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Review Article

Renal Toxicity of Tenofovir: Narrative Review

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Abstract

Tenofovir is a reverse-transcriptase inhibitor based on acyclic nucleotide analogs. Tenofovir is a drug that is often used in treating HIV infection and has also been approved for treating infection by the hepatitis B virus. Despite the fact that its renal safety has been demonstrated in cell culture and clinical trials, clinical use and in vivo animal studies have shown its association with a low, but important, risk of kidney injury. Tenofovir accumulation in these mitochondria-rich cells is explained by proximal tubular cell secretion. Proximal tubular cell dysfunction is a symptom of Tenofovir nephrotoxicity, which might be the leading cause of acute renal injury or chronic diseases of the kidney. A review of articles is performed using keywords related to the topic in the databases of Google Scholar and PubMed, and 54 papers have been included, which were case studies, cross-sectional studies, and in vivo animal studies from 2004 up to 2021. The review aims at explaining the interaction of Tenofovir with kidney tubules, an association of genetic polymorphism, clinical features of Tenofovir-induced renal toxicity, potential mechanisms of Tenofovir-induced renal toxicity, its predisposing conditions and factors, and finally, some proposed strategies and agents to monitor and manage Tenofovir-induced nephrotoxicity.

Keywords: Acute kidney injury, Tenofovir disoproxil fumarate, Reverse-transcriptase inhibitor.

السمية الكلوية للتينوفوفير: مراجعة سردية

الخلاصة

تينوفوفير هو مثبط للنسخ العكسي يعتمد على نظائر النوكليوتيدات غير الحلقية. تينوفوفير دواء يستخدم غالبًا في علاج عدوى فيروس العوز المناعي البشري وقد تمت الموافقة عليه أيضًا لعلاج عدوى فيروس التهاب الكبد ب. على الرغم من حقيقة أن عقار تينوفوفير قد تم إثباته في زراعة الخلايا والتجارب السريرية ، فقد أظهر الاستخدام السريري والدراسات التي أجريت على الحيوانات المختبرية ارتباطه بانخفاض خطر إصابة الكلى، ولكنه مهم. يتم تفسير تراكم في هذه الخلايا الغنية بالميتوكوندريا عن طريق إفراز الخلايا الأنبوبية القريبة. ضعف الخلايا الأنبوبية القريبة هو أحد أعراض السمية الكلوية تينوفوفير ، والتي قد تكون السبب الرئيسي لإصابة الكلى الحادة أو أمراض الكلى المزمنة. تم إجراء مراجعة للمقالات باستخدام الكلمات الرئيسية ذات الصلة بالموضوع في قاعدة بيانات Google Scholar و PubMed اربعة وخمسون بحثًا تم تضمينها والتي كانت دراسات حالة ودراسات مقطعية ودراسات على الحيوانات الحية. تهدف المراجعة الى شرح تفاعل دواء التينوفوفير مع النبيبات الكلوية وترابط تعدد الاشكال الجينية والسمات السريرية للسمية الكلوية التي يسببها والعوامل والاليات المحتملة للتسمم الكلوي، واخيرا عرض بغض الستراتيجيات والعوامل المقترحة لرصد ومنع التاثيرات السمية الكلوية لدواء التينوفوفير.

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INTRODUCTION

Tenofovir disoproxil fumarate (TDF) is a prodrug of Tenofovir available in oral form and is an acyclic nucleotide analog reverse transcriptase inhibitor (NtRTI) with structural similarities to adefovir and cidofovir [1]. Tenofovir diphosphate is a poor inhibitor of mammalian DNA alpha and beta polymerases, as well as mitochondrial DNA polymerase. It is a structural analog of deoxyadenosine-5-triphosphate, the normal substrate for viral RNA-directed DNA polymerase [2]. Tenofovir was the first HIV medication to be licensed by the United States Food and Drug Administration (FDA) in 2001 [1]. In 2008, Tenofovir was approved for the chronic treatment of hepatitis B in adults [3]. On the basis of its effectiveness and tolerability in clinical trials, Tenofovir is now a commonly used part of antiretroviral regimens for both treatment-naive and suffering patients. According to US HIV care recommendations, Tenofovir was used in all preferred antiretroviral regimens for antiretroviral-naive adults and adolescents [4]. Tenofovir comes in a fixed-dose combo with emtricitabine and efavirenz [5]. Through a combing action of proximal tubular secretion and glomerular filtration, Tenofovir is removed unchanged from the urine [6]. Organic anion transporters (OAT1, and to a lesser degree, OAT3) in the membrane of basolateral cells actively transport the drug's 20–30% into kidney proximal tubule cells [9,10]. The transporters of apical membrane MRP-4 and MRP-2 (multidrug resistance proteins, encoded by ABCC4 and ABCC2 genes, respectively) secrete the drug into the tubular lumen [6]. Many drugs interfere with these transporters, resulting in increased drug entry or decreased drug outflow, favoring accumulation of intracellular and enhancing renal toxicity. Tenofovir's most frequent side effects are gastrointestinal symptoms [7]. Acute kidney injury (AKI), chronic kidney disease (CKD), and proximal tubular injury characteristics such as Fanconi syndrome, isolated hypophosphatemia, and reduced bone mineral density may all be caused by kidney toxicity [8,9]. Although TDF has been shown to be successful and reasonably healthy, several studies have suggested that it has nephrotoxic potential, as evidenced by proximal tubular cell injury, which may lead to AKI, CKD, or partial or full Fanconi syndrome [10-12]. This could exacerbate HIV-associated nephropathy (HIVAN), a disorder that is a leading cause of chronic diseases of the kidney and end-stage renal disease (ESRD) and is caused by the Human Immunodeficiency Virus inflicting direct damage to the kidneys [12]. HIVAN is more common in African Americans than in white people, but there is considerable variation among Sub-Saharan African populations [13,14]. AKI is normally treated by stopping the medication, but persistent manifestations can be handled by keeping a closer eye on the patient and treating them symptomatically. Kidney disease, regardless of the underlying cause, can be fatal if left untreated [15]. Patients with an average glomerular filtration rate (eGFR) of less than 50 ml/min/1.73 m^2 who are started on TDF-containing ART have been shown to have an increased risk of renal dysfunction [15]. ART is still given to people with kidney disease in developed countries, but most NRTIs should be given in doses that depend on how well their kidneys work, and some ARVs should be avoided [14,16].

METHODS

A scientific literature search was undertaken in the 2004 to 2021 databases of PubMed and Google Scholar for reviewed studies, and there was no timeframe for other needed documents. A mix of the following keywords is used in the search strategy: Tenofovir, Tenofovir disoproxil fumarate, nephrotoxicity, TDF, renal toxicity, NRTI, HIV, hepatitis, and renal damage. Included are cohort and cross-sectional studies, case studies, and in vivo animal studies investigating the impact of TDF on kidney toxicity in HIV and hepatitis virus-positive patients. The search included all the full-text studies and documents conducted in the English language up to 2021. Ten full-text studies and 44 documents were looked at out of the 85 articles that were found through a literature search in different databases (Figure 1).

RESULTS AND DISCUSSION

Helene Peyriere *et al*. (2004) reported seven cases of renal tubular injury in HIV-positive

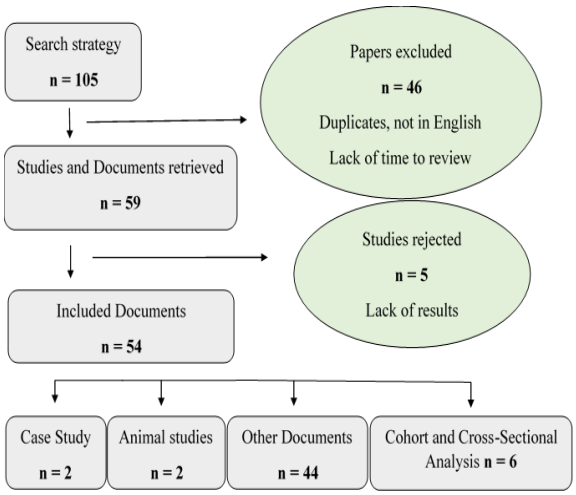

Figure 1: Methodology Flow Chart

patients receiving an antiretroviral regimen containing Tenofovir. In five women and two men, renal tubular dysfunction developed, resulting in a normoglycemic increase in urine glucose, hypophosphatemia, increased protein in the urine, and decreased creatinine clearance. The initial signs and symptoms of renal toxicity appeared between 5 and 64 weeks into Tenofovir treatment and resolved in less than 16 weeks after Tenofovir was discontinued. Six of the patients were considered to be underweight (60 kg). Five patients received ritonavir at a low dose, while one received didanosine. In five of the patients, simply discontinuing the Tenofovir caused the symptoms to resolve. A renal biopsy confirmed the tubule-interstitial injury in one patient. Proximal tubulopathy is a common side effect of long-term Tenofovir therapy. Regular observation of tubulopathy signs in patients with low BMI or moderate preexisting renal disability may guide to early detection of this dysfunction [17] (Table 1). Rodrıguez-Novoa *et al*. (2009) found that around 17% of patients infected with HIV and treated with Tenofovir developed kidney tubular dysfunction (KTD) through increasing proteinuria, glycosuria, and phosphorus wasting. In this population, homozygosity for the C allele at position 24 of the ABCC2 gene was closely linked to KTD. This polymorphism can help distinguish patients who are more likely to develop Tenofovir-associated tubulopathy, and these patients should have their renal function closely monitored [18]. In Herlitz *et al*. (2010), the pathological and clinical results in 13 cases of Tenofovir nephrotoxicity (6 women and 7 men, mean age 51±19.6 years) were investigated. Tenofovir was given to patients for an average of 19.6 months (range: 3 weeks to 8 years; median: 8 months). Nine patients had acute kidney failure, while four others had moderate renal insufficiency and sub-nephrotic proteinuria. At the start of the study, the mean serum creatinine level was 1.3±0.3 mg/dl, rising to 5.7±4.0 mg/dl at the time of biopsy, with a mean proteinuria of 1.6±0.3 g/day. Glycosuria was discovered in seven patients, five of whom did not have diabetes or hyperglycemia. A renal biopsy revealed toxic acute necrosis of tubules with proximal tubular eosinophilic inclusions revealed by light microscopy to be giant mitochondria. Electron microscopy revealed mitochondrial enlargement, degradation, and dysmorphic changes. Clinical follow-up was available for 11 of the 13 patients after Tenofovir discontinuation (mean duration, 13.6 months). All patients, including four who required transient hemodialysis, improved significantly in renal function. TDF nephrotoxicity, according to this study, is primarily a reversible type of toxic acute tubular necrosis affecting the proximal tubules and exhibiting distinct ultrastructural and light microscopic features of mitochondrial injury [19]. Brennan *et al*. (2011) estimated the relationship between renal failure, nephrotoxicity secondary to a toxin (including drugs), and mortality for patients starting Tenofovir-containing regimens using marginal structural models and the inverse likelihood of treatment weights to correct for missed follow-up and confounding. The researchers discovered that renal dysfunction in Tenofovir patients is most likely the result of pre-existing renal pathology, which Tenofovir can exacerbate. With the increased use of Tenofovir, it is crucial to test for renal dysfunction prior to initiation and modify doses to further optimize ART outcomes [15]. Scherzer *et al*. (2012) in

Table1: Summary of Tenofovir's nephrotoxicity studies

Author & year	Type of study	Sample size	Mechanism
Peyriere *et al*., 2004 [17]	Case study	7	Significant tubulopathy Significant ↓ CrCl, ↑ proteinuria
Rodriguez-Novoa *et al*, 2009 [18]	Cross-sectional study	115	17% of HIV patients Developed KTD ↑ proteinuria, glycosuria & phosphorus wasting
Herlitz *et al.*, 2010 [19]	Case study	13	Mitochondrial enlargement, depletion, and dysmorphic changes
Brennan *et al*., 2011 [15]	Retrospective cohort analysis	890	Pre-existing renal disease ↑ TDF induced nephrotoxicity, ↓ CrCl
Scherzer *et al*., 2012 [20]	Cohort analysis	10,841	34% ↑ of proteinuria,33% ↑ of CKD.
Abraham *et al*., 2013 [21]	*In vivo* mice model	12 mice	GSH ↓ 50%, SOD ↓ 57%, GSHR ↓ 150%
Ramamoorthy *et al*., 2014 [22]	*In vivo* mice model	12 mice	ETC I, II, IV, and V ↓ by 46%, 20%, 26% & 21%
Orluwene *et al*., 2015 [24]	Cross-sectional analysis	254	Significant ↑ proteinuria, glycosuria
Wantakisha *et al*., 2017 [23]	Cross-sectional study	445	↑ renal dysfunction in low CD count patients, ↓ CrCl
Nartey *et al*., 2019 [25]	Cohort analysis	300	Significant ↓ CrCl

a study conducted by the Veterans Health Administration, researchers looked at the effects of combined and single Tenofovir exposure on kidney outcomes in 10,841 HIV-infected patients who started antiretroviral therapy. The researchers used Cox proportional hazards and models of marginal structure to look at the links between Tenofovir and 1) proteinuria (two consecutive urine dipstick measurements of 30 mg/dl), 2) rapid decline in kidney function (an annual decline of 3ml/min/1.73 m^2), and 3) CKD (estimated glomerular filtration rate of less than 60 ml/min/1.73 m^2). 3400 proteinuria, 3078 rapid deteriorations, and 533 CKD events occurred over the median follow-up period of 3.9 years (proteinuria) to 5.5 years (CKD). After multivariable adjustment, every year of Tenofovir exposure was linked to an increased risk of proteinuria by 34%, an increased risk of rapid decline by 11%, and an increased risk of CKD by 33% [20]. Abraham *et al*. (2013) investigated the proximal tubular damage as revealed by light microscopy, proximal tubular dysfunction justified by Fanconi syndrome and tubular proteinuria, and severe injury of proximal tubular mitochondria, all of which were observed in adult Wistar rats after chronic Tenofovir administration as shown by electron microscopy. In the renal system of TDF-treated rats, there was a 50% rise in protein carbonyl content as compared to controls. The amount of the body's glutathione was reduced by 50%. In comparison to controls, the activity of superoxide dismutase was reduced by 57%, glutathione peroxidase activity was reduced by 45%, and glutathione reductase activity was reduced by 150%. Carbonic anhydrase activity in TDF-treated rat kidneys was reduced by 45% when compared to controls. Dehydrogenase activity, a marker of mitochondrial activity, was reduced by 29% in TDF-treated rat kidneys compared to controls, implying mitochondrial dysfunction [21]. Ramamoorthy *et al*. (2014) investigated the chronic TDF treatment effects on the function of the proximal tubules, renal mitochondrial function, and electron transport chain (ETC) complex in rats. There was mitochondrial damage in the proximal tubules as well as proximal tubular dysfunction. The respiratory control ratio, 2-(4,5-dimethyl-2-thiazolyl)-3,5-diphenyl-2H-tetrazolium

bromide (MTT) reduction, and mitochondrial swelling were all observed as signs of impaired mitochondrial function. In TDF-treated rat kidneys, the activities of the complexes of electron chains I, II, IV, and V were reduced by 46%, 20%, 26%, and 21%, respectively. TDF-induced mitochondrial proximal tubular dysfunction and ETC defects are thought to disrupt ATP production, leading to proximal tubular dysfunction and damage [22]. Wantakisha *et al*. (2017) performed a cross-sectional analysis of 445 HIV patients' records on a TDF regimen. From 2008 to 2014, patient records in data management software (SMART CARE) were analyzed to assess the proportions of TDF patients who developed renal dysfunction. To assess renal dysfunction, the Cockcroft-Gault formula was used to calculate the glomerular filtration rate (GFR) based on creatinine clearance. Renal dysfunction was demonstrated by a CrCl level of less than 50 mL/min. The researchers used multiple logistic regression to find factors linked to renal dysfunction, and the point prevalence of renal dysfunction among HIV-positive adults exposed to TDF was 18.6% at 18 months. Patients with a CD4+ cell count greater than 350 cells/µl had an 81% lower risk of developing renal dysfunction, with the reduction ranging from 79% to 97% when other covariates were considered [23]. Orluwene and colleagues (2015), to better understand the impact of Tenofovir on the renal tubules, conducted a cross-sectional analysis with 254 HIV-positive patients divided into three groups: TDF (100 patients), non-TDF (102 patients), and naïve (52 patients). Tubular toxicity markers as well as typical indicators of renal damage, were evaluated. Between the various protocol types, there was a substantial difference in the estimation of glomerular filtration rate (eGFR), proteinuria, glycosuria, and uricosuria. The fractional excretion of uric acid, phosphate, and glucose was also higher in the TDF regimen group relative to the treatment naïve and non-TDF groups. As a result, it was concluded that HIV-infected patients exposed to the TDF protocol have proximal tubular toxicity [24]. Nartey *et al*. (2019) investigated TDF's long-term effects on renal function in a cohort of HIV patients. Three hundred HIV-positive patients who started TDF-based antiretroviral treatment in 2008 were randomly selected. As per institutional guidelines for renal function testing, creatinine clearance (CrCl) was measured using the Cockcroft-Gault equation at baseline, and renal impairment was described as CrCl values of 30.0–49.9 mL/min (moderate renal impairment) and 30 mL/min (severe renal impairment). The median time between follow-ups was 2.9 years (IQR 2.3–3.4 years). Of 63 participants, 21.0% had a CrCl rate below 50 ml/min at the study's endpoint, suggesting incident renal impairment, with 18.3% having mild renal impairment and 2.3% having extreme renal impairment. Increased age, a lower baseline creatinine clearance rate, WHO HIV stage III/IV, and participants with a BMI of less than 18.5 kg/m2 were all linked to the development of renal impairment. At the start of ART, people who have known risk factors for kidney disease should be targeted and closely monitored to avoid kidney damage [25].

Drug interactions in the proximal tubule

Because the proximal tubule contributes significantly to drug excretion from the body, there is a risk of TDF and other agents interacting in this nephron segment, potentially leading to toxicity. TDF reaches proximal tubule cells via organic anion transporters on the basolateral transporter [26] and exits via MRP4 on the apical side (multidrug resistance-associated protein 4) [27]. Didanosine, a NRTI, is also a substrate for organic anion transporters, and didanosine and TDF have been shown to potentiate kidney toxicity. As a result, it is not recommended that both medications be given to the same patient at the same time. Ritonavir is an MRP2 substrate [28], and it has been suggested that it may enhance TDF toxicity by preventing TDF from exiting proximal tubule cells and increasing intracellular concentration. Since TDF does not appear to exit via MRP2, the mechanism of this inhibition is unknown [27].

Genetic polymorphism

Although TDF adverse effects on the kidneys are more common in some patients, many others appear to tolerate the drug well. This issue may be related to a genetic variant in renal transporters that causes TDF buildup in proximal tubular cells. ABCC2 (MRP2) haplotypes are related with TDF-induced renal proximal tubulopathy in HIV-infected patients, according to case-control and clinical trial findings on mutation screening in the MRP2 and MRP4 transporter genes. CATC and CGAC were also identified as predisposing and defensive haplotypes, respectively [18,29]. Rodriguez-Novoa *et al*. similarly suggested this genetic relationship in a cross-sectional study, however the research varied on the exact polymorphisms implicated. The reasons for this are unknown, however they may be related to small sample numbers, variations in research methods, and inconsistent notions of tubular dysfunction [18].

Clinical features of tenofovir nephrotoxicity

Tenofovir nephrotoxicity manifests as either (a) proximal tubular dysfunction with preserved renal function or (b) proximal tubular dysfunction with decreased renal function. Acute kidney injury (AKI), chronic kidney disease (CKD), or a glomerular filtration rate (GFR) that is lower than baseline values but within normal limits all represent reduced renal activity. According to current knowledge, they appear to share a common basic pathogenesis and pathology, which will be discussed in conjunction. The majority of Tenofovir-associated nephropathy cases described had partial or complete Fanconi syndrome, which was or was not associated with a decrease in GFR [31-34]. Fanconi syndrome is a type of proximal tubulopathy that is systemic in nature. It encompasses acidosis of the tubules, glycosuria with normal blood glucose levels, hypouricemia, aminoaciduria, tubular proteinuria, hypophosphatemia, and hypouricemia. Tubular proteinuria is an increase in the amount of small proteins in the urine that pass freely through the glomerulus but are reabsorbed by the proximal tubules. Betta2-microglobulinuria is common in patients receiving Tenofovir, even those with normal glomerular filtration rate [35,36]. Additionally, urinary β2-microglobinuria levels are elevated in patients with lower body weights, implying that it is caused by Tenofovir over dosage and resolves when Tenofovir is discontinued [36]. Other symptoms of proximal tubulopathy include osteomalacia and a loss of bone mass as a result of phosphate loss and/or a deficiency of calcitriol, which is produced by mitochondria in proximal tubules [36,37].

Risk factors of TDF-associated nephrotoxicity

Increased age, low body weight, pre-existing decline in kidney function, and concurrent use of nephrotoxic drugs have all been identified as risk factors for developing TDF-associated nephrotoxicity in studies to date. Additionally, there are factors that predispose all HIV-positive patients to kidney disease, which could theoretically exacerbate the harm caused by the majority of nephrotoxic xenobiotics by altering their pharmacokinetics of excretion. It is unknown whether risk factors for tubular toxicity contribute to increased frequency of kidney parameter screening, which may result in a higher detection rate of this complication in observational studies and thus be a significant confounding factor. Nephrotoxicity associated with TDF can occur in people who have no apparent risk factors and can occur at any time after treatment begins. As a result, it is critical to conduct a thorough examination of all TDF patients [38].

Proposed mechanism of toxicity

The kidneys consume approximately 10% of the body's oxygen supply to generate the energy necessary to carry out their primary function of regulating body fluid composition through the filtering, secretion, and reabsorption of nutrients and metabolites. The kidneys, which have the second highest mitochondrial content and thus the highest oxygen consumption in the body, are

particularly mitochondrial-enriched to ensure an adequate supply of ATP. The majority of the ATP produced in the kidneys is used to transport solutes toward (reabsorption) or away from (secretion) the peritubular capillaries via the coordinated action of an array of ATP-binding cassette (ABC) pumps and transporters. ABC pumps require direct ATP hydrolysis to function. Ion electrochemical gradients and membrane potential are generated as a result of asymmetric ion transport across the plasma membrane, which is mediated by ATPase pumps and transporters. Several of these transporters, including the polyspecific organic anion transporters (OATs) that transport TDF, the organic anion transporting polypeptides (OATPs), and the organic cation transporters (OCTs), are highly expressed on the membranes of proximal tubular cells and transport drugs rapidly, resulting in mitochondrial damage and redox reactions [39]. Mitochondrial dysfunction, morphological changes in proximal tubules and tubular mitochondria, and low mitochondrial DNA (mitDNA) copy numbers were all observed after TDF therapy. ADP production is impaired when TDF impairs the function of mitDNA-encoded respiratory chain subunits (including cytochrome c oxidase and NADH dehydrogenase) as well as the activity of electron transport chain (ETC) complexes, resulting in ATP production impairment [40]. On electron microscopy, mitochondrial defects in proximal tubule cells and a decrease in renal mitDNA were observed in TDF-exposed patients who underwent kidney biopsy, similar to the changes seen in mitDNA depletion syndromes. [38,41,42] These results point to mitochondria as a possible target for TDF-induced renal toxicity. [38,19] Various nephrotoxic agents, like NRTIs and disorders like Fanconi syndrome, have an inhibitory effect on DNA polymerase-gamma (and its function in mitDNA replication) in the proximal tubule [21,43]. According to some studies, TDF has a lower affinity for inhibiting DNA polymerase-gamma than some other NRTIs, so it's unlikely that it will influence mitDNA levels through this pathway [44,45]. According to some other studies, TDF partially inhibits DNA polymerase-gamma and could cause mitDNA damage through this pathway [46,47]. Future trials should look at whether TDF has direct toxic effects on the ETC complexes or whether it has an indirect impact by increasing mitochondrial production of reactive oxygen and nitrogen species, which could harm mitochondrial lipids, proteins, and DNA [22]. Following antioxidant depletion, insulted mitochondria are a major source of reactive oxygen species and a site for cellular harm. Antioxidant depletion as a key mechanism for TDF-induced mitochondrial toxicity and its renal toxicity was supported by an increase in oxidative stress signs and a decrease in antioxidant capacities. Reduced succinate dehydrogenase activity, a mitochondrial activity measure, indicates mitochondrial dysfunction during the toxicity process. TDF causes mitochondrial dysfunction and elevated oxidative stress by depleting antioxidant ability, especially glutathione and manganese superoxide dismutase (MnSOD) [21]. Another hypothesis is that phosphorylation of concentrated TDF in the proximal tubules causes a nucleotide pool imbalance, reducing nucleotide availability for mitochondrial DNA synthesis. Understanding the cellular mechanism of TDF-induced nephrotoxicity could aid in the development of preventative measures to counteract this TDF-induced toxicity [21].

TDF-induced nephrotoxicity prevention and treatment

The key to preventing TDF-induced nephrotoxicity is to determine and track renal function at baseline and during TDF care. Biannual measurements of SCr, phosphate, and urine analysis are recommended in candidates for TDF therapy with an eGFR of less than 90 ml/min who are taking concomitant nephrotoxic agents, medications that undergo renal excretion, or diabetes and hypertension [48,49]. When measured eGFR is greater than 50 ml/min, TDF pharmacokinetics remain unchanged and identical to patients with normal renal functioning. With an eGFR of less than 50

ml/min, renal insufficiency induces a substantial decrease in TDF renal clearance, resulting in increased drug exposure. Since TDF has no hepatic removal, a deficiency in liver function has no effect on drug disposition, so there is no need to modify the dosage in this situation [50]. Recent recommendations recommend an annual risk evaluation and renal function monitoring every 3–12 months. Patients with CKD risk factors and nephrotoxic medications should be tracked more regularly. Hypertension, diabetes, CVDs, family history of renal failure, black African ethnicity, concurrent viral hepatitis, low current CD4 count, smoking, older age, and concurrent nephrotoxic status are identified as CKD risk factors in HIV patients. Proteinuria should be tested annually with a urine dipstick and every six months in patients with an eGFR of less than 60 ml/min. Early detection of nephrotoxicity and TDF withdrawal are crucial for preventing irreversible tubulo-interstitial damage. Some proximal renal cell dysfunction warning signs should be considered. Progressive eGFR decline, hypophosphatemia, increased urinary protein/Cr, renal insufficiency (eGFR 60 ml/min), and tubular proteinuria (retinol binding protein, 1- or 2-microglobulinuria, cystatin C, or aminoaciduria) are all indicators. The ratio of phosphate, glucose, and uric acid excretion in the urine to their serum concentrations, as well as urinary pH, are the key indicators of proximal renal tubular injury. Patients with preexisting renal insufficiency (ClCr50 ml/min) or those who experience renal insufficiency while on TDF therapy should have their TDF dose reduced, according to current guidelines. End-stage renal disease (ESRD) patients on hemodialysis showed no extrarenal route of TDF removal [51], and once-weekly TDF dosing is recommended [50]. Modifying the TDF dose interval based on the severity of renal insufficiency (moderate or severe impairment) avoids excessive drug accumulation and achieves steady-state Tenofovir exposures comparable to those observed in subjects with normal renal function receiving a standard daily dose of TDF. TDF should be discontinued if proximal renal tubulopathy develops, as evidenced by progressive decline in eGFR, hypophosphatemia of renal origin, or osteopenia/osteoporosis associated with increased urinary phosphate leak. Due to TDF's nearly 8% plasma protein binding, hemodialysis may be a viable option. TDF is extracted at a rate of 134 ml/min in high-flux environments with a 54% extraction coefficient [52]. Patients with nephrotoxicity caused by TDF may benefit from rosiglitazone. Melatonin pretreatment prevented all known histological changes in proximal tubular mitochondria induced by TDF. MitoQ or Mito-CP, both of which are antioxidants with mitochondria-targeting properties, may protect proximal tubular mitochondria from TDF toxicity. Additionally, vitamin E, ebselen, lipoic acid, plastoquinone, nitroxides, SOD enzyme mimics, Szeto-Schiller (SS) peptides, and quercetin may be used to prevent TDF-induced nephrotoxicity [51].

Conclusion

Proximal tubular cell damage is a symptom of Tenofovir nephrotoxicity, which can manifest as Fanconi syndrome, AKI, or CKD. This typically results in an alteration of the clinical manifestations of kidney injury. Due to their unique collection of drug-transporting cell membrane proteins, proximal tubular cells are particularly susceptible to Tenofovir's toxic effects, presumably by impairing the function of mitochondrial DNA-encoded respiratory chain subunits (including cytochrome c oxidase and NADH dehydrogenase) and decreasing nucleotide availability for mitochondrial DNA synthesis, resulting in impaired ATP production and mitochondrial injury, as well as increased oxidative stress.

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Conflicting interests

The authors declared no conflicts of interest.

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Data sharing statement

N/A

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