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Active hepatitis B virus vaccination in the prevention of viral reactivation in liver transplantation recipients with previous hepatitis B infection: a cohort study

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Summary

BACKGROUND AND AIM OF THE STUDY: For many years, the standard treatment following liver transplantation for hepatitis B has been a combination of hepatitis B immunoglobulin and nucleos(t)ide analogues such as entecavir and tenofovir. However, because of the high costs and logistical challenges of long-term hepatitis B immunoglobulin use, alternative approaches such as vaccination and hepatitis B immunoglobulin-free regimens are being explored. This study gathered information on a potential response (or lack thereof) and addressed the adverse events associated with active immunisation in liver transplant recipients in a Swiss cohort with hepatitis B virus (HBV)-related diseases after discontinuing hepatitis B immunoglobulin.

METHODS: Participants were recruited at the University Hospital of Bern between January 2022 and December 2023. Eligibility was restricted to liver transplant recipients with HBV-related disease who were receiving hepatitis B immunoglobulin and nucleos(t)ide analogue therapy at the time of study entry. The primary outcome was HBV relapse following hepatitis B immunoglobulin discontinuation; secondary outcomes included the response rate to active immunisation and reported adverse events. After exclusion, 18 patients were analysed. These patients, under ongoing immunosuppression and antiviral nucleos(t)ide analogue therapy, received active immunisation a minimum of 4 weeks after stopping hepatitis B immunoglobulin. Blood samples were collected at baseline and 4 weeks after vaccination, with follow-up extending for at least 12 months. Responders were defined as those with anti-HB levels of >10 IU/l. All patients received at least three vaccinations.

RESULTS: Six patients responded to the active immunisation with anti-HBs development, showing a response rate of 33.3%. No side effects or HBV recurrence were reported during the study period.

CONCLUSION: In this cohort, following liver transplantation for hepatitis B, patients who discontinued hepatitis B immunoglobulin while continuing nucleos(t)ide analogue therapy showed no relapse of hepatitis B, and a double-dose vaccination regimen yielded a modest response rate. These findings warrant further investigation into optimising vaccination strategies in this population.

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Introduction

In liver transplantation for diseases related to HBV, preventing HBV recurrence is crucial. In a landmark study in 1991, Samuel et al. reported that post-liver transplantation administration of hepatitis B immunoglobulin (HBIG) reduced the graft infection rate from 75% to 33% and increased 3-year survival from 54% to 83% [1]. Since this study's publication, the standard post-liver transplant care for patients with HBV infection has been parenteral hepatitis B immunoglobulin [2]. After the approval of the first nucleos(t)ide analogue, lamivudine, and later the more effective third-generation nucleos(t)ide analogues, tenofovir and entecavir, the combination regimen of nucleos(t)ide analogues with hepatitis B immunoglobulin became standard. Various studies have shown that combination regimens significantly reduce the risk of graft re-infection to below 5% and improve patient survival rates [3, 4].

For many years, a combination of hepatitis B immunoglobulin and high-barrier nucleos(t)ide analogues such as entecavir and tenofovir has been the standard treatment [2, 5, 6]. However, because of the high costs and logistical challenges associated with long-term hepatitis B immunoglobulin use, alternative approaches such as vaccination and hepatitis B immunoglobulin-free regimens have been investigated. Recent guidelines by the WHO emphasise the need for simplified and expanded access to HBV treatments, underscoring the importance of innovative strategies in managing HBV infection [7]. Although prophylactic HBV vaccines have significantly reduced the prevalence of HBV-related diseases [8], the effectiveness of these vaccines in liver transplant recipients remains under debate [9, 10]. Furthermore, recent research has highlighted the importance of therapeutic vaccines and their poten-

tial to induce a comprehensive immune response, which could be beneficial in the post-transplantation context [11–13]. This study gathered information on a potential response or lack thereof and addressed potential adverse events associated with active immunisation after discontinuing hepatitis B immunoglobulin in conjunction with nucleos(t)ide analogue therapy in liver transplant recipients previously infected with hepatitis B.

Materials and methods

Participant selection

A total of 43 liver transplantation recipients with end-stage liver disease or hepatocellular carcinoma related to HBV infection and active infection at the time of transplantation were identified. The intervention was applied in liver transplant recipients who underwent transplantation between 1994 and 2021 at the University Hospital of Bern. Participants were recruited at the University Hospital of Bern between January 2022 and December 2023. Eligibility was restricted to liver transplant recipients with HBV-related disease who were receiving hepatitis B immunoglobulin and nucleos(t)ide analogue therapy at the time of study entry. An active HBV immunisation protocol was initiated in these patients, who, after discontinuing hepatitis B immunoglobulin in 2022–2023, were receiving ongoing nucleos(t)ide analogue therapy and immunosuppression, as per clinical guidelines. Blood samples for evaluating immunisation response were collected at baseline and 4 weeks after vaccination, with follow-up extending for at least 12 months.

Study protocol

In this open-label cohort study, passive immunisation with hepatitis B immunoglobulin was discontinued at least 4 weeks before the commencement of active immunisation. All patients had negative anti-HBs and viral load at the time of hepatitis B immunoglobulin cessation. The hepatitis B immunoglobulin regimen varied between the participants and was at the treating physician's discretion. Active immunisation was carried out a minimum of 4 weeks after stopping passive immunisation, under ongoing immunosuppression and antiviral therapy with nucleos(t)ide analogue. Blood samples were collected at the beginning of immunisation and 4 weeks after completion. All vaccinations were administered intramuscularly (i.m.), following standard immunisation protocols for liver transplant recipients. Not all patients received their vaccines at the University Hospital of Bern; some participants were vaccinated by their general practitioner.

Data were obtained from patient medical records and laboratory reports. Key variables, such as HBV DNA levels, anti-HBs titres, and demographic data, were assessed through standardised serological testing at baseline and follow-up visits. The immunisation response was measured through anti-HBs titres recorded in laboratory assessments. To minimise selection bias, all eligible patients during the study period were included based on predefined criteria. Observer bias was reduced by relying on objective laboratory measurements for key outcomes and using standardised questions for patient-reported adverse events. Adverse events following vaccination were systematically assessed during clinical visits using structured patient interviews. Patients were specifically asked about any symptoms or discomfort experienced after each vaccination. The questions focused on local reactions (e.g. pain, redness, or swelling at the injection site), systemic symptoms (e.g. fever, fatigue, or nausea), and the presence of severe or unusual side effects. Duration, severity, and the need for medical treatment were also recorded. This approach relied on self-reported data, which, while limited in detecting subclinical adverse events, provided a practical and patient-centred method for adverse event documentation.

The primary outcome was HBV relapse following the discontinuation of hepatitis B immunoglobulin. The secondary outcomes were the response rate to active immunisation and reported adverse events associated with active immunisation.

Following the active immunisation protocol, patients were monitored for a minimum of 12 additional months. Patients were classified as responders if they achieved anti-HBs levels of >10 IU/l at the completion of active immunisation. Non-responders (anti-HBs <10 IU/l) were not reintroduced to passive immunisation but were monitored for hepatitis B recurrence. HBV recurrence was defined as the recurrence of HBsAg and/or HBV DNA. During the follow-up visits, additional laboratory value tests (including haemogramme, liver values, and kidney retention parameters) were obtained. Patients with incomplete data and those lost to follow-up were excluded from the final analysis to ensure data consistency across reported outcomes. Missing data are indicated in table 1, where applicable.

No formal study protocol was registered for this observational study. The study was conducted following international ethical guidelines and with approval from the Cantonal Ethics Commission of Bern, Switzerland (approval number: 2021-00246). No protocol deviations occurred during the study period. The STROBE cohort study reporting guidelines were used to aid in the drafting of this manuscript [14].

Data analysis

Categorical variables are expressed as numbers and percentages. Quantitative variables, such as age and anti-HBs titres, were analysed descriptively and are presented as medians with interquartile ranges. No categorisation of continuous variables was performed due to the small sample size. Data analysis was conducted using Microsoft Excel and R (version 4.2.1), both widely available and supported software packages. No custom analytical code was created for this study.

The study flow diagram shown in figure 1 illustrates the progression from initial patient identification of liver transplant recipients with HBV-related disease to the final analysis of vaccination outcomes. Following the enrolment of 43 liver transplant recipients with end-stage liver disease or hepatocellular carcinoma (HCC) related to HBV, an eligibility and data validation step was conducted to confirm that the patients met the inclusion criteria and that baseline data were accurate. After validation, 19 eligible patients were allocated to receive active HBV vaccination. The figure also details patient exclusions due to death, loss to follow-up, persistent anti-HBs, or patient refusal to

discontinue passive immunisation. The final analysis involved 18 patients who completed the study.

Results

Study inclusion

Twenty-four patients were excluded for the following reasons: death before study enrolment (eight patients), loss to follow-up (eight patients), anti-HBs positivity at the time of transplantation (five patients), and unwillingness to discontinue hepatitis B immunoglobulin (three patients). Additionally, one patient was excluded due to persistent anti-HBs despite cessation of passive immunisation. Consequently, 18 patients were selected to receive active immunisation after discontinuing passive immunisation while continuing immunosuppression and antiviral nucleos(t)ide analogue therapy (figure 1).

Baseline characteristics

A total of 18 patients were enrolled in this study. The indications for liver transplantation included decompensated hepatitis B-related cirrhosis in seven patients (39%), decompensated cirrhosis with hepatitis B/D coinfection in four patients (22%), and hepatocellular carcinoma (with or without cirrhosis) in seven patients (39%) who were HBV-positive. At the time of liver transplantation, only one patient was positive for HBeAg. Eight patients had detectable HBV DNA before transplantation. One patient additionally had alcoholic steatohepatitis, and another had metabolic dysfunction-associated steatohepatitis (MASLD).

The characteristics of each group, including clinical and virological features, are presented in table 1. Most patients were male (72%). The median age at the time of vaccination was 60 years (51, 66.25) in the non-responder group and 61 years (50.50, 69.25) in the responder group. Most patients in both groups were under monotherapy immunosuppression (83.3% in the non-responder group and 66.7% in the responder group). The median number of vaccinations was similar in both groups (median: 3 in non-responders and 3.5 in responders). One participant had positive anti-HBs at the time of transplantation, potentially indicating seroconversion. However, this participant lost anti-HBs by the time of vaccination and was included in the analysis.

Observations of vaccination outcomes

All patients completed a minimum of three vaccinations. Eight patients received more than three vaccine shots (maximum six vaccine shots) in cases of non-response, at the discretion of the treating physician. In all but one patient, a double dose of 40 µg was administered (in two patients, a combination of 20 µg and 40 µg doses was used). At the time of vaccination, six patients had positive anti-HBs (anti-HBs values: 50 IU/l, 83 IU/l, 84 IU/l, 139 IU/l, 235 IU/l, and 283 IU/l). This was attributed to a short interval between hepatitis B immunoglobulin cessation (or, in one case, measurement of anti-HBs while the patient was still receiving hepatitis B immunoglobulin) and anti-HBs measurement, rather than to seroconversion prior to active vaccination. Consequently, these patients were included in the analysis, especially as only one of the six participants showed seroconversion after active vaccination; the other five lacked anti-HBs after vaccination. Upon completion of the vaccination regimen, six patients responded to the active immunisation, resulting in a response rate of 33.3%

Table 1:
Comparison between responders and non-responders. Because of the descriptive nature of this study and the small sample size, no inferential statistics were performed, and p-values have been omitted. The number of participants with missing data is indicated as *n-X*.

Variable		Non-responder (n = 12)	Responder (n = 6)
Sex male (%)		9 (75.0)	4 (66.7)
Before liver transplantation			
Hepatocellular carcinoma (%)		5 (41.7)	2 (33.3)
MELD Score (median [IQR])		13.00 [9.00, 16.50] *n-1*	16.00 [9.00, 17.00] *n-1*
HBsAg positive (%)		12 (100.0)	4 (66.7) *n-1*
Anti-HBs positive (%)		0 (0.0) *n-1*	1 (16.7) *n-1*
HBeAg positive (%)		1 (8.3) *n-1*	1 (16.7) *n-3*
HBV DNA positive (%)		7 (58.3) *n-2*	1 (16.7) *n-2*
At time of vaccination			
Age in years (median [IQR])		60.00 [51.00, 66.25]	61.00 [50.50, 69.25]
Duration from liver transplantation to first vaccination in days (median [IQR])		2555.00 [1368.75, 6218.00]	6387.50 [4562.50, 7665.00]
Number of vaccines (median [IQR])		3.00 [3.00, 4.00]	3.50 [3.00, 4.00]
Anti-HBs positive (%)		5 (41.7)	1 (16.7)
BMI (median [IQR])		27.60 [23.95, 29.00] *n-1*	28.10 [24.90, 29.00] *n-1*
Smoking (%)		1 (8.3)	0 (0.0)
Diabetes mellitus (%)		5 (41.7)	2 (33.3)
Mono-immunosuppression (%)		10 (83.3)	4 (66.7)
Nucleos(t)ide analogue (%)		NA	NA
	Tenofovir alafenamide	7 (58.3)	2 (33.3)
	Tenofovir disoproxil fumarate	1 (8.3)	0 (0.0)
	Entecavir	1 (8.3)	1 (16.7)
	Lamivudine	3 (25.0)	3 (50.0)
Creatinine in µmol/l (median [IQR])		103.00 [87.25, 115.50] *n-2*	96.00 [87.50, 152.50]
Leucocyte × 10^9/l (median [IQR])		4.99 [4.17, 5.49] *n-2*	7.07 [4.12, 7.69]

HBV: hepatitis B virus; MELD: Model for End-Stage Liver Disease; BMI: body mass index.

(6/18). The double-dose vaccine was well tolerated, with no reported side effects. During the study, no recurrence of HBV occurred in either group.

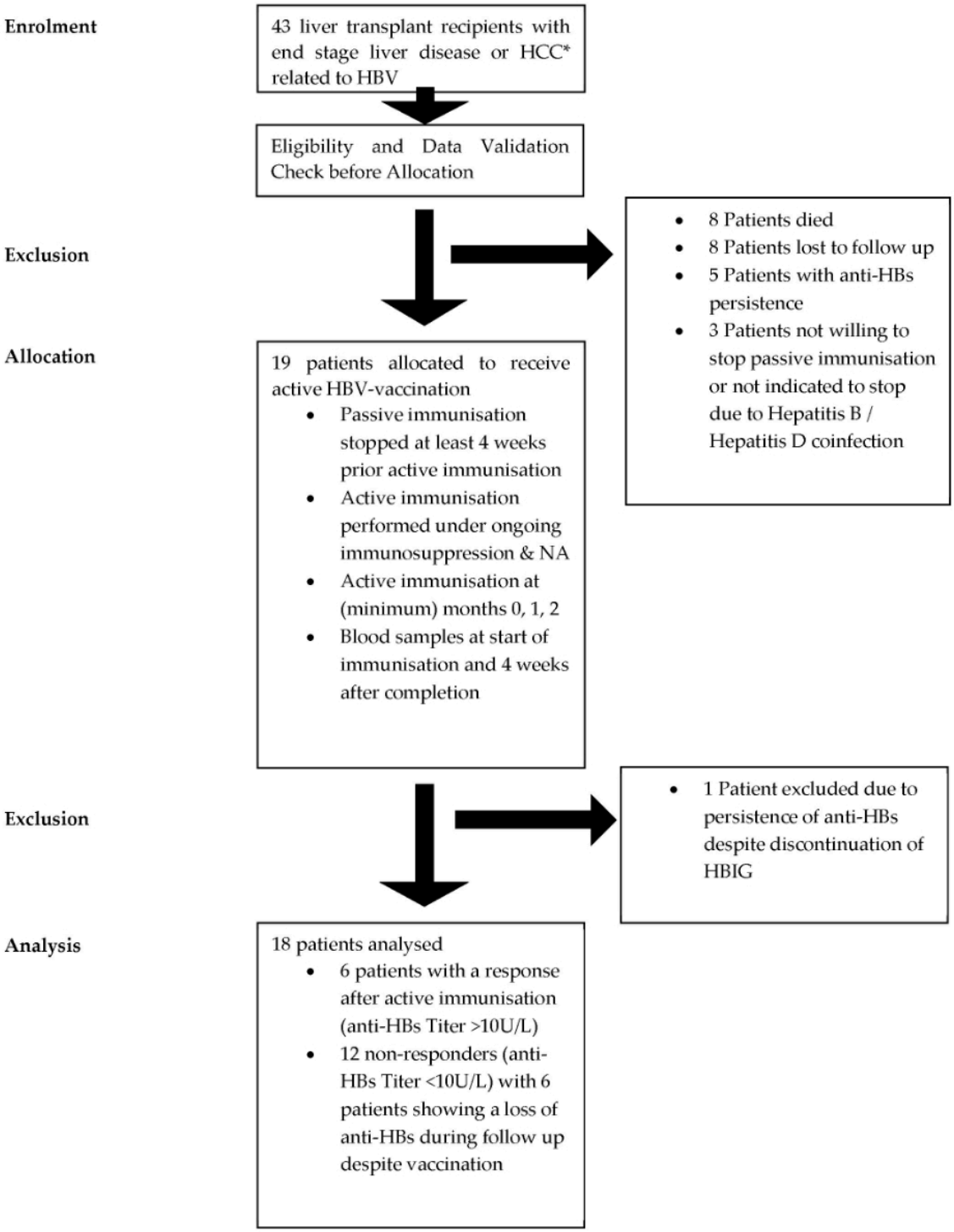
Comparison between responders and non-responders

Differences between responders and non-responders were described based on demographic and clinical characteristics without inferential statistics, given the study's small sample size. Descriptive comparisons highlight variations in age, BMI, and immunosuppression status, as detailed in table 1. Statistical significance testing was not performed, and the results should be interpreted with caution.

Discussion

In this study involving 18 participants, no recurrence of HBV was observed (negative HBsAg and HBV DNA) after at least 12 months of follow-up following the cessation of hepatitis B immunoglobulin. This outcome in-

Figure 1: Study protocol outline. * HCC: hepatocellular carcinoma; HBIG: hepatitis B immunoglobulin; HBV: hepatitis B virus; NA: nucleos(t)ide analogue.



cluded patients who received liver transplants for hepatocellular carcinoma (7 patients) and those with positive HBV DNA at the time of transplantation (8 patients), despite the higher recurrence rates typically reported in these groups [15, 16]. Although third-generation nucleos(t)ide analogues such as entecavir or tenofovir, which have high resistance barriers, have been shown to decrease HBV recurrence rates, residual risk remains [17]. Consequently, active HBV immunisation (vaccination) after parenteral hepatitis B immunoglobulin cessation is an appealing approach to provide additional immunity.

The efficacy of HBV vaccination remains controversial because of variable response rates in patients who are immunosuppressed. In immunocompetent adults, particularly those under 40 years of age, the HBV vaccine demonstrates a 95% seroconversion rate, indicating high effectiveness [18, 19]. The recommended vaccination schedule consists of a 20-µg dose administered at 0, 1, and 6 months [20, 21]. Some studies have shown a greater immune response with a double dose (40 µg) in patients with impaired immune systems [22]. Therefore, our study primarily employed a double-dose vaccine regimen, with 15 of 18 patients receiving 40 µg doses and the remaining patients receiving a combination of 20 µg and 40 µg doses; only one patient received the standard 20 µg dose.

In this study, a relatively low response rate of 33.3%, comparable to that reported in other studies [23–25], was observed after a median of three vaccine shots, with most patients receiving the 40-µg double dose. A cut-off of >10 IU/l for anti-HBs was selected to define a serologic response, as this threshold is widely regarded as protective in immunocompromised populations [26–28]. Measurements were consistently reported in IU/l, following standard laboratory practices at the University Hospital of Bern. In the literature, factors linked to reduced vaccination response include smoking, male sex, obesity, and age over 40 years [29]. In our study, no differences were observed in vaccine response regarding BMI, smoking, diabetes, the interval between vaccination and liver transplantation, or age. However, due to the small sample size, the lack of significant differences for these variables must be interpreted with caution, and causality cannot be confirmed.

The time from liver transplantation to the first active HBV vaccination varied significantly among patients, with a median interval of 2555.00 days for some and 6387.50 days for others. This prolonged interval reflects the clinical caution traditionally exercised in discontinuing hepatitis B immunoglobulin. The shift towards hepatitis B immunoglobulin-free regimens and active immunisation has only gained traction in recent years, influencing the timing of vaccination initiation.

The production of antibodies to HBV is primarily driven by the immune system's response to hepatitis B surface antigen (HBsAg). Consequently, transplant recipients under immunosuppression exhibit a decreased response rate following active immunisation [30, 31]. There was no difference in vaccine response rates between different immunosuppression regimens (monotherapy immunosuppression vs combination therapy), with 83.3% of non-responders on monotherapy immunosuppression compared to 66.7% of responders.

In conclusion, in this prospective cohort study with a short follow-up period, we observed that among 18 patients who underwent liver transplantation due to HBV infection who discontinued parenteral hepatitis B immunoglobulin while continuing nucleos(t)ide analogue therapy, no recurrence of HBV was documented. Furthermore, the response rate of 33.3% following active HBV vaccination was low, despite the administration of a double-dose (40 µg) vaccination regimen in most patients. Lastly, no adverse events were reported after immunisation.

Limitations

The limitations of this study are the small sample size and short follow-up, especially considering that some studies have demonstrated a decline in immunity over time [32]. Due to the small sample size (and lack of a control group), the results must be interpreted with caution, as causality cannot be proven, and therefore, the results are not generalisable. Nonetheless, this study cohort presented a similar response rate to active immunisation compared to similar studies with no adverse events reported from the patients. HBV genotyping was not performed as part of this study, and therefore, no genotype data are available for analysis. This limitation restricts any genotype-specific conclusions regarding immunisation response in our cohort. Another potential limitation is the questioning of patients regarding adverse events after vaccination. This method relied on self-reported data and was not supplemented by formal clinical assessments, which may have limited the detection of subclinical adverse events. However, no patients reported any significant adverse effects during the study period.

Conclusion

In this prospective cohort study with a short follow-up period, we observed that among 18 patients who underwent liver transplantation for HBV infection and discontinued parenteral hepatitis B immunoglobulin while continuing nucleos(t)ide analogue therapy, no recurrence of HBV was documented. Furthermore, the response rate of 33.3% following active HBV vaccination was low, despite the administration of a double dose (40 µg) vaccination regimen in most patients. Lastly, no adverse events were reported after immunisation.

Further studies are needed to assess potential markers for predicting a vaccination response and to optimise vaccination strategies in this population. Additionally, future studies should evaluate whether nucleos(t)ide analogue withdrawal is feasible in vaccine responders.

Data availability

De-identified study data, including the data dictionary, will be made available on the Open Science Framework (OSF). The shared data will include raw data and the statistical analysis plan. The data will be accessible starting on 1 July 2025 for a period of five years. Access will be granted to researchers who submit a reasonable request and whose proposed analyses are ethically justifiable. Requests can be directed to the corresponding author via email.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. EA received support from Gilead Sciences, unrelated to this article, for attending meetings or travel as part of the EASL Congress 2023 and 2024. No other potential conflict of interest related to the content of this manuscript was disclosed.

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