

REVIEW NEPHROLOGY

## Renal Concerns in the Treatment of Chronic Hepatitis B with Tenofovir

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### Abstract

Tenofovir, a third generation oral nucleos(t)ide analogue, currently represents one of the first-line drugs recommended for treating chronic hepatitis B virus (HBV) infection. After oral administration, tenofovir is mostly excreted in the urine by glomerular filtration and proximal tubular secretion. Hence, an impaired kidney function may lead to an increased renal exposure to the drug in patients with coexistent renal damage. This could further worsen kidney disease through different mechanisms of nephrotoxicity such as mitochondrial DNA depletion and tubular cytotoxicity. Despite several studies performed so far to assess tenofovir-related renal toxicity, data in HBV patients are not yet conclusive. Screening of risk factors for kidney disease before starting therapy and a careful monitoring of serum creatinine, glomerular filtration rate, serum phosphate and urine analysis during treatment are advocated to adjust the dose or stop treatment if needed. New biomarkers of tubular injury, such as neutrophil gelatinase associated lipocalin, could become helpful in the future for the timely identification and risk stratification of renal damage induced by tenofovir.

*Keywords:* antiretroviral therapy; hepatitis B; NGAL; nucleos(t)ide analogue; tenofovir

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### Introduction

Chronic hepatitis B virus (HBV) infection is a relevant public health problem all over the world, with different prevalence between low-income and high-income countries. The virus responsible for the disease is a hepatotropic virus belonging to the Hepadnaviridae family (1). Vaccination is recommended by the World Health Organization in all newborns and in unvaccinated subjects, particularly in high-risk individuals including haemodialysis patients, recipients of organ transplantation or blood transfusion, partners of patients with HBV infection and people who travel to endemic areas (2). Nevertheless, HBV

infection is still widespread. Because patients affected are at high risk of morbidity and mortality, primarily related to the development and progression of liver cirrhosis and cancer, identifying the most effective therapeutic options is mandatory (3). The drugs currently recommended as first-line therapy of chronic HBV infection are interferon (IFN) or third-generation oral nucleos(t)ide analogues, such as tenofovir and entecavir (ETV). According to current guidelines, the use of lamivudine (LAM), telbivudine and adefovir (ADV) as first-line drugs is not recommended because of their limited efficacy, their side

effects and the higher rates of drug resistance. IFN is indicated in young patients with mild-to-moderate liver disease, but it cannot be prescribed in patients with non-compensated liver disorder, autoimmune disease, psychosis, depression and during pregnancy. Also, IFN should not be prescribed in renal transplant recipients because of the increased risk of rejection, although this drug has the advantage of limited treatment duration with the hypothetical absence of drug resistance. Long-term treatment with nucleos(t)ide analogues is necessary for patients not achieving sustained virological response or for those needing extended therapy (4).

### Tenofovir: pharmacokinetics and mechanisms of action

Tenofovir disoproxil fumarate (TDF) is a nucleotide reverse transcriptase inhibitor acting as a structural analogue of the usual substrate for viral RNA-directed DNA polymerase used against the human immunodeficiency (HIV) and hepatitis B (HBV) viruses. Tenofovir has been used worldwide since 2001 as part of a highly active antiretroviral therapy (HAART) against HIV infection. Since 2008, it has been indicated for the treatment of adults with chronic HBV infection or HIV/HBV co-infection. It is administered orally as the pro-drug TDF or tenofovir alafenamide (5, 6). Following oral administration, TDF is essentially completely absorbed in the gastrointestinal tract and peak plasma concentrations are reached within 0.25–1.5 h. The prodrug moiety of TDF is efficiently cleaved and minimal intact prodrug is observed in systemic circulation. Major sites of tissue uptake include the liver, kidney and bowel. Half-life of TDF is approximately 17 h. The kidney eliminates TDF with minimal metabolic transformation. After an oral dose, 70%–80% is excreted in the urine unchanged. Although side effects are mostly represented by bone mineral diseases, gastrointestinal disorders and acute pancreatitis, concerns have been raised also about potential renal damage. In fact, specific renal metabolism leads TDF to be eliminated through urine by glomerular filtration (80%) and proximal tubular secretion (20%) (7). Renal clearance abnormalities may affect TDF pharmacokinetics and systemic concentration, and the consequent increased renal exposure to this drug in patients with different degrees of coexistent kidney damage could result in a further decline of renal function (8).

### Mechanisms of tenofovir-induced renal toxicity

TDF nephrotoxicity may be explained by various mechanisms including mitochondrial DNA depletion, tubular cytotoxicity and intra-individual differences in TDF clearance because of polymorphisms in genes encoding for drug transporters (9, 10). TDF acts primarily by disturbing the mitochondrial function through the inhibition of DNA polymerase- $\gamma$  responsible for DNA replication and by depleting different enzymes involved in the electron transport chain function and oxidative

phosphorylation. In vitro experimental studies demonstrated the potential of TDF to induce mitochondrial dysfunction but with a lower toxicity as compared to other nucleoside reverse transcriptase inhibitors (10). After absorption, TDF is phosphorylated in two sites and it is filtered unmodified through the glomerulus, being for little part taken from the blood by the proximal tubular cells (11). As a consequence of phosphorylation, the drug is activated and becomes a structural analogue of the usual substrate of viral RNA-directed DNA polymerase. The drug has the ability to halt viral DNA synthesis by inhibiting the activity of host  $\alpha$ - and  $\beta$ -DNA polymerases and mitochondrial DNA gamma-polymerase. This mechanism is useful to stop viral replication but is also at the basis of TDF-induced mitochondrial pathologies, in particular, in the kidney proximal tubule. In the basolateral membrane of the proximal tubular epithelial cells, provided with numerous mitochondria, TDF is implicated in active cellular uptake by the organic anion transporters hOAT1 and hOAT3. In the apical membrane, TDF takes part in the process of active uptake mediated by multidrug resistance proteins MRP-2 and MRP-4 (12). hOAT-1 and hOAT-3 are responsible for carrying 20%–30% drug into the proximal tubule cells for its elimination by urine. Secretion into the urinary space is mediated also by MRP-2 and MRP-4 on the apical membrane (13). TDF affinity for hOAT-1 and hOAT-3 is at the basis of TDF nephrotoxicity. Moreover, interaction with MRP-2 and MRP-4 may induce mitochondrial DNA depletion and dysfunction, with renal accumulation of the drug (14, 15). TDF may cause different kinds of renal damage, including proximal tubular dysfunction such as Fanconi syndrome, hyperphosphaturia and normal phosphataemia in patients with preserved or decreased renal function, acute interstitial nephritis, acute tubular necrosis and acute kidney injury. Renal biopsies in patients treated with TDF usually show normal glomeruli and necrotic or apoptotic tubular epithelial cells (12, 16). Rats treated with 300 mg/kg of TDF for 28 days showed increased tubular hyaline droplets positive for  $\alpha$ 2-microglobulin; electron microscopy revealed condensed, fibrillar electron-dense material in the proximal convoluted tubule epithelial cells (17).

### Tenofovir and renal function in clinical trials

Renal toxicity due to TDF is clearly described in the literature (11, 18, 19), but many studies were designed to demonstrate the long-term safety and efficacy of TDF in chronic HBV patients with normal or impaired renal function (20). A decline of estimated glomerular filtration rate (eGFR) was observed in patients with mild-to-moderate renal disease before therapy and in patients with normal renal function (13–15). In HIV-infected patients, TDF leads to a significant decline in creatinine clearance (CrCL) compared with non-TDF-containing regimens which is reversible partially or completely after drug discontinuation (8, 21). Clinical trials seem to suggest that TDF does not interfere with renal safety in HBV population and dose adjustment according to basal GFR does not influence viral response to therapy, preventing

renal side effects (22). A similar safety profile has been described in subjects with normal GFR and in those with mild renal impairment at baseline. Fixed thresholds for renal TDF toxicity included an increase of 0.5 mg/dl serum creatinine (sCr) from baseline (23). In a randomised clinical trial (24), patients did not experience renal failure or progressive deterioration in renal function, although the majority (80%) had mild renal impairment. Furthermore, sCr levels remained stable within each CrCL category over the course of the study and the mean CrCL values remained relatively stable over time. In spite of these findings, the severity and the risk of TDF-associated nephrotoxicity in patients with chronic hepatitis B without pre-existing renal disease or facilitating factors for renal involvement are still not well defined (25–27). Moreover, a Cockcroft–Gault estimated CrCL  $\geq 70$  ml/min is an entry criterion for most clinical trials now available, limiting the experience in patients with established renal damage (23). In preliminary data of *naïve* patients treated with TDF or ETV, the risk of renal function worsening was similar in both groups; older age and impaired renal function before starting therapy were predictors of renal damage during treatment (28).

Combined antiviral therapy (TDF *plus* ETV) was not associated with increased risk of renal damage when compared with ETV monotherapy. In a recent study, the increase of sCr values ( $\geq 0.3$  mg/dl) had similar frequency in patients receiving combined therapy or monotherapy at week 96. Elevation of sCr levels above 0.5 mg/dl was more frequent in patients in monotherapy, but in any case, antiviral drug dose reduction was necessary (29). Renal safety profile of the new prodrug tenofovir alafenamide fumarate (TAF) seemed to be different from TDF. TAF showed no *in vitro* interaction with hOAT receptors, which are involved in renal TDF nephrotoxicity (30, 31). A phase 2 study was performed in HIV patients to compare the safety profile of TAF with that of TDF. Patients treated with TAF had a similar virological response, a smaller reduction of CrCL and lower proteinuria than patients treated with TDF after 48 weeks of therapy. TAF effective dosage was lower than TDF (10 mg vs. 300 mg) (32).

### Tenofovir in kidney transplantation and haemodialysis patients

TDF is even less studied and used in kidney transplant recipients, probably because of its potential nephrotoxic effect. After liver transplantation, additional nephrotoxicity should also be considered because of the concomitant use of calcineurin inhibitors (24). Recently, a study was performed using TDF in solid organ recipients, including three kidney transplant recipients. Patients were partial responders to previous therapies with other nucleos(t)ide agents. Renal parameters were stable after 12 months of therapy, and nearly half of the patients were HBV DNA negative at month 12 (33).

In a retrospective community-based cohort study by Gish et al. (23), sCr increased by 0.2 mg/dl from basal levels in

18.8% non-transplant patients receiving TDF; a similar incidence (20.9%) of sCr increase was reported in patients treated with ETV. In this study, transplantation and pre-existing reduced renal function were the only factors independently associated with sCr increase. Long-term studies performed with LAM showed reduced mortality rates and improved patient survival in kidney transplant recipients with HBV infection. Also, in patients undergoing haemodialysis, long-term use of TDF has been poorly studied. Sparse evidence indicates that high-flux haemodialysis is able to remove TDF efficaciously. According to this finding, it is now being recommended to treat HBV patients on haemodialysis with 300 mg TDF once a week after the 12th hour of dialysis (34).

### Dose adjustment of TDF and early diagnosis of TDF-related renal damage

The American Association for the Study of Liver Diseases (AASLD) guidelines recommend to measure eGFR, phosphaturia, urine protein/creatinine ratio, glycosuria and tubular proteinuria in patients with HIV infection every 6 months during TDF therapy. They recommend to reduce TDF dosage if eGFR is below 60 ml/min and to stop TDF treatment if eGFR, phosphaturia, urine protein/creatinine ratio and glycosuria change significantly (35). In patients with chronic HBV infection, sCr, eGFR (with Cockcroft–Gault formula) and phosphataemia should be measured before and every 6 months during TDF exposure. Particular attention has to be given in patients at higher risk for kidney disease and in haemodialysis patients. In patients at risk for renal disease, renal parameters must be measured every month during the first 3 months of therapy, then every 3 months until the end of the first year and every 6 months thereafter. Patients developing eGFR  $< 60$  ml/min and/or serum phosphorus  $< 2$  mg/dl during therapy have to be monitored more closely. TDF dosage adjustment is required in patients with GFR  $< 50$  ml/min (2). Lampertico et al. suggested making dose reduction also in patients with eGFR  $< 60$  ml/min [estimated using Modification of Diet in Renal Disease (MDRD) study equation] and/or low levels of serum phosphorus. In their study cohort, the estimated cumulative probability of dose reduction for renal adverse events was 11% for *naïve* patients and 24% in patients previously treated with ADV at month 48 (36, 37).

Many studies were performed to compare the available equations to calculate eGFR in HBV patients. Indeed, establishing what is the better formula is already a challenging question for practical nephrology. In the general population, the MDRD study equation is usually more accurate than the Cockcroft–Gault equation; however, in some cases, both formulas showed similar results. In particular, the Cockcroft–Gault equation is less accurate than the MDRD equation in older and obese patients, whereas the MDRD study equation should not be applied to children, during pregnancy, to patients aged  $> 85$  years or those belonging to some racial or ethnic subgroups,

such as Hispanic people. MDRD formula is also less accurate in patients affected by diabetes mellitus type 1 without microalbuminuria and in kidney transplant donors (because its accuracy decreases for eGFR >60 ml/min). The Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines recommend to use the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula, which is more accurate than MDRD for eGFR values >60 ml/min and generally improves performances of MDRD equation. Yet, the Cockcroft–Gault equation is still largely used for drug adjustment recommendations, because kidney function was estimated by this formula in the majority of pharmacokinetics studies (38, 39). New markers of tubular dysfunction, such as neutrophil gelatinase-associated lipocalin (NGAL), may be used to evaluate kidney damage during TDF therapy (40–42). In the past, various studies have been published demonstrating the usefulness of NGAL as an early biomarker of tubular damage in HIV-infected patients treated with TDF (43–46). Conversely, the body of evidence in HBV patients, at present, is equivocal. In a randomised clinical trial, HIV patients treated with TDF showed an increase in NGAL values when compared with those treated with abacavir (44); however, more recent studies did not show significant differences in plasma and urinary NGAL after TDF treatment (45, 46).

## Conclusion

Despite a large body of evidence has accrued on the safety profile of TDF therapy in HIV-infected patients, clinical guidance in the chronic hepatitis B population requires further insights, in particular, with respect to renal toxicity and bone mineral disease incidence. Screening of risk factors for renal disease before starting TDF therapy and a careful monitoring of sCr, eGFR, serum phosphate and urine analysis during treatment are important mainstays for guiding the prescription of this drug and to promptly reduce dosage or interrupt therapy if nephrotoxicity occurs. Monitoring early renal damage by implementing new biomarkers such as NGAL could improve timely diagnosis of tubular dysfunction due to TDF. New evidence on TAF, the new oral prodrug of tenofovir, in the HBV population is strongly advocated as this agent has already shown promising results with respect to renal and bone safety in the HIV population.

## Conflict of interest

The authors declare no conflict of interest.

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