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Tenofovir Renal Toxicity: Evaluation of Cohorts and Clinical Studies—Part 2

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ABSTRACT

Tenofovir is a nucleotide reverse transcriptase inhibitor used as part of antiretroviral regimens. It is well tolerated with relative toxicological effects but recent reports have linked it with renal toxicity which is of clinical concern. This study reviews literary work on tenofovir renal toxicity with more light on case reports. Tenofovir renal toxicity manifests as Fanconi's syndrome, nephrogenic diabetes insipidus and acute renal failure. Fanconi's syndrome is characterised by acidosis, protenuria, albuminuria, aminoaciduria, hyperchloremic, metabolic acidosis, hypouricemia, hypophosphatemia and glycosuria. The presence of urine osmolality, polydipsia and polyuria could give credence totenofovir induced nephrogenic diabetes insipidus. In some cases of tenofovir renal toxicity, renal biopsy revealed sclerosed glomeruli with ischemic injury including portal collapse of capillary loops. Histopathological changes in glumeruli include mild mesangial proliferation, increased mesangial matrix and thickened capillary loops. Moderate degenerative tubular changes, loss of tubular mass, interstitial scarring and scattered cellular infiltrates. Pharmacodynamic and pharmacokinetic interactions may occur with the co administration of tenofovir with non steroidal anti-inflammatory drugs, aminoglycosides and some protease inhibitors which may potentiate renal toxicity. Tenofovir renal toxicity is associated with some risk factors including genetic polymorphism as supported by dichotomy in renal toxicity among different race and the association between *ABCC*2 gene and tenofovir kidney tubular dysfunction. The pharmacology of tenofovir renal toxicity is unclear but it is attributed to the interaction between tenofovir and theorganic anion transporters (hOAT1, and to a lesser extent, OAT3) favoring intracellular accumulation in renal proximal tubule cells. This may lead to ultrastructural mitochondrial abnormalities and decreased mtDNA levels which could stimulate reactive oxygen species production, depletion of antioxidants and antioxidant enzymes. These processes can stimulate the destruction of biomolecules such as DNA, proteins, and lipids, thus causing the deregulation of redox-sensitive metabolic pathways, signaling pathways, and cell death. Despite tenofovir renal toxicity it has achieved notable therapeutic success nevertheless patients on tenofovir containing regimens should be monitored for renal function parameters. Co administration with potential nephrotoxic drugs should be avoided except when benefit outweighs risk.

KEYWORDS

Tenofovir; Renal; Toxicity; Interactions; Polymorphism; Pharmacology

1. Introduction

The nephron is the functional unit of the kidney and consists of a continuous tube of highly specialized heterogeneous cells. It is the major organ of excretion and homeostasis for water-soluble molecules; it can concentrate certain substances actively. Its cells can bioconvert chemicals and metabolically activate a variety of chemical substances [1]. To limit both systemic exposure and

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the duration of the pharmacological or toxicological effects, of these substances they are rapidly and efficiently eliminated via the kidney as part of the fundamental defense system of our body. Some drug substances are actively transported across the renal proximal tubule by drug transporters followed by elimination via the urine which is a major pathway in the detoxification process [2]. Some of these eliminated drugs are toxic and their contact with drug transporters in tubular cells is the first fundamental stage in the development of their nephrotoxic process. Most drug substances become nephrotoxic only after transportation into the proximal tubular cells. Recent advances have identified families of drug transporters which are expressed in the proximal tubule [3]. Of the identified transporters, the organic anion transporters (hOAT1, and to a lesser extent, OAT3) in the basolateral membrane are responsible for the active transportation of tenofovir into renal proximal tubule cells [4,5], subsequently the drug is secreted to the tubular lumen by the apical membrane transporters (multidrug resistance proteins, 4 and 2) [6]. Tenofovir may interact with these transporters leading to excessive entry or reduced outflow of tenovoir favoring intracellular accumulation and increasing renal toxicity. Proximal tubular cell secretion of tenofovir explains the accumulation of the drug in these mitochondria-rich cells leading to mitochondrial damage. Despite initial evaluations which gave credence to the renal safety of tenofovir, reports have associated tenofovir with significant risk of renal toxicity in human and animal studies. Tenofovir nephrotoxicity is characterized by proximal tubular cell dysfunction that may be associated with acute kidney injury or chronic kidney injury [7]. Several case reports describing renal toxicity attributable to tenofovir have been published, with manifestations of Fanconi syndrome, nephrogenic diabetes insipidus and acute renal failure being reported [8,9]. Fanconi's syndrome is characterised by acidosis, protenuria, aminoaciduria, hypophosphatamia and glycosuria [10]. In some cases histopathological changes in renal toxicity revealed proximal tubular injury and varying degrees of chronic tubulointerstitial scarring. Prominent eosinophilic inclusions within proximal tubular cell cytoplasm and alteration in mitochondria structure and function were also observed [11,12]. Due to tenofovir reported renal toxicity, in our initial study—Part one, we critically looked at cohorts and clinical studies. In this second part, we are evaluated case reports, genetic factors, pharmacology of tenofovir renal toxicity and the implications of drug-drug interactions on tenofovir renal toxicity.

2. Types of Renal Toxicity in HIV

In spite the fact that some antiretroviral drugs are associated with renal toxicity, HIV is also associated with some forms of renal damage (nephropathy). In the first part of this work we reviewed HIV associated renal nephropathy, HIVAN was observed to be prominent in HIV positive patients of African origin. This observation was reported to have genetic predisposition, and incidence is equally associated with higher viral load. Researchers were able to classify HIV associated renal nephropathy probably due to the evaluation of different and unique characteristic manifestations. Commonly known classifications include HIV associated nephropathy (HIVAN), immune complex-mediated glomerulonephritis, andthrombotic microangiopathies (TMA).

2.1. HIV Associated Nephropathy

It is a disease caused by focal glomerulosclerosis with severe proteinuria, renal failure, and rapid progression to ESRD. It has become the most common cause of end stage renal disease in HIV patients. Studies have shown that HIVAN is more prevalent in patients of African descent [13,14]. The estimated prevalence of HIVAN has ranged from 3.5% in clinical studies to 12% in autopsy studies [15]. Renal biopsy is one of the most fundamental means to establish the diagnosis of HIVAN. Characteristic histopathological findings include collapsing focal and segmental glomerulosclerosis, tubular epithelial atrophy with microcystic dilatation of the tubules and lymphocytic interstitial infiltration [16]. Viral infection of renal cells seems to play an important role in the pathogenesis of HIVAN. In 2002 Marras and others reported that renaltubular cells in patients with HIVN could serve as a reservoir which facilitates active replication of HIV-1 independent of various peripheral blood mononuclear cells [17].

2.2. Immune Complex-Mediated Glomerulonephritis

A multitude of immune complex-mediated glomerulonephritis have been reported as causes of chronic kidney disease in HIV infected patients. The prevalence of HIV associated, immune complex-mediated glomerulonephritis has been estimated to be 15% - 80% in various autopsy and biopsy study in HIV infected patients. According to some authors Immune complex-mediated glomerulonephritis may present as postinfectious glomerulonephritis, membranous nephritis, IgA nephritis, fibrillary glomerulonephritis, immunotactoid glomerulopathy, and membranoproliferative glomerulonephritis [18]. In general, HIVAN is mainly limited to patients of African descent, whereas most cases of renal disease in the white population seem to be immune complex-mediated glomerulonephritis [19].

2.3. Thrombotic Microangiopathies (TMA)

Thrombotic microangiopathies involving kidney was first

described in AIDS patient by Boccia *et al*. in 1984, but subsequently, several hundred cases have been reported worldwide [20]. TMA occurs with an annual incidence of 3.7 cases per 100 000 persons in the general population and is lightly more common in females (female:male ratio 3:2) [21-23]. TMA is a heterogeneous group of disorders characterized by histopathological lesion of vessel wall thickening (mainly arterioles or capillaries), intraluminal platelet thrombosis and obstruction of the vessel lumina. Consumption of platelets and erythrocytes occurs in the microvasculature of kidney, brain and other organs, which causes laboratory features of thrombocytopenia and microangiopathic hemolytic anemia [24]. Haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) are classical forms of thrombotic microangiopathy (TMA) which are characterize by microangiopathic haemolytic anaemia with renal insufficiency along with other features such as thrombocytopenia, fever, and neurological changes [25,26]. It can also be observed in association with pregnancy, cancer, chemotherapy, human immunodeficiency (HIV) infection and malignant hypertension [27].

3. Role of Antiretroviral in HIV Associated Renal Disease

Despite HIV associate renal disease the advent of highly active antiretroviral therapy in the management of HIV hasdecreases the incidence of HIV associated renal disease. One of the primary impacts that is vividly visible is the decrease in HIV associated mortality and morbidity rates. A clearer picture of conspicuous impact could be ascertained from the outstanding literary work of Wyatt and Klotman [28] who reported that the widespread introduction of HAART in 1996, led to a drastic decline in AIDS-related deaths in the United States. They further stated that the proportion of deaths that are attributable to AIDS-defining conditions has continued to decline, with chronic complications such as liver and kidney disease becoming increasingly important contributors to mortality in the HAART era. At the same time, there has been a more subtle decrease in the incidence of ESRD related to HIV, which reached a plateau at approximately 800 to 900 new cases per year in the United States.

Schwartz and colleagues also showed that the introduction of HAART has had a significant impact on the epidemiology of HIV-related kidney disease, the decline in the incidence of HIV-related ESRD after the introduction of HAART strongly suggested a role for antiretroviral therapy in the treatment of HIVAN [29]. This is further supported by reports of clinical and histological improvement in kidney function and architecture after the initiation of HAART [30,31] and by retrospective cohort studies [32]. A number of cohorts have shown tremendous improvement in renal function of HIV patients with renal impairment observed after initiation of HAART. In one of the cohorts HIV positive renal impaired patients improved with HAART treatment with respect to non HAART treated patients [33]. Also Preliminary data from 3313 patients who were enrolled in a randomized antiretroviral trial in Uganda and Zimbabwe demonstrated stabilization or slight improvement in kidney function after the initiation of HAART [34]. In a comparative cohort of patients with HIV biopsy proven HIVAN in the pre-HAART and in the HAART era reports revealed improvement in HIV associated renal function during the HAART era [35]. A cohort of 263 consecutive HIV-infected patients referred to the Johns Hopkins renal clinic from 1995 to 2004 was examined. Patients were included if they had biopsy-proven HIVAN and did not require dialysis within 1 month of their kidney biopsy. Fifty-three patients among 152 biopsied patients had HIVAN. Among 36 patients who met the inclusion criteria, 26 were treated with ART (group I) and 10 patients were not (group II). It was observed that Patients with biopsy-proven HIVAN treated with ART had better renal survival compared with patients who did not receive ART [36].

The beneficial effects of HAART on HIV associated renal disease have been shown in individual clinical observations. There are reports of resolution of renal disease with the administration of HAART, with a recurrence of renal disease after stopping treatment [37]. It is recognized that HAART prevents or reduces the risk of developing HIVAN and if this occurs, HAART treated patients may have a slower course and lower mortality than in untreated patients [38]. Successful transplantations in HIV-infected patients who have received highly active antiretroviral therapy and have undetectable viral loads have been reported. One of these reports can be seen from the work of Murphy and colleagues who transplanted kidneys in 23 patients who were receiving antiretroviral therapy and observed a graft survival rate of 87%. Case reports have also shown the impact of antiretroviral drugs on HIV associated renal disease [39]. Also two African Americans with HIV associated renal impairment exhibited marked improvement after initiation of antiretroviral drugs [40]. Notwithstanding the impact of antiretroviral therapy on HIV associated renal disease is not without its problems. Reports have associated some antiretroviral drugs with renal toxicity which manifested as acute renal failure, Fanconi's syndrome, nephrogenic diabetic insipidus as reviewed bellow.

4. Antiretroviral Induced Renal Toxicity

Regardless of the impact of antiretroviral drugs on ameliorating HIV associated renal disease reports from some

quarters have associated some antiretroviral agents with renal toxicity. One of the classes of antiretroviral drugs with this attribute is the protease inhibitors with respect to indinavir probably due to volume of reports. One of these reports is a cohort reported by Herman which involved 781 patients exposed to indinavir for a median duration of 53 weeks which revealed an incidence of 7 per 100 persons per year [41]. This is in agreement with the work of Dieleman *et al* (2002) [42] who in acohort of 1219 involving 644 patients exposed to indinavir reported an incidence of 8.3 per 100/year vs 0.8 per/year for other PIs on renal toxicity while Kopp *et al.* (2001) [43] reported 3.4% for indinavir associated renal toxicity. A retrospective analysis of 106 HIV infected patients exposed to indinavir revealed (18.6%) had sustained elevation of creatinine [44]. This is consistent with18 % (renal failure) reported by Voigt in a study that involved 72 patients exposed to indinavir. Merck and co (1997) reported incidence within the range of 2.6% - 5% in 2200 patients and 7% when doses exceed the recommended clinical dose [45]. An incidence of 8% out of 240 patients exposed to indinavir was reported by Kopp *et al.* (1997) [46].

In some studies higher incidence of indinavir associated renal toxicity were reported. One of these studies reported incidence of crystalluria as 67% which later decreased to 25% after 2 weeks of therapy in a study which exposed 54 HIV patients to indinavir [47]. An incidence of 23.6% was reported over 2 years in 555 patients exposed to indinavir [48]. A review of 214 patients on indinavir-containing regimens with a median follow up period of 216 (150 - 312) weeks almost half of the patients had significant loss of renal function that was associated with prolonged use of indinavir. Leukocyturia (51.9%) was the most common finding of indinavir-associated renal complications [49]. Some authors have equally linked indinavir withacute andchronic renal failure [50-53].

Some studies have shown that atazavavir a member of the PIs family could be associated with renal toxicity but only few cases have reported. This could be buttressed by a retrospective study involving 1,134 patients who received ritonavir-boosted atazanavir and only 11 cases of atazanavir-associated nephrolithiasis were diagnosed [54]. Similarly, 30 cases of atazanavir-induced nephrolithiasis were recorded without chronic renal failure over a four-year study period [55]. Interstitial nephritis with acute renal failure was described in association with atazanavir or atazanavir/tenofovir therapy [56]. Ritonavir is always used as a booster for other protease inhibitors, it is said to have a safe renal profile probably due few reported cases of reversible renal failure and decline in renal function associated with it [57-59]. Other members of the PI family: nelfinavir, imprenavir, fosamprenavir and lopinavir are reported to have good renal profile due low volume of reports or lack of reports [60]. The non-nucleoside reverse transcriptase inhibitors: nevirapine, efavirenze, and delavirdine have safe renal profile as reported [61]. Nevertheless few cases of Fanconis like syndrome and acute renal failure associated with didanosine, stavudine, lamivudine, and abacavir have been reported [62-65].

Another family of antiretroviral drugs that is associated with nephrotoxicity is the nucleotide reverse transcriptase inhibitors family: Adefovir, cidofovir and tenofovir. They differ from the nucleoside reverse transcriptase inhibitors due to the presence of a cyclic mono phosphate component. Cidofovir and adefovir are nephrotoxic, their accumulation in proximal tubular cells and cytotoxicity may cause direct cytotoxic effects on the renal system [66-69]. Adefovir is currently not approved by USA Food and Drug Administration.

5. Tenofovir Renal Toxicity: Evaluation of Case Reports

In our previous study we evaluated tenofovir associated renal toxicity with emphasis on cohorts, clinical studies and its reversibility. In this second part emphasis is on the evaluation of individual case reports, implications of drug-drug interactions, involvement of genetic factor and the pharmacology of tenofovir associated renal toxicity. Tenofor is associated with Fanconi's syndrome which results from generalized dysfunction of the proximal renal tubule leading to impaired re absorption of amino acids, glucose, urate, bicarbonate, and phosphate and increased excretion of these solutes into the urine [70]. Fanconi's syndrome can either be inherited or acquired. Inherited forms occur in a number of genetic disorders such as, hereditary, tyrosinemia, hepatorenal, cystinosis, Lowe syndrome, galactosemia, fructose intolerance glycogen storage disease type 1 and Wilson's disease [71-76]. It can also be acquired through heavy metal exposure, multiple myeloma, and immunologic disorders [77, 78]. Acquired Fanconi's syndrome has also been associated with the use of a number of medications including aminoglycosides [79]. One of the medications reported to be associated with fanconi's syndrome is tenofovir containing antiretroviral regimens and quite a number of case reports have been documented.

We will start by looking at Kapadia *et al.* 2013 [80] who presented a case of Fanconi' s syndrome in a HIV patient treated with tenofovir containing antiretroviral regimens characterized by eleveated levels of albuminuria and glycosuria with low serum phosphate level. Another case was presented by Irizarry-Alvarado *et al*., 2009 [81] in which laboratory results suggested proximal tubular damage consistent with Fanconi's syndrome due

to the following manifestations: hyperchloremic, non-anion gap metabolic acidosis; hypouricemia; hypophosphatemia; and normoglycemic glycosuria. Mathew and Knaus reported another case of Fanconis syndrome characterisedby hyperchloremic, non-anion gap metabolic acidosis, hypouricemia, hypophosphatemia and glycosuria. The presence of urine osmolality, polydipsia and polyuria gave credence to nephrogenic diabetes insipidus assumed to be related to tenofovir use [82]. Some scholars presented 7 cases of renal injury associated with tenofovir therapy which are consistent with Fanconi's syndrome. Observations revealed proximal renal tubular acidosis, normoglycemic glycosuria, hematuria, hypophosphatemia, hypouricemia, hypokalemia, aminoaciduria, citrullinuria and proteinuria. In one of these cases renal biopsy revealed tubulointerstitial nephropathy with primary lymphocytic infiltrate [83].

Another study presented a HIV patient who was intolerant to some antiretroviral drugs and had persistent virological failure was placed on a new therapeutic regimen containing tenofovir, guided by resistance testing. Due to patient's case presentation, laboratory analysis showed hyperlactatemia, metabolic acidosis, proteinuria, glucosuria, aminoaciduria and elevated serum creatinine which is suggestive of Fanconi's syndrome [84]. Another case of tenofovir induced Fanconi's syndrome in a HIV patient was reported by creput and colleagues. Fanconi's syndrome was diagnosed on the basis of the presence of metabolic acidosis, glycosuria, phosphaturia, proteinuria and hypouricemia. Urinary cytology revealed large amounts of desquamated cells of apparent tubular origin at various stages of degeneration, varying from cells with pyknotic nuclei to anucleate cells and cytoplasmic fragments. There were also rare clusters of mildly atypical squamous cells, and no evidence of crystals. Renal biopsy revealed lesions that were largely localized in the proximal convoluted tubules. There was generalized necrosis and sloughing of tubular cells, with denuding of the tubular basement membrane. When present, the tubular cell cytoplasm appeared thin and often vacuolated. Surrounding the tubules was focal interstitial inflammation of mixed character, without significant destruction of tubular basement membranes [85].

Some case reports showed that tenofovir could induce renal failure and Fanconi's syndrome simultaneously. One of these case reports was reported by Olea and others in a patient on TDF/LOP-RTV containing regimens. Laboratory evaluation revealed glycosuria, aminoaciduria, hyperuricosuria, protenuria, hypercalciuria. This was supported by renal biopsy which revealed acute focal tubule interstitial nephritis with focal tubular atrophy and necrosis [86]. Similar observation was reported by Kapitsinou and Ansari who presented a case of a HIV patient on tenofovir containing antiretroviral regimen who developed acute renal failure and fanconis syndrome characterized by severe metabolic acidosis and acretinine clearance of 9.8 mg/dl [87].

Schaaf and co in 2003 [88] also reported a case of renal failure a HIV patient switched to 3TC/d4T/TDF/LOP-RTV from an initial antiretroviral regimen due to lack of adherence and virological failure. Biochemical evaluation revealed impaired biomarkers of renal function. Renal biopsy showed a mild interstitial infiltrate consisting of lymphocytes, focal atrophic changes in cortical tubules, luminal ectasia and loss of brush border in tubules. The authors attributed this renal failure to tenofovir but could there be potentiation of acute renal failure by lopinavir-rotinavir due to reported cases of nephrotoxicity by these agents.

Patel *et al.* 2007 [89] added their voices by reporting a case of renal failure in HIV positive patient who was treated with some antiretroviral drugs but later switched to 3TC/EFV/TDF. Biochemical evaluation revealed imbalance in renal biochemical parameters which was attributed to tenofovir. Renal biopsy showed sclerosed glomeruli with ischemic injury including portal collapse of the capillary loops. Histopathological changes in glomeruli include mild mesangial proliferation, increased mesangial matrix and thickened capillary loops. Moderate degenerative tubular changes, loss of tubular mass, interstitial scarring and scattered cellular infiltrates were observed. This observation is similar to the work of Lee *et al.* [90] entitled acute tubular necrosis in a patient receiving tenofovir. Collectively they reported tenofovir attributed renal impairment associated with increase cretinine clearance. They further supported their work by a confirmatory renal biopsy which revealed severe tubular necrosis with mild degree of interstitial fibrosis and patchy mild tubular atrophy. In 2006 Zimmermann and co workers [91] reported five cases of HIV positive patient with acute renal failure and Fanconi's syndrome associated with tenofovir containing antiretroviral regimens. In these patients acute tubular necrosis was identified by urinary sediment with pigmented granular casts. Renal biopsy revealed unique lesions due to karyomegaly in proximal tubular nuclei. Similar incidence of tenofovir associated Fanconi's syndrome, nephrogenic diabetes insipidus, and acute renal failure was reported by Verhelst *et al*., 2002 [92].

Karas and colleague reported 3 cases of renal toxicity associated with tenofovir. Renal failure, proximal tubular dysfunction and nephrogenic diabetes insipidus were observed. In 2 of the 3 cases, renal biopsy revealed severe tubular necrosis with characteristic nuclear changes [93]. Another episode of acute renal failure in collaboration with Fanconis's syndrome was made public by Gaspar and friends. Their observation was characterized by glucosuria, aminoaciduria, phosphaturia, calciuria and

uricosuria, hyperchoremic metabolic acidosis and hypokalemia [94]. This observation is in agreement with reports of similar incidence by some authors [95-97].

6. Implications of Drug-Drug Interactions in Tenofovir Renal Toxicity

Drugs are been co administered to increase pharmacological or therapeutic benefits which has been proven in human and animal studies. It is also known that combined use of multiple drugs may cause toxicological effects as a result of drug-drug interactions which could be pharmacodynamic or pharmacokinetic interactions [98]. Antiretroviral regimens contain 3 - 4 drugs which could be administered with other drugs in the presence of co morbidity. There are reported cases of interactions involving antiretroviral drugs and other drugs and one of these interactions is with non steroidal anti-inflammatory drugs (NSAIDs). Cases of renal failure associated with Fanconi's syndrome in HIV patients on tenofovir containing antiretroviral drugs and NSAIDs have been reported [99]. Bicket and colleague reported that drug-drug interaction involving diclofenac could exacerbate tenofovir acute kidney injury. They drew their conclusion from a cohort involving 89 patients on diclofenac of which 61 patients were treated with tenofovir. They observed that 13 patients (14.6%) developed renal impairment [100]. This is in agreement with reports from some quarters on NSAIDS induced renal toxicity in humans [101-105]. In animal studies NSAIDs associated nephrotoxicity was characterized by glomerular degeneration, tubular necrosis, mild interstitial inflammation, glomerulo-nephritis with several proximal convoluted tubules having attenuated and necrotic epithelium. These NSAIDs induced morphological changes are similar to reported tenofovir induced renal changes in animals [106-110]. It was also reported that incidence of acute renal failure associated with NSAIDS account for 15.5% of all cases of drug induced acute renal failure hence combination of tenofovir with other drugs with nephrotoxic potentials should be avoided [111]. Another case of drug-drug interaction that could induce additive, synergistic or potentiate nephrotoxicity is between antiretroviral drugs and aminoglycoside class of antibiotics. HIV is always associated with co morbidity like tuberculosis that may require co administration of antiretrovirals and aminoglycosides. Recent report showed that tenofovir/streptomycin and tenofovir/ kinamycin induced renal toxicity in HIV patients with tuberculosis [112]. Aminoglycosides antibiotics are known to be associated with renal toxicity. Some scholars have reported an incidence of 20% - 50% for aminoglycoside associated renal toxicity [113,114]. In humans aminoglycoside can alter the function and architecture of the kidney [115-118]. In animal studies aminiglycosides induced renal histopathological changes was characterised by glomerular congestion, glomerular degeneration, loss of bowman's capsule space, necrotic changes inform of pale cytoplasm, pkynosis, karyolysis and cellular infiltration in the cortex. Other histopathological changes include basal membrane interruption, mesangial proliferation and apoptosis, indicated by decreases in glomerular filtration and alteration in intraglomerular dynamics [119-121]. Despite few reported cases the co administration of tenofovir and aminiglycosides should be done with caution especially in patients with HIV induced tuberculosis. It is biologically possible that aminoglycosides and tenofovir associated nephrotoxicity may be synergistic in the mitochondria of proximal tubular cells, one suggestive clinical approach is that the combination could be used, but with close monitoring of renal function parameters.

Furthermore synergistic or additive nephrotoxicity can arise from antiretroviral-antiretroviral interactions. One of the suspected interactions is between tenofovir and the protease inhibitors family. Some scholars observed that most patients who developed nephrotoxicity associated with tenofovir received protease inhibitors [122]. In the early part of this study we vividly explain protease inhibitors associated nephrotoxicity with more tribute to indinavir due to available literature. The treatment guideline for HIV management allows the co administration of tenofovir and boosted indinavir [123]. Only few cases of atazanavir induced renal toxicity have been reported as earlier explain in our work but *in vitro* studies, have shown that atazanavir is an inhibitor and inducer of P-glycoprotein and an inhibitor of cytochrome P450 3A activity. This may potentiate the pharmacological profile of some drugs [124]. This can be supported by a report which showed that coadministration of tenofovir with atazanavir could increase the pharmacokinetic parameters of tenofovir and requires patient monitoring [125, 126]. In June 2004, Gilead revised the package insert to include monitoring for adverse effects in patients receiving tenofovir in combination with atazanavir or lopinavir-ritonavir associated with increased tenofovir concentrations, as well as the potential for the development of ARF and Fanconi syndrome.

Didanosine is said to be associated with renal toxicity, an early case report by Crowther *et al*. 1993 [127] described didanosine induced Fanconi's syndrome and nephrogenic diabetes insipidus. Some scholars also have attributed antiretroviral induced renal toxicity to didanosine [128]. Didanosine has been clinically used with tenofovir and there are reported cases of renal toxicity attributed to their co administration [129-131]. Literature showed that coadministration of tenofovir and didanosine have resulted in a significant increase (28%) in maximum serum concentrations of didanosine, leading to an

increased risk of didanosine toxicity [132]. Didanosine is taken up by hOAT1 at the proximal tubules, and it is possible that competition between tenofovir and didanosine for the hOAT1 transporter produces an increase in the didanosine concentration, leading to an increased risk of mitochondrial damage and nephropathy.

In vitro experiments in renal proximal tubule cells have recently shown that didanosine may be very toxic and had negative effects on mitochondrial DNA and cytochrome oxidase II mRNA. This effect was enhanced in the presence of tenofovir, suggesting that didanosine cellular clearance was inhibited [133,134]. Moreover, administration of didanosine to patients also receiving tenofovir may increase the risk of tenofovir-associated proximal tubulopathy and nephrogenic diabetes.

7. Impact of Genetic Polymorphism on Tenofovir Renal Toxicity

TFV-associated kidney tubular damage (KTD) is multifactorial with risk factors including polymorphisms along with nongenetic factors, such as age, and body weight [135,136]. One of these risk factors that have captured attention is the genetic factor which must have introduced dichotomy in the distribution of HIV associated renal damage between the black and the white population.Reports have shown incidence of higher HIV associated renal damage especially HIVN among African-Americans while higher incidence of immune complex-mediated glomerulonephritis occurred among the whites. This is supported with Data from the US Renal Database System (USRDS) which revealed that renal disease attributed to HIVAN recorded in the US nearly 90% are reported in African-Americans [137]. This is consistent with another report from the Veterans Affairs Medical System which showed a higher incidence of end-stage renal disease among HIV-infected African-Americans which may suggests genetic predisposition in HIV associated renal disease [138]. A similar incidence of higher end- stage renal disease in blacks was also reported in a single-center study from Johns Hopkins, with an 18-fold higher risk for progression to ESRD among HIV infected African-Americans compared with HIV-infected Caucasians [139]. The genetic basis of this disparity was further elucidated by Rodrigues-Nova and co who explored the association between kidney tubular dysfunction and polymorphisms in genes encoding drug transporters. They reported that approximately 17% of HIV-infected patients treated with tenofovir had kidney tubular dysfunction homozygosity for the C allele at position −24 of the *ABCC*2 gene which is strongly associated with KTD in this population. This polymorphism may help to identify patients at greater risk for developing tenofovir-associated tubulopathy, and close monitoring of renal function is warranted for these patients [140]. Similar observation was reported by Izzedine *et al.* who assess the influence of single-nucleotide polymorphisms (SNPs) identified in *ABCC*2 and *ABCC*4. They were able to observethat ABCC2 haplotypes are associated with rPT induced by TDF in HIV-1-infected patients. No association was observed between *ABCC*4 polymorphism and TDF-induced rPT in the present study [141].

Pushpakom *et al.* also explored the association of *ABCC*10 transports and*ABCC*10 single-nucleotide polymorphisms (SNPs) with tenofovir induce KTD. They reported that tenofovir is a substrate for *ABCC*10, and genetic variability within the *ABCC*10 gene may influence tenofovir renal tubular transport and contribute to the development of KTD [142]. The association between tenofovir-induced KTD and 14 single nucleotide polymorphisms (SNPs) in the *ABCC*2, *ABCC*4, *ABCC*10, *SCL*22*A*6, and *ABCB*1 genes was investigated in 190 Japanese patients, by Nishijima *et al*., [143] in this study they acknowledge the association between SNPs in *ABCC*2 and tenofovir-induced KTD in an Asian population. These reports leave more rooms for questions, do the African-American population habour genetic polymorphism that is vulnerable or predispose to tenofovir associated renal damage? This calls for more evaluations.

8. Possible Pharmacology of Tenofovir Renal Toxicity

The mechanisms of drug induced renal toxicity can vary largely based on the pharmacologic action, metabolism, and ultimate pathway of excretion of the administered drug. Although several recent studies have revealed the nephrotoxicity of tenofovir, but the mechanism of tenofovir nephrotoxicity is not clear. Studies have suggested that mitochondrial damage may play an important role in TDF induced renal damage [144].

Researchers have shown that tenofovir is eliminated in the kidney by glomerular filtration and tubular secretion. Circulating tenofovir is absorbed from the bloodstream into the proximal tubule cells by the renal organic anion transporters (hOATs) 1 and 3. Efflux from these cells into the tubular lumen is mediated by the multidrug resistance protein (MDR)-4 [145]. The hOATs may generate high intratubular tenofovir concentrations that may interfere with the replication of mitochondrial DNA [146]. Interference with the function of mitochondria can be supported by some animal studies in which administration of TDF 100 mg/kg/day revealed enlargement of mitochondria and disruption of mitochondria crystal in rats [147]. A study in which HIV + transgenic mice and their wild-type littermates were exposed to tenofovir, renal proximal tubules showed ultrastructural mitochondrial abnormalities and decreased mtDNA levels, which

paralleled the ultrastructural mitochondrial abnormalities [148]. Similar observation was reported when Rats were exposed to tenofovir, proximal tubular dilatation, abnormalities in mitochondrial ultrastructure, depleted mtDNA, and depressed respiratory chain enzyme expression (cytochrome *c* oxidase and nicotinamide adenyldinucleotide dehydrogenase) were noted [149].

It is well known that mitochondria are the primary intracellular sources of reactive oxygen species (ROS), as they generate huge numbers of oxidative-reduction reactions and use massive amounts of oxygen [150-152]. Mitochondria damage by tenofovir can stimulate ROS production like superoxide anion, hydrogen peroxide, and hydroxyl radical which can results in oxidative stress in the kidney. Oxidative stress can lead to the destruction of biomolecules such as DNA, proteins, and lipids, thus leading to the accumulation of oxidative damaged products within the cell, causing the deregulation of redox-sensitive metabolic, signaling pathways, and cell death. The activity of tenofovir in the kidney can also deplete the following antioxidants glutathione and antioxidant enzymes such as superoxide dismutases, catalase, glutathione peroxidase, glutathione reductase and glutathione S transferase as observed in some drugs [153-155]. The decrease in the antioxidant system in cells can increase susceptibility of cells to the toxicological effect of ROS resulting in oxidative stress. Thus, oxidative stress can result from overproduction of ROS and/decrease in the antioxidant system in cells.

The above explained mechanism is in agreement with an animal study in which rats were administered by gavage 600 mg/kg body weight tenofovir disoproxil fumarate for 35 days. Tenofovir administration to rats resulted in glomerular and tubular damage. Evaluation with Electron microscope revealed mitochondrial swelling, disruption of cristae and accumulation of amorphous deposits in the matrix. Significant increase in protein carbonyl content, decrease in reduced glutathione and protein thiol, decrease in the activities of the antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, glutathione S transferase and glutathione reductase and a massive increase in myeloperoxidase activity was observed in the kidneys of tenofovir treated rats [155].

9. Conclusion

Despite tenofovir reported renal toxicity; it has achieved a very high and notable clinical success in the management of HIV/AIDS. But renal function status of HIV positive patients should be ascertained and other risk factors ruled out before tenofovir administration. Biomarkers of renal function should be routinely evaluated in patients on tenofovir containing antiretroviral regimens. Co administration with potential nephrotoxic drugs should be avoided except when benefit outweighs risk.

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