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## Hepatitis B reactivation in patients with hepatitis B core antibody positive and surface antigen negative on immunosuppressants

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### Abstract

Hepatitis B viral (HBV) reactivation in the immunosuppressed is a significant problem even in patients who have achieved serological clearance due to the persistence of HBV as cccDNA. HBV reactivation will continue to pose a significant healthcare burden given the high prevalence of HBV and increasing use of immunosuppressants. Screening of hepatitis B surface antigen, antibody to Hepatitis B core antigen antibody and HBV DNA levels should be done routinely in all patients planned for significant immunosuppressant use. We aimed to examine the factors affecting reactivation risk. This depended on HBV disease status, the underlying disease requiring immunosuppression, and the specific immunosuppressive regime. While antiviral prophylaxis can prevent reactivation, it increases cost and still has risk of delayed reactivation after stopping antivirals and close follow-up and on-demand treatment is a good alternative for patients at risk of reactivation.

**Key words:** Previous hepatitis B exposure; Immunosuppression; Cost-effectiveness; Hepatitis B reactivation

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**Core tip:** Hepatitis B reactivation remains a common clinical problem, in countries with high endemicity of Hepatitis B, prevalence of Hepatitis B exposure can be very high where hepatitis B virus (HBV) DNA and HbsAg is negative. This group of patients when undergoing chemotherapy or immunosuppression can have reactivation and HBV DNA can be positive, this review summarizes the key studies and guide in rationale approach.

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## INTRODUCTION

Hepatitis B virus (HBV) is a common disease, with approximately 250 million people being HBsAg positive<sup>[1]</sup> and 1.6 billion people being antibody to hepatitis B core antigen (anti-HBc) positive<sup>[2]</sup>. Even in patients who have achieved serological clearance, HBV persists in the host's hepatocytes as covalently closed circular DNA (cccDNA)<sup>[3]</sup>. The natural history of HBV infection involves an interaction between HBV viral replication and the host's immune response<sup>[4]</sup>. In HBV reactivation, initiation of immunosuppression removes immune surveillance pressure against HBV, enhancing viral replication<sup>[5]</sup>. This phase is defined by an increase in serum HBV DNA levels without any hepatitis. Upon cessation of immunosuppression, host immunity recovers and there is a rapid T-cell-mediated damage of infected hepatocytes, resulting in hepatitis<sup>[6]</sup>. Both processes can occur even in patients with serological clearance of HBV due to its persistence as cccDNA<sup>[3,6]</sup>. Reactivation can lead to hepatitis, liver failure, disruption or delay of immunosuppressive treatment, and can be fatal<sup>[7]</sup>. From an economic point of view, resultant morbidity from HBV reactivation is associated with significant healthcare costs<sup>[8]</sup>.

The management of HBV reactivation in immunosuppressed patients with chronic Hepatitis B is well established<sup>[9-11]</sup>. However, the management of patients with past or resolved HBV infection remains controversial<sup>[12]</sup>. Although patients with hepatitis B surface antigen (HBsAg)-negative, anti-HBc positive patients have a lower risk of HBV reactivation compared to HBsAg-positive patients, the prevalence of anti-HBc is higher than that of HBsAg, ranging from 5% in countries in the western hemisphere, to > 50% in east Asian countries<sup>[7,13]</sup>. Coupled with the increased development and use of immunosuppressants for various conditions<sup>[13]</sup>, HBV reactivation will continue to be an important clinical challenge, with HBsAg-negative, anti-HBc positive patients forming a significant portion of patients at risk of HBV reactivation. In this article, we will review literature pertaining to screening, treatment and follow-up strategies in patients with previous Hepatitis B exposure who are planned for immunosuppression.

In this narrative review, we carried out a search of the PubMed database for studies published until January 2019 using the keywords "Hepatitis B reactivation, HBsAg negative, anti-HBc positive, antiviral prophylaxis, immunosuppression, monitoring, cost-effectiveness" and identified relevant literature. The references cited in these papers were also checked to complement the search.

## IMPORTANT DEFINITIONS

The definition of key terms in the study of HBV reactivation has been varied. This has resulted in a wide range of HBV reactivation rates reported in literature<sup>[14,15]</sup>. Compounded with the lack of systematically collected data, this made it difficult to discern the risk of reactivation in specific populations of immunocompromised individuals and specific classes of immunosuppressants<sup>[10]</sup>. We defined these key terms in accordance with the American Association for the Study of Liver Diseases (AASLD) 2018 Hepatitis B Practice Guidance<sup>[10]</sup> for ease of reference (Table 1). Risk of HBV reactivation was classified as low when the incidence rate of HBV reactivation was < 1%, moderate when the incidence rate was between 1%-10% and high when incidence rate exceeded 10%.

## RISK FACTORS FOR HBV REACTIVATION

The main risk factors for HBV reactivation can be subdivided into: (1) Virologic factors; (2) Patient factors; and (3) Type of immunosuppression (Table 2). The virologic factors associated with an increased risk of reactivation in HBsAg-negative and anti-HBc-positive patients include high baseline HBV DNA levels, absence of anti-HBs antibody and presence of Hepatitis B core-related antigen (HBcrAg). High

**Table 1** Definition of key terms used in the study of hepatitis B virus reactivation

Key term	Definition
Resolved Hepatitis B infection	Negative HBsAg, positive anti-HBc, positive anti-HBs
Past Hepatitis B infection	Negative HBsAg, positive anti-HBc, negative or unknown anti-HBs
HBV reactivation	In HBsAg-negative, anti-HBc-positive patients: Newly detectable HBV DNA level OR; Occurrence of HBsAg sero-reversion (reappearance of HBsAg)
Hepatitis B flare	ALT increase to $\geq 3$ times the baseline level and $> 100$ U/L
HBV-associated liver failure	Impaired synthetic function (Total bilirubin $> 3$ mg/dL or international normalized ratio $> 1.5$ ) OR Ascites OR Encephalopathy OR Death following HBV-associated liver failure attributed to HBV reactivation
Antiviral prophylaxis	Antiviral treatment in a patient where there are no other indications for commencing treatment other than an anticipated HBV reactivation
On-demand treatment	Commencement of antiviral treatment upon diagnosis of HBV reactivation

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; Anti-HBc: Antibody to Hepatitis B core antigen; Anti-HBs: Antibody to Hepatitis B surface antigen.

HBV DNA at baseline was found to be the most important risk factor for HBV reactivation in this population of patients<sup>[16]</sup>, and major guidelines have recommended that HBsAg-negative, anti-HBc positive patients with detectable serum HBV DNA be managed similarly to HBsAg-positive patients, in view of increased HBV reactivation risk<sup>[9]</sup>. A meta-analysis which investigated the effect of anti-HBs status in patients with past Hepatitis B infection found that the presence of anti-HBs reduced HBV reactivation risk overall. The rate of HBV reactivation was 5% in patients who had both positive anti-HBc and anti-HBs serology, compared to 14% in patients who only had a positive anti-HBc<sup>[17]</sup>. This effect was true for higher risk patients who had lymphoma or underwent rituximab-containing chemotherapy<sup>[17]</sup>. Baseline HBcrAg positivity was also associated with increased HBV reactivation risk. In a prospective study involving 124 HBsAg-negative, anti-HBc positive patients undergoing high-risk immunosuppression (either rituximab-containing chemotherapy or allogeneic hematopoietic stem cell transplant, cumulative HBV reactivation rates were significantly higher in HBcrAg patients compared to those who were HBcrAg negative (71.8% vs 31%,  $P = 0.002$ )<sup>[18]</sup>.

Patient factors increasing HBV reactivation risk include increased age, male gender, presence of liver cirrhosis and underlying disease that required immunosuppression<sup>[19,20]</sup>. A meta-analysis performed by Cholongitas *et al*<sup>[21]</sup> showed that rates of HBV reactivation were higher in patients with hematological disease (10.9%) compared to patients with non-hematological disease (3.6%). Patients with liver cirrhosis and hepatocellular carcinoma (HCC) are at a higher risk of chemotherapy-related reactivation of HBV<sup>[22]</sup>.

The type of immunosuppression plays a key role in a patient's HBV reactivation risk. Patients on B-cell depleting-therapies including rituximab have a high risk of HBV reactivation. In a meta-analysis done by Mozessohn *et al*<sup>[23]</sup>, HBsAg-negative and anti-HBc-positive patients on Rituximab had a pooled reactivation rate of 16.4%. B cell-depleting agents also been well described to have a significantly increased risk of HBV-associated liver failure<sup>[24]</sup>. Notably, the increased risk of HBV reactivation appears more pronounced in patients who are on rituximab for hematological malignancies<sup>[17]</sup>, compared to rheumatological conditions such as rheumatoid arthritis<sup>[25,26]</sup>.

Tumor necrosis factor- $\alpha$  inhibitors such as infliximab and tyrosine kinase inhibitors such as imatinib have moderate risk of reactivation in HBsAg-negative, anti-HBc-positive patients<sup>[27,28]</sup>. Anthracycline derivatives such as doxorubicin are associated with a moderate risk of HBV reactivation in patients with previous HBV exposure, and is particularly concerning for patients with HBV-related HCC undergoing doxorubicin-containing transarterial chemoembolization<sup>[5]</sup>. Patients who receive high dose corticosteroids as monotherapy or in conjunction with other immunosuppressive agents have an increased risk of HBV reactivation<sup>[29]</sup>.

Immune checkpoint inhibitors such as anti-CTLA4 (ipilimumab) and anti-PD-L1 (pembrolizumab) have been increasingly used to treat numerous cancers<sup>[30]</sup>. A retrospective study by Wen *et al*<sup>[31]</sup> found that the use of these drugs in HBsAg-negative, anti-HBc-positive patients did not result in any cases of HBV reactivation, even in the absence of antiviral therapy. Thus far, there has only been one reported case of HBV reactivation in a patient with HIV co-infection who received pembrolizumab for treatment of non-small cell lung cancer<sup>[32]</sup>. Data on the risk of HBV

**Table 2 Risk factors determining risk of hepatitis B reactivation in HBsAg negative, anti-HBc positive patients. Hepatitis B chemoprophylaxis can be considered in patients with 2 or more high risk factors for hepatitis B reactivation**

Category	Risk factor
Virological factors	(1) High baseline HBV DNA; (2) Absence of anti-HBs antibody; (3) Presence of Hepatitis B core-related antigen
Patient factors	(1) Male gender; (2) Liver cirrhosis; (3) Immunosuppression required because of hematological malignancy
Type of immunosuppressive regime	High risk: B-cell depleting therapies Medium risk: Anthracycline derivatives, high dose corticosteroids, systemic cancer chemotherapy, cytokine-based therapies, immunophilin inhibitors, tyrosine-kinase inhibitors, protease inhibitors Low risk: Immune checkpoint inhibitors, low-moderate dose corticosteroids, antimetabolite therapies

reactivation in such patients remains limited, and more studies are needed to verify these findings.

## HBV SCREENING

Most patients with previous or chronic HBV infection are asymptomatic and may not be diagnosed prior to commencement of immunosuppression. There is wide variability in the approach to HBV screening before immunosuppression<sup>[33]</sup>. The decision for hepatitis B screening prior in patients who will be receiving immunosuppression is based on a balance between the cost savings of early HBV detection and subsequent administration of antiviral prophylaxis *vs* the cost of screening large numbers of patients.

Major clinical practice guidelines differ in their recommendations for HBV screening in individuals undergoing immunosuppression. The American Society of Clinical Oncology presented a more selective screening strategy<sup>[33]</sup>, and recommended HBV screening only in patients with HBV risk factors<sup>[34,35]</sup> or those who will be receiving cancer therapy associated with a high risk of reactivation, such as B-cell depleting agents or stem cell transplantation<sup>[22]</sup>. A cost effectiveness modelling study<sup>[8]</sup> in a population of patients with hematologic neoplasms at high risk of HBV reactivation showed screening for HBV infection to be both clinically efficacious and cost effective, with initial cost of the screening strategy being offset by monetary savings from prevention of clinical events.

Given the increased use of immunosuppressants, with an increased risk of severe HBV reactivation, universal HBV screening has been found to be cost effective in populations with high prevalence of HBV<sup>[10]</sup>. In populations with lower prevalence of HBV, screening has been found to be cost effective only in patients with higher HBV reactivation risk and those with comorbidities predisposing to higher risk of mortality following reactivation<sup>[36]</sup>. While cost effectiveness arguments are compelling, it is difficult to quantify the negative impact of inability or delay in administration of chemotherapy in patients with HBV reactivation. The AASLD, Asia Pacific Association for the Study of the Liver, European Association for the Study of the Liver are in favor of universal screening prior to commencement of immunosuppressants<sup>[9-11]</sup>. HBV screening should occur at least 1 wk prior to initiation of immunosuppression, with the view of starting antiviral prophylaxis at least 1 wk or as soon as possible upon commencement of immunosuppression.

In the setting of long-term or indefinite immunosuppressive therapy, HBV screening is cost effective even when prevalence of Hepatitis B infection is as low as 0.3%<sup>[22]</sup>. However, HBV screening should not be routine in patients undergoing a low risk immunosuppression regime given that prophylaxis or pre-emptive treatment would not be routinely offered.

Both HBsAg and anti-HBc should be used for HBV screening<sup>[10]</sup> prior to commencement of immunosuppression. Further testing for HBV DNA should be done only if HBsAg is reactive, or in HBsAg-negative patients with positive anti-HBc antibodies. This is to detect occult infection which needs to be managed in the same manner as HBsAg-positive serology. Presence of detectable HBV DNA levels in HBsAg-negative patients with positive anti-HBc antibodies is associated with higher reactivation rates compared to patients who have an undetectable serum HBV DNA<sup>[9]</sup>.

For patients with resolved HBV infection receiving chemotherapy for hematological malignancies, further testing for anti-HBs may be useful to stratify

HBV reactivation risk status. A meta-analysis performed by Paul *et al*<sup>[37]</sup> showed that the absence of anti-HBs increased HBV reactivation risk<sup>[37]</sup>, and such patients should be considered for antiviral prophylaxis. Another study found that patients with resolved HBV infection who underwent allogeneic bone marrow transplant for hematological malignancies and received post-transplant HBV vaccination for augmentation of did not have any cases of HBV reactivation compared to 12 cases of reactivation in patients who did not undergo vaccination. This was postulated to be due to an augmentation of the anti-HBs response<sup>[38]</sup>. The utility of anti-HBs screening in HBsAg-negative, anti-HBc positive patients on other immunosuppressive regimens has not been investigated.

In recent years, HBcrAg has been advocated as a novel biomarker for screening and monitoring of HBsAg-negative, anti-HBc-positive patients who have undetectable HBV DNA titres<sup>[39]</sup>. These patients could either have prior self-limiting HBV exposure or have chronic HBV infection with HBsAg seroclearance, where HBV remains in very low replicative and transcriptional levels despite HBsAg negativity<sup>[40]</sup>. Serum HBcrAg correlates well with intrahepatic cccDNA<sup>[41,42]</sup>, itself being a surrogate measure of the proliferative potential of HBV<sup>[3]</sup>. Seto *et al*<sup>[18]</sup> showed that in HBsAg-negative, anti-HBc-positive patients with lymphoma undergoing rituximab-containing chemotherapy, HBcrAg positivity was associated with HBV reactivation ( $P = 0.011$ , HR: 3.65). This association was found in the same study to be stronger than anti-HBs negativity in predicting HBV reactivation risk<sup>[18]</sup>. The use of HBcrAg for further risk stratification holds much promise in areas of high anti-HBc seroprevalence, where cost effectiveness of antiviral prophylaxis remains a major concern<sup>[43]</sup>. The use of HBcrAg remains nascent and has not entered widespread clinical use<sup>[44]</sup>. Further studies of HBcrAg in patients with moderate and low HBV reactivation risk would enhance the generalizability of this test for screening.

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## TREATMENT STRATEGIES

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Two main strategies - Antiviral prophylaxis and On-demand treatment (Table 1), are used to attenuate the risk of HBV reactivation in HbsAg-negative, anti-HBc positive immunocompromised individuals. Antiviral prophylaxis involves the initiation of HBV antiviral therapy in patients where there are no other indications for commencing treatment other than an anticipated HBV reactivation. On-demand treatment refers to commencement of antiviral treatment only upon diagnosis of HBV reactivation, but usually involves more intensive surveillance both during and after an immunosuppressive regimen.

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## DIFFERENCE IN CLINICAL OUTCOMES BETWEEN TREATMENT STRATEGIES

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Choosing between the two strategies involves weighing the difference in clinical outcomes, and well as cost effectiveness. Major guidelines<sup>[9-11]</sup> acknowledge that HBsAg-negative, anti-HBc-positive patients are generally of a lower risk profile than patients who are HBsAg-positive, and permit close surveillance with early on-demand treatment in patients with a moderate (1%-10%) and low risk (< 1%) risk of HBV reactivation. In patients with high risk of reactivation (> 10%), such as those with hematological malignancies receiving B-cell depleting chemotherapy, antiviral prophylaxis was found to be superior to on-demand treatment<sup>[45]</sup>. Recent studies have shown that on-demand treatment strategy may be comparable to antiviral prophylaxis even in this high-risk group, albeit with some caveats. Liu *et al*<sup>[46]</sup> described a randomized control trial where lymphoma patients with past Hepatitis B infection were randomized to start antiviral prophylaxis with entecavir *vs* close follow-up with on-demand treatment prior to commencement of chemotherapy. The study contained both patients who were receiving B cell-depleting therapy, and those who were not. Despite the incidence of reactivation being higher in the on-demand treatment arm, there were no reported HBV-related liver decompensation events or deaths. It should be noted that a large proportion of patients in this study (73.2%) were anti-HBs-positive, which could have protected against HBV reactivation.

Retrospective analyses<sup>[25,26]</sup> found that patients with past (HBsAg-negative, anti-HBc positive) HBV infection who received rituximab for rheumatological diseases without antiviral prophylaxis had low (3.3%-5%) rates of HBV reactivation. The HBV reactivation episodes were also mild, with no HBV-related hepatitis, hepatic decompensation or death. However, these retrospective studies were done in patients with rheumatological disease, with a lower risk profile than patients undergoing a

similar immunosuppressive regime for hematological malignancy.

## COST EFFECTIVENESS OF TREATMENT STRATEGIES

While cost effectiveness of antiviral prophylaxis in HBsAg-positive patients is known<sup>[10]</sup>, the cost effectiveness of strategies to attenuate the risk of HBV reactivation in patients with past HBV infection is not well established<sup>[9]</sup>. The cost effectiveness of antiviral prophylaxis is broadly dependent on disease prevalence, and the savings arising from the clinical events that are prevented as a result of prophylaxis. In turn, the savings accrued from prevented clinical events is correlated with the severity of the events prevented<sup>[43]</sup>. HBV reactivation in HBsAg-negative, anti-HBc-positive patients are usually milder than patients who are HBsAg positive, and rarely result in hepatitis, hepatic decompensation or death<sup>[25,26,46]</sup>. In a cost effectiveness modelling study<sup>[8]</sup> in a population of patients with hematologic neoplasms at high risk of HBV reactivation, antiviral prophylaxis was found to be cost effective in HBsAg-positive patients, but not in patients who were HBsAg-negative and anti-HBc-positive. A prospective study by Seto *et al*<sup>[47]</sup> found that in HBsAg-negative, anti-HBc-positive patients with lymphoid malignancies undergoing systemic therapy with B-cell depleting agents (Rituximab or obinutuzumab), close biweekly surveillance with early on-demand therapy in event of HBV reactivation was a viable option compared to antiviral prophylaxis, and may be cost effective. Liu *et al*<sup>[46]</sup> also found that patients with past HBV infection, particularly those with positive anti-HBs, had a low risk of HBV reactivation and monitoring HBV DNA and ALT closely was more cost effective than antiviral prophylaxis.

It must be emphasized, however, that a strategy of close HBV serology monitoring with early on-demand treatment is logistically demanding. Patients would be required to come for frequent follow-up appointments and existing cost-effectiveness studies do not take into account the productivity costs borne by the patient as a result of this strategy. Similarly, it is also difficult to quantify the negative impact of inability or delay in administration of chemotherapy in patients with HBV reactivation. Decisions regarding risk attenuation strategies of HBV reactivation in immunocompromised patients with previous HBV exposure must be individualized. We suggest a treatment algorithm (Figure 1) which took into account various factors determining the clinical risk and outcomes of both treatment strategies in HBsAg-negative, anti-HBc-positive patients undergoing immunosuppression.

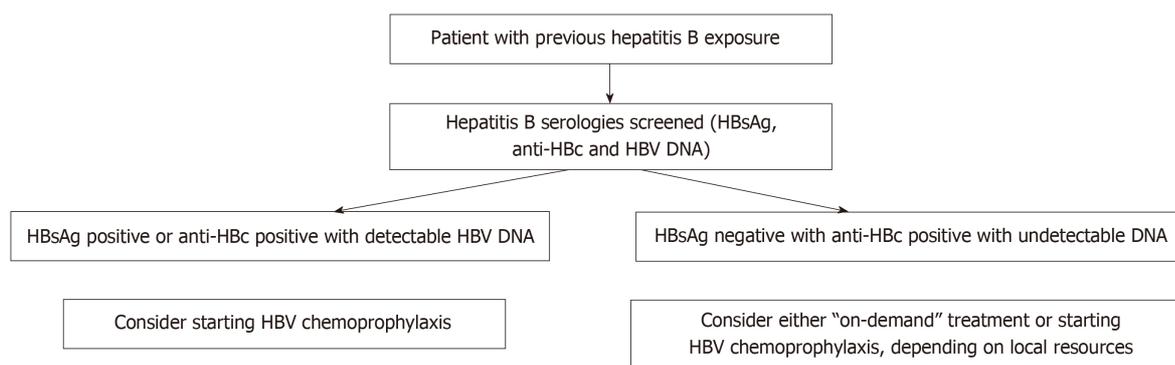
## CHOICE OF TREATMENT AGENT

For patients who are commenced on antiviral treatment either as prophylaxis or as on-demand treatment, antiviral agents with a high genetic barrier to resistance was recommended<sup>[23]</sup>. However, the cost of these medications is high. The major clinical societies' guidelines have noted that in the event of resource constraints, less expensive earlier-generation antivirals with a lower genetic barrier to resistance may be used in patients with a lower risk of resistance (*i.e.*, Undetectable HBV DNA at baseline, and an anticipated prophylaxis duration of less than 6 mo). Patients who are started on antiviral prophylaxis should be continued on antiviral treatment for at least 12 mo after cessation of rituximab-containing immunosuppressants, due to risk of delayed reactivation with rituximab<sup>[48]</sup> and 6 mo for all other immunosuppressive regimes. Patients should undergo routine testing for HBV DNA and serum ALT and AST for 3-6 mo after discontinuation of antiviral therapy to monitor for HBV reactivation post withdrawal.

## CONCLUSION

HBV reactivation remains a concern even after serological clearance due to virus persistence in the host genome as cccDNA. HBV reactivation will continue to remain a significant problem due to high global prevalence of HBV and the increasing use of immunosuppressants. HBV screening with HBsAg, anti-HBc, anti-HBs and HBV DNA should be done in all patients prior to commencement of immunosuppression. HBcrAg shows promise in further characterization of patient's reactivation risk profile. More studies should be done to assess applicability in low and moderate risk immunosuppressants and determining if HBcrAg can be used to identify optimal timepoint of stopping antiviral therapy.

The decision for prophylaxis or close monitoring with early on-demand treatment



**Figure 1** Treatment algorithm for HBsAg negative, anti-HBc positive patients undergoing immunosuppression. Future research may help determine whether HBsAg has a role in determining whether patients with HBsAg negative with anti-HBc positive with undetectable DNA undergo HBV chemoprophylaxis or "on-demand" treatment. HBV: Hepatitis B virus.

needs to be individualized, and depends on the risk of reactivation, cost effectiveness and difference in clinical outcome between the two scenarios. More research is needed to better identify patients who are at elevated risk for HBV reactivation, but concurrently low risk for HBV reactivation associated complications, in order to ascertain the population in whom close monitoring with early on-demand treatment would be a viable option. The risk profile of emerging medications including immune checkpoint mediators needs to be further studied to expand our knowledge on the optimal method of attenuating HBV reactivation risk in immunosuppressed patients with previous HBV exposure.

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