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New Perspectives on Treatment of Hepatitis B Before and After Liver Transplantation

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The hepatitis B virus (HBV) infects more than 260 million people globally, with increasing incidence, especially in developing countries. Despite antiviral therapies, HBV-related end-stage liver disease remains one of the most important indications for liver transplantation worldwide. Although new available treatments have improved the outcome of patients with both compensated and decompensated liver disease in some specific clinical settings as acute-on-chronic liver failure mortality is still high. Moreover, the incidence of HBV-related hepatocellular carcinoma (HCC) seems to be increasing and represents a major challenge for the transplant team. In the post-transplant setting, combination of anti-HBV immunoglobulins and oral nucleos(t)ides provided significant improvement on graft and patient survival. Furthermore, recent data suggested the possibility of personalized therapeutic algorithms based on pre and post-transplant viral and host risk factors. Finally, liver grafts from HBV core antibody (anti-HBc) positive or hepatitis B surface antigen (HBsAg) donors can be safely used in order to expand the donor pool, considering adequate allocation and tailored prophylaxis after LT. In this review we have focused on the evolution of antiviral therapy for HBV, highlighting useful information to aid the transplant hepatologist in clinical practice.

MeSH Keywords: **Antiviral Agents • Hepatitis B • Liver Failure, Acute • Liver Transplantation**

Abbreviations: **ACLF** – acute-on-chronic liver failure; **ADF** – adefovir dipivoxil; **ccc-DNA** – covalently closed circular DNA; **CHB** – chronic hepatitis B; **ESLD** – end-stage liver disease; **ETV** – entecavir; **HBIg** – anti-HBV immunoglobulins; **HCC** – hepatocellular carcinoma; **HRQOL** – health related quality of life; **LAM** – lamivudine; **LT** – liver transplantation; **MELD** – model of end-stage liver disease; **NUC** – nucleos(t)ide analogue; **PEG-IFN** – pegylated interferon; **TBV – telbivudine; TDF – tenofovirdisoproxilfumarate; ETV – entecavir; DDLT – deceased donor liver transplantation; LAM – lamivudine; LT – liver transplantation**

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Background

Despite massive vaccination campaigns, chronic hepatitis B (CHB) remains one of the most important causes of liver disease worldwide. Approximately 350–400 million people are chronic HBV surface antigen (HBsAg) carriers [1]. The spectrum of disease and natural history of chronic HBV infection is protean, ranging from inactive carrier state to progressive chronic hepatitis (CHB), which may lead to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. Longitudinal studies of untreated patients with CHB indicate that the 5-year cumulative incidence of cirrhosis ranges from 8% to 20%. This wide range is due to the fact that different factors (host or virus-related, co-infection with HCV, HDV or HIV viruses, metabolic syndrome, and alcohol) can affect the natural course of HBV infection [2–8]. In this group of patients, the 5-year cumulative incidence of hepatic decompensation is approximately 20% [2–4,9–11]. Decompensation represents a major change in the natural history of liver disease, being associated with poor prognosis (14–35% probability of survival at 5 years) [1,2,9–11]. Finally, it should be pointed out that the annual incidence of HBV-related HCC is particularly high, ranging from 2% to 5% [11]. HBV is responsible for a mortality rate of 2.7 and 3.5 persons per 100 000 inhabitants per year [12]. Furthermore, HBV-related cirrhosis with or without HCC still represents one of the major indications for liver transplantation (LT) [13]. In the last decades, the introduction of new antiviral therapies has dramatically changed the clinical practice both in the pre- and post-transplant setting and, nowadays, from the therapeutic point of view, management of HBV infection can be split up into 2 major chapters: before and after LT.

Antiviral Therapy in HBV-Related Cirrhosis

Compensated disease

The goal of therapy for CHB is to improve survival and health related quality of life (HRQOL) by preventing progression to cirrhosis, decompensated cirrhosis, end-stage liver disease (ESLD), HCC and death. This goal can be achieved if HBV replication is persistently suppressed. However, chronic HBV infection cannot be completely eradicated due to the persistence of covalently closed circular DNA (ccc-DNA) in the nucleus of infected hepatocytes and to the HBV genome integration. Therefore, 2 major clinical implications should be highlighted. First, the risk of HBV reactivation [14–16] implies the need for long-life antiviral therapy when eradication is not feasible. Second, there will never be no risk at all of HCC development [17,18]; therefore, long-term HCC surveillance is mandatory [19].

The first issue is when to start antiviral therapy in this population. Both patients with compensated and decompensated cirrhosis must be considered for treatment, regardless of HBV DNA detectability and/or ALT activity [20]. In this difficult-to-treat population, significant clinical improvement can be obtained with control of viral replication [21–23]. However, antiviral therapy may not be enough to rescue some decompensated patients with very advanced liver disease who should be considered for LT.

The second question is which antiviral therapy should be preferred in case of advanced liver disease. Currently, there are 2 different treatment strategies: treatment of limited duration with PEG-interferon (PEG-IFN) or long-term treatment with nucleos(t)ide analogues (NUCs). Five oral NUCs have been licensed for the treatment of CHB: 3 nucleoside [lamivudine (LAM), telbivudine (TBV), entecavir (ETV)] [1,2] and 2 nucleotide [adefovir dipivoxil (ADF) and tenofovir disoproxil fumarate (TDF)] analogues [20].

PEG-IFN-based antiviral therapy in patients with cirrhosis may increase the risk of bacterial infection and hepatic decompensation [24]. However, PEG-IFN regimens can be used for the treatment of well-compensated cirrhosis [25]. LAM (100 mg/day) was the first NUC approved for treatment of CHB and several randomized controlled trials confirmed its efficacy, showing stabilization or even improvement of liver function [26]. However, long-term LAM monotherapy is unavoidably associated with progressively increasing rates of viral resistance due to YMDD mutations (15–25% at year 1, 65–80% at year 5) [27]. Given that, international guidelines do not recommend LAM monotherapy in patients with HBV cirrhosis [20]. Moreover, high baseline HBV DNA levels are associated with higher risk of LAM resistance, at least in HbeAg-positive patients, as shown by Lau et al. [28].

ADF (10 mg/day) was the second NUC approved. However, as well as for LAM, clinicians must be aware of the risk of resistance during long-term therapy in naive patients (29% at 5 years) [29]. Since then, high costs and risk of renal toxicity [30] caused it to be largely replaced. TBV (600 mg) is a potent nucleoside analogue; however, its use in CHB monotherapy is also associated with YMDD mutations [31], and its use in monotherapy remains a matter of debate. Risk of resistance with ETV/TDF (0.5 mg) is minimal [32]. Thus, both of them are currently considered the treatment of choice in patients with both compensated and decompensated liver disease [20]. Previous history should also be evaluated. In fact, in patients with LAM resistance, ETV monotherapy should be avoided since the risk of resistance rises to 50% after 5 years of ETV treatment [33]. Finally, close monitoring of HBV DNA levels every 3 months, at least during the first year of therapy and until HBV DNA undetectability, remains mandatory because flare-ups of hepatitis B, requiring urgent management, may occur [34]. Finally, in our clinical practice in patients with compensated liver cirrhosis

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and no active HBV replication (HBV DNA-negative), we do not usually suggest NUCs-based antiviral therapy (given the mechanism of action of this category of drugs).

Decompensated disease

Patients with decompensated cirrhosis still represent a major challenge for hepatologists. Since the management of antiviral therapy is complex and these patients may be candidates for LT, they should be treated in specialized liver units. As previously mentioned, antiviral treatment is indicated irrespective of HBV DNA levels. PEG-IFN is contraindicated in this setting, thus second-generation NUCs (ETV/TDF) should be preferred. Recent studies have shown that ETV/TDF drugs are effective and also generally safe in these patients [21–23]. Suppression of HBV replication may lead to clinical improvement over a period of 3–6 months, and then LT may be avoided. In such cases, life-long treatment is needed [20]. Some patients with advanced liver disease may experience a disease progression beyond the "point of no return", and may not benefit, thus requiring LT [35]. In that situation, treatment with NUCs inducing HBV DNA undetectability at LT will decrease the risk of HBV recurrence in the graft [32].

Regarding NUCs adverse effects, lactic acidosis has been reported in small groups of patients with advanced liver disease (MELD score >20)treated with ETV [36]. Therefore, clinical and laboratory parameters should be closely monitored [22].

HBV-Related Acute-on-Chronic Liver Failure

Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity encompassing an acute deterioration of liver function in patients with cirrhosis, either secondary to superimposed liver injury (i.e., active alcoholism, acute reactivation of HBV, and HDV superinfection) or due to extrahepatic precipitating factors such as infection culminating in multi-organ dysfunction [37]. In 40% of cases, no precipitating events can be identified [38]. The prevalence of ACLF in the CANONIC Study was 30% (20% at admission and 10% during hospitalization), being particularly prevalent in alcoholic and HBV-related cirrhosis [38]. It is estimated that approximately 70% of liver failure in China is caused by HBV [39]. HBV infection is a dynamic state of interactions among HBV, hepatocytes, and immune cells of the host. Accordingly, hepatitis activity with alanine aminotransferase (ALT) elevation and episodic abrupt rise of ALT, so-called acute exacerbation or hepatitis flare, may occur spontaneously [40] during or after antiviral therapy or in the setting of immunosuppression and/or chemotherapy [41]. HBV flares occur during the HBeAg-positive immune clearance phase [40,42–44]or in the HBeAg-negative reactive phase, but less frequently [45,46]. The clinical spectrum of HBV flare is wide and varies from totally asymptomatic to a condition of decompensation [45–48], which can culminate in ACLF [49–51]. LT is the only definitive treatment for ACLF in patients who did not respond to supportive measures [52,53], with a 5-year survival rate of around 61% [54].

Antiviral therapy in HBV-related ACLF

As previously mentioned, the efficacy of NUCs has been largely confirmed for treatment of CHB [20]. However, whether NUCs would be effective for HBV-related ACLF remains controversial. The aim of antiviral treatment for ACLF-HBV is to reduce viral load in order to favor reduction in hepatocyte death and improve survival outcomes by prevention of decompensation. Some studies suggested that pretreatment HBV DNA load and its rapid reduction improved outcomes in HBV-related ACLF. More particularly, mortality of patients receiving NUCs was significantly lower than in the placebo group when antiviral therapy was started early [55].

Several studies considered the use of NUCs in patients with HBV-related ACLF. Chan et al. [56] evaluated the role of LAM in treatment of severe HBV flare leading to ACLF in 28 patients *vs.* 18 controls. The authors concluded that LAM administration was not associated with any survival benefit. The same results were described by Tsubota et al. [57] in 25 patients with spontaneous HBV flare treated with LAM. Wong et al. [58] treated 45 patients with severe flare and 31 controls with LAM for a median of 2.8 (range 1.0–7.1) years and 3.8 (range 3.5–8.4) years, respectively. They found that patients with severe acute exacerbation had higher HBeAg seroconversion rates and lower risk of virological breakthrough. However, 33% of patients with severe acute exacerbation still developed LAM resistance and virological breakthrough by 5 years. In a second cohort of 60 consecutive HBV-related ACLF patients treated with LAM, Chen et al. [59] concluded that LAM may prevent death if therapy was started early (before serum bilirubin levels rose over 20 mg/dL). Sun et al. [60], analyzing the factors which could affect prognosis, and found that cumulative survival rates of patients in the LAM group were higher than those of the control group. In the study by Tsang [61], 24 patients treated with LAM were subsequently divided into 2 groups: Group A including patients who survived (33%) and group B including 13 patients who died and 3 patients who underwent LT (67%). Full HBeAg seroconversion was documented in 6 out of 8 (75%) patients after a few months of LAM treatment. However, HBeAg reverted to positive in 4 patients after the end of therapy, leading to recurrent hepatitis. Nevertheless, the authors concluded that LAM may be useful in treating patients with HBV-related ACLF. It should be noted that only 33% of enrolled patients survived without LT. Why was LAM so ineffective in treating this population? Factors other than viral replication have a great impact

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on the prognosis. Livers of these patients have already undergone massive or sub-massive hepatic necrosis. Therefore, suppressing viral replication at this late stage seemed ineffective, as the major determinants for prognosis are liver regeneration and rapid cessation of ongoing inflammation. Neither of these factors are directly dependent on HBV. Moreover, in recent years, LAM therapy for ACLF-HBV has become less appealing due to drug resistance.

Data regarding the use of ADF for ACLF-HBV are very scant [62,63]. In 2 case reports, ADF failed as rescue therapy of LAM resistance after jaundice and development of liver failure. Adefovir has a relatively weak antiviral activity. Therefore, ADF use as a first-line drug in the treatment of acute severe exacerbation seems unfavorable.

Chen et al. administered ETV to 55 patients with severe acute exacerbation of HBV, comparing them with 74 patients who were not treated with any NUC. ETV was capable of a great reduction of HBV replication; however, the MELD score and liver function tests (albumin, bilirubin, and prothrombin time) showed no significant change. Therefore, the authors concluded that short-term suppression of HBV replication may not reduce the progression of liver failure [64]. In 2013, Lai et al. [65] analyzed the data from 182 HBeAg-negative Chinese patients with ACLF (93 treated with ETV and 89 with LAM). HBV DNA levels decreased within 3 months in both groups (P<0.05), regardless of MELD score before treatment. More importantly, 3-month mortality was similar between groups. Given that, they concluded that ETV and LAM are equally effective. Liu et al. [66] performed a similar study, showing no significant differences between virological, biochemical, and clinical outcome in 2 groups of patients treated with ETV *vs.* LAM [36]. In a more recent study by Chen et al. [67], both the safety and efficacy of ETV and TBV were evaluated. Twenty-one consecutive patients with ACLF-HBV were treated with either ETV or TBV. During the course, deterioration of estimated glomerular filtration rate was significant in the entecavir-treated group (P=0.028) but not in telbivudine-treated patients (p=0.8). Furthermore, patients treated with TBV had a significant increase in serum α-fetoprotein (27.9–191.9 ng/mL, P=0.046) in the first 2 weeks, whereas the corresponding increase was not found in those treated with ETV (P=0.139) [67]. The pros and cons of LAM *vs.* ETV in decompensated or severe acute exacerbation of CHB show that ETV seems more effective in promoting faster viral load reduction, albeit its hepatic and extrahepatic adverse effects [68[.

Garg et al. [69] randomized consecutive patients with ACLF due to spontaneous reactivation of CHB to receive either TDF or placebo, with a primary endpoint of 3-month survival. They showed a rapid (>2 log within 2 weeks) decrease in HBV DNA, and reported that TDF-based therapy significantly improved survival in HBV DNA-related ACLF.

Yu et al. [70] recently conducted a meta-analysis of prospective and retrospective studies to examine the efficacy and safety of NUCs in treating HBV-related ACLF. All the ACLF patients included in the studies met the APASL diagnostic criteria [71]. Five eligible studies, 2 RCTs [69,72] and 3 retrospective studies [59,60,73], were identified. Antiviral treatment with NUCs led to significant reduction of HBV DNA [HBV DNA reduction >2 log: 70.4 *vs.* 29%, RR=2.29, 95%CI (1.49, 3.53), P<0.01] and incidence of HBV reactivation [1.80 *vs.* 18.4%, RR=0.11, 95%CI (0.03, 0.43), p<0.01]. Three-month mortality was significantly lower in patients receiving NUCs [44.8 *vs.* 73.3%, RR=0.68, 95%CI (0.54, 0.84), p<0.01] as compared to no treatment. However, 3 studies compared LAM *vs.* ETV as rescue therapy, suggesting no significant difference in the prognosis [36.4 *vs.* 40.5%, RR=0.77, 95%CI (0.45, 1.32), p=0.35]. Given these data, NUCs treatment (LAM with the same result of ETV) seems to reduce short-term mortality as well as reactivation of HBV-related ACLF patients. It should be noted that even in the treatment group, only patients with rapid decline in HBV DNA had a better prognosis [60,69]. Thus, viral factors may participate to the pathogenesis of the severe hepatic necro-inflammation, and subsequently to decompensation. Therefore, appropriate antiviral therapy might prevent, or at least slow, the progression of necro-inflammation and allow hepatic regeneration. However, comparable efficacy was found between ETV and LAM. Nevertheless, it might be possible that the difference between ETV and LAM in suppressing HBV replication was not large enough to affect the prognosis of this difficult-to-treat population.

Other treatments have been evaluated in the setting of HBV-related ACLF (e.g., corticosteroids, granulocyte colony-stimulating factors, artificial liver support systems, immune regulatory therapy, and stem cell therapy) [74]. Some of these therapeutic approaches have been shown to potentially improve liver function and increase patient survival, but most of the studies were not randomized or controlled. Moreover, these kinds of treatment are still experimental and not available in clinical practice. Finally, since patients with ACLF are very challenging and require rapid multidisciplinary evaluation, they should be referred to a tertiary care center when LT is feasible [75].

HBV-Related Acute Liver Failure

HBV is an important cause of acute liver failure (ALF) worldwide. The prognosis is quite poor, with reported LT-free survival ranging from 26% to 53% [76]. Despite recent advances in antiviral agents, there is no definitive evidence that antiviral therapy can modify the natural history of the disease.

To date, no placebo-controlled trials have been published in the setting of HBV-related ALF. Some case series suggested lower mortality in patients with ALF treated with antiviral therapy

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compared to patients without treatment. However, it should be stressed that most of these studies recruited patients before the development of grade 3 or 4 hepatic encephalopathy.

In the multicenter study by Tillmann et al. [77], patients with severe acute or fulminant hepatitis B were treated with LAM in an attempt to prevent HBV reinfection after potential LT. Since September 2000, 17 patients with HBV infection were treated with 100 or 150 mg LAM daily once there was evidence for a severe course as indicated by an INR >2.0. Fourteen of the 17 patients (82.4%) survived with full recovery without LT. All these 14 individuals cleared HBsAg on LAM within 6 months. Twelve patients recovered quickly, as indicated by a normalized prothrombin time within 1 week, while 2 patients had a more prolonged course. None of the patients showed adverse events. Three patients requiring LT despite LAM therapy had more advanced disease at admission. The LAM-treated patients had significantly higher LT-free survival (82.4 *vs.* 20%) if compared with a historic cohort (P<0.001). The authors concluded that LAM seemed safe in patients with severe HBV-related ALF, leading to fast recovery and a potential prevention of liver failure and LT when administered early enough. However, the sample size seems too small for this conclusion. Moreover, the comparison with the historical control group could lead to several biases. Finally, the definition of ALF was based on prolonged INR and not on clinical features (e.g., severe hepatic encephalopathy).

In contrast, in the study by Dao et al. [78], which only included patients with ALF defined by the presence of both encephalopathy and INR >1.5, no beneficial effect of NUCs therapy was described in those with HBV-related ALF. The authors performed a retrospective analysis of the outcome in 85 patients with HBV-related ALF, 43 of whom had received NUCs treatment. Patients were enrolled in 23 centers between 1998 and 2008. No significant differences were found at the baseline between treated and untreated groups. Median duration of NUCs treatment was 6 (range: 1–21) days. Interestingly, overall survival in the NUCs-treated and NUCs-untreated groups were 61% and 64%, respectively (p=0.72). Similarly, rates of transplant-free survival were 21% and 36% in the treated and untreated groups, respectively, p=0.42. Furthermore, multivariate analysis revealed absence of NUCs as a predictor of survival [odds ratio (OR) 4.4, 95% CI 1.1–18.1, p=0.041], as well as hepatic encephalopathy grade I or II [OR 14.4, 95% CI 3.3–62.8, p<0.0001], and prolonged prothrombin time [OR 0.59, 95% CI 0.39–0.89, p<0.012]. Given these results, patients who are admitted with established HBV-ALF seem not to benefit from viral suppression using NUCs. Finally, Kumar et al. [79] performed a prospective randomized study showing no clinical benefit of LAM in acute hepatitis B, even though the decline of serum HBV DNA was faster. Patients with serum bilirubin of more than 5 mg/dL were randomized to receive either 100 mg of LAM daily for 3 months (group 1, n=31) or placebo (group 2, n=40). Patients were considered to have severe acute hepatitis B if they fulfilled 2 of 3 criteria: (1) hepatic encephalopathy; (2) serum bilirubin ≥10.0 mg/dL; and (3) INR ≥1.6. At week 4, HBV DNA levels were significantly lower (P=0.037) in group 1 (median: 3.6721 log copies/mL) than in group 2 (median: 4.2721 log copies/mL), whereas the improvement in serum bilirubin, ALT, and INR values was similar in the 2 groups. Twenty-two patients (71%) in group 1 and 25 patients (62.5%) in group 2 had severe acute hepatitis B. After 12 and 18 months, 93.5% and 92.5%, respectively, of patients in the LAM group and 96.7% and 97.5%, respectively, of patients in the placebo group lost HBsAg. There were no deaths in either group, so it is still uncertain whether these data can be generalized to patients with HBV-related ALF. One of the possible reasons of this clinical finding may be the rapid disease evolution. Blocking the viral replication in this clinical scenario may not be sufficient to stop massive necroinflammation induced by the immune activation. However, despite the lack of benefit, NUCs therapy should be still at least be considered for LT candidates since viral suppression is important to prevent recurrence after grafting [80]. Considering the conflicting results and insufficient data, prospective randomized controlled trials are necessary to assess the role of antiviral therapy in HBV-related ALF. To date, since there is not enough evidence that antiviral therapy or artificial liver support devices can improve patient survival, LT should still be considered as the only effective treatment option that can alter the grave prognosis of HBV-related ALF [75].

Recurrence of HBV Infection After LT

Recurrence of HBV infection after LT was considered a major problem in the past because this risk was higher for HBV-related cirrhosis than for HBV-related ALF. However, newly available weapons led to a significant improvement in graft and patient survival after LT for HBV in recent decades. Data retrieved from the ELTR registry [13] showed a 1-, 3-, 5-, and 10-year graft survival of 83%, 77%, 74%, and 67%, respectively, being significantly better than for HCV related cirrhosis (each p<0.001). Furthermore, short-term survival at 1 and 3 years after LT after the start of the 21st century was significantly higher compared to the previous decade (p<0.001), confirming the improvement in prognosis.

If untreated, recurrence after LT is almost universal, with rapidly progressive hepatitis that jeopardizes long-term patient and allograft survival.

Recurrence is firstly characterized by serum HBsAg and HBV DNA reappearance, followed by biochemical, histological, and clinical evidence of liver disease. Nonetheless, the definition of clinical recurrence after LT is somewhat controversial, because cases with detectable HBsAg, with undetectable HBV

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DNA, normal liver enzymes, and no clinical manifestations of HBV recurrence may not have any clinical impact on long-term graft and patient survival [81].

A landmark multicenter study published in 1993 by Samuel et al. investigated risk factors for recurrence among 201 LT recipients with HBV-related cirrhosis from 17 centers in Europe. They found in multivariate analysis that HBV DNA negativization before LT (P<0.05) was associated with reduced risk of HBV recurrence. Thus, the number of patients with HBV DNA positivity at LT rapidly decreased over time (from 81.2% before 1995 to 51% in 2006–2010), although no significant difference was found in terms of patient and graft survival (p=0.79 and p=0.88, respectively) [13]. Other factors associated with reduced risk of recurrence were HDV co-infection and ALF.

Other studies identified the protective role played by HDV in prevention of HBV recurrence after LT, because HDV exerts a suppressive effect on HBV replication after LT. Regarding HBV-related ALF, the second group at lower risk of HBV recurrence, some authors asserted that the acute and massive necrosis secondary to fulminant infection can led to a natural clearance of the viral load [82,83].

HBIg for HBV prophylaxis after LT

Initially, prophylaxis against HBV reinfection was successfully performed with anti-HBV immunoglobulins (HBIg), as shown by Samuel et al. [83] in 1993. HBIg may help the immune system to protect the graft through binding to circulating virions, blocking the HBV receptor, and inducing lysis of infected cells by antibody-dependent cell-mediated cytotoxicity. The authors demonstrated a significant reduction of reinfection (from 75% to 33%) and an increase of mid-term survival (from 54% to 83%) after LT.

NUCs for HBV prophylaxis after LT

For the second time, the use of LAM opened a new chapter in the history of prophylaxis. In 1996 Grellier [84] showed that mono-prophylaxis with LAM before and after LT provided good short-term outcomes, with 9 out of 12 patients HBV DNA-negative within 6 months after LT. However, subsequent studies revealed a significant relapse due to LAM mutation; Chan [85] evaluated 20 LT recipients receiving LAM mono-prophylaxis after LT for a median time of 2 years, and demonstrated a cumulative probability of developing mutations equal to 34%. Thus, this treatment strategy is considered suboptimal, especially when using LAM mono-prophylaxis.

In the last decade, new-generation NUCs (ETV and TDF) have been tested as mono-prophylaxis in the setting of LT. Fung et al. [86] evaluated 80 consecutive LT recipients with previous chronic HBV liver disease, of which 41% received a DDLT and 74% had detectable HBV DNA at the time of LT. The authors demonstrated that after a median follow-up of 26 months with ETV mono-prophylaxis, 8 patients did not achieve HbsAg sero-clearance, while 10 experienced reappearance of HBsAg after initial sero-clearance; these 18 patients had higher HBsAg levels at the time of transplantation (868.95 *vs.* 415.10 U/mL, respectively; p=0.03), but only 1 patient had HBV DNA positivization. The same group [87] confirmed that mono-prophylaxis with high genetic barrier NUCs was safe in another study comprising 362 patients (38.4% having chronic HBV liver disease), of whom 142 were treated with ETV and 176 with LAM. Type of antiviral therapy (LAM *vs.* ETV), indication to LT (HCC *vs.* decompensated liver disease), and high viral load at LT were significant factors associated with virological rebound in multivariate analysis. More recently, Fernandez et al. [88] prospectively enrolled 58 LT recipients who were mainly at lower risk of reinfection (ALF, HDV co-infection). After 12 months of combined NUCs/HBIg therapy, they were converted to TDF or ETV mono-prophylaxis; 5 patients (8.6%) developed HBsAg detectability, without HBV DNA reappearance.

Thus, ETV and TDF should be the first-line options when a mono-prophylaxis would be adopted; for patients with known LAM resistance, TDF should be the treatment of choice.

Combination therapy

NUCs act directly by reducing viral load in the liver and extrahepatic sites. They determine a synergistic activity between HBIg and NUCs, because reduction of viral load can prevent saturation of HBIg binding sites, and, conversely, HBIg reduces viral mutation [89]. At present, combination with NUCs and HBIg is considered the treatment of choice for prophylaxis of HBV reinfection, since the risk of graft infection is less than 10% [75].

These data came from high-quality studies. A meta-analysis comparing 10 studies, published by Katz et al. [90], demonstrated that combination therapy was significantly better than HBIg monotherapy in preventing reinfection (6.2% *vs.* 21%; RR=0.28; 95%CI: 0.12–0.66) and in reducing mortality (RR=0.44; 95% CI: 0.25–0.77).

Another systematic review aiming to assess any difference between high-barrier NUCs mono-prophylaxis and combination therapy [91] revealed that HBV recurrence was observed significantly less frequently using the latter strategy [26% (29/112) *vs.* 5.9% (109/1834), p<0.0001].

More recently, Wang et al. [92] performed a systematic review of 1484 patients from 19 studies, and demonstrated that combined treatment reduced HBV recurrence (RR=0.16; 95%CI: 0.12–0.20 *p*<0.001) and improved early survival (RR=0.08;

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95%CI: 0.01–0.15; p=0.03). Interestingly, the authors showed that combination therapy was more effective only in the subgroup with HBV DNA detectable before LT (p<0.001; RD=0.42; 95%CI: 0.32–0.52), highlighting the importance of pre-LT viral load, also suggested by the abovementioned study by Fung [87].

Combination prophylaxis: Pros and cons.

In recent years, several factors (e.g., high-barriers NUCs and increasing survival rates, but also costs, treatment adherence, recipients aging, and comorbidities) led hepatologists to look for personalized prophylaxis regimens, which should be simultaneously effective and cost-saving (Table 1).

Regarding costs, combination therapy with high-dose HBIg costs over $100 000/patient in the first year after LT [93], suggesting that this long-life therapy could not be affordable for all the heterogeneous healthcare systems worldwide.

Considering adherence, Chang et al. [94] demonstrated that non-compliance to HBIg was 14% in a small cohort of LT patients, even though anti-HBs titers were satisfactorily achieved. Adherence represents a main goal for LT recipients, independent of etiologies [95].

Different routes of HBIg administration have been proposed to maximize compliance (self-made, home treatment subcutaneous route [96]), and quality of life. Franciosi et al. [97] validated a specific questionnaire for testing HRQOL among HBIg users. Intra-muscle administration provided better scores on the flexibility (81.5±21.4 *vs.* 73.1±24.2, P=0.01) and negative feelings scales (90.1±17.3 *vs.* 85.4±20.7, P=0.04).

On the other hand, long-term NUCs mono-prophylaxis raised some concerns in the setting of LT, mainly due to the possibility of renal dysfunction. Between 30% and 80% of LT recipients develop chronic kidney disease stage 3–4 within the first 10 years post-LT. It can be due to pre-transplant injuries, arterial vasoconstriction due to CNIs, recurrence of hepatitis C, diabetes, and/or metabolic syndrome. Chronic renal disease is associated with a statistically significant increased risk of mortality in the early and late post-LT course [75].

Even though both first- and second-generation NUCs can cause renal tubular dysfunction [98], a single-center observational study [99] did not show significant differences in renal impairment between LT recipients treated with HBIg mono-prophylaxis *vs.* combined prophylaxis (eGFR66.2±25 *vs.* 66.2±18 ml/min; p=0.29). However, the association between NUCs and renal dysfunction should be better evaluated with large-cohort studies, as well as in the long term after LT.

Personalized algorithms for prophylaxis

In recent years, personalized algorithms for prophylaxis of HBV reactivation, balancing risk factors for recurrence and patients' comorbidities, have been proposed.

In a relatively small number of patients (n=102) followed for a median of 24 months [91], Cholongitas et al. confirmed that the use of ETV/TDF prophylaxis after HBIG discontinuation seemed not to be inferior to the combination of NUCs plus HBIg (3.9% *vs.* 1.0%, p=0.17), but also not to be superior to the combination of HBIg and LAM, when the definition of HBV recurrence was based either on HBsAg (3.9% *vs.* 5.9%, p=0.52) or HBV DNA reappearance (0% *vs.* 3.8%, p=0.08). Tandoi et al. [100] proposed an HBIg minimization strategy based on the individual risk profile and on serological targets. In 35 LT recipients (51.4% with HDV co-infection), they used a specific NUCs plus HBIg schedule (10 000 IU during the LT operation and subsequently 5000 IU/day until HBsAg negativization and achievement of an HBsAb protective level >300 mIU/mL, and then pulses of 2500 only if HBsAb titer was <300 mIU/mL). After a median follow-up of 10.5 months, there was no recurrence, and they reported a correlation between quantitative HBsAg level at LT and HBIg administered in the first month after LT.

Similarly, Hu et al. [101] demonstrated that an on-demand HBIg schedule (adjusted for anti-HBs titer) plus ETV was effective in preventing HBV recurrence, which developed in only 2/145 (1.37%) patients. Also, a strategy using early subcutaneous administration of HBIg seemed effective in preventing HBV recurrence. De Simone et al. [102] prospectively switched 49 patients from i.v. to s.c. HBIg administration within 3 weeks after surgery (adjusted dose according to serum anti-HBs titers). All patients receiving combination therapy remained HBV DNA-ve (45/45), and only 1 adverse event (mild injection site hematoma) was assessed as treatment-related.

Lastly, vaccination after LT has been investigated as a potential tool for prophylaxis of HBV recurrence. In a pilot study, Sanchez Fueyo et al. [103] demonstrated that HBV vaccination after 1-year therapy with HBIg was useful and cost-effective in a small cohort of 16 selected recipients. However, long-term follow-up data evaluating this strategy among large cohorts of patients are still missing.

In our opinion, combination therapy of HBIg [at least for a fixed period (1-year)] and NUCs seems to be the safest post-transplant approach. Furthermore, this should be limited to non-HCC patients with no risk factors for HBV recurrence after liver transplantation (i.e., HBV DNA-negative at time of liver transplant). However, mono-prophylaxis strategies with high-barrier NUCs, eventually based on pre-transplant risk factors, should be adopted [75].

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Table 1. Clinical trials evaluating strategies for HBV prophylaxis after LT in the last 10 years.

Authors, year [Ref]	No. of patients	Study design	Mean follow-up (months)	Endpoint	Outcome
Yi, 2013 [70]	29	HBIg + ETV for 5 weeks, then ETV monotherapy	31	Recurrence (HBsAg +)	Recurrence-free survival 96.6% at 1 year
Teperman, 2013 [113]	40 (19 TDF; 18 combo)	combination for 24 weeks, then randomization	18	Recurrence (HBsAg+)	Recurrence-free survival 100% in both groups
Gane, 2013 [114]	26	ADF+LAM before LT. HBIg withdrawal 7 days after LT	57	Recurrence (HBsAg +/HBV DNA –)	Recurrence-free survival 100%
Saab, 2011 [115]	61	HBIg + LAM for 12 months after LT; then, 2 NUCs (nucleotide and nucleoside)	15	Recurrence (HBsAg +), with or without HBV DNA +	RFS 98.3% at 1 year
Kawagishi, 2010 [116]	14	HBIg+ NUCs for 12 months; then only NUCs	30	Recurrence (HBsAg +)	2 out 14 experienced recurrences
Yuefeng, 2011 [117]	15	HBIg + LAM, then LAM alone	Range 42 to 86 months	Recurrence (HBsAg + and HBV DNA +)	2 out of 15 experienced recurrences (LAM resistance)
Angus, 2008 [118]	34 (16 ADF; 18 HBIg)	HBIg + LAM 12 months after LT. Then, randomization to ADF/HBIg	54	Recurrence (HBsAg+)	Recurrence: 1/16 *vs.* 0/18
Buti, 2007 [119]	29 (20 LAM; 9 LAM + HBIg)	HBIg + LAM for 1 month; then, randomization to LAM with or without HBIg	83	Recurrence (HBsAg+)	Recurrence: 3/20 *vs.* 1/14. The mean recurrence-free interval was 92.77 and 92.16 months (P=ns)
Wong, 2007 [120]	21 (15 HBIg + NUCs; 6 NUCs)	HBIg + NUCs for 12 months, then randomization to NUCs with or without HBIg	40	Recurrence (HBsAg + or HBV DNA ≥5 log copies/mL)	0/15 *vs.* 2/6 (both patients with LAM resistance)
Lenci, 2011 [121]	30 (undetectable intrahepatic total and ccc-DNA at time of LT)	HBIg withdrawal and continued lamivudine with monthly HBsAg and HBV DNA monitoring and sequential liver biopsies. If confirmed intrahepatic total and ccc-DNA undetectability 24W after stopping HBIg, → LAM withdrawal	29	Recurrence (HbsAg +)	Five patients became HbsAg-positive: one early after HBIg withdrawal, the other 4 after HBIG and lamivudine withdrawal

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HBV-HDV liver transplant recipients

HDV co-infection is a known risk factor for end-stage liver disease. Co-infection has remained a stable indication for LT in the last 2 decades, with a prevalence of 2% of all LT in Europe [104]. Analyzing data from the ELTR registry [13], HDV co-infection was associated with better short- and long-term patient survival *vs.* HBV mono-infection (1-, 5-, and 10-year survival: 92%, 89%, 86%, and 83%,75%, 60%, respectively, each p<0.001). Encouraging data were also confirmed for grafts (1-, 5-, and 10- year graft survival: 81%, 85%, 80%; 80%, 71%, 64%, respectively, each P < 0.001). Better survival is presumably due to inhibition of the HBV replication cycle [105]. Since specific prophylaxis for HDV reinfection is not available, the most effective strategy to prevent HDV reinfection is the standard HBV prophylaxis with HBIg and antiviral therapy [75].

Treatment of recurrence after liver transplantation

There is no consensus about considering HBV recurrence as HBsAg or HBV DNA reappearance after LT. If untreated, HBV recurrence can cause rapid development of severe liver dysfunction. The aim of therapy is to control HBV replication over time to prevent graft loss [75]. High-barrier NUCs provided good results for treatment of HBV recurrence; however, renal function has to be carefully evaluated. In this setting, ETV may be the preferred option, but attention should be paid to previous LAM therapies.

Use of suboptimal donors: Anti-HBc and HbsAg-positive donors

One of the major problems in the LT setting is the gap between patients in the waiting list and the donor pool. For this reason, suboptimal donors have been used to increase organs availability. Anti-HBc-positive donors are the most common suboptimal liver donors; the anti-HBc donor rate depends on HBV prevalence, being 5.5% in the USA, 10–15% in Europe, and 50% in Asia. Albeit in the absence of detectable serological viremia, anti-HBc-positive subjects can have detectable viremia in hepatocytes because of the ccc-DNA.

This replication could increase during immunodepression or immunosuppression states, as after LT. Thus, use of anti-HBc-positive grafts represents the first cause of *de novo* HBV infection after LT.

Yen et al. identified 90 cases of *de novo* HBV infection among 194 recipients who did not receive antiviral prophylaxis. The majority of infections occurred in HBV non-immune recipients (82/107), but also in previously vaccinated recipients and in isolated anti-HBc recipients. No cases of *de novo* HBV infection were reported among naturally immune (anti-HBc anti-HBs +ve) recipients [106].

Thus, evaluation of recipient's HBV serology before LT is mandatory. This risk has been estimated to be 0–5% in anti-HBs and anti-HBc-positive recipients, 10–18% in isolated anti-HBc or anti-HBs positive ones, and 70–80% in HBV-naive recipients [107].

Prophylaxis after LT is of paramount importance. Different therapeutic strategies have been used. The first approach was mono-prophylaxis with HBIg, which produced a reduction of *de novo* HBV of 31.6% in naive recipients and of 7% in HBc-positive recipients [107]. Then, new therapeutic regimens combining NUCs and HBIg, aiming to limit HBIg over-use and to prevent viral mutations, were proposed. New therapeutic options using HBIg and NUCs or NUCs alone mono-prophylaxis have been proposed. In contrast to HBV +ve recipients, the addition of HBIG to NUCs did not confer higher protection to LAM alone in this cohort of patients [108]. A recent consensus stated that LAM is the treatment of choice as it is the most cost-effective for prophylaxis, while ETV/TDF therapies may also be considered in more selected cases [75,109].

HbsAg-positive donors are another category of suboptimal donors used in recent decades, albeit in limited cases. In these donors with chronic HBV infection, liver biopsy is mandatory to exclude significant liver damage (i.e., inflammation or fibrosis) [109,110].

A retrospective analysis of UNOS data reviewed the outcomes in 92 recipients who received HBsAg +ve grafts [111]. The authors did not show any difference in patient or graft survival when compared to recipients of HBsAg –ve grafts. Yu et al. [70] followed up 23 recipients who received HBsAg +ve grafts and who underwent combination therapy (ETV + HBIg) after LT; the recurrence rate of HBV infection was 100% (23/23) but no HBV-related graft dysfunction nor death were found.

In addition, several studies underlined the importance of not using HBsAg +ve grafts in HDV recipients; in fact, the presence of HBsAg can lead to a rapid and severe HDV reactivation and reinfection [110,112].

Conclusions

Allocation criteria have been proposed for HbsAg-positive donor grafts; they should be firstly allocated to HbsAg-positive recipients, then to those with serological evidence of previous contact with HBV, and as a last choice to naive HBV recipients requesting urgent LT [110]. All patients receiving an HbsAg-positive graft need post-transplant combined prophylaxis with HBIg and NUCs. In addition, HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely thereafter [109[.

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Conflict of interest

None to declare.

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