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BRIEF REPORT

The role of HBIG in real life for patients undergoing liver transplantation due to HDV-related cirrhosis

Sergio Rodríguez-Tajes[1,2] | María García-Eliz[2,3] | Arantxa Caballero Marcos[4] | Isabel Campos-Varela[5] | Alba Cachero Ros[6] | Carmelo Loinaz[7] | Miguel Á. Gómez Bravo[8] | Manuel Rodríguez-Perálvarez[2,9] | Emilio Fabrega[10] | María L. González Diéguez[11] | Carmen Vinaixa[2,3] | José M. Pascasio[2,8] | Inmaculada Fernández Vázquez[7] | Carme Baliellas[6] | Lluis Castells[2,5] | Magdalena Salcedo[4] | Martín Prieto[2,3] | Gonzalo Crespo[1,2] | Sabela Lens[1,2] | Xavier Forns[1,2]

[1]Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, Barcelona, Spain

[2]Consorcio de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas, ISCIII, Madrid, Spain

[3]Liver Unit, Hospital Universitario y Politécnico de La Fe, Valencia, Spain

[4]Liver Transplant Unit, Gregorio Marañón Hospital, Madrid, Spain

[5]Liver Unit, Vall d'Hebron University Hospital, Barcelona, Spain

[6]Liver Unit, Bellvitge University Hospital, L'Hospitalet de Llobregat, Spain

[7]Liver Transplant Unit, University Hospital 12 de Octubre, Madrid, Spain

[8]Liver Unit, Virgen del Rocio Hospital, Sevilla, Spain

[9]Liver Transplant Unit, Hospital Universitario Reina Sofia, Córdoba, Spain

[10]Liver Unit, Marqués de Valdecilla University Hospital, Santander, Spain

[11]Liver Unit, Hospital Universitario Central de Asturias, Oviedo, Spain

Correspondence
Sabela Lens, Liver Unit, Hospital Clínic, University of Barcelona, IDIBAPS, CIBERehd, Villarroel 170, 08036 Barcelona Spain.
Email: slens@clinic.cat

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Abstract

Recommended post-liver transplant (LT) prophylaxis in patients with hepatitis delta includes a nucleos(t)ide analogue (NA) and anti-hepatitis B immunoglobulin (HBIG) indefinitely. We analysed the use of HBIG in real-life clinical practice and its impact on HBV/HDV recurrence in 174 HDV-related LT patients from 10 Spanish liver transplant centres (1988–2018). Median post-LT follow-up was 7.8 (2.3–15.1) years and patient survival at 5 years was 90%. Most patients (97%) received HBIG in the immediate post-LT, but only 42% were on HBIG at the last control. Among those discontinuing HBIG, the median time on treatment was 18 (7–52) months. Post-LT HBsAg+ was detected in 16 (9%) patients and HBV-DNA in 12 (7%). Despite HBsAg positivity, HDV recurrence was reported only in three patients (1.7%), all of whom were not receiving

Abbreviations: anti-HBc, hepatitis B core antibody; anti-HBs, anti HBV surface antigen antibody; CHD, chronic hepatitis delta; DNA, deoxyribonucleic acid; EMA, European Medicines Agency; ETV, entecavir; HBIG, anti-hepatitis B immunoglobulin; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; IQR, interquartile range; LAM, lamivudine; LT, liver transplantation; NA, nucleos(t)ide analogue; NTCP, sodium taurocholate cotransporting polypeptide; peg-IFN, Pegylated interferon; RNA, ribonucleic acid; TDF, tenofovir difumarate.

NA and had discontinued HBIG. Our data suggest that a finite HBIG prophylaxis in HDV-LT is feasible, especially if high-barrier NAs are used.

KEYWORDS
hepatitis B, hepatitis B immunoglobulin, hepatitis delta, liver transplantation

1 | BACKGROUND AND AIMS

Chronic hepatitis delta (CHD) affects at least 15–20 million people worldwide[1] and is the most severe form of viral hepatitis. Compared to HBV monoinfection, coinfection with HDV is associated with accelerated fibrosis progression, earlier hepatic decompensation and an increased risk for the development of hepatocellular carcinoma (HCC) with decreased overall survival.[2] Indeed, the estimated annual rates of cirrhosis and HCC development are 4% and 2.8%, respectively.[3] In addition, HBV/HDV-coinfected patients have a two-fold increased mortality rate compared to HBV monoinfected patients.[4]

Despite the recent conditional EMA approval of the HDV entry inhibitor bulevirtide, the proportion of patients achieving HDV-RNA undetectability is still low, the optimal treatment duration has not yet been defined and data on patients with more advanced disease are very limited.[5] Thus, liver transplantation (LT) remains the only curative option for individuals with CHD and clinical decompensation or hepatocellular carcinoma (HCC).

The combination of HBIG and antivirals is the gold standard for preventing HBV recurrence after LT.[6] To prevent HBsAg reappearance, which may in turn facilitate relapse of hepatitis D, most experts recommend lifelong prophylaxis.[7] Nonetheless, some studies have shown that HDV may protect against HBsAg recurrence after LT[8] and that HBV suppression with NAs would prevent full HBV reactivation, precluding HDV recurrence.[9,10] The latter would imply that life-long HBIG administration may not be necessary.

As data on the use of HDV and HBV prophylaxis in patients with CHD are scarce, particularly in real-life, our aim was to describe HDV/HBV prophylaxis clinical practice among LT recipients in Spain, and to analyse the incidence and impact of HBV and HDV recurrence on graft and patient survival.

Key points

- Patient and graft survival rates in HBV/HDV-related liver transplantation were comparable to those described for HBV monoinfection with a 5-year survival of 90%.
- More than 40% of LT patients discontinued HBIG 1–2 years after transplantation. Despite the latter, HDV reactivation was extremely rare.
- In patients with complete HBV-DNA suppression at the time of LT and when potent NAs are administered as prophylaxis, finite HBIG would be a safe prophylactic approach with a residual risk of HDV reactivation.

2 | METHODS

This multicentre study included 10 Spanish liver transplant centres. We retrospectively analysed all patients who underwent LT for HBV/HDV coinfection between 1988 and 2018. We collected all relevant clinical and virological data before and after LT. The type of HBV prophylaxis administered after LT (HBIG and NAs) and its duration were also recorded. Regarding virological variables, we recorded the following markers during follow-up after LT: HBsAg, anti-HBs, HBV-DNA, HDV-RNA (if available), date of the positive result, as well as HBV vaccination after LT. The periodicity of serum HBV-DNA, HDV-RNA and HBsAg was performed at the physician's discretion. HBV recurrence was defined as HBsAg-positive after LT with or without active replication (HBV-DNA). Finally, we assessed clinical outcomes after LT (cirrhosis development, re-transplantation, death and cause of death).

Continuous variables are reported as median and interquartile range (IQR) and categorical variables are reported as absolute and relative frequencies. Groups were compared using the Mann–Whitney *U* test for continuous variables when appropriate and the Fisher exact test for categorical variables. The cumulative incidences of patient and graft survival were calculated using the Kaplan–Meier method. Statistical significance was established as a two-sided *p* value of .05. The analysis was performed with Stata/IC 14.2 for Mac (StataCorp, Texas).

3 | RESULTS

3.1 | Patient cohort description

A total of 987 patients underwent LT for HBV infection during the study period at the selected centres. Of these, 174 (17%) had HDV coinfection (we recorded data of 173 patients). Baseline characteristics of the cohort, including the indications for LT are depicted in Table 1.

At LT, all patients were HBsAg-positive, only 17% had detectable HBV-DNA as 55% were on antiviral treatment (10% with lamivudine). By definition, all patients were positive for anti-HDV antibodies, but HDV-RNA at LT was available for 76 (44%) patients (Table S1). Of these, 64 (84%) had HDV-positive viremia. Regarding antiviral therapy for HDV, only 12% of the cohort had received peg-IFN. HCV and

TABLE 1 Patient characteristics at LT.

N (%)/med (IQR)	*N* = 173
Sex (male)	130 (75%)
Age	45 (36–52)
Origin	
Spain	133 (77%)
East Europe	26 (15%)
Transplant period	
<1990 (no HBIG)	1 (.6%)
1990–1996 (HBIG monotherapy)	20 (11.6%)
1997–1999 (HBIG+LAM)	11 (6.3%)
>2000 (HBIG+ other NAs)	141 (81%)
Follow-up (years)	7.8 (2.3–15.1)
LT indication	
ALF	6 (4%)
End-stage cirrhosis	117 (68%)
HCC	16 (9%)
End-stage cirrhosis + HCC	32 (19%)
Child-Pugh Score	10 (9–11)
MELD	18 (15–22)
HCV	20 (12%)
HIV	13 (8%)
HBV treatment pre-LT*	
None	70 (45%)
Lamivudine	16 (10%)
Tenofovir/Entecavir	52 (34%)
Others	16 (11%)
HDV treatment pre-LT*	18 (12%)
Virological data	
Detectable HBV-DNA at LT	27 (17%)
Positive HBeAg	12 (7%)
Detectable HDV-RNA at LT**	64 (84%)

Abbreviations: ALF, acute liver failure; HCC, hepatocellular carcinoma. *Data available in 154 patients. **Data based on 76 patients tested for HDV before LT.

HIV coinfections were present in 12% and 8% of the cases, respectively. Most patients received a double or triple regimen based on one calcineurin inhibitor plus 6–12 months of prednisone, with or without mycophenolate mophetil (Table S2). Regarding the donor's HBV serology, 17 were anti-HBc positive and none were HBsAg-positive.

3.2 | HBV prophylaxis

Patients were grouped into different periods according to the available prophylactic therapies after LT: 1 before HBIG introduction (.6%), 20 with HBIG monotherapy (11.5%), 11 HBIG+LAM (6.3%) and 141 HBIG + other NAs (81.5%) including entecavir or tenofovir ($n = 114$) (Table 1).

Immediately after LT, 97% of patients received HBIG but at the time of data collection for the study only 42% of patients were receiving HBIG. The median of follow-up after LT was 7.8 (2.3–15.1) years with a median HBIG treatment duration of 31 (11–82) months. However, when analysing those patients who withdrew from HBIG, the median treatment duration was 18 (7–57) months. The proportion of patients receiving HBIG prophylaxis during follow-up is shown in Figure 1A.

The main reasons for HBIG discontinuation were patient drop-out (9%) and physician's criteria or centre's protocol (76%). HBIG was stopped due to adverse events in two patients. In parallel to HBIG withdrawal, anti-HBs titres declined over time. Figure 1B shows the percentage of patients with positive anti-HBs titres at 1, 3, 5 and 10 years after LT.

Antiviral therapy prophylaxis was associated with the transplant period and changed overtime. Overall, 40% received lamivudine, 40% received tenofovir or entecavir, 10% received other antivirals and a small proportion of patients undergoing LT at early years (10%) did not receive antivirals. At the last follow-up, the proportion of patients receiving tenofovir or entecavir increased to 61% whereas the proportion of patients receiving lamivudine decreased to 26% (25 patients treated with LAM changed to TDF or ETV and other 41 remained with LAM). At the last follow-up there were still eight patients (5%) who were not receiving any antiviral therapy and all had undergone liver transplantation in the early 90's. In addition, five patients received HBIG-free antiviral monotherapy with ETV/TDF.

Regarding HBV vaccination post-LT, only 16 patients (10%) received a full vaccination course (three intramuscular double doses (40ug/dose) at 0, 1 and 6 months). In three of them (18%), HBIG was suspended due to the achievement of anti-HBs titres higher than 100 IU/L. None of these patients stopped NA therapy in the follow-up.

3.3 | HBV and HDV recurrence

During the post-LT follow-up, HBsAg positivity was detected in 16 (9%) patients, 38% within the first year and 25% within the second year. Median time from LT to HBsAg positivity was 16 (6–70) months. The individual patient characteristics are shown in Table S3. Regarding HBIG use, six (38%) patients were still on HBIG at the time of HBsAg+ and in four (25%) other patients, HBsAg was detected within 1 year after HBIG discontinuation. Regarding antiviral prophylaxis, six (37%) patients were not receiving NAs (all undergoing LT before 1999), eight patients were on lamivudine (50%) and only two were on tenofovir (13%), both had an isolated HBsAg-positive determination with negative HBV-DNA and no clinical impact (Table S4).

HBV-DNA was not regularly assessed during follow-up, particularly during the first part of the study, and was usually assessed at the physician's discretion in patients with abnormal liver tests or HBsAg seroreversion. During the study period, recurrence of HBV infection with active replication (HBV-DNA) was detected in 12 liver transplant recipients (7%). HBV-DNA detection coincided with the reappearance of HBsAg in most patients (10/12, 83%), and in

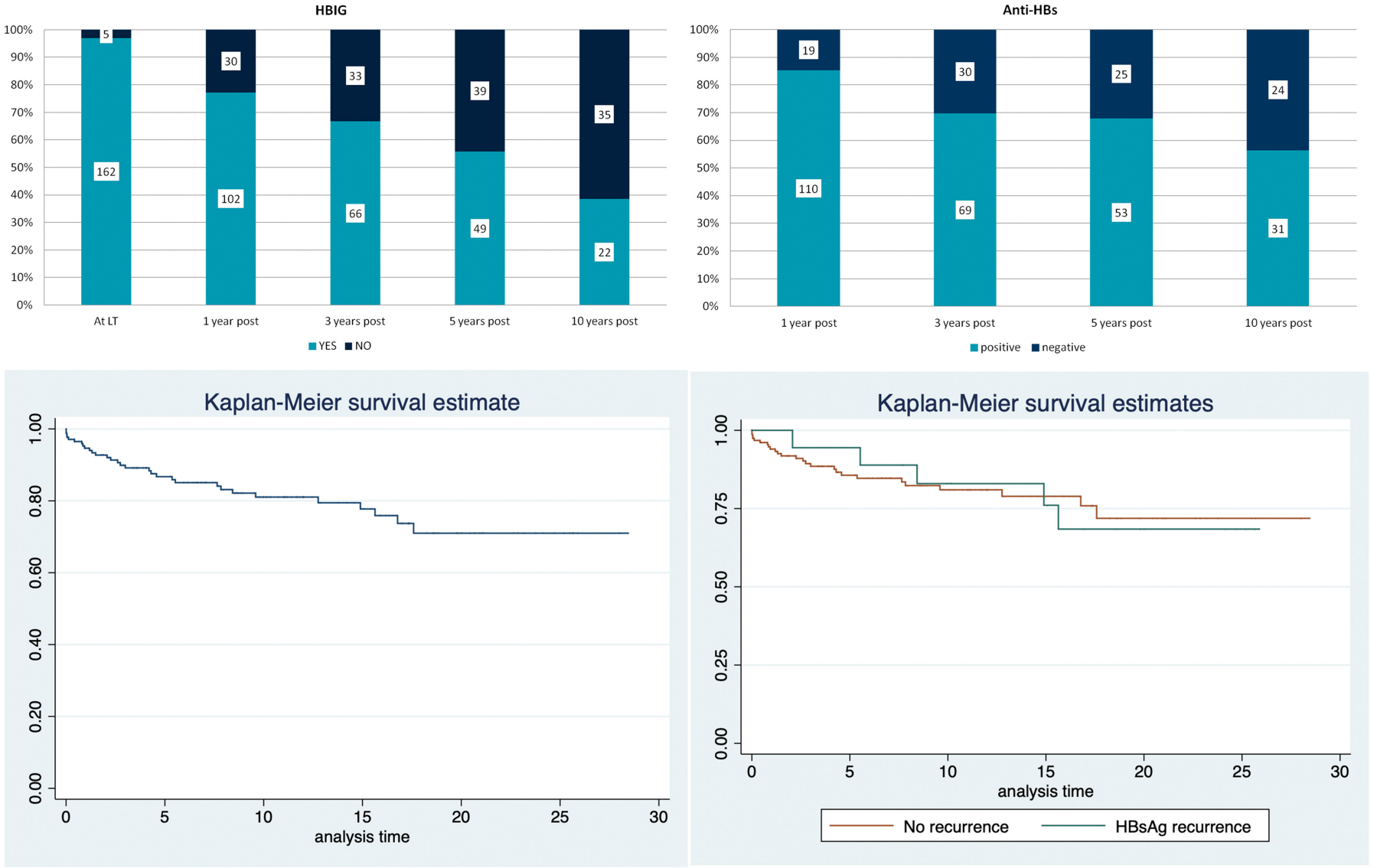

FIGURE 1 (A) Percentage of patients receiving HBIG at 1, 3, 5 and 10 years after LT with the number of patients inside the bars. (B) Percentage of patients with positive anti-HBs titres at 1, 3, 5 and 10 years after LT with the number of patients inside the bars. (C) Total survival (time in years). (D) Survival according to HBsAg recurrence (time in years).

7/12 (63%) it was associated with an increase in transaminase levels. HBV-DNA was detected without HBsAg seroreversion only in two cases; unfortunately, no sequence data were available to discard the presence of HBsAg escape mutants. Importantly, all patients with a positive HBV-DNA determination were either on LAM or not receiving NAs (because they underwent transplantation before NAs implementation).

Regarding HDV recurrence, HDV-RNA was detected only in three patients (1.7% of the total cohort), all with simultaneously positive HBsAg and HBV-DNA. After HDV recurrence, two patients died (one due to HBV/HDV recurrence and another due to HCV-related fibrosing cholestatic hepatitis) and the remaining patient had persistent HBV/HDV coinfection without liver-related complications. All three patients underwent transplantation in the early transplant periods, received HBIG only for approximately 1 year post-LT and were not under NAs prophylaxis at the time of HBV/HDV recurrence (Table S3).

3.4 | Post-transplant patient and graft survival

The survival rates at 1, 5 and 10 years after LT were 94.7%, 90.0% and 88.2%, respectively, and the graft survival rates were 93.5%, 87.1% and 84.1%, respectively (Figure 1C). Besides the small number of cases presenting with HBV or HDV recurrence, a comparison of outcomes between patients who did or did not present with HBsAg recurrence showed no differences in survival ($p > .05$) (Figure 1D).

4 | DISCUSSION

Combined prophylaxis (HBIG and NAs) aims to prevent HBV graft reinfection during and after LT. However, HBIG administration requires parenteral administration, has a high cost and needs frequent assessment of anti-HBs titres. Current data support a short duration of HBIG prophylaxis (an even third generation NAs monoprophylaxis) in HBV monoinfected LT recipients.[11,12] Nevertheless, isolated HBsAg positivity may occur in patients undergoing short HBIG prophylaxis and particularly those not receiving HBIG.[13] The reappearance of HBsAg is a concern for HDV/HBV coinfected patients. As HDV is thought to require only HBsAg to coat its virion[14] and there is no optimal curative therapy, lifelong combination of HBIG with HBV antivirals has been adopted by default as prophylaxis against HDV reinfection. Dual prophylaxis, however, may not be affordable for all centres and patients, which may explain early HBIG therapy discontinuation.

To our knowledge, this is the largest cohort of LT patients with HDV coinfection with a long follow-up period. Importantly, patient and graft survival rates were comparable to those described for HBV monoinfection with a 5 year survival of 90%. In our study, HBV prophylaxis after LT was heterogeneous due to the long follow-up period and the lack of a standardized protocol. However, we believe it is important to include the real-life outcomes of HDV with the different prophylactic strategies to gain further insights into its impact on HDV recurrence. Notably, despite most scientific societies' recommendations, HBIG was discontinued in almost 60% of the patients. The main reason for HBIG discontinuation was the patient's dropout and physician's decision, probably influenced by cost (10%–60% of it not covered by the health-care system) and patient's long-term stability (and survival) after LT.

In our study, post-LT HBsAg positivity at any time point was low (9%) and similar to the HBV recurrence reported in HBV monoinfected LT patients.[15] Despite post-LT HBsAg positivity is more frequent in patients who are not on HBIG, it may also occur in those on combined HBIG/NA therapy and may be independent of anti-HBs titres.[16] Recurrence of HBV infection with active replication (HBV-DNA) occurred in 7% of patients and was accompanied by a biochemical ALT flare in 4% of the total cohort. It is important to highlight that no patient receiving high-barrier o third generation NAs (entecavir or tenofovir), even in absence of HBIG, developed HBV hepatitis recurrence. When individually analysing the characteristics of patients with HBV recurrence, this was associated either to a lack of antiviral prophylaxis or to resistance to low-genetic-barrier NAs (lamivudine). Importantly, despite HBV recurrence (with or without active replication), HDV recurrence occurred in only 3 patients (1.7%) after HBIG discontinuation and in the absence of antiviral prophylaxis. Our data are in accordance with several published studies that, despite including smaller number of patients, indicate a very low HDV recurrence rate after HBIG interruption.[17] A recent review calculated the cumulative rate of HDV infection in these studies resulting in only 2% of the cases.

Interestingly, some studies have revealed that HDV may persist in liver grafts for a long time (HD-Ag positivity in liver biopsies), even in the absence of HBV replication.[18,19] In this scenario, viral RNA is replicated by the host RNA polymerases in the hepatocyte, and therefore persists in the graft for months as a latent infection. In vitro data suggest that the presence of HBsAg and HDV in a cell would be sufficient for HDV to egress from the cell and initiate infection. Indeed, Lempp et al.[20], stably transduced HepG2 cells with genes encoding the NTCP-receptor and the HBV envelope proteins and produced a cell line able to secrete infectious HDV after primary infection. As state above, our data and that from other studies would suggest that HBsAg alone, in the absence of HBV replication (HBV-DNA) may not be sufficient to support HDV reassembly and replication. However, the latter maybe explained by the very low number of hepatocytes co-expressing HBsAg and HD-Ag.

Our study had some limitations. First, the study was retrospective, with no standardized follow-up of patients, resulting in a lack of data at some time points, with different antiviral treatments and with changes in this antiviral treatment during the follow-up as new medications were available. In addition, the virological markers were tested at medical discretion; therefore, we cannot completely discard whether the presence of transient positive HBsAg or HBV-DNA occurred between assessments. Second, HDV-RNA determination was not implemented until recently in some centres. As there was

no commercially available assay the method varied among centres, leading to potential differences in sensitivity.

In conclusion, the main findings of our study indicate that HBV prophylaxis in HBV/HDV-coinfected LT recipients is not homogeneous in real-life practice. Despite most guidelines' recommendations, more than 40% of LT patients withdraw from HBIG 1 to 2 years after transplantation. Despite this, HDV reactivation is rare, even in cases of HBsAg reappearance.

Overall, our results support that HBIG discontinuation after the initial months post-LT in patients with suppressed HBV-DNA at the time of LT would be a safe prophylactic strategy against HDV reinfection, especially when potent NAs are used as prophylaxis.

AUTHOR CONTRIBUTIONS

SRT, SL and XF participated in the concept and design of the study, review and analysis of data, and writing and editing of the manuscript. The rest of the authors participated in the review and analysis of data and in the editing of the manuscript.

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CONFLICT OF INTEREST STATEMENT

XF and SL acted as advisor for Gilead and Abbvie. SL and IF received speaker fees and acted as advisor for Gilead and Abbvie.

DATA AVAILABILITY STATEMENT

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

ETHICS APPROVAL STATEMENT

The study was submitted and approved by the Ethics Committee of our Institution. Each investigator could only identify the patients from their own site, whereas the remaining study investigators could only access patient codes and were not able to retrieve patients' personal data. Given the study design, signed informed consent was not required.

ORCID

Sergio Rodríguez-Tajes https://orcid.org/0000-0002-3189-7557
Isabel Campos-Varela https://orcid.org/0000-0001-6597-3151
Carmen Vinaixa https://orcid.org/0000-0001-5060-4556
Gonzalo Crespo https://orcid.org/0000-0002-1178-4897
Sabela Lens https://orcid.org/0000-0003-4900-411X
Xavier Forns https://orcid.org/0000-0002-8188-1764

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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