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A Comprehensive Narrative Review on the Underlying Mechanisms Diagnosis and Updated Guidelines for Managing Hepatitis B Virus Reactivation during Immunosuppressive Therapy

Tinjauan Naratif Komprehensif mengenai Mekanisme Dasar Diagnosis dan Panduan Terkini untuk Penatalaksanaan Reaktivasi Virus Hepatitis B selama Terapi Imunosupresif

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Abstract

This narrative review aimed to examine the underlying mechanisms of HBV reactivation, identify major risk factors, and review current strategies for diagnosis, risk stratification, antiviral prophylaxis, monitoring, and management. Literature searches were conducted through PubMed/MEDLINE and Google Scholar using terms related to HBV, HBV reactivation, immunosuppressive therapy, diagnosis, prophylaxis, monitoring, chemotherapy, B-cell-depleting therapy, hematopoietic stem cell transplantation, and newer immunomodulatory agents. Original studies, observational studies, systematic reviews, meta-analyses, guidelines, consensus statements, and relevant clinical reviews were considered, with emphasis on recent evidence. The reviewed evidence indicates that HBV reactivation results from impaired immune control, allowing renewed viral replication from persistent HBV reservoirs, followed in some cases by hepatitis during immune restoration. Risk varies according to HBV serological status, baseline viral activity, underlying disease, and the type and intensity of immunosuppression, with particularly high risk associated with B-cell-depleting therapies and hematopoietic stem cell transplantation. Diagnosis requires assessment of HBsAg, anti-HBc, HBV DNA, alanine aminotransferase, and clinical findings before and during therapy. Current evidence supports risk-based antiviral prophylaxis with potent nucleos(t)ide analogues, particularly entecavir or tenofovir, while selected lower-risk patients may undergo regular monitoring. Updated EASL and AGA guidelines provide guidance for screening, prophylaxis, and post-treatment monitoring, although uncertainty remains for several newer immunomodulatory therapies. Individualized risk assessment and continued surveillance are essential to reduce HBV reactivation-related morbidity and mortality.

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health problem, with more than 250 million people living with chronic infection and a substantial burden of cirrhosis, liver failure, and hepatocellular carcinoma (European Association for the Study of the Liver (EASL) 2025). Although nucleos(t)ide analogue therapy can effectively

suppress HBV replication and reduce the risk of liver-related complications, current treatment does not eliminate the viral reservoir within infected hepatocytes. Covalently closed circular DNA (cccDNA) may persist in hepatocytes and allow viral replication to resume when immune surveillance is substantially impaired (Ma *et al*., 2024). This biological persistence is particularly relevant in patients receiving immunosuppressive or immunomodulatory treatment for haematological malignancies, solid tumors, autoimmune diseases, inflammatory disorders, and transplantation (Anvari & Tsoi, 2024; Dossaji *et al*., 2024). The increasing use of these therapies has therefore maintained HBV reactivation (HBVr) as an important clinical concern despite advances in antiviral treatment and HBV management (EASL, 2025; Vutien & Nguyen, 2025).

HBV reactivation is characterized by renewed or increased HBV replication in individuals with current or previous HBV infection and may subsequently result in hepatitis, hepatic dysfunction, or severe liver injury (Cohen *et al*., 2024). The process reflects disruption of the balance between viral replication and host immune control (Anvari & Tsoi, 2024). Immunosuppressive treatment can impair antiviral immune responses involving T cells, B cells, natural killer cells, and antigen-presenting cells, thereby permitting increased HBV replication (Ma *et al*., 2024). Restoration of immune activity after reduction or withdrawal of immunosuppression may then trigger an inflammatory response against HBV-infected hepatocytes and produce a hepatitis flare (Dossaji *et al*., 2024). Importantly, HBVr is not restricted to patients with chronic HBV infection who remain HBsAg-positive. Individuals who are HBsAg-negative but anti-HBc-positive may also remain at risk because previous HBV infection can leave persistent viral material within hepatocytes, particularly when potent immunosuppression is administered (Vutien & Nguyen, 2025). The clinical spectrum ranges from an increase in HBV DNA without symptoms to clinically significant hepatitis, hepatic decompensation, and acute liver failure (Cohen *et al*., 2024).

The probability of HBVr varies according to HBV serological status, baseline viral activity, underlying disease, and the type, intensity, and duration of immunosuppressive therapy (EASL, 2025). HBsAg-positive individuals generally have a higher risk than patients with resolved infection, while B-cell-depleting therapies and hematopoietic stem cell transplantation are among the exposures most strongly associated with reactivation (Anvari & Tsoi, 2024). Other therapies, including corticosteroids, tyrosine kinase inhibitors, cytokine inhibitors, immune checkpoint inhibitors, and cellular immunotherapies, may also be associated with HBVr, although the magnitude of risk differs according to the specific agent and HBV status (Dossaji *et al*., 2024). Evidence from chemotherapy populations further demonstrates the clinical relevance of this problem. A systematic review and meta-analysis involving 86 studies and 21,297 patients reported a pooled HBVr rate of 9%, with rates of 10% among patients with haematological malignancies and 5% among those with solid tumors (Deepan *et al*., 2024). These findings support risk assessment that integrates HBV serology with the planned immunosuppressive regimen rather than relying on a single marker (EASL, 2025).

Accurate diagnosis and risk stratification are essential because HBVr may develop before clinically apparent hepatitis and may interrupt treatment of the underlying disease. Pre-treatment evaluation should therefore establish the patient's HBV status using HBsAg and anti-HBc, while HBV DNA testing provides additional information for patients with current or previous infection (EASL, 2025). During and after immunosuppressive therapy, HBV DNA, HBsAg status, alanine aminotransferase (ALT), and clinical findings should be interpreted together to distinguish virological reactivation from subsequent hepatitis and clinically significant liver injury (Vutien & Nguyen, 2025). Preventive management is based on estimated reactivation risk, with antiviral prophylaxis using potent nucleos(t)ide

analogues recommended for patients at sufficiently high risk, whereas selected lower-risk patients may undergo structured virological monitoring (Ali *et al*., 2025). Evidence from chemotherapy populations supports the effectiveness of antiviral prophylaxis, with lower HBVr rates observed among patients receiving preventive antiviral therapy (Deepan *et al*., 2024).

Despite the growing body of evidence, an important gap remains in the integration of HBVr biology, clinical diagnosis, treatment-specific risk assessment, and rapidly evolving guideline recommendations (Dossaji *et al*., 2024). Previous reviews have addressed HBVr associated with immunosuppressive therapies or specific drug classes, while recent guidelines have provided risk-based recommendations for prophylaxis and monitoring (Vutien & Nguyen, 2025). However, evidence concerning newer immunomodulatory therapies remains heterogeneous, and differences in risk classification, prophylaxis indications, and post-treatment monitoring between contemporary recommendations may complicate clinical decision-making (Ali *et al*., 2025; EASL, 2025). Therefore, an updated synthesis that connects the biological mechanisms of HBVr with its diagnosis and current prevention and management recommendations remains clinically relevant.

The novelty of this review lies in integrating these domains within a single narrative framework, with particular emphasis on the relationship between HBV serological status, immunosuppressive treatment characteristics, diagnostic assessment, antiviral prophylaxis, and recommendations from recently updated international guidelines. This review therefore aims to examine the underlying mechanisms and clinical diagnosis of HBVr, identify major patient- and treatment-related risk factors, and synthesize updated recommendations for risk stratification, antiviral prophylaxis, monitoring, and management during and after immunosuppressive therapy (Ali *et al*., 2025; EASL, 2025).

METHODS

A narrative literature review was conducted to identify and synthesize evidence on the underlying mechanisms, risk factors, diagnosis, prevention, and management of hepatitis B virus reactivation (HBVr) during immunosuppressive therapy. PubMed/MEDLINE was used as the primary database, with the search covering the previous five years and the last search conducted in 5 August 2026. The search strategy used combinations of the terms “hepatitis B virus reactivation,” “HBV reactivation,” “immunosuppressive therapy,” “immunosuppression,” “antiviral prophylaxis,” “HBV screening,” “HBV monitoring,” and “hepatitis B guidelines.” Publications in English were considered. Recent publications were prioritized to reflect current evidence and recommendations, while earlier publications were retained when they provided foundational evidence or established clinical recommendations relevant to HBVr. Google Scholar was used as a supplementary search source to identify potentially relevant publications not retrieved through PubMed/MEDLINE.

Publications were eligible if they were published in English and addressed patients receiving immunosuppressive, anticancer, immunomodulatory, or transplantation-related therapy, with a focus on HBVr or its prevention and management. Eligible publications included clinical practice guidelines, consensus statements, systematic reviews, meta-analyses, cohort studies, clinical studies, and relevant narrative reviews. Publications were included when they provided information on at least one of the following domains: mechanisms of HBVr, patient- or treatment-related risk factors, diagnosis, risk

stratification, antiviral prophylaxis, virological or biochemical monitoring, treatment of HBVr, or clinical practice recommendations. Publications were excluded if they primarily addressed HBV-related conditions unrelated to immunosuppressive therapy, did not provide information relevant to HBVr, were non-English publications, were duplicate records, or lacked sufficient information to address the objectives of the review. When multiple publications addressed substantially overlapping evidence, the most recent or clinically relevant evidence was prioritized.

The PubMed/MEDLINE search identified 718 records. Retrieved publications were screened by title and abstract, followed by full-text assessment of potentially relevant publications. Relevance was determined according to the predefined eligibility criteria and the extent to which each publication contributed to the objectives and five domains of the review. Google Scholar was used as a supplementary search source to identify potentially relevant publications not retrieved through PubMed/MEDLINE. Given the broad scope of results generated by Google Scholar, publications were selectively screened based on title and abstract relevance, publication type, and the predefined eligibility criteria. The literature screening and selection were performed by one reviewer, while the other authors contributed to discussion, verification, and interpretation of the selected evidence. Eleven key publications were ultimately selected for presentation in Table 1 because they represented the principal evidence relevant to the mechanisms, risk assessment, diagnosis, prevention, and management of HBVr. Additional relevant publications, including foundational studies and established guidelines, were incorporated into the narrative synthesis when appropriate.

The selected literature was synthesized narratively across five domains: underlying mechanisms of HBVr, patient- and treatment-related risk factors, diagnosis and risk stratification, antiviral prophylaxis and monitoring, and current management recommendations. For guideline comparison, recommendations from the European Association for the Study of the Liver (EASL), American Gastroenterological Association (AGA), American Society of Clinical Oncology (ASCO), and American Association for the Study of Liver Diseases (AASLD) were assessed according to HBV screening before immunosuppressive therapy, HBVr risk stratification, indications for antiviral prophylaxis, monitoring strategies, and the recommended duration or continuation of prophylaxis. Recent systematic reviews, meta-analyses, cohort studies, consensus statements, and clinical practice guidelines were prioritized when synthesizing evidence concerning established and newer immunomodulatory therapies.

RESULTS AND DISCUSSION

Results

The reviewed literature identified five major domains relevant to hepatitis B virus (HBV) reactivation during immunosuppressive therapy: underlying mechanisms, patient- and treatment-related risk factors, diagnosis and risk stratification, antiviral prophylaxis and monitoring, and updated guideline recommendations. Studies on the biological mechanisms described HBV reactivation as a consequence of disruption of the equilibrium between persistent viral replication and host immune control, with covalently closed circular DNA (cccDNA) remaining within hepatocytes as an important reservoir for renewed viral replication (Ma *et al*., 2024). Immunosuppressive therapies may reduce HBV-specific cellular and humoral immune responses, including the activity of T cells, B cells, natural killer cells, and antigen-presenting cells, allowing HBV replication to increase. Subsequent restoration of immune activity may produce an inflammatory

response against infected hepatocytes and lead to hepatitis and hepatic injury (Cohen *et al*., 2024). The clinical risk is influenced by both HBV status and the immunosuppressive regimen, with HBsAg-positive patients generally having greater risk than individuals with resolved infection (Anvari & Tsoi, 2024).

Risk of HBV reactivation varied substantially according to the immunosuppressive agent and underlying HBV serological status. B-cell-depleting therapies, particularly anti-CD20 agents, and hematopoietic stem cell transplantation remain among the exposures associated with the highest risk, while corticosteroids, tyrosine kinase inhibitors, cytokine inhibitors, immune checkpoint inhibitors, and other immunomodulatory therapies show variable levels of risk (Dossaji *et al*., 2024; EASL, 2025). A systematic review and meta-analysis of 86 studies involving 21,297 patients receiving chemotherapy reported a pooled HBV reactivation rate of 9%, including 10% among patients with haematological malignancies and 5% among those with solid tumors (Deepan *et al*., 2024). More recent real-world data involving 9,422 patients with baseline negative HBV DNA demonstrated measurable reactivation across several treatment categories, including anti-CD20 therapies, anthracyclines, tyrosine kinase inhibitors, corticosteroids, and other immunosuppressive agents (Ikeuchi *et al*., 2026). Evidence from patients receiving Bruton tyrosine kinase inhibitors also demonstrated that HBV reactivation can occur among individuals with past HBV infection, supporting continued surveillance in this population (Azzam *et al*., 2024).

Diagnosis and risk stratification primarily depend on HBV serological testing, virological assessment, liver biochemistry, and characterization of the planned immunosuppressive therapy. Current recommendations emphasize assessment of HBsAg and total anti-HBc before immunosuppressive treatment, with HBV DNA testing used to further characterize infection and reactivation risk when clinically indicated (EASL, 2025). HBV reactivation may initially present as an increase in HBV DNA before the development of alanine aminotransferase elevation or clinical hepatitis, making virological monitoring important for early detection (Cohen *et al*., 2024). The updated AGA guideline recommends antiviral prophylaxis for patients at high risk of HBVr and conditionally favors prophylaxis for those at moderate risk, whereas patients at low risk may be managed with monitoring when appropriate. Monitoring should include HBV viral load and alanine aminotransferase at approximately 1- to 3-month intervals in patients managed without prophylaxis, allowing antiviral treatment to be initiated promptly when reactivation is detected (Ali *et al*., 2025).

Antiviral prophylaxis was consistently associated with a reduction in HBV reactivation among patients receiving immunosuppressive or immunomodulatory therapy. High-potency nucleos(t)ide analogues, particularly entecavir and tenofovir-based agents, are recommended for patients in whom prophylaxis is indicated because of their potent antiviral activity and high barrier to resistance (Vutien & Nguyen, 2025). Evidence from immune checkpoint inhibitor populations demonstrated a lower HBVr incidence among patients with chronic HBV infection receiving antiviral prophylaxis compared with those without prophylaxis, although the absolute risk differed according to baseline HBV status (Ding *et al*., 2023). The effectiveness of prophylaxis has also been demonstrated in broader chemotherapy populations, in which inadequate antiviral protection was associated with greater risk of HBVr (Deepan *et al*., 2024). These findings support the use of antiviral prophylaxis as a central preventive strategy for patients with sufficiently high reactivation risk, while structured monitoring remains appropriate for selected lower-risk populations (Ali *et al*., 2025).

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Table 1. Selected Studies Relevant to HBV Reactivation During Immunosuppressive Therapy

Author, year	Study design	Population/ sample	Main focus	Main finding
Ma *et al*., 2024	Narrative review	Literature on HBV immunology and reactivation	Immunological mechanisms of HBVr	HBVr involves disruption of viral–host immune control, with roles for T cells, B cells, natural killer cells, antigen-presenting cells, cytokines, and persistent cccDNA.
Anvari & Tsoi, 2024	Narrative review	Patients receiving immunosuppressive therapy	HBVr risk and prevention	Patients with chronic HBV infection have greater reactivation risk, while anti-CD20 therapy and hematopoietic stem cell transplantation represent important high-risk exposures.
Cohen *et al*., 2024	Consensus guideline	Patients receiving immunosuppressive immunomodulatory therapy	Screening, detection, monitoring, and management	HBV screening, antiviral prophylaxis, and systematic monitoring can reduce HBVr-related morbidity and mortality.
Dossaji *et al*., 2024	Narrative review	Patients receiving immunosuppressive and immunomodulatory drugs	Risk associated with newer immunomodulators	Risk varies by HBV serological status and treatment class; newer agents, including TKIs, cytokine inhibitors, and immune checkpoint inhibitors, require individualized risk assessment.
Deepan *et al*., 2024	Systematic review and meta-analysis	21,297 cancer patients from 86 studies	HBVr during chemotherapy	The pooled HBVr rate was 9%, with higher rates in haematological malignancies than solid tumors.
Azzam *et al*., 2024	Systematic review and meta-analysis	18 studies of patients receiving BTK inhibitors	HBVr associated with BTK inhibitors	HBVr incidence was 6.6% among patients with past HBV infection receiving ibrutinib, indicating an intermediate level of risk.
Ding *et al*., 2023	Systematic review and meta-analysis	2,561 patients receiving immune checkpoint inhibitors	HBVr during immune checkpoint inhibition	HBVr occurred more frequently in chronic HBV infection than past infection, while antiviral prophylaxis was associated with lower reactivation risk.
Vutien & Nguyen, 2025	Narrative review	Immunosuppressed patients, including transplant populations	Screening, prevention, and management	HBV serology and risk category should guide prophylaxis or monitoring, with entecavir and tenofovir-based agents used for antiviral prevention or treatment.
Ali *et al*., 2025	Clinical practice guideline	Individuals at risk of HBVr	Updated prevention and	Strong recommendation for prophylaxis in high-risk patients, conditional prophylaxis for

			treatment recommendations	moderate-risk patients, and monitoring without prophylaxis for selected low-risk patients.
EASL, 2025	Clinical practice guideline	Patients with HBV infection	Diagnosis, risk assessment, treatment, and HBVr prevention	Updated recommendations incorporate HBV screening, risk stratification, HBV DNA assessment, and prophylaxis during immunosuppressive therapy.
Ikeuchi *et al*., 2026	Retrospective cohort study	9,422 patients receiving immunosuppressive or chemotherapeutic agents	Real-world HBVr incidence	HBVr occurred across multiple treatment categories, including anti-CD20 therapy, anthracyclines, TKIs, corticosteroids, and other immunosuppressive agents.

The studies summarized in Table 1 represent different levels of evidence addressing the mechanisms, risk assessment, diagnosis, prevention, and management of HBVr. Mechanistic literature primarily establishes the biological basis of reactivation through persistent HBV reservoirs and impaired immune surveillance, whereas clinical studies demonstrate substantial variation in risk according to HBV serological status and immunosuppressive drug class (Ma *et al*., 2024; Dossaji *et al*., 2024). Systematic reviews and cohort studies further demonstrate that HBVr remains clinically relevant with both established and newer immunosuppressive therapies, including chemotherapy, BTK inhibitors, and other immunomodulatory agents (Deepan *et al*., 2024; Azzam *et al*., 2024; Ikeuchi *et al*., 2026). Current guidelines consequently emphasize universal or broad HBV screening before relevant immunosuppressive exposure, followed by risk-based selection of antiviral prophylaxis or virological monitoring (Ali *et al*., 2025; EASL, 2025). Overall, the available evidence supports an integrated strategy in which HBV serology, HBV DNA, liver biochemistry, immunosuppressive treatment characteristics, and updated guideline recommendations are considered together when preventing and managing HBVr (Cohen *et al*., 2024).

Discussion

HBV reactivation is primarily driven by disruption of the immune control that normally limits replication from persistent viral reservoirs. Although serum HBV DNA may remain low or undetectable during periods of immune control, HBV DNA persists within hepatocytes, including as covalently closed circular DNA (cccDNA), allowing viral replication to resume when immune surveillance is weakened. The subsequent restoration of immune activity may produce hepatocellular injury, which explains why clinically significant hepatitis can develop after or during recovery from immunosuppression rather than necessarily at the point of maximal immune suppression (Ma *et al*., 2024). This biological sequence is consistent with the established definition of HBVr as renewed viral replication or serological reactivation following loss of immune control and helps explain its occurrence in both chronic and previously resolved HBV infection (Terrault *et al*., 2018). Thus, HBVr should be regarded as a dynamic interaction between viral persistence

and changes in host immunity rather than simply as a consequence of increased viral replication alone (Perrillo, 2015).

The risk of HBVr varies substantially according to baseline HBV serological status and the type of immunosuppressive treatment. HBsAg-positive patients generally have a greater risk because viral replication is more readily re-established when immune control is disrupted, whereas HBsAg-negative, anti-HBc-positive patients have a lower but clinically important risk (EASL, 2025). A systematic review of more than 3,600 HBsAg-negative, anti-HBc-positive patients demonstrated that reactivation risk was particularly relevant among patients with haematological diseases and those receiving rituximab-containing regimens, while anti-HBs positivity was associated with a lower observed risk in several treatment groups (Cholongitas *et al*., 2018). These findings support the continued importance of distinguishing chronic infection from resolved infection before immunosuppressive therapy is initiated. The higher risk associated with B-cell depletion is biologically plausible because prolonged impairment of humoral immunity may persist after treatment has ended (Anvari & Tsoi, 2024).

Treatment-specific risk has become increasingly relevant as immunosuppressive therapy has expanded beyond conventional chemotherapy and anti-CD20 agents. Recent evidence indicates that HBVr may occur with immune checkpoint inhibitors, tyrosine kinase inhibitors, cytokine inhibitors, corticosteroids, and other newer immunomodulatory therapies, although the magnitude of risk differs according to both the drug class and HBV status (Papatheodoridis *et al*., 2022). Real-world data involving more than 9,000 patients similarly demonstrated measurable HBVr incidence across anti-CD20 therapy, anthracyclines, tyrosine kinase inhibitors, and prolonged corticosteroid exposure (Ikeuchi *et al*., 2026). This variability indicates that the immunological mechanism of a drug should be considered together with treatment intensity, duration, underlying disease, and the patient's virological status rather than assigning risk solely according to the drug name. Such treatment-specific distinctions are particularly important for newer agents for which evidence remains limited and heterogeneous (Dossaji *et al*., 2024).

Accurate diagnosis requires recognition that virological reactivation may occur before biochemical hepatitis becomes apparent. HBV DNA can become detectable or increase substantially before alanine aminotransferase elevation, meaning that liver enzyme monitoring alone may fail to identify early reactivation (Terrault *et al*., 2018). Screening before immunosuppressive or anticancer treatment should therefore include HBsAg and total anti-HBc, with HBV DNA assessment used to further characterize patients with evidence of previous or current infection (Hwang *et al*., 2020). This distinction is clinically important because HBVr, HBV-associated hepatitis, and liver failure represent different stages of disease progression and should not be treated as interchangeable outcomes. Integration of serological markers, HBV DNA, ALT, and clinical findings therefore provides a more reliable basis for identifying clinically meaningful reactivation than reliance on any single laboratory parameter (Cohen *et al*., 2024).

Antiviral prophylaxis remains central to preventing severe HBVr, particularly when the anticipated risk is high. Evidence from randomized trials in patients with resolved HBV infection receiving rituximab-based chemotherapy demonstrated substantially fewer reactivation events among patients receiving prophylactic entecavir than among those managed with treatment after reactivation, supporting early antiviral intervention in high-risk settings (Huang *et al*., 2013). More recent guideline recommendations similarly favor

prophylaxis for patients at high risk and permit monitoring without prophylaxis only in selected lower-risk groups in whom reliable follow-up is feasible (Ali *et al*., 2025). The effectiveness of preventive therapy is also supported by data from chemotherapy populations, in which antiviral prophylaxis has been associated with lower rates of HBVr than would otherwise be expected from the underlying treatment risk. These findings support the use of potent nucleos(t)ide analogues as preventive therapy when the probability of clinically significant HBVr is sufficiently high (Deepan *et al*., 2024).

The need for prevention does not end when immunosuppressive treatment is completed. HBVr may develop during the period of immune recovery or after discontinuation of therapy, particularly in patients exposed to prolonged B-cell depletion. A systematic review of patients with haematological malignancies and resolved HBV infection found that prophylactic antiviral therapy was particularly effective in patients receiving anti-CD20 monoclonal antibodies, reinforcing the importance of continued protection in this setting (Cheung *et al*., 2020). Current EASL recommendations extend prophylaxis beyond the end of immunosuppressive therapy, with longer continuation advised for high-risk regimens such as B-cell-depleting treatment (EASL, 2025). For patients managed without prophylaxis, continued HBV DNA and ALT monitoring is necessary because early virological detection permits antiviral treatment before severe hepatitis develops (Ali *et al*., 2025).

Current guidelines have increasingly moved toward risk-based management, although some differences remain between recommendations and evidence gaps persist for newer therapies. EASL 2025 emphasizes the combination of HBsAg, anti-HBc, HBV DNA, and treatment-related risk when determining whether prophylaxis or monitoring is appropriate, while the AGA guideline uses high-, moderate-, and low-risk categories to guide preventive decisions (EASL, 2025; Ali *et al*., 2025). Earlier AASLD guidance similarly established universal HBsAg and anti-HBc screening before immunosuppressive therapy and recommended prophylaxis for patients receiving anti-CD20 therapy or stem cell transplantation (Terrault *et al*., 2018). Despite this broad agreement, uncertainty remains for several newer immunomodulatory agents because available evidence is often derived from retrospective cohorts, small studies, or heterogeneous definitions of HBVr. Continued refinement of risk classification will therefore be necessary as the range of immunosuppressive therapies expands (Papatheodoridis *et al*., 2022).

Overall, HBVr prevention is best understood as a continuum beginning with identification of previous or current HBV infection before immunosuppression and extending through treatment and post-treatment surveillance. The persistence of HBV within hepatocytes means that loss of detectable serum infection does not necessarily represent complete viral eradication, while clinical evidence demonstrates that the probability and consequences of reactivation vary markedly between patients and treatment regimens (Ma *et al*., 2024; Cholongitas *et al*., 2018). Risk-adapted prophylaxis, early virological detection, and appropriate duration of follow-up can reduce preventable HBVr-related morbidity while allowing necessary immunosuppressive therapy to continue (Ali *et al*., 2025). The integration of current guideline recommendations with emerging evidence for newer therapies is therefore essential for maintaining HBV control throughout the entire period of immunosuppression and immune recovery (Cheung *et al*., 2020).

CONCLUSION

Hepatitis B virus reactivation remains an important complication of immunosuppressive therapy because persistent HBV within hepatocytes can resume replication when immune-mediated viral control is impaired. The risk of reactivation varies according to HBV serological status, baseline viral activity, underlying disease, and the type and intensity of immunosuppressive treatment, with particularly high risk associated with B-cell-depleting therapies and hematopoietic stem cell transplantation. Early diagnosis requires HBV screening before immunosuppression and integration of HBsAg, anti-HBc, HBV DNA, alanine aminotransferase, and clinical findings during follow-up. Current evidence supports risk-based antiviral prophylaxis with potent nucleos(t)ide analogues for patients at sufficiently high risk, while selected lower-risk patients may be managed with structured virological monitoring. Updated EASL and AGA recommendations provide a framework for screening, risk stratification, prophylaxis, and monitoring, although uncertainty remains for several newer immunomodulatory therapies. Therefore, individualized assessment and continued surveillance before, during, and after immunosuppressive therapy are essential to minimize preventable HBVr-related morbidity and mortality.

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