

Prevention and Treatment of Recurrent Hepatitis B after Liver Transplantation

Rakhi Maiwall and Manoj Kumar*

Hepatology and Liver Transplantation, Institute of Liver and Biliary Sciences, New Delhi, India

Abstract

Chronic hepatitis B is a global health problem that leads to development of various complications, such as cirrhosis, liver cancer, and liver failure requiring liver transplantation. The recurrence of hepatitis B virus (HBV) post-liver transplantation is a major cause of allograft dysfunction, cirrhosis of the allograft, and graft failure. Patients with high viral load at the time of transplantation, hepatitis B e antigen (HBeAg) positivity, or those with a history of anti-viral drug resistance are considered as high-risk for recurrent HBV post-liver transplantation, while patients with low viral load, including HBeAg negative status, acute liver failure, and hepatitis D virus (HDV) co-infection are considered to be at low-risk for recurrent HBV post-liver transplantation. Antivirals for patients awaiting liver transplantation (LT) cause suppression of HBV replication and reduce the risk of recurrent HBV infection of the allograft and, therefore, all HBV patients with decompensated cirrhosis should be treated with potent antivirals with high genetic barrier to resistance (entecavir or tenofovir) prior to liver transplantation. Prevention of post-liver transplantation recurrence should be done using a combination of hepatitis B immunoglobulin (HBIG) and antivirals in patients at high risk of recurrence. Low dose HBIG, HBIG-free protocols, and monoprophylaxis with high potency antivirals can still be considered in patients at low risk of recurrence. Even, marginal grafts from anti-HBc positive donors can be safely used in hepatitis B surface antigen (HBsAg) negative, preferably in anti-hepatitis B core (HBc)/anti-hepatitis B surface (HBs) positive recipients. In this article, we aim to review the mechanisms and risk factors of HBV recurrence post-LT in addition to the various

treatment strategies proposed for the prevention of recurrent HBV infection

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Introduction

Hepatitis B virus (HBV) infection is a global health problem and is known to be endemic in the Eastern world. An estimated 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen (HBsAg) positive for at least 6 months) and more than 780,000 people die every year due to complications of hepatitis B, including cirrhosis and liver cancer.^{1,2} Chronic infection with HBV results in the development of cirrhosis, liver cancer, and liver failure, necessitating liver transplantation (LT). During the early years of LT in the absence of antiviral prophylaxis, the recurrence of HBV post-liver transplantation was almost universal. Recurrent infection was known to cause allograft dysfunction, cirrhosis of the allograft, and graft failure.² The introduction of intravenous (IV) hepatitis B immunoglobulin (HBIG) in the early 1990s was a major breakthrough in the prevention of post-LT recurrence of hepatitis B. In the current era, more than 90% of recurrent HBV infections can be clinically controlled by treatment with antivirals i.e., nucleos(t)ide analogues (NAs) in combination with HBIG. The use of newer potent antiviral drugs with high genetic barrier to resistance [e.g., entecavir (ETV) or tenofovir (TDF)] has further led to significant improvements in the outcome of patients both pre- and post-liver transplantation. Recent data with these drugs has suggested that a lower dose of HBIG or even HBIG-free protocols could effectively prevent post-liver transplantation recurrence.³ This article details the mechanisms and risk factors of HBV recurrence post-LT and summarizes various treatment strategies proposed for the prevention of recurrent HBV infection.

Immune system in the pathogenesis of HBV

The immune system is inherently capable of clearing more than 90% of HBV infections acquired during adulthood.⁴ Induction of a robust T-cell response accompanied by an increase in the production of interferon gamma (IFN- γ), activation of natural killer cells, and CD8+ T-cell mediated clearance of infected hepatocytes is responsible for acute self-limiting HBV infection.⁵ However, in patients who develop chronic HBV infection, a weak and transient virus-specific T-cell response caused by an excess of inhibitory

Keywords: Hepatitis B; Recurrent; Liver transplant.

Abbreviations: ADV, adefovir; AGL, antigenic loop; APASL, Asia Pacific Association for the Study of Liver; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CI, confidence interval; CTLA-4, Cytotoxic T-lymphocyte-associated protein 4; DNA, deoxyribonucleic acid; ETV, entecavir; HBc, hepatitis B core; HBeAg, hepatitis B e antigen; HBIG, hepatitis B immunoglobulin; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; HDV, Hepatitis D virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IFN- γ , interferon gamma; IM, intramuscular; IV, intravenous; LAM, lamivudine; LT, liver transplantation; MPL, monophosphoryl lipid; NAs, nucleos(t)ide analogues; NTCP, sodium taurocholate co-transporting polypeptide; OLT, orthotopic liver transplantation; PD1, program death receptor 1; RR, response rate; SC, subcutaneous; TDF, tenofovir; TIM3, T-cell immunoglobulin and mucin-domain containing-3.

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*Correspondence to: Manoj Kumar, Department of Hepatology and Liver Transplantation, Institute of Liver and Biliary Sciences, D1 Vasant Kunj, New Delhi, India. Tel: +91-11-4630000, Fax: +91-11-26123504, E-mail: manojkumardm@gmail.com

signals, i.e., cytotoxic T-lymphocyte-associated protein 4 (CTLA-4),⁶ pro-death receptor 1 (PD1),⁷ T-cell immunoglobulin, and mucin-domain containing-3 (TIM3), is predominant. In addition to this, a decrease in the function of regulatory T cells and dendritic cells as well as an unabated activation of natural killer cells is responsible for hepatocyte injury in chronic HBV.⁸ Recent studies have also identified dense non-antigen specific T-cell infiltration as a cause of hepatocyte damage in patients with chronic HBV infection.⁴ In post-LT patients, both B and T-cell mediated adaptive immune response are needed to control the recurrence of infection. Combination treatment with HBIG and NAs is known to mask the adaptive immune response in these patients.^{4,9} Further, the response to therapeutic vaccines is also determined by the adaptive immune response to the virus.

Mechanisms, diagnosis, risk factors, and consequences of HBV recurrence after LT

Mechanisms of HBV recurrence after LT

HBV is a small and enveloped deoxyribonucleic acid (DNA) virus containing a relaxed circular partially double-stranded DNA genome comprised of three surface proteins, i.e., large (L), middle (M), and small (S) proteins.^{10,11} The L protein is required for the release and envelopment of mature virion, which is essential for viral entry.¹² It comprises the PreS1 and PreS2 domains, while the M protein includes the PreS2 domain in the N-terminus.¹⁰ The determinants of infectivity of the virus include the C-terminal of PreS1, the N-terminal of PreS2 protein, and the antigenic loop (AGL) of the S domain. HBIG predominantly targets the AGL-domain of the virus.^{13,14} The various mechanisms by which HBIG prevents HBV transmission include binding to the circulating viral particles by immune complex formation, preventing infection of naïve hepatocytes by blocking the putative HBV receptor, and inhibiting secretion of HBsAg from the infected hepatocytes.¹⁵ NAs inhibit reverse transcription of pregenomic RNA, decreasing synthesis of HBV-DNA, but they do not clear covalently closed circular DNA (cccDNA). This is because the cccDNA episome is the transcriptional template for both HBV messenger RNA and pregenomic RNA.¹⁶ cccDNA is known to persist in the nucleus of infected hepatocytes as a minichromosome and is responsible for viral persistence.¹⁷ Because of this, once infected, HBV stays in the infected hepatocytes for life, despite seroclearance of HBsAg and emergence of anti-HBs antibody.¹⁸ Measurable low levels of HBV DNA in the serum, liver, and peripheral blood mononuclear cells or the presence of cccDNA in the liver tissue has been demonstrated in patients even in the absence of HBsAg. This is called occult HBV infection.¹⁹⁻²³ This becomes of clinical relevance in the context of immunosuppression, which can result in viral flare in patients with occult hepatitis B in the absence of immunoprophylaxis.

Recent studies have identified sodium taurocholate cotransporting polypeptide (NTCP) as a high affinity receptor for HBV entry on the hepatocyte membrane.²⁴ NTCP is known to specifically interact with the PreS1 domain of HBV. The discovery of the NTCP receptor has not only led to unveiling of the mechanism of HBV entry into the hepatocytes but also is considered as an effective therapeutic target to prevent graft liver from HBV infection after orthotopic LT (OLT).^{25,26}

Immunosuppression treatment post-LT is known to induce viral replication, even in HBsAg-negative, anti-HBs antibody-positive patients.^{27,28} Moreover, HBV itself evades the

immune system, and HBV-specific CD4+ and CD8+ T-cell responses have been shown to correlate with viral and hepatitis control during acute and chronic infection.²⁹⁻³¹ Normally, seroconversion of a person from HBsAg-positive to anti-HBs-antibody-positive is a marker for clinical cure and discontinuation of NAs. However, in the context of organ transplant, immunosuppression³² with steroids and calcineurin inhibitors is associated with recurrent hepatitis B characterized by high amounts of HBV-DNA and severe lobular hepatitis with a high incidence of fatal liver failure in the absence of antiviral prophylaxis.³³ HBV reinfection in these patients is primarily a consequence of an immediate reinfection of the graft by circulating HBV particles or a later reinfection from HBV particles coming from extrahepatic sites, such as peripheral blood mononuclear cells, or both. Viral replication has in fact been reported to be maximal after glucocorticoids, which cause enhanced viral replication via direct stimulation of the glucocorticoid responsive enhancer region on the HBV genome.^{2,4} An early withdrawal of steroids has, therefore, been proposed to minimize the incidence of recurrence of HBV and is practiced at most centers, even though there are no large prospective studies that provide evidence in favor of this strategy.^{2,34-36}

Diagnosis and risk factors for HBV recurrence after LT

Recurrence of HBV infection after LT is defined as the reappearance of circulating HBsAg with or without detectable HBV DNA. However, only patients who develop persistently detectable HBV DNA were shown to be at risk for clinical disease and graft loss.^{37,38} Measurable low levels of HBV DNA in serum, liver, and peripheral blood mononuclear cells or the presence of total HBV DNA and cccDNA in liver tissue could also be detected transiently after LT in the absence of a positive HBsAg, irrespective of the type of prophylaxis used.¹⁹⁻²² The significance of these findings is unclear but suggests that occult HBV reinfection occurs in some HBV recipients after LT despite prophylaxis and implies a risk for overt HBV recurrence if the prophylaxis is discontinued.

Various risk factors have been identified for HBV recurrence post-LT. Patients with high viral load at the time of transplantation; HBeAg positivity; history of anti-viral drug resistance; hepatocellular carcinoma (HCC) at LT; HCC recurrence; or chemotherapy used for HCC are considered high-risk for recurrent HBV post-LT, while patients with low viral load (including HBeAg negative status), acute liver failure, and HDV co-infection are considered to be at low-risk for recurrent HBV post-LT.^{2,35,37,38}

The correlation between the viral load at the time of LT and the risk of hepatitis B recurrence was studied by Marzano and colleagues³⁸ in 177 patients with HBV related liver disease who underwent LT. There was a linear correlation between recurrence and viral load at the time of surgery; and in patients with HBV DNA higher than 100,000 copies/mL the recurrence rate was 50% higher ($p=0.003$) than patients with a viral load of 200-99,999 copies/mL, i.e., 7.5%. The recurrence rate was 0% in patients with HBV DNA less than 200 copies/mL.³⁸ Similar results were observed in a multicentric trial conducted in 17 European centers. In this study, 372 consecutive HBsAg-positive patients who underwent LT were studied for HBV recurrence post-LT. The actuarial risk of recurrence of HBV is 50%. This risk was maximal for patients with HBV-related cirrhosis (67%) and lowest for patients with fulminant hepatitis B, i.e., 17%. Further, among patients with

HBV-related cirrhosis, the risk of HBV recurrence was highest (83%) in those who were seropositive for HBV DNA at the time of transplantation and lowest (58%) in those with neither HBV DNA nor HBeAg detectable in serum. The recurrence rates were also lower in patients given prolonged duration of passive prophylaxis with anti-HBs immune globulin. Independent predictors of lower risk of HBV recurrence were long-term administration of the immune globulin, hepatitis delta virus superinfection, and acute liver disease. Importantly, recurrence was also associated with poor survival in these patients.² Considering a direct relationship between HBV viral load at transplantation (i.e., >105 copies/mL) and the rate of HBV recurrence,³⁶ antivirals should be used before transplantation in all patients to achieve undetectable HBV DNA levels to reduce the risk of HBV recurrence.³⁹ In addition, rapid and sustained suppression of HBV-DNA before transplant results in improved survival rates, i.e., 87%, compared to 44% at 3 years in patients with untreated HBV infection.^{39,40}

Presence of HCC at LT, HCC recurrence, and chemotherapy used for HCC are also independently associated with an increased risk of HBV recurrence post-LT. This was demonstrated in a study of 99 patients of HBV related cirrhosis, of which 31 patients had HCC who underwent LT for cirrhosis. It was seen that the presence of HCC, a pre-LT DNA load more than 100,000 copies/mL, and HBIG monoprophyllaxis were significant and independent predictors of HBV recurrence post-LT. Recurrence was significantly more frequent in patients with HCC at time of LT (35% versus 4%, $p < 0.0001$).³⁵

Thus, patients who are considered high-risk for recurrent HBV post-LT include those with high viral load at the time of transplantation, HBeAg positivity, a history of antiviral drug resistance, presence of HCC at LT, HCC recurrence, or chemotherapy used for HCC, while patients with low viral load (including HBeAg negative status), acute liver failure, and HDV co-infection are considered to be at low-risk for recurrent HBV post-LT.

Consequences of HBV recurrence after LT

Todo *et al.*⁴¹ found in patients with recurrent HBV infection post-OLT that the rate of hepatitis development in the graft was accelerated. Further, it was seen that beyond 2 months of transplant the mortality and rate of graft failure were significantly higher in the HBV-related group than in the non-HBV related group. Lerut *et al.*⁴² found the median time to reinfection was 145 days (range 15 to 2,615 days) and reported fibrosing cholestatic hepatitis in three of the 16 HBV reinfected patients, all of whom died within 1 year post-OLT. Liver failure developed in two of these 16 patients, and they died within 2 years post-OLT.⁴³ The presence of HDV co-infection and adequate immunoprophyllaxis were the only significant prognostic variables in these patients. In another study evaluating the histopathological features in patients who underwent transplant for HBV related liver disease, acute cellular rejection was predominantly seen in the first 30 days of OLT, while beyond day 60, acute or chronic hepatitis related to hepatitis B was seen more frequently. Thereafter, a chronic carrier state or chronic active hepatitis and/or cirrhosis were the main features seen on biopsy. The histological findings of graft failure in these patients revealed heterogeneous states, such as massive necrosis, cirrhosis, chronic rejection, or hepatic artery thrombosis. The

recurrence of HBV was not affected by the human leukocyte antigen (HLA) status of the donors, indicating that the viral epitope could be recognized via different HLA and T cell receptors.^{9,43}

Taken together, these findings clearly show that reappearance of HBV in the grafted liver could occur early after OLT with serious consequences, necessitating the need for an adequate immunoprophyllaxis.^{35,38}

Prevention of HBV Recurrence after LT

Before the availability of effective antiviral and immunoprophyllactic agents, high rates of hepatitis B recurrence after LT for chronic hepatitis B (CHB)-related diseases were observed and were almost universal in those with detectable viremia at the time of transplant. Over the past 3 decades, there have been significant advances in both the treatment of CHB and prophylaxis against disease recurrence. Prophylaxis for HBV recurrence post-LT has evolved from using high dose IV HBIG long term to low dose IV/intramuscular (IM)/subcutaneous (SC) HBIG along with antivirals [mainly lamivudine (LAM) and adefovir (ADV)] to HBIG free regimens (either stopping HBIG after a finite duration after LT or no use of HBIG at all) with the availability of highly potent NAs (ETV and TDF).

HBIG containing prophylaxis regimens

Prior to the availability of effective HBV prophylaxis in the 1980s, LT for CHB was a relative contraindication. High rates of graft re-infection led to severe flares, and loss of the graft occurred in the absence of antiviral therapy. HBIG is a polyclonal antibody to HBsAg that is derived from pooled human plasma HBIG, which consists of high-titer antibodies against the AGL domain of the HBsAg L protein.⁴⁴ The use of HBIG after LT was the first major milestone in the prevention of post-transplant HBV recurrence. HBIG monotherapy reduced HBV recurrence approximately by a rate of 70%.⁴⁰ Monoprophyllaxis with high-dose of HBIG in the anhepatic phase, followed by daily and subsequent monthly administration at a fixed dose, was routinely considered prior to the availability of the NAs.⁴⁵⁻⁴⁷ However, the major limitation of such protocols was the high cost associated with HBIG as well as the inconvenience of administering IV injections at frequent intervals to transplanted patients for almost a year.³⁸ Additional limitations included an unreliable supply of the formulation, the local and systemic side effects, and the risk of infection from HBV mutants that escaped neutralization.^{2,37,38}

Further, with experience it became evident that recurrence is not only determined by the dose and duration of the HBIG therapy but also by trough surface antibody titres.^{2,34,37,38}

There are various studies that have assessed HBV recurrence based on the dose, duration, and route of HBIG therapy as well as target titres of anti-HBs. In conventional protocols, HBIG is used at a high dose (e.g., 10,000 IU/day) during the anhepatic phase and the first postoperative week to neutralize HBsAg. In the early post-LT period, some studies reported that high IV HBIG dosage ($\geq 10,000$ IU/day) versus low HBIG dosage ($< 10,000$ IU/day) was associated with a lower frequency of HBV recurrence.² In the medium- and long-term follow-up, IV HBIG was administered in two different ways: at a frequency dictated by the maintenance of specific anti-HBs levels or on a fixed schedule. Although the latter approach is

simpler and requires less monitoring, it is more expensive.⁴⁸ The target levels for anti-HBs titers varied with time after LT: generally, anti-HBs levels were maintained >500 IU/L during months 1–3, >250 IU/L until months 6–12, and >100 IU/L thereafter. Table 1 includes a summary of studies evaluating high dose HBIG for the prevention of post-LT HBV recurrence.

Considering the limitations of IV HBIG, alternative approaches of administering HBIG have also been studied. These strategies include the use of IM or SC preparations of HBIG, which are advantageous because of improved tolerability and the possibility of self-administration by patients at home.⁴⁹

The success of using a low dose of IMHBIG (400–800 IU) in combination with LAM was shown by Gane and colleagues. The rate of HBV recurrence was shown to be as low as 1% at 1 year and 4% at 5 years in their study.⁴⁴ Further, this efficacy was achieved at a reduced cost, which was less than 10% the cost of high dose IV HBIG regimens.⁴⁴ Zheng *et al.* in a retrospective study evaluated 165 patients who received either low dose IM HBIG with LAM (114 patients) or LAM monotherapy (51 patients) post-LT. The low-dose HBIG protocol in their study involved administration of HBIG as 800 IU daily for 6 days, weekly for 3 weeks, and subsequently on a monthly basis.⁵⁰ Again, a superior response rate was demonstrated with the combination treatment in preventing HBV recurrence as compared to LAM monotherapy (13.5% versus 27.4% at 1 year and 15.2% versus 39.7% at 2 years, respectively). Similar to these results, another study done in 183 patients receiving combination prophylaxis with antiviral therapy (mostly LAM monotherapy) with HBIG found no significant

difference in recurrence rates between the different routes and dosages of HBIG therapy. HBIG in this study was given either as IV high-dose regimen (10,000 IU monthly), IV low-dose regimen (3,000–6,000 IU monthly), or as IM low-dose regimen (1,000–1,500 IU every 1–2 months) for a finite duration (median duration 12 months). Multivariate analysis further showed that only positivity for HBeAg and high viral load at transplant, but not the post-transplant HBIG regimen, were associated with HBV recurrence.⁵¹ Interestingly, in all the studies evaluating low-dose IM HBIG, the recurrence rate was primarily affected by the level of viremia pre-LT. Therefore, the success of low-dose HBIG is more likely in patients with a lower level of HBV viremia pre-LT.⁵²

The effectiveness and safety of self-administration of a SC regimen of HBIG was demonstrated by Costanzo *et al.* in a cohort of 135 LT patients who received a 48 week treatment of SC HBIG. The SC preparation was found to be effective in a majority of patients (97.8%), wherein it was able to reach the target anti-HBs titers of more than 150 IU/L.⁴⁹

Combination therapies of antivirals and HBIG

The advent of antiviral therapy further changed the landscape of post-LT prophylaxis for HBV. Because of differences in the mechanisms of action of antivirals and HBIG, combination therapy has become the standard of care for the management of hepatitis B post-LT.^{53,54} The first trial of combination treatment with long-term HBIG with the first-generation NA, i.e., lamivudine (LAM), was conducted in 1998, which showed excellent 1-year survival rates with this therapy.²¹

Table 1. Studies on high dose hepatitis B immunoglobulin (HBIG) to prevent hepatitis B virus (HBV) recurrence post-liver transplantation (LT)

Reference	Number of patients	Anti-viral pre-LT [%]	DNA at LT [IU/mL]	HBIG protocol	Follow up [months]	Recurrence [%]	Antivirals
Markowitz <i>et al.</i> ⁴⁶	14	36	7	100,000IU for 1 month then 10,000IU/month	12.7	0	
Han <i>et al.</i> ⁴⁷	59	34	27	80,000 IU in 1 st month; then 10,000 IU/month	15	0	
Marzano <i>et al.</i> ³⁸	26	100	27	46,500 IU first month; then 5000 IU/month	30	4	
Rosenau <i>et al.</i> ²²	21	52	24	40,000 IU 1stwk; aim for titer > 500IU/L for 1 week and then >100 IU/L	21	10	Lamivudine – resistant pre-LT
Rosenau <i>et al.</i> ⁴⁰	19	100	47	10,000 IU/day until titer >1000 IU/L; then aim for titer >100 IU/L	-	20	Lamivudine – resistant pre-LT
Seehofer <i>et al.</i> ¹⁰³	17	100	29	80,000 IU for 1 month; then aim for titer >100 IU/L	25	18	Lamivudine – resistant pre-LT
Steinmuller <i>et al.</i> ¹⁰⁴	51	100	-	10,000 IU/day until sAg cleared; then aim for titer >100 IU/L	35	8	(3 out of 4 lamivudine resistant pre-LT)

Subsequent reports also described successful control of HBV recurrence with this combination. The major advantage of combination therapy was the reduction in the dose of HBIG and, therefore, the cost of the immunoprophylaxis. The independent and synergistic effects of the combination of HBIG and LAM reduced HBV recurrence to less than 5% at 1 year of follow-up.⁵⁵ Data from a meta-analysis comparing HBIG to combination treatment (including nine studies comparing antivirals to combination treatment and three comparing LAM to HBIG) showed that post-transplant prophylaxis against HBV with combination HBIG and LAM was superior to either agent alone and improved survival compared to HBIG alone. Combination treatment reduced HBsAg reappearance (response rate (RR) 0.28; 95% confidence interval (CI) 0.12–0.66) and was significantly better than antivirals in preventing reappearance of HBsAg (RR 0.31; 95% CI 0.22–0.44), even when low-dose HBIG was given. However, even in combination treatment, the efficacy of HBIG combined with ADV was noted to be superior to that of HBIG combined with LAM.⁴⁵ The superiority of ADV over LAM was also well demonstrated in a systematic review of 46 studies, including 2,162 HBV patients who underwent LT, wherein it was found that patients who received HBIG and LAM experienced HBV recurrence more frequently than patients receiving HBIG and ADV with or without LAM [6.1% versus 2.0%; $p = 0.024$]. Contrary to the combination of HBIG and LAM, where the dose of HBIG determined HBV recurrence, combination of HBIG and ADV was not affected by HBIG dosage, indicating that the dose of HBIG may not be important when used in combination with more potent antivirals.⁵²

HBIG-free prophylactic regimens

Various strategies for HBIG-free therapy have been studied, including withdrawal of HBIG after a finite period, use of newer potent antiviral agents [ETV or TDF] with HBIG for short periods or without HBIG at all, and active immunization with HBV vaccines.⁹

HBIG free protocols were initially studied with LAM. Monotherapy with LAM showed a 10% recurrence rate at 1 year, which was increased to 22–41% at 3 years due to the emergence of escape mutations in the YMDD motif of the polymerase gene.⁵⁶ Recurrence was observed mainly in patients with a high level of HBV replication prior to drug exposure. In contrast, a similar regimen with ADV exhibited superior efficacy to LAM. In a study of 61 LAM-resistant patients who underwent LT, 40% of which received ADV plus/minus LAM prophylaxis without HBIG, no patient had recurrent HBV infection.³⁴ Further, a combination of LAM and ADV was superior to ADV alone, as demonstrated by Gane and colleagues. In their study, no recurrence was observed after a median of 22 months in 18 patients (all with HBV DNA below 3 log 10 IU/ml before LT) treated with combination prophylaxis without HBIG.⁵⁶ Similar results were reported for switching from HBIG after a finite period to a combination of LAM/ADV⁵⁷ or to a combination of emtricitabine/TDF.⁵⁸

The advent of newer and more potent anti-viral drugs with a high genetic barrier to resistance [i.e., ETV or TDF] has led to a decrease in the duration of HBIG use and even to no use of HBIG at all for post-LT HBV prophylaxis.^{59–61} This was demonstrated in a recent systematic review of 519 HBV patients from 17 studies,⁶² in which the efficacy of drugs with high genetic barrier (i.e., ETV or TDF) with or without HBIG as prophylaxis against HBV recurrence after LT were compared

to protocols using LAM and HBIG. It was seen that recurrence developed more often in patients under HBIG and LAM than those with ETV or TDF (6.1% versus 1.0%; $p < 0.001$), and recurrence in HBIG and LAM was lower, albeit insignificantly, than patients who received a newer NA after discontinuation of HBIG [6.1% versus 3.9%; $p = 0.52$]. The use of ETV or TDF alone further was shown to have similar antiviral efficacy as compared to HBIG in combination with LAM, [0.9% vs. 3.8%, $p = 0.11$].

Table 2 shows studies that examined low dose HBIG in patients for the prevention of HBV recurrence post-LT in combination with LAM.

Although the data are not strong enough to suggest the efficacy of monoprophyllaxis with ETV or TDF in reducing post-LT recurrence, this approach continues to be followed in some centers, particularly in patients considered at low-risk of HBV recurrence. Cholangitas *et al*. showed the effectiveness of this approach in 47 recipients of LT who had low-risk of HBV recurrence (4.5% with detectable HBV DNA at the time of LT and 32% with HBV/HDV co-infection) on newer NAs (ETV and TDF monoprophyllaxis) after discontinuation of HBIG. It was seen that recurrence occurred in only three (6.3%) patients based on detectable HBsAg, while all these patients had undetectable HBV DNA and no clinical symptoms secondary to recurrence.⁶³ Similar encouraging results were shown by another study investigating the efficacy of ETV as monoprophyllaxis in 80 patients, wherein no episodes of HBV flares or graft loss were reported secondary to recurrent HBV infection.⁶⁴ Another large and long-term cohort study of 362 CHB post-LT patients receiving only NAs without HBIG showed that at year 8 after LT, 98% had undetectable HBV DNA. Moreover, the survival was also excellent, i.e., 83% at 8 years, with no mortality related to HBV recurrence.⁶⁵ This clearly shows that an HBIG-free regimen with high potency anti-virals (ETV or TDF) is safe, effective, and an appropriate therapeutic approach, specifically in patients with low risk of HBV recurrence.^{66,67} In high-risk patients, HBIG still constitutes an integral part of the antiviral prophylaxis in many transplant centers. Therefore, HBIG free prophylaxis should not be used for those patients with high pretransplant HBV DNA levels, those with limited antiviral options if HBV recurrence occurs (i.e., human immunodeficiency virus (HIV) or HDV coinfection, preexisting drug resistance, or intolerance), those with a HCC at LT, and those with a risk of noncompliance to antiviral therapy.⁶⁸ Amongst these high-risk groups of patients, a withdrawal of HBIG can still be considered with use of high potency NAs, as discussed. The exact time to consider such withdrawal is still controversial; and studies have shown that discontinuation of HBIG 1 year post-transplantation seems to be a safe and feasible approach.^{55,63} In a recent study from India, withdrawal of HBIG therapy 1 year after LT along with use of high potency NAs (ETV and TDF) for the initial 3 months was studied. They included 176 patients (with at least 12 months follow-up) who had HBV cirrhosis or HCC and underwent LT. All included patients received 10,000 IU IVHBIG in an hepatic phase followed by 600–1000 IU IM daily for 7 days, weekly for 3 weeks, and then monthly, to keep anti-HBs levels >100 mIU/mL for 1 year. Further, all these patients received either ETV ($n = 126$, 71.5%) or TDF ($n = 20$, 11.3%), or a combination of ETV and TDF ($n = 30$, 17% for 3 months, followed by ETV alone). Recurrence was noted only in two patients (one of which was due to noncompliance to therapy) during follow-up of 43 (12–117) months.⁶⁹

Table 2. Studies on low dose HBIG in combination with lamivudine (LAM) to prevent HBV recurrence post-LT

Reference	Number of patients	Anti-viral pre-LT [%]	DNA at LT [IU/mL]	HBIG protocol	Follow up [months]	Recurrence [%]	Antivirals
Angus <i>et al.</i> ⁵⁵	32	97	-	800 IU IM at LT and daily for 1 week; 800 IU im monthly	18.4	3	
Ferretti <i>et al.</i> ¹⁰⁵	23	48	13	80,000 IU IV in 1st wk; 1200 IU IM to keep titre >100 IU/L	20	4	
Karademir <i>et al.</i> ¹⁰⁶	35	51	14	4000 IU IM at LT; 2000 IU daily until titer >200 IU/L and then to maintain titres >100 IU/L	16	6	All lamivudine resistant pre-LT
Zheng <i>et al.</i> ⁵⁰	114	-	31	2000 IU IM at LT; 800 IU IM daily for 6 days, weekly for 3 weeks and then monthly	15.8	14	Lamivudine in 99 post-LT
Gane <i>et al.</i> ⁴⁴	147	85	<50	800 IU IM at LT and daily for 6 days; then 800 IU IM monthly	61	4	

Table 3 shows studies of low dose/HBIG-free protocols in combination with antivirals, i.e., LAM, ADV, ETV, or TDF.

Because HBV DNA persists in serum, liver, or peripheral blood mononuclear cells even 10 years after LT and these reservoirs are considered a source of HBV reinfection even in HBsAg negative patients, indefinite long-term prophylactic therapy is the current standard of care in most patients after LT for CHB.^{70,71}

Thus, the assessment of the available data suggest that amongst low risk patients (i.e., those with undetectable HBV DNA levels at the time of transplant), HBIG-free regimens can be used with high potency NAs (ETV or TDF) indefinitely; whereas amongst high risk patients (those with detectable HBV DNA levels at LT, presence of drug-resistant HBV, HIV or HDV coinfection, HCC at LT, or poor compliance to antiviral therapy) 10,000 IU IV HBIG in an hepatic phase should be given followed by 600–1000 IU IM or IV daily for 7 days, then weekly for 3 weeks, and then monthly, to keep anti-HBs levels >100 mIU/mL for 1 year. After 1 year, HBIG may be discontinued. High potency NAs should be continued simultaneously indefinitely in these patients (Fig. 1). The Asia Pacific Association for the Study of Liver (APASL) have recently published the guidelines on the prevention of recurrent HBV post-LT.³

HBIG replacement with vaccination

Another fascinating option in HBIG-free protocols is active immunization using HBV vaccines post-transplantation. The strategy remains controversial because of conflicting results from various studies. Success of the vaccine strategy was reported by Sanchez-Fueyo and colleagues in 14 out of 17 (82%) cases who were treated with HBIG monotherapy followed by one or two courses of double dose vaccination series.⁷² Similarly, Bienzle *et al.* reported success of a vaccine

that was formulated with the new adjuvants 3-deacylated monophosphoryl lipid A (MPL) and Quillaja saponaria in two groups of 10 LT recipients who were HBsAg positive and HBV DNA negative before transplantation. All patients were vaccinated at weeks 0, 2, 4, 16, and 18 and subsequently received three additional doses of vaccine B at bimonthly intervals targeting an antibody titer against anti-HBs greater than 500 IU/L. Response was demonstrated in 16 out of 20 patients (80%) at a median follow up of 13.5 months.⁷³ Subsequently, Angelico *et al.* investigated the efficacy of a triple course of HBV vaccination in 17 patients transplanted for HBsAg-positive cirrhosis. The treatment protocol in the first cycle consisted of three double IM doses (40 µg) of recombinant vaccine at month 0, 1, and 2, respectively, which was followed, in nonresponders, by a second cycle of six intradermal 10 µg doses every 15 days. Further, the nonresponders received a third cycle identical to the first one. The vaccination was initiated 4.5 months after HBIG discontinuation, and LAM (100 mg/day) was given throughout the study. They showed that a vaccination strategy, despite such an aggressive protocol, was ineffective, with success in only 18% of patients.⁷⁴ The ineffectiveness of the vaccine strategy was also demonstrated by Weber *et al.* in 36 patients transplanted for HBV. All received HBIG therapy and an oral antiviral agent from the time of transplant; and subsequently, only 12 patients with a stable postoperative clinical course underwent vaccination after HBIG discontinuation. None of the vaccinated patients maintained HBSAb ≥ 10 IU/L.⁷⁵ Several other trials have also demonstrated poor outcomes with various vaccination strategies, with failure to maintain protective anti-HBs levels over time.^{76–78} The vaccine response is basically determined by the status of immune tolerance in both the donor and the recipient. Patients who are infected with HBV but have still not developed tolerance to the virus, such as patients who develop acute liver failure due to sexual

Table 3. Studies on low dose/HBIG-free protocols in combination with antivirals [LAM, adefovir (ADV), entecavir (ETV), or tenofovir (TDF)]

Study	Number of patients	Treatment protocol	Oral NAs	HBV recurrence	Follow up (in months)	
Perillo <i>et al.</i> ⁶⁵	47	No HBIG	LAM	9/22(41%)	Median 38	Resistance detection 15/47 (32%)
Lo <i>et al.</i> ⁶⁶	31	No HBIG	LAM	1/26	26 alive at median 16	Resistance detection 1/31 (3.2%) at 53 wk
Park <i>et al.</i> ⁶⁷	43	Long term high dose HBIG (n = 20) 1 week high dose HBIG + LMV maintenance (n = 23)	LAM	1/20 (5%) in HBIG 3/23 (13%) in LMV maintenance	Median 17	
Buti <i>et al.</i> ^{53,54}	29	HBIG and LMV for 1 month then randomized to HBIG + LMV continuation (n = 15) or solo LMV (n = 14)	LAM	1/15 (6.7%) in the HBIG + LMV group 3/14 (21.4%) in the LMV group	Mean 83	
Wong <i>et al.</i> ¹⁰⁷	21	At least seven doses of HBIG	LAM	1/21 (4.7%)	Median 40	
Angus <i>et al.</i> ⁵⁵	34	Low dose IM HBIG + LAM (n = 18) versus. (n = 16) discontinued HBIG and Added (LMV + ADV) post-LT	LAM LAM+ADF	0/18 in HBIG + LMV 1/16 (6.3%) in LMV + ADV	Median 34	All patients were ≥12 months post-LT
Yuefeng <i>et al.</i> ¹⁰⁸	15	HBIG for less than 18 months	LAM	2/15(13%)	Mean 56	
Saab <i>et al.</i> ¹⁰⁹	61	IM HBIG for at least 12 months	LAM LAM+ADF ETV+ADF TNF	2/61(3.3%)	Mean 15	
Fung <i>et al.</i> ⁶⁰	23	No HBIG	ETV	18/80(23%)	Median 26	
Wadhawan <i>et al.</i> ⁶¹	75	No HBIG	LAM + ADV (19) ETV (42) TDF (12) ETV + TDF (2)	6/75(8%)	Median 21	
Degertekin <i>et al.</i> ⁵¹	23	HBIG for 12 months	LAM ADV ETV TDF LAM + ADV LAM + TDF ETV + ADV TDF + ADV	3/23(13%)	Median 53	
Nath <i>et al.</i> ¹¹⁰	14	HBIG for 7 days	LAM + ADV	0/14 (0)	Median 14	
Teperman <i>et al.</i> ⁵⁸	16	HBIG for 6 months	FTC + TDF	0/16 (0)	Median 22	
Neff <i>et al.</i> ¹¹¹	10	HBIG for 7 months	LAM + ADV	0/10 (0)	Mean 31	

transmission, and those who receive anti-HBc positive donor livers are good candidates for vaccine strategy.⁷⁹ Another protocol of repeated vaccine administration has been shown to be successful via adoptive transfer of HBV-specific immune

response in patients with post-OLT liver cirrhosis.⁸⁰ In particular, this was seen in donors who were spouses of patients infected with HBV and had high titer anti-HBs before donation.⁸⁰ Lu *et al.* showed that a titer of more than 1000 IU/L

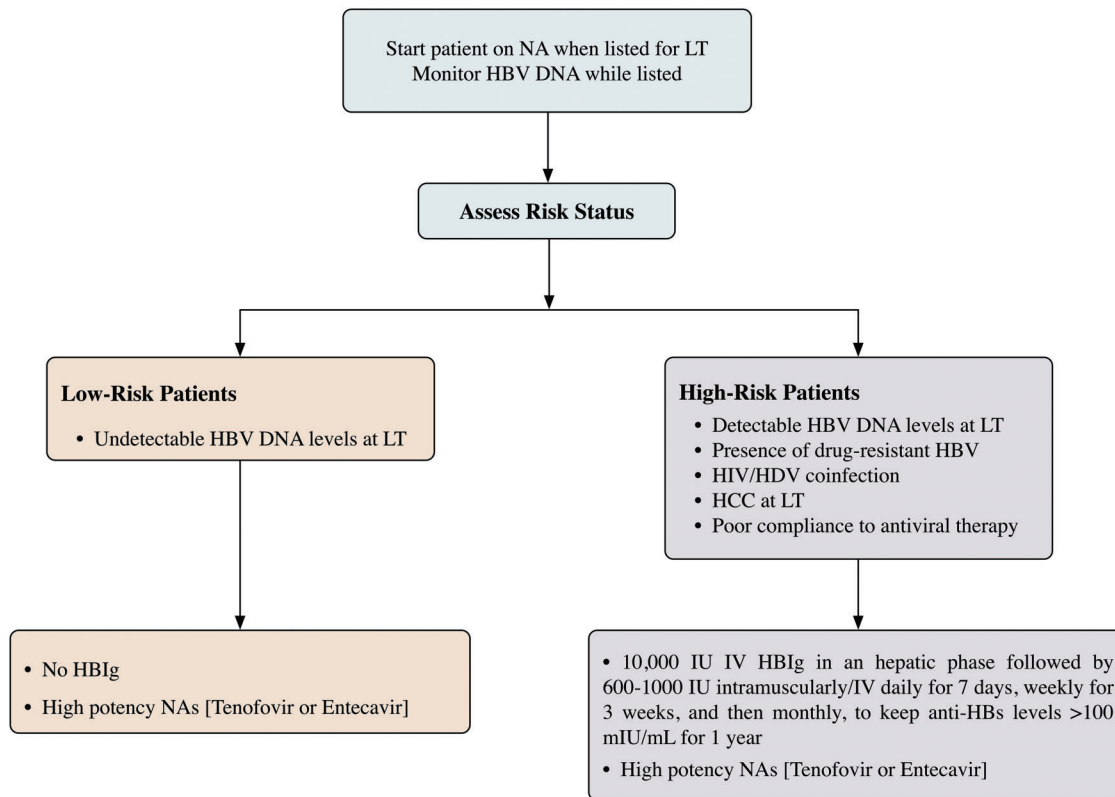


Fig. 1. Proposed algorithm for HBV prophylaxis using HBIG and nucleosides/nucleotides analogues. Abbreviations: HBIG, hepatitis B immune globulin; HBV, hepatitis B virus; HDV, hepatitis delta virus; anti-HBs, hepatitis B surface antibody; LT, liver transplantation; NAs, nucleos(t)ide analogues.

for anti-HBs is required for adoptive transfer of immunity in these patients.⁸¹

Recent data have emerged that suggest the vaccination strategy can be improved by administration of booster doses, double dose third generation recombinant vaccines, or the addition of adjuvants given with the vaccine, which can decrease the formation of escape mutants and the subsequent failure of therapy.^{20,82,83}

Overall, the data regarding use of vaccines is encouraging, but large prospective studies are needed still before such a strategy could be recommended routinely in clinical practice.

Use of grafts from core positive donors

Considering the organ shortage, use of marginal liver grafts obtained from anti-HBc positive donors are frequently considered for patients with HBsAg positive liver disease in countries with high prevalence of this virus. However, there is a risk of virus reactivation post-LT due to the influence of immunosuppression.⁸⁴ Cholongitas and colleagues performed a systematic review of 903 recipients from 39 studies for both the risk of HBV infection after LT with such grafts and the effect of anti-HBV prophylaxis after post-LT recurrence.⁸⁵ Recurrence of HBV infection was noted in 11% of HBsAg-positive LT recipients of anti-HBc positive grafts without any difference in survival when compared to HBsAg-positive recipients of anti-HBc negative grafts. Further, *denovo* HBV infection developed in 19% of HBsAg-negative recipients. Re-infection was more frequent in anti-HBc/

anti-HBs positive than HBV naïve cases without prophylaxis (15% vs 48%, $p < 0.001$). Prophylaxis with HBV included HBIG, LAM, or a combination of both. Use of prophylaxis led to decreased rates of re-infection. The *de novo* infection rates were 19%, 2.6%, and 2.8% in HBsAg-negative recipients under HBIG, LAM, and their combination, respectively.

Based on these results, it was suggested that anti-HBc positive donors can be used safely in HBsAg positive or anti-HBc/anti-HBs positive recipients. Further, patients who are HBsAg-negative should receive prophylaxis with antivirals, and patients who are both anti-HBc/anti-HBs positive recipients may need no prophylaxis at all (Fig. 2). These grafts should be first offered to HBsAg positive, then to anti-HBc and/or HBs positive, and only in the end should be allocated to hepatitis B virus naïve (both anti-HBc and anti-HBs negative) recipients, considering the increased risk of reactivation in the last subgroup of patients

Post-LT HBV Prophylaxis Failure

Because of the persistence of HBV DNA in serum, liver, or peripheral blood mononuclear cells even several years after LT, long-term prophylactic therapy has been recommended for these patients. However, long-lasting treatment in these patients carries a potential risk of prophylaxis failure because of the selection of drug resistant mutants to NAs and HBIG.⁸⁶ The lower diversity of anti-HBs contained in HBIG is one potential reason for HBIG resistance.⁸⁷ The common mutations that have been identified include G145R, G145A, or

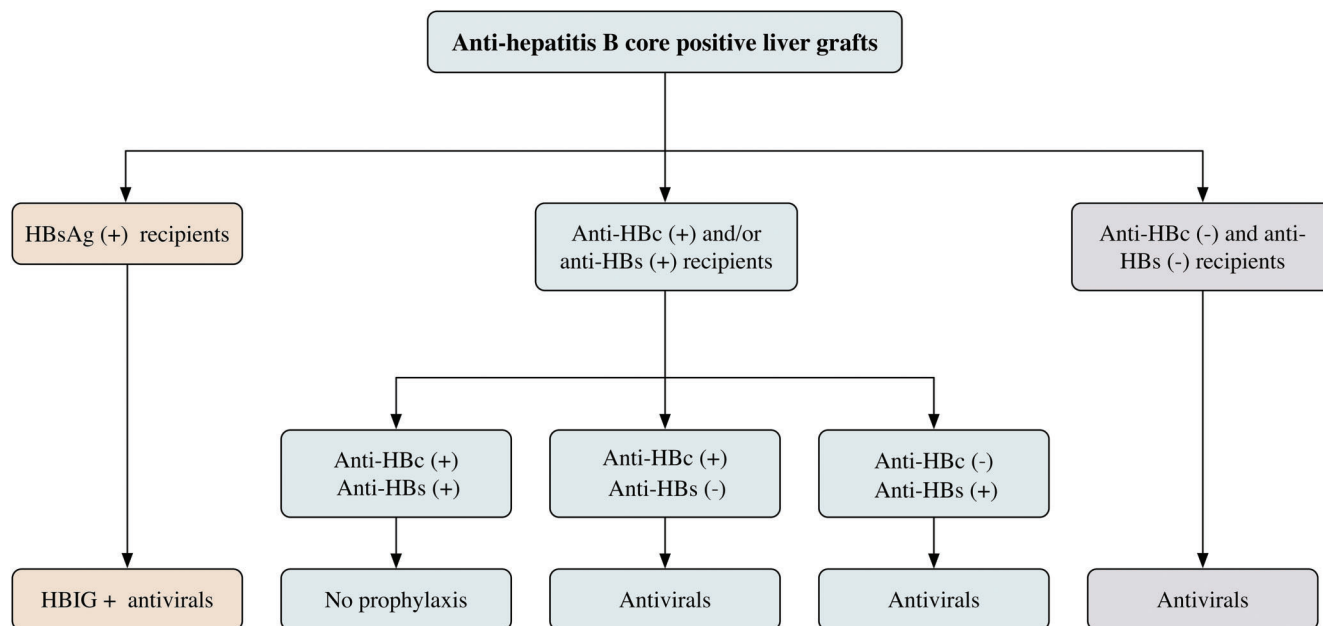


Fig. 2. Proposed algorithm for allocation and management of anti-HBc positive liver grafts. According to the available evidence, these grafts should be offered first to HBsAg positive patients, then to HBc and/or HBs positive patients, and only in the end should be allocated to hepatitis B virus naïve (both anti-HBc and anti-HBs negative) recipients, because of the increased risk of reactivation in the last subgroup of patients. Abbreviations: HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; HBIG, hepatitis B immunoglobulin.

Q129P.⁸⁸ Additionally, longer administration of NAs also involves other problems, such as osteomalacia, Fanconi’s syndrome with ADV,^{89,90} and allergic reactions with HBIG.

Emerging Drug Targets for HBV infection

As already mentioned, NAs do not eliminate cccDNA and; therefore, there is an ongoing discovery for compounds that could directly target cccDNA. Replication of HBV in infected hepatocytes is primarily regulated by acetylation or methylation of histone proteins. The hSirt1/2 activator MC2791 and the JMJD3 inhibitor MC3119 are important drugs that have been tested as epigenetic silencers of cccDNA. Other drug targets that have been evaluated include small-molecule compounds, i.e., CCC-0975 and CCC-0346.^{91,92} Another promising therapeutic approach that has been investigated is blocking the entry receptor of HBV on the hepatocyte. Myrcludex-B is a synthetic lipopeptide derived from the HBV envelope protein that inactivates the HBV pre-S1 receptor,⁹³ and it has been tested in phase 2 trials.^{93,94} Future studies are needed to explore whether a combination of HBIG (targeting the AGL domain) and Myrcludex B (targeting the pre-S1 receptor) as a possible approach to prevent re-infection. A more effective vaccine also has the possibility to induce easier and stronger HBV prophylaxis. Use of several monoclonal antibodies that have stronger reactivity to HBsAg are other options to enable HBsAg clearance. Another novel drug target that has been identified includes the hepatocyte NTCP receptor,^{25,26} which is localized to the sinusoidal membrane and is involved in the enterohepatic circulation of bile salts. Partial blocking of NTCP could result in blocking HBV entry into the hepatocytes and could constitute an important therapeutic modality in preventing viral recurrence post-LT, which needs evaluation in future studies. Considering an inherent potential of the immune system in the clearance of

HBV infection and recent research suggesting clearance of chronic HBV in patients who get bone marrow transplantation from an immune donor, the significance of immunomodulation as a therapeutic approach has been explored for achieving viral clearance in patients with chronic HBV.^{95,96} Immunotherapeutic strategies that are under development for patients with CHB include exogenous administration of cytokines with antiviral activity (IFN-λ) and stimulation of the host T cell immune response. GS-9620, a small orally bioavailable molecule that activates Toll-like receptor 7 signaling, has also been tested in animal models and is currently being evaluated in clinical trials for patients with chronic HBV.⁹⁷⁻¹⁰¹

Thus, although the future therapies for HBV infection has an exciting pipeline, human studies, especially in the context of LT recipients, are needed.

Conclusions

Based on the current evidence, all HBV patients with decompensated cirrhosis should be treated with potent antivirals with high genetic barrier to resistance (ETV or TDF). ETV should be avoided in patients with a previous history of LAM resistance; and, in such patients, TDF should be the drug of choice. TDF should also be the first choice in patients with ETV or telbivudine resistance. Effective pretransplant treatment is the most important factor determining post-transplant HBV recurrence.

To prevent post-LT recurrence, patients with undetectable HBV DNA levels at the time of transplant can be managed using HBIG-free protocols with a high potency antiviral, preferably TDF or ETV. Protocols using short-term HBIG for a year targeting anti-HBs >100 mIU/mL can be an appropriate therapeutic approach for high-risk patients (i.e., detectable HBV DNA levels at LT, HCC at LT, HIV or HDV coinfection, preexisting drug resistance or intolerance, or those with a risk

of noncompliance to antiviral therapy). Finally, marginal grafts from anti-HBc positive donors can be safely used in HBsAg negative, preferably in anti-HBc/anti-HBs positive recipients. Novel drugs that target cccDNA or the NTCP receptor for viral entry or that modulate the immune system hold a lot of promise, which needs to be assessed in future studies. These drugs could not only eliminate the need for life-long therapy but may also cure HBV.

Conflict of interest

None

Author contributions

Writing the article (RM, MK).

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