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CONSENSUS STATEMENT

Consensus Guidelines: Best Practices for the Prevention, Detection and Management of Hepatitis B Virus Reactivation in Clinical Trials with Immunosuppressive/Immunomodulatory Therapy

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Abstract

Hepatitis B virus reactivation (HBVr) during and after immunosuppressive/immunomodulatory (IS/IM) therapy is associated with significant morbidity and mortality, including hepatic decompensation and acute liver failure. The risk of HBVr with IS/IM has been heterogeneous and often unpredictable. As a result, patients with active or previous HBV infection are often excluded from clinical drug trials of such agents. Thorough screening for HBV infection, antiviral prophylaxis, and careful monitoring for HBVr have proven to be effective in reducing the rate of HBVr and improving its outcome in the context of IS/IM. Therefore, safe enrollment and management of certain HBV-marker–positive patients in clinical trials is possible. There is a great, unmet need for consistent, evidence-based recommendations for best practices pertaining to enrollment, monitoring, and management of HBVr in clinical trial participants receiving IS/IM. The aim of these consensus guidelines is to provide a step-by-step blueprint to safely enroll, monitor and manage the patient with inactive chronic or resolved HBV in IS/IM clinical trials from the time of screening through to the end of post-treatment follow up.

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Key Points

The risk of hepatitis B virus reactivation is a significant barrier to the enrollment of patients with active or previous HBV infection into clinical trials with immunosuppressive/immunomodulatory therapy.

Currently, there are no guidelines for Industry to safely enroll and manage patients with active or previous HBV infection in such clinical trials.

These consensus guidelines were developed by the IQ-DILI Initiative to meet this critical unmet need within the biopharmaceutical industry.

1 Introduction

Hepatitis B virus reactivation (HBVr) is a well-recognized complication of immune-altering therapies, and the number of drugs and biologics that are associated with HBVr is constantly expanding. HBVr can be clinically silent or accompanied by hepatitis flares, liver failure, and death [1–7].

HBVr has been reported in patients receiving cancer chemotherapy, B-cell–depleting agents, tumor necrosis factor antagonists, corticosteroids, and other drugs with immunosuppressive effect [1, 2, 8–10]. However, it is also described with drugs having an immunomodulatory mechanism, such as the interferon signaling changes of direct-acting antivirals for hepatitis C virus. These consensus guidelines are designed to apply to both immunosuppressive and immunomodulatory (IS/IM) drugs.

The approach to prevention of HBVr in patients treated with IS/IM is still a matter of debate. The American Gastroenterological Association (AGA) suggested a categorical approach to characterize different anticipated risk levels for HBVr when immunosuppressive therapies are used to treat patients with inactive chronic or resolved HBV [11]. In this approach, the high-risk, moderate-risk, and low-risk categories are defined by treatment-associated HBVr rates of >10%, 1% to 10%, and <1%, respectively. Specific recommendations by the AGA regarding screening for HBV infection prior to starting treatment, as well as HBV DNA monitoring and prophylactic antiviral therapy during treatment varied according to the risk group. Assignment of an HBVr risk level in an individual case is largely determined by the patient's HBV serological status, the specific immunosuppressive agent that is used, and when corticosteroids are on board, the dosing, duration of treatment, and site of their administration. More recently, a systematic review, meta-analysis, and expert opinion by Papatheodoridis et al. endorsed this approach, utilizing a similar categorization of the HBVr risk into low (<1%), moderate/intermediate (1–10%), and high (> 10%) [5].

Despite the growing number of clinical trials assessing new drugs with IS/IM effects, there are no regulatory guidelines or position papers on the prevention, detection, and management of HBVr during clinical trials. Typically, prior to their marketing there is an absence of sufficient data to confidently establish the associated risk of HBVr in hepatitis B surface antigen (HBsAg)-positive or hepatitis B core antibody (HBcAb)-positive patients, especially for first members of a class. As a result, clinical investigators and drug developers face considerable uncertainty when conducting trials using IS/IM drugs. There is a great unmet need for consistent, evidence-based best practices pertaining to the prevention, detection, and management of HBVr in clinical trial participants receiving IS/IM drugs.

The IQ DILI Initiative was launched in June 2016 within the International Consortium for Innovation and Quality in Pharmaceutical Development (also known as the IQ consortium) to reach consensus and propose best practices on topics related to clinical drug-induced liver injury (DILI). The IQ Consortium is a science-focused, not-for-profit organization addressing scientific and technical aspects of drug development and is composed of 48 pharmaceutical and biotechnology companies. The IQ-DILI Initiative is an affiliate of the IQ Consortium, comprising 22 IQ member companies, focused on establishing best practices for monitoring, diagnosing, managing, and preventing DILI. This publication is based on an extensive literature review, and the consensus achieved in structured discussions between IQ DILI members and academic and regulatory experts in a public–private partnership. The recommendations, meant for clinical drug development but not clinical practice, are based on currently available data and opinions of the authors and do not imply a regulatory mandate.

2 Section I: Screening

Patients with chronic HBV are typically excluded from participation in clinical studies with immunosuppressive drugs in early development. However, prevailing opinions among researchers and regulatory agencies are that an all-encompassing exclusion of all patients with serologic footprints of active, as well as inactive chronic or resolved forms of HBV infection for enrollment into clinical trials may impose slow patient accrual, limit patient access, and lead to incomplete

representation of treatment effects in this patient population [12].

There has been inconsistency in the approaches and recommendations of various professional medical societies and regulatory agencies when addressing the screening for HBV infection before starting IS/IM therapies [11, 13–19]. Translating these recommendations into a clinical trial setting poses additional challenges for drug development.

Some recommendations by professional societies suggest that screening for HBV before IS/IM therapy should include three screening tests: HBsAg, anti-HBc, and anti-HBs [14, 20, 21, 44], while others only recommend two screening tests: HBsAg and anti-HBc [11, 15, 16]. According to most guidelines, hepatitis B DNA testing should be done in all patients with HBsAg or isolated HBcAb positivity, as this will determine whether a patient has chronic HBV that may require treatment during and extending beyond IS/IM therapy. The HBV serologic screening results should be applied to the clinical study objectives and target population, as well as inform a determination whether antiviral prophylaxis is needed.

Patients can test negative for HBsAg and still have intermittent, low circulating HBV DNA levels (20–200 IU/mL). These patients are said to have 'occult HBV infection' and are at risk for HBVr [22]. Furthermore, anti-HBc may be the only marker of HBV infection during the 'window' phase of acute hepatitis B [23, 24]. Therefore, it has been recommended to follow a positive anti-HBc test with a sensitive test for HBV DNA [16].

Hepatitis D virus (HDV) requires presence of the HBV surface antigen in its life cycle and is therefore an important pathogenic agent to consider in patients with HBV infection. HBsAg-positive patients should be reflexively screened for HDV infection with HDV antibodies [25, 26].

Considering that a significant portion of infected patients are unaware of their HBV infection, universal HBV marker testing prior to initiation of IS/IM therapy, regardless of the patient's individual risk factors, differences in regional prevalence or immigrant status, or other epidemiologic characteristics of the infection, is seen as a preferred option to reduce the risk of HBVr [13, 16, 20]. Indeed, current recommendations from the CDC call for the screening of all adults for HBV at least once in their lifetime [27].

Consensus statements

1. The risk of HBV reactivation with IS/IM drugs is heterogeneous and unpredictable. In clinical trial programs where drugs have uncertain IS/IM effects, they should be initially managed as if they have these effects.
2. The likelihood of IS/IM effects should be determined by the drug development team based on mechanism of action, results of preclinical or early clinical studies, and class effects.
3. Universal HBV testing in clinical development of IS/IM drugs is recommended to identify patients with prior or chronic HBV infection, before the initiation of IS/IM therapy.
4. The minimum recommended HBV screening tests include serum HBsAg and anti-HBc. Anti-HBs testing is optional and may be useful in specific circumstances. Positive HBsAg or anti-HBc should be followed with HBV DNA testing by a nucleic acid assay (e.g., quantitative PCR). Additional tests could be warranted per local guidelines or specifics of the clinical study.
5. A positive HBsAg result should be followed by testing for HDV with antibodies to HDV.

3 Section II: Enrollment

The decision regarding whether to enroll HBV patients in clinical trials with IS/IM compounds is complex and dependent upon several criteria, including specific characteristics of the investigational drug, the phase of clinical development, target patient population, activity of HBV infection, and severity of pre-existing liver damage.

Automatic exclusion of all HBV patients in trials using IS/IM drugs may inappropriately prevent access to important treatments in the clinical trial or post-marketing setting. Inclusion of patients with certain HBV markers in trials permits the opportunity to learn, in a controlled, well-monitored environment, whether the investigational drug is associated with a true risk of HBV reactivation. Furthermore, eligibility criteria utilized in the clinical development program may have significant effect on future label language and accessibility of an approved drug to certain patients with inactive chronic or resolved HBV infection.

Assessing potency of IS/IM and stratifying risk for HBVr is not always straightforward and is especially difficult if the drug in development is first in a class. A drug's perceived risk for HBVr will impact several other downstream decisions. A recent meta-analysis has provided data on the risk of HBVr associated with new classes of IS/IM therapies [5]. Table 1 can be used as a guide to stratify the relative risk of HBVr associated with various classes of IS/IM. Ultimate determination of HBVr risk, however, will also take host and virologic factors into account. Examples of host factors include male sex, older age, presence of cirrhosis and the type of disease targeted for treatment with immunosuppression; examples of virologic factors associated with increased risk include the presence of HBsAg, HBeAg, and high baseline HBV-DNA levels [28].

Regarding host- and virus-specific variables, there continues to be inconsistency regarding eligibility criteria of patients with positive HBV markers in clinical trials of IS/IM drugs. While some trials specifically exclude patients

with a certain serostatus (e.g., positive HBsAg, positive anti-HBc) [29, 30], others use general non-viral–type specific exclusion criteria such as 'hepatitis,' 'active viral infection,' or 'systemic infection' and leave the final eligibility decision to the investigator [31–33]. In the case of acute HBV infection, where HBsAg is positive and HBcAb IgM may be positive, there is general agreement that all patients should be excluded.

The advent of potent and safe antiviral therapy, for example, nucleos(t)ide analogs (NA) such as tenofovir and entecavir which can provide long-term suppression of HBV replication, has introduced a highly effective risk management strategy in some patients with positive HBV markers by significantly decreasing the risk of HBVr during and after IS/IM therapy [11, 28, 34, 35]. Several studies and meta-analyses have shown that prophylactic NA therapy significantly reduced the risk of HBVr, HBV-related hepatitis, HBV-related acute liver failure, and HBV-related mortality in patients receiving cancer chemotherapy [11, 28, 34, 36–40]. Furthermore, it has been shown that patients treated with certain classes of IS/IM drugs such as tumor necrosis factor antagonists or biologic immunosuppressants, who tested positive for HBsAg, had higher risk of HBVr compared with those who tested negative for HBsAg and positive for anti-HBc (Table 1), and therefore were more likely to benefit from prophylactic therapy [27, 41–44]. Nevertheless, the APASL (Asian Pacific Association for the Study of the Liver), AASLD (American Association for the Study of Liver Diseases), and EASL (European Association for the Study of the Liver) guidelines recommend that HBsAg-negative, anti-HBc–positive patients treated with drugs designed to target B lymphocytes such as rituximab be given NA prophylaxis because these agents have an especially high associated risk of HBVr [15, 16, 20]. In addition, patients with negative HBsAg and positive anti-HBc with detectable HBV DNA levels may be considered to have a similar risk of HBVr as the HBsAg-positive patients and should receive NA prophylaxis [5]. The anti-HBV NA analogs tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), and entecavir are currently among the most potent marketed drugs used to suppress HBV. These drugs are also associated with little drug resistance, are easy to take orally, have few side effects, and generally do not require frequent patient monitoring [45]. Long-acting forms of tenofovir have also been under clinical development and may have the added benefit of sustained

Table 1 Relative risk of HBVr from IS/IM in patients with various HBV serologic profiles

Relative risk	HBsAg-/anti-HBc+ [5]	HBsAg+/anti-HBc+ [5]
Low (< 1%)	Tyrosine kinase inhibitors	
	Anti-TNF agents	
	Immune checkpoint inhibitors	
	T-cell–depleting agents	
	Antiproliferative agents	
	Alkylating agents	
Intermediate (1–10%)	Calcineurin inhibitors	T-cell–depleting agents
	CAR T-cell immunotherapy	
	Corticosteroids (dependent on dose, duration and site of administration)	
	Cytokine inhibitors	
High (>10%)	B-cell–depleting agents	Immune checkpoint inhibitors
	Janus kinase inhibitors	Tyrosine kinase inhibitors
		Cytokine inhibitors
		CAR T-cell immunotherapy
		Corticosteroids (dependent on dose and duration)
		Janus kinase inhibitors
		Alkylating agents
		Anti-proliferative agents
		Calcineurin inhibitors
		Mammalian target of rapamycin (mTOR) inhibitors
		B-cell–depleting agents

anti-HBc hepatitis B core antibody, *CAR* chimeric antigen receptor, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *HBVr* hepatitis B reactivation, *IS/IM* immunosuppression/immunomodulation, *TNF* tumor necrosis factor

therapeutic drug concentrations and improved patient compliance [46].

While some clinical trials have continued to exclude HBV patients, others have expanded their inclusion criteria allowing for HBV prophylaxis with an NA prior to, or at the time of starting the IS/IM study drug, followed by protocol-based monitoring of HBV DNA levels over the duration of the study.

According to the AASLD guidelines, regardless of baseline serum HBV DNA levels, prophylactic antiviral therapy should be administered to patients with chronic hepatitis B at least 7 days before the initiation of anticancer or immunosuppressive therapy, although evidence supporting this schedule is scarce [16]. If IS/IM treatment is needed more urgently, the time interval for antiviral prophylaxis before initiation of treatment can be shortened. When HBVr with liver injury occurs after the start of IS/IM treatment comprising multiple drugs, the reliable identification of the inciting agent may be difficult. The impact on viral reactivation may be additive, even if some IS/IM agents had been started at earlier time points compared with others.

Hepatitis D virus (HDV) may be detected in individuals positive for HBsAg. There is currently no FDA-approved therapy for chronic HDV in the United States. Typically, management of HDV infection requires specialist care. Certain interferon formulations that continue to be available for off-label use in this condition typically entail prolonged treatment and can be difficult to tolerate by some patients. Among emerging novel HDV therapies, bulevirtide has demonstrated promising patient responses in clinical studies but is still not available as a treatment agent in some regulatory jurisdictions [47]. Taken together, enrollment of HDV-positive subjects in IS/IM clinical trials might be possible in certain settings but can add significant challenges for on-treatment and post-treatment protocols and the effective risk management of study subjects.

Consensus statements

6. All patients with acute HBV infection should be excluded from clinical trials of IS/IM drugs, unless the planned indication is acute hepatitis B.
7. With few exceptions (e.g., hepatocellular carcinoma trials), in early phases of clinical development (phase I and early phase II) it is appropriate to exclude patients with positive HBsAg with or without detectable HBV DNA.
8. The decision on whether to exclude patients with negative HBsAg and positive anti-HBc in early clinical trials should be made according to the perceived risk for HBVr based on the type of immunosuppression, status of HBV infection, and patient population under investigation.
9. In late phases of clinical development (late phase II and phases III–IV), it is appropriate to enroll patients with positive HBsAg and patients with detectable HBV DNA, provided that HBV prophylaxis is initiated at least 1 week prior to initiation of IS/IM therapy and that HBV DNA monitoring is implemented (see below).
10. If for some reason, prophylactic therapy with NAs or monitoring of HBV DNA are not possible, it is recommended to exclude patients with positive HBsAg with or without detectable HBV DNA.
11. It is appropriate to exclude patients with positive HBsAg, with or without detectable HBV DNA, if there is evidence in the patient's medical history of an advanced stage of cirrhosis or decompensated chronic liver disease.
12. In general, it is appropriate to enroll patients with negative HBsAg and positive anti-HBc without prophylactic HBV therapy, unless the investigational treatment is recognized to be an IS/IM associated with a high risk for HBVr, or the target treatment population includes patients with an advanced stage of cirrhosis or decompensated chronic liver disease.
13. Patients with negative HBsAg and positive anti-HBc with detectable HBV DNA levels may be considered to have a similar risk of HBVr as the HBsAg patients and should receive NA prophylaxis.
14. If initiation of antiviral treatment or prophylaxis is indicated, it should be started at least 1 week prior to the first exposure of IS/IM therapy. The study participant must be educated regarding the importance of compliance with instructions provided by the study investigators for antiviral treatment or HBVr prophylaxis.

4 Section III: On-Treatment Monitoring and Management

Fundamental criteria for a diagnosis of HBVr are the identification of increased levels of serum HBV DNA compared with baseline levels in patients with inactive chronic or resolved HBV, or of reverse HBSAg seroconversion in patients with previously resolved HBV. In this respect, it should be emphasized that transient therapeutic flares during anti-HBV treatment associated with reduced levels of HBV DNA are distinct effects that do not reflect episodes of HBVr [48].

Clinically, HBVr can manifest in several ways, including (1) silent viral reactivation and elevated viral load without overt hepatitis; (2) HBV-associated hepatitis, elevated viral load and evidence of clinical, biochemical, or histological hepatitis; and (3) fulminant liver failure, elevated viral load

Table 2 Criteria for diagnosis of HBVr [5, 16]

Status of HBV infection	Baseline serologies			HBVr diagnostic criteria
	HBsAg	HBcAb	DNA	
Chronic HBV	+	+	Undetectable	HBV DNA detectable > 1000 IU/mL
	+	+	Detectable	HBV DNA increases > 100-fold or > 2 $\log_{10}$ compared with baseline value
	+	+	Unknown	HBV DNA >10,000 IU/mL
Resolved HBV	−	+	Undetectable	Detection of any DNA (even if not quantifiable) -or- HBs Ag (+) (i.e., reverse seroconversion)
	−	+	Detected but not quantifiable	HBV DNA ≥ 100 IU/mL
	−	+	Detectable and quantifiable	≥ 1 $\log_{10}$ increase in HBV DNA

HBcAb hepatitis B core antibody, *HBsAg* hepatitis B surface antigen, *HBV* hepatitis B virus, *HBVr* hepatitis B reactivation

with hepatic synthetic dysfunction, encephalopathy, and coagulopathy [4]. The time to onset of HBVr is difficult to predict. It can occur within the first 2 weeks of IS/IM exposure or more than a year after cessation of IS/IM, although late viral reactivation is generally uncommon [28, 49].

Life-threatening HBV flares have been reported in the context of immune reconstitution inflammatory syndrome in HIV-positive individuals after initiating antiretroviral therapy [50]. Depending on context, screening positively for HIV Ab has been considered an exclusionary criterion in many IS/IM clinical trials. Although the HIV-positive population might be studied as a distinct treatment stratum in a larger study or in a separate dedicated study, this group of patients has not been a focus for evaluation in these consensus guidelines.

The identification of HBVr prior to occurrence of hepatitis or hepatic failure, whenever possible, should be the goal of any study protocol that includes patients at risk for HBVr. The patient should be instructed to consult the clinical study site investigator or an accessible healthcare provider promptly if there is development of symptoms or signs that suggest new onset or exacerbation of liver disease, including jaundice, abdominal pain, fatigue, anorexia, nausea, and vomiting. Moreover, HBVr can be associated with extrahepatic manifestations of active HBV disease that may involve skin, kidneys, and/or hematologic and immune systems [51]. These manifestations of HBV should be recognized elements for adverse event surveillance, as well as risk analysis and risk management in clinical trials. Clinical and biochemical evaluation as well as HBV testing should be emergently performed to exclude HBVr, since it may be critically important to promptly start antiviral therapy as well as discontinue the study drug.

Reactivation of HBV can be clinically silent even when significant active hepatitis is present and would be detected through frequent routine laboratory monitoring. Table 2 can be used to define HBVr.

Table 3 Routine lab monitoring recommendations for at-risk patients on IS/IM drugs

Guidelines	On antiviral therapy	No antiviral therapy
AASLD (2018) [16]	No comment	Monitor every 1–3 months
AGA (2015) [11]	No comment	No comment
APASL (2016) [15]	No comment	No comment
EASL (2017) [20]	Every 3–6 months during antiviral prophylaxis	Every 1–3 months during IS/IM therapy

AASLD American Association for the Study of Liver Diseases, *AGA* American Gastroenterology Association, *APASL* Asian Pacific Association for the Study of the Liver, *EASL* European Association for the Study of the Liver, *IS/IM* immunosuppression/immunomodulation

Current professional society guidelines are listed in Table 3.

In the absence of full agreement on these guidelines among the societies, the drug developer should use discretion in establishing an optimal frequency for routine lab monitoring of HBV markers and serum biochemical liver tests that is based on the perceived risk for HBVr. Key risk

Table 4 Variables that guide an optimal frequency for routine HBV monitoring in IS/IM clinical trial protocols

	Higher frequency, e.g., monthly	Lower frequency, e.g., every 3 months
Virologic	Positive HBsAg; negative HBsAb	Negative HBsAg
Patient	Off NA prophylaxis	On NA prophylaxis
IS/IM	Drug association with high, intermediate, or unknown risk for HBVr	Low risk of HBVr

HBsAb hepatitis B surface antibody, *HBsAg* hepatitis B surface antigen, *HBVr* hepatitis B virus reactivation, *IS/IM* immunosuppression/immunomodulation, *NA* nucleos(t)ide analog

Table 5 Labs to routinely monitor during IS/IM treatment*

Lab	Rationale
HBV DNA	Essential assay to diagnose HBVr
Liver chemistry (AST, ALT, alkaline phosphatase, total bilirubin)	Essential for diagnosis of HBVr-associated hepatitis; will assist in causality assessment; results available more rapidly vs HBV DNA
Albumin, INR	Important biomarkers of hepatic dysfunction, can be included if liver chemistry is abnormal
HBsAg [if HBsAg (−) and HBcAb (+) at baseline]	To diagnose reverse seroconversion in the cohort with negative HBsAg and positive HBcAb at baseline

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *HBVr* hepatitis B reactivation, *HBcAb* hepatitis B core antibody, *HBsAg* hepatitis B surface antigen, *INR* international normalized ratio, *IS/IM* immunosuppression/immunomodulation

*HBV DNA, liver chemistry and markers of hepatic dysfunction (albumin, INR) should also be performed urgently with new onset or exacerbation of liver disease as part of an assessment

factors for HBVr can be categorized into virologic, host, and IS/IM factors [52]. However, some risk factors (e.g., HBeAg serostatus, presence of cirrhosis, occult HBV infection) may not be known at the time of enrollment.

Table 4 identifies important factors for IS/IM drug developers to consider in determining an optimal frequency for routine HBV laboratory monitoring.

Table 5 provides the recommended lab tests to monitor while on treatment.

Interpretation of laboratory results frequently presents difficulties for the clinician and drug developer alike. The protocol should define management for various laboratory results; for scenarios not covered in the protocol, the investigator should be advised to contact the sponsor.

Table 6 provides recommendations for actions and laboratory testing to be undertaken for selected scenarios.

Post-marketing HBVr monitoring and risk management tools available to healthcare providers and patients should be considered when planning clinical trial protocols for IS/IM drugs. Protocol-based monitoring and clinical management practices implemented in registrational studies may form a frame of reference for best practices in the post-marketing setting. As optimal drug-specific and patient-dependent monitoring practices may evolve over time, subsequent modifications of these practices in the post-marketing phase should be data-driven and based on HBVr events and outcomes that have been observed during clinical trials or in other relevant premarket and postmarket studies.

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15. Recommended frequency of routine clinical and laboratory test monitoring for HBVr is every 1–3 months. The frequency implemented in the protocol will depend primarily on the use of antiviral prophylaxis/therapy, IS/IM potency, and the development program's track record with exposure in patients at risk for HBVr.
16. Laboratory tests to be followed include HBV DNA, liver chemistry (see Table 4), albumin, and INR. HBsAg testing should be regularly performed in patients who are HBsAg (−) and HBcAb (+) at baseline.
17. For cases of possible or confirmed HBVr, patients should be referred to a hepatologist or a clinician with equivalent expertise in viral hepatitis assessment and management, and the IS/IM therapy should be immediately interrupted. General HBV management should be initiated by a hepatologist if HBVr is confirmed. In cases of confirmed HBVr, subsequent rechallenge with IS/IM treatment may put patients at high risk for recurrence of HBVr and possible serious liver injury. As such, rechallenge with IS/IM can be considered for individual study participants in whom benefits strongly outweigh risks and only if NA prophylaxis was not previously instituted. Such patients should start NA prophylaxis in advance of rechallenge with the study drug and be frequently monitored for HBVr recurrence. In addition, they should be given instruction on recognizing and responding to symptoms or signs of recurrence of HBVr.
18. If new-onset symptoms of liver disease appear (e.g., jaundice, fatigue, abdominal pain, nausea/vomiting), the participant should be instructed to discontinue IS/IM treatment, consult with the investigator, seek immediate medical attention, and undergo testing for HBVr.

5 Section IV: Post-Treatment Monitoring and Management

The time to onset of HBVr can vary depending on patient characteristics and the associated risk level of the prescribed IS/IM products. The risk for HBVr after IS/IM discontinuation is variable. If an IS/IM drug is in the high-risk category (>10%), HBVr may occur more than a year after cessation of the treatment. In fact, HBVr has

Table 6 Special laboratory result scenarios to consider

Lab scenario	Clinical interpretation	Actions to be taken with IS/IM	Laboratory testing
Criteria for HBVr are met	Confirmed HBVr	Immediately interrupt IS/IM and refer to specialist* Ensure compliance with NA prophylaxis or initiate anti-HBV treatment	Repeat liver biochemical tests (ALT, AST, alkaline phosphatase, total bilirubin, direct bilirubin, INR, and albumin), check HDV RNA if HDV coinfection is considered; repeat HBV DNA in 1–2 weeks to assess clinical course
HBV DNA is detectable but does not meet threshold for HBVr	Possible HBVr	Immediately interrupt IS/IM and refer to specialist Ensure compliance with NA prophylaxis	Repeat liver biochemical tests, HBV DNA in 1–2 weeks; if trending upwards, manage as HBVr
HBV DNA is detectable but not quantifiable	Possible HBVr	Immediately interrupt IS/IM and refer to specialist Ensure compliance with prophylaxis	Repeat liver biochemical tests, HBV DNA in 1–2 weeks; if trending upwards, manage as HBVr
Elevation in ALT but no change in HBV DNA	Not HBVr. Evaluate for other causes of ALT elevation including DILI	Continue IS/IM, unless ALT, AST, or total bilirubin thresholds meet discontinuation criteria for DILI, per study protocol	As per protocol, for elevation in ALT +/− bilirubin

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *DILI* drug-induced liver injury, *HBcAb* hepatitis B core antibody, *HBsAg* hepatitis B surface antigen, *HBVr* hepatitis B reactivation, *HDV* hepatitis delta virus, *INR* international normalized ratio, *IS/IM* immunosuppression/immunomodulation, *NA* nucleos(t)ide analog

*Rapid withdrawal of IS/IM (especially glucocorticoids) in a study patient with signs of inflammatory HBVr could lead to a paradoxical response and cause a flare of clinical and biochemical hepatitis with histopathological evidence of new or worsening HBV hepatitis on liver biopsy. A 'specialist' refers to an individual with recognized expertise in the assessment and management of viral hepatitis and may opt to initiate NA therapy

been reported in patients treated with rituximab (an agent associated with high HBVr risk) as late as 69 weeks after cessation of therapy. In that cohort containing 19 cases of HBVr, even though earlier seroconversion of HBsAg had occurred prior to rituximab treatment, an undetectable antibody to HBsAg was the only identified risk factor positively associated with HBVr ($p = 0.009$) [53].

Current society guidelines for post IS/IM monitoring and management for HBVr are summarized in Table 7.

Recommendations for monitoring and management of HBVr after last dose of IS/IM therapy in clinical trials is presented in Table 8.

The study patient should be instructed to consult the clinical site study investigator or accessible healthcare provider promptly if there is any development of signs and symptoms of liver disease, including jaundice, abdominal pain, fatigue, anorexia, nausea/vomiting, etc.

Consensus statements

19. Recommended duration of laboratory monitoring after discontinuation of IS/IM is 6 months for all HBV study patients, with a proviso to extend monitoring to 12 months for those at highest risk of HBVr (e.g., rituximab use).
20. Recommended frequency of post-treatment monitoring is 1–3 months according to perceived risk for HBVr; HBV DNA and ALT is recommended at each time point.
21. Duration of NA prophylaxis should be 6 months after final IS/IM exposure. Considerations for shorter (i.e., 3–4 months) or longer (i.e. 12 months) can be considered according to perceived risk of HBVr.
22. During or after the conclusion of a clinical trial with IS/IM, the patient should immediately seek consultation with a physician if there is development of signs or symptoms of liver disease, and testing for HBVr should be performed. Late-onset adverse events (e.g., 12 months after last IS/IM exposure) may still be considered causally associated to IS/IM and require reporting to the sponsor as an adverse event.

6 Conclusions

There is an unmet need in the development of IS/IM therapies to enroll patients with chronic HBV infection or history of exposure to HBV. At present, such patients are often categorically excluded from trial enrollment based upon a positive screening serology. This routine practice of exclusion

Table 7 Post treatment monitoring recommendation in professional society guidelines

Guidelines	Monitoring and management after last dose of immunosuppressive therapy	
	Patients on NA prophylaxis/ treatment	No NA prophylaxis/ treatment
AASLD (2018) [13]	Minimum 6 months and up to 12 months after last dose of immunosuppressive therapy Longer than 12 months for drugs with high risk of HBV reactivation like anti-CD20 therapies	Monitoring for minimum 12 months after discontinuation of NA prophylaxis Monitoring HBV DNA and ALT every 1–3 months On demand anti-viral treatment
EASL (2017) [20]	Minimum 12 months after last dose of immunosuppressive therapy Minimum 18 months for drugs with high risk of HBVr like anti-CD20 therapies	Monitoring for minimum12 months after discontinuation of NA prophylaxis Monitoring HBV DNA and ALT every 1–3 months On demand anti-viral treatment
APASL (2016) [15]	Not discussed	Not discussed
AGA (2015) [11]	Not discussed	Not discussed

AASLD American Association for the Study of Liver Diseases, *AGA* American Gastroenterology Association, *ALT* alanine aminotransferase, *APASL* Asian Pacific Association for the Study of the Liver, *EASL* European Association for the Study of the Liver, *HBVr* hepatitis B reactivation, *NA* nucleos(t)ide analog

Table 8 Post-treatment monitoring and management recommendations

Guidelines	Monitoring and management after last dose of IS/IM therapy	
	On NA prophylaxis*	Not on NA prophylaxis
Duration of lab monitoring post-IS/IM**	12 months	6–12 months
Duration of antiviral	3, 6, or 12 months according to perceived risk of HBVr***	N/A
Labs, frequency	HBV DNA and ALT every 1–3 months	HBV DNA and ALT every 1–3 months
Other recommendations	Refer to specialist after completion of clinical protocol if NA treatment is ongoing	Standard follow-up with generalist after completion of clinical protocol

ALT alanine aminotransferase, *HBVr* hepatitis B virus reactivation, *IS/IM* immunosuppression/immunomodulation, *NA* nucleos(t)ide analog

*If antiviral is being given for treatment, not prophylaxis, then patients should continue NA treatment beyond the end of the clinical trial and follow up with a specialist

**May be longer for IS/IM with effect of longer duration

***High-risk, moderate/intermediate-risk, and low-risk categories are defined by treatment-associated HBVr rates of >10%, 1% to 10%, and <1%, respectively

impacts patient accrual, limits patient access to clinical trials, and leads to incomplete representation of treatment effects in this patient population [12].

These consensus guidelines provide a blueprint to safely enroll and monitor the HBV patient, and prevent, detect, and manage HBVr. The recommendations are made with patient safety top of mind. Feasibility for implementation into clinical trial protocols is also considered. Flexibility is given to the drug developer according to the perceived risk of HBVr, which is often difficult to predict. Some indirect factors that can impact protocol implementation have not been addressed in these guidelines. For example, identifying suitable organizations or institutions that could be responsible for covering the expenses of antiviral prophylaxis when it is recommended has not been discussed. As an important public health-related issue, optimal coverage plans for antiviral prophylaxis can differ between countries and might be influenced by regional HBV endemic rates and variable economic settings. A systematic evaluation of these factors is beyond the scope of this manuscript.

A successful implementation of these consensus guidelines will facilitate further generation of important data relevant to underserved HBV-infected populations. In the future, there will be a need to evaluate novel and dependable

methods that reliably measure HBVr risk, including HBV surface antigen quantification. HDV treatment paradigms in clinical trials with IS/IM will also require further consideration. In principle, clinical trial protocols could be tailored according to evidence-based data regarding specific target HBV-infected populations, that could impact eligibility criteria, as well as IS/IM drug interruption or discontinuation rules and indications for HBVr prophylaxis. Further refinements of these consensus guidelines, such as defining optimal frequencies and durations of HBVr safety surveillance, may be possible when more robust clinical study data become available for analysis.

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