Abstract

Objective: To describe the incidence and characteristics of Tenofovir (TDF) induced nephrotoxicity among people living with HIV/AIDS (PLHA) receiving TDF based anti-retroviral therapy (ART) at Christian Medical College, Vellore.

Method: Medical record review of all the PLHA who is being enrolled and followed up at the ART clinic at CMC, Vellore.

Results: From 2006-11, a total of 274 PLHA have been initiated on TDF based ART. 10 (3.6%) patients developed TDF induced renal dysfunction after a mean duration of 42.6 (SD 19.5) months. 5 patients were female. At the time of initiation of TDF, the mean age was 41.2 (SD 6.1) years and CD4 T-cell count was 281.2 (SD 241.3) cells/µL. 9 patients were started on an NNRTI-based regimen, while only 1 was on a PI/r-based regimen.

5 patients were asymptomatic. Out of the 5 symptomatic patients, 3 patients complained of anorexia and tiredness only; 1 patient had bone pains and proximal pelvic girdle muscle weakness only while 1 patient had both anorexia and proximal pelvic girdle muscle weakness. Urine examination of 8 patients (all symptomatic and 4 asymptomatic patients) revealed proteinuria on urine dip stick assay (1+ to 3+) without active sediments. 9 patients had decline in the estimated creatinine clearance from mean of 84.1 (SD 21.0) to 62.1 (SD 26.3) mL/min/1.73 m². The mean plasma phosphate level was 2.08 (SD 0.45) mg/dL. The mean alkaline phosphatase level increased from 130.7 to 290.8 U/L. Seven patients had features of Fanconi syndrome. All symptomatic patients showed clinical improvement within 2-7 months of discontinuation of TDF and supplementation of phosphate and calcium.

Conclusion: TDF-associated renal dysfunction has a long incubation period during which the patients are largely asymptomatic and reversible. Hence laboratory confirmation is essential with creatinine clearance, urine examination, and phosphate levels. Prompt change of TDF leads to almost complete resolution of the tubular dysfunction.

Introduction

With 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 (TDF), an acyclic nucleoside analogue, is a potent component of first and second line anti-retroviral drug regimens. Approximately 20–30% of the TDF is excreted unchanged in the urine via active secretion by the proximal tubular cells. The free drug is actively taken up by the Organic Anion Transporter (OAT-1) receptor located at the basolateral surface of the tubular cells and concentrated in the cystosol. TDF is excreted into the tubular lumen via the multi-drug resistant proteins (MRP-2 & 4) located at the luminal surface. Although the exact mechanism of TDF induced nephrotoxicity remains unclear, it is proposed that TDF inhibits mitochondrial DNA γ-polymerase and thereby exerts its mitochondrial toxicity and leads to caspase
mediated proximal tubular cell injury. The long term consequence of the damage to the proximal tubular cells leads to variety of nephrotoxic features, which includes Fanconi syndrome, chronic renal failure, acute on chronic renal failure etc.

The incidence of TDF induced renal dysfunction comes mostly from the case series and varies from 1% to 6%,\textsuperscript{2-5} however the true incidence and clinical characteristics remains unclear. Considering the larger number of PLHA being initiated on TDF based ART in India, and paucity of data on TDF induced nephrotoxicity, we aimed to evaluate the incidence of TDF induced renal dysfunction and describe the clinical profile of the PLHA at the tertiary care centre of South-India.

**Material and Methods**

Christian Medical College, Vellore, is a 2000 bedded, tertiary care centre in South India. Department of Medicine Unit-I and Infectious disease provides care to the PLHA from the beginning of the HIV epidemic in India in 1986. An interdisciplinary infectious disease clinic runs on Wednesday afternoon and Friday afternoon, involving medicine, pediatrics, dermatology and venereology and social work provides comprehensive care to PLHIV. We conducted the retrospective case record review of all the PLHA who have been initiated on TDF based ART since 1st January, 2006 to 31st October, 2011. All these patients are followed up at every 6 monthly intervals. During the follow up visit, the history, clinical examination, body mass index, concomitant drug use, co-morbidities, WHO clinical staging and estimated creatinine clearance are recorded. The minimal blood investigations include CD4-T cell count, calcium, phosphate (fasting), creatinine, liver function test, electrolytes, while urine is examined for routine analysis and urine protein: urine creatinine (UP:UC) ratio.

The biochemical grading of TDF toxicity for creatinine, liver function tests and urinary abnormalities were described as per world health organisation guideline (2010 revision) on ART for HIV infection in adults and adolescents. Since this revised guideline does not specify or grade the hypophosphatemia, therefore the cut-off for fasting blood phosphate level below 2.4 mg/dL (lower limit of the normal as per our laboratory cut-off) was described as hypophosphataemia. Fanconi syndrome was diagnosed if there were normoglycaemic glycosuria (≥1+ glycosuria), proteinuria (≥1+ proteinuria or UP: UC ratio > 350 mg albumin/g creatinine) and hypophosphataemia (PO4 < 2.0 mg/dL). Temporal decline in the creatinine clearance over the baseline value was compared. The data was analysed by SPSS (version 16).

**Results**

**Baseline characteristics**

From 1st January, 2006 to 31st October, 2011, total of 274 PLHA have been initiated on TDF-containing ART. Nephrotoxicity was documented among 10 patients (3.6%). Out of these 10 patients, 4 patients received TDF as part of initial ART regimen, 4 patients were substituted to TDF as alternative first line due to toxicity to zidovudine and 2 patients were on TDF as part of a second line ART regimen when the initial regimen failed. Only one patient was receiving boosted protease inhibitor (Lopinavir and Ritonavir) based regimen. No patients received concomitant nephrotoxic drugs.

The mean age was 41.2 years (S.D 6.1; Range 30 to 52 years) at the time of diagnosis of nephrotoxicity and 5 (50%) were male. The baseline body mass index, CD4 T-cell count, creatinine, estimated creatinine clearance (Cr.Cl) and alkaline phosphatase have been shown in Table 1.

**Tenofovir Nephrotoxicity**

After mean duration of 42.6 (SD 19.5) months, 10 patients (3.6%) on TDF therapy developed nephrotoxicity. At the time of presentation, 5 (50%) patients were symptomatic. 3 patients complained of anorexia and tiredness only; 1 patient had bone pains and proximal pelvic girdle muscle weakness only while 1 patient had both anorexia and proximal pelvic girdle muscle weakness. None of the patients reported any change in the quantity or frequency of urine output. The mean change in BMI was from 21.5 (SD 5.2) to 22.5 (SD 2.7) kg/m\(^2\).

The mean estimated creatinine clearance among these ten patients declined from 84.1 (SD 21.0) to 62.1 (SD 26.3) mL/min/1.73 m\(^2\) i.e. 26.8% decline from the baseline (p-value 0.05, 95% CI -64.4 --25.3). The mean creatinine value increased from 0.8 (SD 0.2) to 1.2 (0.4) mg/dL. Interestingly, urine examination was abnormal among 8 (80%) patients only. Proteinuria was the most common urinary abnormality (1+ proteinuria was present among 5 patients and 2+ proteinuria was present among the 3 patients). Among 8 patients with proteinuria, 7 (87.5%) patients fulfilled the criteria for Fanconi syndrome.

**Table 1 : Baseline Characteristics**

<table>
<thead>
<tr>
<th>At the time of initiation of TDF</th>
<th>Mean (N=10)</th>
<th>S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.2</td>
<td>6.1</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>21.5</td>
<td>5.2</td>
</tr>
<tr>
<td>CD(_4)-T-cell count (cells/µL)</td>
<td>281.2</td>
<td>241.3</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Estimated Cr.Cl (mL/min/1.73 m(^2))</td>
<td>84.1</td>
<td>21.0</td>
</tr>
<tr>
<td>Alkaline Phosphatase (U/L)</td>
<td>130.7</td>
<td>100.1</td>
</tr>
</tbody>
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Among the 8 patients with urinary abnormalities, the mean creatinine clearance was 53.1 (SD 20.7) mL/min/1.73 m² while the creatinine clearance among the 2 patients without urinary abnormalities was 98.0 (SD 5.6) mL/min/1.73 m² (p-value < 0.01, 95% CI -64.5 - -25.3). Thus presence of urinary abnormalities was significantly associated with a greater decline in the creatinine clearance at the time of diagnosis of nephrotoxicity.

The mean plasma fasting phosphate level was 2.08 (SD 0.45) mg/dL which was lower than the normal level. Among the 8 patients with urinary abnormalities, the mean phosphate level was 1.97 ±0.42 mg/dL while among the 2 patients without urinary abnormality was 2.50 ± 0.42 mg/dL (p-value 0.29, 95% CI -2.47 – 1.42). There was 195% increase in alkaline phosphatase level from 130.7 ± 100.1 U/L to 290.8 ± 239.8 U/L (p-value 0.06, 95% CI -329.5 – 9.3).

At the time of diagnosis of nephrotoxicity, the mean CD4 T-cell count increased from 281.2 ± 241.3 cells/µL to 483.0 ± 169.3 cells/µL (p-value 0.04, 95%CI -399.2 - -4.3) and the median pVL was < 50 copies/µL.

### Discussion

Among 274 PLHA on Tenofovir based ART regimen, 10 patients (3.6%) developed tenofovir induced nephrotoxicity after a median duration of 42.6 months (S.D. 19.5 months). Though this is in keeping with the earlier published reports from outside India, yet this is lower than the reported rate by Patel et al from India. At the time of the diagnosis of nephrotoxicity, only half of the patients were symptomatic and all the patients showed good clinical response to ART as evidenced by increase in BMI and improvement in the WHO clinical stage of the disease. Thus, unlike adverse drug effect of other antiretroviral drugs, there is a long clinical latency. During this period, the patients show urinary abnormalities, mild proteinuria being the commonest abnormality and 70% had Fanconi syndrome.

The mean creatinine level among the patients remained within normal limits during the follow up. However the estimated creatinine clearance value showed significant decline between pre and post-treatment levels. The decline in the creatinine clearance was significantly more among those showing urinary abnormalities than with normal urine examination. The rate of decline of creatinine clearance was more than the expected healthy population. Hence serum creatinine value in isolation might be misleading and creatinine clearance should replace the traditional monitoring and grading of renal toxicity.

The fasting phosphate level was lower among these patients while there was nearly 200% increase in alkaline phosphatase level which was statistically significant as compared to the pre-treatment value. Since there was no co-existing hepato-biliary pathology evident, the possible source of raised alkaline phosphatase is from bones secondary to hypophosphataemia osteomalacia. However the parathormone, Vitamin D level or Bone Mineral Density at baseline or at the time of diagnosis of nephrotoxicity was not available, hence the diagnosis of hyperparathyroidism, osteomalacia or vitamin D deficiency could not be confirmed.

All the patients had excellent immunological recovery as evidenced by significant improvement in clinical stage and increase in CD4 T-Cell count at the time of diagnosis. The suppression of virological replication was excellent as the patients had plasma viral load below detectable limits of the assay. Hence it can be concluded that even at the time of nephrotoxicity, TDF is a potent backbone of ART.

Tenofovir was withdrawn and switched over to Efavirenz, Abacavir and Lamivudine in 8 patients following the diagnosis of TDF induced renal dysfunction. All the patients were supplemented with oral formulation of vitamin D, calcium and neutral phosphate. Subsequent follow up showed complete resolution of the symptoms in all the 5 symptomatic patients and recovery of the urinary and blood biochemical abnormalities within 2 to 7 months.

### Conclusion

The incidence of TDF induced renal dysfunction remains low. The patients largely remain asymptomatic during the long period of clinical latency. During this period the patients on TDF, should be monitored for nephrotoxicity by laboratory monitoring for proteinuria, decline in creatinine clearance, hypophosphataemia, elevation of alkaline phosphatase levels. Prompt withdrawal of TDF and adequate supplementation with oral formulation of vitamin D, calcium and neutral phosphate leads to complete reversal of renal functions and urinary abnormalities.

### References