

2015 Advances in Liver Transplantation

Application of nucleoside analogues to liver transplant recipients with hepatitis B

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Author contributions: Zheng H conducted the review; Song ZL wrote the paper; Cui YJ, Zheng WP and Teng DH revised the manuscript for important intellectual content.

Supported by National High Technology Research and Development Program (863 Program) of China, Grant No. 2012AA021001.

Conflict-of-interest statement: The authors declare they have no conflicts of interests.

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Received: April 27, 2015
Peer-review started: May 4, 2015
First decision: July 20, 2015
Revised: August 22, 2015
Accepted: September 30, 2015
Article in press: September 30, 2015
Published online: November 14, 2015

Abstract

Hepatitis B is a common yet serious infectious disease of the liver, affecting millions of people worldwide. Liver transplantation is the only possible treatment for those who advance to end-stage liver disease. Donors positive for hepatitis B virus (HBV) core antibody (HBcAb) have previously been considered unsuitable for transplants. However, those who test negative for the more serious hepatitis B surface antigen can now be used as liver donors, thereby reducing organ shortages. Remarkable improvements have been made in the treatment against HBV, most notably with the development of nucleoside analogues (NAs), which markedly lessen cirrhosis and reduce post-transplantation HBV recurrence. However, HBV recurrence still occurs in many patients following liver transplantation due to the development of drug resistance and poor compliance with therapy. Optimized prophylactic treatment with appropriate NA usage is crucial prior to liver transplantation, and undetectable HBV DNA at the time of transplantation should be achieved. NA-based and hepatitis B immune globulin-based treatment regimens can differ between patients depending on the patients' condition, virus status, and presence of drug resistance. This review focuses on the current progress in applying NAs during the perioperative period of liver transplantation and the prophylactic strategies using NAs to prevent *de novo* HBV infection in recipients of HBcAb-positive liver grafts.

Key words: Nucleoside analogues; Liver transplantation; Hepatitis B virus; Hepatitis B immunoglobulin; Hepatitis B core antibody positive donors; *de novo* hepatitis B; Prophylactic regimen

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Core tip: Hepatitis B virus (HBV)-related end-stage liver disease is a common indication for liver transplant. This

review discusses application of nucleoside analogues (NAs) for patients on liver transplant waiting lists, as well as the preventive and therapeutic strategies of NAs for HBV recurrence post-transplantation. The prophylactic role of NAs for recipients of livers from HBV core antibody-positive donors is also discussed. This review will help physicians and surgeons improve management of HBV-related liver transplant patients.

Song ZL, Cui YJ, Zheng WP, Teng DH, Zheng H. Application of nucleoside analogues to liver transplant recipients with hepatitis B. *World J Gastroenterol* 2015; 21(42): 12091-12100 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i42/12091.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i42.12091>

INTRODUCTION

Hepatitis B virus (HBV) infection is the most common chronic viral infection worldwide and ranks as one of the top health burdens^[1]. Serological evidence of current or past HBV infections is found in about 30% of the world's population^[2,3]. Despite the development of management and treatment for chronic HBV infection, some patients still advance to end-stage liver disease, where liver transplantation is the only treatment. In the early 1980s, chronic HBV was regarded as a contraindication for liver transplantation since the results were disappointing, with graft reinfection rates at 80%-100% and two-year graft and patient survival at approximately 50%^[4-6].

In the late 1980s, nucleoside analogues (NAs) and hepatitis B immune globulins (HBIG) were introduced as new prophylaxis strategies against the recurrence of HBV following liver transplantation. As a result, survival rates increased to over 75% and reinfection rates fell to less than 10% after 5 years^[7-9]. In this combination therapy, NAs suppress the replication of HBV and reduce the damage to hepatocytes by hindering the synthesis of reverse transcriptase (RT), which is essential for viral replication^[10]. HBIG is a polyclonal antibody to HBV surface antigen (HBsAg), which performs a central role in prophylaxis against recurrent hepatitis B in liver transplant recipients^[11]. However, the use of HBIG is undermined by its high cost.

Several studies have aimed to minimize or eliminate the use of HBIG without sacrificing low HBV recurrence rates. Today, NAs remain the key therapy for HBV infection in liver transplant recipients.

CLASSIFICATION AND CHARACTERISTICS OF NAs

Classification of NAs

Three main groups of NAs are used, which are based

on their structural classification. The approved NAs include lamivudine (LAM), a deoxycytidine analog with an unnatural L conformation, and the related L-nucleoside, telbivudine (LDT). The second group, the acyclic phosphonates, includes adefovir dipivoxil (ADV), a prodrug for the acyclic 20-deoxy adenosine monophosphate analog adefovir, and the structurally similar tenofovir (TDF). The third group contains a D-cyclopentane sugar moiety and includes the most potent anti-HBV drug discovered to date, the deoxyguanosine analog entecavir (ETV)^[12]. LAM was the first oral antiviral agent against HBV, and initially showed many positive efficacy and tolerability effects. However, it is no longer the treatment of choice due to its high risk of resistance^[13,14]. ADV used to be prescribed for patients with LAM resistance^[15], but they too faced development of resistance against ADV, and better NA alternatives were developed. ETV and TDF are newer antiviral drugs and have superseded other NAs since they have superior antiviral efficacy and are resilient to resistance. For these reasons, ETV and TDF are currently recommended as the first-line therapy for HBV-infected patients^[16].

Drug resistance of NAs

Although NAs can suppress the replication of HBV and control the progression of the disease, drug resistance has limited their long-term effectiveness. Although HBV has a DNA genome, it replicates through reverse transcription of an RNA intermediate. The lack of a proofreading ability of the virally-encoded RNA-dependent DNA polymerase can result in mutations at multiple nucleotide positions in the genome^[17,18]. Viral fitness, potency, and genetic barrier to resistance of the antiviral agents are the major factors associated with the development of antiviral resistance^[19]. For liver transplant recipients, the goal of antiviral therapy is to prevent the reinfection of HBV following transplantation. However, the development of drug resistance is a common problem for such patients because of the need for long-term NA use. It is therefore important to optimize the duration of use, type, and dose of NAs before and after liver transplantation. A summary of the structure, mechanism of action, and incidence of resistance of currently available NAs is listed in Table 1^[12,20,21].

USAGE OF NAs FOR PATIENTS ON LIVER TRANSPLANT WAITING LISTS

Purpose of antiviral therapy in pre-transplantation patients

Every patient with chronic HBV infection is potentially infectious and at risk of developing liver complications. Those who develop complications usually undergo antiviral therapy. However, current medications rarely achieve viral eradication in patients with chronic HBV infection^[22]. Due to the development of antiviral

Table 1 Structure, mechanism of action, and incidence of resistance of currently available nucleoside analogues^[12,20,21]

Drug name	Structure	Mechanism of action	Incidence of drug resistance
LAM	Cytidine analogue	Premature chain termination	High
LDT	Thymidine analogue		High
ETV	Guanosine analogue	Inhibits priming RT Inhibit negative and positive strand synthesis	Low
ADV	Adenosine analogue	Premature chain termination	High
TDF		Inhibit negative strand synthesis	Unknown

ADV: Adefovir dipivoxil; ETV: Entecavir; HBV: Hepatitis B virus; LAM: Lamivudine; LDT: Telbivudine; NA: Nucleoside analogue; RT: Reverse transcriptase; TDF: Tenofovir.

resistance, many patients treated with antiviral drugs nevertheless progress to liver cirrhosis. Once patients develop decompensated cirrhosis, liver transplantation is the only method of treatment available. The goal of antiviral therapy for those who eventually undergo liver transplantation is to decrease the risk of HBV re-infection. Virus levels should be tested every 3 mo^[23]. Antiviral therapy in pre-transplantation patients is important to reduce viral load to low or non-detectable HBV DNA serum levels^[24,25]. All current data suggest that an effective pre-transplantation anti-HBV therapy prevents post-transplantation HBV recurrence^[26]. The appropriate treatment with NAs to HBsAg-positive patients can maintain undetectable HBV DNA, ameliorate liver injury, and improve long-term survival following liver transplantation^[11,27,28]. Physicians should also consider how antivirals are used at other phases of the transplantation process, including (1) those on the waiting list; (2) prophylaxis therapy for transplant recipients; and (3) treatment of recurrent HBV when prophylaxis therapy fails^[23].

LAM and ADV

LAM is the most widely used NA worldwide, due to its low cost. Its efficacy has been confirmed to improve liver function, diminish the incidence of hepatocellular carcinoma^[29], and reduce the need for a liver transplant^[30,31]. However, long-term LAM monotherapy is associated with an increased rate of viral resistance due to YMDD mutations (tyrosine-methionine-aspartate-aspartate mutations), which lead to treatment failure and clinical deterioration. Mutation rates are as high as 70% after 5 years of treatment with LAM^[32,33]. ADV is effective against both wild type and LAM-resistant HBV strains^[34]. It also improves liver function in patients with HBV-related decompensated cirrhosis^[35]. However, its low potency, moderate risk of resistance during long-term therapy, and higher cost tend to impede its widespread use^[29]. Furthermore,

ADV has been found to be associated with adverse renal effects^[36,37]. These drawbacks have fueled research efforts to develop replacements for ADV and LAM. The ideal pre-transplantation therapy will be potent, have a high genetic barrier to resistance, have good virological responses, and show long-term efficacy^[38,39].

ETV and TDF

ETV and TDF are potent antiviral agents with minimal to zero risk of resistance. They are therefore currently recommended as the first line of NAs for pre-transplant therapy for patients with HBV-related decompensated cirrhosis^[16]. ETV has a high genetic barrier to resistance in nucleoside-naïve patients^[40]. A recent study of chronic HBV patients with hepatic decompensation showed that ETV administration significantly decreased mortality. Patients treated with ETV for 24 wk showed a greater reduction in serum alanine aminotransferase levels, which is elevated during acute exacerbation of HBV. Further, these patients had lower model for end-stage liver disease (commonly known as MELD scores) compared to those treated with LAM^[41]. Zhang *et al.*^[42] then reaffirmed that ETV decreases MELD scores and reported that it significantly reduces HBV DNA levels and improves the long-term survival rate in HBV patients with spontaneous acute-on-chronic liver failure. In a retrospective study of patients with chronic HBV, ETV was associated with a significantly lower risk of death compared with LAM^[43]. These findings support the use of ETV over other treatments for patients on the transplant waiting list. TDF is the most recent NA to be approved for chronic HBV treatment. Recent research showed that treatment with TDF monotherapy for 5 years led to prolonged virological remission in the vast majority of patients^[6]. Further, TDF was found to suppress LAM- and ADV-resistant HBV, suggesting that TDF may be an effective treatment for patients who had previously experienced drug resistance^[44]. Due to TDF's high potency and higher genetic barrier, it has also been used on patients with advanced liver fibrosis^[45]. However, TDF has been observed to cause adverse renal effects after 1 year of treatment^[46,47], and ETV has been reported to cause lactic acidosis in patients with severe liver dysfunction^[48]. Studies with larger cohorts did not find any lethal complication with either ETV or TDF^[32]. Despite the higher cost and potential adverse effects of ETV and TDF, they are currently recommended as the first-line therapy for chronic HBV patients and for patients with decompensated cirrhosis awaiting a new liver.

APPLICATION OF NAs IN LIVER TRANSPLANT RECIPIENTS

Prophylactic regimen with HBIG monotherapy

The use of HBIG following a liver transplantation

was the first milestone in the prevention of post-transplantation HBV recurrence. HBIG monotherapy reduced HBV recurrence by approximately 70%^[49]. HBIG monotherapy with high doses (10000 IU) are typically used during the anhepatic phase, and daily doses (10000 IU) are given for the first few days following transplantation. Subsequent doses are administered according to serum HBV titers, and can be either short term (6 to 12 mo) or indefinite^[50]. Long-term HBIG monotherapy is generally well tolerated. However, due to the possibility of late reinfection and mutations of cell surface genes, HBIG monoprophyllaxis may not be a successful solution. For this reason, combination therapy with HBIG and NAs was introduced^[51].

Prophylactic therapy with LAM plus HBIG

The second milestone for preventing HBV recurrence following liver transplantation was the approval of the use of LAM. By combining HBIG with LAM, over 95% of HBV recurrence could be prevented^[52]. However, this kind of treatment also causes several problems. For example, due to the prominent risk of viral resistance, LAM is not considered as an optimal first-line choice^[53]. Also, since HBIG is a type of passive immunization, meaning its effects are immediate and transient, antibody titer must be monitored to guide the therapy. Further, the high cost and inconvenient mode of HBIG administration (*i.e.*, repeated injections) represents a major burden in its use. Many use HBIG as treatment for a finite period of time in parallel with one or two NAs, while some clinicians completely eliminate HBIG in prophylactic regimens^[54].

Discontinuation of HBIG

A study by Buti *et al.*^[55] investigated the risk of HBV recurrence following the discontinuation of HBIG therapy in patients also receiving LAM maintenance therapy. Patients were randomized into either a LAM monotherapy group or an HBIG + LAM group and treated for 1 mo. After 91 months, the two groups had similar recurrence rates of > 10%. In a retrospective study, 132 HBsAg-positive liver transplant recipients received either LAM + HBIG ($n = 97$) or other NA besides LAM + HBIG ($n = 35$). HBV recurrence was only observed in the LAM + HBIG group at 1752 d post-treatment^[56]. Other studies have focused on using more effective NAs, other than LAM, to replace HBIG. Since ADV is a key therapeutic alternative for LAM-resistant patients^[57], it has also been used in combination with LAM to replace HBIG. A multicenter, prospective study showed that all patients who received LAM and ADV after HBIG discontinuation had no HBV recurrence 22 mo after transplantation. Combination therapy with LAM and ADV was therefore deemed safe and effective for HBV recurrence^[58]. Similarly, Nath *et al.*^[59] reported that no recurrence took place following 7 d of high-dose HBIG treatment (10000

IU) followed by LAM and ADV combination treatment. Further, these types of combination therapies are both more convenient and cheaper than using HBIG with LAM^[60,61].

As discussed earlier, ETV and TDF are particularly suitable for patients who are resistant to LAM and ADV. One study analyzed patients with undetectable HBV DNA and HBsAg-negativity at the time of liver transplantation ($n = 29$). These patients were treated with HBIG and ETV for 12 mo, after which the HBIG treatment was discontinued. After 31 mo, only one patient had recurrence^[62]. Teperman *et al.*^[63] recruited patients treated with emtricitabine (a nucleoside reverse transcriptase inhibitor)/TDF and HBIG for at least 24 wk and randomized them into two groups. One group (19 patients) received emtricitabine/TDF combined with HBIG, while the other group (18 patients) was given emtricitabine/TDF alone for an additional 72 wk. None of the study participants experienced HBV recurrence following the 72 wk in either group. After 26 mo of combined therapy with emtricitabine/TDF after HBIG discontinuation, Wesdorp *et al.*^[64] reported that only one out of 17 patients was HBsAg-positive (but without detectable levels of HBV DNA). Stravitz *et al.*^[65] reported similar results, where emtricitabine/TDF was used as a prophylaxis against HBV reinfection after HBIG discontinuation. In a recent study, liver transplant recipients who received combination therapy with HBIG and TDF or ETV were switched to NA monotherapy (ETV or TDF) for 6 mo. No recurrence of HBV was detected^[66]. Cholongitas *et al.*^[67] evaluated the risk of HBV recurrence after withdrawal of HBIG in liver recipients who underwent HBIG/NA combination therapy for at least 12 mo. Patients without HBV recurrence were enrolled for HBIG discontinuation. Of these, 28 patients continued on LAM in combination with ADV or TDF, 10 continued on with TDF monoprophyllaxis, and 9 continued on with ETV monoprophyllaxis. Although three patients developed detectable HBsAg, all of them had undetectable HBV DNA and no clinical signs of HBV recurrence.

Most of the studies examining HBIG-free therapy withdrew HBIG after several months of its application. Studies focusing on a complete HBIG-free prophylactic approach immediately following liver transplantation are limited. However, one study reported on 80 liver recipients who were given ETV without HBIG as the primary prophylaxis against HBV recurrence. Ten patients tested positive for HBsAg, and eight of those remained HBsAg-positive after 26 mo. ETV-related viral resistance was not detected in these patients^[54,68]. In another study, 75 patients with negativity for HBV DNA at the time of liver transplantation were enrolled. A combination of LAM and ADV was administered to 19 patients, 42 were given ETV, 12 received TDF, and 2 received a combination of ETV and TDF after transplantation. Only six patients were positive for HBV

DNA after 21 mo, five of which had stopped taking oral antiviral medication^[69]. Although these studies showed that maintenance therapy with effective NAs after discontinuation of HBIG prophylaxis were effective, further studies in larger cohorts with longer follow-up periods are still needed. Studies that focus on long-term use of NAs without HBIG immediately after liver transplantation are also warranted.

Is HBIG still necessary in the prophylactic regimen with the development of NAs?

The studies described above show that in select patients, HBIG can be successfully discontinued or even excluded. However, although cost and convenience for patients have been the driving force for limiting or eliminating HBIG, it is important to realize that we should not compromise the prevention of disease recurrence. A recent systemic review showed that the application of HBIG reduced HBV recurrence and virus mutants. It also improved 1-year and 3-year survival rates. A sub-group analysis showed that patients with positive pre-transplant HBV DNA status, HBIG was necessary to reduce HBV recurrence rate^[70]. Thus, only patients with an undetectable HBV DNA level prior to transplantation are suited for an HBIG-free strategy. Further, such a strategy is only possible with antiviral treatments that have high efficacy and a high genetic barrier to resistance. For those patients with high pre-transplantation HBV DNA levels or those with limited antiviral options, HBIG-free prophylaxis is not recommended^[11,71]. The duration of prophylaxis should also be considered. It has been thought that adequate prophylaxis must be life-long since NAs cannot eliminate the genomic template of covalently closed circular DNA (cccDNA). As a result, NAs do not eliminate the risk of viral replication in grafts that contain cccDNA^[1]. Consequently, the use of NAs does not eliminate the need for long-term prophylaxis in recipients at risk for recurrent HBV^[9].

RECURRENCE OF POST-TRANSPLANTATION HBV AND ITS TREATMENT STRATEGIES

Causes of HBV recurrence after liver transplantation

With the development of new antiviral agents and appropriate prophylaxis strategies, the recurrence rate of HBV following liver transplantations has significantly decreased in the last decades. However, a 0% recurrence rate has still not been achieved. Several factors contribute to the recurrence of HBV following a liver transplantation. First, pre-transplantation patients with serum HBV DNA ≥ 105 copies/mL have a much higher rate of recurrence compared with those whose HBV DNA is undetectable. Theoretically, undetectable HBV DNA should be achieved in all patients on the waiting list before

they get a new liver^[72]. However, patients that are admitted with severe decompensated cirrhosis or life-threatening complications receive transplants out of urgency, regardless of HBV DNA levels. Second, liver transplant recipients receive immunosuppressant drugs to prevent transplant rejection. It is well known that any type of immunosuppressive therapy can lead to HBV reactivation^[38,73]. Third, drug resistance is always a large risk in anti-HBV therapy—particularly for immunosuppressed patients. It was reported that the LAM resistance is detected in 45% of immunosuppressed patients within the first year following liver transplantation^[10,74], and resistance to HBIG has also been recently reported^[75,76]. Lastly, the compliance of patients also plays a role in recurrence of HBV after transplantations, where low compliance increases the risk of drug resistance^[77].

Treatment strategies for HBV recurrence

Treatment approaches for recurrent HBV in liver recipients is largely based on what we learn about drug resistance in non-transplantation patients. ADV was shown to be an effective rescue therapy for patients with LAM-resistant HBV following liver transplantation^[78,79]. In a retrospective study, five HBV-recurrent liver transplant recipients underwent safe and effective ADV therapy^[80]. ETV and TDF are also considered rescue therapy drugs for recurrent HBV following liver transplantation. ETV has been demonstrated to be safe and effective in prophylaxis treatment, even in combination with immunosuppressive agents^[81]. Fung *et al.*^[68] reported that although only 26% of patients achieved complete viral suppression at the time of transplantation, 98.8% of patients reached undetectable HBV DNA levels with ETV alone following liver transplantation. In a case report, the combined treatment of LAM and TDF effectively suppressed HBV DNA replication in a liver recipient who had LAM, ADV, and HBIG resistance^[82]. Karlas *et al.*^[83] reported that combination therapy with ETV and TDF may be a promising therapy for preventing post-liver transplantation HBV recurrence. The optimal treatment method for HBV recurrence following liver transplantation is still under debate. More clinical studies are needed to thoroughly investigate ideal combinations of antiviral agents. The current treatment selections for liver transplant recipients with HBV recurrence and drug resistance are shown in Table 2^[10,16,84].

USE OF HBcAb-POSITIVE LIVER DONORS AND THE PROPHYLACTIC REGIMEN FOR DE NOVO HBV

Use of HBcAb-positive donors

Liver transplantations have saved thousands of patients worldwide with end-stage liver diseases. However,

Table 2 Treatment selections for liver transplant recipients with HBV recurrence and drug resistance^[10,16,84]

HBV recurrence after liver transplant	LAM resistance ADV resistance ETV resistance HBIG resistance	Add ADV or switch to ETV or TDF Switch to TDF Switch to TDF Switch to NAs monotherapy or combined therapy
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HBV: Hepatitis B virus; LAM: Lamivudine; ADV: Adefovir dipivoxil; ETV: Entecavir; TDF: Tenofovir; HBIG: Hepatitis B immune globulin; NA: Nucleoside analogue.

shortages of donor livers limit their use and impede transplantation research. Thus, several strategies, including the use of HBsAg-negative/HBcAb-positive donors, have been used to expand the liver donor pool. HBcAb-positive donors were previously exposed to HBV, but did not develop chronic infection^[85,86]. The presence of persistent intrahepatic HBV cccDNA in HBcAb-positive donors constitutes a potential reservoir for viral reactivation^[87]. In the absence of prophylaxis, the frequency of HBV transmission ranges from 33% to 100%^[88,89]. It is generally agreed that HBcAb-positive donor livers should be preferentially used in recipients who were HBV-positive prior to transplantation, since these patients require HBV treatment after operation^[90]. For liver recipients unvaccinated and unexposed to HBV and who receive HBcAb-positive livers, prophylactic regimens remain to be defined. If they have never been exposed to any antiviral drugs, LAM and HBIG are regarded as the optimal prophylactic regimens. The infection rates of HBV with LAM alone or combined with HBIG treatments are approximately 10%^[91,92]. In a 12-year study period, Chang *et al.*^[93] reported that LAM monoprophyllaxis was effective in preventing *de novo* HBV in the majority of recipients, with only 8% of patients developing *de novo* HBV. Considering the high resistance rate of LAM, another study applied ADV monotherapy for liver transplant recipients who received HBcAb-positive livers. All recipients had undetectable HBV DNA after a 1.8 years^[94]. The effectiveness of ETV and TDF in this context is still unknown. Recently, Ohno *et al.*^[95] evaluated whether active immunization prevented post-transplantation *de novo* HBV infection in patients who received HBcAb-positive liver grafts. They found that 90% of recipients acquired active immunity after four vaccinations. None had any side effects from HBV vaccination and none developed HBV infection during the study period. These results indicate that vaccination provides a new effective strategy for prevention of *de novo* HBV infection following liver transplantation in recipients who were given HBcAb-positive liver grafts. Furthermore, due to the shortage of donor liver and highly effective antiviral therapy, scientists started to use HBsAg positive donor, Loggi *et al.*^[96] reported 10 patients underwent liver transplant

from HBsAg positive donors, for HBV-related disease ($n = 6$) or HBV-unrelated disease ($n = 4$). With sufficient antiviral therapy, HBV replication was effectively controlled. Besides, more encouraging outcomes of recipients who received HBsAg positive donors were also achieved by other centers^[97,98]. These studies shed light on the new era of liver transplant with HBsAg positive donors.

Prophylaxis for *de novo* HBV following liver transplantation

Although effective antiviral therapy enables the wide use of HBcAb-positive donors, many unanswered questions remain regarding the risk of *de novo* HBV and the appropriate prophylactic measures that should be taken. It should also be noted that the degree of risk also depends on the immune status of recipients^[99]. In our pediatric liver transplantation center, we found that intrahepatic HBV DNA in allografts may be a risk factor for *de novo* HBV infection in pediatric recipients of HBcAb-positive allografts^[100]. While the use of HBcAb-positive donors increases, it is of utmost importance to exercise best preventative practices. *De novo* HBV is caused by two main reasons. First, the incidence rate of *de novo* HBV is significantly higher in the recipients who did not receive any prophylactic therapy compared with those who were treated with NAs^[101]. Second, *de novo* HBV infection occurs in recipients who develop antiviral drug resistance. For these patients, mutant surveillance and change of NAs are necessary^[102]. HBcAb-positive donors can be used as a strategy to increase donor pool on the premise of effective antiviral prophylaxis with NAs and close surveillance. The strategies for preventing HBV recurrence for different groups of HBV-related liver transplant recipients are listed in Table 3.

CONCLUSION

Improvements in the effectiveness and management of antiviral NAs have substantially improved the outcomes of HBV-related liver transplantations. Optimal treatment varies from case to case, but drug resistance is a major consideration in choosing the best option. ETV and TDF are currently the treatment choice for patients with drug resistance, but they are typically combined with HBIG. Since HBIG is costly and inconvenient, HBIG-free regimens are actively explored. Recombinant HBV vaccination is also emerging as an effective strategy for preventing post-transplantation HBV recurrence. Lastly, the ability to use HBcAb-positive donors is an encouraging step to increase the supply of donor livers. Personalized treatment seems to be the key future strategy in the treatment of HBV-infected patients, but novel antiviral agents with a high barrier to resistance should also be pursued to minimize drug resistance and to treat and prevent HBV prevalence.

Table 3 Strategies for preventing hepatitis B virus recurrence for different groups of hepatitis B virus-related liver transplant recipients

Low risk recipient (undetectable HBV DNA before transplantation)	NAs + HBIG ^[52] NAs + short-term HBIG, then switch to NAs combined therapy ^[58,59] or NA monotherapy (ETV or TDF) ^[66] NAs combined therapy ^[54,68] NA monotherapy (ETV or TDF) ^[69] (Further studies are needed) NA + long-term HBIG ^[56]
High risk recipient (detectable HBV DNA before transplantation or with limited antiviral options)	
Recipient with HBcAb positive donors	NA + HBIG ^[91,92] NA monotherapy ^[93,94] Active immunization ^[95]

ADV: Adefovir dipivoxil; ETV: Entecavir; HBcAb: Hepatitis B virus core antibody; HBIG: Hepatitis B immune globulin; HBV: Hepatitis B virus; LAM: Lamivudine; NA: Nucleoside analogue; TDF: Tenofovir.

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P- Reviewer: Fujino Y, Schmidt EE, Tomizawa M **S- Editor:** Ma YJ
L- Editor: A **E- Editor:** Ma S





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