Chapter 17
Organ Transplantation in HBV-Infected Patients

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Introduction

Hepatitis B virus (HBV) infection is associated with liver-related complications that can lead to end stage liver disease (ESLD) and liver failure [1]. Liver transplantation (LT) offers the ultimate cure for patients with chronic hepatitis B (CHB) and is the only treatments available for patients with ESLD [2]. However, HBV recurrence in LT recipients (LTR) can lead to rapid liver disease progression, graft failure, and death [3]. By the 1990s, HBV was considered as a contraindication for LT due to poor outcomes, with a survival rate of only ~50 % at 5 years [4]. The landmark study by Samuel et al. in 1991 [5] showed that passive immunization with Hepatitis B immunoglobulin (HBIG) reduced the HBV recurrence rate to around 30–40 %. Since the approval and use of the first nucleos(t)ide analogue (Nuc) lamivudine (LAM), the combination of HBIG plus LAM has further reduced HBV recurrence and improved survival of HBV-related LT [6–8], and become the standard of care for prophylaxis against HBV recurrence after LT [9]. However, HBIG is expensive, inconvenient, and there is no clear consensus on the optimal dose and schedule for

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the HBIG regimen [6, 8, 10, 11]. The advent of more potent Nuc with high genetic barrier to resistance, i.e., entecavir (ETV) and tenofovir (TDF), has further reduced long-term recurrence rates [12–16]. Recent strategy has suggested the use of HBIG for only a period of time after LT, followed by long-term Nuc alone [17–19]. Till now, the consensus has not been documented.

HBV infection after non-liver organ transplantation is also a problem and was studied more in the setting of renal transplantation (RT). HBV infection is an established cause of morbidity and mortality in RT recipients (RTRs) [20–23]. Immunosuppression post-RT may affect the host's immune responses against HBV [24, 25]. Rates of HBV DNA reactivation of 50–94 % have been reported in the absence of prophylactic antiviral therapy, thereby leading to fatal liver complications [21, 22, 26, 27]. Due to poor patient and graft survivals, RT was not preferred to hemodialysis for HBsAg-positive patients with end-stage renal failure [21]. However, there is a lack of alternative therapy [like hemodialysis for end stage renal disease (ESRD)] in patients with other organ failure [28–33]. With the availability of Nuc since 1998, HBV infection is no longer a risk factor for death or graft failure in organ transplant recipients [34–36].

The advance and the current status of organ transplantation in HBV-infected patients are reviewed in this chapter.

Liver Transplantation

Clinical Course After LT

Definition of HBV Recurrence

Most studies have defined HBV recurrence as the reappearance of hepatitis B surface antigen (HBsAg) and/or HBV DNA post-transplant. Although the reappearance of HBsAg has been considered the marker of recurrent HBV infection, the reappearance of HBV DNA in serum is the most important determinant of prophylaxis failure. With newer and more potent antiviral therapies with high barriers to resistance, patients with the reappearance of HBsAg used to have undetectable HBV DNA in serum and were not associated with graft dysfunction [37–39].

Risk of HBV Recurrence

Many related factors may be responsible for HBV recurrence, including recipient host factors, donor factors and perioperative treatment (use of antiviral agents and immunosuppressants, drug resistance, viral mutations) [40]. Natural history studies from the era before the use of prophylactic therapies showed that the level of HBV DNA at the time of transplantation was the principal factor for HBV recurrence [10, 37, 41, 42]. Of the 372 European HBsAg-positive patients who underwent LT

from 1977 to 1990, the 3-year HBV recurrence rate was highest (83 %) in HBV-related cirrhosis with HBV DNA greater than 10^5 copies/ml at time of LT, intermediate (58 %) in those without detectable HBV DNA or HBeAg, lower (32 %) in those with hepatitis D virus (HDV) co-infection and lowest (17 %) fulminant HBV infection [41, 43]. Even in the current era of routine prophylactic therapies (HBIG + Nuc), HBV recurrence is most consistently associated with levels of HBV DNA before LT [10, 37, 41, 42, 44].

Among other potential factors, HBV variants with antiviral drug-resistant mutation and/or HBIG resistant mutation are the main causes of HBV reinfection [10, 39, 45, 46]. HBsAg escape mutants that harbor single or double point mutations may significantly alter the immunological characteristics of HBsAg, in which most mutations are located within the second "a" determinant loop, with an arginine replacement for glycine at amino acid 145 [47, 48]. It was shown that mutations in the HBsAg (D144E) and the polymerase (L426I/L526M/M550I) of the HBV genome may be responsible for viral breakthrough under combination antiviral prophylaxis with HBIG and LAM [49]. There are also a few studies that investigated the potential influences of precore or BCP mutants on the outcomes of LT [50, 51]. A study showed that infection with precore mutant strains predisposes a patient to early graft loss following transplantation [50]. However, this association has disappeared in the modern era of antiviral prophylaxis of ETV or TDF with or without HBIG.

Other factors identified as being of potential importance are the presence of drug-resistant HBV strains [10, 41, 52] and the recurrence of HCC, possibly due to HBV replication in HCC cells as a source for the recurrence of HBV infection [37, 53]. A recent study in 354 HBV patients with HCC who underwent LT found that patients who had HBV recurrence were 3.6 times more likely to develop HCC recurrence [54]. A study of 154 patients under HBIG + ETV therapy showed an overall HBV recurrence rate of 0.6 %, 1.6 %, and 6.2 % at 1, 2, and 4 years, respectively in which recurrent HCC was an independent risk factor (hazard ratio = 13.5, 95 % confidence interval, 2.4–74.4; $P = 0.006$) [55]. HCC at the time of LT was also a risk factor for post-LT virological rebound. The study of Fung et al. [37] showed a more than sevenfold higher risk of HBV recurrence in patients who had HCC at transplant. In a recent study using pooled data from two cohorts (HBIG + LAM in 171, and HBIG + ETV in 145 patients), predictors of HBV recurrence were Nuc used (LAM), pre-LT HCC, post-LT low anti-HBs (<100 mIU/ml), male gender, and HBsAg (+) in the explanted liver tissue [39].

Evolution of HBV Prophylaxis in LT

HBIG Monotherapy

In 1991 and 1993, Samuel et al. demonstrated that the recurrence rate of HBV after LT is significantly reduced by the intravenous administration of high-dose HBIG [5, 43]. Other studies also demonstrated significantly reduced HBV recurrence after LT

from 90 to 20–40 % by administering high doses of intravenous HBIG 10,000 IU in the anhepatic phase and in the first postoperative week, then monthly [5, 44, 56, 57]. However, HBIG administration is costly, inconvenient and a high dosage of intravenous HBIG after LT may lead to side effects [57], HCV transmission, and allergic reactions [58]. Long-term use of HBIG may also result in the development of genetic HBV mutants, which may cause the virus to become resistant to neutralization [59–62]. Titration of HBIG dose based on anti-HBs titer is an alternative to reduce the need for HBIG. Anti-HBs titer greater than 500 IU/l for the first 3 months, 100–250 IU/l between 3 and 6 months, and 100 IU/l after 6 months post LT are considered to be safe targets of HBV prophylaxis [63].

Subsequently, intramuscular (IM) HBIG has been shown to be as effective as IV HBIG [64, 65]. It can achieve adequate anti-HBs titer to a dose of about 400–2000 IU/month due to slow release. Franciosini et al. [66] noted that patients receiving low-dose IM HBIG reported significantly better health-related quality of life scores, but worse scores on side effects scales compared to patients using IV HBIG. It was also shown in some studies that subcutaneous (SC) HBIG could effectively maintain anti-HBs levels above 100 IU/l, in addition to the advantages of convenience for patients, stable anti-HBs plasma levels, lower dosages of HBIG, and fewer adverse effects [10, 67–69]. But notably, due to it's late introduction, to use intramuscular (IM) or subcutaneous (SC) HBIG for monoprophylaxis post LT is not suggested.

LAM/ADV Monotherapy

At earlier times, LAM has been shown to be safe and effective in patients awaiting LT [70–72]. A multicenter trial conducted at ten centers evaluated the use of LAM as a monotherapy in the pre- and post-liver transplant settings and found that after >12 weeks of post-transplant LAM therapy, 60 % remained HBsAg-negative, a rate comparable to that seen with long-term HBIG monotherapy [73]. Subsequent studies demonstrated that LAM monotherapy in the post-LT setting was associated with 8–32 % HBV recurrence rate at 16–24 months [74–77]. However, high drug resistance rates of 25 %, 30–40 %, and 50 % are found at 1, 4, and 6 years post-LT [73, 78–80].

Adefovir (ADV) appears to be an effective antiviral agent for LT recipients with recurrent HBV infection and LAM-resistance. However, nephrotoxicity was reported and dose adjustment is needed in patients with impaired renal function [8, 81]. In a study of 42 LTRs who developed recurrent HBV or de novo HBV infection with LAM-resistant HBV, switch to ADV achieved complete virological suppression in 27 (64.3 %) during 31 months follow-up without renal dysfunction [82]. Another study showed that ADV monotherapy prior to transplant reduced post-transplant HBV recurrence to only 9 % during a median of 35 months follow-up [83]. Furthermore, HBIG was not required in 18 patients whose pre-LT serum HBV DNA level was suppressed to <3 $\log_{10}$ IU/ml and no HBV recurrence was observed during combined LAM + ADV therapy for a median period of 22 months after LT [18].

Combination of HBIG + Nucs

High-Dose IV HBIG with LAM

The first trial of long-term HBIG combined with LAM was reported in 1998. With monthly HBIG administration plus LAM 150 mg/day, all patients survived without serum HBV DNA positivity 1 year after LT [8]. Thereafter, combination of HBIG and LAM has proved to be more effective in minimizing graft reinfection (≤10 %) and has thus become the standard of care for HBV-infected LTRs [8, 10, 84–86]. Three recent meta-analyses have clearly demonstrated that combination of HBIG and LAM is superior to LAM or HBIG alone [6, 87, 88]. In addition, there was a significant reduction in the development of YMDD (rtM204V) mutants with HBIG + LAM as compared with LAM monotherapy [88].

High-Dose HBIG with ETV vs. LAM

After availability of ETV, a case control study compared the combination of either ETV or LAM with IV HBIG at a dose of 200 IU/Kg intraoperatively and daily for 5 days post-LT followed by interval administration of 1000 IU to maintain anti-HBs titers >500 IU/l during the first 6 months and 200 IU/l thereafter. The results showed no HBV reinfection after 2 years in 26 patients using ETV, but HBV recurred in 4 % after 3 years and 6 % after 5 years in the 63 patients using LAM [13].

Low-Dose IM HBIG with Nuc

Low-dose IM HBIG (300–800 IU) has been suggested as being as effective as intravenous HBIG. A large prospective study of 233 patients receiving IM HBIG 2000 IU intraoperatively, 800 IU IM/day for the first post-LT week and 800 IU IM/month thereafter in combination with LAM reported a 6 % HBV recurrence rate during a mean follow-up of 30 months [89]. A study of 120 patients with prophylaxis using IM HBIG combined with LAM or ETV reported a HBV recurrence rate of 11.1 % in 90 patients in the LAM group but none in the ETV group [90]. Subsequent reports of ETV plus low-dose HBIG revealed that the recurrence rate of HBV was 0–3.2 % [12–16], which was lower than that reported with HBIG + LAM combination [89, 90]. A recent large cohort study of 145 patients using ETV plus low-dose, on-demand (when anti-HBs <100 IU/l) IM HBIG prophylaxis showed a HBV recurrence rate of 1.37 % during a median follow-up of 36 months, in contrast to a rate of 6.4 % (P=0.055) during a median follow-up of 77 months in 171 patients using LAM plus on-demand IM HBIG prophylaxis [39]. The experience of TDF/FTC plus low-dose HBIG therapy was relatively limited, but was associated with good safety and efficacy [12, 19, 91, 92]. A systematic review reported that antiviral prophylaxis with TDF/FTC plus HBIG combination is associated with negligible HBV recurrence post LT [93].

HIBG Discontinuation Followed by Nuc Maintained Therapy

Among the parameters of HBIG evaluated in a systematic review, a high-dosage HBIG during the first week after LT was found to be the only significant factor associated with HBV recurrence [94]. Therefore, the efficacy of HBIG discontinuation has been challenging. Table 17.1 illustrates 4 randomized trials with both study group (HBIG discontinued with Nuc maintained) and control group (HBIG continued with/without Nucs) [17, 19, 95–97]. In an earlier study in 2001, 24 patients (all HBV DNA negative pre-LT) who had received HBIG monotherapy for at least 6 months after LT were randomized into two groups; 12 were switched to LAM, 12 were maintained on HBIG. At 1.5 years post-LT, recurrence of HBV occurred in 2 of 12 in the LAM group compared to 1 of 12 in the HBIG group [95]. In the second randomized study, HBV recurrence was not observed in 29 patients who had HBV DNA levels <2.5 pg/ml spontaneously or with LAM therapy at the time of LT. They received LAM + HBIG combination therapy for the first month after LT then were randomized into either LAM alone or LAM + HBIG therapy. HBV recurrence was not observed during a follow-up of 18 months [97], but developed in 15 % of LAM + HBIG group and 11 % of LAM monotherapy group when follow-up was extended to 83 months. It seems that maintained HBIG has no benefit for the prevention of HBV recurrence [96]. In the third randomized study, LTRs after 1-year therapy with LAM + HBIG were randomized to continue LAM + HBIG or LAM + ADV. HBV recurrence rate in 2-years was 6 % (1/18) in LAM + ADV group and 0 % (0/18) in the LAM + HBIG group [17]. In a recent study, 37 patients maintained on FTC/TDF + HBIG after LT were randomized to either stop the HBIG or continue. No patient experienced HBV recurrence through a median follow-up of 72 weeks [19]. Based on these four studies, we performed a subsequent meta-analysis by using the software package RevMan 5 [98] according to the PRISMA guidelines [99], in which heterogeneity was assessed by formal statistical testing with χ^2 and I^2 [100, 101]. We found that there was no difference in HBV recurrence between the two regimens among four trials ($P = 0.37$; RD = 0.04; 95 % CI = −0.05 to 0.14) (Fig. 17.1). Nuc with continued HBIG did not achieve a favorable outcome compared to Nuc with HBIG discontinued though the HBV recurrence rate was relatively higher in the HBIG discontinued group (6/66, 9.09 %) than that in the HBIG continued group (2/58, 3.44 %).

In addition to randomized control studies, there are also 19 prospective or retrospective studies without control group [16, 18, 41, 102–117] dealing with issues on the discontinuation of HBIG with Nuc maintained (Table 17.2). Maintained Nuc after HBIG withdrawal includes LAM monotherapy in five, ETV in one, LAM + ADV combination in four, TDF + FTC combination in three, and mixed regimens in six studies, all used post LT HBIG + Nuc for a period of time (at least 4 days, mostly 6–12 months) before HBIG withdrawal (Table 17.2). Follow-up periods ranged from 9 to 57 months, with median 24 months. If we combine data from Tables 17.1 and 17.2, in patients with HBIG discontinuation and Nuc maintained, the highest HBV recurrence 8.49 % was observed in the LAM group followed by 4.42 % in the TDF + FTC group, 3.87 % in the LAM + ADV group, and 3.85 % in the ETV group

Table 17.1 Published studies of randomized trials with study (HBIG discontinued with Nucs maintained) and control groups (HBIG continued with/without Nucs) for HBV prophylaxis after liver transplantation

Authors (year) [ref.]	Study year	Patients	Follow-up (median; mo)	Antiviral agent after HBIG withdraw (no. of patients)	Antiviral agent (HBIG continued; no. of patients)	HBV recurrence (%)
Buit, 2007 [97]	1998–2007	*N*=29 (HBIG 1 month)	83	LAM (*n*=20)	LAM+HBIG (*n*=9)	3/20 (15) (LAM) 1/9 (11.1) (LAM+HBIG)
Teperman, 2013 [19]	2007–2011	*N*=37 (HBIG 6 months)	18	FTC+TDF (*n*=18)	FTC+TDF+HBIG (*n*=19)	0 (0) for both group
Naoumov, 2001 [96]	–	*N*=24 (HBIG>6 months)	13	LAM (*n*=12)	HBIG (*n*=12)	1/12 (8.3) (HBIG) 2/12 (16.6) (LAM)
Angus, 2008 [17]	2004–2006	*N*=34 (HBIG 12 months)	21.2	LAM+ADV (*n*=16)	LAM+ HBIG (*n*=18)	1/16 (6.2) (LAM+ADV) 0/18 (0) (LAM+HBIG)

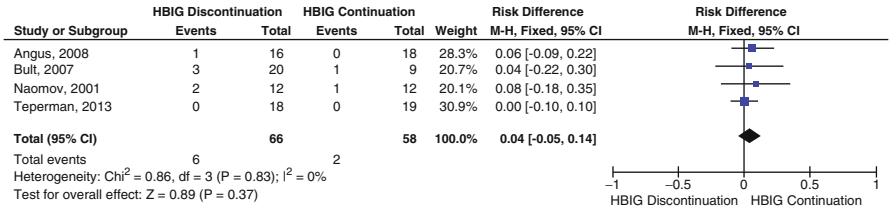


Fig. 17.1 Meta-analysis of four randomized trials with both study group (HBIG discontinued with Nucs maintained) and control group (HBIG continued with/without Nucs) of HBV prophylaxis after liver transplantation

[16–19, 41, 95, 96, 102–117]. There is no significant difference between the four groups (Fig. 17.2). Only the LAM group exhibits a borderline significance of higher rates of HBV recurrence than that of other groups.

Potent Nuc Monotherapy

ETV and TDF are the most recently introduced Nucs with both high antiviral potency and high barriers to resistance. TDF/FTC, TDF, and ETV are all safe and effective antiviral treatment in patients with decompensated liver disease and achieved undetectable HBV DNA (<400 copies/ml) at 48 weeks of treatment in 70.5, 87.8 and 72.7 % of the patients respectively [118]. In a recent study of ETV monoprophylaxis pre and post-LT, HBsAg reappeared in 18/80 patients (22.5 %) by 2 years post-LT, However, all of the patients with HBV DNA <5 $\log_{10}$ IU/ml and HBsAg <3 $\log_{10}$ IU/ml at the time of LT achieved HBsAg seroclearance ad none had genotypic antiviral resistance [38]. In a subsequent report including 362 patients, 176 (49 %), 142 (39 %), and 44 (12 %) were treated with LAM, ETV, and combination therapy (predominantly LAM + ADV) respectively at the time of transplant. The rate of HBsAg seroclearance and HBV DNA suppression to undetectable levels at 8 years was 88 and 98 %, respectively. Overall 8-year survival was not different among the three treatment groups [37]. Wadhawan et al. [119] conducted a prospective trial to evaluate Nuc with HBIG regimen in 89 patients between 2005 and 2012, in which only patients with HBV DNA levels >2000 IU/ml were given HBIG ($n = 14$). Of the remaining 75 patients not receiving HBIG, 19 patients received LAM + ADV, 42 received ETV, 12 received TDF, and 2 received ETV + TDF. At the last follow-up (median = 21 months), 66 patients cleared HBsAg with a HBV recurrence rate of 12 %, and without mortality due to HBV recurrence. Based on these, current data did not recommend LAM monotherapy for post LT prophylaxis due to inadequate potency and high resistance rates. There are now increasing number of reports of HBIG-free antiviral prophylaxis in using ETV or TDF alone or in combination. A completely HBIG-free protocol seems to be better adopted for patients who are HBV DNA negative at the time of LT [37, 38, 93].

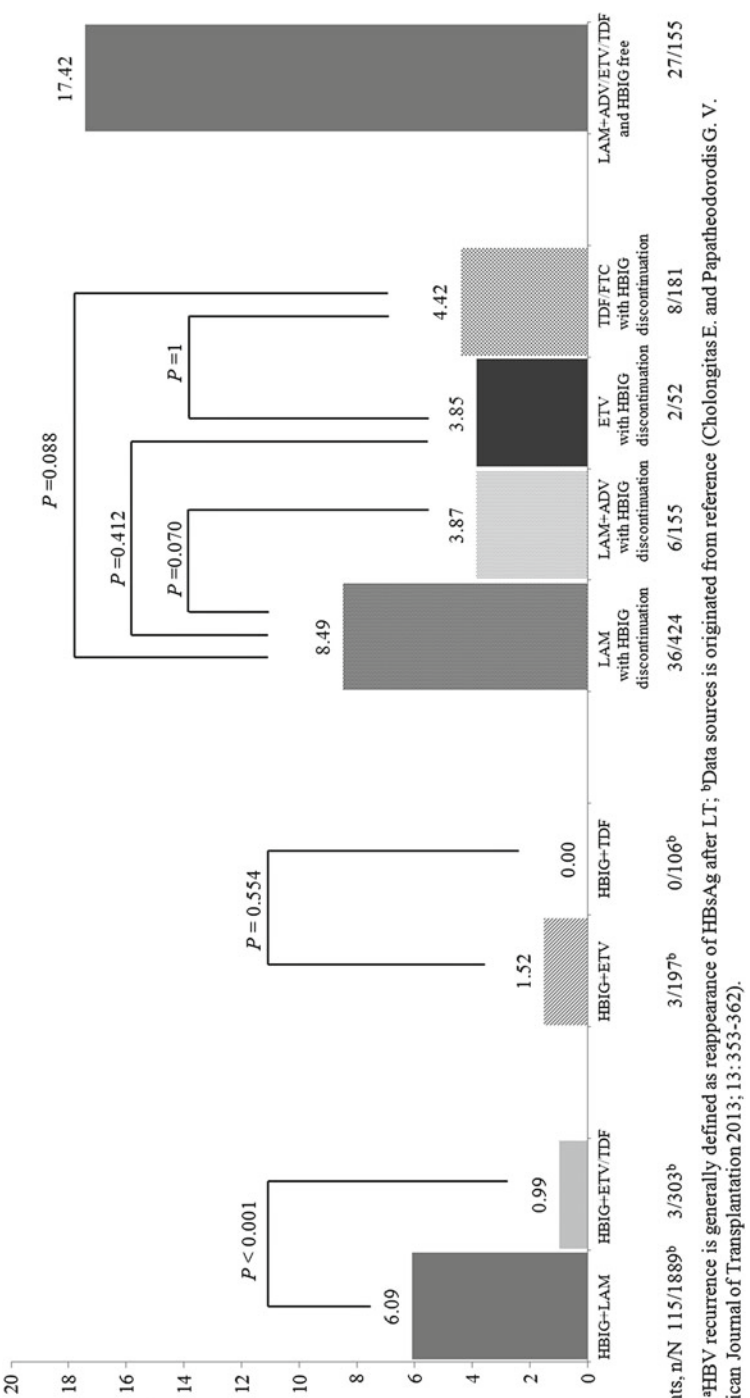
Table 17.2 Published studies on the discontinuation of HBIG with Nucs maintained for HBV prophylaxis after liver transplantation (without control group). They are listed according to the period of HBIG used

Authors, year [ref.]	Study year	Patients	Follow-up (median; months)	Antiviral agent after HBIG withdraw (no. of patients)	HBV recurrence (%)
Park, 2002 [104]	1996–2000	*N*=30 (HBIG 7 days)	9	LAM	3/30 (10.0)
Nath, 2006 [109]	2002–2005	*N*=14 (HBIG 7 days)	14.1	LAM+ADV	0/14 (0)
Gane. 2013 [18]	2003–2007	*N*=20 (HBIG 7 days)	57	LAM+ADV	0/20 (0)
Wong, 2007 [105]	1994–2005	*N*=21 (HBIG>3 months)	40	LAM	1/21 (4.8)
Ahn, 2011 [116]	2002–2007	*N*=24 (HBIG 4 days-6 months)	15.5	LAM (*n*=9) LAM+ADV (*n*=14) TDF+FTC (*n*=1)	0/9 (0) (LAM) 2/14 (14.3) (LAM+ADV) 1/1 [100] (TDF+FTC)
Neff, 2007 [110]	2004–2005	*N*=10 (HBIG 6 months)	31	LAM+ADV	0/10 (0)
Cholongatis, 2014 [118]	2010–2013	*N*=28 (HBIG 6 months)	21	ETV [11] TDF [17]	0 (0)
Shiffman, 2009 [112]	–	*N*=21 (HBIG>6 months)	10.8	TDF+FTC	1/21 (4.7)
Stravitz, 2012 [113]	1958–2009	*N*=21 (HBIG>6 months)	31.1	TDF+FTC	3/21 [14]
Wesdrop, 2013 [111]	1997–2010	*N*=17 (HBIG>6 months)	26.5	TDF+FTC	1/15 (6.7)
Cholongitas,2012 [115]	2007–2011	*N*=47 (HBIG 12 months)	24	LAM+ADV (*n*=23) LAM+TDF (*n*=5) ETV (*n*=9) TDF (*n*=10)	2/23 (8.7) (LAM+ADV) 0/5 (0) (LAM+TDF) 1/9 (11.1) (ETV) 0/10 (0) (TDF)
Yi, 2013 [16]	2007–2009	*N*=26 (HBIG 12 months)	24	ETV	1/26 (3.8)
Tanaka, 2014 [117]	2005–2011	*N*=24 (HBIG 12 months)	29.1	LAM+TDF (*n*=9) TDF (*n*=15)	0 (0)
Lu, 2008 [106]	2002–2006	*N*=122 (HBIG >12 months)	12	LAM	11/122 (9.0)
Sevmis, 2011 [107]	2001–2009	*N*=53 (HBIG>12 months)	46.5	LAM	4/53 (7.5)

(continued)

Table 17.2 (continued)

Authors, year [ref.]	Study year	Patients	Follow-up (median; months)	Antiviral agent after HBIG withdraw (no. of patients)	HBV recurrence (%)
Saab, 2011 [114]	2008–2010	*N*=61 (HBIG >12 months)	15	LAM+ADV (*n*=19) LAM+TDF (*n*=41) ETV+ADV (*n*=1)	0/19 (0) (LAM+ADV) 2/41 (4.9) (LAM+TDF) 0/1 (0) (ETV+ADV)
Dodson, 2000 [103]	1993–1997	*N*=16 (HBIG 24 months)	16.1	LAM	0/16 (0)
Lo, 2005 [108]	1999–2004	*N*=8 (HBIG >24 months)	21.1	LAM+ADV	0/8 (0)
Degertekin, 2010 [41]	2001–2007	*N*=185 (HBIG discontinued after a varying period)	42	LAM (*n*=141) ADV (*n*=16) TDF (*n*=3) ETV (*N*=5) LAM+ADV (*n*=15) LAM+TDF (*n*=3) ADV+TDF (*n*=2)	12/141 (8.5) (LAM) 0/16 (0) (ADV) 0/3 (0) (TDF) 0/5 (0) (ETV) 1/15 (6.7) (LAM+ADV) 0/3 (0) (LAM+TDF) 0/2 (0) (ADV+TDF)



Note. [a]HBV recurrence is generally defined as reappearance of HBsAg after LT; [b]Data sources is originated from reference (Cholongitas E. and Papatheodoridis G. V. American Journal of Transplantation 2013; 13: 353-362).

Fig. 17.2 Risk of HBV recurrence after liver transplantation according to various types of prophylaxis in published studies

Overall Comparison

HBIG Plus Potent Nuc Promise Lowest HBV Recurrence Rates

A systematic review [93] has shown that HBV recurrence was observed to be significantly higher in patients who received Nuc monotherapy or HBIG monotherapy than that of HBIG plus Nuc combination therapies, if the definition of HBV recurrence was based on HBsAg positivity (26 % vs. 5.9 %, $P<0.0001$). In our analysis, HBV recurrence occurred in 27 (17.42 %) of 155 patients with either LAM + ADV, ETV or TDF HBIG-free monotherapy, which was significantly higher than that of HBIG contained regimens [38, 119] (Fig. 17.2). However, if the definition of HBV recurrence was based on HBV DNA detectability, the HBV recurrence rate was similar between HBIG + Nuc combination and potent Nuc monotherapy (0.9 % vs. 3.8 %, $P=0.11$), especially for monotherapy with ETV or TDF [93]. In addition, unlike patients receiving HBIG or Nuc monotherapy, high preoperative viral load seems to be no longer associated with an increased post-LT HBV reinfection in patients given HBIG plus Nuc [39, 120, 121]. Furthermore, LAM + HBIG developed HBV recurrence significantly more frequently when compared to patients under ETV/TDF + HBIG combination (6.1 % vs. 1.0 %, $P<0.001$) [93]. ETV and TDF had similar antiviral efficacy when they combined with HBIG (1.5 % vs. 0 %, respectively, $P>0.05$) [93] (Fig. 17.2). Therefore, the strategy of ETV/TDF + HBIG may still be recommended for patients who are HBV DNA positive at the time of LT.

HIBG Discontinuation Leads to a Higher Rate of HBsAg Reappearance

In considering the fact that waiting list patients are more likely to undergo LT with undetectable HBV DNA, a recent strategy has been to use HBIG for only a finite period of time after LT, followed by long-term Nuc monotherapy. With the encouraging results of previous ETV/TDF + HBIG studies, the experience is increasing. Although the preliminary results of LAM maintained after HBIG withdrawal were good [97], longer follow-up showed that 14 % of patients eventually experienced the recurrence of HBV [96]. Theoretically, ETV and TDF may allow a safer discontinuation of HBIG than LAM due to high potency and very low resistance. In the analysis from Tables 17.1 and 17.2 and Fig. 17.2, LAM maintained group exhibits the highest HBV recurrence (8.49 %) following HBIG discontinuation, but LAM + ADV exhibited a similar HBV recurrence to that of ETV/TDF + FTC following HBIG discontinuation (3.87 % in LAM + ADV; 3.85 % in ETV; 4.42 % in TDF/FTC) (Fig. 17.2). In addition, ETV/TDF + FTC after HBIG discontinuation seems to be slightly inferior to ETV/TDF + FTC with maintained HBIG (4.42 % vs. 0 % in TDF/FTC regimen). But ETV/TDF + FTC after HBIG discontinuation is still superior to ETV/TDF + FTC monoprophylaxis in totally HBIG free regimen ($P<0.05$) (Fig. 17.2). However, there should be some bias in the interpretation of HBV recurrence, because the dose and duration of these studies were highly variable and the data numbers were relatively limited. Nevertheless, HBIG discontinuation under

LAM + ADV, ETV or TDF/FTC therapy may lead to a higher rate of HBsAg reappearance, although with low HBV DNA detectability, than when HBIG is continued long term. Larger studies with longer follow-up are needed for definitive conclusions.

Total Withdrawal of Prophylaxis

Withdrawal of all antiviral prophylaxis with no maintenance HBIG or Nuc therapy can be considered in patients whose intrahepatic HBV DNA, and cccDNA are controlled below the positive titers. A study [122] included 30 patients who were transplanted 64–195 months earlier and were HBsAg-positive, HBeAg and HBV-DNA negative at LT. After verification of no detectable intrahepatic total HBV DNA and ccc-DNA by liver biopsy, all patients underwent HBIG withdrawal and continued LAM with monthly HBsAg and HBV-DNA monitoring and sequential liver biopsies. Thereafter, those with confirmed intrahepatic total and ccc-DNA undetectability 24 weeks after stopping HBIG also underwent LAM withdrawal and were followed-up without prophylaxis. Five of these 30 became HBsAg-positive during a median follow-up of 28.7 months (range 22–42) after LAM withdrawal, but none of these patients experienced clinically relevant events. Of the patients with HBsAg reappearance, one remained HBsAg-positive with detectable HBV-DNA and was successfully treated with TDF. HBsAg-positivity in the remaining patients was transient and followed by anti-HBs seroconversion. They conclude that patients with undetectable HBV viremia at LT and no evidence of intrahepatic total and cccDNA may safely undergo the cautious weaning of prophylaxis. In such a strategy, LAM is cheap and the cost effectiveness on the management of reactivated HBV may be high.

Patient and Graft Survival

It was reported that a high reinfection rate of HBV may accelerate the progression of disease, which resulted in a 5-year survival rate of less than 50 % [3, 123, 124]. The availability and advances in the prophylactic therapies have changed such outcomes of LTRs. In a retrospective study of HBV-infected adults undergoing primary LT in the USA between 1987 and 2002, the 1-year survival probability significantly improved from 71 % in year 1987–1991 to 87 % in year 1997–2002, and the corresponding 5-year survival rate increased from 53 to 76 % ($P < 0.01$) [4]. A large study in 5912 HBV-related LT in Europe over 20 years (1988–2010) showed that the patient and graft survival at 1 and 3 years before 1995 was significantly lower (73%, 65 % and 69 %, 60 %, respectively) when compared with year 1996–2000 (86 %, 81 % and 83 %, 75 %, respectively; each $P < 0.001$), year 2001–2005 (88 %, 83 % and 84 %, 79 %, respectively; each $P < 0.001$), and year 2006–2010 (86 %, 81 % and 83 %, 77 %, respectively; each $P < 0.001$) [125]. This incremental improvement in survival over time reflects the influence of the newer Nuc of ETV and TDF.

After prophylaxis with post-LT HBIG + Nuc, patients' survival continued to improve as 90 % 1-year patient survival was reported in 2007 [126], and 1, 3, 5, and 10 years survival of 93.9, 90.0, 86.9, and 84.1 %, respectively, in 2012 [127]. Even with a totally HBIG-free regimen, patient survival in LTRs could reach 95, 88, and 83 % at 1, 5, and 8 years under potent Nuc prophylaxis [37]. The impact of HBV recurrence on the survival after LT is no longer a significant problem.

Liver Graft from HBsAg-Positive or Anti-HBc-Positive Donor

Regarding donor factors, HBsAg-positive liver grafts can be transplanted to patients with HBV-related diseases [128–130]. Given the shortage of donors, the use of HBV positive grafts in patients with HBV-unrelated diseases could expand the donor pool. A recent study in 42 HBsAg-negative patients using HBsAg-positive liver grafts showed no differences in complications and the patient and graft survivals were comparable to those receiving HBsAg-negative grafts. However, HBsAg persisted after transplant in all patients that received HBsAg-positive grafts though no HBV flare-ups were observed under Nuc therapy with/without HBIG combination [131]. Another study [130] reviewed the outcome of 92 LT using allografts from HBsAg-positive donors in the USA (1990–2009). Allograft and patient survival were comparable between the HBsAg-positive and HBsAg-negative ($n = 82108$) allografts. Utilization of HBsAg-positive liver grafts seems not to increase postoperative morbidity and mortality in the LTR. However, there remains concern of the use of HBsAg-positive live donors, because of the risk of postoperative reactivation and possible liver failure in the donors.

The use of anti-HBc-positive liver grafts is another solution to the current deceased donor shortage. However, the major concern of transplanting such grafts is the transmission of de novo HBV infection to non-HBV recipients. A systematic review [132] including 13 studies showed a 2.7 % incidence of de novo HBV infection during a median period of 25.4 months in patients receiving LAM monotherapy and 3.6 % in patients receiving HBIG + LAM combination therapy during a median period of 31.1 months. Another systematic review [133] including 39 studies showed recurrent HBV infection in 11 % of HBsAg-positive LTRs who received anti-HBc-positive grafts, while survival was similar to HBsAg-positive recipients of anti-HBc-negative grafts. Furthermore, if LTRs did not receive any anti-HBV prophylaxis, de novo HBV infection developed in 47.8 % of 186 HBV naïve recipients, significantly higher than 15.2 % of 138 recipients with serological markers of past HBV infection ($P < 0.001$) or 9.7 % (3/31) of recipients with successful pre-LT vaccination ($P < 0.001$) [134–138]. A study showed that LTRs maintained on ADV therapy had a numerically higher rate (15 %, 5 of 33) of de novo HBV infection than patients maintained on LAM (8 %, 5 of 62) [139]. LAM may be the most cost-effective option for prophylaxis of de novo HBV infection from anti-HBc-positive liver grafts, when compared with newer antivirals (ETV or TDF) [140]. HBIG seems to be unnecessary either as monotherapy or in combination with LAM.

Vaccination Before and After Liver Transplantation

The active immunization of post-LT recipients with HBV vaccine has been tried. Earlier studies reported a successful response to HBV vaccination after LT [141, 142]. However, most studies of post-LT HBV vaccination were of low response rates [143–145]. Patients who were not chronic HBV carriers used to respond well to vaccination. In contrast, the effect of vaccination was disappointing in patients with liver cirrhosis due to immune tolerance [146, 147]. In addition, donors from their spouses with high anti-HBs titers before donation may respond well to vaccine. They undergo adoptive immune transfer from the donor [148, 149]. A study has shown that a high anti-HBs titer (>1000 IU/l) in donors is essential for protective adoptive transfer [150]. Pre-LT HBV vaccination for candidate living donors may facilitate improved post-LT vaccine responses in recipients with liver cirrhosis. LAM or HBIG prophylaxis after LT may be also associated with recurrence due to escape mutants in which second generation recombinant HBV vaccine is not effective [151]. Third-generation recombinant pre-S containing vaccine Sci-B-Vac™ is effective in about 50 % in prevention HBV recurrence due to escape mutants [152].

Notably, considering the extremely high rates of de novo HBV infection after LT in HBV naïve recipients [133] and the successful prevention of de novo HBV infection by pre-LT vaccination [134–138], HBV vaccination should be offered to all naïve HBV patients pre-LT to minimize the need for post-transplant Nuc prophylaxis. Vaccination post-LT may be also tried to enable withdrawal of Nuc prophylaxis if mounting a protective anti-HBs response. However, HBV vaccination alone (without any Nuc) post-LT has been reported to be ineffective in preventing de novo HBV infection [133].

Renal Transplantation

Prevalence of HBV Infection in Renal Transplant Recipients

The prevalence of HBV infection in renal transplant recipients (RTRs) varies between countries, as shown in Table 17.3. With the availability of HBV vaccine in 1980s, the prevalence has been decreasing over time [22, 58, 153, 154]. It decreased from 24.2 % before 1982 to 9.1 % after 1982 ($P<0.001$) in a study [22], and from 6.2 % in 1994 to 2.3 % in 2006 in another study [153]. In countries where hepatitis B is endemic, the prevalence rates are much higher [23, 35, 155–157]. In a 2009 Taiwan study [156], the prevalence of HBV infection in RTRs was 9.2 % (51/554), which is lower than what was reported previously from Taiwan in 2001 (12.9 %, 62/477) and 1994 (20.9 %, 14/67) [23, 157]. The decreasing prevalence of HBV infection may also be attributed to the use of EPO for anemia that consequently decreased the need for blood transfusions during the pre-transplantation period.

Table 17.3 Prevalence rates of HBsAg positivity in renal transplant recipients

Authors, year [ref.]	Study year	Country of origin	HbsAg rate % (no. of patients)
Mathurin, 1999 [22]	1972–1996	France	15.3 (128/834)
Aroldi, 2005 [135]	1972–1989	Italy	14.2 (77/541)
Hu, 1994 [138]	1988–1992	Taiwan	20.9 (14/67)
Lee, 2001 [23]	1984–1999	Taiwan	12.9 (62/477)
Tsai, 2009 [137]	1988–2006	Taiwan	9.2 (51/554)
Santos, 2009 [133]	1992–2006	Portugal	3 (37/1224)
Morales, 2004 [134]	1990–1998	Spain	2.2 (76/3365)
Chan, 2002 [35]	1983–2000	Hong Kong	13.2 (67/509)
Wong, 2001 [136]		Hong Kong	15 (39/265)

Natural History and Outcome of RTRs with HBV Infection

Factors Affecting Progression in HBV-Related Disease After RT

In chronic HBV-infected patients, viral (viral load, genotype, and genomic mutations) host (gender, age, and immune status) and external factors (coinfection with hepatotropic viruses, immunosuppressive therapies, and heavy alcohol consumption) may contribute to the progression of liver disease [1]. Immunosuppression post-RT may affect the host's immune responses against HBV in RTRs [24, 25]. Persistent viral replication and reappearance of HBeAg was observed in 50 % and 30 %, respectively, after RT in 151 HBsAg-positive RTRs [158]. A longitudinal study in 51 HBsAg-positive RTRs showed that 13 (25.5 %) developed cirrhosis (LC) during 57 months follow-up after RT. The study further showed that HBV DNA levels at baseline could not predict LC development while persistent elevation of serum HBV DNA $\geqq 10^5$ copies/ml after RT was a significant risk factor for the development of LC [156]. In contrast, a study in 944 RTRs with HBV infection showed that high pre-RT HBV DNA level $>5 \times 10^4$ IU/ml was a significant predictor ($P=0.007$) for HBV reactivation post-RT [159].

Precore and core promoter mutations are significantly associated with advanced liver disease during the natural course of chronic HBV infection [160]. Similarly, a study with serial HBV DNA sequencing in nine RTRs showed that seven with persistent or increasing amounts of the HBV core gene deletion mutants developed LC, and five died of ESLD [161]. The other study showed that development of T1762/A7164 mutants predicted an increase in HBV DNA, which was associated with eventual development of LC after RT [156]. Another study indicated that in HBV RTRs infected with core promoter mutants, the additional appearance of deletions in the C gene and/or the pre-S region was accompanied by development of LC and ESLD [162].

Histological Progression

The impact of RT on the natural history of HBV has been controversial. A study in 26 HBsAg-positive and 42 HBsAg-negative RTRs showed that HBsAg-positive patients had more severe histological findings, namely chronic persistent hepatitis (CPH) in 38 %, chronic active hepatitis (CAH) in another 38 % and LC in 42 %, in contrast to 17 % ($P=0.08$), 14 % ($P=0.04$) and 19 % ($P=0.07$), respectively, in HBsAg-negative RTRs. During a mean follow-up of 82 ± 58 months, 54 % of HBsAg-positive patients died from liver failure, compared with 12 % of the HBsAg-negative group ($P=0.002$) [163]. This study confirms that HBsAg-positive RTRs had more liver-related complications than HBsAg-negative RTRs.

A prospective study in 20 HBsAg-positive RTRs with serial biopsies during a mean follow-up of 83 months showed that 82 % of RTRs developed CAH or LC. The outcome was much worse than that of ten HBsAg-positive patients who were treated by hemodialysis. They therefore concluded that RT might be inadvisable for HBsAg-positive patients with end stage renal failure [164]. Another large single center study with 310 follow-up liver biopsies in 131 HBsAg-positive RTRs showed that histological deterioration was observed in 85.3 %, with LC development in 28 % and CAH in 42 %, and only 6 % showed a normal liver biopsy during a mean interval of 66 months [158].

Development of Hepatocellular Carcinoma (HCC)

As liver disease may progress in HBV-infected RTRs, HCC may also develop. A nationwide large scale study in 3826 RTRs in Taiwan from 1997 to 2006 showed a higher incidence of HCC in HBV-RTRs than that of non-HBV RTRs, during a mean follow-up period of 7.4 years, despite the availability of anti-HBV drug therapy [165]. The incidence of HCC was significantly greater in the HBV group at years 1 (7.84 vs. 0.70 per 100 person-years), 3 (2.82 vs. 0.26 per 100 person-years), and 5 (1.86 vs. 0.17 per 100 person-years) [165]. Another study reported a 10-year HCC incidence of 4.2 % in HBV-infected RTRs with post-transplant LAM therapy in contrast to 34 % ($P=0.008$) in HBsAg-positive RTRs who did not receive any antiviral therapy [166]. Notably, the histological progression was all reported before the era of antiviral therapies.

Anti-HBV Therapy for RTRs

The efficacy of currently available antiviral therapy options in RTRs with HBV infection is presented in Table 17.4. In general, interferon (IFN) based therapy is not recommended for RTRs. Previous studies reported an increase in acute allograft rejection, immne-mediated renal allograft injury, and graft loss following IFN therapy [167–170].

Table 17.4 Characteristics of antiviral agents for HBV therapy in patients of renal transplant recipients

Antiviral agent	Approved therapy (year)	Consideration in RTRs of HBV [Ref.]
LAM	1998	• Approved worldwide for the treatment of chronic hepatitis B both in organ transplant patients, with evidence of meta-analysis (high rate of drug resistance) [35, 74, 171–183]
ADV	2002	• Good evidence of treatment in LAM resistant RVRs • Potential renal toxicity for RTRs [184–186]
ETV	2005	• Good effect but relatively limited data in RTRs • Preferred choice for first line treatment HBV reactivation of RTRs • No nephrotoxicity [183, 187, 188, 192, 196–198]
LdT	2006	• Lack of evidence for RTRs • May be considered combination therapy in patients of renal function impairment who need ADV or TDF treatment [196–201]
TDF	2008	• Rare evidence for RTRs • Reported renal toxicity in HIV patients [189, 190, 194, 195]

Lamivudine

It has been approved worldwide for the treatment of chronic hepatitis B in organ transplant patients [35, 74, 171–183]. A meta-analysis including 181 RTRs in 14 clinical prospective cohort studies showed that LAM therapy resulted in a mean overall HBV DNA clearance in 91 % and HBeAg loss in 27 % but LAM resistance was reported in 18 %. The increased duration of LAM therapy was directly correlated with the frequency of HBeAg loss ($r=0.51$, $P=0.039$) and LAM resistance ($r=0.620$, $P=0.019$).

Adefovir Dipivoxil

A retrospective study showed that ADV add on LAM therapy was superior to ADV monotherapy in achieving undetectable HBV DNA at month 24 (44.4 vs. 20 %) in RTRs with LAM resistance, but 4 (29 %) of the 14 RTRs developed moderate to severe impaired renal function [184]. Another study showed that both serum creatinine and 24-h proteinuria increased significantly during 2-year ADV therapy in 11 HBV-infected patients with LAM resistance [185]. In contrast, no significant renal function impairment has been observed during long-term ADV plus LAM combination therapy in RTRs with LAM resistance [186]. However, with the availability of ETV and TDF, ADV may no longer be used to treat HBV in patients with renal impairment or post RT

Entecavir and Tenofovir

More recent study on ETV monotherapy in 27 Nuc-naïve or LAM experienced HBV-infected RTRs showed undetectable HBV DNA in 96 % at month 12 and 100 % at months 24 of therapy without viral resistance [187]. Studies also show that ETV is more effective than LAM in reducing HBV DNA levels in RTRs [183, 187, 188]. The experience of TDF for RTRs was very limited, only described in sporadic case reports [189, 190].

Selection of Antiviral Therapy

Given the drug potency, safety, and resistance issues during long-term therapy, LAM, ADV, and telbivudine (LdT) are no longer recommended for patients with organ transplantation [58, 183, 191–194]. Instead, potent Nuc with low resistance should be used for RTRs. Since long-term use of TDF in HIV patients has been associated with possible renal toxicity, as well as metabolic bone disease and osteomalacia [194, 195], it has been suggested that ETV may be preferred over TDF in RT population because no nephrotoxicity has been reported in chronic hepatitis or cirrhotic populations [187, 192, 196–198]. TDF adapted to creatinine clearance could be a safe alternative in RTRs with drug resistance [189]. If renal allograft dysfunction is in progress, the inception of LdT, in theory, could potentially lead to renal function improvement. This is attributed to LdT having exhibited a better eGFR evolution among HBV patients during long-term antiviral therapy [196–199]. LdT is also associated with improvement of renal function in liver transplant setting [200, 201] who are considered at high risk for renal dysfunction due to the concomitant use of the nephrotoxic calcineurin inhibitors (CNIs) [202].

Timing and Duration for Antiviral Therapy

At present, the general consensus is that Nuc therapy should be commenced pre RT in those with active CHB and start at time of transplant in those without CHB as the majority of patients will have increase in HBV DNA under immunosuppression [193]. Actually, there are two principal approaches to preventing HBV reactivation after RT: prophylactic and preemptive. A study showed that preemptive LAM therapy improved the survival of HBV-infected RTRs [35], while others showed that prophylactic LAM treatment might provide benefits in RTRs [177, 182], but salvage treatment after hepatic dysfunction during HBV recurrence was less effective [180].

The duration of anti-HBV therapy in RTR should also be considered. In the era of LAM, prolonged therapy is associated with drug resistance [183, 203], while withdrawal of LAM may be adversely associated with a high risk of relapse and liver failure. A recent small study showed a high rate (75 %, 9/12) of virological relapse (defined as HBV DNA >2000 IU/ml) during a median follow-up of 65 weeks (range 8–194 weeks) in patients who had completed 2-year LAM treatment and

discontinued therapy after demonstration of undetectable HBV DNA at two occasions 6-month apart [183]. However, another study in 12 low risk RTRs (more than 9 months therapy, HBV DNA and HBeAg-negative, stable immunosuppression) showed that five (41.7 %) of them achieved successful Nuc withdrawal, with two (16.7 %) patients maintaining undetectable serum HBV DNA for more than 18 months after cessation of LAM therapy [35]. It was also reported that no liver related mortality was recorded in 20 HBsAg-positive kidney or heart transplant recipients after LAM treatment was discontinued [204]. Recent study also reported the successful withdrawal of antiviral agents in six of 14 HBV-RTRs who met the following criteria: no cirrhosis; normal liver biochemistry; negative HBeAg; no viral resistance; antiviral therapy >9 months; maintenance dosage of immunosuppressant for >3 months; and no acute rejection during recent 6 months. Four (66.7 %) of these six patients successfully withdrew Nuc and remained HBV DNA negative for a median period of 60.5 months [205]. Taken together, the therapeutic strategy is complex and the results inconsistent, making it difficult to reach a conclusive recommendation. In high risk patients with high levels of HBV DNA at baseline, or those who are maintained with a high dose of immunosuppressant, long-term therapy may be needed [192, 193].

Patient and Graft Survival After Renal Transplantation

The impact of HBV infection in the survival of RTRs has also been debated and remains controversial. Some studies showed no significant difference in 5-year survival between HBsAg-positive and negative RTRs [206, 207]. Other larger and longer studies showed negative impact of HBV infection on patient and graft survival [21–23, 36, 208]. Lee and colleagues [23] reported that the 10 year patient and graft survival was significantly higher in the HBV-negative RTRs (82.8 and 74.2 % respectively) than in the HBV-infected RTRs (51.4 and 44 % respectively). Mathurin and colleagues [22] further showed that the 10-year survivals of HBV-infected patients (55 ± 6 %) and HCV-infected patients (65 ± 5 %) were significantly lower than that of patients without HBV or HCV infection (80 ± 3 %, $P < .001$). The most important predictor of outcome following RT in HBsAg-positive RTR is the presence of cirrhosis prior to transplant. A meta-analysis including 6050 RTRs indicated clearly that serum HBsAg was an independent risk factor for death (relative risk: 2.49, $P < 0.0001$) and allograft loss (relative risk of 1.44, 95 % CI of 1.02–2.04) after RT [21]. However, most of these studies were conducted in the era before oral anti-HBV therapy was available. A guideline has suggested that the best predictor for liver mortality following renal transplantation in an HBsAg-positive recipient is with cirrhosis at the time of transplant, and liver biopsy should be considered in all potential HBsAg-positive renal transplant candidates. Established cirrhosis with active viral infection should be considered a relative contraindication to RT [209].

The availability of LAM in 1998 marked the new era of oral therapy. A study from Hong Kong showed that the survival of HBsAg-positive RTRs who received preemptive LAM treatment (transplanted after 1996) was similar to that of

HBsAg-negative controls, whereas HBsAg-positive RTRs who did not receive LAM treatment (transplanted before 1996) had significantly increased liver related mortality (relative risk 68, 95 % CI, 8.7–533.2) and lower survival (relative risk, 9.4, $P<0.001$) [35]. A large study in RTRs in the USA from 2001 to 2007 also reported that HBV infection was no longer a risk factor for death or kidney failure, although 5-year cumulative incidence of hepatic failure was higher in 1346 HBV-RTRs (1.3 % vs. 0.2 %; $P<0.001$), compared with 74,355 HBV-negative RTRs [34]. Notably, a large retrospective study showed that the 10 year patient and graft survival rates in 66 HBsAg-positive RTRs were significantly lower than those in 2054 non-HBV RTRs (64.4/36.6 % vs. 88.2/70.5 %, respectively, $P<0.0001$). In contrast, patients with LAM therapy had significant improvement in both 10 year patient and graft survivals, as compared to HBV RTRs who did not take LAM (85.3/59.2 % vs. 49.9/22.7 %, respectively, $P<0.0001$) [36]. A nationwide large-scale study of 3826 RTRs in Taiwan from 1997 to 2006 also reported that there were no differences between the HBV and non-HBV groups in patient or graft survival rates during a mean period of 7.4 years follow-up [165]. A more recent study indicated that patient and graft survival rates of LAM prophylactic HBV-RTRs were significantly higher than those of historical control (never LAM treated HBV-RTRs) ($P=0.001$ and 0.017, respectively) from 2000–2009 [166].

HBsAg-Positive Renal Transplant Donors

Kidneys from HBsAg-positive donors were previously not acceptable for RT, because of the potential risk of HBV transmission to recipients. Obviously, the extremely high prevalence of HBsAg in Asian populations would limit the donor pool. In some situations, it is acceptable for renal grafts from HBsAg-positive donors to HBsAg-positive or HBsAg-negative recipients with long-term Nuc administration with or without HBIG [210–213]. One study compared 14 anti-HBs-positive patients who received kidneys from HBsAg-positive donors and 27 HBsAg-positive patients who received kidneys from HBsAg-negative donors, and found that the ten year patient survival (92.8 % vs. 62.5 %, $P=0.14$) was higher but not significantly different [214]. There are also reports on LAM combined with HBIG in anti-HBs-positive recipients who received grafts from HBsAg-positive donors [213, 215]. A prospective non-randomized controlled study in 373 HBsAg-positive RTRs who received a kidney from either HBsAg-positive donor ($n=65$) or HBsAg-negative donor ($n=308$) using a standardized immunosuppressive and antiviral regimen (400 U HBIG once for HBsAg-negative graft recipients and twice for HBsAg-positive graft recipient, 400 U HBIG weekly for 3 months and LAM 100 mg daily for 6 months for recipients with HBV DNA-positive grafts) showed no significant differences in liver injury and patient survival among these 2 groups of RTRs [213]. A latest study from Thailand used the propensity score matching technique to compare outcomes of 43 HBsAg-negative recipients with anti-HBs titer above 100 mIU/ml (by natural or vaccination) who received RT from HBsAg-positive donors versus 86 HBsAg-negative donors, and found no significant difference in

graft and patient survival during a median follow-up duration of 58.2 months and no HBV-infective markers were detected in the HBsAg-positive donor group [216]. Notably, most of these reports regarding the safety of HBsAg-positive renal donors to HBsAg-negative recipients were all from Asia where HBV infection is highly endemic. Therefore, considering the remarkable impact of renal transplantation on patients' survival and life quality as well as recent progress in anti-HBV therapy, the benefit of renal graft absolutely overweighs the risk of HBV transmission, which was also shown in liver transplant recipients [129, 130].

Anti-HBc-Positive Renal Transplant Donors

The exclusion of anti-HBc-positive renal donors would limit the donor pool because of the extremely high prevalence of natural immunity from childhood HBV exposure in Asian populations. However, it was shown that the de novo HBV infection rate from anti-HBc-positive kidney and heart allografts was significantly lower than that from liver allografts [217]. In a systematic review of 1385 anti-HBc-seropositive renal donors, seroconversion of anti-HBc, anti-HBs or both occurs in 3 % of RTRs, and only 0.28 % of the recipients develop HBsAg seroconversion. Furthermore, there was no symptomatic hepatitis, higher mortality, or shorter renal graft survival among these patients [218]. Since there was a very low risk of seroconversion, renal grafts from anti-HBc-positive donors is not contraindicated [219, 220]. However, monitoring of serum HBV markers is still required after RT. Nuc therapy initiation is indicated only when there is seroconversion of HBsAg or an increase in viral load, and may be interrupted after immunosuppression is reduced and complete viral clearance has been achieved [221]. Pre-transplant immunization may be helpful to further reduce the risk of HBV transmission [210, 222].

Comments on HBV-Positive Renal Transplant Donors

Finally, it is important to emphasize that use of either HBsAg-positive or anti-HBc-positive donors in RT is a completely different scenario and risk profile than the risks in LT. In RT, anti-HBc-positive kidneys have never been an issue whilst HBsAg-positive kidneys can be safely used provided the recipient has protective immunity (natural or post-vaccination) or receives antiviral prophylaxis following transplantation [129].

Renal Recipients with Markers of Past HBV Infection

Reactivation of HBV infection can also occur at a rate of 0.9–5 %, during a period ranging from 8 weeks to 15 years in HBsAg-negative but anti-HBs- and anti-HBc-positive RTRs [25, 223–228]. It may sometimes be difficult to distinguish these

from patients with de novo infection by receiving anti-HBc-positive renal graft. It is indicated that the odds ratio for HBV reactivation in patients without anti-HBs antibodies at transplantation compared to those with anti-HBs antibodies was 26 (95 % CI [2.8–240.5], $P=0.0012$) [227]. Notably, the 1-, 3-, 5-, and 10-year patient survival was 86.7, 79.4, 72.2, and 65.0 % respectively in the de novo HBV group, and was 96.1, 93.8, 91.5, and 84.5 % respectively in the non-HBV reactivation group (log-rank 4.12, $P=0.042$) [228]. However, since there are low rates of de novo HBV infection, routine antiviral prophylaxis in this group cannot be recommended. Suggestions have advocated monitoring of HBsAg or HBV DNA and institution of preemptive antiviral therapy if HBV DNA progressively rises [192].

Organ Transplantation Other Than LT and RT

Besides RT, there is less data available for other non-liver organ transplantation [229, 230]. HBV reactivation after heart transplantations was common but usually well controlled with LAM treatment. HBsAg-positive donor hearts were safely transplanted into anti-HBs-positive recipients; Therefore, HBV carrier status should not contraindicate heart transplantation [230]. It is also reasonable to consider recommendations similar to that for the RT setting [28–33]. Among these, bone marrow transplantation (BMT) is the most serious one that should be briefly addressed. Immunosuppression in BMT can result in reactivation not only among HBV patients, but also in those immune to HBV. Among patients with resolved hepatitis B before BMT, the anti-HBs titer may decline and serum HBV DNA may become detectable [231]. Chemotherapy which was used before BMT may further reactivate HBV infection. An earlier study reported 100 Hong Kong patients undergoing chemotherapy for lymphoma and found that the development of HBV-related hepatitis in 13 (48 %) of 27 HBsAg-positive patients; 2 (3.9 %) of 51 HBsAg-negative, anti-HBc-positive patients; and none (0 %) of 22 HBsAg-negative, anti-HBc-negative patients [232]. A study of 137 consecutive patients (23 HBsAg-positive, 37 anti-HBs-positive, and 77 negative for HBV) who underwent hematopoietic cell transplantation (HCT) showed that hepatitis due to HBV reactivation was more common in HBsAg-positive patients than in HBsAg-negative patients (hazard ratio, 33.3; $P<0.0001$). Furthermore, HBsAg-positive patients with detectable HBV DNA before HCT had a significantly higher risk of hepatitis flare than HBsAg-positive patients without detectable HBV DNA (adjusted hazard ratio, 9.35; $P=0.012$) [233]. It has also been reported that adoptive transfer of immunity against HBV leading to clearance of HBV infection was found in patients undergoing BMT in which the donors had recovered from prior HBV infection or had been actively immunized against hepatitis B [233, 234]. Overall, prophylactic antiviral therapy is recommended for all HBsAg-positive patients undergoing BMT regardless of HBV DNA status, and should be continued for at least 6 months or longer according to baseline serum HBV DNA levels [235–238]. Finally, transplanting avascular organs such as the cornea carries very low risk of HBV transmission, even from HBsAg-positive donors [239–241]. Antiviral prophylaxis is not recommended for this transplant setting.

Summary and Conclusion

Organ transplantation in the HBsAg-positive patient is effective and life saving, but the prevention or management of HBV recurrence and/or reactivation has been a challenge. For LTRs, high genetic barrier Nuc plus HBIG is still the standard of care to prevent HBV recurrence post LT. HBIG discontinuation after a period of time after LT seems to be safe, but might lead to a higher HBsAg reappearance rate, although most are with undetectable HBV DNA after HBsAg reappearance. Even with higher rates of HBsAg reappearance than HBIG contained regimens, HBIG free with potent Nuc therapy could also achieve similar clinical outcomes. However, the clinical significance and long-term outcomes of HBsAg reappearance in LTRs are unknown. Larger studies with longer follow-up are needed for a definitive conclusion.

The reported prevalence of chronic HBV carriers receiving RT is decreasing, but it is still not negligible, especially in endemic areas of HBV infection. HBV has conferred a high risk of morbidity and mortality in RTRs before the advent of Nuc. At present, HBsAg-positive or anti-HBc-positive donors can be safely used in RTRs. Flow diagram of management algorithm for RTRs with HBV infection is illustrated in Fig. 17.3. Considering long-term treatment, antiviral agents with a high genetic barrier to resistance (ETV or TDF) and lack of nephrotoxicity (e.g., ETV) are recommended.

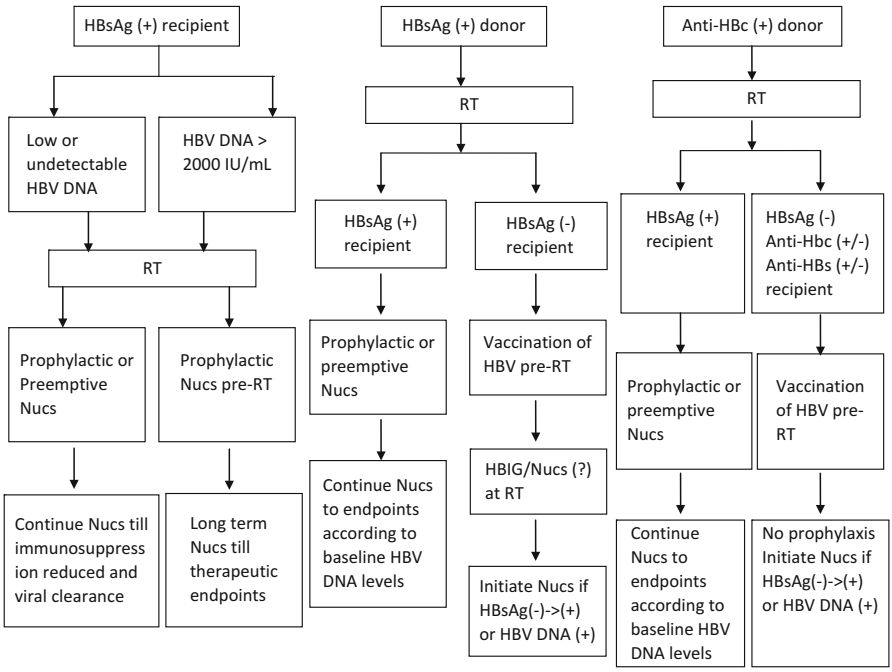


Fig. 17.3 Flow diagram of management algorithm for renal transplant recipients with HBV infection

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