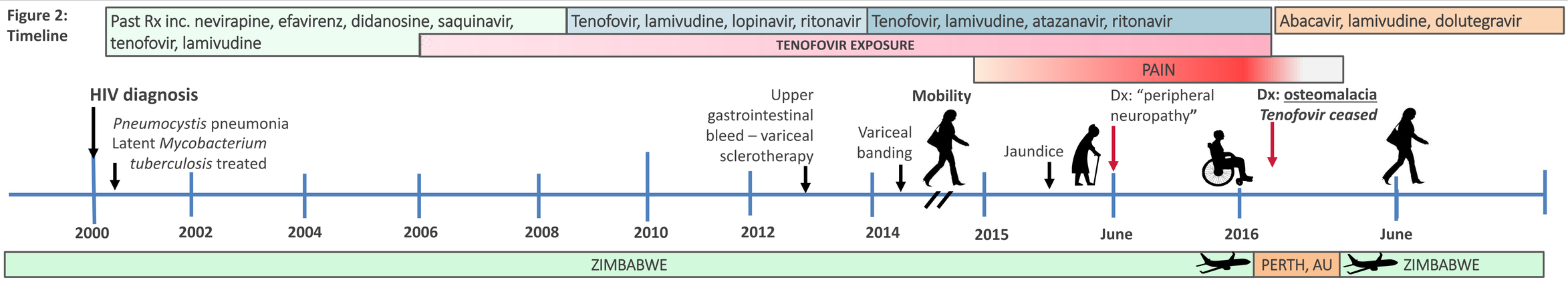


Figure 1: Areas of tenderness

Figure 2: Timeline



4. INVESTIGATIONS

Laboratory findings revealed severe hypophosphatemia, hypouricemia, acidosis, proteinuria and raised alkaline phosphatase. A bone scan (Figure 4) revealed multiple insufficiency fractures in the axial spine and proximal long bones.

Patient bloods: March '16		Reference range
Haemoglobin	124	115-160 g/L
White cell count	4.82	4-11 x 10^9/L
Platelets	**58**	150-400 x 10^9/L
Sodium	140	135-145 mmol/L
Potassium	3.9	3.5-5.2 mmol/L
Bicarbonate	**17**	22-32 mmol/L
Creatinine	83	45-90 umol/L
Bilirubin	**56**	<20 umol/L
ALT	34	<35 U/L
Alk phos	**460**	30-110 U/L
GGT	**100**	<40 U/L
Albumin	38	35-50 g/L
INR	1.2	0.9-1.3
Calcium	2.23	2.1-2.6 mmol/L
Phosphate	**0.39**	0.75-1.5 mmol/L
PTH	2.1	1.6-6.9 pmol/L
Vitamin D	121	>50 nmol/L
CK	45	30-170 U/L
Urine P:Cr ratio	**139**	<13 mg/mmol
HLA B57 typing	HLA B*5701 is ABSENT	
Schistosoma serology	**POSITIVE:** past or recent Schistosoma infection	

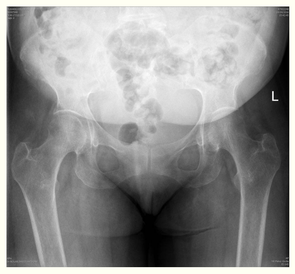


Figure 3: Normal pelvic x-ray

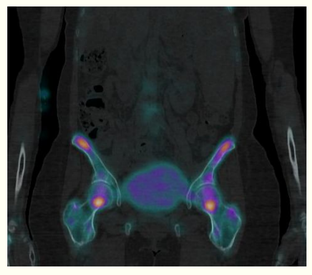
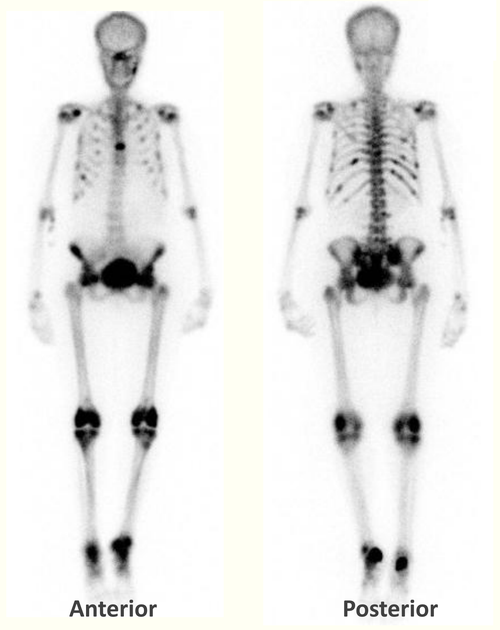


Figure 4a: 99mTc scan: pelvic, femoral microfractures



Anterior **Posterior**

Figure 4b: 99mTc Whole body bone scan: multiple insufficiency fractures (#)

5. DIAGNOSES & MANAGEMENT

Investigations confirmed suspected diagnoses of:

1. **Tenofovir-induced osteomalacia**
2. **Non-cirrhotic portal hypertension – likely associated with past didanosine exposure and/or schistosomiasis**
3. **Hyperbilirubinemia secondary to atazanavir**

- **Tenofovir was discontinued**
- **Following HLA typing, abacavir / lamivudine / dolutegravir was commenced**
- **Praziquantel treatment was provided for schistosomiasis**
- **Pain and mobility improved significantly over the subsequent two months**
- **The patient was able to mobilise independently by the end of her visit to Perth**

6. CONCLUSIONS

This case of tenofovir-induced Fanconi's syndrome with osteomalacia, highlights:

1. **The importance of surveillance and early recognition of Fanconi's syndrome**
2. **The wide range of iatrogenic complications that can arise from past ART**
3. **The complexities of HIV management in short-term visitors to Australia**

- Fanconi's syndrome is characterised by proximal tubule renal dysfunction
- Major features: hypophosphatemia, hypokalemia, glycosuria, hypouricemia, proteinuria and non-anion gap metabolic acidosis [1]
- Severe hypophosphatemia (<0.65 mmol/L) leads to impaired bone mineralisation (osteomalacia), cognitive slowing and myopathy [1]
- Current guidelines recommend monitoring patients on tenofovir (TDF) by checking creatinine, phosphate, urine glucose & protein:creatinine ratio 3 monthly for 1st year of therapy, then 6-12 monthly thereafter [2]
- New formulations of tenofovir alafenamide (TAF) are significantly less likely to cause Fanconi's syndrome due to reduced off-target (e.g. renal) drug exposure [3]

1. Mateo L, Holgado S, Marinoso M et al. Hypophosphatemic osteomalacia induced by tenofovir in HIV-infected patients. *Clinical Rheumatology.* 2016, 35:1271-1279.
2. Holt S, Gracey D, Levy M et al. A consensus statement on the renal monitoring of Australian patients receiving tenofovir based antiviral therapy for HIV/HBV infection. *AIDS Research and Therapy*. 2014, 11:35.
3. Ray A, Fordyce M, Hitchcock M. Tenofovir alafenamide: a novel prodrug of tenofovir for the treatment of Human Immunodeficiency Virus. *Antiviral Research.* 2016, 125:63-70.