ABSTRACT

Tenofovir is an antiretroviral drug used in combination with other antiretroviral agents. It is an effective therapy for HIV infection. Kidney injury induced by this drug has been known to occur in the HIV positive patients. When given in titrated doses, it is safe and should be combined with regular monitoring of renal function and serum phosphate levels. We present a case report of Tenofovir induced nephropathy in a patient diagnosed to have acquired immunodeficiency syndrome 8 years ago and was on TDF based anti-retroviral therapy. The patient had normal serum creatinine, normal blood glucose levels, raised serum bilirubin and amylase levels, mild anemia with glycosuria and proteinuria. Renal biopsy revealed normal glomeruli with dilated proximal tubules and attenuation of brush border. Our case reverted back to normal upon withdrawal of drug. We present this case to emphasize that the clinician should be aware of TDF induced acute kidney injury (AKI) presentation.

Keywords: Tenofovir; retroviral disease; acute toxic tubular injury.

1. INTRODUCTION

Tenofovir Disoproxil Fumarate (TDF) is the nucleotide reverse transcriptase inhibitor approved for the treatment of Human Immunodeficiency Virus (HIV) infection, which became available in 2001. TDF is one of the most commonly prescribed antiretroviral drugs...
around the world and is generally considered safe [1-3]. It has gained widespread use on the basis of its high efficacy, tolerability, and patient-friendly dosage schedule. TDF is extensively excreted by glomerular filtration with 20-30% being actively transported into renal proximal tubule cells by organic anion transporter-1. Renal toxicity is the most severe adverse effect but it is uncommon, with an incidence of <1% [2]. First case of Fanconi syndrome and renal failure induced by tenofovir was reported in 2001 and published in American Journal of Kidney disease [4]. TDF nephrotoxicity usually manifest as proximal tubular dysfunction with Fanconi syndrome, isolated hypophosphatemia and decreased bone mineral density. We report a case of TDF nephrotoxicity associated with anemia and osteomalacia that resolved after discontinuation of TDF.

2. CASE REPORT: CLINICAL HISTORY

A 45 year old male presented with complains of hip pain, difficulty in walking and right sided weakness since 2 months. He was diagnosed to have acquired immunodeficiency syndrome 8 years ago and was on tenofovir based anti-retroviral therapy, the TLE (TDF, Lamivudine and EFV) regime with Tenofovir in dosage of 300mg once daily. The patient had no comorbidities like hypertension and diabetes. On examination, he was afebrile with normal blood pressure. Investigations revealed slightly decreased haemoglobin - 11.8 gm/dl and normal TLC – 11.74 x 10³ / mm³ with other haematological parameters within normal limits. PT and INR were normal. Serum creatinine, serum electrolytes and blood sugar were within normal limits. Liver function test showed increased serum bilirubin levels (Total bilirubin 4.96 mg/dl; Direct bilirubin 1.24 mg/dl) with near normal SGOT and SGPT levels. Serum amylase (119.53U/L) and CPK-MB (106.93 U/L) were also raised. Urine examination showed glycosuria and proteinuria.

Other viral markers for Hepatitis B and Hepatitis C were negative. MRI of lumbosacral spine showed the osteoporotic changes.

3. KIDNEY BIOPSY

Renal Biopsy was performed and studied for routine light microscopy and Immunofluorescence. The biopsy sample consisted of appropriate number of glomeruli that is 8 and all of which were normal. However, the pathology was found in tubulointerstitial compartment. The tubules showed dilatation with flattening of epithelial lining and attenuation of brush borders, some tubules showed enlarged nuclei and occasional mitosis. (Fig. 1A and B). The lumen contained eosinophilic cellular debris and crystalline precipitate along with few
Fig. 1. Normocellular glomeruli with normal thickness of glomerular basement membrane. Dilated proximal tubules with flattening of cells and attenuation of brush border. A. H&E (400x) B. Silver Methenamine (400x)

hyaline cast. Mild tubular atrophy (10%) was noted. The interstitium showed edema with mild mixed inflammatory infiltrate. Blood vessels appeared unremarkable. Tissue submitted for IF studies showed 7 glomeruli, IgG, IgM, IgA, Kappa, Lambda were negative and C3 was trace positive.

3.1 Impression

The diagnosis of acute toxic tubular injury was given and as the patient was on TLE regime for retroviral disease, Tenofovir as the etiological agent was suggested.

4. DISCUSSION

In the era of HAART, tubulointerstitial injury has become a prominent form of renal disease in HIV infected individuals. Infectious disease society of America recommended that all the HIV positive patients should be assessed for kidney disease. If there is greater than 1+ proteinuria or eGFR less than 60ml/min/1.73m², renal biopsy is indicated. The main clinical presentations of tenofovir nephrotoxicity are (a) proximal tubular dysfunction with preserved renal function and (b) proximal tubular dysfunction associated with decreased renal function [5]. Decreased renal function may be classified as acute kidney injury (AKI), chronic kidney disease (CKD) or a glomerular filtration rate (GFR) that is decreased. Drug induced tubular dysfunction associated with HAART agents may produce fannconi syndrome, acid base disorders and increased or decreased electrolyte concentrations.

The microscopic change of acute tubular necrosis is characterized by flattening of the epithelium along with loss of proximal brush border staining. Foci of denuded tubular basement membrane and crystalline precipitate of medications accumulated in tubular lumina of distal tubules is also seen. Reverse transcriptase inhibitor, usually Tenofovir inhibits human mitochondrial DNA polymerase-γ, inhibiting DNA synthesis and subsequent mitochondrial DNA depletion. The proximal tubule is responsible for the reabsorption of glucose, uric acid, amino acids, small proteins and phosphates, the secretion of hydrogen ions and the synthesis of calcitriol. Damage to the proximal tubules leads to wasting of these elements in urine, renal tubular acidosis and Vitamin D deficiency.

Factors associated with increased risk of TDF toxicity include dose and duration of treatment, advanced age, low body weight, low CD4 count, ABCC2 gene polymorphism (encoding for MRP2
transporter), co prescription of other nephrotoxic drug such as aminoglycoside, HCV coinfection [2,5]. The TDF introduction in treatment regime and onset of AKI may vary from weeks to years (1month-8 years) [6,7]. Our patient also presented with the features of acute tubular injury and revealed the histopathologic findings of tenofovir induced tubular damage. Renal functions generally improve in the month following TDF withdrawal. However, AKI does not always revert completely.

5. CONCLUSION
TDF induced AKI nephrotoxicity can present with proteinuria, glycosuria, anemia and Fanconi syndrome. As the use of TDF-based HARRT is widely spread, clinician should be aware of the complexity of TDF induced AKI and carefully evaluate all patient on TDF with decrease GFR. Regular follow up of these patients is recommended with urine analysis and creatinine and electrolytes. Early detection of nephrotoxicity and tenofovir withdrawal are key to avoid irreversible tubulointerstitial damage. Further research need to be conducted in order to evaluate the magnitude of this adverse effect associated with this important drug.

DISCLAIMER
The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL
As per international standard or university standard guideline participant consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES