Tenofovir-induced delayed nephro-osteo toxicity

Bhargavi Kumar[1], Rajgokul Prabhakar[2], Saravanan Thangavelu[3]

Abstract

Tenofovir disoproxil fumarate (TDF) is the foundation nucleotide reverse-transcriptase inhibitor in the recommended first-line regimen for all naive human immunodeficiency virus-1 (HIV-1) patients whose age is more than 10 years and body weight is more than 30 kg. Although it has a good safety profile overall, nephrotoxicity is a concern and its overall incidence is 1–6% with a long period of clinical latency. Nephrotoxicity may manifest as either proximal renal tubule dysfunction in the form of a partial or complete Fanconi syndrome or as decreased renal function leading to acute or chronic kidney injury. Osteomalacia can also develop secondary to complicating hypophosphataemia and low calcitriol levels. Here we report a 50-year-old HIV-positive male on tenofovir who presented with proximal renal tubular acidosis and fracture of left neck of femur four years after initiation of the drug.

Correspondence to:
Saravanan Thangavelu
No. 4 Thasami Park
Residency
Singanallur
Coimbatore-641005
Tamil Nadu
India

Email:
dr_saravanan12@yahoo.co.in

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Introduction

Tenofovir disoproxil fumarate (TDF) is an oral acyclic nucleotide analogue reverse transcriptase inhibitor used in the treatment of HIV-1 infection approved by the Food and Drug Administration (FDA) in 2001.[1] Tenofovir has found a major role in the fixed-dose combination along with lamivudine and efavirenz or doultegravir.[2] It has an added advantage in HIV-hepatitis B co-infection. It has an overall good safety profile, a relatively long half-life and allows once-daily dosing ensuring good patient compliance with relatively rare side effects.

Tenofoviris is actively transported into the mitochondria of proximal tubule cells of the kidney and thereby can lead to proximal tubular dysfunction in long-term use.[1] Proximal renal tubular acidosis is characterised by defective proximal tubular reabsorption associated with phosphaturia, glycosuria, aminoaciduria, bicarbonaturia resulting in hypophosphataemia, hypokalaemia and metabolic acidosis. Overt Fanconi syndrome is rare, but can occur as a delayed presentation with incidence being 1.09 per 1000 patient years.[3]

Osteotoxicity can occur either due to direct effect of the drug itself or secondary to hypophosphataemia as a result of renal toxicity.[4] Hence routine and careful monitoring for these toxicities is absolutely essential as they may occur even after a long asymptomatic period.

Case presentation

A 50-year-old male presented with poor appetite, significant weight loss of 6 kg in 2 months and progressively painful difficulty in walking over 8 months. He was diagnosed with HIV-1 8 years ago and was on regular treatment with tenofovir, lamivudine, atazanavir and ritonavir for 4 years elsewhere. CD4 count done 3 months previously was 118 cells/mm^3. He took diclofenac 50 mg intermittently over the previous 2 months.

On examination, he was thin, pale and had a limited range of movements in both lower limbs and left shoulder due to pain. His body mass index (BMI) was 16.5 kg/m^2.

Preliminary investigations showed macrocytic normochromic anaemia, elevated creatinine levels, hypokalaemia, hypophosphataemia, low bicarbonate levels and elevated serum alkaline phosphatase (ALP) levels. Arterial blood gas analysis revealed metabolic acidosis. Urine examination showed mild albuminuria and glycosuria (serum glucose was normal) with no pus cells. Results are shown in Table 1. Ultrasonography of the abdomen and pelvis revealed chronic renal parenchymal changes and renal artery Doppler study was normal.

X-ray pelvis showed an undisplaced fracture in the left neck of femur and an old displaced fracture in right neck of femur

[1]Assistant Professor, [2]Junior Resident, [3]Professor and HOD, Department of Medicine, PSG, IMS&R, Coimbatore, Tamil Nadu, India

Table 1

Lab parameters	Day 1	Day 2	Day 3	Day 5	2 weeks after discharge	1 month after discharge	Reference range
pH	7.23	7.259	7.266		7.34		7.35–7.45
Acid base excess mmol/l	-14.4	-12.2	-11.6	-8.8			-2 – +3
Serum sodium (mEQ/l)	139		144	143	138	143	136–146
Serum potassium (mEQ/l)	2.45	3.22	3.24	4.60	5.5	3.66	3.5–5.0
Serum bicarbonate (mEQ/l)	12.5	14.7	14.2	15.9	15.7	21.6	22–30
Serum chloride (mEQ/l)	107		105			105	102–109
Serum phosphorous (mg/dl)		1.3		2.1	4.7		2.7–4.5
Serum creatinine (mg/dl)	1.75			1.24		1.26	0.8–1.25
Creatinine clearance (mL/min)	39.29			55		54.56	97–137
Serum ALP(U/l)	459						40–129
Serum Vitamin D (ng/ml)	31.08						Deficient <20 Insufficient 21–29 Normal 30–70
Urine pH	6.8			>9.0			4.6–8.0
Urine glucose		4+			3+	1+	negative
Urine albumin		3+				1+	negative

confirmed on computed tomographic scanning. Serum vitamin D levels were normal. HIV viral load was undetermined and CD4 counts were 327.

Tenofovir-induced proximal renal tubular acidosis and pathological fracture was suspected and tenofovir withheld. He was treated with intravenous fluids, appropriate bicarbonate correction, thiazide diuretics, potassium citrate and his acidosis gradually improved. He was discharged on a high-potassium diet with oral potassium citrate, calcium and oral sodium bicarbonate supplements. At follow-up two weeks later he had an improving appetite and decreased pain in his legs. His electrolytes were normal with decreasing trend of creatinine levels. He was started on abacavir after hypersensitivity testing with HLAB5701 along with lamivudine and doultegravir. His bicarbonate, creatinine clearance, urine albuminuria and glycosuria improved significantly and he was able to attend to his activities of daily living.

Discussion

According to the India HIV Estimation 2017 report, national adult (15–49 years) HIV prevalence in India is estimated at 0.22% (0.16%–0.30%).[2] India has the third largest HIV epidemic in the world, with 2.14 million people living with HIV as per the UNAIDS 2018 data. 56% of adults are on antiretroviral treatment.

Kidney disease in HIV-affected individuals may be attributed to a variety of causes which include: HIV-associated nephropathy (HIVAN) presenting with focal segmental glomerulosclerosis, HIV-associated immune complex kidney disease (HIVICK), acute kidney injury or chronic kidney disease.[5] The common antiretroviral therapy (ART) causes include tenofovir (tubular toxicity), protease inhibitor indinavir (nephrolithiasis, crystal nephropathy and interstitial nephritis) and enfuviritide (glomerulopathy).[6]

Tenofovir-induced nephrotoxicity is quite rare with most studies estimating it between 1–6%.[7] Tenofovir-induced nephrotoxicity could present as proximal tubular dysfunction with preserved renal function (14%) or proximal tubular dysfunction associated with decreased renal function – which can either be acute kidney injury (1.6 %) or chronic kidney disease (8%).[1] Our patient also presented with proteinuria, glycosuria along with elevated creatinine levels and chronic renal parenchymal changes on ultrasonography.

About 20–30% of TDF is actively transported into the renal proximal tubule cells by organic anion transporters (OAT 1 and 3) located in the basolateral membrane and then subsequently secreted to the tubular lumen by the apical membrane transporters MRP-4 and MRP-2 (multidrug resistance proteins).[8] Any factor which causes overexpression of OAT1 and 3 or inhibits MRP-4 will cause tenofovir to accumulate within the cells, which in turn causes mitochondrial toxicity.

Rarely, distal renal tubular acidosis has also been encountered (<5%), although the exact mechanism is not known.[9]

Risk factors include old age, low BMI, prior history of renal disease, reduced baseline glomerular filtration rate (eGFR), diabetes mellitus, hypertension, hepatitis C co-infection and genetic polymorphisms (APOL1G1 gene).[8] The index patient's BMI at the time of presentation was quite low. However, his BMI at the time of initiation with tenofovir was not known. Factors which inhibit MRP-4 include anti-inflammatory drugs like diclofenac, ibuprofen as well as protease inhibitors. The index patient was on concomitant ritonavir and diclofenac, both of which might have added to the toxicity.

Nephrotoxicity can occur after years of tenofovir therapy as a delayed presentation with the median duration of presentation ranging between 16 months to 5 years.[10] Casado et al. observed a 32% prevalence of proximal tubulopathy after a median time of 5 years on tenofovir.[11] Our patient presented with nephrotoxicty 4 years after ART initiation with tenofovir. He had asthenia, loss of appetite, significant weight loss, muscle pain, easy fatigability and poor quality of life despite improvement in CD4 count, which prompted us to probe drug-related toxicities.

Osteotoxicity in HIV may be multifactorial. HIV can cause direct bone damage due to its effects on bone remodelling. Tenofovir can cause osteotoxicity through secondary effects of proximal renal tubular acidosis and its resultant hypophosphataemia. Because renal metabolism of vitamin D to its active form dihydroxyl cholecalciferol also occurs in proximal tubular cells, serum vitamin D levels can also be low in these patients. In addition, tenofovir can influence phosphate metabolism through circulating factors like phosphatonins.[4] In our patient vitamin D levels were normal but hypophosphataemia and elevated alkaline phosphate levels were noted and were probable contributors to bone toxicity and resultant pathological fracture.

This combined presentation of renal and bone toxicity with tenofovir therapy is quite rare, with few case reports available.[12,13] Lucey et al. reported a teenage boy with HIV infection on tenofovir presenting four years later with Fanconi syndrome and stress fracture of bilateral metatarsals.[13]

The early stages of proximal tubulopathy can be diagnosed by urine analysis of beta 2 microglobulin. In a study from Christian Medical College, South India, alkaline phosphatase (ALP) levels increased by nearly 200% after treatment with tenofovir. It was statistically significant thereby rendering it an important marker for monitoring of toxicity.[7] This is similar to the observation by Woodward et al. in which 89.5% of patients on tenofovir who developed hypophosphataemia had elevated ALP levels after a median time of seven years on ART.[12] It was also observed that creatinine clearance was a more valuable indicator compared to absolute creatinine values. National AIDS Control Organisation guidelines 2018 suggest measuring creatinine clearance and assessing risk factors for renal toxicity prior to starting tenofovir therapy. eGFR, urine protein/creatinine ratio, urine glucose and urine phosphates need to be monitored every three months for one year and then biannually.[2]

It is recommended to switch to alternative nucleoside reverse transcriptase inhibitors whenever tenofovir toxicity is encountered. However, even in those patients where tenofovir-related toxicities are encountered, it is still noted that the patients had a strong clinical and immunological response.

Ideally, if tenofovir entry to proximal tubule cells is prevented or exit is facilitated, renal toxicity may be averted. Drugs like probenecid which is an inhibitor of OAT1 and rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist that induces the expression of many proximal tubular cell transporters were studied in the past.[1] However, both had dose-limiting side effects.

Conclusion

Although antiretroviral therapy has given hope and life to HIV patients, it is important to be aware of the potential side effects and thereby monitor for the associated toxicities.

Early diagnosis of tubulopathy by urinary protein excretion, glycosuria assessment, creatinine clearance evaluation and alkaline phosphate assessment can be of central importance in identifying kidney and bone toxicities. Prompt recognition of toxicity and withdrawal of the drug can significantly improve or even reverse tubular damage in most patients, thereby avoiding chronic kidney damage.

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