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2020 position statement and recommendations of the European Liver and Intestine Transplantation Association (ELITA): management of hepatitis B virus-related infection before and after liver transplantation

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Summary

Background: Prophylaxis of HBV recurrence is critical after liver transplantation in HBV patients. Despite new prophylactic schemes, most European LT centres persist on a conservative approach combining hepatitis B immunoglobulin (HBIG) and nucleos(t)ides analogues (NA).

Aim: This setting prompted the European Liver Intestine Transplantation Association (ELITA) to look for a consensus on the prevention of HBV recurrence.

Methods: Based on a 4-round Delphi process, ELITA investigated 16 research questions and established 50 recommendations.

Results: Prophylaxis should be driven according to 3 simplified risk groups: Low and high virological risk patients, with undetectable and detectable HBV DNA pre-LT, respectively, and special populations (HDV, HCC, poorly adherent patients). In low-risk patients, short-term (4 weeks) combination of third-generation NA+ HBIG, or third generation NA monotherapy can be considered as prophylactic options. In high-risk patients, HBIG can be discontinued once HBV DNA undetectable. Combined therapy for 1 year is advised. HBV-HCC patients should be treated according to their virological risk. In HDV/HBV patients, indefinite dual prophylaxis remains the gold standard. Full withdrawal of HBV prophylaxis following or not HBV vaccination should only be attempted in the setting of clinical trials. Organs from HBsAg+ve donors may be considered after assessment of risks, benefits, and patient consent. They should not be used if HDV is present. In poorly adherent patients, dual long-term prophylaxis is

Abbreviations: ACLF, acute on chronic liver failure; ALF, acute liver failure; cccDNA, covalently closed DNA; CHB, chronic hepatitis B; CHC, chronic hepatitis C; DDI, drug-to-drug interactions; ETV, entecavir; HBIG, hepatitis B immunoglobulins; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LMV, lamivudine; LT, liver transplantation; NA, nucleoside analogues; TAF, tenofovir alafenamide; TDF, tenofovir.

Luca S. Belli is the co-first author.

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recommended. Budget impact analysis should be taken into account to drive prophylactic regimen.

Conclusions: These ELITA recommendations should stimulate a more rational and homogeneous approach to HBV prophylaxis across LT programs.

1 | INTRODUCTION

Hepatitis B virus (HBV) infection is a common indication for liver transplantation (LT) affecting nowadays 10%-15% of LT candidates.[1-3] These figures include HDV/HVB-related liver diseases, which, based on data of the European Liver Transplantation Registry (ELTR) (Figure 1), currently account for 2% of LT indications and 20% of LT indications in HBV positive patients. In the early LT era, HBV was considered a contraindication due to the high risk of graft loss associated with HBV recurrence, resulting in poor survival rates (<40% at 5 years),[4] particularly in patients with high HBV DNA levels at LT. The introduction of hepatitis B immunoglobulin (HBIG) in the early 1990s improved outcomes by reducing recurrence by 60%.[5] However, patients with high HBV DNA levels at LT remained at risk of HBV recurrence because of insufficient neutralising antibodies. Another disadvantage of HBIG prophylaxis was its very high cost. In the late 1990s lamivudine (LMV), despite its high resistance rate, when combined with HBIG, allowed 90% of recurrent HBV infections to be clinically controlled.[6] In the early 2000s, third generation of nucleos(t)ide analogues (NAs) with a high genetic barrier to resistance, such as entecavir (ETV) or tenofovir (TDF) led to further significant improvements,[7] including prophylaxis without HBIG.[8] Surprisingly, despite these advances, guidelines covering in-depth all aspects of this topic have not been proposed so far. Two recent surveys conducted simultaneously in France and Italy (European Liver and Intestine Transplant Association [ELITA] meeting 2016) showed that HBIG remains widely used in European centres often at the same doses used 20 years ago, despite combination with third generation NAs. To stimulate a more rational approach to managing HBV prophylaxis, an ELITA consensus meeting was held and this document provides the conclusions of this Conference.

2 | SEARCH STRATEGY; SELECTION CRITERIA

The promoter, ELITA, selected a scientific board of 15 international experts and identified 16 relevant topics, each one assigned to two experts. The consensus meeting was endorsed by the European Association for the Study of the Liver (EASL) and the Italian Association for the study of the Liver (AISF). Experts independently carried out an English language literature search of PubMed, Embase and Scopus databases, and the Cochrane central register of controlled trials. Text, keywords and medical subject heading terms were used. Search terms and dates varied according to the topic. Quality of evidence and strength of recommendations were graded according to the EASL/GRADE

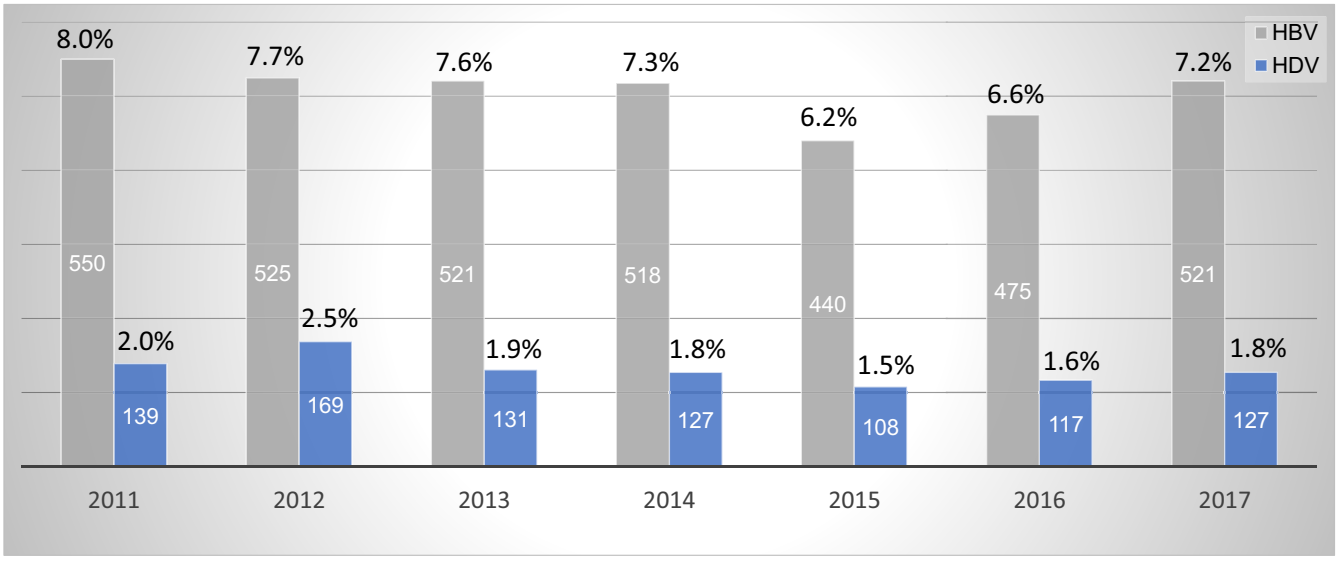

FIGURE 1 Prevalence of liver transplantation for HBV or HDV in Europe between 2011 and 2017 (ELTR data–www.eltr.org)

system[9] (Table S1) and circulated to the whole panel. Following a Delphi process[10] the experts were asked to approve each recommendation and if not, to justify their disagreement. Experts' opinions were ranked as strong disagreement, disagreement, neutral, agreement, strong agreement, further merged as disagreement, neutral, agreement. Recommendations were adjusted after each round of the Delphi process according to the experts' suggestions. After four rounds, >70% agreement and <20% disagreement rates were achieved for 49 out of 50 proposals (Figure S1). A preliminary budget impact analysis was also set up to compare historical prophylactic strategies to those derived from these recommendations.

The short version of ELITA recommendations is presented herein. Individual contributions of the experts exploring more in detail the rational and background of each issue will be presented elsewhere.

2.1 | Definitions and risk stratification

2.1.1 | Research questions

Q1 How to define HBV recurrence after LT in HBV+ve candidates?

The 4-5 dynamic phases which characterise the natural course of chronic HBV infection/hepatitis in the nontransplant individual[11,12] cannot be strictly transferred to the LT patient.

1. In the LT setting,[13] low levels of HBs Ag[14] can persist for a limited period post-LT then spontaneously disappear with HBsAg half-life estimated to be close to 7 days.[15] Residual HBV particles may rapidly infect the liver leading to cccDNA formation and potentially to viral genome integration, since NAs cannot prevent de novo infection of hepatocytes.[16,17] Yet, most patients on NA monoprophylaxis become HBsAg −ve in the first 3 months after LT, suggesting that the immune system can clear the residual HBsAg, while HBV replication is efficiently suppressed by NA.
2. Historically, on HBIG monoprophylaxis, emergence of escape mutations in the "a" determinant region were reported.[18-23] The associated serologic profile combined HBV DNA +ve and HBs Ag +ve or −ve, since mutations in the "a" determinant might result in false-negative immunoassay diagnostic tests. With the use of NAs with high barrier to resistance and improved performances of HBs Ag diagnostic assays now able to detect most of the S gene mutants[24,25] this scenario has vanished but indicates that under some circumstances, HBs Ag cannot be considered the gold standard to diagnose HBV recurrence.
3. HBV reactivation can occur in recipients receiving anti-HBc +ve HBAg-ve liver grafts.

Thus, the clinical significance of HBs Ag after LT differs from the non-transplant setting. HBs Ag may persist transiently with no detectable HBV DNA, and in other settings, active replication can be detected with no detection of HBsAg. Therefore, HBsAg cannot be considered the gold standard for active HBV infection after LT. Rather, HBV DNA has emerged as an associated marker of active HBV infection. The optimal clinical monitoring of HBV recurrence on the liver graft should, therefore, rely on both HBsAg and HBV DNA detection/quantification. On this ground, ELITA proposes to individualise five different patterns of HBV infection after LT (see recommendation 2 and Table 1) and to adopt these standardised scenarios as a reference in the perspective of future clinical trials.

TABLE 1 ELITA definitions of HBV status after liver transplantation for HBV-related liver diseases

	HBV DNA	HBs antigen	Liver enzymes	Other
Pattern 1				
Recurrence of HBV infection with active replication	+	+	Normal	
Pattern 2				
Recurrence of HBV infection with active replication and surface gene escape mutant	+	−	Normal	
Pattern 3				
Recurrence of HBV infection with controlled replication by NA	−	+ (transient or persistent)	Normal	
Pattern 4				
Recurrence of HBV hepatitis	+	+ or − (if surface gene escape mutation)	Abnormal	
Pattern 5				
Occult infection	−	−	Normal	Detection of ccc DNA in the liver
True HBs Ag clearance	−	−	Normal	—

Abbreviations: HBs antigen, Hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogues.

Recommendations	Level of evidence	Strength Agreement Score
R1. Definition of HBV recurrence should be based on both HBsAg and HBV DNA detection/quantification which provide complementary information and should be used together to have a full picture of the situation	III	Strong 93.3%/6.7%/0% 4.6/5 (4-5)
R2. In the perspective of future clinical trials, HBV recurrence should be classified/standardised according to five scenarios (Table 1) 1. Recurrence of HBV infection with active replication: defined by any serum HBV DNA persistence or reappearance after LT with detectable HBsAg+ and liver enzymes in a normal range. 2. Recurrence of HBV infection with active replication: defined by any serum HBV DNA persistence or reappearance after LT without detectable HBsAg and liver enzymes in a normal range 3. Recurrence of HBV infection with controlled replication by NA: defined by transient or persistent detection of HBsAg and undetectable HBV DNA on NA. 4. Recurrence of HBV hepatitis: defined by serum HBV DNA positivity with or without HBsAg detection + abnormal liver enzymes and compatible histology (liver inflammation) 5. Occult infection: this pattern combines the detection of cccDNA in the liver with no detection of HBsAg nor HBV DNA in the serum. It should be distinguished from trueHBs Ag/HBV clearance (see future prospects section)	III	Strong 86.7%/13.3%/0% 4.5/5 (4 -5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

Q2 How to stratify the risk of HBV recurrence?

Failure of prophylaxis has been most consistently predicted by pre-transplant HBV DNA levels.[26-28] In the past, patients had been divided into two risk categories: (a) those at increased risk, with viral load >4 log and surrogate markers of high HBV DNA levels, such as HBeAg positivity, a history of antiviral drug resistance, poor adherence, HIV co-infection and (b) those at low risk, with a low viral load <4 log, HBeAg negative status, acute liver failure and HDV co-infection.[29] The presence of hepatocellular carcinoma (HCC) at transplantation was also reported to be associated with HBV recurrence.[30-32] Currently, most patients are at low risk at LT with HBV DNA usually undetectable on third generation NA.[11] In patients with HCC, only those with a high risk of tumour recurrence have an increased risk of HBV recurrence (see Question 7), indicating that currently, most HCC patients, because of strict selection criteria, are not exposed to HBV recurrence. Thus, the traditional predictors separating high and low risks of recurrence should be revisited accordingly. An agreement between experts was achieved to abandon the historical pre-LT HBV DNA cut-off of 4 log and, in the era of third generation NA, HBe Ag as an independent risk factor of recurrence. A proposal was made to separate patients on the sole ground of HBV DNA detectability.[1] Also, the proposal was made to no longer consider HCC patients as a high-risk group, but as a special population not requiring specific prophylaxis since ultimately, re-appearance of HBV DNA or HBs Ag in this subpopulation can be considered as a surrogate marker of HCC recurrence, this latter event driving outcome (see Question 7 for more details).

Recommendations	Level of evidence	Strength Agreement Score
R3: Prophylaxis against HBV recurrence should be tailored according to three risk groups defined as follows: *Low virological risk patients*: patients with undetectable HBV DNA pre-LT, irrespective of LT indication (cirrhosis or fulminant hepatitis), *High virological risk patients*: • Patients with detectable HBV DNA at LT • Patients with HBV reactivation resulting in HBV-related acute on chronic liver failure *Special populations*: • Patients with HDV co-infection, at low virological risk but deserving full prophylaxis • HCC patients, at higher virological risk in case of HCC recurrence but not requiring specific prophylaxis • Patients at risk of poor adherence to antiviral therapy post-LT	III	Strong 86.7%/13.3%/0% 4.3/4(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

2.2 | Pre-transplant issues

2.2.1 | Research questions

Q3 How to treat patients on the waiting list?

Modalities of treatment in patients listed for HBV-related cirrhosis and persistent HBV replication have been extensively reviewed elsewhere.[11,12] The consensus is to treat all patients listed for HBV liver disease with persistent active HBV replication.[11,33] The goals are to improve liver function and to achieve further delisting when feasible, and in patients maintained on the wait-list to achieve the abolition of HBV replication to prevent reinfection.

Recommendations	Level of evidence	Strength Agreement Score
R4: Patients with compensated cirrhosis listed for LT and detectable HBV DNA at listing, typically HCC patients, should be treated with NA with high genetic barrier to resistance (entecavir or tenofovir disoproxil fumarate or TAF), irrespective of HBV replication level to minimise the risk of HBV recurrence. These drugs can be safely used in patients with compensated cirrhosis (Child-Pugh A)	II-2	Strong 92.9%/0%/7.1% 4.8/4(4-5)
R5: Patients with decompensated cirrhosis listed for LT should be treated with NA with high genetic barrier to resistance (entecavir, 1 mg/day or tenofovir disoproxil fumarate or TAF) in order to minimise the risk of HBV recurrence, to improve liver function and to achieve further delisting when appropriate. Careful monitoring of side effects such as lactic acidosis and kidney dysfunction is still required	II-2	Strong 85.7%/14.3%/0% 4.6/5(5-5)
R6: In case of previous resistance to lamivudine, tenofovir is the drug of choice; in case of resistance to adefovir, entecavir is recommended. Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LMV exposure and TAF availability	II-1	Strong 100%/0%/0% 4.8/5(5-5)
R7: All patients treated with NAs should be followed with periodic assessments including ALT, serum HBV DNA and MELD score on a 3-month-basis. In patients with decompensated cirrhosis and significant MELD score improvement on NA, inactive status on the waitlist and eventually delisting should be considered on a case by case basis	III	Strong 100%/0%/0% 4.8/5(5-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement;Recommendation score from 0 to 5: Mean, median (IQ).

Q4—Is transplantation feasible in HBV DNA+ve patients in the NA era?

Q4a—Is pre-LT full HBV abolition of replication mandatory in chronically infected patients?. In the LMV era, HBV DNA level before LT was the major risk factor for HBV disease recurrence.[26] This implied that any effort had to be made to achieve HBV DNA negativity before LT. The availability of third generation NA has permitted favourable long-term results in patients with high HBV DNA levels.[8,13,14]

Recommendation	Level of evidence	Strength Agreement Score
R8: For HBV DNA-positive patients in urgent need of LT for chronic HBV-related liver disease, the operation should be considered even in the presence of very high HBV DNA levels or in the setting of a declining HBV viral load on NAs. These patients are at high risk of HBV recurrence and their post-LT prophylactic regimen should be adjusted accordingly	II-2	Strong 92.9%/7.1%/0% 4.4/5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

Q4b: Is pre-LT treatment mandatory in urgent situations (fulminant and acute-on-chronic)?. The majority of patients with HBV-related acute liver failure (ALF) have low level of circulating HBV.[34,35] In the era of high genetic barrier NA, there is no evidence that pre-LT antiviral therapy is associated with lower mortality or with reduced post-transplant recurrence. Moreover, there is no evidence against the use of antiviral agents before LT since there is no evidence that they are harmful. Overall, the rate of recurrence, with or without HBIG is very low.[36] For patients with HBV-related ALF receiving auxiliary LT, HBV infection may not recur and withdrawal of prophylaxis after the regeneration of the native liver was shown to be feasible with complete atrophy of the partial graft and withdrawal of immunosuppression.[37,38]

In contrast to ALF, HBV-related acute on chronic liver failure (ACLF) is characterised by relatively high levels of serum HBV DNA[39,40] and NAs are associated with a significant decrease in HBV DNA.[39,40] Overall, ETV or TDF-based prophylaxis, with or without HBIG are associated with a very low recurrence rate, whether patients test positive or not for serum HBV DNA before LT.[14,41,42]

Recommendations	Level of evidence	Strength Agreement Score
R9: In urgent settings, as in HBV-related ALF and ACLF, pre-LT serum HBV DNA positivity should not be a contraindication for LT, even in patients with high viral load	II-2	Strong 85.7%/14.3%/0 4.6/5(5-5)
R10: HBV-related ALF may not be a contraindication for auxiliary LT	III	Weak 78.6%/7.1%/14.3% 4.1/4(4-5)
R11: There is neither rationale nor evidence for or against the use of antiviral agents before transplantation in patients with HBV-related ALF. The decision to treat or not can be taken on a case-by-case basis, taking into account (a) serum HBV DNA levels which are usually very low, (b) the decision of LT on an emergency setting, prior to HBV DNA status availability, and (c) the risk of post-transplant recurrence which is low with current prophylaxis regimens	II-2	Strong 85.7%/7.1%/7.1% 4.4/5(4-5)
R12: In patients with HBV-related ACLF, a trial testing the benefit of antiviral agents may be recommended as (a) serum HBV DNA levels are generally high, (b) preliminary data suggest that antiviral agents may be associated with higher survival rates and (c) the safety profile of the new antiviral agents is presumably good in this population	III	Strong 92.9%/0%/7.1% 4.4/ 5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement;Recommendation score from 0 to 5: Mean, median (IQ). NA: not applicable.

2.3 | Adjusting prophylaxis to the patient profile

2.3.1 | Research questions

Q5. Can we optimise/customise combined prophylaxis in de novo patients receiving NAs with high genetic barrier to resistance? Anti-HBs targets, HBIG dosing and duration. In Western countries, long-term combination of HBIG and third generation NAs has become the standard of care for preventing recurrence,[11,12,33] with duration and dosing of HBV prophylaxis being adjusted to the risk of recurrence. With third generation NAs, the originally proposed high targets of anti-HBs titres could be reduced. For low-risk patients, lower HBIG doses and discontinuation of HBIG became possible provided patients continued on third generation NA long-term (Table 2).[42-56] The type of prophylaxis in low-risk patients (combined short-term HIBG + NA vs NA monotherapy with no HBIG) was extensively discussed amongst the panel. Pros and cons of both strategies are summarised in Table S2. The consensus choice was made to leave both options available (see algorithm 1 in Figure 2 and recommendation 17), taking into account the local prevalence of HBV diseases amongst LT candidates as well as the availability and cost of HBIG. However, since evidence supporting NA mono-prophylaxis in these patients is still limited (ie, one retrospective study with standardised follow-up[8] and 2 uncontrolled prospective studies,[54,57] Table 3), the panel recommended to preferentially consider NA monotherapy in the setting of prospective clinical trials or observational cohorts. Proposed ELITA recommendations adjusted on the risk profile are presented in the table below and in Figure 2. The expert panel acknowledges that over-treatment with HBIG cannot be excluded on the basis of studies, suggesting that the combination of NA with very low dose HBIG are effective. However, the eventually selected strategy reflects the consensus achieved after the fourth round of the Delphi process, balancing opinions of experts favouring low dosing with those favouring a more conservative approach.

Choice of 3rd generation NA. The choice of third generation NA, life-long, should be driven by virological and clinical considerations as in the non-transplant population.[11] In patients with a history of resistance to LMV or ETV, TFV is advised. In patients with no history of resistance to LMV, ETV, 0.5 mg/day can be used, especially in case of renal failure or severe osteoporosis. In patients with post-LT renal impairment, ETV adjusted to DFG can be considered. As far as TAF is concerned, TAF has recently been studied in a retrospective study and in a registry study,[58,59] as a switch from other NAs after LT. From these small groups of patients, the overall observation suggests that switching to TAF led to the reduction in ALT and a trend towards improvement in renal function (eGFR). Viral suppression was maintained and calcineurin inhibitor levels were not modified by TAF administration. In countries where TAF is available, it might be considered, especially to preserve kidney function. Since evidence is still low, prospective long-term studies testing TAF post-LT are awaited in LT patients with deterioration of renal function or severe osteoporosis pre-or post-LT, to provide stronger recommendations.

Recommendations	Evidence level	Strength Agreement Score
R13: HBIG duration and anti-HBs targets In low-risk patients receiving third generation NA pre-LT, short-term combination of third generation NA+ HBIG or third generation NA monotherapy post-LT (see question 6 recommendation 17) can be considered prophylactic options. In case of short-term combination, best duration of HBIG is not established but combined therapy ensuring anti-HBs levels between 50 and 100 mIU/mL for 4 weeks post-LT is advised*. NA monotherapy should preferentially be considered in the setting of prospective observational cohorts or clinical trials. *Note: Keeping in mind that when using HBIG IV post-operatively for 5-7 days, anti-HBs titres will remain beyond the target for much longer than 4 weeks, in general 3 months. In high-risk patients, receiving third generation NA post-LT, HBIG can be discontinued once HBV DNA is undetectable. Optimal duration period of HBIG has not been established but combined therapy for at least 1 year is advised. The anti-HBs levels should be maintained >500 IU/L until month 3, >100-250 IU/L until month 6 and >50-100 IU/L thereafter	II-2	Strong 86.7%/13.3%/0% 4.2/4(4-5)
R 14: Doses of HBIG and schedule HBIG prophylaxis should be adapted to formulations of HBIG available in different countries. On-demand administration is more cost-effective and should be preferred, except in poorly adherent patients in whom a fixed schedule is preferred Patients with low risk of recurrence 10 000 IU during the anhepatic phase, then 5000 IU IV/day (or every other day) for the first post-operative week (7 days), then on-demand, or on the fixed schedule in non-adherent patients. For maintenance, HBIG administration can be IV, IM or subcutaneous, as per centre practice to maintain anti-HBs levels according to recommendation 13 Patients at high risk of recurrence 10 000 IU during the anhepatic phase then 10 000 IU IV/day for the first post-operative week (7 days), then on-demand HBIG administration (or on the fixed schedule in non-adherent patients) to maintain anti-HBs levels according to recommendation 13. For HBIG maintenance, the route of administration can be IV, IM or subcutaneous as per centre practice	II-3	Strong 86.7%/6.7%/6.7% 4.1/4(4-5)
R 15: The choice of third generation NA, life-long, should be driven by virological and clinical considerations. In patients with a history of resistance to LMV or ETV, TFV is advised. In patients with no history of resistance to LMV, ETV, 0.5 mg/day can be used, especially in the case of renal failure or severe osteoporosis. In patients with post-LT renal impairment, ETV adjusted to DFG can be considered. Testing TAF in specific trials post-LT is recommended in patients with renal failure or severe osteoporosis pre-or post-LT	II-2	Strong 93.3%/0%/6.7% 4.7/5(5-5)
R 16: A detailed cost-effectiveness analysis is advised to identify the best cost-effective approach in the different risk groups	III	Strong 81.3%/18.8%/0% 4.6/5(4.5-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ). NA: not applicable.

Q6. Can NA monoprophylaxis be considered?

An HBIG-free regimen is desirable as it obviates the high cost including the need for regular parenteral administration. A major concern of an HBIG free regimen is the higher rate of HBsAg positivity that may occur following LT. Whether this represents a failure to eradicate HBV or a true recurrence remains highly debatable. Indeed, NAs do not prevent the infection of hepatocytes,[16,17] ie, they do not prevent cccDNA establishment and viral genome integration but inhibit viral replication at post-cccDNA steps in the viral life cycle. However, there appears to be the minimal consequence of seropositivity for HBV on the background of complete viral suppression, and although additional HBIG will render HBsAg

TABLE 2 *Studies on prevention of HBV recurrence under third generation nucleotide analogues after discontinuation of HBIG*

Study First author (ref no.)	Pts, n	Positive DNA at LT (%)	POST LT HBIG (anhepatic/ first week/follow up)	Duration HBIG	Type of NA post-HBIG withdrawal	Follow up, (months)	HBV recurrence, N (%)	Recurrence definition (positivity of)
Buti[52]	15	0	10 000 IU IO, 5000 IU ev for 7 days, 4000 IU IM for 3 weeks	1 month	LAM	18	3 (20%) [3 HBsAg −/DNA +]	HBVDNA
Degertekin[43]	23	47.8	Different protocols	12 months	ETV or TDF	53	3 (13%)	HBsAg or HBVDNA
Saab[44]	61	78	Different protocols	>12 months	LMV or ETV+ ADV or TDF	15	2 (3%) [2 HBsAg +/DNA−]	HBsAg or HBVDNA
Stravitz[45]	21	56	10 000 IV/1500 iv per day/ IM based on anti-HBs	>6 months	TDF + Emcitrabine	31	3 (14%) [2 HBsAg +/ DNA −, and 1 HBs Ag +/DNA +]	HBsAg or HBVDNA
Tanaka[53]	132	41	2000 IU for 7 days, 2000 IU for 3 weeks, 2000 IU for 11 months	12 months	LAM [97], ADV [17], TDF (13), ETV (5)	68 for LAM, 32 for non-LAM	9 (9.3%) only in the lam group	HBsAg or HBVDNA
Teperman[46]	16	100	No data	>9 months	TDF+ Emcitrabine	18	0 (0%)	HBsAg or HBVDNA
Wesdorp[47]	17	89	10 000 IV daily for 7 days then 10 000 IV /2 months	>6 months	TDF + Emcitrabine	26	2 (11.8%) [2 HBsAg +/DNA −]	HBsAg or HBVDNA
Gane 2013[54]	20	65	800 IU for 7 days	7 days	LAM+ADV	57	0 (0%)[a]	HBsAg or HBVDNA
Tanaka[48]	24	50	2000 IV/2000 IV per day/2000 IM/months	12 months	TDF (±LMV)	29	0 (0%)	HBsAg or HBVDNA
Cholongitas[42]	28	0	1.000 IM daily for 7 day then 1.000 IM/month	6 months	ETV or TDF	21	0 (0%)	HBsAg or HBVDNA
Fernandez[55]	58	26	2000 IU IM every month	>20 months	ETV or TDF	28	5 (8.6%) [5 HBsAg +/DNA −]	HBsAg or HBVDNA
Radhakrishnan[49]	42 (95% HCC)	All <100 IU	5000 IV/5000 IV for 5 days/ stop	5 days	ETV or TDF	37	2 (5.%) [1 HBsAg +/DNA−and 1 HBsAg -/DNA +] both with HCC rec	HBsAg or HBVDNA
Lens[50]	222	19	5.000 IV/5000 IV per day/1000 IM or sc based on anti-HBs targets	6-12 months	LMV or ETV or TDF	72	Not available	HBsAg or HBVDNA
Manini[51]	69	65	Variable	>6 months	ETV or TDF	69	6 [6 HBsAg +/DNA −]	HBsAg or HBVDNA
Dobrindt[56]	65	Not available	10 000 IU IO followed by 2000 IV every 6 weeks	<36 months	LAM or ETF or TDF	51	3 (4.6%) [3HBsAg +/DNA −]	HBsAg or HBVDNA

Abbreviations: ETV, entecavir; HBIG, hepatitis B immunoglobulins; HCC, hepatocellular carcinoma; LMV, Lamivudine; LT, liver transplantation; NA, nucleoside analogues; TDF, tenofovir.

[a]HBs Ag seroclearance 100% on M6 post LT; one case on transient reappearance on M41 due to HCC recurrence, disappearing after excision of the metastasis. HBV undetectable in 100% of cases.

undetectable, it is unlikely to confer an additional advantage in graft and patient survival. In a study of 80 patients in Hong Kong receiving ETV monotherapy without HBIG followed up for a median of 26 months, the HBsAg seroclearance rate was 91% at 2 years without any virological relapse or graft loss secondary to recurrence.[14] There were no significant differences in pre-LT HBV DNA levels between those who did or did not have HBsAg reappearance or persistence after transplant (3.2 vs 3.7 log copies per ml, respectively, $P = 0.94$). A larger study of 256 patients on ETV monotherapy demonstrated 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. In a study of oral NA only (176 LMV, 142 ETV and 44 combination NA, median follow-up: 53 months), the rate of HBsAg negativity and undetectable HBV DNA at 8 years was 88% and 98%, respectively.[8,60] The highest recurrence rate was observed in those taking LMV, highlighting the importance of using a NA with low resistance rates. Patients with HBV DNA at LT up to 10^4 showed a similarly low rate of HBsAg positivity (below 2% after 8 years) as those who were HBV DNA negative. Survival was 83% without any HBV-related mortality. These studies show that NA alone are safe and effective in preventing HBV graft hepatitis and graft loss, with excellent long-term survival, irrespective of pre-transplant viral load. Whether the presence of HBsAg may stay as an innocent bystander in the longer term deserves further observational studies. Collection of data on long-term consequences of cccDNA establishment and/or HBV integration is, therefore, advised in Western countries before implementing early NAs monotherapy in high-risk patients.

Recommendations	Evidence level	Strength Agreement Score
R17: Third generation NA monoprophylaxis without HBIG should be considered as an alternative prophylactic strategy after LT in patients with no detectable HBV DNA before LT, especially in patients without HDV co-infection and in countries that have no access to HBIG	II-2	Strong 75.0%/6.3%/18.7% 4.2/5(3.5-5)
R 18: Although prophylaxis based on third generation NA without HBIG has also been shown feasible in patients with detectable HBV DNA at transplant in Asian countries, collection of data on long-term consequences of cccDNA establishment and/or HBV integration is recommended in Western countries before implementing such a strategy in high-risk patients	III	Weak 66.7%/26.6%/6.7% 4.1/5(3-5)
R19: For patients with evidence of prior drug resistance, the use of a single agent without cross-resistance or combination of a nucleoside and nucleotide analogue with high barrier to resistance should be considered	I	Strong 93.8%/6.3%/0% 4.9/5(5-5)
R20: HBV-HCC patients should be treated according to their virological risk profile as in non-HCC patients	III	Strong 86.7%/0%/13.3% 4.3/5(4-5)
R21: In LT patients with HBV recurrence associated with HCC recurrence, treatment of HBV infection should be undertaken on a case-by-case basis. A shift from NA prescribed at baseline to another compound can be considered. Removal of a single metastasis is advised as it may not only abolish HBV replication but also improve tumour status and survival	III	Weak 73.3%/20%/6.7% 4.1/4(3.5-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreementRecommendation score from 0 to 5: Mean, median (IQ).

Q7. Do HCC patients require special prophylaxis?

HCC-HBV LT candidates are at higher risk of HBV recurrence (2%-35%) than those without HCC (1%-9.7%) and the risk of HBV recurrence is more pronounced in patients transplanted with advanced tumours.[30,61] HBV reinfection is strongly associated with HCC recurrence, either in the liver graft or as post-LT extra-hepatic metastasis.[30-32,61-64] In about 80% of cases, HCC recurrence is diagnosed before or concurrently to HBV detection post-LT.[30-32] The association between HCC and HBV recurrences suggests that extrahepatic HCC metastatic cells may act as a viral reservoir for late HBV recurrence and graft reinfection; of note, HBV recurrence has been reported in patients receiving HBIG or NA monoprophylaxis or both.[62] This suggests that HBV virions in tumours cells might not be fully accessible to NA. HCC cells might be, therefore, considered as an HBV sanctuary. HCC LT candidates are usually selected on the ground of HCC recurrence risk around 10%[65] with prognosis and post-LT mortality typically driven by the recurrence of HCC and not that of HBV (Table 4). Therefore, adopting combined long-term HBV prophylaxis in all HBV-HCC patients would result in over prophylaxis in 90% of these candidates.

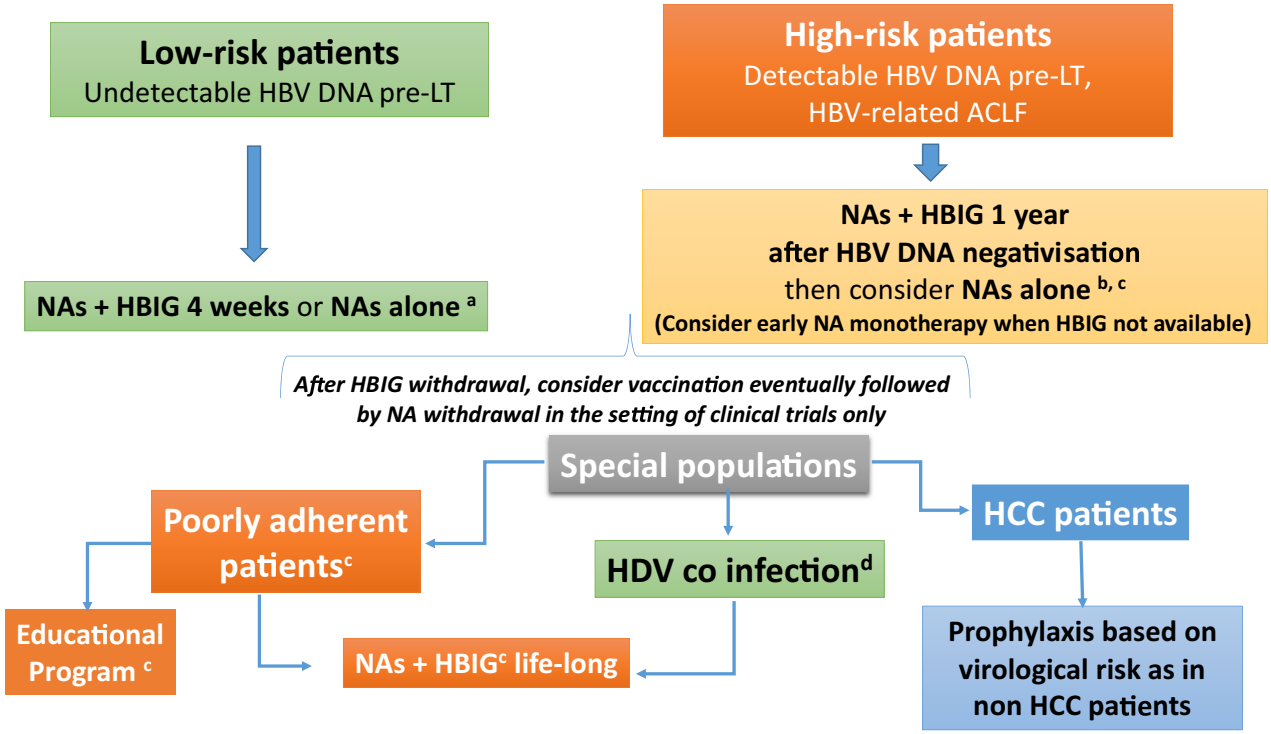

FIGURE 2 2020 ELITA algorithm for de novo prophylaxis of HBV recurrence after liver transplantation for HBV-related liver disease. A, In Western countries, early NAs monoprophylaxis should preferentially be undertaken in the setting of prospective cohorts or clinical trials addressing the prevalence of ccc DNA and DNA integration. B, Registries are encouraged after late HBIG withdrawal to generate more data about this strategy. C, Consider specific educational programmes in poorly adherent patients and in patients receiving NAs alone or subcutaneous HBIG in the long term. D, In HDV population, HBIG withdrawal can be considered in the setting of clinical trials. Abbreviations: HBIG : hepatitis B immunoglobulins; HBV: Hepatitis B virus. HDV: Hepatitis D virus; NA: nucleoside analogues

TABLE 3 *Studies on prevention of HBV recurrence under new nucleotide analogues monoprophylaxis without HBIG in low-risk patients*

Study First author year (ref no.)	Design	Pts, n	DNA at LT (%)	Type of NA	Follow up, months	HBV DNA negative post LT (end FoU)	HBs Ag clearance/ anti-HBs positive (%)	Survival
Fung[8]	Retrospective	265		ETV	59	100%	8-year: 92%	9-year: 85%
Wadhawan[57]	Prospective (LRLT)	75	<3 log 100% Undetectable 57/75 (76%)	LMV+ADV 19 ETV 4 2 TDF12 ETV+TDF 2	21	100%[a]	2-year 92%[a]/25%[b]	7-year: 73.7%[a]
Gane[54]	Prospective	18	<3 log	LMV+ ADV	20	100%	100%	2-year: 100%

ADV, adefovir; ETV, entecavir; FoU, follow-up; HBs Ag, hepatitis B surface antigen; HBV, hepatitis B virus; LMV, lamivudine; LRLT, living-related LT; LT, liver transplantation; TDF, tenofovir.

6 HBs Ag recurrences with transient positivity of HBV DNA: 1 ETV resistance; 6 adherence issues; 6 HBs Ag recurrences with transient positivity of HBV DNA: 1 ETV resistance; 6 adherence issues.

[a]No death due to HBV recurrence.

[b]19 patients with HBs antibodies >10 m IU/mL.

Q8. Do HDV+ve recipients require specific prophylaxis?

As HDV requires concomitant infection with HBV,[66] prevention of hepatitis D relies on the same measures used to prevent HBV re-infection.[67] HBIG based prophylaxis has been associated with a recurrence rate <20% because of usually minimal HBV replication in the majority of HDV candidates.[5,68,69] The combination of

HBIG with NAs was subsequently adopted as standard prophylaxis with virtually no relapse of hepatitis D reported since its inception in 2007.[70,71] Recently, long-term prophylaxis with NA alone after HBIG discontinuation was reported in 65 HDV patients from 4 Centres.[55,72-74] After a 28 month- to 20 year-follow-up, one patient (1.5%) relapsed with HBV/HDV disease, suggesting that NA alone prophylaxis may be also effective against HDV re-infection. However, in one report, HDV infection recurred four years after LT, accompanied by an HBV flare 10 months after the discontinuation of HBIG.[75] This raised the concern that the reappearance of HBsAg provides the substrate to the reactivation of a latent HDV infection. Indeed, inside the hepatocytes, HDV is replicated by the host enzymes[76] and can establish a latent state independently from HBV.[77,78] The use of an antiviral alone guarantees the abolition of HBV replication but not the emergence or persistence of HBsAg, necessary for HDV to become infectious, thereby facilitating relapse of hepatitis D. This assumption remains controversial yet because without a full HBV reactivation, HDV infection remains clinically abortive with no productive infection, thus precluding HDV recurrence.[79]

Recommendations	Evidence level	Strength Agreement Score
R 22: Indefinite combination of antiviral agents and HBIG post–transplant remains at present the gold standard for prophylaxis against recurrence of hepatitis D	II-2	Strong 81.3%/12.4%/6.3% 4.3/4(4-5)
R23: Based on recent data, discontinuation of HBIG followed by NA monoprophylaxis or in combination with entry inhibitors may be considered, particularly in the setting of clinical trials	III	Weak 75.0%/6.3%/18.7% 3.9/4(3.5-5)
R24: Organs from HBsAg-positive donors should be prohibited in HDV-positive recipients	III	Strong 100%/0%/0% 4.7/5(4-5)
R25: The combination of antiviral and HBIG post–transplants remains at present the gold standard for prophylaxis in HDV transplants receiving an HBc Ab-positive liver	II-2	Strong 81.3%/12.5%/6.3% 4.33/ 5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

Q9: Shifting "historical," long-term patients from HBIG plus NA to third generation NA monoprophylaxis. Who, when and how?

According to ELTR Registry, 12 000 HBV+ve liver transplant recipients are currently alive.[1] Most are maintained on combined NA + HBIG prophylaxis as demonstrated by recent surveys conducted in Italy[80] and France. A major issue is which of these patients can be safely shifted to NA mono-prophylaxis. The policy of stopping HBIG administration and to continue with NA monoprophylaxis in patients who are HBs-Ag negative, HBVDNA negative, HDV negative and with normal liver biochemistry long term following LT, has already been adopted by some groups.[42-51] From these studies, the following factors should be taken into account in patients treated with third generation NA:

- a time interval of at least 6 months from LT is adequate before considering HBIG withdrawal;
- the risk of HBV recurrence after HBIG withdrawal (HBs-Ag positivity) varies between 0 and 20% (Table 2);
- very few patients with recurrent HBV infection after HBIG withdrawal become HBV DNA positive with or without abnormal liver biochemistry (recurrent HBV hepatitis). This condition typically occurs in patients non-adherent to NA mono-prophylaxis.

Of note, data regarding the persistence of HBs Ab after HBIG withdrawal are scarce. A recent study reported on around 10% of patients presenting with persistent HBsAb.[51] Identifying patients developing natural anti-HBV immunity after HBIG withdrawal may open the door to further NAs withdrawal or, on the opposite, to vaccination in patients without natural HBs Ab. Monitoring HBs antibodies decline after HBIG withdrawal, therefore, provides the transplant hepatologist with relevant information to guide the prophylactic management, and should be considered in some circumstances as the first step before participation in prospective studies testing NAs withdrawal or HBV vaccination, depending on patients' profile.

Corresponding ELITA recommendations according to two scenarios are presented in Figure 3.

TABLE 4 HBV recurrence in patients transplanted for HCC and HBV-related liver disease

	N HBV Pts	N HCC pts (%)	Type of prophylaxis Post LT	Definition of HBV recurrence	HBV Recurrence (n, %)	HCC recurrence	% of HCC recurrence amongst pts with HBV recurrence	% of HBV recurrence in pts with HCC recurrence	HBV recurrence in pts with HCC vs non HCC	Hazard ratio for HCC as a risk factor for HBV recurrence (95% CI)	Timing of HBV/HCC recurrence	Outcome of HCC/HBV recurrence
Kim[62]	154	NA	ETV + HBIG	HBsAg +	5 (3.2)	19/?	4/5 (80%)	4/19 (21%)	NA	13.5 (2.4-74.4)	HCC first in 4 cases 9.4 months before HBV	Death from HCC: 3/5 1 pt alive with lung metastasis
Kiyici[63]	287	72 (25%)	LMV + HBIg low dose	HBsAg +	29/287 (10.1%)	8/72 (11%)	7/29 (24.1%)	7/8 (87.5%)	23.6% vs 5.5% (17/72 vs 12/215)	26.9 (10.8-67.1)	HBV first 2 HCC first 2 Concurrent 3	Unknown
Faria[30]	99	31 (31.3%)	HBIG + LMV or ADF	HBsAg +	14/99 (14.1%)	8/31 (25.8%)	7/14 (50%)	7/8 (87.5%) (vs 4/23 (17.4%) in HCC pt with no recurrence	35.4% vs 4.4% (11/31 vs 3/68)	Beyond Milan: 18.1 (4.6-72) <0.0001 Within Milan 4.2 (0.9-18.9)	HBV first 3 HCC first 0 Concurrent 4	HCC related death? Liver injury ?
Vigano[64]	101	101 (100%)	HBIG + LMV or ADF/TDF or ETV	HBsAg +	2/101 (1.98%)	11/101 (10.8%)	2/2 (100%)	2/11 (18.2%)	1.9% (2/101 vs NA)	ND	ND	2 deaths from HCC progression Within 1 year
Saab[31]	175	88 (50.2%)	HBIG + NA Mainly LMV	HBsAg + + HBV DNA	12/175 (6.9%)	13/88 (14.8%)	5/12 (41.7%)	5/13 (38.5%)	(83.3% vs 2.3%) 10/12 vs 2/87	4.93 (1.27-19.24) (univariate analysis)	HCC first 4 HBV first 1	4/5 deaths from HCC recurrence
Chun[32]	209	106 (50.7%)	NA + HBIG (LMV) :90% HBIG : 10%	HBsAg +	22 (10.5%)	19/106 (17.9%)	6/22 (27.3%)	6/12 (50%)	11.3% vs 9.7% (12/106 vs 10/103)	8.47 (2.88-24.9)	HCC first 6, 3.9 months before HBV recurrence	19 HCC recurrences Died from HCC (median time 14 months)

Abbreviations: ADF, adefovir; ETV, entecavir; FoU, follow-up; HBIG, hepatitis B immunoglobulines; HBs Ag, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LMV, lamivudine; LT, liver transplantation; NA, nucleoside analogues; ND, not determined; pt, patient; TDF, tenofovir.

Recommendations	Evidence level	Strength Agreement Score
R 26. Before withdrawing HBIG in stable long-term patients without signs of HBV recurrence (HBsAg negative and HBV DNA negative), the following factors need to be considered: adherence, presence of HDV co-infection and the type of NA, while on dual prophylaxis (first/second generation NA or third-generation NA)	III	Strong 92.9%/7.1%/0% 4.5/ 5(4-5)
R27. Withdrawing HBIG in long-term patients should follow the following scenarios Scenario 1: In patients who are adherent while on prophylaxis combining third generation NA and HBIG and without HDV coinfection, HBIG withdrawal should always be considered while continuing third generation NA. Monitoring for anti-HBs can be considered when appropriate. Scenario 2: In patients who are adherent while on prophylaxis combining first generation NA and HBIG and without HDV coinfection, HBIG withdrawal should be always considered but only after shifting to third-generation NA. Monitoring for anti-HBs can be considered when appropriate	II-2-3	Strong 85.7%/7.1%/7.1% 4.3/5(4-5)
R28: Patients with HDV co-infection and patients who are at risk of poor adherence should be kept on dual prophylaxis (see questions 8 & 14). A shift to 3rd generation NAs is advised in patients on first/second generation NAs	III	Strong 85.7%/14.3%/0% 4.5/ 5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement;Recommendation score from 0 to 5: Mean, median (IQ).

Q10. Is full withdrawal of prophylaxis feasible?

The concept that prophylaxis against HBV recurrence after LT should be indefinite is based on several indirect findings. Around 45% of LT recipients under continuous HBIG prophylaxis have evidence of persistent HBV DNA in serum, PBMC, or liver up to 10 years following LT.[81] Also, intrahepatic HBV DNA, or ccc DNA has been found in a high proportion of LT recipients.[82,83] Recently, Lenci et al investigated the presence of total HBV DNA and ccc DNA in the liver of 44 long-term LT survivours with low or undetectable viremia at LT.[84] Three (10%) and one patients tested positive for total HBV DNA and cccDNA, respectively, identifying recipients "at low risk of HBV recurrence." In a subsequent study,[85] full prophylaxis withdrawal was shown feasible and safe in 30 low-risk patients with undetectable serum and intrahepatic HBV DNA and negative cccDNA at enrolment. After 5 years on combined prophylaxis, stepwise HBIG and NA withdrawal were performed over two 6-month periods, under strict monitoring of serum and tissue HBV virology. After 2 years, 25 (83%) patients did not experience HBV recurrence. After an extended 6-year follow-up,[86] HBV recurrence occurred in a total of 6 (20%) patients, with only one additional late recurrence. Only three patients (10%) required reinstitution of HBV prophylaxis. At the end of follow-up, 90% of patients were still prophylaxis-free, 93.3% were HBsAg negative and 100% HBV DNA negative. In another retrospective report dealing with full prophylaxis withdrawal,[87] 10/190 Chinese patients who were HBeAg negative and HBV DNA negative at the time of LT completely stopped HBIG and NA 2 years after LT, due to poor compliance. Nine patients (90%) had no evidence of HBV recurrence after 4-year follow-up. The only patient who recurred was successfully treated with ETV.

Recommendations	Evidence level	Strength Agreement Score
R 29: At the present stage of knowledge, full HBV prophylaxis withdrawal cannot be recommended after LT	II-2	Strong 100%/0%/0% 4.7/5 (4-5)
R 30: Although full HBV prophylaxis withdrawal is probably feasible and safe in selected LT recipients, HBV prophylaxis withdrawal should be yet currently attempted in the setting of controlled clinical trials only	II-2	Strong 93.8%/6.2%/0% 4.4/4(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

Q11: Is there a role for active prophylaxis (vaccination)?

After LT, protective HBV antibodies decline, particularly if acquired by vaccination.[88] The seroprotection rate of HBV vaccination is also low,[89-99] especially early post-LT. Strategies to improve the response rate have included accelerated double-douse schedules and/or the use of vaccine adjuvants.[98] Studies investigating whether HBIG could be discontinued after HBV vaccination (Table S3) were limited by small sample size and lack of randomisation. Most used extra adjuvants in the vaccines. Discontinuation of HBIG was only feasible in highly selected patients, mostly under low-dose immunosuppression, not taking corticosteroids and with a low need of HBIG.

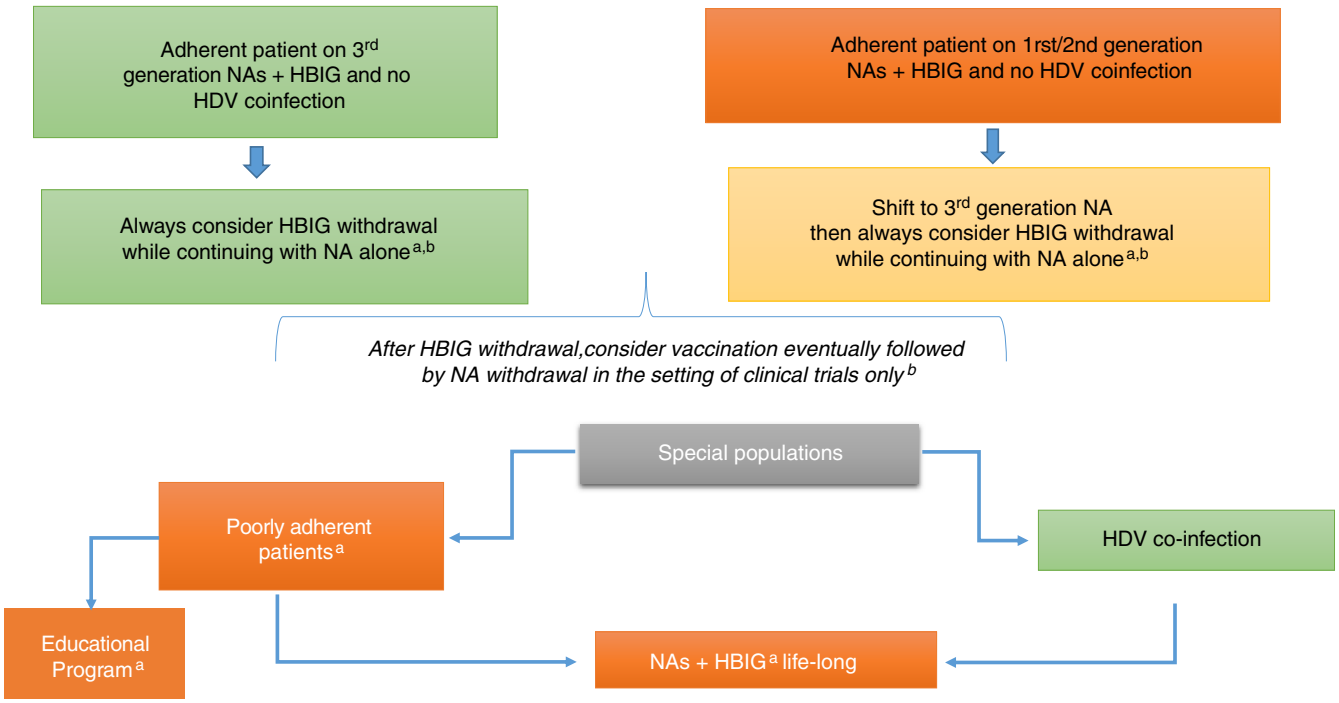

FIGURE 3 2020 ELITA algorithm for long-term prophylaxis of HBV recurrence in patients transplanted for HBV-related liver disease. a—Consider specific educational programmes in poorly adherent patients and in patients receiving NAs alone or sub-cutaneous HBIG in the long term. b—Consider monitoring of anti-HBs titre in patients amenable to active vaccination protocols after HBIG withdrawal. c—In HDV population, HBIG withdrawal can be considered in the setting of clinical trials. Abbreviations: HBIG, hepatitis B immunoglobulins; HBV, Hepatitis B virus; HDV, hepatitis D virus; NA: nucleoside analogues

Recommendations	Evidence level	Strength Agreement Score
R31 Hepatitis B vaccination should be performed in all patients with chronic liver disease at the early stage of the disease	III	Strong
R32: Patients on the waiting list for LT can be vaccinated with an accelerated double-dose schedule. The use of adjuvant vaccines is advised in the setting of clinical trials	II-2	Strong 92.9%/7.1%/0% 4.46/ 5(4-5)
R33 Post-LT HBV vaccination to discontinue prophylaxis against HBV recurrence in HBV positive recipients should be undertaken in the setting of controlled trials only	II-3	Strong 92.9%/7.1%/0% 4.5/ 5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement;Recommendation score from 0 to 5: Mean, median (IQ).

2.4 | Use of HBV liver grafts

2.4.1 | Research questions

Q12. Use of anti-HBc +ve liver grafts. Which recipient, Which prophylaxis?

The prevalence of anti-HBc +ve donors varies from 2% to 3% in the United States, around 10% in Europe to more than 50% in Asia (Figure 4).[100] Using such grafts in HBsAg-ve recipients has a potential for transmitting HBV infection even in the absence of detectable viremia due to ccc-DNA in the donor hepatocytes. The risk varies from 10% to 80% with the HBV serological status of the recipient. Without prophylaxis, it is highest in naïve recipients[101] and lowest in anti-HBsAg+ve/anti-HBc+ve ones.[100]

HBV prophylaxis reduces the risk from 47.8% to 12% in naïve recipients and from 15.2% to 3.4% in anti-HBc +ve recipients.[100] Systematic reviews failed to demonstrate any significant advantage of HBV prophylaxis in anti-HBs +ve recipients because of the low rate of de novo HBV infection of about 4%-9%.[100,101] Given the small number of de novo HBV infection and the lack of randomised studies, it is difficult to establish superiority between NA alone and NA±HBIG[102] in HBV+ve/HDV-ve recipients or between different NA. Lamivudine has been consistently proved cost-effective for prophylaxis in this setting. However, the cost of third generation NAs with high barrier to resistance has been significantly reduced over the last years and ETV/TDF therapies can nowadays be considered when available.[102-104] In 72 HDV-positive patients receiving HBcAb-positive grafts treated with

NA plus HBIG post-transplant, none experienced HBV/HDV recurrence. These data indicate that, in contrast to the risk of HDV recurrence with an HBsAg-positive liver,[105] an HBcAb-positive liver can be safely given to HDV recipients protected long-term with combination therapy. However, data on NA monoprophylaxis are lacking.

Recommendations	Evidence level	Strength Agreement Score
R34 Anti-HBc +ve liver grafts should be considered for all adult recipients after informed consent and be preferentially proposed to HBsAg +ve recipients as these patients have been already planned to receive HBV prophylaxis and further to patients with detectable anti-HBs and/or anti-HBc antibodies	II-2	Strong 78.6%/14.3%/7.1% 4.2/ 4.5(4-5)
R35: In HBs Ag -ve recipients, prophylaxis should be based on NA long term. Third-generation NAs or Lamivudine can be proposed, depending on cost and availability	II-2	Strong 92.9%/0%/7.1% 4.4/ 5(4-5)
R36: Cohort studies aiming at quantifying the risk of HCC in patients receiving anti-HBc liver grafts are recommended since these patients are perceived at risk, albeit low, of HCC but the actual risk is unknown	III	Weak 92.9%/0%/7.1% 4.4/ 5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

Q13. Use of HBsAg +ve liver graft. Which recipient, which prophylaxis?

Transplantation from HBsAg+ve donors is a safe way to expand the donor pool[106-108] provided certain measures are undertaken including strict donor selection criteria (absence of delta co-infection[109] and liver damage) and adequate antiviral therapy. The main conclusions drawn from the studies are: (a) HBsAg+ve grafts have preferentially been allocated to HBsAg+ve recipients,[110,111] or in exceptional cases to HBsAg -ve recipients with high MELD scores[112]; in this latter scenario information on the potential risk of de novo HCC is advised. (b) The use of HBsAg+ve grafts is safe and comparable in outcome, even in terms of long-term survival, to the use of HBs -ve grafts[107,113]; (c) Despite the lack of signs of HBV-disease and the use of immunoglobulins, most patients continue to be HBsAg-positive,[112] thus the value of using HBIG remains unclear; (d) Prevention of HBV-liver disease can only be guaranteed by antiviral prophylaxis.[112] To establish graft suitability, the following criteria are required: normal liver function profile, donor and recipient HDV negativity, and in some but not all studies, donor pathology excluding fibrosis or significant inflammation. While most studies recommend chronically HBV infected recipients as preferred target recipients, a study suggested that the best candidates to receive HBV-infected organs are those with previously controlled HBV-infection (HBcAb-positive or both HBcAb and HBsAb positive) because they were able to mount an effective viral response when faced with a new HBV infection.[114] Although scant, HBsAg+ve donors have also been used in LDLT[115,116] provided NA prophylaxis of the donor was used for at least 2 years following donation.

Recommendations	Evidence level	Strength Agreement Score
R37. Organs from HBsAg+ve donors may be considered after an individualised assessment of the risk and benefits and appropriate patient consent. In HBAg-ve recipients, information on the potential risk of de novo HCC is advised	III	Strong 78.6%/14.3%/7.1% 4.2/ 4.5(4-5)
R38. Use of grafts from HBsAg+ve donors should only be considered when significant donor liver disease has been ruled out by histological examination	III	Strong 92.9%/0%/7.1% 4.6/5(4.25-5)
R39. Use of HBsAg+ve grafts should only be considered if there is an option for indefinite prophylaxis with entecavir or tenofovir	III	Strong 92.9%/7.1%/0% 4.7/5(5-5)
R40. HBsAg+ve grafts should not be used if HDV is present in either the donor or the recipient	III	Strong 100%/0%/0% 4.9/5(5-5)
R41. Recipients with chronic HBV infection should be managed according to existing guidelines irrespective of the donor HBV status and should be kept on third generation NA long term with no HBIG post-LT (HBs Ag +ve patients, see questions 5 and 6)	III	Strong 85.7%/14.3%/0% 4.4/5(4-5)

Recommendations	Evidence level	Strength Agreement Score
R42. Strict post-transplantation monitoring including clinical, biochemical and sero-virological assessment every 3 months for 1 year and then every 3–6 months indefinitely, in addition to liver ultrasound every 6-12 months, is recommended	III	Strong 100%/0%/0% 4.6/5(4-5)
R43. HBIg prophylaxis is not recommended in HBs Ag negative recipients regardless of the presence or not of anti-HBcore and/or anti-HBs	III	Weak 78.6%/7.1%/14.3% 4.3/ 5(4-5)
R44. HBsAg+ve grafts should target first HBs +ve recipients, followed by HBs –ve but anti-HBcore/antiHBs (+) recipients. In case of emergency, HBsAg+ve grafts may be used in HBV naïve patients only if the first four recommendations are guaranteed	III	Strong 80%/6.7%/13.3% 4.1/ 4(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

2.5 | Adherence, economic impact and perspectives

2.5.1 | 2.2.1. Research questions

Q14 Impact of non-adherence on prophylactic anti-HBV therapy after LT

Non-adherence to medical prescriptions refers not only to patients failing to take their medicine but also to errors in medicine dosage and timing of administration. Risk factors include young age and transition phase, conditions requiring long-term therapy,[117] but also understanding the disease,[118] personality, family or social relationships and supports.[119,120] As patients have different barriers to adherence, interventions tailored to individual risk factors are warranted. They may include counselling, educational programmes and specific devices to improve and check adherence (behavioural intervention), as well as an increase in the frequency of clinical or nurse visits or regular feedback (emotional intervention).[121] In LT, non-adherence to immunosuppressive drugs ranges from 15% to 40% in adults, whereas the rate of non-adherence to clinical appointments ranges from 3% to 47%.[122] In addition, more than 50% of HBV cases failing long-term NA are related to non-adherence. Strategies to counteract poor adherence include its detection, educational programmes and specific prophylactic regimens based on long-term combined HBIG +NA prophylaxis.

Recommendations	Evidence level	Strength Agreement Score
R 45 Risk factors of non-adherence to prophylactic antiviral medication should be carefully assessed during the waiting phase and before prescribing anti-HBV prophylaxis. Such an evaluation should include: (a) age; (b) previous non-adherent behaviour especially in the pre-LT setting; (c) misunderstanding of the risk associated with viral infection post-LT and/or therapeutic modalities; (d) lack of external (social/familial) support and caregiver	III	Strong 92.9%/0%/7.1% 4.5/4(4-5)
R46 In patients at high risk of poor/non-adherence (see above), dual long-term prophylaxis combining NA+ in-hospital HBIG (whatever the formulation) can be recommended	III	Strong 78.6%/14.3%/7.1% 4.1/ 4(4-5)
R47 Regardless of the risk of non-adherence and the type of anti-HBV prophylactic treatment, adherence to antiviral prophylaxis should be systematically evaluated during post-LT follow-up on a quarterly basis (Expert opinion). Self-reporting questionnaire and detection of HBV DNA/HBs Ag (plus HBs Ab when HBIG are used) on a quarterly basis can reasonably be proposed as first line tests	III	Strong 92.9%/7.1%/0% 4.2/4(4-5)
R48 Patient should benefit from a dedicated educational programme especially when subcutaneous HBIG or oral NA monotherapy are considered	III	Strong 92.9%/7.1%/0% 4.4/4.5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement;Recommendation score from 0 to 5: Mean, median (IQ).

Q15. Economic considerations associated with new ELITA prophylactic regimens

To evaluate the economic impact of the new ELITA HBV prophylaxis regimens, a budget impact analysis was performed assuming that all new HBV transplanted patients would be treated accordingly. Costs derived from the new ELITA regimen were compared with those associated with historical protocols.[123] The reference costs of each drug were based on the average price reported in

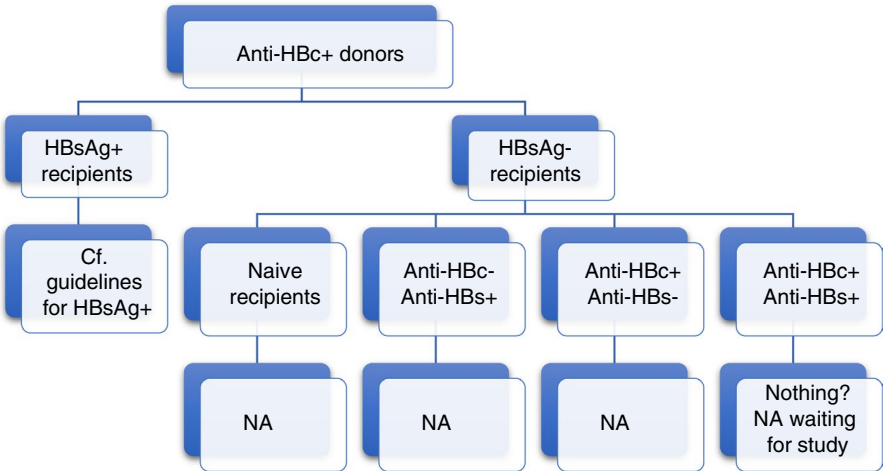

FIGURE 4 Prophylactic strategies after liver transplantation using an anti-HBc +ve liver allograft.

Spain, Italy, France, Austria, Belgium and Poland (Drugs average price: HBIG IV (5000 IU), € 1589.6; HBIG IM (1000 IU), €248.7; HBIG SC (1000 IU), € 496.4; Entecavir (1 mg), €10.1 mg; Tenofovir (245 mg), €8.4; Lamivudine (100 mg), €1.6). Based on ELTR Registry data, 600 HBV new patients are transplanted per year across Europe with early 3-months mortality after LT and a 10-year survival probability of 8% and 70%, respectively.[3,124] Based on expert opinions, assumptions for the prevalence of risk groups were made as follows 60%-, 10%- and 30%-prevalences of low-risk, high-risk and special population patients, respectively.

On this ground, the developed budget impact model estimated a 10-year cost reduction per patient of € 76 000 in "low risk" and € 67 000 in "high risk" patients. For special populations, no difference in cost was observed. Based on an estimation of 600 new LTs performed yearly in Europe in HBV recipients,[3,124] the target population will be 4835 patients after 10 years, resulting in €45.0 million cost-saving after 5 years and € 170.0 million after 10 years (Figure S2). A sensitivity analysis was also performed to estimate the impact of possible treatment cost reduction and variations in the incidence of new HBV LTs in Europe. Assuming a 50% reduction in treatment price, the model estimates a €19.0 million cost-saving after 5 years and € 84.0 million after 10 years. Assuming a 30% reduction of new HBV liver transplant per year (420 instead of 600) in Europe, the target population would be 3384 patients after 10 years for a €28.0 million cost-saving after 5 years and € 119.0 million after 10 years.

Finally, based on available data, around 6000 patients have been transplanted for HBV-related liver diseases in the last 10 years, 4835 of these patients being currently alive.[3,124] The cost-saving resulting from switching all these historical patients to new ELITA regimens would be around €30.0 million in only one year (Figure S3). Assuming a 50% reduction of treatment price, the cost-saving would be around €15.5 million in only 1 year.

Recommendations	Evidence level	Strength Agreement Score
R49: Budget impact analysis should be taken into account by stakeholders to nationally drive HBV prophylactic regimen according to HBV risk profiles amongst LT candidates	III	Strong 80.0%/13.3%/6.7% 4.2/ 4(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement ;Recommendation score from 0 to 5: Mean, median (IQ).

Q16. Future perspectives for HBV prophylaxis after LT

Novel direct antivirals that target different steps of the viral life cycle are being developed to achieve a functional cure for infection. The main viral target under study is the viral covalently closed circular DNA (cccDNA) which is responsible for viral persistence. Several agents may show promise in the setting of HBV prophylaxis after LT. These include:

1. Myrcludex-B, a pre-S1 myristylated peptide, specifically blocks the interaction of HBV with its receptor, hNTCP. This entry inhibitor, administered by SC route, is being evaluated in patients with chronic hepatitis B (CHB) and with HBV/HDV co-infections.[125,126] Its clinical value for LT patients should be evaluated in clinical trials as a potential substitute for HBIG.

2. Capsid assembly modulators are currently evaluated in Phase 1b/2a clinical trials as oral antiviral agents for the treatment of CHB. These compounds might have the potential to decrease profoundly the pool of intrahepatic cccDNA.[127-129] Combinations with NAs in LT patients should be evaluated to see if they would allow the depletion of cccDNA and a more rapid withdrawal of HBIG.
3. Drugs targeting cccDNA are being evaluated in pre-clinical models. They may offer novel perspectives for simplified prophylactic strategies in the future.[130,131]
4. Other viral targets are under pre-clinical or early phase clinical studies (siRNA, Nucleic acid polymers, HBx inhibitors).[130,131]

Recommendations	Evidence level	Strength Agreement Score
R50 Clinical trials in LT patients should be performed with Entry inhibitors or Capsid assembly modulators as soon as sufficient clinical efficacy and safety data have been generated in patients with CHB or CHD	III	Strong 78.6%/14.3%/7.1% 4.2/5(4-5)

Agreement amongst experts: % Agreement/neutral opinion/disagreement.Recommendation score from 0 to 5: Mean, median (IQ).

2.6 | Future prospects

Considerable improvement was achieved over the last two decades in the management of HBV infection pre-LT and its prevention post-LT. Current approaches combining NA+ HBIG or even NA alone post-LT are now consistent with excellent mid- and long-term survivals whatever the replicative status of HBV before transplantation. The current ELITA guidelines provide up-dated evidence to adopt these new prophylactic strategies on a large scale and to move out of a conservative policy which has been the rule until recently across Europe.[80] Yet there are still unmet medical needs and area of knowledge to explore in the close future.

Efficacy of new prophylactic protocols based on HBIG withdrawal and long-term NA monoprophylaxis should certainly be investigated in the long term through observatory studies to assess the magnitude of prophylaxis failure due to underestimated poor adherence.

Additional data should be collected in Western centres which are keen to adopt full NA monoprophylaxis. It is, indeed, of major importance to verify across Europe that the encouraging results reported by Fung et al[8] can be reproduced in Western populations and that LT in HBV patients, especially in those with positive HBV DNA before LT, is not hampered by unexpected serious events. Ideally, those issues should be investigated by setting up randomised controlled studies comparing different prophylactic approaches on endpoints such as recurrent HBV infection or hepatitis, HBs Ag persistence, intra-hepatic detection of ccc DNA and even de novo HCC following HBV genome integration in graft cells.

While waiting for such controlled studies, an ELITA survey in centres using NA monoprophylaxis across Europe will be launched and a prospective cohort of patients on NA monoprophylaxis will be considered.

In HDV+ve candidates, discontinuation of HBIg followed by NA monoprophylaxis or in combination with entry inhibitors will have to be considered in the setting of clinical trials.

Specific controlled prospective studies should also be designed in HBV +ve recipients to re-assess the feasibility and efficacy of full prophylaxis withdrawal under strict circumstances, in highly selected patients (HBeAg negative patients, transplanted with undetectable viremia, with at least a few years of recurrence-free follow-up after LT). Such an approach can be easily reconsidered nowadays, thanks to third generation NAs with high genetic resistance which can be promptly administered as "rescue therapy" in case of HBsAg seroreversion and/or HBV DNA detectability, with rapid suppression of viral replication and effective long-term disease control, even if serum HBsAg remains detectable.

Such an approach should also be combined with investigation of new vaccination protocols with vaccination to be started in patients on NA post-LT, after withdrawal of HBIg, targeting first patients who show HBs Ag –ve/anti-HBs -ve after HBIg withdrawal and after the minimisation of immunosuppression and not during the first 6 months post-LT. Other innovative approaches based on new adjuvant vaccines and myrcludex peptide as a pre-S1 vaccine are also attractive to test in LT patients.

As stated in Question 16 alternative prophylactic strategies should be eagerly explored including the entry inhibitor Myrcludex-B as a potential substitute for HBIG in combination with NAs. Clinical trials in LT patients should also be performed with capsid assembly modulators as soon as sufficient clinical efficacy and safety data have been generated in non-LT patients with CHB or CHD.

Eventually, long-term risks associated with the use of anti-HBc +ve and Hbs Ag +ve liver grafts should be investigated prospectively.

3 | CONCLUSIONS

The aim of these ELITA HBV practical guidelines was primarily to revisit, in the long story of LT, the major issue of how to prevent recurrence of HBV infection. In light of recent advances and peculiarities of LT, ELITA experts propose to reconsider the definitions of HBV infection post-LT and the risk groups for HBV recurrence. They also propose new, simple and cheaper prophylactic strategies adjusted to these risk groups and recommendations on the use of expanded criteria grafts to

safely expand the liver pool. Eventually, they suggest rooms for investigation to next-generation researchers committed with LT.

These ELITA HBV practical guidelines provide clinicians with an official, reliable and comprehensive source of information and recommendations to guide LT practitioners in adopting new prophylactic strategies in HBV patients. This is a major step forward in the modern era of LT. ELITA acknowledges yet that moving forward will deserve careful assessment of the proposed strategies and plans to endorse any future initiative aiming at pushing these new limits.

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AUTHORSHIP

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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