

Reactivation of hepatitis B after liver transplantation: Current knowledge, molecular mechanisms and implications in management

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Abstract

Chronic hepatitis B (CHB) is a major global health problem affecting an estimated 350 million people with more than 786000 individuals dying annually due to complications, such as cirrhosis, liver failure and hepatocellular carcinoma (HCC). Liver transplantation (LT) is considered gold standard for treatment of hepatitis B virus (HBV)-related liver failure and HCC. However, post-transplant viral reactivation can be detrimental to allograft function, leading to poor survival. Prophylaxis with high-dose hepatitis B immunoglobulin (HBIG) and anti-viral drugs have achieved remarkable progress in LT by suppressing

viral replication and improving long-term survival. The combination of lamivudine (LAM) plus HBIG has been for many years the most widely used. However, life-long HBIG use is both cumbersome and costly, whereas long-term use of LAM results in resistant virus. Recently, in an effort to develop HBIG-free protocols, high potency nucleos(t)ide analogues, such as Entecavir or Tenofovir, have been tried either as monotherapy or in combination with low-dose HBIG with excellent results. Current focus is on novel antiviral targets, especially for covalently closed circular DNA (cccDNA), in an effort to eradicate HBV infection instead of viral suppression. However, there are several other molecular mechanisms through which HBV may reactivate and need equal attention. The purpose of this review is to address post-LT HBV reactivation, its risk factors, underlying molecular mechanisms, and recent advancements and future of anti-viral therapy.

Key words: Hepatitis B virus; Liver transplantation; Reactivation; Hepatitis B immunoglobulin; Recurrence; Prophylaxis; Antivirals

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Core tip: Aim of this review is to summarize the current concepts and management of hepatitis B after liver transplantation (LT). There are no clear guidelines regarding hepatitis B therapy after transplantation. Hepatitis B immunoglobulin (HBIG) is expensive and cumbersome to administer and there is no definite time point for discontinuation of HBIG after LT. Here we summarize the indications and duration of hepatitis B immunoglobulin and nucleoside analogs. This review also addresses key molecular mechanisms and the risk factors which are associated with hepatitis B virus reactivation post LT. This review provides up-to-date information not only for the liver transplant specialists but also for the virologists and scientists working in this field.

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INTRODUCTION

Chronic hepatitis B (CHB) caused by hepatitis B virus (HBV) infection remains a major global health problem affecting an estimated 350 million people worldwide with more than 786000 individuals dying annually due to complications of CHB, including cirrhosis and liver cancer. CHB is the leading cause of hepatocellular carcinoma (HCC) accounting for at least 50% of

newly diagnosed cases^[1]. Furthermore, HCC is the third leading cause of cancer-related mortality in the world^[2] with a dismal 5 year survival and the fastest growing rate of cancer death in North America^[3]. Liver transplantation (LT) is the most effective treatment in patients with CHB-related liver failure, cirrhosis and HCC. However, HBV reactivation following LT emerges as a major clinical challenge^[4].

Over the past decade, a substantial advancement has been made in the treatment of CHB, and to date several potent antiviral medications are available for the treatment of HBV infection, mainly gaining long-term viral suppression^[5,6]. However, despite of having strong suppressive antiviral therapy for chronically HBV-infected patients, some patients still develop HCC possibly due to the presence of minimal residual viremia (MRV) and irreversible HBV DNA integration into liver genome. MRV is a consequence of persistent, low-level virus replication in the liver and at the extrahepatic sites, particularly in peripheral blood mononuclear cells (PBMC), coinciding with circulation of virus traces^[7-10]. Despite long-term antiviral treatment with suppression of viral DNA, MRV commonly persist^[7,11]. One of the major sources of MRV is supercoiled HBV covalently closed circular DNA (cccDNA) and its persistence is mainly responsible for recurrent HBV infection post-LT^[12,13]. Prior to introduction of hepatitis B immunoglobulin (HBIG) in 1990s, HBV recurrence in LT was as high as 75% to 89% of patients with 3-year survival rate in 54%^[14,15]. The introduction of viral suppression strategy using combination of HBIG and more potent nucleos(t)ide analogs (NAs) has significantly decreased the HBV recurrence in vast majority of these patients improving their long-term survival^[16]. However, this strategy does not completely eradicate HBV and, therefore, does not protect against future recurrence of symptomatic HBV infection. It also requires monitoring of LT patients for life, thus significantly increasing the economic burden and manpower engagement.

Evaluating the risk of HBV recurrence is crucial in devising effective strategy against post-LT reactivation. The factors associated with high rates of HBV reactivation are high viral load prior to the transplant, HBV e antigen (HBeAg) reactivity, co-infection with human immunodeficiency virus type 1 (HIV), non-compliance with drug therapy, HCC at the time of LT, and anti-viral drug resistance. On the other hand, low viral load, anti-HBe positivity and anti-HBs presence are factors with lower risk of HBV reactivation^[15,17-21].

MOLECULAR MECHANISMS OF HEPATITIS B REACTIVATION IN LIVER TRANSPLANTATION

cccDNA and its role in HBV reactivation

Although HBV is a DNA virus, it replicates by reverse transcription intermediate^[22]. Establishment of cccDNA is crucial in the HBV life cycle. This nuclear cccDNA

minichromosomal acts as the powerhouse of HBV transcriptional machinery and constitutes a molecular basis for virus reactivation^[12]. HBV cccDNA chronically exists throughout the natural history of HBV infection^[23] and it is not yet possible to eradicate this HBV molecule even with current potent anti-viral therapies, such as Entecavir (ETV) or Tenofovir disoproxil fumarate (TDF)^[24]. A recent study by Papatheodoritis *et al*^[25] showed that despite of the anti-HBV therapy, HCC develops in the context of the cccDNA presence and, thus, MRV and reactivation cannot be ruled out.

When recipients receive transplantation with liver from donors with previous history of HBV infection, but with negative serum HBsAg and HBV DNA, intrahepatic cccDNA could still be detected after LT^[4,26]. Notably, detection of anti-HBc alone in the absence of HBsAg and HBV DNA in a donor should be treated as an indicator of occult infection and a low-level virus replication in the liver, which could be reactivated post-LT^[18,27,28]. On the other hand, patients with undetectable HBV viremia at LT and no evidence of cccDNA and intrahepatic HBV DNA on repeat examinations -may be safely withdrawn from long-term prophylaxis^[29]. However, safe withdrawal also depends on the level of the sensitivity of the assays used for detecting HBV viremia, HBV cccDNA in the liver and the existence of HBV replication at the extrahepatic sites [e.g., peripheral blood mononuclear cells (PBMC)], which in occult cases may be missed even using ultrasensitive tests.

Genotype-specific recurrence of HBV

Ten different HBV genotypes have been identified which are scattered in an ethno-geographically specific manner. Ample of evidence suggested the role of HBV genotypes in disease progression, mode of transmission, disease severity, HCC risk, and response to therapy^[30]. Compared to genotype D, HBV genotype A responds well to the interferon therapy^[31]. Numerous reports across the globe documented association of HBV genotype B and C with severe liver disease including development of HCC^[32], while HBV genotype C has higher risk for mother to child transmission^[33]. Since virus evolves within the host, study of HBV genotype is important prior to LT, especially in genotypes, which are associated with the occult HBV infection^[34,35]. A study by Devarbhavi *et al*^[34] demonstrated that patients with HBV genotype D have the highest risk of HBV recurrence and mortality compared to genotype A. In our recent study, we demonstrated that viral genotypes fluctuate while patient is on the Tenofovir therapy, revealing two important phenomena, first, there is mixture of viral populations present in HBV infected patient and secondly, at a given time, only one of the viral strain is inhibited/exhibits^[36]. Although, not with regard to the HBV genotypes, but from the point of HBV quasispecies an elegant study by Buti *et al*^[37] identified HBV quasi-species evolution after LT in patients under long-term lamivudine prophylaxis with or without HBIG

and there was low transient viremia detected even in the absence of serum HBsAg, showing importance of continuing HBV prophylaxis. In the same context, a recent case study by Mina *et al*^[38] showed that HBV genotypes fluctuates after LT, which could possibly be the main reason behind the HBV reactivation in liver transplant settings. Since, in diagnostic assays, the possible source of HBV reactivation is negated, it is an open question, if extrahepatic tissues should be tested to find the origin of such reactivation. Studies focusing on HBV recurrence based on genotype are summarized in Table 1. It would be worthwhile to consider HBV genotyping in both donor and recipient so that each viral strain is tracked in case of the mixed genotype infections, which are emerging as important hidden source for reactivation.

Co-existing hepatitis D virus infection and HBV reactivation

Hepatitis delta virus (HDV) consists of a single-stranded RNA molecule enveloped by hepatitis B surface antigen (HBsAg)^[39]. One of the risk factors of HBV recurrence in LT patients is the co-infection with hepatitis delta virus (HDV)^[40]. Fulminant hepatitis B reactivation in co-infected patients has been reported^[40,41]. HBsAg-positive liver grafts in HBsAg-positive recipients with HDV co-infection has been reported to result in virological recurrence and rapid development of liver cirrhosis, and need for re-transplant^[42,43]. HDV is a RNA pathogenic virus that requires presence of HBV for its survival^[44]. Studies on post-LT patients suggest that the absence of HBV prophylaxis or lack of proper function of HBIG leads to higher incidence of both HBV and HDV reinfection^[43,45,46].

The co-existence or co-infection of HBV and HDV is very commonly observed, obviously due to the dependence of HDV infection on HBV. For instance, 11.9% of HBV-positive patients were also positive for HDV in an Italian liver patient cohort, with a higher incident in patients older than 50 years^[47]. It also appears to have a geographical connection, as co-infection HBV-HDV in LT patients was found to be low in Japan^[48], possibly due to the differential geographical distribution of HDV genotypes I and II between other parts of the world and Asian countries, respectively^[49]. The helper functions of HBV provide the support to HDV for cell entry, replication, virion assembly and export^[50]. The interactions between HBV-HDV occur in two phases, the first phase of active HDV replication occurs with the suppression of HBV, followed by reactivation of HBV and reduction in HDV in the second phase^[51]. Due to this nature of HDV and HBV interactions, early recurrence of HDV has been detected in many patients in the absence of HBV recurrence^[52]. Studies also imply that HDV could be a cause for many subclinical infections and symptoms develop rapidly upon recurrence of HBV^[45]. HBV recurrence has been shown to cause atypical reappearance of HBV infection and HDV relapse in the

Table 1 Recurrence of hepatitis B virus in different genotypes

HBV genotype	No. of patients	Median follow-up (mo)	HBV recurrence number (%)	Mortality number (%)
Girlanda <i>et al.</i> ^[175] , 2004				
A	15	56	4 (27)	2 (13)
D	13	67	7 (54)	5 (38)
A/D	12	43	4 (33)	2 (17)
A/C	2	66	1 (50)	0
E	2	45	1 (50)	1 (50)
C	1	106	1 (100)	0
Devarbhavi <i>et al.</i> ^[134] , 2002				
A	10	56	3 (30)	1 (10)
C	6	22.5	3 (50)	1 (10)
D	5	15	3 (60)	1 (10)
E	1	1	0	Lost follow-up
Gaglio <i>et al.</i> ^[176] , 2008				
A	28	24	3 (10.7)	3 (10.7)
B	8	24	1 (12.5)	1 (12.5)
C	18	24	1 (5.5)	5 (5.5)
D	6	24	0	0
Lo <i>et al.</i> ^[177] , 2005				
B	43	36	4 (2)	7 (17)
C	74	36	21 (15)	7.5 (11)

HBV: Hepatitis B virus.

allografts^[53]. Additionally, the recurrence of HBV-HDV post-LT is the cause of death for many LT patients, prompting need for more research on this subject^[45,54]. In a recent study, recurrence rate of HBV after LT was not different from the recurrence rate of HBV-HDV co-infection on long-term low-dose HBIG prophylaxis along with TDF^[55].

Genetic variations of host genetic makeup in predicting HBV reactivation

Genetic variations of host genetic makeup may play some role in increased/reduced risk of HBV reactivation after LT. Single-nucleotide polymorphisms (SNP) of two-gene locus cytotoxic T lymphocyte antigen-4 (CTLA-4) +49 and CD86 +1057 were previously reported to influence the outcome of LT with respect to allograft acceptance^[56,57]. Homozygosity for CTLA-4 +49 (G/G genotype) was reported to be associated with reduced risk of HBV recurrence in post-LT Chinese patients^[56]. CD86 and CTLA-4 are known to stimulate and inhibit T cell activation, respectively.

Role of superinfection in HBV reactivation

Superinfection is defined as the infection with a second virus or a different strain of virus at a later time point, after the establishment of persistent infection of the first virus^[51,58].

Superinfection with HDV of an individual chronically infected with HBV may have deleterious consequences^[59]. This pattern of infection causes a severe acute hepatitis that may be self-limited but that in most cases (up to 80%) progresses to chronicity^[60]. The resultant chronic HDV infection usually exacerbates the preexisting CHB^[60]. It is to be noted that HBV replication is usually suppressed by HDV, and this suppression

becomes persistent in the case of a chronic HDV infection^[61,62]. Due to concern for HDV superinfection in post-LT setting, it is of utmost importance to prevent HBV recurrence after LT. Nonetheless, patients chronically co-infected with HDV are less at risk of HBV recurrence and have a better survival rate than patients infected with HBV alone. Patients co-infected with HDV generally do not require pre-transplant antiviral therapy due to HBV suppression and low viral load. Although potent HBV DNA-polymerase inhibitors can control HBV replication, reappearance of HBsAg and/or the persistence of HBV DNA in serum, liver, or PBMC might have deleterious consequences in the setting of HBV-HDV co-infection as they may provide the biologic substrate to the reactivation of HDV^[40]. No effective antiviral drug is available for the treatment of graft infection with HDV, and potentially the best approach is to keep them on long-term potent antiviral therapy along with low dose of HBIG (Figure 1).

As mentioned before, HBV has ten genotypes named A-J, and they influence the disease outcome and treatment to antiviral therapy^[63]. Depending on the geographical location, patients may have one or mixed genotypes of HBV in infected patients and consequences of which possibly have the recombinant HBV genotypes^[64-66]. The genotype C of HBV was observed in majority of the HBV-infected patients with acute exacerbation^[67]. An earlier published review reported that HBV genotypes D and C are associated with a lower rate of favorable response to alpha-interferon and pegylated-interferon alpha-2b therapy than genotypes A and B^[68]. The rate of resistance to lamivudine (LAM) was higher in patients with genotype A infection than in patients infected by genotype D, whereas no difference in the risk of LAM resistance is found between patients

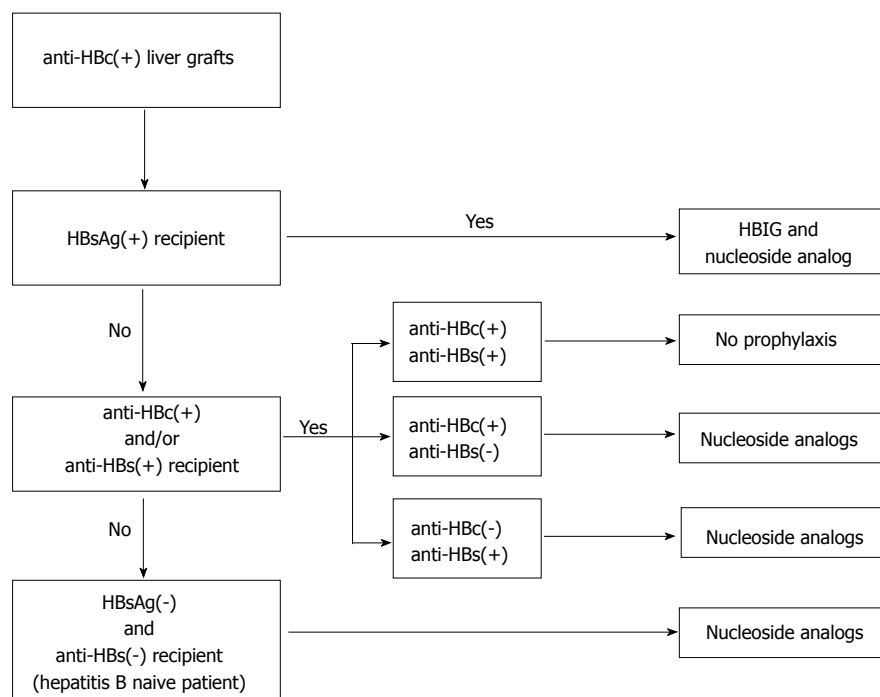


Figure 1 Stepwise approach of anti-hepatitis B core positive grafts allocated to recipients based on their hepatitis B serology. In chronic hepatitis B patients with HBsAg positive and who receive Anti-HBc positive liver grafts should be treated with HBIG and nucleoside analogs. If the recipient is HBsAg negative and Anti-HBc positive and/or anti HBs positive, NA is used for prophylaxis based on anti HBc and anti HBs serologies. No prophylaxis is recommended for anti-HBc positive and anti-HBs positive liver in LT recipient without HBsAg positive serology. These patients should be followed with periodic HBV DNA level guided by ALT to monitor for any relapse. In Hepatitis B naïve patients, NA is recommended for prophylaxis. HBIG: Hepatitis B Immunoglobulin; HBsAg: Hepatitis B surface antigen; Anti-HBs: Hepatitis B surface antibody; Anti-HBc: Hepatitis B core antibody.

with genotype B and patients with genotype C^[68]. Later studies using potent nucleotide analogue have shown no genotype specific differences in treatment responses^[69]. Another challenge with HBV is the generation of HBV variants through splicing. These variants may get activated with the disease progression post-LT leading to undesirable clinical outcomes as well as the development of drug resistance^[70].

Role of HBV integration in HBV reactivation after LT

The role of HBV DNA integration in the genome of host liver cells has been studied from the early 1980s and it had long been postulated to have implications for the antiviral therapy for HBV^[71,72]. Recent study demonstrated that HBV can integrate into the host genome immediately after its invasion^[73]. HBV DNA integration has been detected in all the stages of HBV infection including occult HBV infection^[74]. The potential for oncogenicity has been proven in the woodchuck model with occult WHV infection^[75]. In a study from Japan, eighty-two consecutive Japanese patients with cirrhosis, who were negative for serum HBsAg and antibody to hepatitis C virus (anti-HCV) were observed for a median of 5.8 years^[76]. The HCC development rates in the patients HBV DNA-positive and HBV DNA-negative were 27.0% and 11.8% at the end of the 5th year, and 100% and 17.6% at the 10th year, respectively.

The clinical significance of occult HBV infection has not been well studied in LT recipients. A recent study investigated the prevalence of occult HBV infection in

cirrhotic patients undergoing LT in a Brazilian referral center^[77]. Liver samples from 68 adults were analyzed using a nested polymerase chain reaction assay for HBV DNA and occult HBV infection was diagnosed in three (4.4%) patients. Markers of previous HBV infection were available in two patients with occult HBV infection and were negative in both. Clinical impact of occult HBV infection in immunosuppressed individuals has been recently reviewed^[78]. These results suggest potential for HBV reactivation post-LT from occult HBV infection. In fact, a recent study with 43 patients with alcoholic cirrhosis, who were negative for serum HBsAg before LT, detectable HBV DNA in the explanted liver was evident in 41.9%^[79]. *De novo* HBV infection occurred in 18.6% (8/43) of the recipients at a median of 10 mo after LT.

Extrahepatic replication of HBV and its role in HBV reactivation

Numerous reports demonstrated the presence of HBV DNA, virus genome replicative intermediates and viral proteins in hepatic tissue, and HBV DNA and HBsAg in serum of HBV-infected persons, but the existence of extrahepatic sites of HBV replication are not as well recognized. Nonetheless, the accumulated data indicate that PBMC and different immune cell types can support HBV replication^[27,80-83]. Stronger evidence came from the woodchuck model of HBV infection^[27,75,84-87]. There are also occasional observations that endothelial cells, epithelial cells, neurons, macrophages and polymorphonuclear leukocytes could be permissive to

HBV infection in humans^[88]. HBV replication was also demonstrated in *in vitro* bone marrow cultures and lymphatic tissues of patients with CHB^[89-91]. In the woodchuck model of hepatitis B, extrahepatic replication of the woodchuck hepatitis virus and infectivity of the virus derived from lymphoid cells were clearly delineated^[75,87]. Interestingly, in some situations, the lymphatic (immune) system might be the only site of virus replication in this model^[75,86,87,92].

In one of the xenotransplantation study in patients with baboon liver transplants, Lanford *et al.*^[93] demonstrated the persistence of HBV DNA in several extrahepatic tissues after HBV replication halted in the liver. In the woodchuck model, the mothers with resident hepadnaviral infection cells transmit the infection to their offspring which is predominantly restricted to their lymphatic system^[84]. These observations suggest that the attachment preferences of HBV to cellular receptors on diverse cell types might be responsible for the quasispecies specific compartmentalization of HBV^[94]. Studies related to genetic variability, drug resistance and potential immune evasion mechanisms of virus in plasma and PBMC of patients with CHB have also been investigated^[95,96]. Because of the diverse nature of the HBV in hepatic and extrahepatic tissues, the response to therapy has been shown to be different in PBMC-restricted HBV compared to hepatic HBV^[95]. In these studies, liver, plasma as well as PBMC samples were evaluated using ultrasensitive assays for the quasispecies compatibility in LT patients under long term prophylaxis. The authors inferred that extrahepatic HBV is always detectable in the serum, liver, and PBMC of almost all patients despite prophylaxis, supporting continuation of anti-HBV therapy^[95,96]. However, there is not a study yet that demonstrated that reactivation can solely originate from extrahepatic sites.

THE RISK OF HBV REACTIVATION IN LIVER TRANSPLANT PATIENTS UNDERGOING IMMUNOSUPPRESSION THERAPY

Upon HBV entry, the level at which HBV persists depends on the interplay between the viral replication rate and the host immune response. LT patients with prior HBV infection could experience a reactivation of HBV following LT due to immunosuppressive therapy, potentially leading to deleterious consequences, including graft failure and death^[97-99].

HBV reactivation in immunosuppressed patients

Immune mechanism: HBV cccDNA and low levels of HBV DNA and RNA remain detectable in host hepatocytes even in patients exposed to HBV who have developed anti-HBs after apparent complete clearance of serum HBsAg and HBV DNA from a recent infection^[87,100]. Hence, there seems to be a balance between host HBV-specific T cell and

innate immune responses and virus replication that maintains the latency of the viral infection^[80,101,102]. Immunosuppressive therapy or cancer chemotherapy may lead to induce imbalance of these mechanisms which causes HBV reactivation^[101,103].

Non-immune mechanism: HBV infection can also be flared by steroids^[104]. This may include stimulation of a glucocorticoid-responsive element (GRE) in the HBV genome which leads to up regulation of HBV gene expression^[105]. In addition, mechanistic target of rapamycin (mTOR) inhibitors, like rapamycin, that are used as immunosuppressive drugs in LT patients and certain cancers, are reported to enhance HBV reactivation in patients^[106]. It is also shown that maintaining an immunosuppressive regimen using mTOR-inhibitors post-LT commonly reactivate HBV infection, along with infections with other viruses, such as HCV, cytomegalovirus (CMV), HIV-1, human papilloma virus (HPV), Epstein Barr virus (EBV) and herpes simplex virus (HSV) as well^[107].

HCC recurrence after LT

In a Chinese registry study, patients undergoing LT due to HBV-related HCC vs HCV-related HCC demonstrated recurrence of HCC at a significantly higher rate in HBV-HCC cohort (26.39%) compared to that in HCV-HCC cohort (9.07%) ($P < 0.001$)^[108]. The risk factors for HCC recurrence were: elevated serum alpha fetoprotein, large tumor volume, microvascular invasion, high serum HBV DNA and HBsAg levels, and immunosuppression^[109,110].

Younger age has been suggested as a significant risk factor for HBV infection-related HCC recurrence after LT. It has been proposed that this could be due to the vertical transmission of HBV from the occult HBV infection harboring mother and HBV immune tolerant state of the younger patients, triggering HCC recurrence^[111,112].

PROPHYLAXIS FOR HBV REACTIVATION AFTER LT

HBsAg-positive patients

Introduction of HBIG in prevention of HBV reactivation following LT was a major milestone. HBIG is pooled polyclonal antibody against HBsAg. Although its mechanism of action remains incompletely understood, it is believed that it prohibits binding of virions to hepatocytes or promotes lysis of infected hepatocytes^[113]. In the initial days, prophylaxis for recurrent HBV infection was administered to HBsAg-positive patients using HBIG or LAM monotherapy. This strategy showed significant reduction in re-infection and improvement of graft survival after LT^[14,15,114]. Although graft survival was largely improved with either HBIG or LAM monotherapy, the re-infection rates were continued to be 30%-40% of patients^[15,19,115]. Furthermore, LAM monotherapy

resulted in development of HBV reverse transcriptase mutations that lead to antiviral drug resistance. When LT patients were on only HBIG prophylactic therapy, their chance of developing HBV escape mutations was significantly higher^[116], and this led to *de novo* HBV infection in some patients after LT^[17,117]. First described in 1998, combination therapies of HBIG with NA were successful in controlling HBV infection in most of the patients. None of the 59 patients undergoing LT for HBV-related liver failure who received high dose of HBIG intra- and post-operatively in combination with LAM as prophylaxis, showed detectable HBV DNA after 459 days of treatment^[118]. By combining LAM with HBIG, the HBV recurrence rate further dropped to less than 5%. The success of this combination regimen led it to become the most favored antiviral prophylactic regimen in ILT centers worldwide. Despite being effective, HBIG was very expensive and unavailable to a significant percentage of the patient population, and it requires regular parental injections and monitoring. In view of this, lower-dose HBIG in combination with LAM was evaluated and was found to be equally effective^[119-121]. However, this combination approach of HBIG with an oral antiviral medication is of historical value only and neither alone was sufficient in preventing HBV reactivation or recurrence. With the availability of newer and more potent oral NA, there has been a shift from HBIG combination therapy to NA alone. A systematic review by Cholongitas *et al.*^[122] noted a higher recurrence rate with combination of HBIG plus LAM compared to HBIG plus ETV/TDF (6.1% vs 1%, $P = 0.004$). A meta-analysis has shown that compared to high dose HBIG-LAM combination, low dose HBIG and potent NAs (TDF or ETV) demonstrated significantly lesser HBV recurrence^[123]. Both ETV and TDF have been associated with resistance rate of less than 2% after 5 years in patients with HBV infection^[124]. Several earlier studies have demonstrated usefulness of long term HBIG, and more recent studies have demonstrated safe withdrawal of HBIG with continuation of oral antiviral therapies alone by adopting a limited duration of HBIG use in the protocol^[119,121,125-138] (Tables 2 and 3).

Hepatitis B core antibody-positive liver donor

LT from hepatitis B core antibody (anti-HBc)-positive donors is being increasingly used due to the shortage of organs. However, due to immunosuppressive therapy, the risk of HBV reactivation is higher after LT in these patients^[139]. In a systematic review of 39 studies involving 903 LT patients, Cholongitas *et al.*^[139] evaluated the risk of HBV recurrence after LT with grafts from anti-HBc-positive donors and effect of anti-HBV prophylaxis. HBV recurrence was found to be 11% in HBsAg-positive LT patients who received anti-HBc-positive grafts compared to anti-HBc-negative grafts, but overall survival was same in both groups. They also noted that *de novo* HBV infection occurred in 19% of HBsAg-negative patients receiving anti-HBc-positive grafts. Without prophylaxis, HBV re-activation

was 15% in anti-HBc/anti-HBs-positive recipients and 48% in HBV naïve patients. However, prophylaxis using HBIG, LAM or a combination decreased re-infection rate significantly. Similarly, *de novo* HBV infection rates in HBsAg-negative patients decreased to 19%, 2.6% and 2.8% using HBIG, LAM and combination, respectively.

This study suggests that anti-HBc positive grafts can be donated safely to HBsAg-positive and anti-HBc/anti-HBs-positive sub groups, and antiviral prophylaxis decreases post-LT reactivation significantly. Due to high risk of reactivation in HBV-naïve patients, anti-HBc-positive grafts should only be considered if other two sub-group recipients are not available^[140]. Figure 2 shows stepwise approach in allocating anti-HBc-positive grafts based on recipients HBV serology and prophylaxis after LT.

Anti-HBs and Anti- HBc-positive recipients

De novo HBV infection is substantially lower in anti-HBc and/or anti-HBs-positive compared to HBV-naïve recipients^[141]. The presence of anti-HBs seems to protect from *de novo* HBV infection and both anti-HBc and anti-HBs-positive recipients represent a group that can safely receive anti-HBc-positive liver grafts without any post-transplant HBV prophylaxis (probability of *de novo* HBV infection < 2%)^[142-151]. These patients should however be followed with periodic HBV DNA level guided by ALT to monitor for any relapse. Despite this low risk, many centers prefer to continue with NA without HBIG in this subgroup of patients, and future studies will further clarify this concept (author's personal communication). Figure 3 shows stepwise approach in allocating anti-HBc-positive grafts based on recipients HBV serology and prophylaxis after LT.

Duration of HBIG administration

Currently, there is no consensus regarding the duration of use and dose of HBIG as a component of prophylaxis, and many experts believe in an individualized approach to use of HBIG in prophylaxis^[152-154]. A recent study has demonstrated that in HBV-infected patients undergoing LT, who have HBV DNA levels less than 100 U/L and an absence of co-infection with HIV or HDV, a very short course of HBIG in combination with long-term antiviral therapy is highly effective in preventing HBV recurrence^[130]. Chen *et al.*^[131] has shown infusion of two high doses of HBIG during surgery in combination with ETV significantly prevented HBV recurrence and improved the 3-year survival after LY. Another, potential cost saving approach could be combination of ETV plus low-dose on-demand HBIG^[155]. Additionally, HBIG-free approach has recently been advocated and is discussed in the later part of this review.

HBIG-free prophylaxis and treatment options

Advent of newer and more-potent NAs with high genetic barrier for resistance such as ETV and TDF, have shown great therapeutic potential as prophylactic agents, and achieved a stronger viral suppression,

Table 2 The results of combination therapy of low-dose hepatitis B immunoglobulin and nucleos(t)ide analogues and the effects of withdrawal of hepatitis B immunoglobulin from combination therapy

Ref.	NA	HBIG protocol	Median follow-up (mo)	HBV recurrence
Angus <i>et al</i> ^[119] , 2000	32 LAM	400 IU or 800 IU/d for 1 wk from LT followed by 400 IU or 800 IU/ monthly thereafter	18.4	3.1% HBsAg + and 0% HBV DNA+
Gane <i>et al</i> ^[121] , 2007	147 LAM	400 IU or 800 IU/d for 1 wk followed by 400 IU or 800 IU/ monthly thereafter	62	1% at 1 yr and 4% at 5 yr. Baseline HBV DNA was associated with HBV recurrence
Karademir <i>et al</i> ^[125] , 2006	33 LAM, 2 LAM + ADV	All patients received 4000 IU of intramuscular HBIG during surgery, 2000 IU intramuscular daily thereafter, until the HBsAb titer > 200 IU/mL and the HBsAg was seronegative, followed by lifelong 1200 to 2000 IU HBIG on-demand if HBsAb titer fell below 100 IU/mL	16	5.7% (2 of 35 patients) had HBV DNA recurrence. They were LAM resistant
Iacob <i>et al</i> ^[126] , 2008	42 LAM	10000 IU within anhepatic phase and daily within the first postoperative week, followed by 2500 IU on demand	21.6	HBV recurrence rate was 4.8% after a median of 1.8 yr
Jiang <i>et al</i> ^[127] , 2010	254 LAM	2000 IU in anhepatic phase, followed by 800 IU/d for first day then weekly for the rest of 3 wk in the first post-operative month, then 800 IU monthly	41.2	1-, 3- and 5-yr HBV recurrence rates were 2.3%, 6.2% and 8.2%, respectively 5 cases have YVDD mutations
Nath <i>et al</i> ^[128] , 2006	14 LAM + ADV	1000 IU HBIG in anhepatic phase 1000 IU/daily for week 1, then HBIG withdrawn, replaced with oral ADV	14.1	7.1%
Saab <i>et al</i> ^[129] , 2011	18 LAM + HBIG, 16 LAM to LAM + ADV	Randomized trial Patients treated with low dose HBIG + LAM ≥ 1-yr post LT 18 patients continued HBIG 16 patients discontinued HBIG and ADV added	21	0% in HBIG + LMV 6.1% in LMV + ADV Recurrent case: HBsAg + /HBV DNA (-)
Saab <i>et al</i> ^[129] , 2011	19 LAM to LAM + ADV, 41 LAM to LAM + TDF, 1 ETV to ETV + ADV	All patients treated with low dose HBIG + LAM ≥ 1-yr post-LT. All patients discontinued HBIG	15	3.3% recurrent cases: HBsAg (+)/ HBV DNA (-)
Radhakrishnan <i>et al</i> ^[130] , 2017	42 (ETV (12%), TDF (83%), or TDF/FTC (5%))	HBIG 5000 IU given in anhepatic phase and daily for 5 d together with nucleos(t)ide analogues after LT and then continued indefinitely.	36	1- and 3-year cumulative incidences of recurrence, defined by positive serum HBsAg of 2.9%
Chen <i>et al</i> ^[131] , 2015	50 (ETV before and after LT)	Two doses of HBIG-First dose anhepatic phase (10000 IU) and other dose (10000 IU) during surgery (additional doses as needed to maintain HBIG level > 300 IU/mL from 6 wk to 12 mo)	36	0% recurrence at 3 years defined as reappearance of HBsAg and HBV DNA level
Cholangitas <i>et al</i> ^[132] , 2016	34 (LAM = 2, AFV = 1, ETV = 9, TDF = 12)	HBIG 1000-10000 IU bolus during anhepatic phase, followed by daily × 7 d, and then monthly 1000-2000 IU intramuscularly for 6-12 mo post-LT and then discontinued NA were continued indefinitely	28	5.8% recurrence defined as reappearance of serum HDV in LT recipients with detectable serum HBsAg and/or HBV DNA
Wesdorp <i>et al</i> ^[133] , 2013	17 (15 of 17 converted from LAM/ADV to TDF/FTC)	All received HBIG ± (10000 IU given during anhepatic phase followed by a 4-7 d course of 10000 IU of IV HBIG daily, and then monthly intramuscularly for > 6 mo and then switched to TDF/FTC	24	No recurrence defined by HBsAg and HBV-DNA positivity. However, 6.7% had isolated HBsAg recurrence
Stravitz <i>et al</i> ^[134] , 2012	21 (Patients were initially on LAM = 11, ETV = 4, AFV = 2, LAM + ADV = 2, LAM + ADV = 2. All patients were converted to TDF/FTC)	HBIG ± nucleos(t)ide > 6 mo, then substituted with TDF/FTC	31	0% recurrence of HBV DNA after switching to TDF/FTC
Taperman <i>et al</i> ^[135] , 2013	37 patients were randomized to TDF/FTC plus HBIG (n = 19) or receive (TDF/FTC) alone (n = 18)	HBIG ± nucleos(t)ide for 24 wk, then randomized to TDF/FTC plus HBIG (n = 19) or receive TDF/FTC alone (n = 18) for an additional 72 wk	72	0% recurrence of HBV DNA in both arms

Gane <i>et al</i> ^[136] , 2013	20 patients with initial HBIG for 7 d and then switched to LAM+ ADV	HBIG 800 intramuscularly given immediately after LT and the daily for 7 d and then switched to LAM/ADV	57	0% recurrence defined as reappearance of HBsAg and HBV DNA
McGonigal <i>et al</i> ^[137,141] , 2013	4 (ETV = 2, LAM = 1, TDF = 1)	HBIG + NA for more than one year and switched to TDF/FTC	15	0% recurrence of HBsAg and HBV DNA
Angus <i>et al</i> ^[138] , 2008	34 patients randomized after 12 mo of HBIG +LAM to ADV (<i>n</i> = 16) with and without HBIG (<i>n</i> = 18)	Low dose HBIG × 12 mo along with LAM	4.4 yr for the LAM/ADV and 4.6 yr for the HBIG/LAM group	1 of 15 (6%) in the LAM/ADV and 0 of 15 (0%) in the HBIG/LAM group had HBsAg positive at last follow up

HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; HDV: Hepatitis delta virus; LAM: Lamivudine; LT: Liver transplantation; ETV: Entecavir; TDF: Tenofovir.

Table 3 Hepatitis B immunoglobulin-free regimens in preventing recurrence of hepatitis B virus infection after liver transplantation

Ref.	No. of patients	Median duration of follow-up (mo)	Therapy	HBsAg loss	Undetectable HBV DNA
Fung <i>et al</i> ^[161] , 2017	265	59	ETV	At 1, 3, 5, and 8 yr of follow up, 85%, 88%, 87.0%, and 92% were negative for HBsAg, respectively	At 1, 3, 5 and 8 yr of follow up, 95%, 99%, 100%, and 100% had undetectable HBV DNA, respectively
Fung <i>et al</i> ^[158] , 2013	362	53	LAM = 176 (49%), ETV = 142 (39%), and 44 (12%) were on combination therapy (Either LAM or ETV) plus nucleotide analog (either ADV or TDF)	HBsAg seronegativity at 1, 3, 5 and 8 yr was 80%, 82%, 82% and 88%	HBV DNA suppression to undetectable levels at 1, 3, 5 and 8 yr was 94%, 96%, 96%, and 98%. Rate of HBV DNA suppression for LAM, combination therapy, and ETV at 1 yr was 97%, 94%, and 95%, respectively
Fung <i>et al</i> ^[159] , 2011	80	26	ETV	The cumulative rate of HBsAg loss was 86% and 91% after 1 and 2 yr, respectively	95% with undetectable HBV DNA and 5% had low level viremia
Wadhawan <i>et al</i> ^[157] , 2013	75	21	19 patients received a combination of LAM+ADV, 42 received entecavir, 12 received TDF, and 2 received a combination of ETV + TDF	The cumulative probabilities of clearing HBsAg were 90% and 92% at 1 and 2 yr after transplantation, respectively	Nine patients were HBsAg-positive with undetectable DNA at the last follow-up. The recurrence rate in our series was 8% (6/75)

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; LAM: Lamivudine; ETV: Entecavir; TDF: Tenofovir.

paving the way for a HBIG free regimen for antiviral prophylaxis^[13,156]. In a multicenter trial by Gane *et al*^[136], no HBV recurrence was detected in 28 HBV patients who received a combination of LAM and ADV after a median follow-up of 22 mo when the pre-transplant HBV-DNA level was below 3 log(10) IU/mL. In a later study of 75 HBV patients who received different oral antiviral treatment after LT (19 received a combination of LAM and ADV, 42 ETV, 12 TDF, and 2 received a combination of ETV and TDF), the HBV recurrence rate was merely 8% at a median follow-up of 21 mo and there was no mortality related to HBV recurrence^[157]. There was no significant difference in HBsAg clearance and HBV-DNA suppression between those on LAM, combination treatment, or ETV, but virological relapse rate at 3 years was 17%, 7%, and 0%, respectively (*P* < 0.001).

Fung *et al*^[158] evaluated monotherapy with NAs (LAM, ETV or LAM plus ADV) without HBIG in a large, long-term cohort study involving 362 LT patients with CHB. At the end of 8 years of follow-up, 98%

showed undetectable HBV DNA in serum by clinical assay. Overall 8-year survival rate was 83% with no difference between these three treatment groups and, importantly, no mortality was observed due to HBV recurrence in any of the 362 patients. This study showed that at least in low risk patients, HBIG-free regimen with high potency NAs was safe and effective in preventing post-LT HBV reactivation. For patients without preexisting LAM-resistant mutation, the use of ETV as a standalone treatment remains an ideal choice given its lack of nephrotoxicity. In a study of 80 CHB patients undergoing LT where ETV was used alone in a completely HBIG-free regimen with a median follow-up of 26 mo a high HBsAg seroclearance rate of 86 and 91% after 1 and 2 years respectively was observed^[159]. Thirteen percent of patients had HBsAg positivity either from reappearance of HBsAg after initial seroclearance or from persistence of HBsAg-positive status after transplantation. It is important to note that there was no incidence of virological rebound or

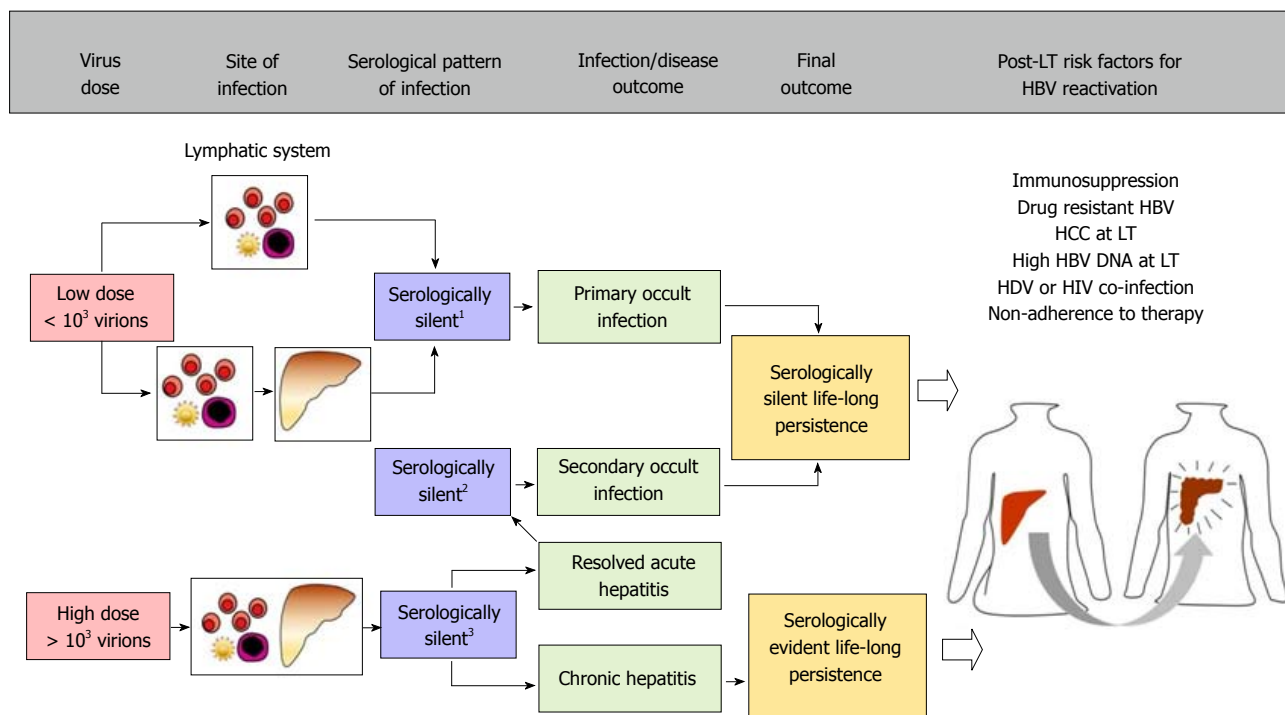


Figure 2 Generalized concept of overt and occult hepatitis B virus infections based on the data from the woodchuck model of hepatitis B, their long-term outcomes, and associated risk factors for hepatitis B virus reactivation following liver transplant. Based on experimental infection in the woodchuck model (Mulrooney-Cousins PM, Michalak TI, 2015^[92]). ¹Serologically silent infection: HBsAg, anti-HBc and anti-HBs negative; HBV DNA positive; ²Serologically silent infection: HBsAg negative, anti-HBc positive, anti-HBs positive or negative; HBV DNA positive; ³Serologically evident infection: HBsAg and anti-HBc positive, anti-HBs negative. HBV DNA positive. SOI: Secondary occult infection; POI: Primary occult infection; LT: Liver transplant; HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HDV: Hepatitis D virus; HBsAg: HBV surface antigen; anti-HBc: Antibodies to HBV core antigen; anti-HBs: Antibodies to HBV surface antigen.

resistance, nor any HBV-related graft hepatitis, graft loss, or mortality. The same group later also followed histological outcomes of CHB patients treated with an HBIG-free regimen, 42 patients were treated with ETV monotherapy who underwent liver biopsies after LT at a median time of 10 mo. Of these, 9 were serum HBsAg-positive at the time of biopsy. All patients were serum HBV DNA-negative- at the time of biopsy. None of these patients had histological evidence of HBV-related graft hepatitis and positive immunohistochemical staining for HBsAg^[160]. Fung *et al*^[161] also shown the long-term efficacy of using ETV monotherapy in a study involving 165 LT recipients with HBV. The study demonstrated that ETV monotherapy is highly effective at preventing HBV reactivation after LT for CHB, with a durable HBsAg seroclearance rate of 92%, an undetectable HBV DNA rate of 100% at 8 years, and excellent long-term survival of 85% at 9 years.

This approach has been supported by another recent study by Chongitas *et al*^[132]. They have shown that maintenance therapy with NAs prophylaxis after HBIG discontinuation was effective against HBV/HDV recurrence, but it seems that a longer period of HBIG administration might be needed before it is withdrawn after LT. Another large study from Asia has shown long-term ETV monotherapy (without HBIG) is highly effective at preventing HBV reactivation after LT for CHB, with a durable HBsAg seroclearance rate of 92%, an undetectable HBV DNA rate of 100% at 8 years, and

excellent long-term survival of 85% at 9 years. The positive outcomes with the use of ETV monotherapy without HBIG has challenged the need for HBIG post-LT^[161] A recent network metanalysis has shown that ETV resulted with the highest probability (31%) as the best prophylactic option on reducing the risk of HBV recurrence. ETV is the preferred oral NAs treatment compared to other five different prophylactic regimens (LAM, TDF, ADV, LAM plus ADV, LAM plus TDF) in the prevention of HBV recurrence after LT^[162]. With currently preferred antivirals, namely, those with high barrier to resistance, more patients are likely to have low or undetectable viral load at the time of transplantation and an HBIG-free regimen will more likely be acceptable in the vast majority (Figures 2 and 4). On the other hand, HBIG is still an integral part of prophylaxis in high-risk patients with high pre-transplant HBV DNA level, presence of HCC at LT, co-infection with HIV and HDV, presence of drug-resistance and non-compliance with therapy^[152]. However, duration of HBIG in such patients can be guided by testing of serial serum HBV DNA level, and HBsAg status (Figures 2 and 4). A recent study however has challenged this notion, and noted that oral antiviral therapy alone without HBIG is highly effective in preventing reactivation of HBV infection and graft loss from recurrent hepatitis B after LT in patients with preexisting HBV LAM resistance^[163]. The cumulative rate of HBsAg seroclearance at 1, 5, and 10 years was 82%, 88%, and 91%, respectively. At the time

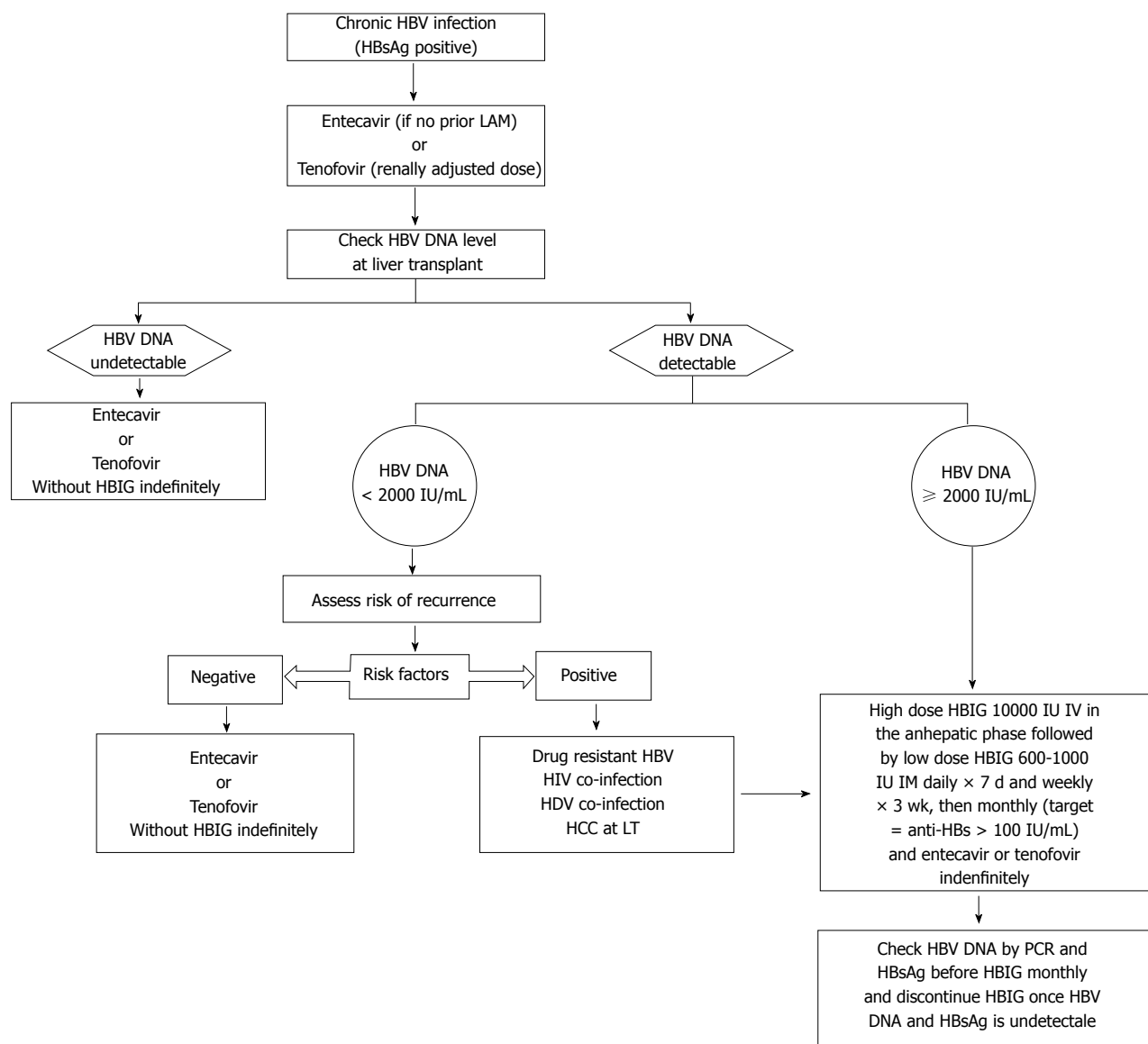


Figure 3 Proposed algorithm for hepatitis B prophylaxis in liver transplant patients. In chronic hepatitis B patients Entecavir (if no prior Lamivudine therapy) or Tenofovir (adjusted to renal function) is recommended as the first line therapy. Based on HBV DNA level at the time of transplant and risk factors, HBIG should be initiated, if associated risk factors for HBV recurrence post LT. High risk patients include drug resistant HBV, HIV co-infection, HDV co-infection, HCC. This group of patients receive high dose IV HBIG 10000 IU given during the anhepatic phase followed by low dose HBIG to achieve target anti HBs > 100 IU/mL along with NAs. HBIG is discontinued once HBV DNA is undetectable and loss of HBsAg is achieved. HBIG: Hepatitis B immunoglobulin; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HCC: Hepatocellular carcinoma; HIV: Human immunodeficiency virus; HDV: Hepatitis delta virus; LAM: Lamivudine; LT: Liver transplantation.

of transplantation, 39 (72%) patients had detectable HBV DNA, with a median of 4.5 log copies/mL. The cumulative rate of HBV undetectability was 91% at 1 year, increasing to 100% by 5 years. After 1 year of LT, over 90% of the patients had undetectable HBV DNA, and from 8 years onward, 100% had undetectable HBV DNA in serum. The long-term outcome was excellent, with survival of 87% at 12 years after transplantation, without any mortality related to HBV reactivation. However, HBIG does provide additional benefits beyond preventing HBV recurrence in LT recipients such as its association with reduced rates of rejection^[164,165], and modifying risk of developing HCC post-LT^[166]. Another important consideration is the potential for preventing graft reinfection such that subsequent discontinuation

of all immunoprophylaxis can be considered^[167]. The proposed algorithm for HBV prophylaxis for CHB patients undergoing LT is summarized in Figures 1 and 3.

Complete discontinuation of all prophylaxis

Based on the previous data and clinical studies, lifelong prophylaxis is currently advocated to LT patients to prevent HBV recurrence. Lenci *et al*^[167] investigated the safety of withdrawal of prophylactic measures in selected LT patients using a stepwise protocol. The LT patients underwent liver biopsies after receiving a HBIG-LAM combination therapy. It was shown that careful withdrawal of HBIG was safe in patients with undetectable HBV viremia at transplantation and no evidence of total and intrahepatic cccDNA.

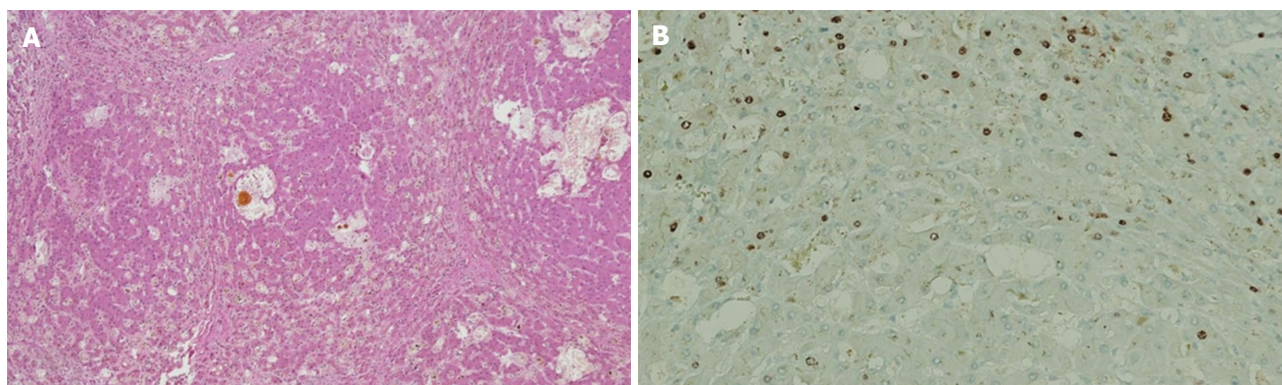


Figure 4 Immunostaining. A: Recurrent hepatitis B virus infection leading to cirrhosis in a post-liver transplantation patient. Figure shows cirrhotic nodules with cholestasis but no appreciable inflammation; B: Immunostaining for hepatitis B core antigen shows strong nuclear accumulation of antigen in a small proportion of hepatocytes indicating active virus propagation.

More recent study showed that complete prophylaxis withdrawal is safe in patients transplanted for HBV-related disease at low risk of recurrence and is often followed by spontaneous anti-HBs seroconversion^[168]. However, based on previous studies many centers continue prophylaxis indefinitely as low level HBV viremia is known to persist even after many years of therapy^[167,169], and complete discontinuation of all preventative therapy cannot be recommended at this time and should only be performed in the setting of a clinical trial^[170].

HBV vaccination and active immunity

Although there is no effective clearance, to ensure a maximum suppression of HBV in LT patients and avoidance of escape mutations caused by long-term administration of HBIG or NAs, it is crucial to develop a strong and long lasting immune response against HBV. Several trials have noted an increase in anti-HBs titer in up to 65% of patients who received HBV vaccination after LT following HBIG withdrawal^[141]. More recent study looking at active immunization in *de novo* HBV infection after LT with a HBV core antigen-positive graft have shown that active immunization is effective in preventing *de novo* infection if the post-transplant anti-HBs level is maintained above 100 IU/L with vaccination and antiviral prophylaxis. Prophylaxis can be safely discontinued in this group of patients who obtain this immunity^[171].

Emerging therapies and the future of HBV treatment

Current HBV prophylaxis and treatment modalities can only suppress but do not eradicate HBV infection completely; therefore there is a lifelong need for the therapy. Recently, there is a renewed interest to target various stages HBV replication cycle and its interaction with the host.

DAA and host-targeting agents (HTA) are the two major categories that are being developed and are at various phases of clinical trials^[2,13]. Among these, DAAs act by inhibiting viral enzymatic activities or protein function, and generally have excellent safety

profile, therefore present an attractive option for drug manufacturers. Major HBV target-specific classes of DAAs that are being developed are inhibitors of cccDNA (e.g., CRISPR/Cas9, sirt1/2, MC2792), hepatocyte entry receptor inhibitors (*via* NTCP; *i.e.*, mycludex, ezetimibe), HBV DNA polymerase inhibitors (HB pol; e.g., GS-7340, besifovir), siRNA target (ARC-520/521), core allosteric modulators (CpAM; e.g., NVR 3-778), immune modulators (e.g., GS9620, nivolumab, pidilizumab), and therapeutic vaccines (e.g., TG-1050)^[2,172-177]. These drugs are at various stages of clinical trials and they indicate a promising future for HBV prophylaxis and treatment.

CONCLUSION

With the advent of LT is currently regarded as the ultimate option for treatment for liver cirrhosis, liver failure and HCC associated with chronic HBV infection. Phenomenal success in allograft survival has been achieved by use of HBIG and oral antiviral medications. Prophylaxis with low dose HBIG and oral anti-HBV nucleotides is universally accepted as an effective option to reduce post-transplant viral reactivation. Availability of newer oral anti-HBV nucleos(t)ide analogs (NA), such as ETV and TDF, with higher barriers to resistance and better knowledge of risk factors associated with post-LT HBV reactivation have allowed incorporating these newer NA as part of the antiviral regimen after LT for CHB patients. The use of combination HBIG and lamivudine remains only of historical interest at this time as neither alone was sufficient to prevent HBV recurrence. ETV with its excellent safety profile, low nephrotoxicity, remains the agent of choice for patients without prior lamivudine resistance. For those with prior resistance, the addition of TDF is likely the best treatment option. LT with anti-HBc-positive donors is now possible due to better understanding of the balance between recurrence risk and availability of individualized prophylaxis strategies, and has expanded the pool of donor in an era with high demand for cadaveric donor with scarce supply. Current treatment regimen for

HBV can only control HBV replication, but cannot fully eradicate. As such, efficacy of HBV prophylaxis should be measured by its ability to prevent graft hepatitis and loss secondary to HBV infection, and not in terms of achieving a cure. With currently available potent NA we can achieve substantial suppression of HBV replication, but we are far from achieving viral eradication, although newer antiviral treatments approaches are in development. Hence, a positive HBsAg in post-LT period does not necessarily means HBV recurrence, as the patient has never achieved a virological cure. It is for the same reason we can argue that continuation of HBIG to achieve seroclearance of HBsAg does not achieve any clinical utility as long as viral suppression is achieved with NA. By administering HBIG to keep the antibody titers above a certain arbitrary level, serum HBsAg logically becomes undetectable because of the formation of immune complexes, which evades detection. However, this does not equate to complete eradication, nor the reappearance of serum HBsAg upon stopping HBIG signifies reactivation. In fact, hepatitis B core antigen remains detectable in the liver throughout HBIG administration despite serum HBsAg negativity. As such, long-term prophylaxis with HBIG does not serve any clinical utility and early discontinuation of this practice should be considered as long as complete viral suppression is achieved.

Emerging therapies are now focusing on newer targets of HBV replication and virus-host interaction with an ambitious goal of eradicating HBV infection in the near future rather than mere viral suppression.

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