

Antiviral treatment for chronic hepatitis B in renal transplant patients

Ezequiel Ridruejo

Ezequiel Ridruejo, Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Ciudad Autónoma de Buenos Aires, C1425ASG Buenos Aires, Argentina

Ezequiel Ridruejo, Hepatology and Liver Transplant Unit, Hospital Universitario Austral, Pilar, 1629 Provincia de Buenos Aires, Argentina

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Correspondence to: Ezequiel Ridruejo, MD, Hepatology Section, Department of Medicine, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC", Avda. Las Heras 2939, C1425ASG Buenos Aires, Argentina. eridruejo@gmail.com

Telephone: +54-11-48091980

Fax: +54-11-48091992

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showing a favorable safety and efficacy profile of nucleos(t)ide analogue (NUC) treatment in the renal transplant setting. Entecavir, a drug without major signs of nephrotoxicity, appears to be the first option for NUC naïve patients and tenofovir remains the preferred choice for patients with previous resistance to lamivudine or any other NUC. Renal transplant recipients under antiHBV therapy should be monitored for its efficacy against HBV but also for its safety with a close renal monitoring. Studies including a large number of patients with long term treatment and follow up are still needed to better demonstrate the safety and efficacy of newer NUCs in this population.

Key words: Tenofovir; Long term outcome; Hepatitis B; Renal transplantation; Entecavir

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Core tip: Nucleos(t)ide analogue treatment is safe and effective in renal transplant patients. It improves long term patients and graft survival.

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Abstract

Chronic hepatitis B infection is frequent in renal transplant patients. It negatively impacts long term outcomes reducing graft and patient survival. Current guidelines clearly define who needs treatment, when to start, what is the first line therapy, how to monitor treatment response, when to stop, and how patients must be controlled for its safety. There is some data

INTRODUCTION

Renal transplantation (RT) is the preferred treatment for patients with end-stage renal disease (ESRD) undergoing renal replacement therapy. Moreover, RT improves quality of life and survival when compared with remaining on the waiting list^[1]. In the last twenty years, improvement in immunosuppressive therapy resulted in a decline in acute rejection

prevalence and in 1-year improvement in graft survival. In spite of short-term survival, both long-term patients and graft survival has not improved as expected^[2,3]. Cardiovascular diseases, malignancy and infections are the most frequent determinants of death in RT recipients. Liver failure appears as the fourth cause of death in long-term survivors after RT^[3-6]. In these patients liver failure is mostly related to chronic viral hepatitis B (HBV) and C (HCV). Both HBV and HCV negatively impact on renal transplantation outcomes by reducing long term graft and patient survival; the magnitude of this impact may vary between these viruses and may differ from different series. Treatment strategies of these viruses are clearly different in patients with ESRD. Nowadays HCV must be treated with Peg-interferon combined with low dose ribavirin before transplantation; in the near future new antivirals will allow HCV treatment after renal transplantation. Conversely, HBV can be treated with the same drugs across all stages of chronic renal disease: before and in dialysis, and after RT.

In the last decades HBV prevalence has decreased in dialysis units due to the implementation vaccination programs and infection control procedures. Today it varies between 0% to 20% according to different sources^[7,8]. But prevalence in RT patients tends to vary and can be higher since some of these patients were transplanted before these programs were widely available. The present review focuses on the current management of patients with HBV after renal transplantation.

PRE-TRANSPLANT EVALUATION

Chronic HBV infected patients with ESRD must be adequately evaluated before being transplanted. Two key aspects must be taken into account: evaluation of HBV status and the severity of liver disease. Regarding HBV status, all HBsAg (hepatitis B surface antigen) positive patients and all patients with previous known history of acute or chronic hepatitis B or the presence of antiHBc (hepatitis B core antibody) with/without antiHBs (hepatitis B surface antibody) require a full virological evaluation including HBeAg (hepatitis B envelope antigen) and antiHBe (hepatitis B envelope antibody) determination and HBV DNA levels measurement. This evaluation will allow classifying these patients into different clinical situations^[9,10].

Chronic hepatitis B: (1) HBsAg positive for more than 6 mo; (2) Serum HBV DNA \geq 2000 (EASL)-20000 (AASLD) IU/mL (10^4 - 10^5 copies/mL), lower values 2000-20000 IU/mL (10^4 - 10^5 copies/mL) are often seen in HBeAg-negative chronic hepatitis B; (3) Persistent or intermittent elevation in ALT/AST levels; (4) Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation; and (5)

Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.

Inactive HBsAg carrier state: (1) HBsAg positive for more than 6 mo; (2) HBeAg negative, antiHBe positive; (3) Serum HBV DNA < 2000 IU/mL; (4) Persistently normal ALT/AST levels; and (5) Liver biopsy confirms absence of significant hepatitis.

Resolved hepatitis B: (1) Previous known history of acute or chronic hepatitis B or the presence of antiHBc with/without antiHBs; (2) HBsAg negative; (3) Undetectable serum HBV DNA; and (4) Normal ALT levels.

Concomitantly, the severity of liver disease must be evaluated before RT usually by obtaining a liver biopsy. There is some debate about the better route to perform the liver biopsy given that patients with ESRD undergoing hemodialysis have an increased risk of bleeding associated with clotting diseases, uremia-associated platelet dysfunction and intradialysis antiaggregants and anticoagulant treatments^[11]. Once transplanted this risk disappears with the restoration of normal renal function. In some centres the transjugular route is the preferred one since is associated with less a reduced risk of bleeding and pain, and may allow measuring the hepatic venous pressure gradient (HVPG) for confirming and grading portal hypertension^[12,13]. However in many centres the percutaneous trans-thoracic route is still widely and safely used^[14].

There are some noninvasive tests to evaluate the severity of liver fibrosis but they have not been widely evaluated in dialysis and RT patients^[11,15]. FibroTest (FT) and liver stiffness measurement (LSM) for noninvasive assessment of liver fibrosis had been evaluated in RT patients with chronic HBV or HCV infection^[16]. It had been reported that FT and LSM are sufficiently accurate for diagnosing mild liver fibrosis (\leq F2), but differed by 38.4% from the histological data in patients with more severe fibrosis (\geq F3); their predictive value for diagnosing severe liver disease needs to be confirmed. More information is needed in HBV infection to recommend its use.

Once the HBV clinical situation and the severity of liver diseases have been established, treatment indication and possibility of RT has to be defined. HBsAg positive patients receiving immunosuppressive therapy after renal transplantation must antiHBV prophylaxis or treatment (based on HBV DNA levels) with a NUC.

In the general population HBV inactive carriers do not need to be treated^[9,10]. But RT candidates who are inactive carriers have a higher risk of reactivation after transplantation. In HBsAg positive inactive carriers, treatment can be used as prophylactic (HBV DNA undetectable, no hepatocellular injury), preemptive (HBV DNA < 2000 IU/mL, no hepatocellular injury), and salvage

Table 1 Dosage adjustment of nucleos(t)ide analogue for patients with reduced creatinine clearance

	Recommended dosage		Dosage forms	
Creatinine clearance (mL/min)	Lamivudine ^[25]		Lamivudine ^[25]	
	> 50	100 mg once daily	Tablets: 100 mg	
	30-49	100 mg first dose, then 50 mg once daily	Oral solution: 10 mg/mL	
	15-29	100 mg first dose, then 25 mg once daily		
	5-14	35 mg first dose, then 15 mg once daily		
< 5	35 mg first dose, then 10 mg once daily			
> 50	Adefovir ^[26]		Adefovir ^[26]	
	10 mg every 24 h		Tablets: 10 mg	
	30-49	10 mg every 48 h	Oral solution: not available	
	10-29	10 mg every 72 h		
	Hemodialysis	10 mg every 7 d following dialysis		
> 50	Telbivudine ^[27]		Telbivudine ^[27]	
	600 mg every 24 h		Tablets: 600 mg	
	30-49	600 mg every 48 h	Oral solution: 100 mg/5 mL	
	10-29	600 mg every 72 h		
	Hemodialysis	600 mg every 96 h following dialysis		
> 50	Entecavir ^[28]	Entecavir in Lamivudine-Refractory ^[28]	Entecavir ^[28]	
	0.5 mg once daily	1 mg once daily	Tablets: 0.5 mg and 1 mg	
	30-49	0.25 mg once daily OR	0.5 mg once daily OR	Oral solution: 0.05 mg/mL
		0.5 mg every 48 h	1 mg every 48 h	
	10-29	0.15 mg once daily OR	0.3 mg once daily OR	
		0.5 mg every 72 h	1 mg every 72 h	
	Hemodialysis	0.05 mg once daily OR	0.1 mg once daily OR	
		0.5 mg every 7 d following dialysis	1 mg every 7 d following dialysis	
		Tenofovir ^[29]		Tenofovir ^[29]
	> 50	300 mg every 24 h		Tablets: 300 mg
30-49	300 mg every 48 h		Oral powder: 40 mg per 1 g of oral powder	
10-29	300 mg every 72 to 96 h			
Hemodialysis	300 mg every 7 d or after approximately 12 h of dialysis			

therapy after reactivation (HBV DNA > 2000 IU/mL, with hepatocellular injury). Even if the prophylactic/preemptive initiation is the generally accepted treatment, the data comparing these treatments are few^[17]. All RT candidates with *chronic HBV* need to be treated before transplantation with NUCs^[9,10]. Patients with *resolved HBV* have a low reactivation risk in the RT setting varying between 0.6% to 6%^[18-20]. Since there is a low reactivation risk in HBsAg negative patients, universal prophylaxis is not recommended in them. Among antiHbC positive patients, those having low antiHBs titers (< 100 IU/mL) have the higher risk of reactivation. Even though there is limited evidence, repeat vaccination may be considered for this group. Current HBV DNA tests allows to diagnose true occult infection in patients with isolated antiHbC positive serology. There is not enough information about the absolute risk of reactivation in this sub-population, so it is unclear whether prophylaxis is beneficial^[21].

The severity of liver disease will determine if the patient is a good candidate for RT or not. Evidence of decompensated liver disease (ascites, encephalopathy, variceal bleeding, etc.) precludes RT and is a clear indication of combined liver-renal transplantation (LRT). The presence of compensated cirrhosis with signs of portal hypertension is also an indication for LRT. Cirrhotic patients without portal hypertension must be carefully evaluated

for RT since cirrhosis is correlated with an higher mortality risk^[22]. Non cirrhotic patients are adequate candidates for RT.

TREATMENT

There are many guidelines regarding HBV treatment. Patients with ESRD and RT can be considered a special population and there are particular recommendations for them that may vary from those implemented in the general population^[9,10,15,23]. Patients with chronic hepatitis B are candidates for treatment and those inactive hepatitis B carriers are candidates for prophylactic or preemptive therapy.

There are two main treatment options in hepatitis B: interferon and NUCs. Interferon therapy has many disadvantages when compared with NUCs: poorly tolerated due to side effects, limited efficacy in this populations, subcutaneous administration and there is certain risk of graft rejection^[24]. So, there is agreement that in RT patients with chronic HBV infection interferon based therapy should be avoided^[15,21,23]. On the contrary, NUCs have a high antiviral potency, have a good safety and tolerability profile and can be orally administrated. These drugs can be easily used in RT and doses can be adjusted according to creatinine clearance^[25-29] (Table 1). The main limitations of NUCs include the need for long-

term therapy, which may be for indefinite time in HBeAg negative patients; the risk of development of NUC's resistant viral strains; and the unknown safety profile with long-term treatment^[11].

Regarding NUCs, there are five drugs currently approved for HBV treatment: lamivudine (LAM), adefovir (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir disoproxil fumarate (TDF). Treatment with TDF or ETV is preferable to LAM in NUC naïve patients, since they are more effective due to a high antiviral potency and have a high barrier to resistance reducing the risk of drug resistance and treatment failure^[9,10,15,21,23].

Since LAM was the first NUC approved for clinical use, it has yielded the majority of data on the management of HBsAg-positive renal transplant recipients. Several observational studies have shown that LAM can improve liver function^[15]. A meta-analysis including 14 prospective cohort studies (184 patients) showed that LAM normalized ALT levels in 81% (95%CI: 70%-92%), cleared HBV-DNA in 91% (95%CI: 86%-96%) cleared HBeAg in 27% (95%CI: 16%-39%) of the patients. In most studies (11 of 14) LAM was administered for 6 to 12 mo^[30]. Even though LAM was associated with significantly improved patient survival^[31], prolonged treatment is associated with progressive increase in drug resistance and the cumulative probability of developing LAM resistance (LAM-R) was approximately 60% after 69 mo^[30,32,33]. LAM-R leads to treatment failure and can be associated with progressive liver disease and a negative impact in patient and graft survival. Fortunately today there are good treatment options for LAM-R. Given that there are better options for HBV treatment, LAM cannot be consider within the first treatment choices for these patients^[9,10,15,21,23].

Adefovir was the second available oral drug for HBV treatment infection. It has similar antiviral activity against both LAM-R and wild-type HBV, but it may be nephrotoxic (especially in high doses). Currently its major clinical application is as add on therapy for the management of lamivudine-resistance since it has lower antiviral activity than ETV and TDF for naïve patients^[9,10,15].

There have been reports on ADV short-term efficacy either as mono- or add-on therapy in LAM-R RT patients^[34-39]. One year ADV monotherapy showed a significant viral response in 11 patients with a median HBV DNA decline of 5.5 log₁₀. Only one patient cleared HBV DNA, one of the six HBeAg positive patients cleared HBeAg but without antiHBe seroconversion; none cleared HBsAg. Importantly, there were no significant clinical and laboratory adverse events^[34]. ADV as add-on therapy to LAM resulted in significant HBV suppression LAM-R RT recipients^[38,39]. In 11 ADV add on treated patients, HBV DNA was undetectable in 80%-83% after 36 to 42 mo^[38]. However, six patients (54%) had to lower

ADV dose due to a decline in glomerular filtration rate after a median of 11 mo (range: 9-42)^[38]. After 12, 24 and 36 mo of ADV treatment treatment 35.7%, 42.8% and 88.0% of treated patients cleared HBV DNA; there was no virological breakthrough and 92.8% of patients achieved normal ALT levels after 12 mo of treatment^[39]. Patients treated with add-on ADV therapy tended to normalize ALT levels and to reduce HBV DNA levels more effectively than those treated with ADV monotherapy^[39]. In this study 29% of the participants developed moderate to severe renal failure^[39].

However, when compared with treatment-naïve the virological response could be fluctuating and relatively slow in LAM-R patients^[40]. Nevertheless, rescue therapy with ADV resulted in significantly better viral suppression and liver biochemistry compared with continuation of LAM (75% vs 14.3% had persistent normalization of ALT), and the clinical response was sustained for at least 24 mo^[31]. Evidence of nephrotoxicity in the absence of proximal tubulopathy, despite dosage adjustment, was frequently observed, and could necessitate treatment discontinuation^[38,39]. ADV has a low antiviral potency at the currently approved dose and its efficacy could be further reduced with dose adjustment according to renal dysfunction. For these reasons ADV is not a first line option for naïve patients and its benefits for LAM-R may be less when compared with TDF.

There are currently no results about telbivudine treatment in RT recipients but it would be worthwhile to explore the use of this agent in treatment-naïve kidney allograft recipients given its relatively low resistance rate, lack of nephrotoxicity, and the relatively lower cost compared with other nucleoside/tide analogues^[40].

Entecavir is one of the first line treatment options for HBV^[9,10]. This drug has a high antiviral potency, a high genetic barrier for resistance and a good safety profile. It is very effective for treatment naïve patients but has a lower efficacy for LAM-R patients, and it is not the first option for this latter population^[9,10,15]. A recent 2-year prospective study included 27 RT patients, 18 (67%) were treatment naïve and 9 (33%) had been previously treated with LAM but had no resistant mutations. ETV cleared HBV DNA in 70%, 74%, 96% and 100% of patients after 12, 24, 52 and 104 wk respectively^[41]. There was no change of creatinine clearance, and no episodes of lactic acidosis or muscle damage during treatment. There were higher rates of undetectable HBV DNA levels in ETV treated than LAM treated patients (32%, 37%, 63% and 63% at 12, 24, 52 and 104 wk, respectively; $P < 0.005$)^[41]. In an analysis excluding 9 patients from the ETV group who were also LAM experienced, the remaining 18 ETV naïve subjects exhibited a better virological response at 52 and 104 wk than 19 previously treated with LAM ($P < 0.05$)^[41].

Other studies reported results with ETV in cohorts including both naïve and LAM-R patients, unfortunately with limited number of patient^[42-45]. Experience regarding the use of ETV in RT recipients who had developed LAM- or ADV-resistance had been examined in a small study with 10 solid organ transplant recipients (8 kidney allograft recipients)^[42]. Treatment with ETV resulted in an appreciable drop in HBV DNA levels and a 50% HBV undetectability in both HBeAg positive and HBeAg negative patients after 16.5 mo of treatment without significant changes in glomerular filtration rate^[42]. In our small experience we reported ETV use in 11 patients with several chronic renal diseases: 1 with stage 4 CKD, 7 in dialysis, and 3 RT recipients^[43,44]. HBV DNA was cleared in 54.5% ($n = 6$); 77.7% of HBeAg-positive patients (7/9) seroconverted to antiHBe positive; and only one patient (9.1%) showed antiHBs seroconversion. There were no significant changes in renal or hematological biochemical parameters^[43,44]. In the most recent report, twenty-one RT patients (10 treatment naïve, 11 with LAM resistance) were treated with ETV for 34.7 ± 22.9 mo (range 6-75 mo)^[45]. The cumulative rate of HBV DNA undetectability at 12, 24, and 36 mo was 60%, 100%, and 100% for treatment naïve group, and 27%, 45%, and 45% for LAM-R group, respectively. Genotypic resistance to ETV emerged after 20.0 ± 3.5 mo with increase in ALT and HBV DNA in two patients with LAM-R, but was not observed in the treatment-naïve group. There were no significant changes in glomerular filtration rate^[45]. Also, ETV was used in RT patients who developed hepatic flares due to the appearance of LAM-R^[46]. Four patients were treated with ADV and two with ETV. After 18 mo, HBV DNA was $< 10^5$ copies/mL in 4 subjects and $< 10^2$ copies/mL in 1 subject. There were no remarkable adverse events and no changes in renal function^[46]. ETV appears as one of the best options for NUC naïve RT patients; it is less effective in LAM-R and better options are available.

Tenofovir was the last NUC to be approved for HBV mono-infection and is the other first line option together with ETV^[9,10,15]. It has a high antiviral potency, a high genetic barrier for resistance and a good safety profile^[9,10,15], but there is some concern about its potential nephrotoxicity^[47]. There is little data in the renal transplant setting: only one study reports the results of three RT treated patients together with 3 liver, and 1 heart transplant recipients^[48]. HBV DNA viral became significantly decreased and 3 patients cleared HBV DNA at the end of the study period. There were no adverse events related to tenofovir treatment. No episodes of acute rejection were reported under therapy. There were no statistically significant changes in renal function represented by stable creatinine levels, estimated creatinine clearance, serum phosphorus level, or daily microalbuminuria level^[48]. TDF appears

as one of the best options for both NUC naïve and LAM-R RT patients; treatment results have to be extrapolated from the general population since there is little experience in RT.

TIMING OF INITIATION OF TREATMENT: PREEMPTIVE OR PROPHYLACTIC THERAPY

Patients with chronic renal disease go through different phases: varying stages of renal failure, ESRD, hemodialysis (HD)/peritoneal dialysis (PD), and transplantation. Once transplanted could suffer various kidney disease and finally lose the graft and return to dialysis. HBV infection will go with the patient along the road. The timing of HBV treatment initiation may vary depending on the stage of renal disease.

Patients undergoing HD or PD who are not RT candidates can start NUC therapy if HBV DNA levels are ≥ 2000 IU/mL regardless of ALT levels, especially if they have moderate fibrosis in the liver biopsy (METAVR score $F \geq 2$) or estimated by a non-invasive methods^[11].

All HBsAg-positive RT recipients are considered candidates for NUC treatment. RT candidates with HBV DNA levels > 2000 IU/mL must initiate treatment at HBV diagnosis, those with HBV DNA ≤ 2000 IU/mL should start therapy at least 2 wk before RT. NUC therapy has to be continued indefinitely as long as the patients are under any immunosuppressive treatment^[9,10,11,15]. It should be remembered that compensated cirrhotic patients are not candidates for RT, and cirrhotic patients with decompensated disease should be evaluated for combined liver-kidney transplantation^[11,49].

As previously mentioned, RT candidates who are inactive carriers have an increased reactivation risk after transplantation. In this subgroup of HBsAg positive patients treatment can be used as prophylactic (HBV DNA undetectable, no hepatocellular injury), preemptive (HBV DNA ≤ 2000 IU/mL, no hepatocellular injury), and salvage therapy after reactivation (HBV DNA > 2000 IU/mL, with hepatocellular injury). Even if the prophylactic/preemptive initiation is the generally accepted treatment, the data comparing these treatments are few. The disappearance of viral load is a prerequisite for a HBV positive patient on hemodialysis to be enrolled in the RT list. Therapy with ETV, TDF or LAM on adjusted doses for renal function is included in the current guidelines for prophylaxis of HBV positive RT candidates. The optimal NUC regimen has not been proposed yet, so prophylaxis may start before or at the time of RT and continue thereafter^[9,10,15,50]. ETV should be the first line option for avoidance of short term resistance and ADV nephrotoxicity, while TDF had better be applied in case of LAM-R^[9,10,50].

Lamivudine is the most extensively drug used in prophylactic/preemptive therapy in RT patients. In a small study, LAM given as either prophylactic or preemptive treatment was proven superior to salvage therapy when liver dysfunction is evident^[51]. None of the HBsAg positive patients receiving prophylactic or pre-emptive therapy developed reactivation, while 50% of the patients not been treated suffered reactivation^[51,52]. These results were confirmed by others, but there is some controversy about the clinical impact of prophylactic/preemptive therapy vs salvage therapy^[51-55]. One study showed that there was no differences in survival between HBsAg positive RT patients treated preemptively with LAM and HBsAg negative controls. HBsAg positive patients transplanted without preemptive therapy had an increased mortality rate [relative risk of death, 9.7 ($P < 0.001$); relative risk of liver-related mortality, 68.0 ($P < 0.0001$)^[53]. Twenty five RT candidates received pre-transplantation prophylactic/preemptive NUC therapy, 22 (88%) were treated with LAM and 3 (12%) with ETV^[54]. When compared with a historical control group NUC treated patients has a significant improvement in 10 year graft (82% vs 34%) and patient (91% vs 57%) survivals. There was no liver-related death in NUC treated patients. In contrast, in untreated controls patient death (68%) was the most frequent cause of graft failure, which was mostly caused by liver diseases. Prophylactic and preemptive therapy resulted in the same graft and patient survival, but patients receiving preemptive therapy had a higher HBV reactivation incidence. NUC treatment was independently associated with better patient survival ($P = 0.005$)^[54]. On the contrary, a retrospective analysis using LAM in the majority of patients found no benefit of prophylactic/preemptive treatment^[55]. Ninety four RT candidates were evaluated, 56 received antiviral prophylaxis (Group 1), 51 with LAM and 5 with ETV, and 38 did not (Group 2). In group 2 20 patients experienced HBV reactivation: 16 received LAM, 2 received ETV and 2 received no antiviral treatment. Using the Cox-regression model, prophylactic treatment did not improve patient survival (OR = 1.29, 95%CI: 0.37-4.49, $P = 0.693$), graft survival (OR = 1.25, 95%CI: 0.45-3.46, $P = 0.666$) or reduce the risk of hepatic decompensation (OR = 2.01, 0.35-11.57, $P = 0.434$)^[55]. LAM-R occurred in 21 LAM-treated Group 1 and 4 LAM-treated Group 2 patients ($P = 0.243$), with mean times of resistance after RT of 82 and 132 mo, respectively ($P = 0.001$)^[55].

A recent retrospective study compared both treatment strategies^[17]. It included 58 HBsAg positive RT recipients: 24 in the prophylactic group (all patients used LAM) and the 34 in the preemptive group (32 patients used LAM and 2 patients used ETV). The graft/patient survival rates for HBsAg positive were the same as those of hepatitis-free recipients ($P = 0.18$). In the prophylactic group,

there were fewer hepatic dysfunctions (12.5% vs 30%, $P = 0.12$), viral breakthroughs (16% vs 32%, $P = 0.17$) and elevated alanine aminotransferase concentrations (37% vs 52%, $P = 0.24$), however these differences were not statistically significant. In the prophylactic group, one patient was switched to ETV and then to TDF due to partial response finally achieving complete virological response. In the preemptive group, LAM was withdrawn and changed to TDF in 3 patients and to ADV in another one achieving an adequate virologic/biochemical response. These NUCs were almost as safe as LAM, as there were no significant differences among proteinuria and estimated glomerular filtration rate^[17].

Results from these studies support the clinical guidelines recommendations: prophylactic or preemptive therapy with NUCs provides comparable graft/patient survival with hepatitis-free RT recipients and may be better in preventing hepatic dysfunction than salvage therapy. Given its high risk for developing resistant mutations, LAM is no longer a first option, and ETV should be the first one. TDF can be an effective and safe treatment for LAM-R in RT recipients (Figure 1)^[9,11,15,21,56].

TREATMENT IMPACT ON LONG TERM EVOLUTION

In the last years, several cohort studies had demonstrated that HBV infection is associated with higher patient mortality and risk of graft failure in RT patients^[15,40,50,57]. These results had been validated in two meta-analysis^[58,59]. The first meta-analysis was published in 2005 and included 6050 patients from six observational cohort retrospective studies. Pooled results showed that HBsAg positive status was a significant predictor for death (RR = 2.49, 95%CI: 1.64-3.78) and for graft loss after RT, when compared to seronegative patients (RR = 1.44, 95%CI: 1.02-2.04) (homogeneity test, $P < 0.0001$)^[58]. These results have been updated in 2014: ten observational studies involving 82690 unique RT recipients were included. In this study, HBsAg positive status was associated with an increase risk for all-cause mortality (adjusted RR = 2.214, 95%CI: 1.56-3.137, $P < 0.0001$) and for all-cause graft failure (aRR = 1.44, 95%CI: 1.26-1.63, $P < 0.0001$)^[59]. Both meta-analyses of observational studies concluded that untreated RT HBsAg positive patients have an reduced patient and graft survival.

As previously mentioned oral NUC therapy safely and effectively can suppress HBV replication in RT recipients. Several studies had shown that this antiviral effect may impact on long term graft and patients outcome^[31,54,60-62]. In 63 LAM treated HBsAg positive RT recipients 10-year survival rate was 81% and such results were nearly comparable to HBsAg

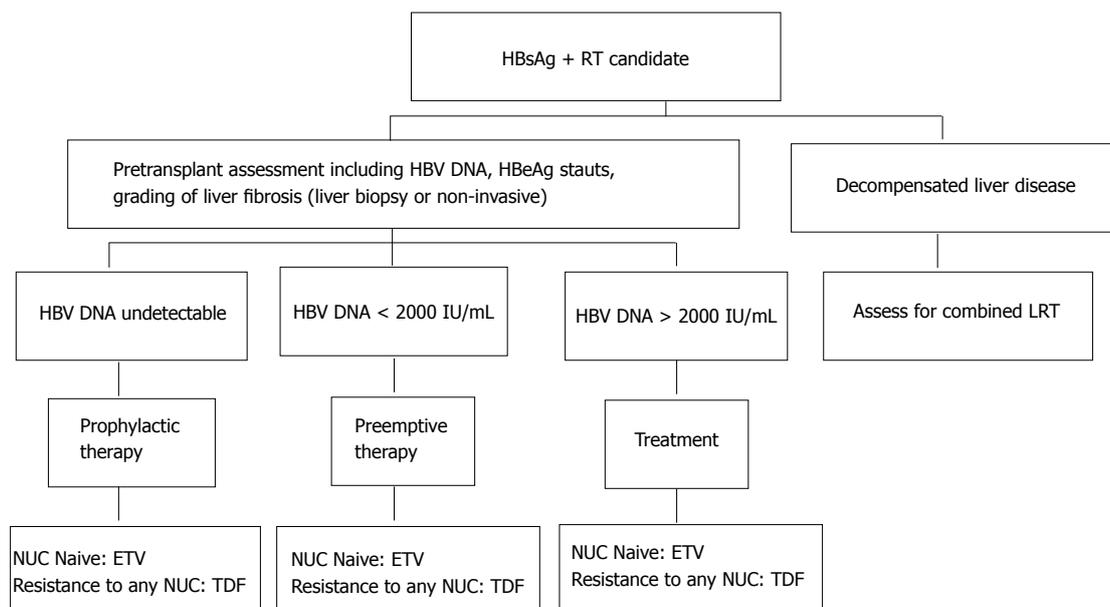


Figure 1 Treatment algorithm for management of renal transplant candidates with chronic hepatitis B virus infection. RT: Renal transplantation; LRT: Liver renal transplantation; NUC: Nucleos(t)ide analogue; ETV: Entecavir; TDF: Tenofovir disoproxil fumarate.

negative patients^[31]. Initiating treatment with LAM is associated with a 62% chance of developing drug resistance after 4 years of continuous therapy. Six months after beginning rescue therapy with ADV or ETV, HBV DNA decrease three-log in 75% of patients without significant adverse effects. When compared with untreated patients, those treated with NUCs showed a significant improvement in survival after 20 years of follow up (34% vs 83% respectively, $P < 0.006$). Even though NUC therapy reduced overall mortality by reducing liver related disease ($P < 0.036$), 40% of death in chronic HBV infected patients are still related to liver complications and 22.2% of them developed in patients being treated^[31].

Forty two RT patients were treated for long term with different NUCs regimens: at the end of follow up 18 patients were receiving monotherapy (9 LAM, 2 ADV, and ETV) and 24 combination therapy (11 LAM + ADV, 2 LAM + TDF, 4 ETV + ADV, 6 ETV + TDF and 1 TDF + emtricitabine, FTC)^[60]. At the end of the study 100% (18/18) of patients under monotherapy and 87.5% (21/24) of patients under combination therapy cleared HBV DNA. The 3 patients (12.5%) in the combination therapy group with detectable HBV DNA, had HBV DNA levels below 300 IU/mL. At the end of follow up, 92.8% of the entire cohort had cleared HBV DNA. Patient survival was 97.6% at 10 years, 95.2% at 15 years, and 90.4% at 20 years after renal transplantation, while graft survival was 100% at 5 years, 97.6% at 10 years, 95.2% at 15 years, and 88.1% at 20 years after renal transplantation. At the end of the study, 8 patients (19.04%) died and 1 received a liver transplantation due to end stage liver disease. Four

deaths were liver related: 4 patients (3 cirrhotics and 1 with only mild fibrosis at baseline) developed an hepatocellular carcinoma (HCC) despite complete virological response; three of the other patients died of non liver cancer and the remaining from stroke^[60]. During the study, 11.9% (6/42) of patients returned to dialysis due to chronic rejection leading to graft failure. The NUC dose was modified according to creatinine clearance in 45.2% (19/42) of the patients^[60].

Thirty RT patients underwent long term NUC therapy; at the end of follow up 25 were still alive and being treated and 24 were HBV DNA non detectable. Eight patients were receiving LAM monotherapy, 1 on ETV, 1 on TDF, 6 on LAM + ADV combination and 9 LAM + TDF^[61]. Five patients died from no liver related disease and 9 returned to dialysis after graft failure due to chronic allograft nephropathy. In this cohort, 10 year patient survival was 92% and 10 year graft survival was 86%. There were no renal adverse effects related to ADV/TDF therapy^[61].

Twenty five patients received pre-RT treatment with LAM (22 patients) and ETV (3 patients): 18 were HBV DNA undetectable (prophylactic group) and 8 were HBV DNA positive (preemptive group), and were compared to a historical control group^[54]. Unadjusted 10-year graft survival rates in the treatment cohort vs historical control cohort were 81.8% and 34.3%, respectively ($P = 0.003$). Graft lost occurred more frequently in the historical control than in the treated cohort (70.3% vs 4.3%, respectively); this was mainly related to patient death. Treated patients showed a better 10-year patient survival than the control group: 90.0% vs 57.4%; $P = 0.013$. Pre-transplantation NUC

Table 2 Definition of response to nucleos(t)ide analogue antiviral therapy of chronic hepatitis B

Category of response	
Biochemical (BR)	Decrease in serum ALT to within the normal range
Virologic (VR)	Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg positive
Primary non-response	Decrease in serum HBV DNA by 2 log ₁₀ IU/mL after at least 24 wk of therapy
Virologic relapse	Increase in serum HBV DNA of 1 log ₁₀ IU/mL after discontinuation of treatment in at least two determinations more than 4 wk apart
Histologic (HR)	Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy
Complete (CR)	Fulfill criteria of biochemical and virological response and loss of HBsAg
Time of assessment	
On-therapy	During therapy
Maintained	Persist throughout the course of treatment
End-of-treatment	At the end of a defined course of therapy
Off-therapy	After discontinuation of therapy
Sustained (SR-6)	6 mo after discontinuation of therapy
Sustained (SR-12)	12 mo after discontinuation of therapy

HBV: Hepatitis B; HBsAg: Hepatitis B surface antigen.

treatment was an independent factor for the improved patient survival [odds ratio (OR) = 0.052; $P = 0.005$]. Liver-related disease was the main cause of death in the historical control cohort (84.6% of the cases); sepsis was the second most frequent cause (15.4% of the cases)^[54]. Overall, graft (100% vs 71.4%) and patient survivals (100% vs 85.7%) were similar in the 2 treated cohorts ($P = 0.601$)^[54].

Only one study showed some conflicting results on NUC therapy impact in patients' survival^[62]. The study included 94 HBV-positive and 282 age/sex-matched HBV negative RT patients: 56 patients received an antiviral agent for prophylaxis (LAM 51, ETV 5), and other 18 for HBV reactivation. Although the patient survival rate was lower for HBV positive than HBV negative RTRs (89% vs 94% at 5 years, 78% vs 88% at 10 years, $P = 0.031$), there was no difference in graft survival between the two groups (86% vs 92% at 5 years, 73% vs 81% at 10 years, $P = 0.113$). In multivariate analysis, HBsAg positive status was a significant risk factor for death (OR = 2.19, 95%CI: 1.14-4.20, $P = 0.019$), but not significant for graft loss (OR = 1.64, 95%CI: 0.94-2.86, $P = 0.079$)^[62]. HBeAg and HBV DNA Pretransplant status was not available for all the patients. Of the 26 HBeAg-positive patients, 14 were receiving antiviral prophylaxis at transplantation: 8 showed reactivation while 6/12 of the untreated developed reactivation. All survived with stable liver chemistry, except for one dying from an HCC. Of 57 HBeAg-negative patients, 35 were started on antiviral prophylaxis at transplantation: 14 showed reactivation while 14/22 of the untreated developed reactivation. Among them, 12 died,

whereas the remaining 45 survived without hepatic dysfunction^[62]. Even though treated patients showed a reduced survival, it appears to be better than the survival reported in untreated patients.

NUC therapy in HBsAg positive RT patients is associated with a higher long term patient and graft survival rate. Studies have some limitations since most of the used LAM, which is not the best treatment option. More potent NUCs may add some benefit over LAM, but this still has to be demonstrated. Salvage therapy with TDF or ADV is safe and effective in patients developing LAM-R. Despite this clear benefit, all HBV infected patients must be closely follow up and HCC screening must be performed every six months, since the risk of HCC development may not entirely disappears even in the presence of virological response^[60,63].

DURATION OF THERAPY AND EVALUATION OF RESPONSE

In RT patients it is unclear what is the optimal treatment extent that assures long term viral suppression, preserving adequate liver function with the minimal risk of viral resistance development^[15]. Current guidelines clearly define how to monitor on treatment response, what are the therapeutic endpoints and when it is possible to stop treatment (Table 2)^[9,10]. In the case of NUC therapy, there are some terms regarding resistance that have also been defined. These is particularly important in this population, since some patients had initiated treatment long time ago with old NUCs such as LAM (Table 3)^[9,10].

Table 3 Definition of terms relating to antiviral resistance to nucleos(t)ide analogue treatment

Term	Definition
Virologic breakthrough	Increase in serum HBV DNA by > 1 log ₁₀ (10-fold) above nadir after achieving virologic response, during continued treatment
Viral rebound	Increase in serum HBV DNA to > 20000 IU/mL or above pretreatment level after achieving virologic response, during continued treatment
Biochemical breakthrough	Increase in ALT above upper limit of normal after achieving normalization, during continued treatment
Genotypic resistance	Detection of mutations that have been shown in "in vitro" studies to confer resistance to the NA that is being administered
Phenotypic resistance	<i>In vitro</i> confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitory concentrations) to the NUC administered

NUC: Nucleos(t)ide analogue.

The duration of treatment depends on HBeAg status. HBeAg positive patients should be treated until HBV DNA and HBeAg are cleared and antiHBe seroconversion develops. Additional treatment, also known as "consolidation therapy", is needed for at least 6 to 12 mo after antiHBe seroconversion to prevent virological relapse. It is recommended to closely monitoring for relapse after treatment withdrawal. Relapse, even in patients achieving adequate virological response is a possibility, but their rates tend to be low^[64]. HBeAg negative patients should treated until HBsAg clearance is achieve^[9,10]. These recommendations might be applied to treatment in RT recipients to ensure treatment success, but outcomes after NUCs withdrawal in RT immunosuppressed patients is unknown.

A small recent study evaluated the long term results in HBV positive RT patients after NUC treatment discontinuation^[65]. Fourteen patients treated with LAM (11 patients), ADV (1 patient), ETV (1 patient), and LdT (1 patient) were included in this study. Patients were allowed to discontinue treatment if they have all of the following: (1) no clinical and histologic evidence of cirrhosis; (2) normal liver biochemistry; (3) negative for both HBV DNA and HBeAg; (4) no viral resistance; (5) antiviral therapy > 9 mo; (6) maintenance dosage of immunosuppressant for > 3 mo; and (7) no history of acute rejection during recent 6 mo^[65]. All patients were followed at 3 to 6 mo interval for liver biochemistry, viral serology, and HBV DNA level after treatment discontinuation. In 6 (42.9%) of 14 patients who meet the pre-specified criteria treatment was discontinued. In 4 of them (66.7%) it was successfully discontinued and HBV DNA was still undetectable for a median 60.5 mo (range, 47-82 mo). In the other 2 patients HBV reactivated, but HBV DNA was again cleared after immediately resuming NUC therapy^[65]. On the contrary, in LAM treatment discontinuation in 19 RT recipients after 2 years of treatment without adequate virological response, relapse rate was high (75%)^[66]. Even though evidence is scarce, it seems that in certain RT patients, after complete viral suppression

and sufficient duration, antiviral therapy can be successfully and safely withdrawn.

IMPACT OF NUCLEOS(T)IDE ANALOGUES ON RENAL FUNCTION

Nucleos(t)ide analogues are primarily eliminated without changes in the urine following ingestion, and appropriate dose modifications are proposed for patients with impaired renal function (eGFR < 50 mL/min) (Table 1). Treatment guidelines recommend that all patients initiating NUC treatment should be tested for serum creatinine levels and estimated creatinine clearance before therapy; and baseline renal risk should be assessed for all of them^[9,10]. High baseline renal risk includes one or more of the following clinical situations: decompensated cirrhosis, creatinine clearance < 60 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic medications and solid organ transplantation. In consequence, RT recipients may have many of these basal renal risk factors.

In clinical trials outside renal transplant setting, minimal decline in renal function have been showed with all NUCs, except for LdT which appears to improve renal function^[67,68]. Impact of LdT on renal function was analyzed from a database including all patients treated in the GLOBE Study (2 years), in the long term extension study CN04E1 (4 to 6 years) and in patients with decompensated cirrhosis (2 years)^[69]. Renal function improved in LdT treated patients in GLOBE trial (+8.5% increase in mean eGFR,) and it was sustained for 4 to 6 years. Improvement in renal function in LdT treated patients was also observed in those at increased risk for renal impairment: patients with baseline eGFRs of 60-89 mL/min per 1.73 m² (+17.2%), > 50 years (+11.4%), and with advanced liver fibrosis or cirrhosis (+7.2% for patients with Ishak fibrosis score 5-6). In patients with the highest renal risk such as decompensated cirrhotics, eGFR was also improved with LdT (+2.0%). In patients who received 2 years of LAM in GLOBE/015 studies and

rolled over to extension study to receive LdT for 2 additional years, eGFR also improved after treatment switch (+8.9%)^[69]. Although this data may suggest that LdT may be renal protective, it is not clear whether this protective effect is specific to this NUC. This potential benefit, particularly relevant in the RT population, does not overcome the high risk of treatment resistance and neuromuscular adverse events. As previously mentioned, this beneficial safety profile does not support the use of LdT as a first-line NUC in hepatitis B treatment^[69].

Nucleotide, specially ADV, appear to be more nephrotoxic than nucleoside analogues^[70-74]. In a real-life setting study, 145 patients ADV treated patients were compared with 145 untreated patients regarding its impact on renal function^[71]. During follow-up, 30% of ADV treated patients show a mild decrease in renal function (10%-20% reduction in eGFR from baseline) compared with 16% in the untreated group, 15% vs 6% showed a moderate decrease (20%-30%), and 7% vs 1% showed a severe decrease (> 30%) respectively ($P > 0.0001$). In the ADV group 6.9% of the patients discontinued treatment ($P > 0.004$). In a multivariate analysis ADV treatment significantly predicts renal dysfunction [hazard ratio (HR) = 3.94, $P = 0.03$]. In the same analysis, age > 50 years (HR = 3.49, $p = 0.087$), baseline mild renal dysfunction (HR = 4.49, $P = 0.073$), and hypertension and/or diabetes mellitus (HR = 2.36, $P = 0.074$) were not significant predictors^[71]. In a retrospective study, 687 patients receiving ADV monotherapy (18.2%) or in combination with LAM (81.8%) for 1 year or more were enrolled to evaluate the incidence and risk factors of renal impairment^[72]. Renal dysfunction was defined as mild (20%-30% reduction in eGFR), moderate (30%-50%), or severe (more than 50%). Patients were treated for a median of 27 mo, 10.5% ($n = 72$) developed renal dysfunction being mild in 77.8% of patients, moderate in 20.8% of patients, and severe in only 1 patient. The cumulative incidence of renal dysfunction at 1, 3, and 5 years was 2.6%, 14.8%, and 34.7%, respectively. ADV dose was modified in 7 patients and it was discontinued in 3 patients; after these changes, eGFR remained stable^[72]. In 271 ADV treated patients, after 6 years of treatment GFR ≤ 60 mL/min incidence was 38.3% and after 5 years, serum creatinine increased ≥ 0.5 mg/dL in 21.48%. Switching ADV to other NUC or reducing its dose was associated with reversal of renal dysfunction in almost all patients; there were no differences between the two approaches ($P = 0.737$)^[73]. On the contrary, a study including 46 HBeAg negative LAM-R patients treated with ADV add on for up to 90 mo found no impact on renal function when compared with a matched control group of untreated inactive HBV carriers^[74].

The number of patients treated with ADV in the

RT setting is smaller than in the general population. In this subgroup, ADV treatment may also impact on renal function. A significant decrease of estimated GFR and an increase in serum creatinine from 1.42 (± 0.39) to 1.6 (± 0.36) mg/dL, ($P = 0.02$) was found in 11 patients treated for 2 or more years^[37]. It was also associated with an increase in proteinuria, changes in renal tubular parameters and changes in phospho-calcic metabolism^[37]. Another study including also 11 LAM-R patients did not show significant changes in median creatinine clearance (CLcr), in serum phosphorus or in urinary protein level from baseline to the last available visit. However, after a median treatment time of 11 mo (range: 9-42), 54% ($n = 6$) of patients reduce ADV dose due to renal dysfunction. Renal function remained stable ($n = 5$) or improved ($n = 1$) 22 mo (range: 6-34) after dose modification^[38].

Fourteen patients were treated with long term ADV (5 monotherapy, and 9 ADV + LAM combination therapy). Eight patients (57.2%) developed impaired renal function; it was mild (5%-20% reduction in the eGFR compared to baseline values) in 4, moderate (20%-30%) in 2, and severe (> 30%) in the 2 remaining patients. Acute graft rejection was diagnosed by kidney biopsy in 2 of these patients. Calcineurin inhibitors nephrotoxicity was presumed in 2 of these patients and their doses were accordingly adjusted. ADV dose was reduced in 3 patients due to severe renal dysfunction (eGFR 30-50 mL/min) and it was discontinued in 1 patient (eGFR < 20 mL/min) without impact on virological response^[39]. Renal dysfunction in long-term ADV treated patients appears relatively frequent, but serious nephrotoxicity is unusual. Renal dysfunction can be safely managed by dose reduction or switching to another NUC without impact on virological response.

In TDF treated patients, also a nucleotide analogue, renal dysfunction is less frequently seen than with ADV. The majority of previously nephrotoxic events reported, which were similar to those reported under ADV treatment, were in HIV infected patients^[68]. There is recently presented data about TDF impact on renal function in HBV mono-infected patients^[75-80]. A study evaluated the pooled results from three global randomized clinical trials including 426 TDF treated patients for 144 wk. In this study 0.5% (2/426) of patients developed a creatinine increase ≥ 0.5 mg/dL from pre-treatment values and none showed an eGFR decrease < 50 mL/min, showing a minimal impact of TDF on renal function even in high risk patients such as cirrhotics or diabetics^[75]. Moreover, when 74 patients with mild renal dysfunction (CrCl 50-80 mL/min) were compared with 206 with normal renal function (CrCl ≥ 80 mL/min), none of them showed signs of renal impairment defined as a creatinine increase ≥ 0.5 mg/dL after 96 wk of therapy^[76]. Among 441 patients from the Vireal cohort, 114 with baseline impaired

renal function were classified as stage 2 (GFR 60-89 mL/min), stage 3 (GFR 30-59 mL/min), stage 4 (GFR 15-29 mL/min) and stage 5 (GFR < 15 mL/min or dialysis) and included in the study. When compared from baseline, after 48 wk of treatment, TDF did not significantly modified GFR in patients with stage 2 (76 mL/min vs 77 mL/min), 3 (50 mL/min vs 49 mL/min), or 4 (23 mL/min vs 23 mL/min) renal failure^[77]. Two RT recipients were included and had a stable GFR under therapy. Nine patients needed to adjust TDF dose. At the end of the study, 67% had a stable renal failure stage, 22% had an improvement and 11% had a decreased in it^[77]. In a retrospective study, 195 refractory patients were treated with TDF monotherapy for 30 ± 16 (6-90) mo were compared with 89 asymptomatic HBsAg carriers^[78]. After 48 mo, TDF treated patients in showed a significantly greater reduction in eGFR when compared to untreated patients [-16 ± 36 (-48 - +23) and -9.6 ± 36 (-21 - +22) mL/min, respectively, $P = 0.03$]. TDF dose was reduced in only 1 patient after 15 mo of treatment due to a 0.38 mg/dL increase in creatinine levels^[78]. In 26 LAM-R patients treated with TDF, there were no significant variations in phosphatemia and GFR from baseline after one year of treatment^[79]. Even if there is no impairment on renal function, TDF may have some potential effects on the proximal tubule. In 61 TDF treated patients for a mean time of 29 mo, there were no significant change in mean GFR in the overall population but 58% of patients showed an impairment in GFR (median 8.1%, range 0.01% to 20.5%) and two patients developed an GFR to < 60 mL/min^[80]. At least one sign of proximal tubular damage appeared in 26 (42%) individuals: glucosuria without diabetes mellitus, increased alpha1-microglobulinuria/creatinine ratio, hypophosphatemia, reduced tubular resorption of phosphate rate and reduced tubular maximum reabsorption rate^[80]. The effects of TDF on renal function were evaluated in 321 naïve patients treated for 4 years in clinical practice^[81]. In this large European cohort, there were no modifications in creatinine and phosphorus serum levels and eGFR was reduced from 84 to 80 mL/min. At year 4, patients with eGFR < 50 increased from 2% to 3% and those with eGFR < 60 mL/min increased from 7% to 11%. At the same time point, hypophosphatemia (serum phosphate < 2.3 mg/dL) increased from 2% to 5.1 %, while 1% of the patients had phosphate levels < 2.0 along the study period. TDF dose was reduced in 17 patients due to reduction in eGFR and in 2 due to hypophosphatemia. Seven patients had to withdraw treatment and were switched to ETV. Overall, some renal adverse effect was reported in 26 patients (7%)^[81].

In comparison to nucleotide analogues, nucleoside analogues, such as ETV and LdT, show not significant renal toxicity^[67,68]. Studies have been performed

comparing ETV and TDF nephrotoxicity^[82-86]. After 2 years of treatment, there was no significant modifications in eGFR in 74 ETV and 50 TDF ± LAM treated patients^[82]. In the ETV group 2.7% showed a reduction $\geq 40\%$ in eGFR vs 3.92% in the TDF ± LMV group ($P = NS$). When compared with an untreated control group, in ETV treated patients eGFR was reduced by -7.6 mL/min (95%CI: -15.8+0.6, $P = 0.07$) and by -8.7 mL/min (95%CI: -18.3+1.0, $P = 0.08$) in TDF ± LMV treated patients. In untreated controls, eGFR remained stable or even improved by +7.4 mL/min (95%CI: 0.78-14.1, $P = 0.03$)^[82]. In another real-life cohort of 212 patients were treated with TDF and 79 with ETV and its impact on renal function was evaluated^[83]. No significant differences were found in urea, creatinine and phosphorus levels and in eGFR after 12 mo of TDF treatment. Also in the same group, there was no difference in the proportion of patients with eGFR < 60 mL/min when compared with baseline levels. In ETV treated patients, there was a significantly reduction in serum phosphorus (0.96 vs 1.06, $P = 0.016$), increased in creatinine levels (1.0 vs 0.89, $P < 0.05$) and reduction in eGFR (80 vs 89, $P < 0.05$) after 12 mo of treatment. In ETV treated patients, 3.8% of patients had a 25% increase in creatinine levels while 0.47% of TDF treated patients had a 25% decrease in eGFR after 12 mo of treatment^[83]. In a community-based retrospective cohort study, 80 patients treated with TDF monotherapy or in combination with other NUCs were matched with 80 ETV treated patients and incidences of serum creatinine increments and eGFR decrease were evaluated^[84,85]. More patients in the ETV group had creatinine increments ≥ 0.5 mg/dL (3 vs 11; $P = 0.025$), whereas more patients treated with TDF had eGFR reductions of < 60 mL/min (15 vs 6; $P = 0.022$) and at least 1 dose modification (13 vs 4; $P = 0.021$). In a multivariate analysis, previous organ transplantation (aOR, 6.740; 95%CI: 1.799-28.250; $P = 0.005$) and pre-treatment renal failure (aOR, 10.960; 95%CI: 2.419-48.850; $P = 0.002$) were significantly associated with increases in serum creatinine levels^[84]. Renal function was evaluated in 197 HBV mono-infected patients from two outpatient clinics and who were classified according to the received treatment: LAM ($n = 36$), ADV ($n = 32$), ETV ($n = 32$), TDF ($n = 37$), and untreated HBsAg-positive patients ($n = 60$)^[86]. The CKD-EPI equation was used to calculate eGFR and the individual change in eGFR over time was modeled with linear mixed effects models. Patients with previous renal dysfunction, diabetes mellitus, or arterial hypertension were excluded from the analysis. The yearly predicted median individual changes in eGFR according to this model were: -2.05 mL/min in untreated patients, and -0.92 mL/min, -1.02 mL/min, -1.00 mL/min, and -0.92 mL/min in LAM, ADV, ETV and TDF treated patients,

respectively. A decrease of eGFR > 20 mL/min from baseline developed in 3.3% of untreated patients, and in 5.5%, 0%, 6.25%, and 2.7% in LAM, ADV, ETV and TDF treated patients, respectively. Renal insufficiency stage 3 (eGFR of < 60 mL/min) was uncommon and not different between all patient groups^[86].

First line NUCs, ETV and TDF, appears to have little impact on renal function in the general population when compared with untreated controls and with the others NUCs. Markers of renal function indicated that TDF treated patients, suspected to be more nephrotoxic, have similar risks of developing changes in renal function than ETV treated patients. Although there is some evidence showing some degree of renal dysfunction in ETV treated patients, its clinical significance remains unclear and it may represent a physiological decrease in renal function in this group and/or reflect the potential limitations of standard biochemical tests of renal function in patients with liver disease^[83]. Baseline renal risk factors may play a role in the nephrotoxic effects of NUCs. Data on RT patients is limited but these results can be extrapolated to this population, taking into account that these RT recipients can be considered within the high renal risk group. Therefore, it is recommended in all HBV treated patients to measure serum creatinine levels and estimated creatinine clearance, and in ADV or TDF treated patients it is also recommended to measure serum phosphate levels, especially in patients at high renal risk. In patients at low renal risk these tests can be performed every 3 mo during the first year and every 6 mo thereafter, in case of no renal adverse events. In patients at high renal risk these tests can be performed every month for the first 3 mo, every 3 mo until the end of the first year and every 6 mo thereafter, in case of no renal adverse events. Closer renal monitoring is required in patients who develop reductions in creatinine clearance < 60 mL/min or reductions in serum phosphate levels < 2 mg/dL^[9,10,15,87].

CONCLUSION

Current guidelines clearly define who needs treatment, when to start, what is the first line therapy, how to monitor treatment response, when to stop, and how patients must be controlled for its safety. There is some data showing a favorable safety and efficacy profile of NUC treatment in the renal transplant setting. ETV, an agent without signs of major nephrotoxicity, appears to be the best option for NUC naïve patients and TDF is still the preferred agent in patients with resistance to LAM or any other NUC. Renal transplant recipients under antiHBV treatment should be closely monitored for its efficacy against HBV and for its safety, especially regarding its impact on renal function. Studies including a large

number of patients with long term treatment and follow up are still needed to better demonstrate the safety and efficacy of newer NUCs in this population.

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