Toxicological Impact of Co-treatment with Rifampicin and Tenofovir on the Renal Function of Male Albino Rats

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Abstract This experimental study comparatively evaluated the toxicological effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin (TDF-RIF) combination on kidney function and histology of male albino rats. Male albino rats used in this study were divided into five (5) groups A-E of sixteen (16) animals each. Animals in group A, (placebo control) were treated orally with normal saline, group B (solvent control) were treated orally with 0.1% ethanol while groups C-E were treated orally with 80 mg/kg of RIF, 32 mg/kg of TDF and a combination of TDF-RIF for 2-8 weeks respectively. Animals were sacrificed at the end of drug therapy, blood sample was collected, centrifuged and serum extracted for creatinine, urea and uric acid evaluation. Kidney was harvested, weighed and examined for histopathological changes. Treatment with tenofovir-rifampicin combination had no significant (p<0.05) effect on absolute kidney weight when compared with treatment using individual doses of these drugs. Insufficient (p>0.05) time-dependent increases in serum creatinine, urea and uric acid levels were observed in animals treated with tenofovir-rifampicin combination when compared with treatment using individual doses of these drugs. Acute tubular necrosis, enlarged glomeruli and obliteration of the Bowman's capsule were observed in the kidneys of rats treated with tenofovir, rifampicin and a combination of tenofovir-rifampicin. This result shows that treatment with tenofovir-rifampicin combination in the management of human immunodeficiency virus/tuberculosis (HIV/TB) co-infection may not be associated with synergistic renal toxicity at the dose level used in this study.

Keywords Renal, Toxicity, Co-treatment, Tenofovir, Rifampicin, Rats

1. Introduction

Tenofovir is an acyclic nucleotide phosphonate diester analog of adenosine monophosphate. Similar to many Nucleoside Reverse Transcriptase Inhibitors (NRTIs) tenofovir inhibits HIV-1 reverse transcriptase by competing with the natural substrate deoxyadenosine 5′-triphosphate, which is part of the nucleotide pools used by virus in generating cDNA [1, 2]. It is an orally bioavailable prodrug that is widely prescribed due to its potency, convenient dosing, and a favorable safety and tolerability profile. It was approved by the US Food and Drug Administration (FDA) in 2001 and is recommended by World Health Organization (WHO) for use in adults and adolescents as preferred first-line nucleotide reverse transcriptase inhibitors in combination with other antiretrovirals (ARVs) to make dual or triple once-daily fixed-dose combinations. When administered, tenofovir is eliminated by active tubular secretion and glomerular filtration with predominant accumulation in proximal renal tubular cells. [4,5]. The use of tenofovir is associated with proximal tubular dysfunction with or without decreased renal function. Renal impairments, characterized by acute renal failure, interstitial nephritis and Fanconi’s syndrome, have been reported with the use of tenofovir in humans and animals [6, 7]. Animal studies and case reports in humans showed that tenofovir might be associated with various degrees of kidney histopathological damage characterized by proximal tubular necrosis, chronic tubulointerstitial scarring, and ultrastructural mitochondrial abnormalities [8-10].

Rifampin is a large lipid soluble semisynthetic macrocyclic antibiotic produced from streptomyces mediterranei. It is a first-line drug mostly used in combination with isoniazid, ethambutol and pyrazinamide in the treatment of all forms of tuberculosis caused by organisms with known or presumed sensitivity to the drug. It has activity against organisms that are dividing rapidly (early bactericidal activity) and against semidormant bacterial populations, thus accounting for its sterilizing activity [11].
It acts by binding to β subunit of bacterial DNA-dependent RNA polymerase in prokaryotic, but not in eukaryotic cells thereby inhibiting RNA synthesis [12]. Rifampicin is said to be safe, but it has been associated with adverse reactions such as nephrotoxicity sometimes resulting in acute renal failure [13]. Although deterioration of renal function, associated with acute tubulointerstitial nephritis and/or acute tubular necrosis, typically appears in patients receiving intermittent rifampicin therapy, some authors have also reported cases occurring during continuous rifampicin therapy [14, 15]. Studies have shown that rifampicin is associated with histopathological changes characterized by glomerular distortion glomerulonephritis, interstitial nephritis and/or acute tubular necrosis [16, 17].

Despite the fact that rifampicin and tenofovir are individually associated with renal toxicity these drugs are usually co-administered in the management of human immunodeficiency virus/ tuberculosis co-infection [18, 19]. The direct exposure of the kidney to co-administered rifampicin - tenofovir could be associated with overlapping nephrotoxic effects [22]. This study was therefore designed to investigate the effects of co-treatment with tenofovir- rifampicin on kidney function and histology of adult male albino rats.

2. Materials and Methods

Animals

Eighty (80) adult male albino rats of average weight 350 ±5 g which were divided into five groups A-E of sixteen (16) animals each were used in this study. The animals were obtained from the animal house of the Department of Pharmacology and Toxicology, Madonna University, Elele, Rivers State. The animals were allowed to acclimatize for 14 days and had free access to food and water ad libitum.

Drugs

Rifampicin used in this study was manufactured by Mancare Pharmaceuticals, India while pure sample of tenofovir disoproxil fumarate was purchased from Shijiazhuang Aopharm Import & Export Trading Co., Ltd. Shijiazhuang, China. Both drugs were of analytical grade. The doses of rifampicin and tenofovir disoproxil fumarate used in this study are 80mg/kg and 32 mg/kg respectively which are higher than the clinically recommended doses [23, 24]. Rifampicin was dissolved in 0.1% ethanol while tenofovir disoproxil fumarate powder was suspended in normal saline [25, 26].

Grouping of Animals and Drug Administration

Animals were group into five groups A- E of 16 animals per group. Animals in each group were further sub divided into four groups of four animals each. Animals in group A (placebo control) were treated with normal saline, while animals in group B (solvent control) were treated with 0.1% ethanol orally. Animals in groups C-E were treated with 80 mg/kg of RIF, 32 mg/kg of TDF and a combination of TDF-RIF orally for 2-8 weeks respectively.

Collection of Sample for Analysis

At 2, 4 6 and 8 weeks, after overnight fast, 2mls of blood samples were collected from the rats under chloroform anesthesia by cardiac puncture into sterile sample container and allowed to clot. Thereafter, plasma was separated by centrifugation at 1200 rmp for 15 min and used for analysis. The animals were then killed by over dose of chloroform anesthesia; kidneys were dissected out, cleaned off the extraneous tissue, weighed and evaluated for histopathological changes.

Evaluation of Serum Renal Function Parameters

Serum urea, uric acid and creatinine levels were determined as described by Kind & King 1954 [27] Annino & Giese 1979[28] Toro & Ackermann 1975[29] .

Histopathological Analysis

Kidney tissue was fixed in 10% buffered formalin for 24 h at room temperature; the slices were embedded in paraffin and then sectioned. Four micrometer-thick paraffin sections were stained with hematoxylin and eosin for light microscope examination. The photomicrographs of the relevant stained sections were taken with the aid of a light microscope.

Statistical Analysis

Data were expressed as mean values ± SEM. Analysis of data was performed with one-way analysis of variance (ANOVA).Statistical significance was set at p< 0.05.

3. Results

Effects on absolute Kidney Weight and Serum Creatinine

There wasn’t any significant (p>0.05) change in kidney weight of animals treated with TDF, RIF and a combination of TDF- RIF with respect to the control [Table 1]. In our study, we observed that treatment with TDF time-dependently increased serum creatinine level to 109.2±2.20, 117.1±3.21, 124.1±2.12 and 146.2±0.13 while treatment with RIF increased serum creatinine level.
time-dependently to 106.6±0.71, 113.75±1.21, 123.5±3.00 and 144.7±2.14. These increases were found to be significant ($p<0.05$) only at week 8 when compared with the control. Treatment with a combination of TDF – RIF produced insignificant ($p>0.05$) time- dependent increases in creatinine level when compared with treatment with individual doses of TDF and RIF, but increase was significant ($p<0.05$) at week 8 when compared with the control [Table 2].

### Table 1. Effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin combination on absolute kidney weight (g) in rats

| Dose       | WK2       | WK4       | WK6       | WK8       |
|------------|-----------|-----------|-----------|-----------|
| Control    | 0.63±1.15 | 0.66±2.15 | 0.65±3.00 | 0.62±1.13 |
| TDF 80mg/kg| 0.67±3.22 | 0.64±2.43 | 0.66±2.43 | 0.63±2.04 |
| RIF 32mg/kg| 0.65±2.10 | 0.64±2.72 | 0.70±1.33 | 0.63±2.51 |
| TDF/RIF    | 0.70±2.31 | 0.67±3.21 | 0.71±1.20 | 0.64±1.16 |

TDF: tenofovir, RIF: rifampicin. Results are expressed as mean ± SEM.

### Table 2. Effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin combination on serum creatinine (µmol/l) in rats

| Dose       | WK2       | WK4       | WK6       | WK8       |
|------------|-----------|-----------|-----------|-----------|
| Control    | 101.7±1.21| 102.2±2.10| 105.3±3.12| 103.1±0.15|
| TDF 80mg/kg| 109.2±2.20| 117.1±3.21| 124.1±2.12| 146.2±0.13*|
| RIF 32mg/kg| 106.6±0.71| 113.75±1.21| 123.5±3.00| 144.7±2.14*|
| TDF/RIF    | 110.1±1.22| 119.25±1.25| 124.3±1.25| 149.3±1.22*|

TDF: tenofovir, RIF: rifampicin. Results are expressed as mean ± SEM, the superscript (*) means significant difference with respect to the control at $p<0.05$(ANOVA).

### Effects on Serum Urea

Treatment with TDF produced time-dependent increases in serum urea, but significant ($p<0.05$) increase to 6.5±0.03 was only observed at week 8 only with respect to the control. Also RIF treated animals showed time-dependent increases in serum urea with significant ($p<0.05$) increase observed only at week 8 when compared with the control. Furthermore combined treatment with TDF-RIF time-dependently increased serum urea to 4.97±3.00, 5.21±2.12, 5.42 ±0.21 and 6.70±1.12 for 2-8 weeks respectively. These increases were insignificant ($p>0.05$) when compared with treatment using individual doses of TDF and RIF [Table 3].

### Table 3. Effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin combination on serum urea (mmol/l) in rats

| Dose       | WK2       | WK4       | WK6       | WK8       |
|------------|-----------|-----------|-----------|-----------|
| Control    | 4.32±2.20 | 4.40±1.20 | 4.61±0.14 | 4.41±0.31 |
| TDF 80mg/kg| 4.71±2.21 | 5.02±2.13 | 5.31±2.11 | 6.58±0.03*|
| RIF 32mg/kg| 4.60±2.13 | 4.72±1.23 | 5.13±0.23 | 6.37±2.11*|
| TDF/RIF    | 4.97±3.00 | 5.21±2.12 | 5.42±0.21 | 6.70±1.12*|

TDF: tenofovir, RIF: rifampicin. Results are expressed as mean ± SEM, the superscript (*) means significant difference with respect to the control at $p<0.05$(ANOVA).

### Effects on Serum Uric Acid and Kidney Histology

Treatment with TDF produced insignificant ($p>0.05$) time-dependent increases in serum uric acid when compared with the control. Treatment with RIF also produced insignificant ($p>0.05$) time-dependent increases in serum uric acid when compared with the control. In animals treated with a combination of TDF- RIF, time-dependent increases in serum uric acid levels were observed. These increases were insignificant ($p>0.05$) when compared with treatment using individual doses of these drugs [Table 4]. Kidney of animals’ exposure to TDF, RIF, and a combination of TDF- RIF showed histopathological changes characterized by tubular necrosis, enlarged glomeruli and obliteration of the Bowman’s capsule [Fig 2-4].

![Figure 1. Photomicrograph of H and E stained section of the kidney of control rat treated with 0.1% ethanol for 8 weeks showing normal kidney histology. (x400)](image1)

![Figure 2. Photomicrograph of H and E stained section of the kidney of control rat treated with 80mg/kg of rifampicin showing acute tubular necrosis. (x400)](image2)
Figure 3. Photomicrograph of H and E stained section of the kidney of rat treated with 32mg/kg of tenofovir for 8 weeks showing acute tubular necrosis and enlarged glomeruli and obliteration of the Bowman’s capsule. (x400)

Figure 4. Photomicrograph of H and E stained section of the kidney of rat treated with combined doses of 80mg/kg of rifampicin and 32mg/kg of tenofovir for 8 weeks showing acute tubular necrosis and enlarged glomeruli obliteration of the Bowman’s capsule. (x400)

Table 4. Effects of treatment with tenofovir, rifampicin and tenofovir-rifampicin combination on serum uric acid (mg/dl) in rats

| Dose    | WK2     | WK4     | WK6     | WK8     |
|---------|---------|---------|---------|---------|
| Control | 1.51±2.00 | 1.53±1.13 | 1.50±3.12 | 1.52±1.12 |
| TDF 80mg/kg | 1.57±2.30 | 1.60±3.10 | 1.65±1.15 | 1.77±0.74 |
| RIF 32mg/kg | 1.54±1.53 | 1.57±0.64 | 1.60±3.10 | 1.67±1.12 |
| TDF/RIF | 1.59±2.70 | 1.65±3.12 | 1.68±3.13 | 1.79±2.14 |

TDF: tenofovir, RIF: rifampicin. Results are expressed as mean ± SEM.

4. Discussion

Toxic effects on the kidney related to medications are both common and expected, given the kidney’s roles in plasma filtration and maintenance of metabolic homeostasis. Renal dysfunction and injury secondary to medications can present as subtle injury and/or overt renal failure. Some drugs perturb renal perfusion and induce loss of filtration capacity while others directly injure vascular, tubular, glomerular and interstitial cells [30]. This study comparatively assessed time-dependent toxicological effects of treatment with tenofovir, rifampicin, and tenofovir-rifampicin combination on kidney function and histology of adult male albino rats which no study has been done. Evaluation of the effects of drugs on organ weight is an essential aspect of toxicological assessment [31]. In this study, treatment with a combination of tenofovir-rifampicin did not produce any significant (p>0.05) change in absolute kidney weight when compared with treatment using individual doses of these drugs [32, 33]. Co-treatment with tenofovir-rifampicin produced time-dependent increases in creatinine, urea and uric acid, but increases were not significant (p>0.05) when compared with treatment using individual doses of tenofovir and rifampicin. Observation in the study shows that co-therapy with tenofovir-rifampicin in HIV/TB co-infection may not be associated with synergistic renal toxicity.

In this study, we observed a time-dependent increase in serum creatinine level in tenofovir treated animals which is a sign of renal toxicity and is consistent with previous studies that were not time-correlated [34, 35]. Noted increase in serum urea in tenofovir treated animals was time-dependent and is also a sign of renal toxicity. This observation is consistent with the work of Adaramoye and others who reported increase in serum urea in rats treated with 50mg/kg of TDF for 4 weeks [36, 37]. Our current study observed increase in serum uric acid in tenofovir treated animals which agree with the work of Abraham and others who reported increase in serum uric acid in rats treated with 600mg/kg of TDF for 5 weeks [38]. Histopathological examination of the kidney of tenofovir treated animals revealed kidney damage characterized by acute tubular necrosis, enlarged glomeruli and obliteration of the Bowman’s capsule. This finding is consistent with a study which shows that animals treated with 600mg/kg of tenofovir for 35 days produced proximal tubular and glomerular damage [39]. Lebrecht and colleagues also exposed rats to tenofovir and reported proximal tubular dilatation and necrosis which is consistent with our observation [40]. Tenofovir induced kidney damage observed in our current study could be attributed to tenofovir induced oxidative stress. Reports have associated tenofovir with accumulation in renal tubules, lipid peroxidation, generation of oxidative radicals and the down regulation of kidney antioxidants [41].

Furthermore, we observed increases in serum creatinine and urea levels in rifampicin treated animals which is in agreement with previous reports [42- 46]. The increase in
serum uric acid level in rifampicin treated animals observed in this study agrees with a reported investigation by Shabana and colleagues who treated rats with 200mg/kg of rifampicin for 30 days [47]. In this present study, histopathological examination of kidney of rifampicin treated animals revealed tubular necrosis which is in resonance with reported observations by Tada and co-researchers who observed rifampicin induced mild nephrotic syndrome, showing glomerular abnormalities and slight interstitial changes [48]. Our findings are validated by the work of De Vriese et al [49] who reported that acute tubular necrosis is the predominant pattern in renal biopsies during acute renal failure attributed to intermittent rifampicin therapy. The mechanism by which rifampicin induced kidney damage has been attributed to immune complex deposition in the blood vessels or interstitium which may cause glomerular endotheliosis leading to tubular injury [50]. Interestingly, observed increases in serum urea, creatinine, and uric acid induced by these drugs could be correlated with histopathological changes observed in the kidney of treated animals.

5. Conclusions

Treatment with tenofovir-rifampicin combination produced time-dependent increases in creatinine, urea, and uric acid levels, but increases were not significant (p>0.05) when compared with treating using individual doses of these drugs. Histopathological damage characterized by acute tubular necrosis, enlarged glomeruli and obliteration of the Bowman’s capsule were observed with treatment with tenofovir-rifampicin combination. Treatment with tenofovir-rifampicin combination in the management of HIV/TB may not be associated with synergistic renal toxicity, but patients renal function status should be considered before co-administration of tenofovir-rifampicin.

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