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Tenofovir-Induced Fanconi Syndrome in an HIV Infected Nigerian: A Case Report

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ABSTRACT

***Background*:** While TenofovirDisoproxil Fumarate (TDF) has achieved great success in the treatment of HIV infection, there have been reports of TDF-induced Fanconi syndrome. TDF is a key component of first line antiretroviral regimens with increasing use, particularly in developing countries. Whereas, much attention has been focused on other renal complications of TDF, very little has been studied in Nigeria to address the potential proximal renal tubular dysfunction with its attendant complications, such as osteomalacia.

Case Report: We describe the case of a 52 year old HIV infected Nigerian woman on TDF plusEmtricitabine plus ritonavir-boosted LopinavirAntiretroviral Therapy (ART) who presented with osteomalacia and micro fractures due to renal phosphate wasting which resolved following discontinuation of TDF and supplementation with Calcium (Calcium Sandoz 1000mg OD), Vitamin D (Cholecalciferol 1000mg BID and alfacalcidol 0.5mg OD) and Phosphate (Potassium phosphate monobasic, sodium phosphate dibasic dihydrate 1 BID).

Conclusion: This case highlights the importance of considering the diagnosis of osteomalacia among HIV infected Nigerians on TDF containing ART. We recommend regular monitoring of renal tubular function, bone alkaline phosphatase, serum calcium and phosphorus, as part of routine management for patients on TDF-based ART.

Keywords: *HIV, tenofovir, nephropathy, fanconi syndrome, osteomalacia, Nigeria*

INTRODUCTION

Tenofovir Disoproxil Fumarate (TDF) is considered a first-line drug for the treatment of HIV and exposure to it is increasing, particularly in developing countries with high burden of HIV infection.[1] TDF is frequently used because of its demonstrated efficacy,[2] its activity against hepatitis B virus,[3] and co-formulation with emtricitabine and efavirenz to provide a potent antiretroviral regimen involving a single pill per day. TDF is an oral prodrug of tenofovir, which is a Nucleotide Reverse Transcriptase Inhibitor (NRTI). TDF is rapidly hydrolyzed and largely eliminated unchanged by the kidney, through a combination of glomerular filtration and active tubular secretion. [4]

TDF has a favourable safety profile. However, over the past few years, nephrotoxicitydue to TDF use has been reported. Renal toxicity may manifest as Acute Kidney Injury (AKI), Chronic Kidney Disease (CKD), and features of proximal tubular injury,

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including Fanconi syndrome, isolated hypophosphatemia, and decreased bone mineral density. [5] Some patients seem to be more vulnerable than others to these adverse renal effects such as diabetics, patients with hypertensive nephropathy and those on ART with ritonavir-boosted protease inhibitors (PI/r).[6]

Fanconi syndrome is a generalized proximal tubulopathy. In its complete form it is associated with renal tubular acidosis, glycosuria with normoglycemia, aminoaciduria, hypophosphatemia, hypouricemia, and tubular proteinuria. [7] Other manifestations of proximal tubulopathy in individual patients include osteomalacia and decreased bone mass due to phosphate wasting and/or calcitriol deficiency, since calcitriol is synthesized by mitochondria in proximal tubules. [7]

We report a case of a 52 year old HIV infected woman on TDF-based ART who developed hypophosphataemicosteomalacia from renal phosphate wasting, and reversal of the clinical condition following discontinuation and supplementation with Calcium (Calcium Sandoz 1000mg OD), Vitamin D (Cholecalciferol 1000mg BID and alfacalcidol 0.5mg OD) and Phosphate (Potassium phosphate monobasic, sodium phosphate dibasic dehydrate BID)

CASE REPORT

The index case was a 52 year old Nigerian female diagnosed with HIV-1 infection in 2003. Her initial HIV treatment consisted of zidovudine 300mg and lamivudine 150mg BID as part of a trial programme for the first two years. Her antiretroviral regimen was changed in 2005 to TDF 300mg daily, lamivudine 150mg BID and efavirenz 600mg taken at nightas more antiretroviral drugs became available in Nigeria through support from the United States President's Emergency Plan For AIDS Relief (PEPFAR) program. Her serum creatinine and estimated Glomerular Filtration Rate (eGFR) at initiation of TDF-based treatment were 75.5 µmols/L and 84.03mls/min, respectively. However, serum calcium, phosphorus, alkaline phosphatase and urinary protein, phosphate, glucose and bicarbonate were not estimated at baseline as these tests were not recommended by the National HIV treatment guidelines at this time. She was switched toTDF 300mgPlus Emtricitabine 200mg (TRUVADA®) and ritonavir-boosted Lopinavir (LPV/r) 400mg/100mg BID, due to virologic failure in 2006. She had good virologic and immunologic response to therapy. Her HIV RNA levels remained below 400 copies/ ml and CD4 count was consistently above 500cells/mm^3.

In 2006, she developed lower back pain; which progressively worsened over time. The pain was non-radicular with associated progressive weakness of the lower limbs so that she could not walk without support. She also had weakness of the upper limbs and the associated joints. She has been confined to a wheelchair over the last two years. There was no history of trauma, infections, diarrhoea or conjunctivitis, and she had no urogenital symptoms. Other medications she received at various times in the course of her ill health on account of pain included: Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), opiate analgesics and corticosteroids; without improvement in symptoms.

Examination revealed a middle- aged lady in good nutritional state but in painful distress. She weighed 62kg and was 153cm tall. She was not febrile and she had no skin changes. Cardiovascular examination was essentially normal with a pulse of 75 beats/ minute and a blood pressure of 130/80 mmHg. Auscultation of her lungs revealed no abnormality. She had healed lower abdominal wall scars on account of previous caesarean section and hysterectomy. Other abdominal findings were essentially negative. Her higher cerebral functions were intact, and she had no paresis or sensory impairment. She had swelling of the knee and ankle joints, and also joints of the hands; with no evidence of inflammation. There was severe restriction of movement of the shoulder and elbow joints due to pain and weakness but this was less severe in the joints of the hands and fingers. She had severe joint pain in both lower limbs with resultant restriction of passive movement of the hip and knee joints.

Test results at initial evaluation in 2010 showed normal hematologic parameters. Serum levels of aspartate transaminase (AST),alanine transaminase (ALT), urea, creatinine, uric acid, potassium and sodium were also within normal limits. She however had hypophosphataemia (1.5mg/dL, normal range: 2.6-4.5mg/dL), low vitamin D levels (17ng/L, normal range: 30-70ng/L), hyperglycaemia (117mg/dL, normal range: 70-100mg/dL)and metabolic acidosis(Serum Bicarbonate: 15mmols/L, normal range: 21-31mmols/L). Estimated GFR ranged between 59.14 to 73.65 ml /min. DXA bone density measurement of the second to fourth lumbar

vertebrae and left femur revealed scores in keeping with very severe osteopenia (T scores -4.8 and -6.4 respectively). Radiograms of hands, feet, pelvis and knees showed pronounced demineralization but no evidence of fractures, arthritic or anthrotic joint changes. Magnetic resonance imaging (MRI) of the vertebral column showed pronounced osteopenia. Chest radiogram, cranial MRI, abdomino-pelvic ultrasound scan and heart echocardiogram were essentially normal. Based on the clinical, laboratory and imaging findings, an assessment of osteomalacia arising from hypophosphataemia which resulted from a proximal tubular dysfunction caused by TDF was made.

The antiretroviral agent, TDF was discontinued (replaced with Raltegravir) while Lopinavir/Ritonavir combination was continued. She also had Calcium (Calcium Sandoz 1000mg OD), Vitamin D (Cholecalciferol 1000mg BID and alfacalcidol 0.5mg OD) and Phosphate (Potassium phosphate monobasic, sodium phosphate dibasic dehydrate BID) supplementation. An Angiotensin converting enzyme inhibitor (ACEI), Ramipril was added to her therapy to treat the proteinuria. In addition, she had regular physiotherapy. Subsequent review six months after initiation of treatment showed increased mobility, reduced pain and improvement in laboratory parameters (Table 1).

DISCUSSION

We present the case of an HIV-infected Nigerian woman on TDF-containingART regimen who developed Fanconi and hypophosphataemic osteomalacia. The case had an unusual presentation with severe bone pain to the point that she could not walk and was wheelchair bound for a couple of years. She had severe BMD loss at cortical and trabecular sites. Laboratory reports supported the features of Fanconi syndrome with decreased plasma phosphorus and hypo-uricaemia. The patient was on various combinations of ART since onset of HIV diagnosis. However, of these ART drugs, Fanconi syndrome is a potential side effect of TDF. Laboratory changes demonstrated mild decrease in estimated Glomerular filtration rate (eGFR), a striking rise in alkaline phosphatase, and bone density loss. Worthy of note is the fact that this patient was on ritonavir as part of her anti-retroviral drug combination. Ritonavir has been shown to increase the concentration of TDF by 30-40% and has been anecdotally linked to TDF renal tubular disease. [5]This may have further worsened the renal tubular toxicity associated with TDF-based ART therapy in this patient. Interestingly, she had resolution of her bone pain and biochemical abnormalities upon discontinuation of TDF and supplementation with phosphate and vitamin D.

Although Fanconi syndrome and nephrotoxicity associated with TDF is clearly documented in the

Table 1: Laboratory results of the index patient with TDF-Induced fanconi syndrome

Parameter	Normal Range	After 5 years on TDF	6 months after TDF
Serum Creatinine (umol/L)	72-126	146.44	49.97
eGFR (ml/min)	>90	59.14-73.65	100.1
Serum Phosphate(mmols/L)	0.8-1.4	0.48	1.26
Serum Calcium (mmols/l)	2.15-2.55	2.19	2.55
25-hydroxy vitaminD (µg/l)	20-70	16	40
Vitamin D3(ng/l)	30-70	17	124
Serum *ALP (U/L)	35-104	451	297
Serum Uric Acid (mg/dl)	2.4-5.7	1.7	4.0
**CRP (mg/dl)	<.5	10.11	0.28

** ALP=Alkaline Phosphatase*
***CRP=C-Reactive Protein*

literature; there are only a few descriptions of Fanconi syndrome with severe bone pains as manifested by our patient. The prolonged exposure to TDF-based ART in this patient may have being a contributory factor. Perrot et al reported a case of chronic bone pain related to TDF and suggested that factors associated with TDF toxicity included: low BMI, concomitant use of NSAIDs, and other ART drugs like RTV;[8]. The patient we describe was also on RTV as part of her ART regimen. This may have further predisposed the patient to the renal toxicity. Parsonage *et al.* described 2 cases of myopathy in HIV-infected patients receiving TDF that were associated with hypophosphatemic osteomalacia.[9]

This patient presented with features to suggest myopathy. Woodward et al identified 22 patients (1.6% of their clinic patients who received TDF) and subsequently developed TDF-associated renal toxicity. All these patients had proteinuria, a rise in serum creatinine and drop ineGFR, most had a drop in serum phosphate level and an increase in serum alkaline phosphatase level. In all, 12 presented with bone pain and osteomalacia. The diagnosis of TDF-associated renal toxicity in their patients was supported by the improvement of renal function abnormalities on discontinuation of TDF, suggesting that TDF toxicity is at least partially reversible. [10]

The findings of TDF-induced Fanconi syndrome presenting with hypophosphataemic osteomalacia, reversal with discontinuation of TDF and supplementation with Vitamin D, Calcium and Phosphate as described with our index patient have been reported by other workers .[11] There is an underlying high prevalence of osteopenia and osteoporosis in HIV-infected patients and the reason for this appears to be multifactorial. In a meta-analysis, the prevalence of osteoporosis in HAART-exposed patients was 3 times more likely compared to HIV-uninfected controls.[12] The mechanism for BMD loss in HIV-infected patients has been conjectured to be related to renal phosphate wasting possibly from renal proximal tubular dysfunction resulting from viral infection or drug-induced toxicity.[10]

Possible mechanisms of renal toxicity by TDF have been proposed by several authors. [13, 14] The proximal tubular cell is the main target of TDF toxicity due to its complement of cell membrane transporters that favour TDF accumulation.[7] Current evidence also suggests that mitochondria are the target organelles of TDF cytotoxicity.[7] Inhibition of mtDNA polymerase $\tilde{a}$ has been proposed to have a central role in TDF-related mitochondrial toxicity[7] and the accompanying proximal renal tubular dysfunction.The cause of severe bone pain in our patient appears to be related to TDF, especially as there was reversal with cessation of TDF.

This case highlights the occurrence of Fanconi syndrome and hypophosphataemic osteomalacia in a patient on TDF-containing ART in Nigeria. With the scale up of TDF use as a first-line ARV in Nigeria, we recommend routinemonitoring of renal function including assessments for renal tubular dysfunction, alkaline phosphatase (bone fraction) and plasma phosphorus for HIV-infected patients on TDF-containing ART. This will ensure early detection and substitution of TDF with other non-nephrotoxic antiretroviral agents to prevent and possibly reverse the renal toxicity associated with TDF use.

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