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Hepatitis B Immunoglobulins Withdrawal in Hepatitis B Virus Mono-Infected Liver Transplant Recipients: An Italian Multicentre Prospective Study

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ABSTRACT

Background & Aims: Despite recommendations from scientific societies that hepatitis B immunoglobulin (HBIG) can be safely discontinued, centres across Europe continue to use the combination nucleoside analogues (NAs) plus HBIG for long-term prophylaxis against hepatitis B virus (HBV) recurrence after liver transplant (LT). The aim of this study was to evaluate the safety of HBIG withdrawal in a cohort of LT recipients on long-term HBIG+NAs.

Methods: All patients under third-generation NAs + HBIG and who adhered to the INSIGHT-B protocol were followed up after HBIG withdrawal, in a multicentre, prospective, Italian cohort study, to evaluate the risk of HBV reactivation. The probability of HBsAg reappearance after HBIG withdrawal, stratified by presence of HCC at LT, was estimated through Kaplan–Meier curves and Log-rank tests.

Results: Between February 2021 and January 2024, 222 liver transplant (LT) recipients withdrew HBIG 11.6 (IQR 6.7–17.0) years after LT and were followed up for a median time of 24 months. After HBIG withdrawal, Hepatitis B surface antigen (HBsAg) reappearance

Abbreviations: ELITA, European liver and intestine transplantation association; ELTR, European liver transplantation registry; ETV, entecavir; EVL, everolimus; HBIG, hepatitis B immunoglobulins; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDV, hepatitis D virus; hgb-NA, high genetic barrier nucleos(t)idic analogue; LAM, lamivudine; LFTs, liver function tests; LGB, low genetic barrier; LLOD, lower limit of detection; LT, liver transplantation; MMF, mycophenolate mofetil; NAs, nucleoside or nucleotide analogues; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

was observed in 12 patients (5.4%) with a cumulative 1-, 2- and 3-year recurrence rate of 4.08%, 5.36% and 6.89% respectively. HBsAg serum levels remained very low over the entire period of observation (median 9 months, range 3–20), and in four cases fluctuated around the detectability threshold. In all cases, HBV-DNA persisted undetectable, liver function tests (LFTs) remained within the normal range, and neither HBV-related hepatitis nor HCC were observed. No baseline patients' features were found to be significantly associated with the likelihood of HBsAg reappearance after HBIG withdrawal, including the presence of HCC at transplantation.
Conclusions: HBIG could be safely withdrawn in HBV mono-infected LT recipients on long-term combination HBIG plus third generation NAs.

1 | Introduction

Hepatitis B virus (HBV) infection represents a common indication for liver transplantation (LT) in Europe, involving 10%–15% of LT candidates, based on data from the European Liver Transplantation Registry (ELTR). These figures also include HBV/Hepatitis D virus (HDV)-related liver diseases [1–3].

In the initial experience of LT, HBV was considered a contraindication to LT due to the high risk of graft loss secondary to HBV recurrence, resulting in poor survival rates (< 40% at 5 years) particularly in patients with elevated HBV-DNA serum levels at the time of LT [4]. The introduction of hepatitis B immunoglobulin (HBIG) in the early 1990s reduced HBV recurrence by 60%, dramatically improving both graft and patient survival [5]. However, patients with elevated HBV-DNA serum levels at LT still remained at risk of HBV recurrence mainly as a consequence of insufficient circulating neutralising antibody levels despite frequent HBIG i.v. infusion which were cumbersome for the patients and costly for the healthcare system.

In the late 1990s, the advent of lamivudine (LAM), the first nucleoside analogue (NA) against HBV, allowed 90% of recurrent HBV infections to be clinically controlled when used in combination with long-term HBIG [6]. The main downside of LAM was its low genetic barrier (lgb) which favoured the emergence of drug-resistant YMDD mutations.

In the early 2000s, more potent second-generation NAs such as Adefovir dipyvoxil, shortly followed by potent third-generation NUCs with a high genetic barrier (hgb), such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), led to virtually universal prevention of HBV reactivation [7]; thus paving the way for HBIG-free prophylaxis [8, 9].

More recently, international guidelines suggested that 'de novo' patients undergoing LT should be treated with NA in combination with HBIG only for a limited period of time after LT, varying between 4 and 52 weeks depending on HBV-DNA levels at the time of LT, and that adherent, 'historical patient' on dual prophylaxis should have HBIG withdrawn and maintained on hgb-NA monotherapy [10–12].

Despite the availability of clear international recommendations, most Centres across Europe are still maintaining life-long combination prophylaxis for patients undergoing LT for HBV-related liver disease [13, 14].

It must be acknowledged that this 'conservative' approach is sustained by both the high effectiveness of the combination prophylaxis against HBV reactivation and the concern of the potential consequences of HBsAg reappearance after HBIG withdrawal, especially in patients undergoing LT with active HCC. Moreover, HBIG withdrawal policies have been mainly explored with excellent results in observational, retrospective cohorts from the far East, where HBV viral strains are different from those circulating in Europe. This study aims to evaluate both the safety and effectiveness of hgb-NAs monotherapy in a large cohort of historical LT recipients who had been on dual prophylaxis for at least 1 year (median 10 years), therefore providing further evidence to support the reconsideration of related concerns.

2 | Material and Methods

2.1 | Study Design

This is a multicentric, prospective, cohort study from seven Italian centres that includes HBsAg-positive LT recipients who received standard immune-prophylaxis with HBIG + NAs for at least 12 months after LT, and who agreed on HBIG withdrawal while being maintained or started on long-term ETV or TDF or tenofovir alafenamide (TAF). Patients were consecutively enrolled at the time of their routine annual follow-up visit at each site. All HBsAg-positive patients received iv HBIG during transplantation and for the first postoperative week aiming for detectable anti-HBs titres (ideally > 300 IU/mL), followed by periodic (from weekly to monthly) subcutaneous or intramuscular injections in order to maintain anti-HBs protective titres (ideally > 100 IU/mL). Target serum anti-HBs levels, however, could vary according to each centre policy. At LT, HBIG infusions were added to the ongoing NA treatment, that is, LAM from 2000 to 2007, Adefovir + LAM in 2007–2009, TDF from 2009 or ETV from 2008. After 2017, LT recipients under TDF could be switched from TDF to TAF according to Italian reimbursement criteria (for age, or renal and/or bone disease).

2.2 | Study Population

Patients transplanted between 1 January 1991 and 31 December 2023 were considered for HBIG withdrawal on occasion of the scheduled follow-up visit in the clinic at each site (Milano-Niguarda, Milano-Policlinico, Bergamo-ASST Papa San Giovanni XXXIII; Pisa-Cisanello; Roma-Umberto I; Torino-Molinette and Palermo-ISMETT). Informed consent was obtained from all patients before HBIG discontinuation. The study was approved by the Institutional Review Boards of Milano Niguarda with approval code Number 611–11102022. Ethics approval was also obtained from all participating centres. The

study complied with the Declaration of Helsinki and good clinical practice guidelines.

2.3 | Inclusion Criteria

The following inclusion criteria were required at enrolment.

Age > 18 years. No HDV coinfection at LT. No graft from HBsAg-positive donors. At least 12 months of combined HBIG prophylaxis after LT. HBsAg and HBV-DNA undetectable at enrolment. Normal liver function tests. Past adherence to regular post-LT follow-up visits and medication intake. Maintained or switched to third-generation NA (TDF, ETV or TAF) at HBIG withdrawal. Patients still on LAM were switched either to TDF or ETV, at the discretion of the clinician managing the patient. Signed informed consent.

2.4 | Exclusion Criteria

Coinfection with HDV. Receiving a graft from an HBsAg positive donor. Nonadherence to past outpatient visit and medication intake. Refusal to release the consent to the study.

2.5 | Endpoints

The primary endpoint was HBsAg reappearance after HBIG withdrawal. Secondary endpoints were recurrence of HBV (defined as the reappearance of both HBsAg and HBV-DNA), recurrence of HBV-related disease (defined as HBV reinfection associated with increase of LFTs) and changes in renal function in patients who were switched from LAM to TDF or ETV at the time of HBIG withdrawal.

2.6 | Antiviral Protocol Following HBIG Withdrawal

ETV or TDF dose was adjusted for renal function (GFR); patient could be switched to TAF according to Italian regulatory agency switching criteria.

2.7 | Data Collection and Follow Up After HBIG Withdrawal

A standardised protocol for the prospective collection of data following HBIG withdrawal was established.

Patients underwent outpatient visits at least at 3, 6, 12, 18, 24, 30 and 36 months after stopping HBIG, with the following biochemical and serological tests prospectively collected: LFTs, creatinine, HBsAg (with titre when positive), HBV-DNA, anti-HBs titre. The qualitative HBsAg tests were performed using the Architect HBsAg assay (Abbott Diagnostics, Abbott Park, IL, USA), with a lower limit of detection (LLOD) of 0.05 IU/mL. Anti-HBs were measured using the Architect anti-HBs assay (Abbott Diagnostics, Abbott Park, IL, USA), with a LLOD of 10 mIU/mL. HBV-DNA was measured with the COBAS Taqman assay (Roche Molecular Systems, Branchburg, NJ) with a LLOD of 10 IU/mL.

Change in renal function was monitored in patients who were on LAM before HBIG discontinuation. Patients' drug compliance was monitored by the clinician at each follow-up visit.

2.8 | Policy in Case of HBsAg Reappearance

Prior to starting the study, HBIG re-administration was not considered an effective option in the case of HBsAg reappearance. However, the final decision on HBIG re-administration was left to local clinicians' discretion.

2.9 | Statistical Analysis

The characteristics of the study population were assessed through a descriptive analysis, with categorical variables described through absolute and relative frequencies and continuous variables through median and interquartile range. Analyses were carried out on the whole population and stratified by reappearance of HBsAg. The probability of HBsAg reappearance, starting from the date of HBIG withdrawal and stratified by presence of HCC at LT, was estimated through Kaplan–Meier curves and Log-rank tests.

Univariate Cox proportional hazard models were used to evaluate the association between HBsAg reappearance and selected variables collected at LT and at HBIG withdrawal.

3 | Results

Between February 2021 and January 2024, 238 LT recipients on long-term HBIG + NA were assessed for inclusion in this study. Fifteen (6%) were excluded for the following reasons: two for receiving a graft from an HBsAg-positive donor, one for noncompliance, one for intolerance to third-generation NAs analogues and 11 for refusing consent (Figure 1). One additional patient was excluded from the analysis because of voluntary withdrawal of all post-LT drugs including NA and immunosuppressants. A total of 222 patients were eventually included in the analysis. The main patient's characteristics at transplant and at the time of HBIG withdrawal are summarised in Table 1. Most patients were middle-aged male; the majority of them were of Caucasian origin. At LT, 43 (19%) patients were HBV DNA positive. 22% of donors were anti-HBc positive. HBIG was stopped after a median time from LT of 11.6 years (rage 1–31 years).

3.1 | HBsAg Reappearance in the Serum

During the 24 months (IQR 17–32) of post HBIG withdrawal, HBsAg reappeared in the serum in 12 patients (5.4%). The corresponding cumulative 1-, 2- and 3-year HBsAg reappearance rate was 4.08%, 5.37% and 6.89% respectively. The median

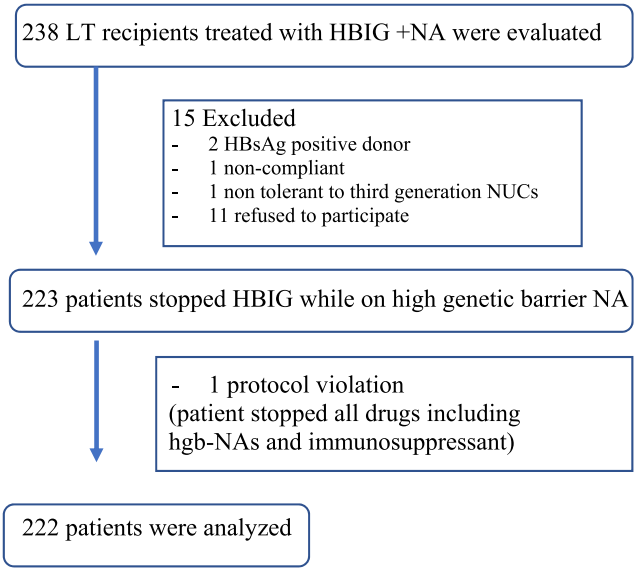

FIGURE 1 | Patient disposition. HBIG, hepatitis B immunoglobulins; hgb, high genetic barrier.

time of HBsAg reappearance from HBIG discontinuation was 9 (IQR 4.5–15) months. At the time of HBsAg reappearance, the median serum HBsAg and anti-HBs titres were 0.08 (IQR 0.06–0.18) IU/mL and 0 (IQR 0–0) respectively. Ten out of 12 patients experiencing HBsAg reappearance were continued on HBIG alone, while two were restarted on HBIG (in 1 case for patient preference, in the other on clinician advise). Both patients were restarted on the same HBIG dose they were taking before withdrawal, and both became HBsAg negative. Median follow up after HBsAg reappearance was 9 months (range 3–30 months).

Table 2 shows HBsAg titre kinetics for the 12 patients who became HBsAg positive. In four patients, HBsAg recurrence was transient while in the remaining eight patients HBsAg positivity persisted over the entire period of observation.

No 'HBV reinfection' or 'HBV disease' recurrence was observed as HBV-DNA remained undetectable and LFTs normal in all cases. All patients with HBsAg reappearance underwent elastography which was normal.

Abdominal ultrasound or CT scan, according to local policies, was performed to exclude HCC recurrence.

3.2 | Predictors of HBsAg Reappearance

At univariate analysis, no baseline features (at LT and at HBIG withdrawal) showed to be significantly associated with the risk of HBsAg reappearance. In the absence of significant associations at univariate analysis, multivariate analysis was not performed (Table 3). Notably, the reappearance of HBsAg was independent of the duration of HBIG administration. For greater clarity, patients who had HBIG withdrawn between 0–3, 3–5, 5–10 and >10 years after transplant were compared, and no statistical difference between groups was found (Table 4).

Finally, the cumulative probability of HBsAg reappearance according to the presence of pre-LT HCC at LT was similar ($p = 0.2$) (Figure 2) in keeping with the multivariable analysis (Table 3).

3.3 | Renal Function Changes

Seventy-seven patients (27%) were on LAM at the time of HBIG withdrawal and were switched either to ETV (49%) or to TDF/TAF (51%). 24/77 patients with eGFR <60 mL/min/1.73 m2 at the time of HBIG discontinuation were switched to TAF. No significant worsening in renal function was observed during the follow up (Figure 3).

3.4 | Survival

By the end of the study, four patients died after 34, 50, 56 and 71 months since HBIG withdrawal. The causes of death were bacterial infections (one pneumonia and one sepsis) for two patients, while the remaining two died of cardiovascular causes. No patient experienced HCC recurrence or de-novo HCC during the follow-up period.

4 | Discussion

According to ELTR Registry, at least 15 000 HBV positive LT recipients are currently alive and most of them are maintained long-term on combined NAs + HBIG, as shown in recent studies conducted in France, Spain and Italy [13, 14]. This conservative approach is quite surprising in light of the proven efficacy of hgb-NA monotherapy and the recent recommendations from the European Liver and Intestine Transplantation Association (ELITA) consensus [10].

In this study, we describe the risk and characteristics of HBV recurrence in 'historical' HBsAg positive Caucasian LT recipients, who after a median period of 11.6 years of dual therapy with HBIG plus NA, had HBIG withdrawn, and were consequently treated with hgb-NAs mono-therapy to prevent HBV reactivation. The cumulative probability of HBsAg reappearance and HBV-DNA recurrence at 3 years was 6.89% (12/222) and 0% respectively. Furthermore, no patient experienced biochemical signs of HBV-related disease, confirming results from previous studies [8, 15, 16].

More in detail, in our 12 cases of HBsAg reappearance, HBsAg titres persisted at very low levels over a median period of 9 months (range 3–30 months) and often fluctuated around the detectability threshold. Notably, in four patients, HBsAg became undetectable after initial reappearance. These results are again in line with what was described by Fung et al. [8] in a large cohort of patients from Asia. Similar observations were reported by Xu et al. in 46 patients from the United States [15] and by Manini et al. in 70 patients from United Kingdom [16]. However, only 37 of these patients were Caucasians.

Regarding the interpretation of these findings, it is well documented that HBV can persist in extrahepatic sites such as pancreatic islet cells, renal proximal tubular epithelium and

TABLE 1 | Patient characteristics, 222 cases, at LT and at HBIG withdrawal.

Demographics	
Male gender – N (%)	185 (83%)
Ethnicity – N (%)	
Caucasian	209 (94.1%)
Africans	5 (2.2%)
Asian	8 (3.6%)
Characteristics at LT	
Age, years*	55 (46–61)
LT indication	
Decompensated cirrhosis	98 (44.1%)
Hepatocellular carcinoma	108 (48.6%)
Acute liver failure	16 (7.2%)
Virological features – N (%)	
HBV-DNA positive	43 (19.4%)
HBV-DNA negative	151 (68.0%)
HBV-DNA missing	28 (12.6%)
Type of antiviral, N (%)	
LAM ± ADV	92 (41.4%)
ETV o TDF	127 (57.2%)
None	3 (1.3%)
Donor serology	
Anti-HBc positive	49 (22.1%)
Anti-HBc negative	150 (76.5%)
Not available	23 (10.4%)
Characteristics at HBIG withdrawal	
Time (years) from LT*	11.6 (6.7–17.0)
Age, years*	67 (59.7–72.4)
Duration (years) of HBIG Prophylaxis*	10.0 (5.0–15.0)
Duration of HBIG Prophylaxis	
0–3 years	37 (16.67%)
3–5 years	25 (11.26%)
5–10 years	51 (22.97%)
> 10 years	109 (49.10%)
Type of antiviral	
LAM	77 (34.7%)
ETV or TDF/TAF	145 (65.3%)
Type of HBIG	
IM	128 (57.7%)
SC	94 (42.3%)
Anti-HBs titre (mIU/mL)*	150.0 (107.0–211.0)
Laboratory test	
ALT, UI/L*	20.0 (15.0–25.0)
Bilirubin, mg/dL*	0.7 (0.5–1.0)
Creatinine mg/dL*	1.1 (0.9–1.3)
Immunosuppression	
Tacrolimus	170 (76.6%)
Cyclosporine	33 (14.9%)
MMF	73 (32.9%)
EVL	19 (8.6%)
Follow-up time (months) from HBIG withdrawal*	24.0 (17.0–32.0)

Abbreviations: ETV, entecavir; HBIG, hepatitis B immunoglobulins; LAM, lamivudine; LT, Liver transplantation; TDF, tenofovir disoproxil fumarate.
*Median (Q1–Q3).

lymphocytes, which can represent a source of HBV recurrence after LT [17]. In addition, it has been shown that a very early recurrence of HBV in the graft can be observed in half of the biopsy samples obtained at the time of graft reperfusion or early in the postoperatory setting, despite the use of high-dose HBIG during the transplant procedure [17]. Therefore, the role of prophylaxis is to prevent reactivation of HBV rather than actual reinfection; hence the hypothesised need for lifelong prophylaxis [18, 19].

HBsAg has historically been regarded as an important marker of reactivation, especially prior to the advent of oral NA. With NA treatment, the clinical significance of HBsAg positivity has declined, except when using low genetic barrier NA such as LAM, where a positive HBsAg may indicate underlying resistance, preceding HBV-DNA reappearance and eventually graft hepatitis. Conversely, in patients receiving high genetic barrier-NA monoprophylaxis, reappearance of HBsAg is not associated with hepatitis when serum HBV-DNA is not detectable. The presence of serum HBsAg without HBV-DNA is likely due to the production of subviral particles not blocked by NA while HBsAg particles are blocked by HBIG in immune complexes. It is therefore plausible that in the era of potent NA, isolated HBsAg reappearance after LT does not represent a reliable marker of HBV-related disease recurrence, but merely a serological finding with no clinical implication.

We were not able to find any donor, transplant, or recipient-related factor associated with the likelihood of HBsAg reappearance after HBIG withdrawal; although the low frequency of observed events makes the identification of predictive factors statistically more challenging. In this regard, HCC has always been under the spotlight given the well described association

TABLE 2 | Description of HBsAg reappearance in the serum*.

Pz ID	Year of LT	HCC at LT	HBIG withdrawal	Time of HBsAg reappearance after HBIG withdrawal						
				3 months	6 months	12 months	18 months	24 months	30 months	36 months
23	2013	Yes	Apr 2023	**Neg****	**0.09**	Restart HBIG				
94	2006	No	Feb2022	**0.2**	**0.2**	Restart HBIG				
141	2007	Yes	Apr 2022	**Neg**	**Neg**	**Neg**	**0.06**	**0.06**	**Neg**	
157	2008	Yes	Apr 2022	**Neg**	**Neg**	**Neg**	**Neg**	**Neg**	**0.06**	
159	2005	No	Jun 2023	**Neg**	**0.08**	**Neg**	**Neg**			
174	2009	No	Jun 2023	**Neg**	**Neg**	**0.07**	**Neg**			
177	2007	Yes	Mar 2022	**0.3**	**0.46**	**0.46**	**0.6**	**0.57**	**0.57**	
191	2006	Yes	Mar 2022	**Neg**	**Neg**	**Neg**	**0.06**	**0.07**	**0.07**	
214	2017	Yes	Feb2023	**Neg**	**Neg**	**0.36**	**0.63**			
215	2010	Yes	Mar2023	**Neg**	**Neg**	**0.07**	**Neg**			
221	2012	Yes	Dec 2023	**Neg**	**Neg**	**0.05**				
223	2016	No	Jan 2024	**0.16**	**0.41**	**0.41**				

Abbreviations: HBIG, hepatitis B immunoglobulins; HCC, hepatocellular carcinoma; LT, liver transplantation.
*Expressed as IU/mL.
**Neg means below 0.05IU/mL.

TABLE 3 | Analysis of predictors of post-LT HBsAg reappearance following HBIG withdrawal.

	HBsAg reappearance		Univariate analysis	
Variable	**Yes (*N* = 12)***	**No (*N* = 210)**	**HR (95% CI)**	***p***
Male gender	10 (83%)	175 (83%)	1.00 (0.22–4.58)	0.99
Ethnicity				
Caucasian	11 (92%)	198 (94%)	0.68 (0.09–5.25)	0.70
Non-Caucasian	1 (8%)	12 (6%)		
Age at LT	53.4 (45.3–61.3)	55.39 (46.4–61.2)	0.99 (0.94–1.05)	0.77
HCC at LT	8 (66.6%)	100 (47.6%)	2.14 (0.64–7.10)	0.21
ALF at LT	0 (0.0%)	16 (7.6%)	NA**	NA
HBV-DNA at LT (pos vs. neg)	2 (16.6%)	41 (19.5%)	1.12 (0.23–5.38)	0.89
Anti-HBc +ve donor	4 (33.3%)	45 (21.4%)	2.16 (0.61–7.69)	0.23
Duration of HBIG (years)	12.82 (10.5–14.6)	10 (5–15)	1.04 (0.96–1.13)	0.31
Age at HBIG w/d	67.2 (57.9–77.0)	67.6 (59.7–72.4)	1.00 (0.94–1.06)	0.96
Tacro at HBIG w/d	9 (75.0%)	161 (76.7%)	0.99 (0.27–3.67)	0.98
Anti-HBs titre at HBIG w/d	159 (99–183)	149.(107–212)	1.00 (0.99–1.00)	0.47

*One patient who stopped all drugs, including immunosuppressants and hgb-NA, was excluded from the analysis.
**Not adequate because of 0 events.

TABLE 4 | Rate of HBsAg reappearance following HBIG withdrawal, stratified for different duration of HBIG after LT: < 3 years, 3–5 years, > 5 years and > 10 years.

Duration of HBIG prophylaxis	**HBsAg reappearance**	
	Yes (*N* = 12)	**No (*N* = 210)**
0–3 years	0 (0%)	37 (17.62%)
3–5 years	0 (0%)	25 (11.9%)
5–10 years	3 (25%)	48 (22.86%)
> 10 years	9 (75%)	100 (47.62%)

Note: p value: 0.1906.

between HBV recurrence and HCC recurrence, with HCC behaving as a sanctuary of HBV, without any evidence of direct causality [19]. In the study from Manini et al. [16] HBsAg reappearance after HBIG withdrawal was observed only in patients with HCC at LT (but without HCC recurrence after LT). In our study, HCC at LT did not predict HBsAg reappearance after LT.

Another potential concern is the residual risk of de novo HCC based on reported rates of HCC/year of 0.5%–1.4% for noncirrhotic HBV patients on treatment with third generation NAs warranting enrolment of these patients in HCC surveillance programmes [20, 21]. The absence of de novo HCC in our cohort is in line with the reassuring data coming from the landmark study of Fung et al. [8] where no cases of de novo HCC were reported over a period of 8 years and these results are confirmed after extended follow up (unpublished data). In a subsequent study from Fung et al. [22] 114 HCC LT recipients receiving prophylaxis with ETV alone were monitored for the reappearance of HBsAg using a high sensitivity test with a LLOD of 0.0005 IU/mL at regular intervals after LT. The HBsAg and HCC recurrence rates at 1, 2, 3 and 5 years were 8.5%, 18%, 21.9% and 26% for HBsAg and 9%, 14.4%, 20.7% and 24.3% respectively. Notably, early reappearance of HBsAg (within 3 months from LT) was associated with a significantly higher rate of HCC recurrence compared to those who remained HBsAg negative (56.1% vs. 7%, respectively, at 5 years posttransplant, $p < 0.001$). While waiting for confirmation from other studies, this finding is intriguing as the traditional HBsAg test with a LLOD of 0.05 IU/mL would not have detected this correlation, and it suggests that the risk of HBV/HCC recurrence is already established early after LT. From a very practical point of view, it is to be highlighted that the concern of the potential consequences of HBsAg reappearance in patients undergoing LT with active HCC is virtually absent after 3–5 years from LT when the risk of HCC recurrence is virtually zero, and this is the case for the vast majority of historical patients.

Notably, two patients in our series were restarted on HBIG soon after HBsAg reappearance using the same HBIG doses they were on before withdrawal, and both rapidly returned HBsAg negative. Although the clinical benefit of this approach is questionable, it may represent an option to reassure the very few patients who may feel uncomfortable about returning HBsAg positive and to remove the fear of 'potential' long-term risk of developing HBV-related complications in the context of complete viral suppression. Moreover, the similar results in terms of HBsAg reappearance between patients who had HBIG withdrawn at different time intervals from LT confirm that HBIG can be stopped much earlier in line with what is suggested by current guidelines.

These results should be framed also from a health economic perspective, as they highlight the potential cost-effectiveness of the new approach [23]. Cortesi et al. performed an economic

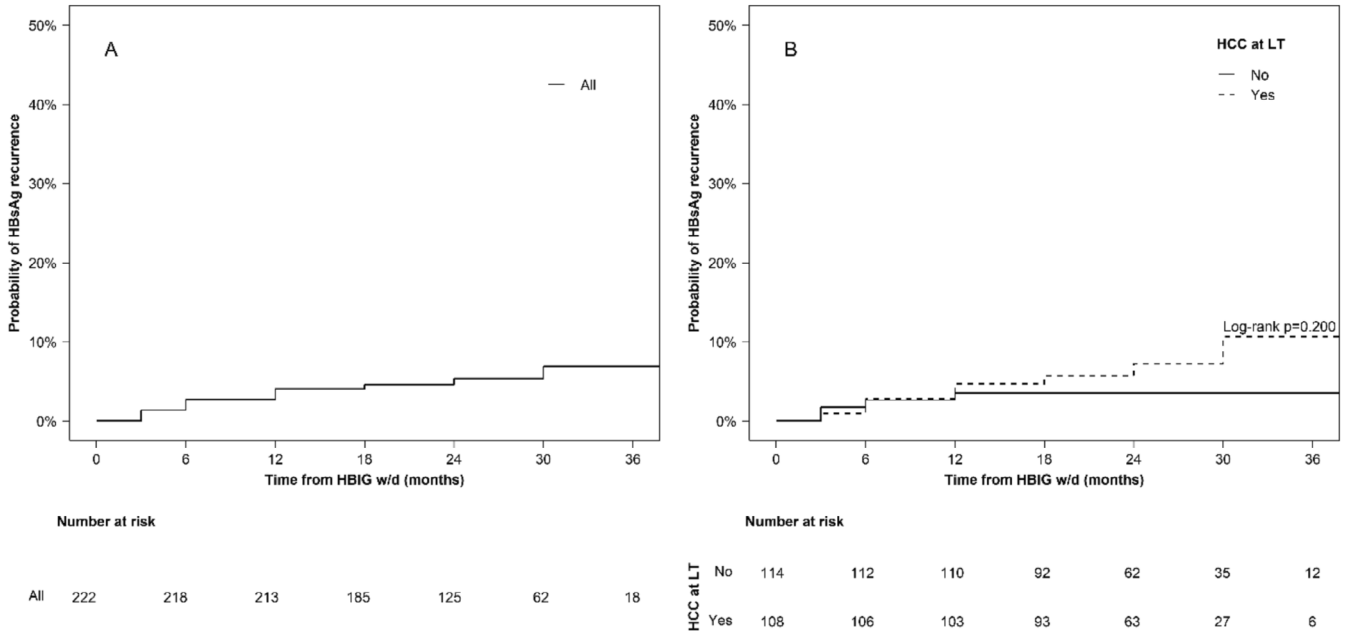

FIGURE 2 | Cumulative probability of HBsAg reappearance (12 cases) overall (panel A) and according to the presence of pre-LT HCC (panel B).

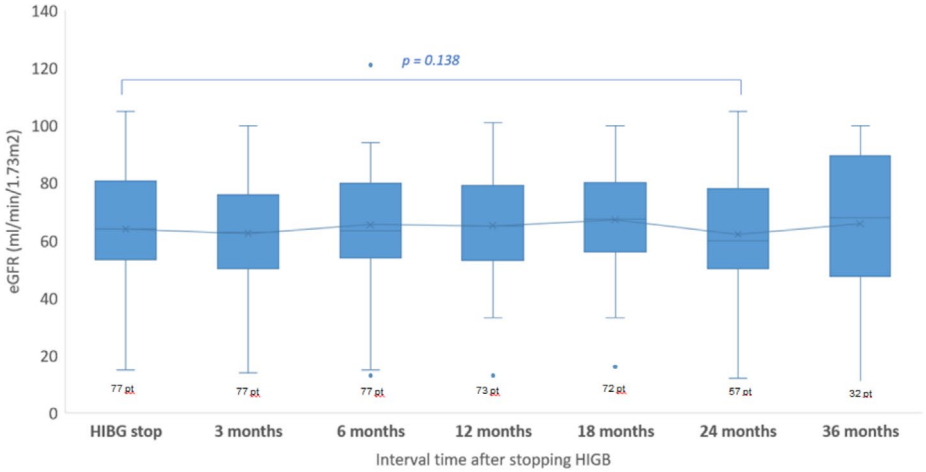

FIGURE 3 | Patients shifted from LAM to TDF/TAF at the time of HBIG withdrawal: EGFR over time after shifting.

impact analysis associated with the implementation of the new ELITA recommendations [24]. The authors assumed an average price of 327 Euro for 1.000 IU of HBIG marketed in Spain, Italy, France, Austria, Belgium and Poland and therefore an annual cost of 4.250 Euro for each patient treated with 1.000 IU IM or SC HBIG every 4 weeks, which represents the most common 'low dose' maintenance regimen in Italy. If we consider that 5.627 historical HBV LT patients were alive at the time of the report by Adams et al. [3], the cost saving of stopping HBIG would be at least 20.000.000 Euro per year at European level. Applied to our study, the 223 patients who had HBIG stopped favoured an annual cost saving of approximately 1.000.000 Euro. We believe that the money saved with this strategy could be effectively re-allocated by the healthcare system to invest where it is more needed. Finally, patients were happy to stop HBIG for the negative effect of injections on broader aspects of quality of life encompassing physical functioning (pain during injections), psychological well-being (negative feelings such as anxiety and fatigue) and social functioning (lower flexibility in daily activities).

There are some limitations for this study. First, there was heterogeneity in the antiviral regimens used prior to HBIG withdrawal, including variations in the schedule of HBIG prophylaxis and the types of antiviral drugs prescribed across the seven participating centres. Second, although the risk of HBsAg recurrence in smaller series has been shown to reach a plateau after 3 years, its definite estimate would require longer follow-up. Third, the follow-up of patients who experience HBsAg reappearance is too short, median 9 months, for a clear assessment of its clinical impact. Fourth, the study is subject to survivorship bias, as we were unable to include historical HBV patients who died prior to the study's initiation, potentially affecting the generalisability of the results to all patients with HBV. This also explains why the well-known association between HBsAg reappearance and HCC recurrence did not emerge [25].

In conclusion, our study provides additional evidence in favour of discontinuing HBIG in 'historical' HBV transplant recipients as the great majority, 95%, will remain HBsAg negative. To the best of our knowledge, this is the largest study on this topic so far. Avoiding overtreatment is highly relevant because it is cumbersome for patients and costly for the health-care systems. This policy would be applicable and safe for historical patients transplanted for HCC and with a follow-up after LT longer than 5 years, as they would no longer be at risk for HCC recurrence.

Author Contributions

Raffaella Viganò: conceptualization, data curation, writing – original draft, writing – review and editing. **Alessandro Loglio:** data curation, writing – review and editing. **Clara Dibenedetto:** data curation, writing – review and editing. **Paola Carrai:** data curation, writing – review and editing. **Silvia Martini:** data curation, writing – review and editing. **Ilaria Lenci:** data curation, writing – review and editing. **Bianca Magro:** data curation, writing – review and editing. **Sara Conti:** formal analysis. **Paolo Angelo Cortesi:** formal analysis. **Chiara Mazzarelli:** data curation, writing – review and editing. **Chiara Becchetti:** data curation, writing – review and editing. **Giovanni Perricone:** data curation, writing – review and editing. **Monica Cucco:** data curation, writing – review and editing. **Marco Carbone:** writing – review and editing. **Donatella Cocchis:** data curation, writing – review and editing. **Elisa Farina:** data curation, writing – review and editing. **Luisa Pasulo:** data curation, writing – review and editing. **Mauro Viganò:** data curation, writing – review and editing. **Michele Sagasta:** data curation, writing – review and editing. **Elisabetta Degasperi:** writing – review and editing. **Davide Ghinolfi:** data curation, writing – review and editing. **Pietro Lampertico:** supervision, writing – review and editing. **Stefano Fagiuoli:** supervision, writing – review and editing. **Luca Saverio Belli:** conceptualization, writing – original draft, writing – review and editing, data curation.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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