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METABOLIC BONE DISEASE AND RENAL TUBULAR ACIDOSIS: A RARE MANIFESTATION OF TENOFOVIR IN A NON-RENAL-IMPAIRED PATIENTS

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ABSTRACT

Tenofovir disoproxil fumarate, a key nucleotide analog reverse transcriptase inhibitor in antiretroviral therapy (ART), is essential for HIV and chronic hepatitis B management. Although TDF effectively suppresses viral replication, prolonged use can lead to renal and bone complications, including acute kidney injury, chronic kidney disease, and osteomalacia. This report highlights two cases illustrating Tenofovir disoproxil fumarate's impact on bone health and renal function. A 48-year-old female with a 20-year HIV history on TDF-based Anti-Retroviral Therapy developed osteomalacia, experiencing pain and pseudo-fractures. Switching to abacavir improved her symptoms and lab markers rapidly. In a 61-year-old male, long-term TDF use led to an intertrochanteric femur fracture, renal impairment, and metabolic bone disease, requiring ART modification and supportive care. These cases emphasize the need for routine renal and bone health monitoring in TDF-treated patients. Early detection and timely ART adjustments can mitigate complications, improving outcomes and quality of life.

Keywords: Tenofovir disoproxil fumarate, Antiretroviral Therapy, Metabolic bone Disease, HIV Related Complication, Renal Tubular Acidosis

INTRODUCTION

Nucleotide analog reverse transcriptase inhibitors (NtARTIs), including tenofovir disoproxil (TDF), are frequently used to treat HIV and chronic hepatitis B infections.[1] TDF is an essential component of antiretroviral therapy, significantly enhancing patient outcomes and extending survival [2]. However, despite its effectiveness, TDF is not without risks. The acyclic adenine nucleotide analog, tenofovir, inhibits HBV DNA polymerase. [3] After oral administration, TDF is hydrolyzed within cells to tenofovir, phosphorylated to produce the active form, tenofovir diphosphate. Approximately 20–30% of the medication is actively transported into renal proximal tubule cells by organic anion transporters, At the same time, the remainder is excreted into the tubular lumen by the apical membrane transporters MRP-4 and MRP-2, encoded by the ABCC4 and ABCC2 genes. [4] Although tenofovir is primarily associated with gastrointestinal side effects, post-marketing surveillance has reported kidney toxicity events, including acute kidney injury, chronic kidney disease, and proximal tubulopathy. [5] These conditions can lead to hypophosphatemia, decreased bone mineral density, and Fanconi syndrome (FS).[6] Clinical trials have linked tenofovir disoproxil fumarate (TDF) doses of 300 mg or more to an increased risk of acute renal failure (ARF) due to decreased excretion via the human organic anion transporter.[7] HIV patients treated with TDF have also been observed to have elevated levels of total cholesterol and low-density lipoprotein (LDL), potentially exacerbating renal and bone toxicities.[8]

CASE REPORT 1:

This 48-year-old female patient presented at the endocrinologist outpatient department complaining of right ankle pain that had been becoming worse over a year. She has no history of fractures, proximal myopathy, or impaired vision. Pedal edema and lipodystrophy were observed in the patient during the local assessment. The patient's right leg was swollen from knee to toe. The respiratory and cardiovascular systems passed the systemic testing. She has been receiving antiretroviral medication (Tenofovir Disoproxil Fumarate 300mg daily, lamivudine 300mg, and Dolutegravir50mg) for her 20-year history of HIV infection. Following a laboratory investigation, the osteoporosis profile reveals the following: normal calcium levels (9.13 mg/dL, normal range 8.1–10.4), normal phosphorus levels (3.20, normal range 2.7–4.5 mg/dL), normal albumin levels (3.98, normal range 3.5–5.0 g/dL), normal S.PTH levels (37.81, normal range 15–65 pg/mL), normal vitamin D levels (39.0, normal range >20 ng/ml deficiency), normal creatinine levels (0.81 Normal value 0.5-1.2 mg/dL), and an elevated S.Alkaline Phosphatase (337.6, normal range 30-120U/L) that is uncommon in osteomalacia. Additionally, the electrolytes display S. Bicarbonate 23.9 mmol/L, (Normal range 23–29 mmol/L), S. Chloride 106 mmol/L, (Normal range 96–106 mmol/L), S. Potassium 5.25 mmol/L, (Normal range 3.5 – 5.5 mmol/L), and S. Sodium 143 mmol/L, (Normal range 136–145 mmol/L).

The diagnostic test, Xray reveals that the lower end of the tibia has a pseudo-involuntary fracture or looser zones, which appear as linear radiolucent bands perpendicular to the long axis of the bone (Figure 1 and 2). Investigations revealed that it is osteomalacia, a metabolic bone condition that is causing the pseudofracture, which was caused by TDF, a nuclear reverse transcriptase inhibitor. The ART protocol was thus modified with Abacavir 600mg, Lamivudine 300mg, Doultegravir 50mg, and within a week the

patient noticed the pain and swelling had fully subsided and appeared to be reverting to normal.

CASE REPORT 2:

A 61-year-old male patient presented to a tertiary care hospital on 18/02/2024, following an alleged history of an irrelevant skip and fall, resulting in an injury to his right hip. The patient experienced significant pain and was unable to bear weight on his right lower limb (RLL). Physical examination revealed tenderness in the RLL and an inability to perform a straight leg raise. Radiographic imaging identified an intertrochanteric femur fracture on the right side, while a CT scan showed diffuse sclerosis of the femoral head with subchondral cystic changes. The patient had a known history of HIV, confirmed by a viral load test and a CD4 count of 148, with a low-normal CD4/CD8 ratio. He was on antiretroviral therapy (ART) with Tenofovir 600 mg, Dolutegravir 50 mg, and Lamivudine 300 mg, and had a history of pulmonary tuberculosis treated three years prior. On day 9 post-admission, the patient underwent surgery for trochanteric fixation nail-advanced (TFN-A) to address the right intertrochanteric fracture.

Laboratory investigations revealed decreased hemoglobin and red blood cell levels, along with elevated mean corpuscular volume, mean corpuscular hemoglobin, blood urea nitrogen, and serum creatinine levels, suggestive of anemia and potential kidney injury. The patient was transfused with 1 pint of packed red blood cells. Metabolic acidosis with compensatory respiratory alkalosis was also noted and managed with spirometry and incentive spirometry. Given the patient's HIV status, lymphocytes, eosinophils, and basophils were initially decreased but improved after adjusting the ART regimen. An osteoporosis profile indicated low serum potassium, bicarbonate, and calcium levels, with increased alkaline phosphatase, serum parathormone, and serum chloride levels. The endocrinologist diagnosed the patient with vitamin D deficiency and osteomalacia, a metabolic bone disease, and initiated treatment with Syrup Vitamin D3 weekly for 8 weeks, Sodium Acid Phosphate sachet twice daily, fluids (2.5L/day), Tablet spironolactone 25 mg twice daily, Syrup Potassium Chloride 15 ml four times daily, Injection Sodium Bicarbonate 50 ml over 30 minutes, a potassium-rich diet, and Injection Magnex Forte D5 1.5g after post-operative day 1. The patient also had dyselectrolytemia, which was corrected with appropriate medications. The ART regimen was modified by withholding Tenofovir due to suspected tenofovir-induced renal tubular acidosis and metabolic bone disease. The specialists suggested that Tenofovir might have contributed to bone weakness, leading to the fracture. Subsequent diagnostic tests, including USG KUB, revealed bilateral renal parenchymal disease and diffuse urinary bladder wall thickening. The ART regimen was revised to include Abacavir 600 mg, Dolutegravir 50 mg, and Lamivudine 300 mg. Following the initiation of this new regimen, the patient's renal function stabilized, and he showed improved mobility, being able to perform toe and ankle movements and participate in physiotherapy by day 12. On day 13, the patient was discharged with prescriptions for Paracetamol 1g, Pantoprazole 40 mg, Calcium for metabolic bone disease, Sachet Nodosis 2g, Alpha ketoanalogues, and Capsule probiotics for kidney injury. He was also advised to continue the new ART regimen for 1 month.

DISCUSSION:

Highly active antiretroviral treatment (HAART) is based on nucleoside reverse transcriptase inhibitors

(NRTIs). In 2001, the nucleotide analogue tenofovir was approved for the treatment of HIV and, more recently, chronic hepatitis B infection. Clinical reports of tenofovir-related adverse effects, including bone loss, have been made despite its effectiveness. [9] A similar study by David Verhelst *et.al.,* stated simultaneous osteoblast inhibition and osteoclast activity stimulation, lead to bone loss and osteoporosis. It can additionally cause proximal renal tubular dysfunction leading to hypophosphatemia due to phosphate wasting [10]and calcium anomalies, which can interfere with bone mineralization and lead to osteoporosis and secondary hyperparathyroidism, aggravating bone loss, which is similar to the study's findings on osteomalacia. [11] Dirk Lebrecht *et al.,* discussed that Tenofovir had been associated with mitochondrial toxicity, which can impair cellular function, including in bone cells, interfering with normal bone metabolism parallel to the first case study leading to osteomalacia. [12] According to Tarantal *et al.*, some animal's bone metabolism may be affected by long-term prenatal and postnatal tenofovir. [13] McComsey *et al.,* and Stellbrink *et al.,* stated that metabolic bone disorders are found in TDF regimens than abacavir/lamivudine. In the first study, a tibial fracture and an intertrochanteric fracture developed in the second study due to bone loss associated with TDF regimens, as reported by Duvivier *et al*., [14]. The first two case studies presented with BMD loss due to TDF regimens reversible after the drug withdrawal which correlates the study done by Lisa Hamzah *et al.*, [15] Compared to TDF, Abacavir is linked to fewer renal and bone-related adverse effects. It increases bone mineral density which in contrast to the study stated that tenofovir alafenamide has fewer renal and bone-related adverse effects [16].Grant *et al.*, observed that patients treated with TDF had more BMD loss and increased bone turnover than non-TDF users. Furthermore, though rare, TDF can produce acquired Fanconi syndrome, a proximal tubular malfunction characterized by phosphate wasting that leads to hypophosphatemia, osteomalacia, and muscular weakness [17].

Our case indicates the importance of physicians anticipating and managing TDF's adverse effects on bone, which include calcium and vitamin D supplements, regular BMD monitoring, lifestyle changes, and consideration of alternative antiretrovirals with a better bone safety profile. Vitamin D, bisphosphates, and calcium supplements have been shown to improve BMD in HIV patients on ART.

CONCLUSION:

Both case studies highlight the difficulty of maintaining long-term ART in HIV-positive patients, particularly those on Tenofovir-based regimens. While TDF remains an effective HIV therapy, its potential for renal and bone damage should not be underestimated. Renal function, bone density, and electrolyte levels must be monitored regularly in patients on long-term TDF treatment. Early detection of adverse medication effects and prompt adjustment of the ART regimen can help to minimize problems like osteomalacia, improve patient outcomes, and improve the quality of life for people living with HIV.

ABBREVIATIONS:

HIV: Human Immunodeficiency Virus; TDF: Tenofovir Disoproxil Fumarate; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; HAART: Highly Active Antiretroviral Treatment; RLL: Right Lower Limb; TFN-A: Trochanteric Fixation Nail-Advanced; ART: Anti-Retroviral Therapy

INFORMED CONSENT: Informed Consent was obtained from both the patients.
CONFLICT OF INTEREST: The Authors declares no conflict of interest

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