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Potential Kidney Toxicity from the Antiviral Drug Tenofovir: New Indications, New Formulations, and a New Prodrug

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Abstract

Purpose of Review—The antiviral agent tenofovir is highly effective for the treatment of HIV and Hepatitis B virus (HBV) infections, and the older prodrug tenofovir disoproxil fumarate (TDF) is also a component of daily pre-exposure prophylaxis (PrEP) to reduce the risk of HIV infection in high-risk populations. Although TDF is well tolerated, the potential for kidney and bone toxicity has important implications for public health given the large number of individuals exposed to TDF worldwide. This review summarizes the recent literature on kidney and bone health in individuals treated with TDF and the newer prodrug tenofovir alafenamide (TAF).

Recent Findings—Risk factors for TDF toxicity appear to be similar in patients treated for HIV or HBV and in HIV-uninfected PrEP users, although drug-drug interactions are a more important concern in HIV-positive individuals. The risk of toxicity appears to be lower with TAF, but further studies are needed to confirm the safety of long-term use and to evaluate the efficacy of TAF-based PrEP.

Summary—Nephrologists should be aware of the potential kidney and bone toxicity of TDF, as well as unique situations in which the newer prodrug TAF may contribute to kidney injury.

Keywords

tenofovir disoproxil fumarate; tenofovir alafenamide; proximal tubulopathy; hepatitis B virus; pre-exposure prophylaxis

Introduction

The widely used antiviral agent tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir, a member of the nucleos(t)ide reverse-transcriptase inhibitor (NRTI) class of antiretrovirals and a potent inhibitor of the Hepatitis B virus (HBV) DNA polymerase. TDF is approved for the treatment of HIV and HBV infections and to reduce the risk of HIV infection in high-risk populations. While TDF is well tolerated, it has been linked with adverse effects on kidney and bone. This review focuses on the potential kidney and bone toxicity of TDF in individuals with HIV or HBV infection and in healthy adults taking TDF for HIV prevention, and will review the available data on safety of the newer prodrug, tenofovir alafenamide (TAF).

Potential toxicity of TDF in HIV-positive individuals

Tenofovir belongs to a family of acyclic nucleotide analogues that also includes cidofovir and adefovir, both of which exhibit dose-limiting proximal tubulopathy. Tenofovir must be provided as a prodrug because of limited oral bioavailability, and is itself di-phosphorylated to its active antiviral form inside cells of the immune system and liver.

When combined with 2 additional antiretrovirals, TDF is considered first-line therapy for HIV infection.^{1,2} Pre-marketing clinical trials did not demonstrate significant nephrotoxicity when used in carefully selected clinical trial participants; however, several manifestations of nephrotoxicity have been linked to TDF use in clinical practice.

Proximal tubulopathy

The proximal tubules are especially vulnerable to TDF toxicity, and subclinical evidence of proximal tubular dysfunction is common in observational studies of TDF users. Current, past, and cumulative TDF use have been associated with increased levels of urinary low molecular weight proteins and other biomarkers of proximal tubular dysfunction or injury, although it is not clear whether these subclinical markers predict clinically relevant proximal tubular injury or decline in glomerular filtration rate (GFR).^{3–5} Biomarkers that have been proposed for the evaluation of TDF kidney toxicity in clinical practice or for research purposes are summarized in Table 1.

In contrast to the high frequency of subclinical proximal tubulopathy, the incidence of overt Fanconi syndrome is low, with estimates ranging from <0.1% in clinical trial follow-up to 1.5% in single-center case series.^{6,7} In addition to evidence of proximal tubulopathy, patients with Fanconi syndrome may present with a decline in GFR, bone pain, or pathologic fractures. Review of published case series found that Fanconi syndrome developed a mean of 11 months (range 1 – 29 months) after TDF initiation; however, Fanconi syndrome has also been reported after 8 years of treatment.^{8,9} Symptoms and proximal tubular abnormalities typically resolve with cessation of TDF; however, proteinuria and decreased GFR may persist.¹⁰

Although the diagnosis of TDF-induced proximal tubulopathy is typically made clinically, kidney biopsy can confirm the diagnosis by demonstrating acute tubular necrosis with dysmorphic mitochondria in proximal tubule cells^{6,11} (Figures 1 and 2). Consistent with these findings, the mechanism of tenofovir nephrotoxicity is thought to involve mitochondrial dysfunction, which is known to cause the lactic acidosis more commonly linked with other NRTIs. TDF toxicity in animal models is also characterized by depletion of mitochondrial DNA.¹² Lactic acidosis is a rare complication of TDF use, but the proximal tubule may be especially vulnerable to mitochondrial dysfunction as it has limited anaerobic ATP-generating capacity.

Tenofovir enters proximal tubule cells through basolateral organic anion transporters (OAT) and exits primarily through the apical transporter multidrug resistance-associated protein (MRP) 4.¹³ Concomitant medications that block these transporters can increase the nephrotoxicity of TDF by raising plasma concentrations of tenofovir. For example,

concurrent exposure to didanosine, a substrate for OAT, has been strongly linked to TDF nephrotoxicity. Ritonavir, a substrate for MRP2, has also been associated with increased risk of TDF nephrotoxicity. It is unclear whether the increased risk with concomitant ritonavir involves interference with tenofovir clearance or increased plasma tenofovir concentrations as a result of increased intestinal absorption.

Established risk factors for TDF-induced proximal tubulopathy include older age, lower baseline creatinine clearance (CrCl), concomitant ritonavir-boosted protease inhibitors (PI), and longer duration of TDF exposure.^{5,14} Although not well-studied, the newer pharmacoenhancer cobicistat also increases tenofovir exposure and may increase the risk of nephrotoxicity.¹⁵ Genetic polymorphisms in proximal tubule transporters may explain why some individuals are more susceptible to TDF nephrotoxicity, although further studies are required.¹⁶

Decreased GFR

In contrast to the low risk of nephrotoxicity observed in pre-marketing clinical trials, observational studies have demonstrated higher rates of GFR decline with TDF use.^{14,17,18} In a Spanish cohort, the incidence of CrCl < 60 ml/min was 29.2/1000 person-years.¹⁴ A similar incidence of CrCl < 60 ml/min was observed in a 12-year observational cohort study in Tokyo (20.6/1000 person-years), with a rapid drop in eGFR occurring within the first 3 months of TDF use (−26.4 versus 7.4 mL/min/1.73 m²/year in the control group).¹⁷ While some experts have suggested that this initial decline in eGFR might reflect interference with tubular creatinine secretion rather than a true decline in GFR, TDF use was also associated with an 11% increased risk of rapid eGFR decline, defined as an annual decline of 3 mL/min/1.73 m² for two consecutive years.¹⁷

Prolonged cumulative exposure to TDF has also been linked to eGFR decline and decreased kidney function. In observational studies, every year of TDF use was associated with a 14–33% increase in risk of decreased kidney function.^{14,18,19} Other risk factors included baseline chronic kidney disease (CKD), older age, and CD4+ cell count below 50.^{14,20} Importantly, cumulative use of ritonavir-boosted PI, both with and without concomitant TDF, has also been associated with increased risk of decreased eGFR.^{18,19}

While GFR may recover after discontinuation of TDF, some patients experience persistent declines. In one study of patients with eGFR decline, proteinuria, hypophosphatemia, and/or euglycemic glycosuria, cessation of TDF led to initial resolution of renal abnormalities in 97% of subjects; however, at 18 months at least one of these abnormalities was present in 41%.²¹ Older age and longer duration of HIV infection were associated with lower odds of full and rapid renal recovery.

Risk scores have been developed to help providers predict the risk of CKD in HIV-positive adults so that TDF can be avoided in high-risk individuals.^{22,23} Further studies are needed to validate these risk scores in more diverse patient populations.

Proteinuria

Proteinuria is the most common TDF-associated kidney abnormality, occurring in up to 37–40% of subjects in some studies.^{5,21} Most cases are mild, with 70% of affected individuals having < 1 g/g. One study found that every year of TDF use was associated with a 34% increase in the risk of proteinuria, even after adjustment for age, gender, and race.¹⁹ Resolution of proteinuria occurred in 23% of patients with cessation of TDF. While TDF-induced proteinuria is predominantly non-albumin or “tubular” proteinuria, albuminuria is also more common with TDF use.²⁴

Bone Mineral Density Decline

HIV-positive individuals have higher rates of osteopenia and osteoporosis, and antiretroviral therapy is associated with further declines in bone mineral density (BMD).²⁵ TDF-associated proximal tubulopathy can lead to phosphate wasting, hypophosphatemia, acidosis, and decreased bone mineralization. Even in the absence of proximal tubulopathy, TDF use is associated with a greater decline in BMD. In one study, the incidence of fractures in patients who ever received TDF was double that of patients who never received TDF (8.1 versus 4.7/1000 person years), and longer time on treatment was associated with higher fracture rates.²⁶ Studies continue to investigate the contribution of vitamin D insufficiency and mild elevations in parathyroid hormone (PTH) that occur with TDF use.

Available Formulations and Drug-Drug Interactions

TDF is a component of several fixed dose combination pills, and all currently approved single-tablet antiretroviral regimens contain either tenofovir or the alternative NRTI abacavir (Table 2).

Several commonly used medications increase the plasma concentration of tenofovir, including the pharmacoenhancers ritonavir and cobicistat and the antiviral agent ledipasvir, which is approved in combination with sofosbuvir to treat Hepatitis C virus infection. Concomitant use of any of these agents may increase the risk for TDF nephrotoxicity, and combination of TDF with a ritonavir-boosted PI and ledipasvir is contraindicated.

In addition, several agents frequently used in combination with TDF interfere with tubular secretion of creatinine, causing an immediate and non-progressive decline in creatinine-based eGFR and CrCl, but no associated decline in measured GFR. A clinically relevant effect on creatinine-based eGFR has been best demonstrated with cobicistat and the integrase inhibitor dolutegravir, although ritonavir and rilpivirine exhibit a similar effect *in vitro*.²⁷ Some experts have suggested that tenofovir may also interfere with creatinine secretion, based on the early decline in eGFR observed across studies. The extent to which small effects on creatinine secretion impact the epidemiologic association of TDF and boosted PIs with eGFR decline is unknown, but this is unlikely to explain the clinically relevant declines in eGFR associated with cumulative use.

Potential toxicity of TDF as PrEP

In addition to use as HIV treatment, TDF combined with emtricitabine (FTC) is the only FDA-approved regimen for use as daily pre-exposure prophylaxis (PrEP).²⁸ Alternate regimens, including TAF, have limited or unproven efficacy as PrEP.²⁹ TDF-based PrEP has been shown to reduce HIV acquisition in men who have sex with men (MSM), individuals in serodiscordant relationships, and people who inject drugs.²⁹ The efficacy of TDF-based PrEP varies from 70% to > 90% depending on the population^{30,31} and the level of adherence.^{32,33} Although data on real-world outcomes are limited, one observational study of 657 mostly MSM PrEP users achieved 100% effectiveness.³⁴ PrEP has the potential to change the course of the HIV epidemic when used in combination with other evidence-based prevention tools, but TDF exposure in healthy, HIV-negative persons requires careful consideration of toxicities. Because data on serum creatinine were collected routinely in clinical trials, available data on safety are largely based on eGFR trajectories, with more limited data on tubular function and bone health.

GFR Decline

In previously healthy individuals, TDF-based PrEP has been associated with a statistically significant but largely reversible decline in kidney function. In the iPrEx trial, healthy HIV-negative men and transgender women were assigned to receive FTC-TDF or placebo.³⁵ Within 4 weeks of study drug initiation, there was a small but statistically significant decrease in CrCl for the active arm relative to placebo (-2.4 mL/min versus -1 mL/min).⁸ This difference persisted over the 144-week study, but resolved upon study drug discontinuation. In the Partners PrEP study, HIV-negative members of heterosexual, serodiscordant African couples were randomized to receive TDF, FTC-TDF, or placebo.³⁶ At 18 months, the absolute mean eGFR change associated with FTC-TDF PrEP was $-1.59\text{ mL/min/1.73 m}^2$ (95% CI: -2.44 to -0.74). Like the iPrEx study, the small differences in mean eGFR between treatment arms were reversed following discontinuation of study drug.³⁷

An additional analysis compared participants in the Partners PrEP Study,³⁶ which monitored creatinine at 3-month intervals, and the Partners Demonstration Project, an open-label study of PrEP recipients that monitored creatinine at 6-month intervals.³⁸ CrCl $<60\text{ mL/min}$ occurred in $<1\%$ of participants over 24 months and was not significantly different between the two monitoring strategies. Older age, lower body weight, and baseline CrCl $<90\text{ mL/min}$ were independently associated with development of CrCl $<60\text{ mL/min}$. Similar risk factors were identified for GFR decline below 70 mL/min/1.73m^2 in the United States (US) Demonstration Project., an open-label study of daily FTC-TDF PrEP in men and transgender women.³⁹

A meta-analysis of randomized trials evaluating the risk of renal adverse events in 17,222 healthy individuals randomized to TDF-based PrEP versus placebo found that most creatinine elevations were Grade 1, defined as an increase in creatinine to 1.1–1.3 times the upper limit of normal ($\times\text{ ULN}$).⁴⁰ Only 16 participants randomized to PrEP experienced a Grade 2 elevation, defined as $1.4\text{--}1.8 \times\text{ ULN}$. TDF-based PrEP was associated with increased risk of Grade 1+ creatinine events (pooled odds ratio (OR)= 1.36, 95% CI: 1.09 to

1.71), but the absolute increase in graded creatinine events was small, translating to a number needed to harm of 167.⁴⁰

Proximal Tubulopathy and Proteinuria

In the Partners PrEP cohort, the FTC-TDF and placebo arms were compared using archived urine and serum samples obtained at the 24-month study visit or last on-treatment visit. Tubulopathy was defined as any 2 of the following: tubular proteinuria, euglycemic glycosuria, increased urinary phosphate excretion, or increased uric acid excretion.⁴¹ Thirteen (1.7%) FTC-TDF recipients and 10 (1.3%) placebo recipients met criteria for tubulopathy (OR=1.30; 95% CI: 0.52 to 3.33; $p = 0.68$).⁴¹ Similar results were observed in a substudy of iPrEx, with no statistically significant difference in the rates of proximal tubulopathy between the active PrEP and placebo arms.³⁵ Nonetheless, a single Partners PrEP participant assigned to FTC-TDF demonstrated overt Fanconi syndrome with multiple manifestations of proximal tubulopathy accompanied by eGFR decline. Although the urine results were not available during the trial, study drug was permanently discontinued because of graded creatinine elevations.⁴¹

In a nested case-control analysis in Partners PrEP, rates of tubulopathy did not differ between those who did and did not subsequently experience a clinically significant decline in GFR of $\geq 25\%$.⁴¹ Monitoring for tubulopathy therefore appears to be an ineffective strategy to identify those at risk for TDF-associated GFR decline.

Tubular proteinuria, defined by spot urine protein: creatinine ratio >200 mg/g with urine albumin–total protein ratio <0.4 , was significantly more frequent in Partners PrEP participants on FTC-TDF relative to placebo (7% versus 4%; $P = .01$).⁴¹ Worsening dipstick proteinuria was also observed in 16% of participants receiving daily FTC-TDF in the US Demonstration Project.³⁹ Because proteinuria has been associated with adverse outcomes, additional study is needed to understand the implications of this finding in healthy persons receiving PrEP.

Bone Mineral Density Decline

Although BMD declines with PrEP use, increased fractures have not been demonstrated. Much like GFR, the observed changes in BMD appear to reverse after FTC-TDF is discontinued.⁴² A substudy of iPrEx analyzed changes in BMD using dual-energy X-ray absorptiometry (DXA) at baseline and at 24 week intervals.⁴³ By 24 weeks, there was a statistically significant decline in BMD at both hip and spine in those randomized to FTC-TDF. Changes over subsequent study intervals did not reach statistical significance. At 24 weeks, participants who adhered to FTC-TDF (based on intracellular levels of tenofovir-diphosphate) experienced significantly greater BMD losses than the placebo arm. There were no differences in fractures or low BMD between the 2 groups over the 2 year study period.⁴³

The risk and implications of BMD decline may be greater in adolescents, who have not yet achieved peak bone mass. In two open-label Adolescent Trials Network Studies enrolling HIV-negative MSM ages 15 to 22, spine, hip, and whole body DXA scans were performed at baseline and weeks 24 and 48 in a subgroup of participants on daily FTC-TDF PrEP.⁴⁴

There were statistically significant declines in BMD at the hip and in BMD z scores at the lumbar spine, hip, and total body at both 24 and 48 weeks. There was a strong relationship between drug exposure, measured by tenofovir-diphosphate concentrations in dried blood spots, and change in hip BMD at week 48. Compared to participants with low drug exposure, those with high drug concentrations also had a greater increase in PTH and a decrease in fibroblast growth factor (FGF23). These changes led the authors to conclude that BMD changes are likely related to endocrine effects rather than kidney toxicity.⁴⁴

Potential toxicity of TDF in Hepatitis B virus infection

Tenofovir is also highly effective for the treatment of chronic HBV infection, with a high barrier to resistance. As a result, tenofovir or the alternative nucleoside analogue entecavir are recommended as first-line therapy for HBV mono-infection, while tenofovir-containing ART is recommended as first-line therapy for HIV-HBV co-infection.^{45,46} Similar to HIV, chronic HBV infection requires lifelong suppressive therapy, increasing the risk for cumulative toxicity. This risk may be lower in persons living with chronic HBV mono-infection, who typically experience fewer significant drug-drug interactions; nonetheless, observational studies and case reports have confirmed the potential for TDF-induced kidney and bone toxicity in this population.

GFR decline

The initial clinical trials of TDF for HBV infection were conducted in individuals with HIV-HBV co-infection, in whom practice guidelines continue to recommend tenofovir as a component of dual therapy for HBV.^{45,46} In the definitive phase 3 trials comparing TDF versus adefovir for HBV mono-infection, there were no renal adverse events reported among 426 participants randomized to 48 weeks of TDF; however, only increases in serum creatinine of 0.5 mg/dL were reported.⁴⁷ Trial participants who enrolled in the open-label phase experienced a small number of renal adverse events over 7 years of follow-up, including 6 cases of CrCl decline to < 50 ml/min, largely in participants with traditional CKD risk factors.⁴⁸ In a smaller randomized trial among adolescents with HBV mono-infection, 6/52 (11.5%) participants randomized to TDF experienced a confirmed serum creatinine increase 0.3 mg/dL, but no participant experienced an increase in creatinine 0.5 mg/dL.⁴⁹ Several small observational studies have demonstrated a modest but statistically significant decline in eGFR in individuals treated with TDF for HBV mono-infection.^{50,51} Practice guidelines recommend periodic monitoring of eGFR in HBV-positive individuals treated with TDF, with increased frequency of monitoring in individuals with CKD risk factors.^{45,46}

Proximal Tubulopathy and Proteinuria

Overt proximal tubulopathy is rare in individuals treated with TDF for HBV mono-infection. Case reports of TDF-induced Fanconi syndrome in HBV-positive individuals suggest that this complication is more likely to occur in persons with traditional CKD risk factors. Evidence of proximal tubulopathy resolved after the discontinuation of TDF in most but not all of the published cases.^{52,53} As in HIV-positive individuals, there appears to be a higher prevalence of subclinical proximal tubular dysfunction among HBV-positive individuals

treated with TDF. In a small cross-sectional study of HBV mono-infected individuals receiving TDF (n=69) or entecavir (n=89), TDF use was associated with higher levels of urinary retinol-binding protein, higher fractional excretion of uric acid, and higher urine protein: creatinine ratio.⁵⁴ Subjects on TDF also had higher levels of PTH and procollagen 1 N-terminal (P1NP), a marker of bone formation. In adjusted analysis, TDF use remained independently associated with higher levels of urinary retinol binding protein, suggesting an association with subclinical proximal tubular dysfunction.

Bone mineral density decline

Few studies have considered the impact of TDF use on bone health in individuals with HBV mono-infection. The phase 3 trials comparing TDF versus adefovir did not include baseline measurements of BMD⁴⁷; however, there was no significant change in BMD from Year 4 to Year 7 in the open-label follow-up study.⁴⁸ In the randomized trial of TDF in adolescents with HBV mono-infection, no participants met the pre-specified safety endpoint of 6% decline in lumbar spine BMD through week 72.⁴⁹ An observational study of participants who switched from lamivudine and adefovir to TDF demonstrated a high prevalence of osteopenia at baseline, but only transient worsening of BMD following the switch to TDF. These investigators observed no significant change in PTH during the study period, and suggested that this may have contributed to the lack of impact on bone.⁵⁰

Potential for improved safety profile with tenofovir alafenamide

The alternative tenofovir prodrug TAF was approved in 2015 for the treatment of HIV and is currently included as a component of several first-line antiretroviral regimens.¹ In 2016, TAF was approved for the treatment of HBV as monotherapy or in combination with FTC (Table 2). Ongoing studies are evaluating the efficacy of FTC-TAF as PrEP.

High plasma levels of tenofovir are thought to promote kidney and bone toxicity.⁵⁵ TAF is more stable in plasma, and is largely converted to tenofovir intracellularly. Therefore, TAF achieves higher intracellular tenofovir-diphosphate levels in target cells of the immune system and liver and lower plasma tenofovir exposure at approximately 1/10 lower dose compared to TDF.⁵⁶

Phase 3 clinical trials in HIV-positive, antiretroviral-naïve adults demonstrated that TAF was non-inferior to TDF in terms of efficacy, with a more favorable toxicity profile including fewer creatinine increases, lower proteinuria, and smaller declines in BMD at 48 weeks.⁵⁷ The 96-week results continue to demonstrate significantly smaller declines in BMD and CrCl, and fewer participants with proteinuria in the TAF arm.⁵⁸ In an open label phase 3 trial, participants who were switched from TDF-containing regimens to a TAF-containing regimen had stable eGFR and improvements in proteinuria, albuminuria, and BMD at 48 weeks.⁵⁹ Review of the literature identified a single published case report of possible TAF-associated nephrotoxicity in an HIV-positive patient with multiple risk factors;⁶⁰ a second possible case was recently reported at the American Society of Nephrology Kidney Week (abstract SA-PO983).

Phase 3 clinical trials in individuals with HBV infection have also demonstrated non-inferior efficacy of TAF compared to TDF, with similar improvements in measures of subclinical kidney and bone toxicity.^{61,62}

All formulations of TAF are approved for individuals with HIV and CrCl > 30 ml/min, including the first two single-tablet HIV regimens for individuals with CrCl between 30–50 ml/min (Table 2). TAF is also approved to treat HBV in individuals with CrCl as low as 15 ml/min. It is important to note that tenofovir plasma concentrations increase significantly as CrCl decreases⁶³, potentially increasing the risk for toxicity in individuals near the dosing threshold. This risk may be higher in the setting of drug-drug interactions and in individuals with low body weight.

Conclusion

With growing numbers of individuals worldwide exposed to the antiviral agent tenofovir, nephrologists should be aware of the potential for kidney and bone toxicity in individuals with HIV or HBV infection and in healthy persons taking TDF to reduce the risk of HIV infection. While the risk of toxicity appears to be lower with the newer prodrug TAF, further studies are needed to confirm the safety of long-term TAF use in individuals with CKD and in those taking concomitant medications that influence tenofovir exposure.

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Figure 1. Light microscopic findings in tenofovir toxicity

(a) Proximal tubules exhibit diffuse and severe acute degenerative changes including luminal ectasia, cytoplasmic simplification, irregular luminal contours, loss of brush border, and focal apoptosis with epithelial desquamation, with adjacent interstitial edema. These findings are typical of toxic acute tubular necrosis (hematoxylin and eosin, $\times 400$). (b) A low-power view demonstrates tubular simplification, as well as more chronic tubular atrophy and interstitial fibrosis. These light microscopic findings are consistent with an acute and chronic tubulointerstitial nephropathy (periodic acid-Schiff, $\times 200$). (c) A characteristic feature of TDF nephrotoxicity is eosinophilic intracytoplasmic inclusions within proximal tubular epithelial cells, corresponding to the giant mitochondria seen ultrastructurally (hematoxylin and eosin, $\times 600$). (d) The proximal tubular inclusions stain red (or fuchsinophilic) with trichrome stain ($\times 1000$). Reproduced with permission from Herlitz L et al. *Kidney Int* 2010; 78: 1171–1177.

Figure 2. Ultrastructural findings in tenofovir toxicity

(a) A low-magnification field demonstrates the wide range in size and shape of mitochondria within proximal tubular epithelial cells ($\times 5000$). (b) Markedly enlarged mitochondria are interspersed with normal-sized mitochondria in proximal tubular cells. One cell is undergoing degeneration with shedding of cytoplasmic fragments into the tubular lumen ($\times 5000$). (c) At higher magnification, the enlarged mitochondria are largely devoid of cristae. In contrast, cristae are easily identified in adjacent, normal-sized mitochondria ($\times 8000$). (d) Abnormalities in the number and distribution of mitochondrial cristae are best appreciated at high magnification. In this field, there is focal loss of cristae, as well as clustering of residual cristae at the peripheral mitochondrial membrane ($\times 20,000$). Reproduced with permission from Herlitz L et al. *Kidney Int* 2010; 78: 1171–1177.

Table 1

Evaluation of tenofovir kidney toxicity in clinical practice and clinical research

Estimated glomerular filtration rate	<ul style="list-style-type: none"> Recommended at least q6months in stable patients (IDSA guidelines) *
Creatine-based estimates	<ul style="list-style-type: none"> CKD-EPI eGFR is the preferred estimate in clinical practice Affected by extremes of muscle mass and by medications that interfere with creatinine secretion
Cystatin C-based estimates	<ul style="list-style-type: none"> Useful alternative to creatinine-based eGFR in the setting of medications that interfere with creatinine secretion Affected by systemic inflammation
Proteinuria	<ul style="list-style-type: none"> Recommended at least annually in stable patients (IDSA guidelines) *
Urinalysis	<ul style="list-style-type: none"> Reasonable screening assay, but poor sensitivity for LMW proteinuria if toxicity is suspected May also detect glycosuria & RTA
Urine protein: creatinine ratio	<ul style="list-style-type: none"> Most sensitive for LMW proteinuria, but may not be cost-effective for screening in low-risk individuals
Urine albumin: creatinine ratio	<ul style="list-style-type: none"> Least sensitive for tenofovir toxicity, but may be elevated because of failure to reabsorb filtered albumin
Ratio of urine albumin: protein	<ul style="list-style-type: none"> Ratio <0.4 has been used as a marker of “tubular” proteinuria in research studies
Markers of proximal tubular function	<ul style="list-style-type: none"> No guidelines for use in clinical practice
Hypophosphatemia	<ul style="list-style-type: none"> May reflect proximal tubulopathy Highly influenced by dietary intake
Euglycemic glycosuria	<ul style="list-style-type: none"> Dipstick glucose in the absence of diabetes or hyperglycemia is a rare but specific marker of proximal tubulopathy
Phosphaturia	<ul style="list-style-type: none"> Fractional excretion of phosphate can be used to confirm suspected proximal tubulopathy
Aminoaciduria	<ul style="list-style-type: none"> Abnormal urinary excretion of amino acids can be used to confirm suspected proximal tubulopathy
Increased uric acid excretion	<ul style="list-style-type: none"> Increased fractional excretion of uric acid can be used to confirm suspected proximal tubulopathy
Urinary biomarkers	<ul style="list-style-type: none"> Elevated levels of multiple urinary biomarkers including RBP, IL-18, KIM1, α1 microglobulin, β2 microglobulin have been associated with TDF use in research studies
Kidney biopsy	<ul style="list-style-type: none"> Kidney biopsy is particularly useful in patients with an unclear diagnosis or a compelling reason to continue tenofovir

eGFR, estimated glomerular filtration rate; IDSA, Infectious Disease Society of America; LMW, low molecular weight proteins that may indicate proximal tubular dysfunction; RTA, renal tubular acidosis; RBP, retinol binding protein; IL-18, interleukin-18; KIM1, kidney injury molecule 1

* Lucas GM, Ross MJ, Stock PG et al. Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected with HIV: 2014 Update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2014; 59: e96–e138.

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Table 2

Tenofovir: Available Formulations, Indications, and Renal Dosing

Brand Name	Components	Approved Indications	Renal Dosing
Viread®	TDF 300mg	HIV (in combination therapy) Hepatitis B	CrCl ≥ 50 (daily) CrCl 30–49 (q48hrs) CrCl 10–29 (q72–96 hrs) Hemodialysis (qweek)
Truvada®	TDF 300mg Emtricitabine	HIV (in combination therapy) Hepatitis B HIV PrEP	CrCl ≥ 50 (daily) CrCl 30–49 (q48hrs)
Atripla®	TDF 300mg Emtricitabine/Efavirenz	HIV (single tablet regimen)	CrCl ≥ 50
Complera®	TDF 300mg Emtricitabine/Rilpivirine	HIV (single tablet regimen)	CrCl ≥ 50
Stribild®	TDF 300mg Emtricitabine/Elvitegravir/Cobicistat	HIV (single tablet regimen)	CrCl ≥ 70 to initiate; CrCl ≥ 50 to continue
Vemlidy®	TAF 25mg	Hepatitis B	CrCl ≥ 15
Descovy®	TAF 25mg Emtricitabine	HIV (in combination therapy) Hepatitis B	CrCl ≥ 30
Odefsy®	TAF 25 mg Emtricitabine/Rilpivirine	HIV (single tablet regimen)	CrCl ≥ 30
Genvoya®	TAF 10mg* Emtricitabine/Elvitegravir/Cobicistat	HIV (single tablet regimen)	CrCl ≥ 30

Brand names are provided for clarity because the fixed dose combination pills are widely known by their commercial names. TDF, tenofovir disoproxil fumarate 300 mg; TAF, tenofovir alafenamide; PrEP, HIV pre-exposure prophylaxis; CrCl, Cockcroft-Gault creatinine clearance in ml/min.

* A lower dose of TAF is included in fixed dose combination with the pharmacoenhancer cobicistat, which increases plasma tenofovir exposure.