**ANTIVIRAL TREATMENT FOR CHRONIC HEPATITIS B IN RENAL TRANSPLANT PATIENTS**

Running title: NUC treatment in RT patients

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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 showing a favorable safety and efficacy profile of nucleos(t)ide analogue (NUC) treatment in the renal transplant setting. Entecavir, an agent without signs of major nephrotoxicity, appears to be the preferred option for NUC naïve patients and tenofovir remains the agent of choice for patients with prior resistance to lamivudine or any other NUC. Renal transplant recipients under antiHBV therapy should be followed not only for the treatment efficacy against HBV but also with a thorough renal monitoring as well. 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.

**Keywords**: Hepatitis B; Renal Transplantation; Entecavir; Tenofovir; Long Term Outcome

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

**INTRODUCTION**

Renal transplantation (RT) is the treatment of choice for patients with end-stage renal disease (ESRD) undergoing renal replacement therapy. Moreover, RT is associated with better quality of life and survival when compared with those remaining on the waiting list [1]. During the last two decades, the introduction of new immunosuppressants has been associated with a decline in the prevalence of acute rejection and with an improvement in 1-year graft survival. However, in contrast to the short-term survival, the long-term outcome of both transplant recipients and their grafts has not improved as expected [2-3]. Cardiovascular diseases, malignancy and infections are the most common causes of death in RT patients. 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 months.

2. Serum HBV DNA ≥2000 (EASL)-20,000 (AASLD) IU/mL (104-105 copies/mL), lower values 2,000-20,000 IU/mL (104-105 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.

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 months.

2. HBeAg negative, antiHBe positive.

3. Serum HBV DNA<2,000 IU/mL.

4. Persistently normal ALT/AST levels.

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.

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 bleeding risk associated with clotting disorders, uremia-associated platelet dysfunction and intradialysis anti-platelet and anticoagulant therapies [11]. Once transplanted this risk disappears with the restoration of normal renal function. In some centres the transyugular 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 transthoracic 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 extensively evaluated in this group of 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 acceptably accurate for diagnosing mild liver fibrosis (≤F2), but differed by 38.4% from the liver biopsy data in patients with more severe fibrosis (≥F3); their diagnostic value for predicting 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. Every HBsAg positive patient who undergoes renal transplantation and receives immunosuppressive agents should receive antiHBV prophylaxis or treatment (based on HBV DNA levels) with a nucleos(t)ide analogue (NUC).

In the general population HBV inactive carriers do not need to be treated [9,10]. But RT candidates who are *inactive carriers* are at an increased risk of reactivation 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 [17]. All RT candidateswith *chronic**HBV* need to be treated before transplantation with NUCs [9,10]. Patients with *resolved HBV* are at low risk of reactivation in the RT setting varying between 0.6 to 6% [18-20]. Given the low risk of reactivation of patients who are HBsAg negative it is not recommended that universal prophylaxis is given. Limited evidence suggests that amongst those positive for antiHBc, those with low titers of antiHBs (<100 IU/ml) are at greatest risk and repeat vaccination should be considered for this group. Amongst those with isolated antiHBc positive serology sensitive HBV DNA assays may detect those with true occult infection. However data on the absolute risk of reactivation is lacking and it is unclear if prophylaxis is warranted [21].

The severity of liver disease will determine if the patient is a good candidate for RT or not. The presence 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 evidence of portal hypertension is also an indication for LRT. Cirrhotic patients without portal hypertension must be carefully evaluated for RT since cirrhosis is associated with an increased risk of mortality [22]. Patients without cirrhosis 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 interferon treatment should generally be avoided in HBV infected RT patients [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, perhaps indefinite, therapy, particularly in HBeAg negative patients, the risk of viral resistance and the unknown long-term safety [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. The utility of LAM in stabilization of liver function was shown in several observational studies [15]. A meta-analysis that included 14 prospective cohort studies (184 patients) determined the mean overall estimate for ALT normalization, and HBV-DNA and HBeAg clearance at 81% (95% CI 70-92%), 91% (95%CI 86-96%) and 27% (95% CI 16-39%), respectively. The duration of LAM therapy was 6 to 12 months in the majority (11 of 14) of the studies [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 months [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 is no longer a first line treatment for these patients [9,10,15,21,23].

Adefovir was the second available oral drug for HBV treatment infection. It has similar activity against both wild-type and LAM-R 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 resulted in a significant virological 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 lost HBeAg but without antiHBe seroconversion; none had HBs Ag loss. Importantly, there were no significant clinical and biochemical adverse effects [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 months [38]. However, six patients (54%) had to reduce ADV dose because of creatinine clearance decline after a median of 11 months (range: 9–42) [38]. After 12, 24 and 36 months of ADV treatment treatment 35.7%, 42.8% and 88.0% of treated patients achieved undetectable HBV DNA levels; there was no virological breakthrough and normalization of ALT was achieved in 92.8% of patients after 12 months of treatment [39]. Patients treated with AVD add on 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 patients developed moderate to severe renal insufficiency [39].

However, the virological response could be variable and relatively slow when compared with treatment-naïve subjects [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 months [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 is currently no data on the use of telbivudine in renal transplant 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 NUC naïve and 9 (33%) were LAM experienced patients without YMDD mutations. ETV resulted in undetectable HBV DNA levels in 70%, 74%, 96% and 100% of patients after 12, 24, 52 and 104 weeks respectively [41]. There was no change of glomerular filtration rate, and no lactic acidosis or myopathy during treatment. ETV treated patients presented higher rates of undetectable HBV DNA than LAM treated (32%, 37%, 63% and 63% at 12, 24, 52 and 104 weeks, 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 weeks 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 months of therapy without significant changes in renal function [42]. In our small experience we reported ETV use in 11 patients with several chronic renal diseases: 1 with stage 4 CKD, 7 undergoing hemodialysis, and 3 RT recipients [43,44]. The rate of HBV DNA clearance was 54.5% (n = 6); the rate of antiHBe seroconversion was 77.7% (7/9 HBeAg-positive patients). The rate of antiHBs seroconversion was 9.1% (1/11 patients). There were no significant changes in renal function or hematological 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 months (range 6-75 months) [45]. The cumulative rate of HBV DNA undetectability at 12, 24, and 36 months 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 months with increase in ALT and HBV DNA in two patients with LAM resistance, but was not observed in the treatment-naïve group. There were no significant changes in renal function [45]. Also, ETV was used in RT patients who developed hepatic flares duo to the appearance of LAM-R [46]. Four patients were treated with ADV and two with ETV. After 18 months, HBV DNA was <105 copies/mL in four patients and <102 copies/mL in one patient. Treatment was well-tolerated and renal function remained stable [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 monoinfection 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 three liver, and one cardiac transplant recipients [48]. HBV DNA viral became significantly decreased and three patients were HBV DNA negative at last follow-up. Clinical tolerance to tenofovir therapy was good. There were no occurrences of rejection during treatment. As far as renal function was concerned, there were no statistically significant changes in creatinine level, 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.

In patients undergoing HD or PD who are not RT candidates can start NUC therapy with HBV DNA >2000 IU/mL regardless of ALT activity, particularly if they have at least moderate histological liver lesions at liver biopsy or at least moderate fibrosis estimated by a non-invasive marker [11].

Treatment with NUCs is recommended for all HBsAg-positive RT recipients. NUC therapy should ideally start at HBV diagnosis in RT candidates with HBV DNA >2000 IU/mL or 2 weeks before RT in candidates with HBV DNA ≤2000 IU/mL and should continue for life as long as the patients remain under any immunosuppressive agent [9,10,11,15]. It should be remembered that patients with compensated cirrhosis are precluded from RT, while patients with decompensated cirrhosis may only undergo combined liver and kidney transplantation [11,49].

As previously mentioned, RT candidates who are *inactive carriers* are at an increased risk of reactivation 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 pre-emptive 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 versus salvage therapy [51-55]. One study showed that the survival of RT patients preemptively managed with LAM was similar to that of HBsAg negative controls, whereas HBsAg positive patients who underwent transplantation without preemptive treatment had inferior survival (relative risk of death, 9.7 [P <0.001]; relative risk of liver-related mortality, 68.0 [P <0.0001]) [53]. Twenty five RT patients received pre-transplantation prophylactic/preemptive antiviral therapy, 22 (88%) and 3 (12%) were prescribed lamivudine and entecavir, respectively [54]. The treatment group, when compared with a historical control group, showed a significant improvement in 10 year graft (82% vs. 34%) and patient (91% vs. 57%) survivals. Among the historical control group, the main causes of graft failure were patient deaths (68%), which were mostly caused by liver diseases. In contrast, there was no liver-related death in the treatment group. In addition, there was no difference in graft or patient survival between the prophylactic and preemptive groups, but the incidence of HBV reactivation was lower in the prophylactic group. Antiviral therapy was an independent factor for the improved patient survival (P = .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. Cox-regression analysis showed that antiviral prophylaxis had no benefit on patient death (OR 1.29, 95% CI 0.37 - 4.49, p = 0.693), graft failure (OR 1.25, 95% CI 0.45-3.46, p = 0.666) or 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 months, 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 did not reach statistical significance. 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. Due to high rates of resistance 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) [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 reduced patient and graft survival in RT recipients [15,40,50,57]. These results had been validated in two meta-analysis [58,59]. In 2005, six observational cohort retrospective studies (6050 unique patients) were included in the first meta-analysis. Pooling of study results demonstrated that HBsAg in serum was an independent and significant risk factor for death (relative risk 2.49, 95% CI: 1.64-3.78) and for graft failure after RT, when compared to seronegative patients (relative risk 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 82 690 unique RT recipients were included. The summary estimate for adjusted relative risk (aRR) of all-cause mortality was 2.214 (95% CI: 1.56-3.137, p < 0.0001) and for all-cause graft loss aRR was 1.44 (95% CI: 1.26-1.63, p < 0.0001) [59]. Both meta-analyses of observational studies support the notion that untreated HBsAg positive patients after RT have an increased risk of mortality and graft loss.

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 [31,60-63]. In 63 LAM treated HBsAg positive RT recipients 10-year survival rate was 81% and such results were nearly comparable to HBsAg negative patients [31]. With LAM as initial treatment, 62% of patients developed drug resistance after 4 years. Salvage treatment with ADV or ETV was well tolerated, and resulted in a three-log decrease in HBV DNA after 6 months of treatment in 75% of patients. Treatment of hepatitis B with NUCs resulted in significantly improved patient survival (83% vs. 34% at 20 years, p < 0.006). Although antiviral treatment was associated with reduced mortality because of liver complications (p < 0.036), liver-related deaths still accounted for 40% of mortalities in HBsAg positive patients in the era of antiviral therapies and 22.2% of all deaths that occurred in patients who had received antiviral treatment [31].

Forty two RT patients were treated for long term with different NUCs regimens: at the end of the study 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]. All the 18 monotherapy patients had undetectable HBV DNA at the end of follow-up while 21 of the 24 patients under combination therapy (87.5%) had undetectable HBV DNA and 3 (12.5%) were still detectable but with HBV DNA titers below 300 IU/ml. Overall, 92.8% of the patients had undetectable HBV DNA at the last visit. Patient survival was 97.6% (41/42) at 10 years, 95.2% (40/42) at 15 years, and 90.4% (38/42) at 20 years post-transplantation, while graft survival was 100% at 5 years, 97.6% (41/42) at 10 years, 95.2% (40/42) at 15 years, and 88.1% (38/42) at 20 years. At the end of follow-up, 8 patients (19.04%) died and one underwent a liver transplantation for decompensated cirrhosis. Four deaths were related to hepatocellular carcinoma (HCC), despite complete viral suppression, in 3 patients with baseline cirrhosis and in one patient with baseline mild liver fibrosis; the other 4 deaths were related to extrahepatic diseases [60]. During follow-up, 6 of the 42 patients (11.9%) lost their graft and resumed dialysis, mainly due to chronic rejection. Nineteen of the 42 patients (45.2%) required NUC dose adjustment to renal function [60].

Thirty RT patients underwent long term NUC treatment; at the end of the study 25 were still living and on treatment and 24 have undetectable viremia. Eight patients remain on LAM monotherapy, 1 on ETV, 1 on TDF, 6 on LAM + ADV combination and 9 LAM + TDF [61]. Five patients died with no relation to the liver disease and 9 lost their graft due to chronic allograft nephropathy. In this cohort, 10 year patient survival was 92% and 10 year graft survival was 86%. No renal toxicities related to ADV/TDF were observed [61].

Twenty five patients received pre-RT treatment with LAM (22 patients) and ETV (3 patients): 18 were HBV DNA negative (prophylactic group) and 8 were HBV DNA positive (preemptive group), and were compared to a historical control group [62]. Unadjusted 10-year graft survival rates in the treated subjects versus historical control subjects were 81.8% and 34.3%, respectively (p = 0.003). Graft failure among the treatment group occurred in 4.3% whereas 70.3% historical control subjects experienced graft failures, mainly due to patient death. Treated patients showed a better 10-year patient survival than the historical cohort: 90.0% vs. 57.4%; p = 0.013. Pre-transplantation antiviral therapy was an independent factor for the improved patient survival (odds ratio 0.052; p = 0.005). Among the historical control group, liver-related mortality was the leading cause of death, accounting for 84.6% of the cases, with sepsis contributing to 15.4% of them [62]. There were no significant differences in graft (100% vs. 71.4%) and patient survivals (100% vs. 85.7%) between the 2 treatment groups (p = 0.601) [62].

 Only one study showed some conflicting results on NUC therapy impact in patients’ survival [63]. The study included 94 HBV-positive and 282 age/sex-matched HBV-negative patients who underwent RT: 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), graft survival was comparable (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) [63]. 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 who died of hepatocellular carcinoma. 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 [63]. Even though treated patients showed a reduced survival, it appears to be better than the survival reported in untreated patients.

Treatment of HBsAg RT recipients with NUCs analogues confers a long term patient and graft survival benefit. 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. Rescue therapy with TDF or ADV is effective and well tolerated in patients who had developed 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 [60,64].

**DURATION OF THERAPY AND EVALUATION OF RESPONSE**

The optimal duration of therapy that ensures long term remission of viremia and maintenance of normal liver function and minimizes the development of resistance in RT recipients is not known [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].

The duration of treatment depends on HBeAg status. In HBeAg positive chronic hepatitis B patients, NUC treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 6 to 12 months of additional treatment (consolidation therapy) after appearance of antiHBe. 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 [65]. In the case of HBeAg negative chronic hepatitis B patients, NUC treatment should be continued until the patient has achieved HBsAg clearance [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 outcomes after withdrawal of an antiviral agent in RT patients with chronic HBV [66]. Fourteen patients treated with LAM (11 patients), ADV (1 patient), ETV (1 patient), and LdT (1 patient) were included in this study. Treatments were withdrawn in patients who met all of the following 7 criteria: (i) no clinical and histologic evidence of cirrhosis, (ii) normal liver biochemistry, (iii) negative for both HBV DNA and hepatitis B envelope antigen (HBeAg), (iv) no resistance to antiviral agent, (v) antiviral therapy > 9 months, (vi) maintenance dosage of immunosuppressant for > 3 months, and (vii) no history of acute rejection during recent 6 months [66]. All patients were followed regularly at approximately 3-6 months for liver enzyme, viral markers, and HBV DNA level after antiviral withdrawal. Discontinuation of antiviral agent was attempted in 6 (42.9%) of 14 patients who satisfied the criteria. Four (66.7%) of 6 patients were successfully withdrawn and remained negative for HBV DNA for a median 60.5 months (range, 47-82 months). Two reactivated patients resumed antiviral treatment immediately, with subsequent normalization of HBV DNA [66]. 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%) [67]. Even though evidence is scarce, it seems that NUC therapy can be discontinued successfully and safely in selected RT recipients, after complete suppression of HBV and sufficient duration of antiviral therapy.

**IMPACT OF NUCLEOS(T)IDE ANALOGUES ON RENAL FUNCTION**

Nucleos(t)ide analogues are primarily excreted unchanged in the urine following ingestion, and appropriate dosing adjustments are recommended for patients with creatinine clearance <50 ml/min (Table 1). Treatment guidelines recommend that all patients starting NUC therapy should be tested for serum creatinine levels and estimated creatinine clearance before treatment; and baseline renal risk should be assessed for all patients [9,10]. High baseline renal risk includes one or more of the following factors: decompensated cirrhosis, creatinine clearance <60 ml/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs 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 rates of renal function decline have been reported with all NUCs, except perhaps for LdT which seems to improve the creatinine clearance [68,69]. Impact of LdT on renal function was analyzed from a database including all patients treated in the GLOBE Study (2 Years), long term extension study CN04E1 (4 to 6 years) as well as in patients with decompensated cirrhosis (2 years) [70]. Renal function improved in LdT treated patients during the 2-year GLOBE study (+ 8.5% increase in mean eGFR,) and this improvement was maintained for 4-6 years. Increased eGFR with LdT treatment was also observed in patients at increased risk for renal impairment: patients with baseline eGFRs of 60-89 mL/min/1.73 m(2) (+17.2%), older than 50 years (+11.4%), and with liver fibrosis/cirrhosis (+7.2% for patients with Ishak fibrosis score at 5-6). In decompensated patients with high renal risk, eGFR was also improved on telbivudine (+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%) [70]. 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 outweigh the high rate of antiviral drug resistance and neuromuscular adverse effects. As previously mentioned, this beneficial safety profile does not support the use of LdT as a first-line NUC in hepatitis B treatment [70].

The nephrotoxic potential seems to be higher for nucleotide analogues, particularly ADV [72-75]. In a real-life setting study, the severity and incidence of renal dysfunction in 145 patients treated with 10 mg ADV was evaluated, and compared to 145 patients unexposed to ADV [72]. A mild decrease of eGFR (10%-20%) from baseline was observed in a total of 30% in the ADV group versus 16% among the unexposed group during follow-up, a moderate decrease (20%-30%) was observed in 15% versus 6%, and a severe decrease (>30%) was observed in 7% versus 1% (p > 0.0001). Discontinuation of treatment was observed in 10 (6.9%) patients on 10 mg ADV compared with 0 (0%) patients in the unexposed group (p > 0.004). On Cox proportional hazard analysis also inclusive of sex, ADV was a significant predictor of significant renal dysfunction (hazard ratio [HR] 3.94, P = 0.03). There were also significant trends for age >50 years (HR 3.49, p = 0.087), mild renal impairment at baseline (HR 4.49, p = 0.073), and hypertension and/or diabetes mellitus (HR 2.36, p = 0.074) [72]. In a retrospective study, 687 patients treated with ADV alone (18.2%) or in combination with LAM (81.8%) for more than 12 months were enrolled to evaluate the incidence and risk factors of renal impairment in patients treated with ADV [73]. Renal function was measured using the estimated glomerular filtration rate (eGFR), and renal dysfunction was defined as mild (20-30% decrease), moderate (30-50%), or severe (more than 50%). During the median treatment duration of 27 months, 72 patients (10.5%) developed renal impairment, which was mild in 77.8% of cases, moderate in 20.8% of cases, and severe in one patient. The cumulative incidence of renal impairment at 1, 3, and 5 years was 2.6%, 14.8%, and 34.7%, respectively. Modification of the dosing interval or discontinuation of ADV was required in seven and three patients, respectively, and none of them showed a further decline in the eGFR [73]. In 271 ADV treated patients, GFR ≤60 mL/min was 38.3% by 6 years, while serum creatinine increase ≥0.5 mg/dL was 21.48% by 5 years. Renal dysfunction resolved in almost all patients after either switching therapy or reducing adefovir dose, with no difference between the two strategies (p = 0.737) [74]. On the contrary, a study including 46 HBeAg-negative patients with LAM-R treated were treated with ADV + LAM for up to 90 months found no impact on renal function when compared with a matched control group of untreated inactive hepatitis B virus carriers [75].

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, six patients (54%) had to reduce ADV dose because of CLcr decline after a median of 11 months (range: 9–42). Twenty-two months (range: 6–34) after dose adjustment, CLcr either remained stable (n = 5) or improved (n = 1) [38].

Fourteen patients were treated with long term ADV (5 monotherapy, and 9 ADV + LAM combination therapy). Renal dysfunction was diagnosed in eight patients (57.2%) ; a mild decrease in eGFR (5-20%) from the baseline was observed in four patients, a moderate decrease (20-30%) was noted in two patients, and a severe decrease (> 30%) was noted in two patients. Among these, graft rejection was verified in two patients by renal biopsy. Calcineurin inhibitors toxicity was considered to be the cause of nephrotoxicity in two patients, and the use of immunosuppressive agents was adjusted accordingly. Nephrotoxicity led to a decrease in ADV dosage in three patients (eGFR diminished to 30-50 mL/minute) and withdrawal in one patient (eGFR < 20 mL/min) without impact on virological response [39]. Renal impairment in long-term ADV users appears relatively frequent, but serious renal toxicity is rare. 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. Most of the previous reported nephrotoxic events, which were similar to those observed with ADV therapy, were in HIV infected patients [69]. There is recently presented data about TDF impact on renal function in HBV mono-infected patients [76-81]. A study evaluated the pooled results from three global randomized clinical trials including 426 patients receiving TDF over 144 weeks. There were no clinically relevant changes in renal function, with two (0.5%) patients having an increase in Cr ≥ 0.5 mg/dL from baseline and no patients with eGFR < 50 mL/min, even in high risk patients such as cirrhotics or diabetics [76]. Moreover, in a study comparing 74 patients with mild renal impairment (CrCl 50 - 80 mL/min) with 206 with normal renal function (CrCl ≥ 80 mL/min), there was no evidence of increased risk for renal complications: none of the patients had a confirmed increase in serum creatinine of ≥0.5 mg/dL after 96 weeks of therapy [77]. Among 441 patients from the Vireal cohort, 114 with baseline decreased glomerular filtration rate 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. After 48 weeks of treatment, TDF did not significantly alter renal function in patients with stages 2, 3, and 4 renal disease (76 vs. 77 mL/min, 50 vs. 49 mL/min, and 23 vs. 23 mL/min, respectively) [78]. Two RT recipients were included and had constant GFR during treatment. TDF dose adjustments were performed in 9 patients. Regarding renal disease stage, 67% were stable, 22% improved and 11% decreased renal function at the end of the study [78]. In a retrospective study, 195 patients with previous failed NUC therapy and treated with TDF monotherapy for 30±16 (6-90) months were compared with 89 asymptomatic HBsAg carriers [79]. By month 48, patients in the TDF group had a significantly greater decrease in eGFR as compared to the control group (−16±36 [−48 – +23] and −9.6±36 [−21 – +22]mL/min, respectively, p = 0.03). Only one patient required dose reduction after 15 months of therapy following an increase of Cr from 0.8 to 1.18 mg/dL [79]. In 26 LAM-R patients treated with TDF, there were no significant changes from baseline in phosphatemia and GFR after one year of treatment [80]. Despite the lack of significant GFR changes, caution must still be taken with potential proximal tubule effects. In a study of 61 patients treated with TDF, mean GFR (102±21.8 ml/min/1.73m2 (48-161)) showed no significant change compared to baseline (p=n.s.), 35 (58%) patients showed a GFR decline (median 8.1%, range 0.01% to 20.5%) and 2 had decrease of GFR to < 60 ml/min/1.73m2 after a mean treatment duration of 29 months [81]. At least one sign of proximal tubular damage appeared in 26 (42%) individuals: glucosuria without DM, increased alpha1-microglobulinuria/creatinine ratio, hypophosphatemia, reduced tubular resorption of phosphate rate and reduced tubular maximum reabsorption rate [81]. The effects of TDF on renal function were evaluated in 321 naïve patients treated for 4 years in clinical practice [82]. In this large European cohort, serum creatinine and phosphorus blood levels remained unchanged over time (0.90 mg/dl; 3.3 mg/dl) while eGFR declined from 84 to 80 ml/min. The proportion of patients with eGFR<50 and <60 ml/min (MDRD) increased from 2% to 3% and from 7% to 11% at year 4, respectively. The proportion of patients with blood phosphate below 2.3 mg/dl increased from 2% (baseline) to 5.1 % at year 4, while 1% of the patients had phosphate <2.0 throughout the study period. Due to renal events, TDF dose was adjusted in 19 (5%) patients (eGFR decline in 17; low phosphate in 2) and discontinued in additional 7 (2%) patients who were switched to ETV. Overall, renal events were reported in 26 patients (7%) [82].

In contrast to nucleotide analogues, nucleoside analogues, including ETV and LdT, did not show a significant renal toxicity [68,69]. Studies have been performed comparing ETV and TDF nephrotoxicity [83-87]. A 2-year study of patients on ETV (n = 74) and TDF ± LAM (n = 50) showed no significant changes in eGFR [83]. The proportion of patients with ≥40% reduction in eGFR from baseline was 3.92% in the TDF ± LMV group vs. 2.7% in the ETV group (p=NS). In the univariate mixed linear model, compared to control subjects at baseline, eGFR at 2 years declined in the ETV group by -7.6 ml/min (95% CI -15.8-+0.6, p=0.07) and -8.7 ml/min (CI -18.3-+1.0,p=0.08) in the TDF ± LMV group while in the control it remained stable at +7.4 ml/min (CI 0.78-14.1,p=0.03) [83]. In another real-life cohort of 212 patients were treated with TDF and 79 with ETV and its impact on renal function was evaluated [84]. After 6 and 12 months of TDF use, no significant difference was found in urea, creatinine, eGFR and PO4 (p=NS). No significant difference found in proportions of patients with eGFR <60 at baseline and after 12 months of TDF use (p=NS). After 12 months of therapy, ETV group had significantly decreased PO4 (0.96 vs. 1.06, p=0.016), increased creatinine (1.0 vs. 0.89, p<0.05) and decreased eGFR (80 vs. 89, p<0.05). Three patients (3.8%) in the ETV group had 25% increment in Cr while 1 patient (0.47%) in the TDF group had 25% reduction in eGFR after 12 months of therapy. In a community-based, retrospective cohort study of 80 patients who received TDF, alone or in a combination regimen were matched with 80 patients who received only ETV and incidences of serum creatinine (SCr) increase and eGFR were recorded [85-86]. More patients in the ETV group had increases in SCr ≥0.5 mg/dL (3 vs. 11; p = .025), whereas more patients treated with TDF had eGFR of <60 mL/min (15 vs. 6; p = .022) and at least 1 dose adjustment (13 vs. 4; p = .021). By multivariate analysis, the only significant factors associated with an increase in SCr were a history of organ transplantation (aOR, 6.740; 95% CI, 1.799-28.250; p = .005) and pre-existing renal insufficiency (aOR, 10.960; 95% CI, 2.419-48.850; p = .002) [85]. Renal function was evaluated in 197 HBV mono-infected patients from two outpatient clinics and who were categorized according to therapy: LAM (n = 36), ADV (n = 32), ETV (n = 32), TDF (n = 37), and untreated HBsAg-positive patients (n = 60) [87]. The CKD-EPI equation was used to calculate eGFR in this study and the individual change in eGFR over time was modeled with linear mixed effects models. Patients with pre-existing renal disease, Diabetes mellitus, or arterial hypertension were excluded from the analysis. The yearly predicted median individual changes in eGFR according to this model were: HBV untreated -2.05 ml/min, LAM -0.92 ml/min, ADV -1.02 ml/min, ETV -1.00 ml/min, and TDF -0.92 ml/min. A decrease of eGFR >20 ml/min from baseline confirmed by two measurements was observed in 2/60 HBV untreated patients, in 2/36 HBV lamivudine treated patients, 2/32 HBV entecavir treated patients, 0/32 HBV adefovir treated patients, and 1/37 HBV tenofovir treated patients. Patients achieving an eGFR of <60 ml/min (renal insufficiency stage 3) were infrequent and not different between HBV patient groups [87].

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 patients treated with TDF, suspected to be more nephrotoxic, were no more likely to have changes in renal function than patients treated with ETV. One study found that in ETV cohort there was evidence for a degree of deterioration in renal function, although authors reported that its clinical significance is unclear and may represent a physiological decrease in renal function in this cohort and/or reflect the potential limitations of standard biochemical measures of renal function in patients with liver disease [84]. 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 seems appropriate to monitor for adverse renal effects with serum creatinine (estimated creatinine clearance) and serum phosphate levels during ADV or TDF therapy in all HBV patients and with serum creatinine levels (estimated creatinine clearance) during NUC therapy in patients at high renal risk. The frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, in case of no worsening, in patients at low renal risk as well as every month for the first 3 months, every 3 months until the end of the first year and every 6 months thereafter, in case of no worsening, in patients at high renal risk. Closer renal monitoring is required in patients who develop creatinine clearance <60 ml/min or serum phosphate levels <2 mg/dl) [9,10,15,88].

**CONCLUSIONS**

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 preferred option for NUC naïve patients and TDF remains the agent of choice for patients with prior resistance to LAM or any other NUC. Renal transplant recipients under antiHBV therapy should be followed not only for the treatment efficacy against HBV but also with a thorough renal monitoring as well. 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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|  | **Recommended Dosage** | **Dosage Forms** |
| **Creatinine Clearance****(mL/min)** | **Lamivudine[25]** | **Lamivudine[25]** |
| >50 | 100 mg once daily | Tablets: 100 mg, Oral solution: 10 mg/mL |
| 30-49 | 100 mg first dose, then 50 mg once daily |
| 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 |
|  | **Adefovir[26]** | **Adefovir[26]** |
| >50 | 10 mg every 24 hours | Tablets: 10 mg, Oral solution: not available |
| 30-49 | 10 mg every 48 hours |
| 10-29 | 10 mg every 72 hours |
| Hemodialysis | 10 mg every 7 days following dialysis  |
|  | **Telbivudine[27]** | **Telbivudine[27]** |
| >50 | 600 mg every 24 hours | Tablets: 600 mg, Oral solution: 100mg/5ml |
| 30-49 | 600 mg every 48 hours |
| 10-29 | 600 mg every 72 hours |
| Hemodialysis | 600 mg every 96 hours following dialysis  |
|  | **Entecavir [28]** | **Entecavir in Lamivudine-Refractory [28]** | **Entecavir [28]** |
| >50 | 0.5 mg once daily  | 1 mg once daily | Tablets: 0.5 mg and 1 mg, Oral solution: 0.05 mg/mL |
| 30-49 | 0.25 mg once daily OR0.5 mg every 48 hours | 0.5 mg once daily OR1 mg every 48 hours |
| 10-29 | 0.15 mg once daily OR0.5 mg every 72 hours | 0.3 mg once daily OR1 mg every 72 hours |
| Hemodialysis | 0.05 mg once daily OR 0.5 mg every 7 days following dialysis | 0.1 mg once daily OR 1 mg every 7 days following dialysis |
|  | **Tenofovir [29]** | **Tenofovir [29]** |
| >50 | 300 mg every 24 hours | Tablets: 300 mg,Oral Powder: 40 mg per 1 g of oral powder |
| 30-49 | 300 mg every 48 hours |
| 10-29 | 300 mg every 72 to 96 hours |
| Hemodialysis | 300 mg every 7 days or after approximately 12 hours of dialysis |

**Table 1:** **Dosage Adjustment of Nucleos(t)ide Analogue for Patients with Reduced Creatinine Clearance**

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| **Category of Response** |
| Biochemical (BR) | Decrease in serum ALT to within the normal range |
| Virologic (VR) | Decrease in serum HBV DNA to undetectablelevels by PCR assays, and loss of HBeAg inpatients who were initially HBeAg positive |
| Primary non-response | Decrease in serum HBV DNA by 2 log10 IU/mLafter at least 24 weeks of therapy |
| Virologic relapse | Increase in serum HBV DNA of 1 log10 IU/mLafter discontinuation of treatment in at leasttwo determinations more than 4 weeks apart |
| Histologic (HR) | Decrease in histology activity index by at least 2points and no worsening of fibrosis scorecompared to pre-treatment liver biopsy |
| Complete (CR) | Fulfill criteria of biochemical and virologicalresponse 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 months after discontinuation of therapy |
| Sustained (SR-12) | 12 months after discontinuation of therapy |

**Table 2. Definition of Response to Nucleos(t)ide Analogue Antiviral Therapy of Chronic Hepatitis B**

|  |  |
| --- | --- |
| **Term** | **Definition** |
| Virologic breakthrough | Increase in serum HBV DNA by >1 log10 (10-fold) above nadir after achieving virologic response, during continued treatment |
| Viral rebound | Increase in serum HBV DNA to > 20,000 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  | In vitro confirmation that the mutation detected decreases susceptibility (as demonstrated by increase in inhibitoryconcentrations) to the NUC administered |

**Table 3. Definition of Terms Relating to Antiviral Resistance to Nucleos(t)ide Analogue Treatment**

Figure 1: Treatment algorithm for management of renal transplant candidates with chronic hepatitis B virus (HBV) infection.

Abbreviations; RT: renal transplantation; LRT: liver renal transplantation; NUC: nucleos(t)ide analogue; ETV: entecavir; TDF: tenofovir.