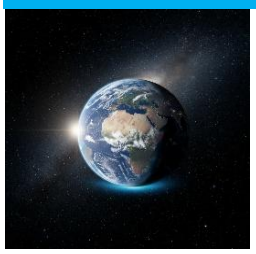
NICOLAUS COPERNICUS UNIVERSITY IN TORUŃ



Journal of Education, Health and Sport. eISSN 2391-8306.

Journal Home Page
https://apcz.umk.pl/JEHS/index

ALEKSANDROWICZ, Hanna, KALINOWSKA, Zuzanna, SOKOŁOWSKA, Julia, DAWIDOWICZ, Marcel, KUCHARSKI, Kacper, SZAFRANIEC, Artur and RYBIŃSKA, Marcelina. HBV reactivation after immunosuppressive therapy and allogeneic HSCT – a silent threat in patients with chronic hepatitis B: a literature review. Journal of Education, Health and Sport. 2026;88:69714. eISSN 2391-8306. https://doi.org/10.12775/JEHS.2026.88.69714

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 11.03.2026. Revised: 16.03.2026. Accepted: 17.03.2026. Published: 21.03.2026.

HBV reactivation after immunosuppressive therapy and allogeneic HSCT – a silent threat in patients with chronic hepatitis B: a literature review

Hanna Aleksandrowicz [1] ORCID: https://orcid.org/0009-0006-3686-3942

E-mail: hania.aleks24@gmail.com

[1] Lower Silesian Centre for Oncology, Pulmonology and Haematology

plac Hirszfelda 12, 53-413 Wrocław

Zuzanna Kalinowska[1] ORCID: https://orcid.org/0009-0005-3940-3987

E-mail: zsujankalinowska@gmail.com

[1] Lower Silesian Centre for Oncology, Pulmonology and Haematology

plac Hirszfelda 12, 53-413 Wrocław

Julia Sokołowska[1] ORCID: https://orcid.org/0000-0002-7042-0348
E-mail: jsokoo008@gmail.com
[1] Lower Silesian Centre for Oncology, Pulmonology and Haematology
plac Hirszfelda 12, 53-413 Wrocław

Marcel Dawidowicz[1] ORCID: https://orcid.org/0009-0000-5297-3507
E-mail: mardawidowicz@int.pl
[1]Lower Silesian Centre for Oncology, Pulmonology and Haematology
plac Hirszfelda 12, 53-413 Wrocław

Kacper Kucharski [2] ORCID: https://orcid.org/0009-0004-5709-8974
E-mail: kacper.kucharski1129@gmail.com
[2] Jan Mikulicz-Radecki University Clinical Hospital,
Borowska 213, 50-556 Wrocław

Artur Szafraniec [1] ORCID: https://orcid.org/0000-0002-9991-2039
E-mail: aszafraniec15@gmail.com
[1]Lower Silesian Centre for Oncology, Pulmonology and Haematology
plac Hirszfelda 12, 53-413 Wrocław

Marcelina Rybińska [3] ORCID: https://orcid.org/0009-0000-1580-8705
E-mail: marcelina.rybinska@gmail.com
[3] 4. Military Clinical Hospital and Polyclinic IPHC
Rudolfa Weigla 5, 53-114 Wrocław

Corresponding author:
Hanna Aleksandrowicz
694731213
hania.aleks24@gmail.com
ul. Słonimskiego 11/3
50-304 Wrocław

Abstract

Chronic hepatitis B is a disease caused by infection with the hepatitis B virus (HBV), whose genetic material may exist either in an integrated form within the hepatocyte genome or as episomal covalently closed circular DNA (cccDNA). The persistence of cccDNA in host cells prevents complete viral eradication, even with effective antiviral therapy. In patients with undetectable surface antigen (HBsAg) and absent HBV DNA replication, infection may remain in an occult phase (OBI – *occult HBV infection*). However, during states of immunosuppression—such as oncologic or hematologic treatment and allogeneic hematopoietic stem cell transplantation (allo-HSCT)—there is a significant risk of viral reactivation, which may result in severe liver injury and worsen clinical outcomes. The aim of this review is to summarize current data on the mechanisms of HBV reactivation, risk factors, preventive strategies, and monitoring approaches in patients after immunosuppressive therapy or allo-HSCT. Particular emphasis is placed on the need for individualized therapeutic management and regular monitoring of liver function markers, as the clinical presentation does not always reflect the true extent of liver injury. Understanding the pathomechanisms of HBV reactivation and implementing appropriate preventive strategies remain crucial for improving the safety and efficacy of treatment in patients undergoing allo-HSCT.

Objective

The aim of this review was to summarize current knowledge on HBV reactivation after immunosuppressive therapy and allogeneic hematopoietic stem cell transplantation and to discuss its clinical significance, risk factors, and preventive strategies, highlighting key aspects of diagnosis and management.

Materials and methods

This article presents a comprehensive narrative review of the current scientific literature on hepatitis B virus (HBV) reactivation following allogeneic hematopoietic stem cell transplantation (allo-HSCT) or immunosuppressive therapy in general. The review focuses on the mechanisms, clinical implications, risk factors, and preventive strategies associated with HBV reactivation in this patient population. Relevant publications were identified through systematic searches conducted in the PubMed, Google Scholar, and Web of Science databases. Additionally, the reference lists of selected articles were reviewed to identify additional studies not captured in the primary search. The search strategy included the following key terms and

their combinations: “HBV reactivation,” “hepatitis B virus,” “chronic hepatitis B,” “allogeneic hematopoietic stem cell transplantation,” “HBV reactivation after allo-HSCT”, “immunosuppression,” “antiviral prophylaxis,” and “occult HBV infection.” Inclusion criteria comprised: original research articles, clinical studies, case reports, systematic or narrative reviews, and clinical guidelines, studies describing clinical outcomes, risk factors, mechanisms, or preventive approaches related to HBV reactivation in the context of immunosuppressive therapy and allo-HSCT; publications available in English or Polish and accessible in full text. Exclusion criteria included: articles not directly related to HBV infection or its reactivation after allo-HSCT; papers lacking clinical or mechanistic data; duplicated reports; and conference abstracts without peer-reviewed full-text versions. The search and selection process was conducted in January 2026. All identified studies were critically analyzed and synthesized to provide an updated overview of current knowledge and clinical recommendations concerning HBV reactivation.

Keywords

Hepatitis B virus; HBV reactivation; allogeneic hematopoietic stem cell transplantation; allo-HSCT; chronic hepatitis B; immunosuppression; antiviral prophylaxis; reactivation risk factors.

Introduction

Reactivation of hepatitis B virus (HBV) infection is a rapid increase in viral replication in individuals with chronic infection (HBsAg-positive) or in patients with a history of infection (HBsAg-negative, anti-HBc-positive), which can lead to severe hepatitis, organ decompensation and death (Koffas and Gill, 2023; Shi and Zheng, 2020). By definition, this condition is a sudden, at least 100-fold increase in HBV DNA concentration in individuals with pre-existing viraemia or the detection of HBV DNA or HBsAg in a patient who was previously negative for these parameters (Pawłowska et al., 2019). A key element in the pathogenesis of HBV reactivation is the persistent presence of covalently closed circular DNA (cccDNA) in hepatocyte nuclei. This form constitutes a stable transcriptional template that persists in the host organism even after the clinical elimination of surface antigen (HBsAg) from the blood serum (Koffas and Gill, 2023; Maya et al., 2007). In a state of immunological homeostasis, viral replication is inhibited by a specific cellular and humoral response. The introduction of immunosuppressive factors leads to a breakdown in immunological control, resulting in a rapid increase in HBV DNA titres and increased expression of viral antigens. As viremia increases, hepatocytes are damaged (ALT and AST levels rise), which can cause liver dysfunction

manifested, for example, by hyperbilirubinemia, coagulopathy or hypoalbuminaemia. This phase may progress to fulminant hepatitis (less common, can be fatal) or end with suppression of the inflammatory process through fibrosis, which promotes the development of cirrhosis and increases the risk of developing hepatocellular carcinoma (HCC) (Shi and Zheng, 2020). Liver cell damage often occurs during the immune reconstitution phase, when the reviving immune system recognises and attacks infected hepatocytes, triggering an inflammatory cascade (Choi et al., 2019).

In this paper, we present a review of the available literature describing the scale of the problem, risk factors and cases of HBV reactivation (HBVr) in patients undergoing immunosuppressive treatment, including those who have undergone allogeneic haematopoietic stem cell transplantation (allo-HSCT). In addition, we attempt to answer the question of whether and how these conditions can be prevented.

Discussion

Risk Factors

The risk of reactivation is determined by the characteristics of the virus, the physiological condition of the host and the immunosuppressive strength of the treatment used. The most important factor determining the risk of reactivation is the patient's initial serological status – HBsAg-positive individuals (carriers) are 5 to 8 times more likely to experience reactivation than individuals with latent infection (HBsAg-negative/anti-HBc-positive) (Vutien and Nguyen, 2025). An example of such a high viral predisposition is also a high baseline HBV DNA titre (> 2000 IU/ml) and the presence of HBeAg, which indicates intense replication before the start of treatment (Elharabi et al., 2025). The risk is also higher in men, who experience almost three times more reactivations. Exposure also increases in older people (over 65 years of age), which may be due to weakened immune surveillance associated with the ageing process (Mak et al., 2023). Liver condition is also an important factor – patients with cirrhosis or advanced fibrosis not only experience reactivation more often, but also suffer from more severe hepatitis (Flisiak et al., 2018). Patients with haematological malignancies, such as non-Hodgkin's lymphoma (NHL), acute lymphoblastic leukaemia (ALL) or multiple myeloma, have a significantly higher reactivation rate than those with solid tumours (Mak et al., 2023). This is due to profound impairment of humoral and cellular immunity, which under normal conditions controls the latency of HBV. During immunosuppressive treatment, the highest risk is posed by therapies targeting B lymphocytes, i.e.:

• Anti-CD20 antibodies (e.g., rituximab, obinutuzumab). These cause profound B-cell depletion, which removes control over the virus's cccDNA and can lead to reactivation even a year after the end of therapy (Vutien and Nguyen, 2025; Yeo et al., 2008).

• CAR-T cell therapies. Modern treatments using programmed T lymphocytes lead to long-term B lymphocyte aplasia, which creates a risk of very late reactivation (Gentile and Antonelli, 2019).

• Anthracyclines (e.g., doxorubicin). These drugs can directly stimulate viral replication by affecting viral promoters (p21 pathway) (Pawłowska et al., 2019; Mak et al., 2023).

• Glucocorticosteroids: The use of doses above 20 mg of prednisone per day for more than 4 weeks classifies the patient as high risk, as steroids directly stimulate HBV gene expression through specific steroid response elements in the viral genome (Pawłowska et al., 2019; Vutien and Nguyen, 2025).

Anti-cancer therapies with drugs such as tyrosine kinase inhibitors (TKIs), checkpoint inhibitors (ICIs) and proteasome inhibitors also carry risks (Elharabi et al., 2025; Doyle et al., 2019).

Analysis of current epidemiological data and the results of multicentre clinical trials indicates that the scale of HBV reactivation is closely correlated with the patient's serological profile and the aggressiveness of the therapeutic protocol used. In HBsAg-positive patients (carriers) undergoing standard anticancer chemotherapy without antiviral protection, the frequency of reactivation is estimated at 20–50%, with peak replication usually occurring shortly after the withdrawal of cytostatics (Pawłowska et al., 2019). In extremely high-risk groups, such as patients with lymphomas or those undergoing transplantation procedures, these rates are even more alarming. Without pharmacological prophylaxis, reactivation is reported in 45–81% of carriers with lymphoma, and in the case of allogeneic stem cell transplantation (allo-HSCT), the frequency ranges from 14% to 78%. An extremely high risk, ranging from 50% to 94%, also applies to kidney transplant recipients who are HBV carriers, which drastically reduces the patient's chances of survival without appropriate treatment (Shi and Zheng, 2020; Liu et al., 2022; Scott and Chan, 2017).

In the population of patients with past or latent infection (HBsAg-negative, anti-HBc-positive), the overall risk of reactivation is lower, typically ranging from 0.3% to 10% (Pawłowska et al., 2019; Shi and Zheng, 2020). Statistics show a clear disproportion between haematological diseases, where the reactivation rate averages 10.9%, and non-haematological diseases, where the rate drops to 3.6%. The use of rituximab (anti-CD20) is particularly dangerous – in this group, the cumulative 2-year risk of replication recurrence in people with latent HBV reaches

as high as 41.5% (Papatheodoridis et al., 2022). In the course of allo-HSCT procedures in patients with a history of HBV infection, the frequency of reactivation varies widely from 2.6% to 42.9%, depending on the depth of immunosuppression and the presence of graft-versus-host disease (Viganò et al., 2010; Hammond et al., 2009). In rheumatology, on the other hand, in patients receiving anti-TNF treatment, the risk is relatively lower, ranging from 1.7% to 5% (Shi and Zheng, 2020).

The introduction of modern targeted and cell therapies increases the population of patients who should be monitored for HBV reactivation. In patients with DLBCL who are HBV carriers undergoing CAR-T cell therapy, reactivation is reported at a rate of 20%, despite the use of prophylaxis in some of them (Mak et al., 2023). In the treatment of multiple myeloma with anti-CD38 antibody (daratumumab), the risk in patients with a history of infection is approximately 6.5% (Pawłowska et al., 2019). Tyrosine kinase inhibitors (TKIs) used in leukaemia are also associated with a 26% reactivation rate in HBV carriers, while checkpoint inhibitors (ICIs) show a risk of between 0.5% and 5.3% (Agency for Health Technology Assessment and Tariff System [AOTMiT], 2019).

The clinical consequences of the lack of virological surveillance and reactivation prophylaxis are significant: nearly 40% of patients with reactivation develop clinically overt hepatitis, and the mortality rate in the event of organ failure in this population is reported to be between 30% and even 50% (Cui et al. , 2010; Garg et al., 2010). These statistics confirm that the implementation of prophylaxis based on potent nucleoside analogues (entecavir, tenofovir) is essential, as it reduces the above risks to below 2–6% (Su et al., 2018; Cheung et al., 2020).

Literature review

Analysis of documented clinical cases of HBV reactivation reveals an extremely diverse pathophysiological picture, in which the course of the phenomenon depends on the precise interaction between the biology of the haematological tumour and the mechanism of action of the immunotherapy used. The spectrum of clinical manifestations described in the literature ranges from asymptomatic virological incidents, detected only through rigorous monitoring of HBV DNA titres, to fulminant liver failure with a high mortality rate. Cases involving modern therapeutic protocols, such as CAR-T cell therapies or the use of monoclonal antibodies, as well as stem cell transplantation, which, due to the induction of profound and persistent B-cell aplasia, pose a risk of atypical or very late reactivation, occurring even more than a year after the end of oncological treatment. The following summary of case reports illustrates the critical diagnostic challenges faced by clinicians in the era of personalised medicine, taking into

account both standard replication recurrences and rarer phenomena such as reactivation despite acquired post-vaccination immunity.

The problem of reactivation of latent HBV infection was addressed in the literature more than 20 years ago. At that time, Knöll et al. described a series of cases of patients after allo-HSCT with current latent HBV infection. The study showed that 50% of patients (3 out of 6 studied) experienced so-called reverse seroconversion, i.e. the reappearance of HBsAg antigen in serum. This is a significantly higher rate than that reported in earlier studies (the authors report a range of 14–20%). Reactivation occurred on average between 12 and 22 months after transplantation. In most patients (2 out of 3), it proceeded without obvious clinical symptoms or liver damage, but these patients became chronic carriers of the virus with high viremia levels. Only one patient showed a moderate increase in liver enzymes (ALT), followed by spontaneous elimination of HBsAg. The authors emphasise that the use of sensitive HBV-DNA tests allows the detection of reactivation as early as 2 –4 months before the onset of serological changes, which justifies the need for rigorous genetic monitoring of all patients with a history of HBV infection, especially those undergoing intensive immunosuppression or struggling with chronic graft-versus-host disease (Knöll et al., 2004).

M. Yamamoto et al. describe the case of an 18-year-old patient diagnosed with acute lymphoblastic leukaemia (ALL) who, after chemotherapy and bone marrow transplantation, experienced reactivation of the infection despite having been vaccinated in childhood. During virus genotyping tests, it was determined that the patient had been infected during delivery by his sick mother. Despite this, the body managed to keep the HBV infection latent for the next 18 years – prior to allo-HSCT, the patient's serological status was negative (Yamamoto et al., 2019). This situation illustrates how profound immune suppression can be in haematological cancer patients. It has been repeatedly shown that chemotherapy can contribute to the disappearance of anti-Hbs antibodies, especially if they were present in low titres before the start of treatment (Choi et al., 2019). Such patients are particularly vulnerable to the development of overt infection.

Cases of reactivation have also been reported in patients with chronic myeloid leukaemia treated with tyrosine kinase inhibitors (e.g. imatinib). An article by Hailan et al. from 2021 describes the clinical case of a 46-year-old man diagnosed with chronic myeloid leukaemia (CML) in the chronic phase with a history of hepatitis B virus (HBV) infection. As part of first-line therapy, the patient was treated with imatinib, a tyrosine kinase inhibitor (TKI). Due to the growing number of reports of HBV reactivation (HBVr) in patients treated with TKIs, the doctors decided to include lamivudine prophylaxis, despite the lack of clear guidelines in

international recommendations for this group of drugs. After 6 months of therapy, the patient achieved an optimal response to CML treatment (a significant decrease in BCR-ABL1 levels from 84% to 3% IS). The combination therapy (imatinib and lamivudine) was well tolerated, with no adverse events or signs of HBV reactivation. The paper highlights the lack of clear guidelines on HBVr prophylaxis and monitoring in the context of TKI use, suggesting the need for routine screening before starting treatment. It is crucial to determine baseline liver function and monitor it regularly (in the case described, at 1, 3 and 6 months of treatment) (Hailan et al., 2021).

In addition, as advances are made in the treatment of haematological diseases, new treatment strategies are emerging. Although the risk of adverse events during such therapies is still being explored, there are reports of HBV reactivation in patients undergoing CAR-T therapy. Monoclonal antibodies used after allo-HSCT in the treatment of chronic graft-versus-host disease (GVHD), i.e. blinatumomab in the case of disease recurrence, as well as rituximab, ruxolitinib, and ibrutinib acting on B and/or T lymphocytes, may lead to virus reactivation, as confirmed by numerous case reports (Li et al., 2022; Wei et al., 2019; Yang et al., 2020).

Noteworthy is the case report by Li et al. (2022) of a 3-year-old girl with relapsed acute T-cell lymphoblastic leukaemia and concomitant HBV infection (baseline viraemia >10^8 IU/ml). The young patient underwent CAR-T (CD7) cell therapy as a bridge to allogeneic haematopoietic stem cell transplantation (HSCT). Thanks to intensive antiviral treatment (entecavir, tenofovir, HBIG immunoglobulins), liver function was maintained within normal limits and viraemia was reduced to undetectable levels, making this the first report on the safety of CAR-T in such a young child with HBV. The relationship between cancer therapy and the course of HBV is critical in this case, as the intensive treatment protocol (conditioning for transplantation and the action of CAR-T lymphocytes) led to a complete breakdown of immune surveillance of the virus, which, in the absence of pharmacological protection, would allow uncontrolled replication from the persistent form of cccDNA and the development of fulminant hepatitis (Li et al., 2022). This case emphasises that in the era of modern immunotherapies, even unusual treatment regimens for haematological malignancies require rigorous virological monitoring and often indefinite use of antiviral drugs in patients with HBV.

In contrast to the above success, there are also unsuccessful cases of reactivation of infection, as reported in an article by Wei J. et al. A 54-year-old female patient with diffuse large B-cell lymphoma (DLBCL) was described as having a resolved HBV infection – HBsAg-negative among with presence of anti-HBc and anti-HBs antibodies. As part of her cancer treatment, the patient received sequential infusions of anti-CD19 and anti-CD22 CAR-T cells. Despite long-

term, 26-month antiviral prophylaxis, the patient discontinued treatment on her own shortly after completing immunotherapy. After remission of the underlying disease, severe HBV reactivation occurred, manifesting as acute liver damage. Despite the reintroduction of antiviral treatment, liver failure progressed. Despite the addition of entecavir, the treatment proved ineffective. The patient died due to rapid deterioration of liver function and hepatic coma. This case highlights the importance of reactivation prophylaxis in patients with a history of HBV infection, both before and after immunosuppressive treatment (Wei et al., 2019).

Prophylaxis

In many countries around the world, including Poland, recommendations are in place regarding procedures to prevent HBV reactivation. Depending on the risk of this phenomenon occurring, strict monitoring of the patient's serological status and liver function is carried out, or antiviral prophylaxis is administered. It is therefore essential to identify infected patients before starting any anticancer therapy.

Comprehensive screening and risk-adjusted prophylaxis are key to preventing hepatitis B virus (HBV) reactivation in patients undergoing any immunosuppressive or anticancer therapy. All leading scientific societies, including AGA, APASL, AASLD, EASL and ASCO, recommend determining basic virological parameters before starting treatment (Cornberg et al., 2025; Lau et al., 2021; Hwang et al., 2020; Conners et al., 2023; Chou et al., 2020). The recommended test panel includes:

- HBsAg (surface antigen) – as an indicator of active infection.
- anti-HBc (antibodies against core antigen) – a key marker of past contact with the virus, indicating the presence of cccDNA in the liver.
- anti-HBs – a marker of immunity (post-vaccination or post-infection).
- HBV DNA (quantitative) – recommended for all HBsAg-positive and anti-HBc-positive individuals prior to high-risk therapies (Mak et al. 2023).

The anti-HBc test is particularly important because it enables the detection of patients with latent or healed infection in whom the virus persists in the liver in the form of cccDNA despite negative HBsAg (Raimondo et al., 2006, Yuen et al., 2008). In this case, patients may often be unaware of the presence of infection. If HBsAg or anti-HBc is positive, quantitative HBV DNA testing is necessary as a starting point for monitoring and evaluating the effectiveness of prophylaxis (Ali et al., 2025).

The choice of pharmacological prophylaxis strategy depends on the serological profile and planned treatment. In HBsAg-positive patients (regardless of HBV DNA level) who are at high risk of reactivation (up to 70% in lymphomas), mandatory antiviral prophylaxis is significantly

more effective than pre-emptive treatment, and the number of patients needed to treat to prevent one reactivation (NNT) is only three (Cornberg et al., 2025; AOTMiT, 2019; Hsu et al., 2008; Lau et al., 2003). In HBsAg-negative, anti-HBc-positive patients, the risk of reactivation depends on the therapy used; with high-risk drugs such as anti-CD20 antibodies or haematopoietic stem cell transplantation (HSCT), routine pharmacological prophylaxis is recommended, as the cumulative 2 -year risk of reactivation can reach 10–41.5%, while in moderate- or low-risk therapy, a pre-emptive treatment strategy is acceptable, consisting of monitoring ALT activity and HBV DNA levels every 1–3 months (Mak et al., 2023; Seto, 2015). Currently, prophylaxis is based on potent nucleoside or nucleotide analogues with a high genetic barrier to resistance, such as entecavir (ETV), tenofovir disoproxil (TDF) or tenofovir alafenamide (TAF); the use of lamivudine is no longer recommended due to the high risk of developing resistant strains. Studies have shown that ETV reduces the risk of reactivation to 6.6% compared to 30% for LMV (AOTMiT, 2019; Chou et al., 2020; Cornberg et al., 2025). Modern therapies, including CAR-T cell therapy, BTK inhibitors and checkpoint inhibitors, are associated with profound and prolonged immunosuppression, requiring prolonged prophylaxis or close monitoring of patients. Individuals undergoing allogeneic HSCT are an extreme risk group, with a reactivation rate without prophylaxis of 14–78% and mortality rates as high as 22%; prophylaxis should be started at least one week before conditioning, also taking into account the serological status of the donor (Mindikoglu et al., 2006; Gentile et al., 2017). The duration of prophylaxis should be individualised: in standard moderate-risk chemotherapy, drugs are used for 12 months after the end of treatment, while in high-risk therapy (anti-CD20, CAR-T, HSCT), prophylaxis is continued for 18–24 months, and in allo-HSCT recipients with chronic graft-versus-host disease, antiviral treatment may be continued indefinitely during immunosuppression or the presence of GVHD (Ali et al., 2025; AOTMiT, 2019; Pawłowska et al., 2019). Both before deciding to discontinue therapy and after discontinuing antiviral treatment, it is necessary to monitor ALAT and HBV DNA every 3 months for at least one year for early detection of late reactivation (Pawłowska et al., 2019).

In Poland, funding is available under the drug programme for two antiviral drugs that are nucleoside/nucleotide analogues (AN): entecavir and tenofovir for patients who have undergone organ/haematopoietic cell transplantation or who are eligible for biological treatment with a high/intermediate risk of reactivation or who are being treated for HCC. The drug is provided for the entire duration of therapy associated with the above-mentioned risk and additionally for 18 months after its completion, and if the relevant criteria are met, even without time limits (AOTMiT, 2019). On the other hand, patients with a previously established

diagnosis of HBV infection who are treated with AN should continue this therapy if it is effective (HBV DNA remains undetectable) (Pawłowska et al., 2019).

The implementation of systematic screening and prophylaxis based on modern analogues allows for the safe conduct of the most aggressive haematological therapies, minimising the risk of death from liver causes.

It should be remembered that despite following the recommendations, long-term treatment after allo-HSCT and good tolerance of the therapy, immunological destabilisation may occur, resulting in HBV reactivation and massive virus replication, leading to acute liver damage. This is consistent with meta-analyses documenting that the use of reactivation prophylaxis reduces the risk of its occurrence but does not eliminate it completely (Su et al., 2018; Cheung et al., 2020). The effectiveness of antiviral treatment depends on many factors related to the patient's health, underlying disease, treatment used, and serological status prior to the start of immunosuppression.

Summary

Reactivation of chronic, latent HBV infection is a significant problem in patients undergoing immunomodulatory therapies. Hematooncology patients, particularly those following allogeneic hematopoietic cell transplantation, are at significant risk, particularly due to the need for both chemotherapy and immunosuppressive medications. Despite recommendations for the prevention of HBV reactivation, the complexity of treatment in similar cases requires individualization of the therapeutic process, depending on the patient's clinical condition, comorbidities, and existing pharmacotherapy. Furthermore, the lack of correlation between the clinical presentation (patient well-being, abnormalities in physical examination) and the stage of disease progression, as reflected in laboratory tests, is worth emphasizing. In each case of reactivation of the infection, the primary goal should be to normalize liver enzyme activity as quickly as possible, which translates into minimizing the risk of liver damage, and then to achieve seroconversion in the "e" system (obtaining anti-HBe antibodies in HBeAg-positive patients) and a state in which viral DNA is no longer present in the blood, which means the infection has returned to a latent state. More importantly, reactivation of HBV infection should be prevented by identifying and then monitoring patients at risk.

Disclosure

Author's contribution: Conceptualization: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; methodology: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; software: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; validation: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; formal analysis: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; investigation: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.;

resources: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; data curation: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; writing—original draft preparation: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; writing—review and editing: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; visualization: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.; supervision: H.A., Z.K.; project administration: H.A., Z.K., J.S., M.D., K.K., A.S., M.R.

All authors have read and agreed to the published version of the manuscript.

Funding Statement: This Research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

Conflicts of Interests: The authors declare no conflict of interest.

Declaration of the Use of Generative AI and AI-Assisted Technologies in the Writing Process: During the preparation of this manuscript, the authors utilized Google's Gemini to improve the academic quality of the English language. The tool was employed to enhance clarity, coherence, consistency, and compliance with scientific writing conventions, as well as to refine grammar and stylistic elements in the presentation of the results. Following its use, the authors carefully reviewed and revised the text where necessary and assume full responsibility for the final content and its scientific integrity.

Bibliography

Agency for Health Technology Assessment and Tariff System (AOTMiT). Entecavir and tenofovir in the prophylaxis of hepatitis B virus (HBV) reactivation. Report No. OT.4320.16.2019. Warsaw, Poland; September 25, 2019. https://bip.aotm.gov.pl/assets/files/zlecenia_mz/2019/189/RPT/OT.4320.16.2019_ENT_TDF_reaktywacja_WZW_B_2019.09.25.pdf. Accessed January, 2026.

Ali, F. S., Nguyen, M. H., Hernaez, R., Huang, D. Q., Wilder, J., Piscoya, A., Simon, T. G., & Falck-Ytter, Y. (2025). AGA Clinical Practice Guideline on the Prevention and Treatment of Hepatitis B virus reactivation in At-Risk individuals. *Gastroenterology*, *168*(2), 267–284. https://doi.org/10.1053/j.gastro.2024.11.008

Cheung, C. K. M., Law, M. F., Chao, D. C., Wong, S. H., Ho, R., Chao, A. C. W., Lai, J. W. Y., Chan, T. Y. T., Tam, M. T. K., Lau, S. L. F., & Tam, T. H. C. (2020). Prevention of hepatitis B virus reactivation in patients with hematological malignancies and resolved hepatitis B virus infection: a systematic review and meta-analysis. *Journal of Digestive Diseases*, *21*(3), 160–169. https://doi.org/10.1111/1751-2980.12848

Choi, Y. B., Lee, N. H., Yi, E. S., Kim, Y., & Koo, H. H. (2019). Changes in hepatitis B antibody status after chemotherapy in children with acute lymphoblastic leukemia. *Pediatric Blood & Cancer*, *66*(12), e27904. https://doi.org/10.1002/pbc.27904

Chou, R., Blazina, I., Bougatsos, C., Holmes, R., Selph, S., Grusing, S., & Jou, J. (2020). Screening for hepatitis B virus infection in nonpregnant adolescents and adults. *JAMA*, *324*(23), 2423. https://doi.org/10.1001/jama.2020.19750

Conners, E. E., Panagiotakopoulos, L., Hofmeister, M. G., Spradling, P. R., Hagan, L. M., Harris, A. M., Rogers-Brown, J. S., Wester, C., Nelson, N. P., Contributors, Rapposelli, K., Sandul, A. L., Choi, E., Coffin, C., Marks, K., Thomas, D. L., & Wang, S. H. (2023). Screening and testing for hepatitis B virus infection: CDC Recommendations — United States, 2023. *MMWR Recommendations and Reports*, *72*(1), 1–25. https://doi.org/10.15585/mmwr.rr7201a1

Cornberg, M., Sandmann, L., Jaroszewicz, J., Kennedy, P., Lampertico, P., Lemoine, M., Lens, S., Testoni, B., Wong, G. L., & Russo, F. P. (2025). EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology*, *83*(2), 502–583. https://doi.org/10.1016/j.jhep.2025.03.018

Cui, Y., Yan, F., Wang, Y., Song, X., Liu, L., Lei, X., Zheng, M., Tang, H., & Feng, P. (2010). Nucleoside Analogue Can Improve the Long-Term Prognosis of Patients with Hepatitis B Virus Infection-Associated Acute on Chronic Liver Failure. *Digestive Diseases and Sciences*, *55*(8), 2373–2380. https://doi.org/10.1007/s10620-010-1257-7

Doyle, J., Raggatt, M., Slavin, M., McLachlan, S., Strasser, S. I., Sasadeusz, J. J., Howell, J., Hajkowicz, K., Nandurkar, H., Johnston, A., Bak, N., & Thompson, A. J. (2019). Hepatitis B management during immunosuppression for haematological and solid organ malignancies: an Australian consensus statement. *The Medical Journal of Australia*, *210*(10), 462–468. https://doi.org/10.5694/mja2.50160

Elharabi Z, Saba J, Akin H. Navigating the Latest Hepatitis B Virus Reactivation Guidelines. Diseases. 2025; 13(11):355. https://doi.org/10.3390/diseases13110355

Flisiak R, Halota W, Jaroszewicz J, i in. (2018). Zalecenia Polskiej Grupy Ekspertów HBV dotyczące leczenia przewlekłego wirusowego zapalenia wątroby typu B w 2018 roku. Medical Science Review-Hepatologia; https://doi.org/10.5114/hepatologia.2018.75975 (in Polish)

Garg, H., Sarin, S. K., Kumar, M., Garg, V., Sharma, B. C., & Kumar, A. (2010). Tenofovir Improves the Outcome in Patients with Spontaneous Reactivation of Hepatitis B Presenting as Acute-On-Chronic Liver Failure. *Hepatology*, *53*(3), 774–780. https://doi.org/10.1002/hep.24109

Gentile, G., Andreoni, M., Antonelli, G., & Sarmati, L. (2017). Screening, monitoring, prevention, prophylaxis and therapy for hepatitis B virus reactivation in patients with haematologic malignancies and patients who underwent haematologic stem cell transplantation: a systematic review. *Clinical Microbiology and Infection*, *23*(12), 916–923. https://doi.org/10.1016/j.cmi.2017.06.024

Gentile, G., & Antonelli, G. (2019). HBV reactivation in patients undergoing hematopoietic stem cell transplantation: A narrative review. *Viruses*, *11*(11), 1049. https://doi.org/10.3390/v11111049

Hailan, Y. M. A., Mudawi, D., & Yassin, M. A. (2021). Chronic Myeloid Leukemia in a Patient with Hepatitis B Virus Infection: A Case Report. *Case Reports in Oncology*, *14*(2), 1004–1009. https://doi.org/10.1159/000516747

Hammond, S. P., Borchelt, A. M., Ukomadu, C., Ho, V. T., Baden, L. R., & Marty, F. M. (2009). Hepatitis B Virus Reactivation following Allogeneic Hematopoietic Stem Cell Transplantation. *Biology of Blood and Marrow Transplantation*, *15*(9), 1049–1059. https://doi.org/10.1016/j.bbmt.2009.05.001

Hsu, C., Hsiung, C. A., Su, I., Hwang, W., Wang, M., Lin, S., Lin, T., Hsiao, H., Young, J., Chang, M., Liao, Y., Li, C., Wu, H., Tien, H., Chao, T., Liu, T., Cheng, A., & Chen, P. (2008). A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: A randomized trial. *Hepatology*, *47*(3), 844–853. https://doi.org/10.1002/hep.22106

Hwang, J. P., Feld, J. J., Hammond, S. P., Wang, S. H., Alston-Johnson, D. E., Cryer, D. R., Hershman, D. L., Loehrer, A. P., Sabichi, A. L., Symington, B. E., Terrault, N., Wong, M. L., Somerfield, M. R., & Artz, A. S. (2020). Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO Provisional Clinical Opinion update. *Journal of Clinical Oncology*, *38*(31), 3698–3715. https://doi.org/10.1200/jco.20.01757

Knöll, A., Boehm, S., Hahn, J., Holler, E., & Jilg, W. (2004). Reactivation of resolved hepatitis B virus infection after allogeneic haematopoietic stem cell transplantation. *Bone Marrow Transplantation*, *33*(9), 925–929. https://doi.org/10.1038/sj.bmt.1704457

Koffas, A., & Gill, U. S. (2023). Hepatitis B and D: an overview of the diagnosis and management. *Medicine*, *51*(5), 351–355. https://doi.org/10.1016/j.mpmed.2023.02.013

Lau, G. K., Yiu, H. H., Fong, D. Y., Cheng, H., Au, W., Lai, L. S., Cheung, M., Zhang, H., Lie, A., Ngan, R., & Liang, R. (2003). Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. *Gastroenterology*, *125*(6), 1742–1749. https://doi.org/10.1053/j.gastro.2003.09.026

Lau, G., Yu, M., Wong, G., Thompson, A., Ghazinian, H., Hou, J., Piratvisuth, T., Jia, J., Mizokami, M., Cheng, G., Chen, G., Liu, Z., Baatarkhuu, O., Cheng, A. L., Ng, W. L., Lau, P., Mok, T., Chang, J., Hamid, S., . . . Omata, M. (2021). APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatology International*, *15*(5), 1031–1048. https://doi.org/10.1007/s12072-021-10239-x

Li, Z., Meng, F., Li, J., & Wu, T. (2022). Donor-Derived CD7 CAR-T therapy followed by allogeneic hematopoietic stem cell transplantation for acute T-Lymphocytic leukemia associated with hepatitis B: a case report. *Frontiers in Immunology*, *13*, 931452. https://doi.org/10.3389/fimmu.2022.931452

Liu, J. K., Vutien, P., Huang, D. Q., Ishigami, M., Landis, C. S., Nguyen, M. H., Daniel, P. C. N., Ito, T., Dang, H., Maeda, M., & Leong, J. (2022). Renal outcomes with tenofovir alafenamide in liver transplant recipients. *Clinical Gastroenterology and Hepatology*, *21*(2), 538-540.e4. https://doi.org/10.1016/j.cgh.2022.01.035

Mak, J. W. Y., Law, A. W. H., Law, K. W. T., Ho, R., Cheung, C. K. M., & Law, M. F. (2023). Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies in the targeted therapy era. *World Journal of Gastroenterology*, *29*(33), 4942–4961. https://doi.org/10.3748/wjg.v29.i33.4942

Maya, R., Gershwin, M. E., & Shoenfeld, Y. (2007). Hepatitis B virus (HBV) and autoimmune disease. *Clinical Reviews in Allergy & Immunology*, *34*(1), 85–102. https://doi.org/10.1007/s12016-007-8013-6

Mindikoglu, A. L., Regev, A., & Schiff, E. R. (2006). Hepatitis B virus reactivation after cytotoxic chemotherapy: The disease and its prevention. *Clinical Gastroenterology and Hepatology*, *4*(9), 1076–1081. https://doi.org/10.1016/j.cgh.2006.05.027

Papatheodoridis, G. V., Lekakis, V., Voulgaris, T., Lampertico, P., Berg, T., Chan, H. L., Kao, J., Terrault, N., Lok, A. S., & Reddy, K. R. (2022). Hepatitis B virus reactivation associated with new classes of immunosuppressants and immunomodulators: A systematic review, meta-analysis, and expert opinion. Journal of Hepatology, 77(6), 1670–1689. https://doi.org/10.1016/j.jhep.2022.07.003

Pawłowska, M., Flisiak, R., Gil, L., Horban, A., Hus, I., Jaroszewicz, J., Lech-Marańda, E., & Styczyński, J. (2019). Profilaktyka reaktywacji zakażeń HBV – rekomendacje grupy roboczej profilaktyki reaktywacji HBV. *Acta Haematologica Polonica*, *50*(4), 192–198. https://doi.org/10.2478/ahp-2019-0031 (in Polish)

Raimondo, G., Pollicino, T., Cacciola, I., & Squadrito, G. (2006). Occult hepatitis B virus infection. *Journal of Hepatology*, *46*(1), 160–170. https://doi.org/10.1016/j.jhep.2006.10.007

Scott, L. J., & Chan, H. L. Y. (2017). Tenofovir alafenamide: A review in chronic hepatitis B. *Drugs*, *77*(9), 1017–1028. https://doi.org/10.1007/s40265-017-0754-9

Seto, W. (2015). Hepatitis B virus reactivation during immunosuppressive therapy: Appropriate risk stratification. *World Journal of Hepatology*, *7*(6), 825. https://doi.org/10.4254/wjh.v7.i6.825

Shi, Y., & Zheng, M. (2020). Hepatitis B virus persistence and reactivation. *BMJ*, *370*, m2200. https://doi.org/10.1136/bmj.m2200

Su, Y., Lin, P., Yu, H., & Wu, C. (2018). Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. *European Journal of Clinical Pharmacology*, *74*(9), 1111–1119. https://doi.org/10.1007/s00228-018-2487-4

Viganò, M., Vener, C., Lampertico, P., Annaloro, C., Pichoud, C., Zoulim, F., Facchetti, F., Poli, F., Scalamogna, M., Deliliers, G. L., & Colombo, M. (2010). Risk of hepatitis B surface antigen seroreversion after allogeneic hematopoietic SCT. *Bone Marrow Transplantation*, *46*(1), 125–131. https://doi.org/10.1038/bmt.2010.70

Vutien P, Nguyen MH. HBV Reactivation in Immunosuppressed Patients: Screening, Prevention, and Management Including Solid Organ Transplant Recipients. Viruses. 2025; 17(3):388. https://doi.org/10.3390/v17030388

Wei, J., Zhu, X., Mao, X., Huang, L., Meng, F., & Zhou, J. (2019). Severe early hepatitis B reactivation in a patient receiving anti-CD19 and anti-CD22 CAR T cells for the treatment of diffuse large B-cell lymphoma. *Journal for ImmunoTherapy of Cancer*, *7*(1), 315. https://doi.org/10.1186/s40425-019-0790-y

Yamamoto, M., Ikuta, K., Sawada, K., Shindo, M., Torimoto, Y., & Okumura, T. (2019). Hepatitis B virus (HBV) reactivation in an acute lymphoblastic leukemia patient despite being vaccinated against HBV in infancy. *Digestive and Liver Disease*, *51*(10), 1487–1488. https://doi.org/10.1016/j.dld.2019.07.003

Yang, C., Xie, M., Zhang, K., Liu, H., Liang, A., Young, K. H., & Qian, W. (2020). Risk of HBV reactivation post CD19-CAR-T cell therapy in DLBCL patients with concomitant chronic HBV infection. *Leukemia*, *34*(11), 3055–3059. https://doi.org/10.1038/s41375-020-0913-y

Yeo, W., Chan, T. C., Leung, N. W., Lam, W. Y., Mo, F. K., Chu, M. T., Chan, H. L., Hui, E. P., Lei, K. I., Mok, T. S., & Chan, P. K. (2008). Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab. *Journal of Clinical Oncology*, *27*(4), 605–611. https://doi.org/10.1200/jco.2008.18.0182

Yuen, M., Wong, D. K., Fung, J., Ip, P., But, D., Hung, I., Lau, K., Yuen, J. C., & Lai, C. (2008). HBSAG seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology*, *135*(4), 1192–1199. https://doi.org/10.1053/j.gastro.2008.07.008