TENOFOVIR INDUCED NEPHROTOXICITY – A CASE REPORT

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ABSTRACT
Tenofovir disoproxil Fumarate (TDF) is an antiretroviral medication used to prevent and treat HIV/AIDS and to treat chronic hepatitis B. It is a defective adenosine nucleotide that selectively interferes with the action of reverse transcriptase. The most common side effects associated with Tenofovir include nausea, vomiting, diarrhea, and asthenia. Less frequent side effects include hepatotoxicity, abdominal pain and flatulence. Here we report a case of nephrotoxicity which resulted from long time usage of Tenofovir as the patient is HIV positive for last 15 years. Data regarding effectiveness of nephro-protective agents against TDF-induced nephrotoxicity are not conclusive. Before extrapolation of the preclinical evidence to clinical practice, this evidence should be confirmed in future human studies.

KEYWORDS: Tenofovir, Nephrotoxicity, Retroviral Disease, Acute kidney injury.

INTRODUCTION
The kidney is an essential organ required by the body to perform several important functions including the maintenance of homeostasis, regulation of the extracellular environment, such as detoxification and excretion of toxic metabolites and drugs. Therefore, the kidney can be considered as a major target organ for exogenous toxicants. Nephrotoxicity is a kidney-specific feature in which excretion does not go smoothly owing to toxic chemicals or drugs.[1] Approximately 20% of nephrotoxicity is induced by drugs, but medication of the elderly increases the incidence of nephrotoxicity up to 66% as the average life span increases. Nephrotoxicity can be diagnosed through a simple blood test. Evaluation of nephrotoxicity through blood tests includes the measurements of blood urea nitrogen (BUN), concentration of serum creatinine, glomerular filtration rate and creatinine clearance.[2] The expansion of access to anti-retroviral therapy (ART) in India, larger numbers of people living with HIV/AIDS (PLHA) are initiated on ART. Tenofovir disoproxil fumarate (TDF) is an oral pro drug of Tenofovir, an acyclic nucleoside phosphate. TDF is first nucleotide analogue reverse transcriptase inhibitors to be approved for the treatment of HIV infection.[2,3] However, frequent laboratory monitoring for very rare toxicity may unnecessarily limit the use of TDF in resource-limited settings. Therefore, a more precise estimate of the risk of nephrotoxicity would be useful for clinicians and policy makers.[4]

MOA
Accumulation of tenofovir in the proximal tubular cells, which plays an important role in drug excretion from the body. TDF enters proximal tubule cells through organic anion transporters and exist via the apical transporter and MRP4 (multi resistance associated protein).[5]

Clinical Features of Tenofovir Nephrotoxicity
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. Decreased renal function may be classier as AKI, CKD, or a glomerular filtration rate (GFR) that is decreased when compared with baseline values, albeit within normal limits.[7]

CASE PRESENTATION
52 yr old female admitted in General Medicine Department in a tertiary care hospital with chief complaints vomiting and loose stools since 1 week. On general examination, she was found to be normal. Blood pressure: 140/90mm Hg. Past History: On her past medical history she was known to of HIV since 15 years on antiretroviral therapy, diabetes mellitus since 6 months.

Laboratory Investigations
Here laboratory investigation was performed. Serum creatinine level and random blood sugar was increased than normal levels. Fasting blood glucose and CD4 cell count was decreased. Biochemistry report revealed...
Serum creatinine levels decreased to 4.9mg/dl after stopping suspected drug (tenofovir), CD4 T-cell count was normal 276ug/ml (500-1500), Random blood sugar of 232 mg/dl (140-150), Fasting blood glucose was normal.

Table: Demonstration of serum creatinine levels.

<table>
<thead>
<tr>
<th>S.no</th>
<th>Serum Creatinine level</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.4mg/dl</td>
<td>06/01/2016</td>
</tr>
<tr>
<td>2</td>
<td>4.9mg/dl</td>
<td>18/01/2016</td>
</tr>
</tbody>
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Blood gas report: P\textsuperscript{o}$_2$-7.25 (7.36mmhg), Pco\textsubscript{o}$_2$-26 (32mmhg), Po$_2$-26.6 (75mmhg), Na’-150 (134-146mol/L) and cl-111(96-108mol/L) level was increased comparing to normal level. Complete urine exam report revealed Color: pale yellow, Reaction: acidic, Albumin: +, Sugar: ++, Pus cell: 5-6cells/Hpf, Epithelial cells: 3-4cells/Hpf. USG abdomen impression confirmed hepatomegaly, cystitis, grade1 increased renal echotexture.

Differential Diagnosis
Based on patient medical history of HIV and DM. Correlating her past medication history and laboratory test results, condition was finally confirmed as Retroviral Disease (Z+ve) with AKI, **Tenofovir induced nephrotoxicity**.

Treatment
Initially suspected drug Tenofovir was stopped and condition was managed with Inj. Ceftriaxone 1g/IV/BID, Inj. Insulin-R 10U/SC/TID, Tab. Pantoprazole 40mg/BID, Tab. B complex/OD which was continued for 2 days then Tab.Nimodipine-20mg/TID and Tab. Calcium D$_3$/OD added to plan continued for 10 days.

Outcome and follow-up
Patient was advised to have a regular check up for levels of creatinine levels, blood sugar and urine examination.

DISCUSSION
Treatment with TDF induced a broad spectrum of nephrotoxicity, including renal failure, proximal tubular injury and reduced urinary concentration ability.\textsuperscript{[5]} Thus, unlike adverse drug effect of other anti-retroviral drugs, there is a long clinical latency. The patient had excellent immunological recovery as evidenced by significant improvement in clinical stage and increase in CD4 T-Cell count at the time of diagnosis Most importantly Rosiglitazone reversed all TDF induced renal alteration, it has been demonstrated that changes in expression of membrane protein transporters can occurs in many forms of acute kidney injury, including those caused by ischemic or nephrotoxicity.\textsuperscript{[6]}

In this case patient was diagnosed with retroviral disease, DM, acute kidney injury and had high serum creatinine level (7.4mg/dl) due prolonged usage of Tenofovir. Nephrotoxicity was confirmed based on the Sr Cr levels and finally condition was managed by stopping corresponding drug (Tenofovir).

CONCLUSION
Several predisposing factors including elevated baseline Serum Creatinine, concomitant nephrotoxic medications, low body weight, advanced age, tenofovir disoprophil fumarate (TDF) dose and duration of treatment and lower CD4 cell count were identified as risk factors for development of TDF-induced nephrotoxicity. Rosiglitazone may be helpful in patients presenting with TDF-induced nephrotoxicity. Pre-treatment with melatonin prevented all known histological changes in proximal tubular mitochondria induced by TDF. Vitamin E, lipoic acid, plastoquinone, nitroxides, SOD enzyme mimetics are other potential agents for prevention of TDF-induced nephrotoxicity.

However, data regarding effectiveness of nephroprotective agents against TDF-induced nephrotoxicity are not conclusive. Before extrapolation of the preclinical evidence to clinical practice, this evidence should be confirmed in future human studies.

REFERENCES