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REVIEW

A Review of Hepatitis B Reactivation Risk on Immunosuppressants with a Focus on Newer Immunomodulators

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Abstract

Purpose of Review Hepatitis B virus reactivation (HBVr) can complicate the use of immunosuppressive, antiviral, and chemotherapeutic medications in individuals with a history of prior exposure to HBV or chronic infection. Timely management is crucial to prevent fatalities. This review focuses on the various classes of biologics linked to the risk of HBVr, with emphasis on newer immunosuppressive and immunomodulator therapies.

Recent Findings Immune checkpoint inhibitors, tyrosine kinase inhibitors, cytokine inhibitors, and chimeric antigen receptor T-cell immunotherapies are associated with a high risk of hepatitis B virus reactivation (HBVr) in patients who are hepatitis B surface antigen-positive (HbsAg-positive). This risk decreases significantly when patients start nucleoside analogue (NA) prophylaxis. It is recommended to use NA prophylaxis alongside these medications and closely monitor for reactivation upon discontinuation of NA prophylaxis.

Summary To minimize the risk of reactivation when starting immunosuppressive, antiviral, and chemotherapeutic agents in individuals at high, intermediate, and low risk for hepatitis B virus reactivation (HBVr), it is crucial to employ specific strategies for risk assessment, monitoring, and management.

Keywords Hepatitis B · Reactivation hepatitis B · Immunosuppression · Immunotherapy · Chemotherapy · Immunomodulators

Introduction

Hepatitis B virus (HBV) infection is a public health threat worldwide that can result in chronic hepatitis with progression to liver cirrhosis and/or cancer [1]. It is estimated that 3.2% of the global population lives with chronic HBV, amounting to 257.5 million individuals worldwide with over 2 billion individuals who have been exposed to HBV (anti-HBc +) [2]. An estimated 13% of these individuals are diagnosed, and only 8.2% of those eligible for treatment are receiving it. HBV infection causes up to 858,000 deaths per year, projected to increase to 1,149,000 deaths by 2030 [2, 3]. In the USA alone, up to 2.4 million people are affected [4•]. Higher incidences of HBV infection are observed in Asia, Africa, Eastern Europe, the Mediterranean, and Central South America [2].

HBV Triple Panel

The Centers for Disease Control and Prevention (CDC) issued guidance in March 2023 that recommends universal testing of HBV with a triple test screen for all adults; the triple screen includes hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and total antibody to hepatitis B core antigen (anti-HBc) [5••]. Table 1 lists the interpretations of the possible results.

Non-immune individuals typically have never been vaccinated and are without HBV infection. Past HBV infection with resolution and immune control indicates HBsAg loss and anti-HBs-positive and is characterized by low or undetectable serum HBV DNA, normal alanine transaminase (ALT) levels, and resolution of liver inflammation. Immune-protected persons have been vaccinated, have anti-HBs,

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Table 1 Interpretation of results from triple screening of hepatitis B [5••]

Testing results			Interpretation
HBsAg	Anti-HBs	Anti-HBc*	
-	-	-	Non-immune, vaccinate
-	+	+	Immune-control
-	+	-	Immune-protected
+	-	+	Infected
-	-	+	Exposed

*False positive rate for core antibody is 1 in 500 patients; consider workup for occult hepatitis B, do not vaccinate, and educate about possible reactivation [6]

and never had HBV infection before testing. "Infected" indicates evidence of current infection (i.e., HBsAg-positive). Exposed individuals have recovered from a prior HBV infection and may or may not have immune control. Finally, possibly infected individuals have ambiguous results that require further tests to reveal their underlying status, including the workup for occult HBV infection (including patients who are anti-HBc-positive alone). Vaccination is recommended in non-immune, nonexposed individuals and is not needed in exposed, immune-controlled, and immune-protected persons [4•]. Post-vaccination testing and boosting are not recommended due to their high cost and do not have a proven clinical benefit [4•, 6]. Specifically, no data shows a benefit to "boost" these individuals with additional doses of HBV vaccine.

HBV Reactivation

HBV reactivation (HBVr) occurs as a complication of immunomodulation, anti-hepatitis C virus (HCV) medications, and immunosuppressive therapy in people with prior exposure to HBV or chronic HBV infection. Those experiencing HBVr can have different levels of hepatitis flares, ranging from elevated liver tests with no symptoms to severe hepatitis including jaundice [7]. Table 2 summarizes the definitions for HBVr and hepatitis flare according to American Association for the Study of Liver Diseases (AASLD) and Asian-Pacific Association for the Study of the Liver (APASL) guidelines [7].

Risk Factors for HBV Reactivation

Both host and virologic factors, along with the degree of immunosuppression, contribute to the risk of HBVr [7]. Virologic factors include higher baseline HBV DNA levels, chronic hepatitis B (CHB) diagnosis, positive hepatitis B e-antigen (HBeAg), co-infection with other viruses, and HBV genotype [7]. Many host factors can heighten susceptibility to HBVr, including male gender, advanced age, liver cirrhosis, and underlying comorbidities necessitating immunosuppression. The intensity and the number of administered therapies determine the level of immune suppression. Immunosuppressive drugs are classified based on their risk of HBVr as high (> 10%), moderate (1–10%), and low (< 1%) [7–9].

Role of Different Serologic Combinations in HBV Reactivation

In relation to HBVr, the risk is notably higher in patients who are HBsAg-positive/anti-HBc-positive compared to those with only anti-HBc positivity, and this risk is even lower when anti-HBc is combined with anti-HBs positivity (especially with high titers). Individuals with detectable HBsAg face an up to eightfold increased risk of reactivation [7]. The highest risk is seen in patients who are HBeAg/HBsAg-positive [10]. Several drugs further elevate the risk for HBsAg-positive patients, including tumor necrosis factor-alpha (TNF-α) inhibitors, chemotherapy for hematologic and solid organ malignancies, anthracyclines, B-cell-depleting agents, and chronic steroid therapy [11••].

Another marker that can contribute to a higher rate of HBVr is high levels of anti-HBc. A higher titer of anti-HBc (≥ 6.41 IU/mL) indicates an increased risk of reactivation [10]. Several studies have demonstrated that individuals with anti-HBs exhibit a shielding effect due to an enhanced

Table 2 Definitions of HBV reactivation and hepatitis flare [7]

	AASLD	APASL	EASL
HBV reactivation	-HBV DNA elevation compared to baseline, or any increase if no baseline available -Previously HBsAg-negative and anti-HBc-positive persons with seroconversion to HBsAg positivity	-HBV DNA ≥ 2 log increase, or newly appearing HBV DNA to a level ≥ 100 IU/mL in previously stable or undetectable persons -HBV DNA at a level ≥ 20,000 IU/mL in a person with no previous baseline level	Not clearly defined
Hepatitis flare	Elevation of ALT 3 times greater than the baseline and at a level > 100 U/L	Elevation of aminotransferase levels > 5 times the upper limit of normal and twice the value at baseline	Not clearly defined

humoral and T-cell HBV immune response [10]. One study found that in 157 patients with rheumatoid arthritis, those who tested positive for anti-HBs and received rituximab had a lower HBVr rate (4.8%) compared to those who tested negative for anti- HBs (20%) [12].

Clinical Manifestations of HBV Reactivation

The clinical manifestation of HBVr can involve a resurgence of liver disease activity and abnormalities in liver enzymes with or without abnormal liver function tests. Acute liver failure is a potential outcome for a minority of patients. It is characterized by coagulopathy and encephalopathy and can be associated with ascites and bleeding. This condition could lead to a liver transplant or even death. Since many patients have had recent cancers, a liver transplant is rarely an option. Less severe presentations of HBVr include symptoms such as right upper quadrant abdominal pain and jaundice [11••].

HBVr might remain entirely asymptomatic in certain instances and only become evident through laboratory investigations. These findings are summarized in Table 3 [7, 11••].

Timely management of HBVr is crucial to prevent liver failure, need for a liver transplant, and potential fatalities. Patients with CHB who experience disease exacerbations largely through non-adherence to their antiviral treatment have a high rate of HBVr (51.9%) [13]. Among those with cirrhosis, the liver failure rate is 45.0%, in contrast to the 20.3% rate in patients without cirrhosis. In the same study, short-term mortality among patients with cirrhosis and HBVr reached 14.0% at 28 days and 23.3% at 90 days. Prompt antiviral treatment initiation and monitoring compliance and resistance can prevent HBVr and complications.

Updated HBV Markers to Monitor Reactivation

Novel biomarkers, including anti-HBs and anti-HBc titers, HBV-core related antigen (HBcrAg), HBcAg, ultra-sensitive HBsAg assessment, and HBV RNA quantitative, are being used or studied for their potential in assessing the risk of HBVr during immunosuppressive treatments. The utility of these markers is summarized in Table 4 [14••]. Currently, anti-HBs and anti-HBc are the most used in clinical practice. While these new biomarkers, such as HBcrAg, have been associated with various phases of HBV infection, more research is needed to determine their reliability in diagnosing and monitoring HBVr [14••].

HBV Reactivation Diagnostic Challenges

Viral covalently closed circular DNA (cccDNA) in liver cells has made it impossible to eradicate the HBV virus completely. cccDNA provides the basis for virion replication in all exposed patients [15]. Viral cccDNA can be used to quantify the viral load in the liver cell, but requires sampling of an infected hepatocyte. Potential alternative markers for intrahepatic cccDNA are HBcrAg and HBcAg, which have shown a strong correlation with cccDNA transcriptional activity in both HBeAg-positive and HBeAg-negative patients. This represents a marked improvement over HBsAg, as HBsAg can be derived from integrated truncated

Table 3 Clinical signs, symptoms, and laboratory value abnormalities in HBVr [7, 11••]

Clinical signs	Clinical symptoms	Laboratory value abnormalities
Ascites, portal hypertension, jaundice, altered mental status	Right upper quadrant abdominal pain, generalized abdominal pain, nausea, vomiting, fatigue, body aches, diarrhea	• Increase in ALT and aspartate aminotransferase • Increase in bilirubin • Increase in prothrombin time

Table 4 Old and new HBV markers to monitor patients at risk for HBV reactivation [14••]

Marker titers	Findings
Anti-HBs titers (standard)	Titer level inversely correlated with HBVr risk
HBV DNA quantitative titers (standard)	A greater than 100-fold increase compared to the previously undetectable DNA baseline
Anti-HBc titers (new)	Higher levels correlated with HBeAg clearance, antiviral therapy effectiveness, and decreased risk of HBVr after stopping treatment
HBcrAg and HBcAg (new)	Marker of intrahepatic HBV cccDNA activity and positivity correlates to higher HBVr risk
Serum HBV RNA quantitative (new)	Marker of number of virions containing pre-genomic RNA released from infected hepatocytes. Its role in HBVr is unknown
Standard (normal tool) and ultra-sensitive quantitative HBsAg (new)	New assays with a 0.5 mIU/mL detection for HBsAg compared to the current 5 mIU/mL limit could identify minimal HBV replication in resolved infections. However, its use is limited in immunocompromised patients

HBsAg genomes. Accurately assessing a patient's risk of HBVr remains a challenge, especially in patients undergoing immunosuppressive therapy, since HBV can stay hidden in the liver as quiescent cccDNA [16].

HBV Reactivation Risk Associated with Immunosuppressive Medications

Immunosuppressants and chemotherapeutic medications pose the greatest risk of causing HBVr. Drugs that have the potential to cause HBVr in > 10% of cases are classified as high risk. This category includes B-cell-depleting agents such as rituximab and ofatumumab, anthracycline derivatives like doxorubicin and epirubicin, as well as moderate-dose corticosteroid therapy or high-dose steroid therapy lasting for > 4 weeks [9] or when steroids are used in combination with other immunosuppressants. These drugs can trigger HBVr in patients who have previously recovered from HBV infections, regardless of whether they have detectable or undetectable HBV DNA in the serum. The likelihood of HBVr occurring is also contingent upon the patient's HBsAg status, and patients who are HBsAg-positive are at higher risk for HBVr compared to those who are HBsAg-negative/anti-HBc-positive [8].

Classes of moderate HBVr risk, with an incidence of 1–10%, include drugs like TNF-α inhibitors (etanercept, adalimumab, certolizumab, infliximab), cytokine and integrin inhibitors (abatacept, ustekinumab, natalizumab, vedolizumab), and tyrosine kinase inhibitors (TKIs; imatinib and nilotinib) [9].

Drugs that carry an anticipated HBVr risk < 1% include traditional immunosuppressive agents such as azathioprine and methotrexate, as well as low-dose corticosteroid therapy administered for < 1 month [9]. Table 5 summarizes the mechanisms associated with HBV in each drug class and their corresponding risk of HBVr.

Prevalence of Immunosuppressant Therapy

In 2013, the Centers for Disease Control (CDC) determined that approximately 2.7% of individuals are taking immunosuppressants or have been given immunosuppressants at any given time. A more recent study exploring these drugs' use in insured adults found that about 2.8% of adults took immunosuppressants between 2018 and 2019 [21]. The study revealed that the most prescribed were prednisone, methylprednisolone, and methotrexate, often combined with TNF-α inhibitors, anti-rejection transplant medications, disease-modifying antirheumatic drugs, and antineoplastic medications [21]. Unfortunately, more data is needed about the worldwide use of immunosuppressant therapies.

The Risk of HBV Reactivation in Newer Agents

B-Cell-Depleting Agents

Rituximab poses a high risk of HBVr in up to 28.5% of patients who do not receive antiviral prophylaxis [22]. A recent study found that none of the 63 allogeneic stem cell transplant recipients with resolved HBV infection treated with rituximab experienced HBVr while receiving prophylaxis with lamivudine (LAM) from 2009 to 2016 [23]. However, one patient had reactivation after discontinuing prophylaxis. The authors of the study concluded that LAM might be reserved for HBV viremic of HBsAg-positive patients as there are no current study or convincing data comparing different nucleoside analogues (NAs) in resolved HBV infections among stem cell transplant (SCT) recipients. However, these authors would strongly advise the use of first-line agents such as tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir (ETV) for prophylaxis since there is no risk of resistance with these medications in these settings. Additionally, patients should be monitored for at least 12 months after stopping the antiviral agent. Patients taking other anti-CD20 agents—such as ofatumumab, ocrelizumab, obinutuzumab, and ibritumomab—are also at high risk of HBVr [17].

A newer agent, daratumumab, was recently developed for the treatment of relapsed or refractory multiple myeloma. Few reported studies have shown the potential for HBVr after daratumumab therapy in patients with past or chronic HBVr. In a multicenter randomized trial of 259 patients with relapsed or refractory multiple myeloma treated with daratumumab, only 1 patient with past HBV infection experienced HBVr, resulting in death [24]. In a separate study involving 93 patients with past HBV infection and multiple myeloma treated with daratumumab, 6 patients (6.5%) experienced HBVr, with 4 of them being anti-HBs-positive. Tragically, 1 patient who was anti-HBs-negative developed hepatic encephalopathy and succumbed to hepatic failure after just 17 days of treatment [25•].

A recent case report from China detailed the condition of an 88-year-old man who developed HBVr 7 years after undergoing therapy for diffuse large B-cell lymphoma (DLBCL) with rituximab, cyclophosphamide, doxorubicin hydrochloride, oncovin, and prednisone (R-CHOP). The patient had a documented HBV infection prior to chemotherapy and received close monitoring. Subsequently, the patient underwent treatment for prostate cancer using leuprorelin acetate (luteinizing hormone–releasing hormone agonist), during which elevated liver enzymes and increased HBV DNA levels were observed, confirming a case of late HBVr [26].

Table 5 Overview of mechanisms and risk of HBV reactivation in common immunosuppressants

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
B-cell-depleting agents Humanized antibodies	Rituximab, alemtuzumab, obinutuzumab, ocrelizumab, ofatumumab	Commonly prescribed for active RA and is a key component of B-cell non-Hodgkin lymphoma treatment regimens	Target CD20 sites on B lymphocyte cells, suppressing humoral immunity that controls HBV by generating neutralizing antibodies against circulating viruses	High risk; use prophylaxis	High risk; use prophylaxis
T-cell activation blocking agents Monoclonal antibody	Belatacept, abatacept, secukinumab, mogamulizumab	Belatacept is used in combination with other agents as prophylaxis for kidney transplant rejection. Abatacept is used for different autoimmune arthritic conditions, including RA, psoriatic arthritis, and juvenile idiopathic arthritis	These agents hinder CD2-mediated T-cell co-stimulation. Belatacept blocks T-cell activation by inhibiting the CD80/CD86 binding costimulatory signal. In contrast, alefacept disrupts CD2-mediated T cell co-stimulation, resulting in T cell depletion involving natural killer cells [17] Secukinumab impedes the IL-17 pathway of pro-inflammatory cytokines released from immune cells, including T-helper cells. Mogamulizumab targets the C–C chemokine receptor 4 used for the treatment of relapse/refractory adult T cell leukemia/lymphoma [73] Mechanism of HBVr remains unclear	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis. In a recent study of patients with a kidney transplant receiving belatacept, 16.7% of 32 anti-HBc-positive patients encountered HBVr [18]
Immune checkpoint inhibitors	Durvalumab, atezolizumab, nivolumab, pembrolizumab, ipilimumab, tremelimumab, camrelizumab	Durvalumab and atezolizumab primarily treat NSCLC but may be used in treating other malignancies like HCC and melanomas, often in combination with other drugs. Nivolumab and pembrolizumab primarily treat melanomas and NSCLC. Ipilimumab is primarily used for melanomas. Tremelimumab combined with durvalumab or camrelizumab combined with apatinib can be used to treat HCC	Activate cytotoxic T cells by inhibiting immune-suppressive molecules like PD-1, PD-L1, and CTLA-4. Mechanism of HBVr remains unclear	Low risk when treated with concurrent HBV prophylaxis and/or treatment [19]	N/A

Table 5 (continued)

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
TKIs	Imatinib, nilotinib, erlotinib, dasatinib, ibrutinib	Used in hematologic malignancies such as chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom macroglobulinemia	Competitively inhibit ATP at the catalytic binding site of tyrosine kinase, potentially affecting HBV-specific immune control by disrupting kinase signaling pathways and lymphocyte proliferation crucial for immune activation [11••]	Moderate risk; use prophylaxis. In a retrospective study, it was estimated that 9.36% of HBsAg (+) patients had HBVr [20••]	Moderate risk; use prophylaxis
TNF-α inhibitors	Adalimumab, etanercept, certolizumab, infliximab	Used in the treatment of immune-related diseases such as IBD, RA, spondylarthritis, and psoriasis	Inhibit TNF, which triggers various pro-inflammatory signaling pathways. They can result in reduced cytokine cascade involved in HBV clearance, decreased lymphocyte clearance and apoptosis, and insufficient T-cell response [11••]. TNF may also activate a unique host antiviral pathway that can cause regulate cccDNA, so blocking it with these agents can predispose one to HBVr [11••]	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis
Proteasome inhibitors. Small molecule inhibitor	Bortezomib, carfilzomib, ixazomib	Used for the treatment of multiple myeloma and mantle cell lymphoma	Block proteasomes, potentially preventing the breakdown of pro-apoptotic factors and triggering programmed cell death in cancerous cells. They are believed to disrupt pathways essential for the proliferation of vital B and plasma cells that play a key role in HBV immune control [11••]	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis
Anthracyclines Intercalating agent	Doxorubicin, epirubicin, daunorubicin	Used for the treatment of neoplastic conditions, including metastatic breast cancer, acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma	DNA intercalating agents and topoisomerase II inhibitors. Mechanism of HBVr remains unclear	High risk; Use prophylaxis. A prospective study found that 41% of HBsAg-positive patients treated with doxorubicin had HBVr [10]	Moderate risk; Use prophylaxis

Table 5 (continued)

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
Corticosteroids	Prednisone, prednisolone, methylprednisolone, dexamethasone	Used for a variety of conditions: RA, IBD, asthma, and chronic obstructive pulmonary disease	These agents work primarily by binding to the glucocorticoid receptor, which leads to inhibition of pro-inflammatory signals and promotion of anti-inflammatory signals. Mechanism of HBVr involves suppression of cell-mediated immunity by inhibiting interleukin production, which are in turn important for T and B-cell production [11••]	High risk *For intra-articular steroids in any dose* ≤ 1 week: low risk; no prophylaxis; monitor HBV DNA and ALT every 3 months ≥ 10 mg/day for ≥ 4 weeks: high risk; use prophylaxis ≤ 10 mg/day for ≥ 4 weeks: moderate risk; use prophylaxis	Intermediate risk *For intra-articular steroids in any dose* ≤ 1 week: low risk; no prophylaxis; monitor HBsAg, HBV DNA, and ALT every 3 months ≥ 10 mg/day for ≥ 4 weeks: moderate risk; use prophylaxis
Other immunosuppressive agents	Azathioprine, 6-mercaptopurine, methotrexate	Used for a variety of conditions: transplant anti-rejection medication, multiple sclerosis, IBD, RA	Azathioprine works as a purine metabolism antagonist, resulting in inhibition of DNA and RNA synthesis. 6-mercaptopurine works as a phosphoribosyl pyrophosphate amidotransferase inhibitor, inhibiting the synthesis of DNA and RNA [9] Methotrexate inhibits dihydrofolate reductase, which ultimately results in purine and thymidylate deficiencies and consequently, reduction in DNA synthesis [21]	Low risk; no prophylaxis needed. Monitor HBV DNA and ALT every 3 months	Low risk; no prophylaxis needed Monitor HBsAg, HBV DNA, and ALT every 3 months

CTLA-4, cytotoxic T-lymphocyte-associated protein 4; *HCC*, hepatocellular carcinoma; *IBD*, inflammatory bowel disease; *N/A*, not applicable; *NSCLC*, non-small cell lung cancer; *PD-1*, programmed cell death protein 1; *PD-L1*, programmed death-ligand 1; *RA*, rheumatoid arthritis

Agents Targeting T-Cell Activation

In a study evaluating the safety profile of secukinumab for psoriasis, it was observed that 15.2% (7/46) of HBV-positive patients experienced HBVr during secukinumab therapy without antiviral prophylaxis. The risk of reactivation was significantly higher in patients who were HBsAg-positive compared to those who were HBsAg-negative/anti-HBc-positive (24.0% vs. 4.17%, $P = 0.047$) [27].

CAR-T-Cell Therapy

Researchers investigated the safety and effectiveness of chimeric antigen receptor (CAR)-T-cell therapy targeting B-cell maturation agent (BCMA) in 9 patients with refractory/relapsed multiple myeloma and chronic or resolved HBV [28]. During a follow-up period of 9.8 months after CAR-T therapy, 1 patient with HBsAg-positive status showed no HBVr when given anti-HBV medications prophylactically. Among 8 patients with resolved HBV infection, 2 who received prophylactic anti-HBV drugs also did not experience HBVr. Of the 6 patients who did not use prophylactic antiviral drugs, 5 showed no HBVr, while 1 had a recurrence of HBsAg without detectable HBV DNA or liver function damage. The results revealed that CAR-T-cell therapy demonstrated an overall favorable safety profile in these patients despite chronic HBV infection [28].

However, a case reported in China described severe early HBVr resulting in mortality following CAR-T therapy [29]. The patient was HBsAg- and anti-HBc-positive, with undetectable serum HBV DNA levels, and was treated with anti-CD19 and anti-CD22 CAR-T-cell immunotherapy for refractory/relapsed DLBCL [29]. Another post hoc analysis studied HBVr in patients with resolved HBV infection who received anti-CD19 CAR-T-cell therapy without antiviral prophylaxis. Among 30 patients, 2 experienced HBVr, indicating an incidence of 6.67% [30]. In patients with chronic HBV infection, the risk of HBVr with CD19 CAR-T-cell therapy is higher, especially in those who are HBeAg-positive [31].

Immune Checkpoint Inhibitors for Solid Tumors

A study analyzing the use of checkpoint inhibitors (ICIs) for patients with non-small cell lung cancer (NSCLC) investigated 32 HBV-infected patients undergoing anti-PD-1 treatment, of whom 6 experienced hepatitis, but the difference compared to non-HBV patients was not statistically significant (18.8% vs. 8.91%) [32]. Among the 16 patients with chronic HBV, 3 experienced viral reactivations or flares during anti-PD-1 treatment. One patient's HBV DNA seroconverted from undetectable to 1484 IU/mL after starting pembrolizumab but returned to undetectable levels after entecavir treatment. Another patient's HBV DNA level increased after nivolumab treatment despite taking tenofovir prior. A third patient's HBV DNA level increased after pembrolizumab treatment but later dropped while continuing pembrolizumab and entecavir treatment.

Another study on patients with unresectable hepatocellular carcinoma (HCC) receiving nivolumab or pembrolizumab and simultaneous treatment with NAs noted that no HBVr occurred in the 35 patients with HBV DNA < 100 IU/mL [33]. However, the study did not mention the HBV status of these patients.

PD-1 inhibitors have gained recent popularity in treating solid tumors. A more recent study identified 990 patients (HBsAg-positive, 397; HBsAg-negative, 593) in Hong Kong receiving one of the following: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies (ipilimumab and tremelimumab), programmed cell death protein 1 (PD-1) antibodies (nivolumab, pembrolizumab, and spartalizumab), or programmed death-ligand 1 (PD-L1) inhibitors (atezolizumab, avelumab, and durvalumab). All HBsAg-positive patients received antiviral therapy. HBVr, defined by a 2-log increase in HBV DNA from baseline, occurred in only 2 HBsAg-positive patients and none of the HBsAg-negative patients. Only 1 patient who was HBsAg-negative had seroconversion following nivolumab for 72 days [34, 35].

A recent retrospective study noted that of 114 patients treated with anti-PD-1/anti-PD-L1 agents, 6 with chronic HBV with undetectable viral loads prior to treatment underwent HBVr. They were treated with camrelizumab, nivolumab, pembrolizumab, and toripalimab [37]. A larger retrospective study with 3465 patients had an even lower reactivation rate of only 1% of HBsAg-positive (5/511) patients previously treated with antiviral therapy with 2 HBsAg-positive patients even experiencing HBsAg seroclearance after ICI treatment [36•]. Among the patients with reactivation, the mean age was 61.8. Two patients were treated with nivolumab, 2 with pembrolizumab, and 1 with a combination of nivolumab and ipilimumab.

Multiple professional societies in the USA and Europe have recommended HBV prophylaxis for patients with chronic HBV infection, as this approach has proven to be effective in preventing HBVr after ICIs.

Tyrosine Kinase Inhibitors

Two separate case reports identified a case of HBVr that occurred during ibrutinib treatment despite negative HBsAg. In both patients, increased serum HBV DNA levels were controlled with entecavir, but it took over a year to achieve undetectable levels [37, 38]. In a study of 48 patients with chronic lymphocytic leukemia treated with acalabrutinib, 1 with past HBV infection experienced HBVr, leading to

an HBV-related death despite receiving entecavir treatment after reactivation [39].

Epidermal growth factor receptor (EGFR) TKIs, such as gefitinib, erlotinib, osimertinib, and afatinib, are now first-line therapies for NSCLC [18]. A study found that patients with NSCLC receiving EGFR TKI treatment had a clinically meaningful risk of HBVr during treatment, with an incidence of 9.36% [19].

Transcatheter Arterial Chemoembolization for HCC

In a recent retrospective analysis of 108 patients with HCC and HBV infection who underwent transcatheter arterial chemoembolization (TACE), 42 patients (38.9%) experienced HBVr [40]. Notably, individuals with a detected HBV DNA level ≥ 10^4 exhibited a significantly higher reactivation rate of 65.8% (25/38), compared to cases where HBV DNA level was < 10^4, resulting in a reactivation rate of 24.3% (17/70). A different multicenter clinical trial sought to study whether HBVr rates were lower in those who underwent antiviral therapy prior to starting radiotherapy for HCC [41]. The study found that patients in the antiviral group had lower rates of HBVr than those in the non-antiviral group (7.5% vs. 33.3%, $P < 0.001$) [41]. A meta-analysis of 11 studies also aimed to evaluate the impact of TACE and preventive antiviral therapy on HBVr risk. The analysis echoed similar findings that while TACE increased the risk of HBVr and hepatitis in patients with HCC, preventive antiviral therapy reduced the HBVr rate significantly (odds ratio [OR], 0.08; 95% CI, 0.02–0.32; $P < 0.01$) [42].

Furthermore, there have been reports indicating a higher occurrence of HBVr in patients with HCC receiving combined therapy of TKIs like lenvatinib or sorafenib along with PD-1 inhibitors such as sintilimab or camrelizumab, compared to those undergoing TKIs monotherapy [43•]. Consequently, the combination of TACE with TKIs and ICIs could also lead to higher HBVr rates, as seen in a single-center retrospective study involving 119 patients with HBV-related advanced unresectable HCC who underwent this triple-therapy approach [44].

Stem Cell Transplant

HBVr is commonly reported in patients after hematopoietic stem cell transplant (HSCT), with a reported incidence of 11% [45]. A prospective trial investigated the effectiveness of the HBV vaccine in preventing HBVr after HSCT. Among 50 patients with resolved HBV infections, 6 experienced reactivation following vaccination, resulting in a 2-year cumulative incidence of 22.2% [45].

Another study aimed to determine whether quantification of anti-HBs and anti-HBc could predict the risk of HBVr in 533 patients with leukemia undergoing immunosuppression. They found that high anti-HBs or low anti-HBc levels at baseline were associated with a lower risk of HBVr. Anti-HBe status did not affect HBVr incidence, but the predictive ability of baseline antibodies was significant only in patients with negative anti-HBe [46].

Tumor Necrosis Factor-Alpha Inhibitors

The reactivation rate was lower in a large, single-center retrospective cohort study of 120 HBsAg-negative, anti-HBc-positive patients receiving anti-TNF therapy. One patient (0.8%) with a detectable HBV viral load (< 20) before starting treatment experienced reactivation with seroconversion, while 3 patients (2.5%) developed detectable viral load during anti-TNF therapy despite having undetectable levels initially [47]. In a recent study in Turkey, 266 patients with resolved or past HBV infections receiving immunosuppressive drug therapy and 246 patients receiving antineoplastic therapy were followed over 24 months. All participants had undetectable HBV DNA levels at baseline, and resolved infections were defined as HBsAg-negative/anti-HBc-positive/anti-HBs-positive, while past infections were defined as isolated anti-HBc-positive. No cases of HBVr were detected among patients receiving rituximab, TNF inhibitors, or high-dose glucocorticoids for 4 weeks, even in those with isolated anti-HBc positivity [48].

Janus Kinase Inhibitors

A recent prospective study analyzed a cohort of patients with myeloproliferative neoplasms and occult HBV infection (HBsAg-negative/anti-HBc +) treated with ruxolitinib [49]. HBVr occurred in approximately 26.7% (4/15) of patients.

Guidelines for Monitoring Hepatitis B Reactivation

Guidelines for preventing HBVr in patients receiving immunosuppression should emphasize vigilant screening for HBV before initiating immunosuppression, risk stratification based on HBV serology and the type of immunosuppression being contemplated, as well as the duration of therapy and the implementation of suitable prophylaxis and/or monitoring for HBVr. These principles are reflected by most major societies [9, 50, 51, 52•].

The AASLD recommends monitoring of HBV DNA, HBsAg, and ALT levels every 1–3 months in patients with chronic and resolved HBV receiving prophylaxis or on-demand therapy and up to 12 months after withdrawing NA therapy. APASL recommends monitoring ALT and HBV DNA every 1–3 months with undetectable HBV DNA when patients are receiving on-demand therapy for resolved HBV.

Finally, EASL recommends monitoring HBsAg and/or HBV DNA every 1–3 months in moderate or low risk resolved HBV and on-demand therapy to treat if DNA is positive or there is evidence of reverse seroconversion. Subject to more recent updates to these guidelines, the authors suggest 2–3 years of monitoring after discontinuing any immunosuppressants or immunomodulator therapy.

The American Society of Clinical Oncology made a clinical opinion update in 2010 recommending that those with previous or current HBV infection undergoing cancer treatment with a high-risk treatment group should continue prophylactic treatment for a minimum of 12 months following the conclusion of cancer therapy treatment [53]. These patients should also be referred to hepatology or gastroenterology for close monitoring if NAs are discontinued. HBV DNA should be followed every 6 months for these individuals for a minimum of 2 years or HBV DNA quantitative should be assessed with any change in liver enzymes. In addition, the NCCN Guidelines recommend that centers not conducting routine risk-based screening should adopt universal screening using HBsAg and anti-HBc [54]. It is imperative to screen patients considering undergoing immunosuppressive therapy using the triple panel, as appropriate serology stratifies the risk for HBVr. Those who are found to have HBsAg-positive and/or HBV DNA-positive should be started on the appropriate prophylaxis as proper management based on this stratification, to decrease morbidity and mortality [55].

Management of Hepatitis B Reactivation

Antiviral prophylaxis has been heavily studied to manage and prevent HBVr in patients receiving immunosuppressants. Several studies have demonstrated the effectiveness of NA therapy in preventing HBVr. Among NA therapies, several recent meta-analyses and randomized controlled trials have demonstrated the superiority of third-generation NAs ETV and TDF/TAF in the prophylaxis of HBVr compared to LAM [16, 56–59]. The decreased efficacy of LAM has been attributed to increased resistance to LAM, as well as concern for withdrawal flares upon its cessation [60].

Due to these studies, the most updated guidelines from several studies recommend ETV and TDF/TAF as the preferred antivirals of choice. However, do not overlook the ample evidence supporting the efficacy of LAM [61–64]. Antiviral cost and availability should be considered when prophylaxis is indicated [4•]. The expected duration of prophylaxis should also factor into the decision of which NA to use, as LAM resistance has been demonstrated to increase exponentially over time [65]. Although there is no consensus on how long NAs should be administered, the determination of prophylaxis duration will typically require consideration of whether the patient has chronic or resolved HBV infection based on serology, as well as the type and intensity of immunosuppression being considered or used in the past [11••].

Hepatitis B Reactivation Management Guidelines in Special Populations

Liver Transplant Recipients

CHB is the leading cause of HCC worldwide, with > 50% of patients with HCC being HBsAg-positive or anti-HBc-positive [66]. Following liver transplantation, reactivation rates of HBV were high prior to the use of hepatitis B immune globulin (HBIG) with NAs, which presented a clinical challenge for many countries, providers, and patients. Historically, HBVr after liver transplantation resulted in poor survival rates.

During liver transplantation, it is crucial to assess the HBV status of both the donor and the recipient [67]. In liver transplantations involving recipients and/or donors who test positive for anti-HBc, providing lifelong HBV prophylaxis to recipients in conjunction with their immunosuppression is recommended. However, HBIG administration is not recommended due to our current NA therapies' high efficacy and extremely low resistance rates. For recipients exhibiting negative results for all 3 HBV seromarkers, HBV vaccination is strongly advised before liver transplantation.

TAF and ETV stand as the preferred HBV prophylactic agents, and their administration is recommended for patients at the time of transplantation. This proactive approach helps to mitigate potential HBV-related complications and ensures a more favorable post-transplantation outcome. TDF is not preferred due to the risk of renal toxicity, particularly in transplant recipients who frequently experience renal impairment and are on calcineurin inhibitors [67].

HIV Patients

HBV co-infection is present in about 7% of HIV-positive patients, making up a significant portion of the HBV population [68]. HBVr can occur as a major complication with co-infected patients. Reactivation can occur in patients with untreated HIV as a result of the immune system's decline but may also occur in those who have sudden withdrawal of HIV antiretroviral treatment (ART) that contains anti-HBV agents as well. It is also suggested that a longer duration after agent withdrawal with medicines such as TDF and TAF resulted in a higher level of HBV DNA compared to baseline [68], reflecting the higher rate of replication that can occur with medication cessation. If managed incorrectly, this subset of patients may have a worse prognosis compared to those with only HBV infection, including a more rapid progression to cirrhosis, HCC development, and mortality related to hepatic compromise [68].

Immune reconstitution syndrome, a well-recognized syndrome that typically occurs after the initiation of ART, is another way HBVr can present. It is estimated that 20–25% of HIV-HBV co-infection cases can have HBVr because of ART initiation [69]. To prevent reactivation, it is recommended that antiretroviral and HBV therapies be concurrently administered [69]. In addition, if changing ART in patients due to treatment failure, adverse effects, comorbidities, or a desire for pregnancy, providers should ensure that drugs containing anti-HBV activity are part of the new regimen [70]. New forms of HIV treatment include injection therapy every 1–3 months. However, these regimens do not contain TDF/TAF or ETV, and fatal reactivation of HBV has occurred when stopping tenofovir-based therapies as part of the switch.

Hepatitis C Virus Patients

The worldwide prevalence of HBV-HCV co-infection is 5–10% of HBV-infected individuals [71]. Patients with HBV-HCV co-infections have also been identified as having a higher risk of HBVr. Direct-acting antivirals (DAAs) used to treat HCV have been shown to be a potential cause of HBVr, especially in those who are HBsAg-positive. This is because DAAs have been noted to elevate both HBV DNA levels in HBsAg-positive patients and ALT levels with reactivation. Most of these events have been reported to occur between 4 and 12 weeks after DAA treatment initiation. Given this HBVr risk, HBV DNA level monitoring is recommended every 4 to 8 weeks during HCV treatment and repeated 3 months after treatment [51].

The induction of DAAs can result in devastating complications, including fulminant liver failure and even death, although the latter is much less common [71]. The risk of HBVr tends to be higher in those with HBsAg positivity [7]. Although the risk of HBVr is low in HBV-HCV co-infected patients, the potential for devastating complications does suggest that all HCV-infected patients should be screened for HBV prior to induction of DAAs. Nonetheless, HBV antiviral therapy is still recommended to be started along with DAA therapy, with ETV, TAF, and TDF being the antivirals of choice [51].

Patients who are HBsAg-negative and anti-HBc-positive with HCV infection, however, are typically at a low risk of reactivation with DAA therapy. However, some authors and guidelines still recommended that ALT levels be monitored during treatment, at the end of treatment, and during follow-up. If ALT levels are seen to increase or fail to become normal during or after DAA therapy, HBV DNA load and HBsAg should be tested [51]. Importantly, new minimal monitoring regimens, tests for HCV, and treatment without follow-up tests have not led to any new cases of HBV reactivation that have been reported or published.

Informed Consent

It is strongly recommended to obtain informed consent prior to the commencement of immunosuppressive drugs as these carry serious side effects [72]. Patients should be made aware of the seriousness of the side effects, such as tuberculosis and reactivation of underlying hepatitis, in a simple and easy-to-understand manner. The reliance on forms is outdated; societies encourage an open discussion between physicians and their patients to allow enough time for the patient to formulate questions and clear up misunderstandings.

Conclusions

The indications of immunosuppressive therapies encompass a diverse range of conditions, ranging from autoimmune disorders like systemic lupus erythematosus to solid and hematologic malignancies, inflammatory bowel disease (IBD), post-transplant scenarios, dermatologic conditions like eczema, and neurological disorders including multiple sclerosis [11••]. The substantial prevalence of these treated conditions, along with the extensive use of immunosuppressive drugs and the potential coexistence of CHB, collectively heighten the risk of HBVr. This risk is further increased when antiviral regimens for HBV are suddenly discontinued or in patients undergoing DAA treatment for HCV.

Although current HBV therapies can suppress the virus, complete eradication remains elusive, necessitating lifelong monitoring [66]. Effective and timely management of HBV is crucial to avoid complications. Typically, treatment begins with potent agents like TDF/TAF or ETV [10]. For patients who have undergone prior LAM treatment, initiating TDF/TAF is recommended due to observed instances of high resistance. The future direction of HBV treatment aims to target specific stages of the HBV replication cycle. Several clinical trials aimed at targeting the lifecycle of HBV replication, cccDNA formation, and HBV integration are currently underway.

With the emergence of new anticancer and immunosuppressant therapies, it is vital for clinicians to understand the reactivation risk in patients with HBV. Healthcare providers can integrate universal HBV screening for immunocompromised patients by incorporating clinical algorithms into routine practices. Robust screening can be achieved by engaging providers, streamlining testing protocols, and facilitating electronic health record integration to ensure effective linkage to care [53]. Ensuring help from clinicians for screening and implementing appropriate antiviral prophylaxis is essential to prevent HBVr. Furthermore, no established markers or validated tests predict the risk of HBVr associated with specific medication. Therefore, future studies and periodic updates to recommendations on preventing HBVr are of critical importance.

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Declarations

Competing interests The authors declare no competing interests.

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- • Of importance
- •• Of major importance

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