CASE REPORT

Tenofovir-related Fanconi's syndrome and osteomalacia in a teenager with HIV

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SUMMARY

A teenage boy with vertically acquired-HIV presented with bone pain of 6 months duration. His antiretroviral therapy (ART) consisted of tenofovir disoproxil fumarate (TDF), emtricitabine and ritonavir-boosted lopinavir. Plain X-rays showed stress fractures of metatarsals bilaterally. A dual emission X-ray absorptiometry scan revealed osteomalacia. Raised serum creatine, hypophosphataemia, glycosuria and metabolic acidosis supported a diagnosis of Fanconi's syndrome. Serum vitamin D levels were low.

Discontinuation of TDF led to improvement in renal function, increase in serum phosphate and resolution of bone pain. This case uniquely features renal and skeletal toxicities with resultant metatarsal stress fractures. Children and adolescents on combined ART which include tenofovir should be screened for the early detection of proximal tubulopathy, with the measurement of renal function, phosphate, vitamin D and urinary phosphate excretion. Although uncommon and mostly reversible, recognition of tenofovir-related effects is paramount as prolonged exposure may lead to persistent renal tubular damage and osteomalacia.

BACKGROUND

Tenofovir disoproxil fumarate (TDF) is an adenine analogue reverse transcriptase inhibitor, used in combination with other antiretroviral therapy (ART) for the treatment of HIV, which received Food and Drug Administration approval in 2001. Reports of TDF-related renal toxicities in adults followed in 2002¹ with the first paediatric case being reported in 2006.² Decreased bone mineral density with TDF use in HIV-infected populations, particularly prepubertal and young adolescents is a known adverse effect of TDF especially when used with a boosted protease inhibitor (PI).³ We describe a 17-year-old boy who developed Fanconi's syndrome and osteomalacia while taking ART which included TDF.

CASE PRESENTATION

The teenager of Aboriginal and Torres Strait Islander descent was diagnosed with perinatally acquired HIV at 2 years of age. With a CD4 count of $554 \times 10^6/L$ (18%), he started combined antiretroviral therapy (cART) at 3 years of age with lamivudine, zidovudine and didanosine. Owing to hyperlipidaemia, his cART was modified to tenofovir/emtricitabine and lopinavir/ritonavir at 13 years of age. He remained adherent to his ART regimen having an undetectable viral load for over a decade and CD4 counts between 600 and $700 \times 10^6/L$ (21–23%).

At 17 years of age, he was admitted to a hospital with a 6-month history of bilateral foot pain, precipitated by jumping off a 2 m wall. He also complained of lower back pain of 3 months duration which necessitated the use of a walking-aid to mobilise. He was a thin teenager of slight frame, with a body mass index (BMI) of 21 kg/m². Vital signs including serial blood pressures were all normal. Clinical examination revealed focal tenderness in his lower back and the dorsum of both feet.

INVESTIGATIONS

Marked osteopenia was seen on X-rays of his spine and feet, with healed stress fractures in the fourth metatarsal of both feet. No vertebral fractures were noted. His bone mineral density (BMD) scan was markedly abnormal, with a T score of -3.65 (Z score -2.3) at the lumbar spine and -5.86 (Z score -3.24) at the femoral neck indicating a low BMD for his chronological age. He had an isolated rise in alkaline phosphatase (ALP) of 353 U/L (38–140) and an elevated parathyroid hormone (PTH) of 7.5 pmol/L (1.1–6.9) with hypophosphataemia (PO_4 0.37 mmol/L (0.80–1.5)) suggestive of increased bone resorption. Furthermore, his initial 25-hydroxy-vitamin D level was moderately deficient at 21 nmol/L (50–75).

Additional investigations revealed significantly impaired renal function (creatinine 1.59 mg/dL (0.5–1.2), which had been deteriorating over 2 years, but was not previously addressed. He had significant proteinuria (1.93 g/24 h), glycosuria (2+ on dipstick) and metabolic acidosis (venous gas pH 7.27, HCO_3^- 19 mmol/L, CO_2 44 mm Hg). The tubular reabsorption of phosphate (TRP) was significantly reduced at 0.34 mg/dL (2.6–4.4 mg/dL).

A renal biopsy was performed, predominantly showing tubular damage (figure 1).

DIFFERENTIAL DIAGNOSIS

The findings of glycosuria, hypophosphataemia with altered bone profile (ALP and PTH both elevated), low TRP and impaired creatine suggested a diagnosis of Fanconi's syndrome with proximal tubulopathy. This resulted in secondary osteomalacia, which led to bone pain and metatarsal fractures. This was attributed to the prolonged use of tenofovir.⁴

Other HIV-associated renal pathologies such as nephrotic syndrome with minimal change disease and focal segmental glomerulosclerosis (FSGS) were considered. However, the fact that these pathologies usually occur in uncontrolled HIV infection did not support the diagnosis of an underlying

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Figure 1 Mild tubular cell vacuolisation (black arrow) and flattened epithelium (broken arrow due to tenofovir toxicity).

renal pathology in this teenager who had remained virally suppressed for over a decade.⁵ Furthermore, electron microscopy of his renal biopsy showed a normal-looking glomerulus, which made FSGS less likely.

Protease inhibitors have been linked with interstitial nephritis albeit rarely. Ritonavir (RV) has been associated with ARF in a few reports, but without histopathological characterisation. Lopinavir (LPV) has not been associated with any significant renal toxicity. However, cotreatment with (LPV/RV) may have increased TDF toxicity in our patient, as LPV/RV increases plasma TDF concentrations by inhibiting apical membrane transporters (possibly by inhibiting the tubular multidrug resistance protein 4 (MRP4)), which is responsible for the efflux of tenofovir from tubular cells.⁶ The patient's ART regimen included LPV/RV taken concomitantly with TDF for almost 4 years.

TREATMENT

Tenofovir was discontinued and replaced with abacavir/lamivudine (HLA B*5701 allele analysis was negative). In most cases, Fanconi's syndrome and proximal tubulopathy are reversible within a few months of tenofovir cessation. Phosphate, bicarbonate, potassium and calcium supplements were started to replace his solute loss and treat osteomalacia. By WHO definitions, osteoporosis is defined with a BMD of 2.5 SD or more below that of a 'young normal' adult (T-score at or below -2.5). A BMD between 1.0 and 2.5 SD suggests osteopenia. In premenopausal women, in men less than 50 years of age and in children, the WHO BMD diagnostic classification is not applied. The International Society for Clinical Densitometry recommends that instead of T-scores, ethnic or race-adjusted Z-scores should be used, with Z-scores of -2.0 or lower defined as either 'low bone mineral density for chronological age' or 'below the expected range for age' and those above -2.0 being 'within the expected range for age'.⁷

In addition, his vitamin D deficiency was treated with 2000 IU/day of 1,25-OH vitamin D₃ therapy for 6 weeks until levels had rose to 64 nmol/L. He was then switched to maintenance therapy of 1000 IU/day of vitamin D₃.⁸

OUTCOME AND FOLLOW-UP

Clinically, he showed rapid improvement. Two months after changing the treatment, he was pain-free and mobilising independently. Despite initial biochemical improvement,

hypophosphataemia and proteinuria persisted 6 months after ceasing tenofovir, at which time his serum creatine was 1.45 mg/dL and phosphate was 0.78 mmol/L.

DISCUSSION

TDF is now recommended as first-line therapy in US Department of Health and Human Services guidelines in HIV management in adults and postpubertal/Tanner stage 4 children (DHHS 2010).⁹ It belongs to the same class of drugs as adefovir and cidofovir, which have nephrotoxic effects on the proximal tubules, although tenofovir is less nephrotoxic. The renal proximal tubule is a major site for the excretion of TDF. Proximal tubular dysfunction leads to the wasting of substances in the urine that are normally freely filtered by the glomerulus and then reabsorbed by the proximal tubules, such as low-molecular weight proteins (LMWPs), phosphate and glucose. Mild proximal tubular dysfunction may be detected by the asymptomatic presence of LMWPs in the urine, such as retinol-binding protein, whereas severe disease results in the classical renal Fanconi syndrome which the patient developed while taking ART, which included TDF over a 4-year period. Our patient's renal function had been deteriorating over 24 months since starting TDF, which unfortunately was not addressed. This highlights the importance for clinicians to be aware of the potential nephrotoxicity associated with tenofovir as well as bone demineralisation risk.

Renal biopsy is not necessary to diagnose tenofovir-related nephrotoxicity in the vast majority of the cases since the diagnosis can be implied based on increased creatine and characteristic findings of Fanconi's syndrome on urinalysis. Glycosuria without hyperglycaemia is also a hallmark. With tenofovir tubulopathy, proteinuria up to 2 g/day is common. Nephrotoxic effects of TDF have usually resolved by 6 months postceasing TDF.¹⁰ Although our patient's renal function improved, proteinuria and phosphate wasting persisted at review 9 months post-cessation of TDF. A likely explanation for his continuing renal dysfunction would be residual tubular damage from prolonged TDF exposure, which has been shown to be a risk factor for persistent pathology.¹¹ This is differentiated from the underlying glomerulosclerosis by the presence of urinary low molecular weight proteins rather than albuminuria. The patient's urine was negative for albumin.

Adult data show the time between the initiation of tenofovir treatment and the detection of renal abnormalities varies from 1 to 26 months.¹² In our patient, it appears that the renal deterioration occurred 24–26 months after the initiation of TDF therapy.

Our patient's osteomalacia was probably secondary to hypophosphataemia. A recent nested case-control cohort showed that hypophosphataemia was uncommon (4%), but associated with prolonged TDF use, and generally reversible following TDF withdrawal.¹³ Purdy *et al*¹⁴ observed >6% BMD loss with TDF-containing ART in heavy treatment-experienced prepubertal children or those in early puberty which seemed to recover with discontinuation of TDF.

Previous reports of Fanconi-related osteomalacia in HIV-infected adults showed duration of tenofovir use more associated with tenofovir-related bone abnormalities than in tenofovir-related acute renal failure.¹⁵ It is evident that without ceasing TDF, hypophosphataemia would worsen, thus further skeletal compromise would follow.

The patient's vitamin D deficiency may have contributed to his osteomalacia also. Renal metabolism of vitamin D to the active form: di-hydroxyvitamin D, occurs at the site of the

proximal renal tubule. Thus, potential effects of tenofovir on decreasing bone mineralisation may be at least partially dependent on vitamin D status.

Several studies have highlighted vitamin D deficiency in HIV-positive patients, related both to low dietary intake and access to sunlight.¹⁶ As vitamin D deficiency may potentiate the deleterious effects of tenofovir on bone metabolism, monitoring of vitamin D status in all patients with HIV is important.

Monitoring for highly active antiretroviral therapy toxicity can be challenging in a resource-poor setting where TDF is also recommended as part of the first-line therapy. Globally, the largest burden of HIV infection lies in countries with limited resources (eg, in Sub-Saharan Africa); the potential risks of TDF usage in these environments include the high prevalence of pre-existing chronic kidney disease (CKD), malnutrition and low body weight, and a lack of facilities to perform appropriate monitoring for nephrotoxicity.¹⁷ The prevalence of pre-existing stage 3 CKD (eGFR < 60 mL/min) in HIV-infected patients starting ART has been estimated to be around 25% in resource-poor settings.¹⁸ Nevertheless, the WHO recommends TDF as a first-line therapy for HIV infection, on the grounds of simplicity of use (once-daily dosing) and treatment of hepatitis B virus co-infection and advises monitoring of creatine clearance (CrCl) every 6 months if possible. In these patients, the potential risks of toxicity have to be balanced with the benefit of treating a virus that has a significant impact on life expectancy. In such scenarios, the WHO guidelines recommend that the inability to perform

CrCl should not be a barrier to TDF use. Given that TDF toxicity occurs more frequently in HIV-infected patients on concomitant PIs, a combination with a non-nucleoside reverse transcriptase inhibitor may be a better strategy for first-line therapy.

The WHO also recommends symptom-directed laboratory monitoring for drug toxicity. Clinical monitoring (weekly home visits by trained lay person using standardised symptom questionnaire) in resource-poor settings should be augmented with basic urinalysis screening for glycosuria and proteinuria. Where possible, any positive findings should prompt laboratory investigation. When TDF toxicity is suspected, WHO recommend switching to an alternative nucleoside reverse transcriptase inhibitor, for example, abacavir or zidovudine.¹⁹

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REFERENCES

- Verhelst D, Monge M, Meynard JL, *et al.* Fanconi syndrome and renal failure induced by tenofovir: a first case report. *Am J Kidney Dis* 2002;40:1331–3.
- Hussain S, Khayat A, Tolaymat A, *et al.* Nephrotoxicity in a child with perinatal HIV on tenofovir, didanosine and lopinavir/ritonavir. *Pediatr Nephrol* 2006;21:1034–6.
- Gafni RI, Hazra R, Reynolds JC, *et al.* Tenofovir disoproxil fumarate and an optimized background regimen of antiretroviral agents as salvage therapy: impact on bone mineral density in HIV-infected children. *Pediatrics* 2006;118:e711–18.
- Laprise C, Baril J, Dufresne S, *et al.* Association between tenofovir exposure and reduced kidney function in a cohort of HIV-positive patients: results from 10 Years of follow-up. *Clin Infect Dis* 2013;56:567–75.
- Viani RM, Dankner WM, Muelenaer PA, *et al.* Resolution of HIV-associated nephrotic syndrome with highly active antiretroviral therapy delivered by gastrostomy tube. *Pediatrics* 1999;104:1394–6.
- Zimmermann AE, Pizzoferrato T, Bedford J, *et al.* Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006;42:283–90.
- International Society for Clinical Densitometry Official Positions. <http://www.iscd.org>. Updated 2007. (accessed Jul 2012).
- Holick M, Binkley N, Bischoff-Ferrari H, *et al.* Clinical practice guideline: evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2011;96:1911–30.
- <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf> (accessed on 14 Feb 2013, p. 41).
- Onyeador N, Patel D, Lyall H, *et al.* Renal tubular dysfunction associated with tenofovir based HAART in perinatally acquired HIV: the need for paediatric formulations and pharmacokinetic studies (Abstracts of the 14th Annual Conference of the British HIV Association). *HIV Med* 2008;9(Suppl 1):26.
- Wever K, van Agtmael M, Carr A. Incomplete reversibility of tenofovir-related renal toxicity in HIV-infected men. *J AIDS* 2010;55:78–81.
- Williams J, Chadwick DR. Tenofovir-induced renal tubular dysfunction presenting with hypocalcaemia. *J Infect* 2006;52:107–8.
- Judd A, Boyd KL, Stöhr W, *et al.* Effect of tenofovir disoproxil fumarate on risk of renal abnormality in HIV-1-infected children on antiretroviral therapy: a nested case-control study. *AIDS* 2010;24:525–34.
- Purdy JB, Gafni RI, Reynolds JC, *et al.* Decreased bone mineral density with off-label use of Tenofovir in HIV-infected children and adolescents. *J Paediatr* 2008;152:582–4.
- Wanner DP, Tyndall A, Walker U. Tenofovir-induced osteomalacia. *Clin Exp Rheumatol* 2009;27:1001–3.
- Rodriguez M, Daniels B, Gunawardene S, *et al.* High frequency of vitamin D deficiency in ambulatory HIV positive patients. *Aids Res Hum Retro* 2009;25:9–14.
- Wools-Kaloustian KK, Gupta SK. Will there be an epidemic of HIV-related chronic kidney disease in sub-Saharan Africa? Too soon to tell. *Kidney Int* 2008;74:845–7.
- Mulenga LB, Kruse G, Lakhi S, *et al.* Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. *AIDS* 2008;22:1821–7.
- WHO. *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach*. <http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf> (accessed 5 Apr 2013). 2010.
- Department of Health and Human Services. *Guidelines for the use of antiretroviral Agents in pediatric HIV infection*. DHSS. 2012. <http://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv-guidelines/0> (accessed 5 Feb 2013).

Learning points

This case demonstrates the multifactorial nature of bone and renal toxicity in patients with HIV treated with cART.

- Given that tenofovir disoproxil fumarate (TDF) is now recommended as the first-line therapy for HIV-infected adults and postpubertal children, serum parathyroid hormone (PTH), calcium, alkaline phosphatase (ALP), phosphate levels should be monitored 3–4 monthly with vitamin D levels checked 6 monthly (also include when PTH is raised).²⁰
- Early diagnosis of tubulopathy is important, as in most cases the toxicities resolve after cessation of TDF, but prolonged exposure may lead to persistent renal tubular damage. Urinalysis, serum creatine, spot urine protein/creatinine ratio and fractional excretion of urinary phosphate should be determined at each clinic visit.
- If people taking TDF develop hypophosphataemia, then the drug should be stopped immediately.
- Dual emission X-ray absorptiometry (DEXA) scanning should be performed in cases of limb pain, before the occurrence of more severe bone complications leading to immobility. Some experts obtain a DEXA at baseline and every 6–12 months for prepubertal children and those in early puberty who are initiating treatment with TDF.²⁰
- WHO recommends TDF as part of the first-line therapy in resource-poor settings also. The lack of facilities for regular creatine clearance screening should not be a barrier to TDF use. Symptom-directed laboratory monitoring for drug toxicity in resource-poor settings. Combination with a non-nucleoside reverse transcriptase inhibitor may be a better strategy for first-line therapy, for example, TDF plus efavirenz.

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