**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 63502

**Manuscript Type:** MINIREVIEWS

**Prevention of hepatitis B reactivation in patients requiring chemotherapy and immunosuppressive therapy**

Shih CA *et al*. Prevention of hepatitis B reactivation

Chih-An Shih, Wen-Chi Chen

**Chih-An Shih, Wen-Chi Chen,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung 813, Taiwan

**Chih-An Shih,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, Antai Medical Care Corporation, Antai Tian-Sheng Memorial Hospital, Pingtung County 928, Taiwan

**Chih-An Shih,** Department of Nursing, Meiho University, Pingtung County 928, Taiwan

**Wen-Chi Chen,** Faculty of Medicine, School of Medicine, National Yang Ming Chiao Tung University, Taipei 112, Taiwan

**Wen-Chi Chen,** Institute of Biomedical Sciences, College of Science, National Sun Yat-sen University, Kaohsiung 8424, Taiwan

**Author contributions:** Shih CA and Chen WC designed the research study, performed the research and wrote the manuscript; All authors have read and approved the final manuscript.

**Corresponding author: Wen-Chi Chen, MD, Chief,** Division of Gastroenterology and Hepatology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, No. 386 Ta-Chung 1st Road, Kaohsiung 813, Taiwan. wcchen@vghks.gov.tw

**Received:** January 29, 2021

**Revised:** April 12, 2021

**Accepted:** June 2, 2021

**Published online:**

**Abstract**

Hepatitis B virus (HBV) reactivation can lead to severe acute hepatic failure and death in patients with HBV infection. HBV reactivation (HBVr) most commonly develops in patients undergoing cancer chemotherapy, especially B cell-depleting agent therapy such as rituximab and ofatumumab for hematological or solid organ malignancies and that receiving hematopoietic stem cell transplantation without antiviral prophylaxis. In addition, the potential consequences of HBVr is particularly a concern when patients are exposed to either immunosuppressive or biologic therapies for the management of rheumatologic diseases, inﬂammatory bowel disease and dermatologic diseases. Thus, screening with HBV serological markers and prophylactic or pre-emptive antiviral treatment with nucleos(t)ide analogues should be considered in these patients to diminish the risk of HBVr. This review discusses the clinical manifestation, prognosis and management of HBVr, risk stratifications of cancer chemotherapy and immunosuppressive therapy and international guideline recommendations for the prevention of HBVr in patients with HBV infection and resolved hepatitis B.

**Key Words:** Hepatitis B virus; Reactivation; Chemotherapy; Immunosuppression; Prevention

Shih CA, Chen WC. Prevention of hepatitis B reactivation in patients requiring chemotherapy and immunosuppressive therapy. *World J Clin Cases* 2021; In press

**Core Tip:** Reactivation of hepatitis B virus (HBV) could be fatal in the patients with hepatitis B infection and chemotherapy or immunosuppressive therapy. We review the risk of HBV reactivation, screening of HBV infection and the strategies of prophylaxis of HBV reactivation in patients requiring chemotherapy and immunosuppressive therapy.

**INTRODUCTION**

***Global epidemiology of hepatitis B***

Hepatitis B virus (HBV) is a virus containing a DNA genome of 3226 base pairs that can cause a potentially life-threatening liver infection[[1](#_ENREF_1),[2](#_ENREF_2)]. About 2 billion people have been infected with HBV worldwide; of which, 350 million are in chronic infection status[[3](#_ENREF_3),[4](#_ENREF_4)]. HBV is one of the most frequently identiﬁed pathogens that lead to acute and chronic hepatitis, acute liver failure and death in East Asia. Three quarters of the HBV carries reside in the Asia-Paciﬁc region[[5](#_ENREF_5)]. Nevertheless, northern, western and central Europe, North America and Australia are among the lowest prevalence area of chronic HBV infection [hepatitis B surface antigen (HBsAg)-positive, 0.2% to 0.5%] and HBV exposure [HBsAg-negative but hepatitis B core antibodies (anti-HBc)-positive, 4% to 6%], while Eastern Europe, the Mediterranean, Russia, Southwest Asia and Central and South America have higher prevalence rates (2% to 7% chronically infected and 20% to 55% exposed). Southeast Asia, China and tropical Africa have the highest prevalence rates (8% to 20% chronically infected and 70% to 95% exposed)[[3](#_ENREF_3" \o "Pattullo, 2015 #21)].

Patients infected with HBV, either chronic or resolved HBV infection cases, are at risk of HBV reactivation (HBVr) when they undergo chemotherapy. HBVr could occur in patients receiving chemotherapy for hematological malignancies or hematopoietic stem cell transplantation (HSCT) recipients as well as patients receiving treatment for solid tumors such as breast cancer[[6](#_ENREF_6)]. In HBsAg-positive lymphoma patients undergoing rituximab plus steroid combination chemotherapy and HSCT, HBVr rates could be up to 24% to 88%[[7-10](#_ENREF_7)]. Increasingly, patients with solid tumors receiving chemotherapy, particularly in breast cancer patients receiving anthracycline-based regimens, are also at risk of HBVr[[10](#_ENREF_10)].

**DEFINITION OF HBVr**

The recent American Association for the Study of Liver Diseases (AASLD) recommendation guideline defined HBVr in HBsAg-positive, anti-HBc-positive patients as any of the followings: (1) at least 2 log (or 100-fold) increase in HBV DNA compared to baseline; (2) HBV DNA at least 3 log (or 1000) IU/mL in a patient with previously undetectable HBV DNA level; or (3) HBV DNA at least 4 log (or 10000) IU/mL if baseline level is not available[[11](#_ENREF_11)]. For HBsAg-negative, anti-HBc-positive patients, HBVr could be defined as: (1) HBV DNA is detectable; or (2) reverse HBsAg seroconversion occurs (reappearance of HBsAg)[[11](#_ENREF_11)].

**CLINICAL MANIFESTATION OF HBVr**

The clinical manifestations of HBVr vary from absence of symptoms to liver decompensation and mortality. An abrupt surge in HBV DNA levels without symptoms, elevated aminotransferases, symptomatic hepatitis and acute liver failure were encountered in most of the cases with HBVr by severity[[12](#_ENREF_12" \o "Choi, 2017 #12)].

The occurrence of HBVr largely depends on the primary disease requiring chemotherapy or immunosuppressive therapy, host immunity, underlying disease and the immunosuppressive agents used. HBVr may occur as early as within the ﬁrst 2 wk or up to a year after the cessation of chemotherapy and immunosuppressive therapy. Identifying the risk factors and mechanisms associated with HBVr could help quantify the risk of HBVr and manage the clinical consequences[[13](#_ENREF_13)].

The clinical course of HBVr could be divided into three stages[[14](#_ENREF_14),[15](#_ENREF_15)]. During the ﬁrst stage, there is a gradual or abrupt increase in serum levels of HBV DNA in HBsAg-positive patients, reappearance of serum HBsAg in patients previously seronegative for HBsAg or reappearance of serum HBV DNA in patients with undetectable HBV DNA before chemotherapy and immunosuppressive therapy. Symptoms of hepatitis are usually absent and the levels of aminotransferases are not elevated at this stage[[6](#_ENREF_6)]. During the second stage, serum HBV DNA levels increase persistently with elevated aminotransferases levels. The symptoms associated with hepatitis could be present or absent. In cases with severe hepatitis flare up, hepatic injury could further progress and cause liver failure and even death. These changes could occur during treatment duration of chemotherapy and immunosuppressive therapy or after discontinuation of the treatments and may occur with restoration of the host immunity[[6](#_ENREF_6),[16](#_ENREF_16)]. During the third stage, liver injury could resolve after withholding chemotherapy and immunosuppression agents or administration of antivirals[[6](#_ENREF_6)].

HBVr could develop during or after discontinuation of chemotherapy and immunosuppressive therapy. For patients undergoing chemotherapy for lymphoma, HBVr usually occurs after the second or third courses of treatments. Among non-Hodgkin’s lymphoma patients receiving rituximab-containing therapy, HBVr could develop after six doses of rituximab and within 1 year after the last dose[[17](#_ENREF_17)].

Occurrence of HBVr may delay or hamper scheduled chemotherapy or immunosuppressive therapy and result in progression of underlying diseases. A study of patients receiving chemotherapy for breast cancer revealed that early discontinuation of chemotherapy or a delay in the scheduled therapy occurred in about 70% of cases with HBVr, corresponding to the figure of only 33% in cases without HBVr[[18](#_ENREF_18" \o "Yeo, 2003 #59)].

**RISK FACTORS FOR HBVr AND UNDERLYING DISEASES**

The main risk factors associated with HBVr could be divided into three categories: (1) host factors; (2) virological factors; and (3) type of immunosuppressive regimen. The host factors include male sex, older age, presence of liver cirrhosis and type of diseases requiring immunosuppression[[19](#_ENREF_19),[20](#_ENREF_20)].

***Host factor***

Younger age and male gender are among the risk factors for HBVr[[20](#_ENREF_20)]. On the contrary, another study reported old age as a risk factor[[12](#_ENREF_12),[21](#_ENREF_21)]. It has also been found that patients with older age tend to have more virologic conditions (HBsAg positivity, persistently detectable serum HBV DNA and presence of covalently closed circular DNA in the liver), which increase the risk of HBVr[[22](#_ENREF_22),[23](#_ENREF_23)].

***Virological factor***

The extent of HBV replication before the start of chemotherapy and immunosuppressive therapy is an important risk factor for HBVr. Patients seropositive for HBsAg are at a higher risk of HBVr than those seronegative for HBsAg and seropositive for anti-HBc. Patients seropositive for HBsAg are at a 5- to 8-fold risk for HBVr[[6](#_ENREF_6" \o "Law, 2016 #19),[24](#_ENREF_24)]. In the patients receiving chemotherapy for lymphoma, the prevalence rate of HBVr could be 48% in HBsAg-positive patients, 4% in HBsAg-negative/anti-HBc-positive patients and 0% in HBsAg-negative/anti-HBc-negative patients[[12](#_ENREF_12),[25](#_ENREF_25)]. The liver failure could occur in 7% of HBsAg-positive patients, 2% of HBsAg-negative/anti-HBc-positive patients and 0% of HBsAg-negative/anti-HBc-negative patients[[12](#_ENREF_12),[25](#_ENREF_25)].

Patients with resolved HBV infection (HBsAg-negative, anti-HBc-positive) could have occult HBV infection with persistent detectable HBV DNA[[26-28](#_ENREF_26)]. The HBVr rate ranges from 8.9% to 41.5% in occult HBV infection patients receiving rituximab-containing chemotherapy in different studies using the definitions of HBsAg seroreversion or detectable HBV DNA[[29-31](#_ENREF_29)]. In a multicenter, randomized, phase 3 study of 326 diffuse large B-cell lymphoma or follicular lymphoma patients with resolved HBV infection, 27 (8.2%) had HBVr that occurred at a median of 125 d after the first dose of obinutuzumab or rituximab immunochemotherapy. Twenty-five of 232 patients (10.8%) without prophylactic nucleos(t)ides had HBVr while only 2 of 94 patients (2.1%) with prophylactic nucleos(t)ides had HBVr[[32](#_ENREF_32)]. Thus, prophylactic nucleos(t)ides should be used in resolved HBV infection patients receiving rituximab-containing regimens for hematological or rheumatological disease[[33](#_ENREF_33)].

***Immunosuppressive regimen***

The risk of HBVr could be graded according to the potency of immunosuppression agents used as followed: (1) high risk: HBVr rate of more than 10% (anti-CD20 monoclonal antibodies including rituximab; systemic cancer chemotherapy agents such as doxorubicin); (2) moderate risk: HBVr rate of 1% to 10% (imatinib, ibrutinib and other tyrosine kinase inhibitors; corticosteroids dosage equivalent to more than prednisone 20 mg daily use for more than 4 wk); and (3) low risk: HBVr rate of less than 1% (traditional immunosuppressive agents such as azathioprine and methotrexate; corticosteroids use for less than 4 wk) (Table 1)[[22](#_ENREF_22)].

**UNDERLYING DISEASES**

***Hematologic malignancies***

The studies of chemotherapy-associated HBVr were most often investigated in hematologic malignancies such as non-Hodgkin’s lymphoma[[7](#_ENREF_7),[25](#_ENREF_25),[34](#_ENREF_34)]. B-cell proliferation and lymphocytes infected by HBV also could be observed in non-Hodgkin’s lymphoma patients seronegative for HBsAg[[22](#_ENREF_22" \o "Sagnelli, 2019 #20)]. HBVr has been investigated in multiple myeloma patients seropositive for HBsAg or seronegative for HBsAg but seropositive for anti-HBc[[35-37](#_ENREF_35" \o "Mya, 2012 #53)]. Multiple myeloma patients with immune dysfunction are prone to develop HBVr[[38](#_ENREF_38)]. We recommend antiviral prophylaxis in HBsAg-positive patients from 1 wk before starting immunosuppressive agents and until 12 mo after discontinuation of the agents. We also recommend that patients seronegative for HBsAg but seropositive for anti-HBc on drugs targeting B lymphocytes should be provided with antiviral prophylaxis.

***Solid tumors***

The incidence of HBVr associated with systemic cytotoxic chemotherapy ranged from 20% to 36% in solid tumor patients including breast cancer, lung cancer, hepatocellular carcinoma (HCC) and nasopharyngeal cancer who were seropositive for HBsAg[[39](#_ENREF_39" \o "Chen, 2015 #102)]**.** Severe HBVr may occur in 4.3% of HBsAg-positive patients with solid tumors who received chemotherapy without antiviral prophylaxis[[7](#_ENREF_7)].Breast cancer patients undergoing chemotherapy are associated with 25% to 40% incidence of HBVr[[18](#_ENREF_18" \o "Yeo, 2003 #59),[40](#_ENREF_40)]. The HBVr rate associated with breast cancer is higher than that associated with other solid cancers (7% to 29%) because anthracycline and corticosteroids are frequently used[[41](#_ENREF_41)]. We recommend antiviral prophylaxis in HBsAg-positive patients from 1 wk before starting immunosuppressive agents until 12 mo after discontinuation of the agents. At present there are insufficient data to recommend antiviral prophylaxis in HBsAg-negative/anti-HBc-positive patients.

***HCC***

The incidence of HBVr in patients with HCC ranges between 4% and 67%[[12](#_ENREF_12),[42](#_ENREF_42)]. In fact, HBVr can occur during curative or palliative therapies for HCC such as hepatectomy, local ablation, transarterial chemoembolization, systemic chemotherapy and radiation therapy[[43](#_ENREF_43" \o "Jang, 2004 #57)]. In HBsAg-positive patients with HCC who were treated with transarterial chemoembolization, 33.7% had HBVr[[43](#_ENREF_43" \o "Jang, 2004 #57)]. Of the patients seronegative for HBsAg and treated with transarterial chemoembolization, 11% developed HBVr[[44](#_ENREF_44" \o "Jang, 2015 #58)]. Due to the high incidence of HBVr, we recommend to initiate antiviral therapy in all patients with HBV related HCC undergoing chemoradiation, locoregional or systemic therapy.

***HSCT***

Patients undergoing allogeneic HSCT are at the highest risk of HBVr because of high-dose chemotherapy and potent immunosuppressive agents to prevent the rejection of the graft[[6](#_ENREF_6)]. In HBsAg-positive patients receiving HSCT, 57.6% developed HBVr[[45](#_ENREF_45)]. HBVr is also not uncommon in patients seronegative for HBsAg but seropositive for anti-HBc undergoing HSCT, with a rate of HBsAg seroreversion of 20% in a retrospective study[[46](#_ENREF_46)]. We recommend prophylactic antivirals for patients administered with high-risk therapies such as anti-CD20 antibodies or HSCT recipients.

***Rheumatologic diseases***

The incidences of HBVr in patients with rheumatologic disease such as rheumatoid arthritis could be up to 12.3% in patients seropositive for HBsAg[[47](#_ENREF_47)] and 3% to 5% in patients seronegative for HBsAg but seropositive for anti-HBc-positive[[12](#_ENREF_12),[48](#_ENREF_48)]. Tumor necrosis factor α inhibitors (*e.g.*, etanercept, inﬂiximab and adalimumab) when administered in rheumatoid arthritis and psoriasis patients seropositive for HBsAg are associated with an HBVr rate of 1% to 10%. On the contrary, the reactivation risk is only around 1% in patients seronegative for HBsAg but seropositive for anti-HBc[[49](#_ENREF_49)]. Therefore, we recommend that HBV prophylaxis may not be indicated in patients seronegative for HBsAg but seropositive for anti-HBc-positive while they could be monitored for hepatic biochemical flare during immunosuppression.

***Inflammatory bowel disease***

The HBVr rates in patients with inflammatory bowel disease range between 0.6% and 36.0% for patients seropositive for HBsAg[50]. The rate ranges between 1.6% and 42.0% for patients seronegative for HBsAg but seropositive for anti-HBc[[50](#_ENREF_50" \o "Loras, 2010 #64)]. With the use of tumor necrosis factor α inhibitors and other biologic agents, HBVr including hepatic failure has been reported[[51](#_ENREF_51),[52](#_ENREF_52)]. We recommend that HBsAg-negative, anti-HBc-positive patients with inﬂammatory bowel disease treated with tumor necrosis factor inhibitors, biologicals or conventional immunosuppressive therapies could be monitored without anti-HBV prophylaxis.

**PREVENTION OF HBVr**

***Strategy of screening***

The strategies of screening for HBV before starting chemotherapy and immunosuppressive therapies vary between the recommendations[[53-57](#_ENREF_53)]. The patients undergoing these therapies that carry a high or moderate risk of HBVr should be screened for HBsAg and anti-HBc with or without checking anti-HBs. The patients seronegative for HBsAg, anti-HBc and anti-HBs could be vaccinated against HBV[[13](#_ENREF_13" \o "Loomba, 2017 #2)].

***Risk stratification of HBVr***

The risk of HBVr could be categorized into high risk (> 10%), moderate risk (1%-10%) and low risk (< 1%) according to the risk of reactivation (Table 1)[[49](#_ENREF_49),[54](#_ENREF_54),[58](#_ENREF_58)].

***High-risk patients (> 10%)***

B-cell depleting agents such as rituximab are associated with a high risk for HBVr and thus antiviral prophylaxis should be administered in the patients exposed to HBV regardless of the HBsAg status[[59](#_ENREF_59)]. These patients should be given prophylactic antivirals (entecavir or tenofovir preferred) before the start of chemotherapy and immunosuppressive treatments[[12](#_ENREF_12)]. Monitoring for HBVr should continue for another 6 to 12 mo after the cessation of prophylactic antivirals[[60](#_ENREF_60)].

***Moderate-risk patients (1%-10%)***

Pre-emptive therapy is defined as antivirals initiated at the rise of serum HBV DNA or alanine aminotransferase (ALT) levels but before the onset of hepatitis symptoms or liver failure. Primary prophylaxis therapy is defined as antivirals started before or at the initiation of immunosuppressive agents and before rise in HBV DNA or ALT levels. In HBsAg-negative and anti-HBc positive subjects with moderate (< 10%) or low (< 1%) risk of HBVr, pre-emptive therapy, instead of prophylactic therapy, is generally recommended[[60](#_ENREF_60)]. Pre-emptive therapy is based on monitoring HBsAg and/or HBV DNA at 1 to 3 mo intervals during and after immunosuppression and starting antiviral therapy in case of detectable HBV DNA or HBsAg seroreversion[[60](#_ENREF_60" \o ", 2017 #81)].

***Low-risk patients (< 1%)***

Close monitoring of HBsAg, HBV DNA and ALT levels with on-demand antiviral therapy could be offered for the patients who carry a low risk for HBVr.

***Screening***

Screening of HBV using tests including HBsAg, anti-HBc and anti-HBs should be performed before the initiation of chemotherapy or immunosuppressive agents. Patients seropositive for HBsAg with serum HBV DNA level of equal to or greater than 2000 IU/mL and an increased ALT level should start nucleos(t)ide analogues as recommended by the American Association for the Study of Liver Diseases guidelines[[11](#_ENREF_11" \o "Terrault, 2018 #25)]. A proposed algorithm of HBVr prophylaxis and treatment for patients receiving chemotherapy and immunosuppressive therapy are described in Figure 1[[11](#_ENREF_11),[58](#_ENREF_58),[60](#_ENREF_60),[61](#_ENREF_61)].

Given the fact that screening for HBV before chemotherapy and immunosuppressive therapy with prophylactic antiviral agents could significantly decrease the occurrence of HBVr, the screening rates remain relatively low in non-HBV endemic countries such as the United States (17%) and Canada (14% to 31%)[[62-64](#_ENREF_62)]. A retrospective cohort study from Taiwan, which included 2512 cancer patients receiving chemotherapy, found that a computerized order entry-based alert system (e-REMINDER) and a therapeutic control system (e-CONTROL) achieved a very high pre-chemotherapy HBV screening rate (99.3%) and a high antiviral agents prophylactic rate (95.8%) without any event of severe or acute HBVr (Figure 2)[[65](#_ENREF_65)].

**OPTIMAL ANTIVIRAL AGENT PROPHYLAXIS**

Prophylactic lamivudine signiﬁcantly decreases the risk of HBVr, hepatitis and mortality in patients undergoing chemotherapy[[19](#_ENREF_19" \o "Loomba, 2008 #34),[66](#_ENREF_66)]. Pre-emptive therapy with lamivudine before the initiation of chemotherapy also decreases the risk of interruption of cancer chemotherapy.

The main concern about lamivudine is that the genetic barrier is relatively low, although it is effective for the prophylaxis of HBVr[[19](#_ENREF_19),[55](#_ENREF_55)]. The resistance rates of lamivudine are 20% and 30% at 1 and 2 years, respectively, and increase exponentially thereafter[[55](#_ENREF_55)]. In some countries, the use of lamivudine, adefovir and telbivudine (agents with low genetic barriers) may be considered because of the low cost. This is particularly true for patients seropositive for HBsAg with undetectable or very low levels of serum HBV DNA[[13](#_ENREF_13" \o "Loomba, 2017 #2)]. Entecavir or tenofovir is the agent of choice for the prophylaxis of HBVr because these antivirals have a high genetic barrier[[54](#_ENREF_54),[55](#_ENREF_55),[67](#_ENREF_67)]. In a randomized, controlled trial comparing entecavir 0.5 mg daily and lamivudine 100 mg daily in prophylaxis of HBVr in lymphoma patients seropositive for HBsAg receiving rituximab-containing chemotherapy, entecavir was superior to lamivudine in terms of decreasing the risk of developing hepatitis (0% *vs* 13.3%), HBVr (6.6% *vs* 30.0%) and disruption of chemotherapy (1.6% *vs* 18.3%)[[67](#_ENREF_67)]. As for the patients undergoing systemic cytotoxic chemotherapy for solid tumors, antiviral prophylaxis reduced the risk for HBVr, HBV-related hepatitis and chemotherapy interruption[[68](#_ENREF_68)]. Entecavir was superior to lamivudine with less incidence of HBVr in the patients with a baseline HBV DNA level ≥ 2000 IU/mL[[39](#_ENREF_39)]. A recent meta-analysis revealed that both tenofovir and entecavir could be the most efﬁcacious therapies in the prophylaxis of HBVr[[69](#_ENREF_69)]. Table 2 summarizes the recommendations for treatment and follow-up in different clinical scenarios and choice of antiviral agents.Most experts recommend routine screening before cancer chemotherapy[[70](#_ENREF_70),[71](#_ENREF_71)].

No standard strategy has hitherto been established to prevent HBVr in patients with resolved HBV infection. A recent meta-analysis with 13 studies showed no association between antiviral prophylaxis and risk of HBVr in patients with resolved hepatitis B[[72](#_ENREF_72)]. Nevertheless, providing antiviral prophylaxis to the patients receiving rituximab-containing therapy could be considered[[72](#_ENREF_72)]. Huang *et al*[[27](#_ENREF_27)] recently revealed that HBVr and HBsAg seroreversion were not uncommon in patients with lymphoma and resolved hepatitis B, and entecavir prophylaxis could signiﬁcantly prevent rituximab-associated HBVr[[27](#_ENREF_27)]. In patients with hematological malignancy and resolved hepatitis B receiving rituximab-containing regimens, tenofovir effectively prevents the occurrence of HBVr[[73](#_ENREF_73)]. Prophylactic lamivudine may be considered only in the patients without HBV viremia[[74](#_ENREF_74)].

**CONCLUSION**

HBVr is increasingly recognized as a clinical challenge with a risk of signiﬁcant morbidity and mortality. Development of HBVr with an increase in serum HBV DNA and aminotransferases could occur in 20% to 50% of HBV carriers undergoing cytotoxic chemotherapy for cancer treatment or immunosuppressive therapy with a mortality rate of approximately 5%[[75](#_ENREF_75)].

Screening for HBV before immunosuppression and chemotherapy is required to prevent the occurrence of HBVr. Screening tests including HBsAg and anti-HBc with or without anti-HBs in the patients about to start anticancer and immunosuppressive therapy is recommended. An integrated strategy involving screening the patients at risk, stratifying the patients for risk according to the status of HBV and the type of immunosuppressive agents administered and careful evaluation of the prophylactic therapy could significantly lower the risk of HBVr.

Entecavir or tenofovir are preferred over lamivudine as antiviral therapy for the prophylaxis of HBVr. The optimal duration of prophylactic antiviral therapy remains to be defined. Current international guidelines suggest administration of prophylactic antiviral therapy for at least 6 to 12 mo after the completion of chemotherapy and even longer for rituximab users or patients with high serum HBV DNA levels before the start of chemotherapy. However, patients with chronic hepatitis B or cirrhosis should continue antiviral therapy regardless of the duration of chemotherapy. Aggressive screening of HBV with adequate antiviral prophylaxis is the optimal strategy for preventing HBVr during chemotherapy and immunosuppressive therapy.

**REFERENCES**

1 **Kawsar HI**, Shahnewaz J, Gopalakrishna KV, Spiro TP, Daw HA. Hepatitis B reactivation in cancer patients: role of prechemotherapy screening and antiviral prophylaxis. *Clin Adv Hematol Oncol* 2012; **10**: 370-378 [PMID: 22895238]

2 **Liaw YF**, Chu CM. Hepatitis B virus infection. *Lancet* 2009; **373**: 582-592 [PMID: 19217993 DOI: 10.1016/S0140-6736(09)60207-5]

3 **Pattullo V**. Hepatitis B reactivation in the setting of chemotherapy and immunosuppression - prevention is better than cure. *World J Hepatol* 2015; **7**: 954-967 [PMID: 25954478 DOI: 10.4254/wjh.v7.i7.954]

4 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745 [PMID: 9392700 DOI: 10.1056/NEJM199712113372406]

5 **Mohamed R**, Desmond P, Suh DJ, Amarapurkar D, Gane E, Guangbi Y, Hou JL, Jafri W, Lai CL, Lee CH, Lee SD, Lim SG, Guan R, Phiet PH, Piratvisuth T, Sollano J, Wu JC. Practical difficulties in the management of hepatitis B in the Asia-Pacific region. *J Gastroenterol Hepatol* 2004; **19**: 958-969 [PMID: 15304110 DOI: 10.1111/j.1440-1746.2004.03420.x]

6 **Law MF**, Ho R, Cheung CK, Tam LH, Ma K, So KC, Ip B, So J, Lai J, Ng J, Tam TH. Prevention and management of hepatitis B virus reactivation in patients with hematological malignancies treated with anticancer therapy. *World J Gastroenterol* 2016; **22**: 6484-6500 [PMID: 27605883 DOI: 10.3748/wjg.v22.i28.6484]

7 **Shih CA**, Chen WC, Yu HC, Cheng JS, Lai KH, Hsu JT, Chen HC, Hsu PI. Risk of Severe Acute Exacerbation of Chronic HBV Infection Cancer Patients Who Underwent Chemotherapy and Did Not Receive Anti-Viral Prophylaxis. *PLoS One* 2015; **10**: e0132426 [PMID: 26274393 DOI: 10.1371/journal.pone.0132426]

8 **Ling WH**, Soe PP, Pang AS, Lee SC. Hepatitis B virus reactivation risk varies with different chemotherapy regimens commonly used in solid tumours. *Br J Cancer* 2013; **108**: 1931-1935 [PMID: 23652302 DOI: 10.1038/bjc.2013.225]

9 **Lau GK**, Liang R, Chiu EK, Lee CK, Lam SK. Hepatic events after bone marrow transplantation in patients with hepatitis B infection: a case controlled study. *Bone Marrow Transplant* 1997; **19**: 795-799 [PMID: 9134171 DOI: 10.1038/sj.bmt.1700744]

10 **Dai MS**, Wu PF, Shyu RY, Lu JJ, Chao TY. Hepatitis B virus reactivation in breast cancer patients undergoing cytotoxic chemotherapy and the role of preemptive lamivudine administration. *Liver Int* 2004; **24**: 540-546 [PMID: 15566502 DOI: 10.1111/j.1478-3231.2004.0964.x]

11 **Terrault NA**, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, Brown RS Jr, Bzowej NH, Wong JB. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560-1599 [PMID: 29405329 DOI: 10.1002/hep.29800]

12 **Choi J**, Lim YS. Characteristics, Prevention, and Management of Hepatitis B Virus (HBV) Reactivation in HBV-Infected Patients Who Require Immunosuppressive Therapy. *J Infect Dis* 2017; **216**: S778-S784 [PMID: 29156044 DOI: 10.1093/infdis/jix178]

13 **Loomba R**, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. *Gastroenterology* 2017; **152**: 1297-1309 [PMID: 28219691 DOI: 10.1053/j.gastro.2017.02.009]

14 **Hwang JP**, Lok AS. Management of patients with hepatitis B who require immunosuppressive therapy. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 209-219 [PMID: 24247262 DOI: 10.1038/nrgastro.2013.216]

15 **Hoofnagle JH**. Reactivation of hepatitis B. *Hepatology* 2009; **49**: S156-S165 [PMID: 19399803 DOI: 10.1002/hep.22945]

16 **Lalazar G**, Rund D, Shouval D. Screening, prevention and treatment of viral hepatitis B reactivation in patients with haematological malignancies. *Br J Haematol* 2007; **136**: 699-712 [PMID: 17338776 DOI: 10.1111/j.1365-2141.2006.06465.x]

17 **Evens AM**, Jovanovic BD, Su YC, Raisch DW, Ganger D, Belknap SM, Dai MS, Chiu BC, Fintel B, Cheng Y, Chuang SS, Lee MY, Chen TY, Lin SF, Kuo CY. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol* 2011; **22**: 1170-1180 [PMID: 21115603 DOI: 10.1093/annonc/mdq583]

18 **Yeo W**, Chan PK, Hui P, Ho WM, Lam KC, Kwan WH, Zhong S, Johnson PJ. Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. *J Med Virol* 2003; **70**: 553-561 [PMID: 12794717 DOI: 10.1002/jmv.10430]

19 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948 DOI: 10.7326/0003-4819-148-7-200804010-00008]

20 **Yeo W**, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, Leung NW, Zee B, Johnson PJ. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. *J Med Virol* 2000; **62**: 299-307 [PMID: 11055239 DOI: 10.1002/1096-9071(200011)62:3<299::aid-jmv1>3.0.co;2-0]

21 **An J**, Shim JH, Kim SO, Choi J, Kim SW, Lee D, Kim KM, Lim YS, Lee HC, Chung YH, Lee YS, Suh DJ. Comprehensive outcomes of on- and off-antiviral prophylaxis in hepatitis B patients undergoing cancer chemotherapy: A competing risks analysis. *J Med Virol* 2016; **88**: 1576-1586 [PMID: 26945543 DOI: 10.1002/jmv.24512]

22 **Sagnelli C**, Pisaturo M, Calò F, Martini S, Sagnelli E, Coppola N. Reactivation of hepatitis B virus infection in patients with hemo-lymphoproliferative diseases, and its prevention. *World J Gastroenterol* 2019; **25**: 3299-3312 [PMID: 31341357 DOI: 10.3748/wjg.v25.i26.3299]

23 **Yuen MF**, Wong DK, Fung J, Ip P, But D, Hung I, Lau K, Yuen JC, Lai CL. HBsAg Seroclearance in chronic hepatitis B in Asian patients: replicative level and risk of hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1192-1199 [PMID: 18722377 DOI: 10.1053/j.gastro.2008.07.008]

24 **Shouval D**, Shibolet O. Immunosuppression and HBV reactivation. *Semin Liver Dis* 2013; **33**: 167-177 [PMID: 23749673 DOI: 10.1055/s-0033-1345722]

25 **Lok AS**, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy. Report of a prospective study. *Gastroenterology* 1991; **100**: 182-188 [PMID: 1983820 DOI: 10.1016/0016-5085(91)90599-g]

26 **Fopa D**, Candotti D, Tagny CT, Doux C, Mbanya D, Murphy EL, Kenawy HI, El Chenawi F, Laperche S. Occult hepatitis B infection among blood donors from Yaoundé, Cameroon. *Blood Transfus* 2019; **17**: 403-408 [PMID: 31846605 DOI: 10.2450/2019.0182-19]

27 **Huang YH**, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, Yang MH, Tzeng CH, Lee PC, Lin HC, Lee SD. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. *J Clin Oncol* 2013; **31**: 2765-2772 [PMID: 23775967 DOI: 10.1200/JCO.2012.48.5938]

28 **Di Bisceglie AM**, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? *Hepatology* 2015; **61**: 703-711 [PMID: 25412906 DOI: 10.1002/hep.27609]

29 **Hsu C**, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, Kao WY, Chiu CF, Lin SF, Lin J, Chang CS, Tien HF, Liu TW, Chen PJ, Cheng AL; Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: a prospective study. *Hepatology* 2014; **59**: 2092-2100 [PMID: 24002804 DOI: 10.1002/hep.26718]

30 **Matsue K**, Kimura S, Takanashi Y, Iwama K, Fujiwara H, Yamakura M, Takeuchi M. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. *Cancer* 2010; **116**: 4769-4776 [PMID: 20597091 DOI: 10.1002/cncr.25253]

31 **Seto WK**, Chan TS, Hwang YY, Wong DK, Fung J, Liu KS, Gill H, Lam YF, Lie AK, Lai CL, Kwong YL, Yuen MF. Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: a prospective study. *J Clin Oncol* 2014; **32**: 3736-3743 [PMID: 25287829 DOI: 10.1200/JCO.2014.56.7081]

32 **Kusumoto S**, Arcaini L, Hong X, Jin J, Kim WS, Kwong YL, Peters MG, Tanaka Y, Zelenetz AD, Kuriki H, Fingerle-Rowson G, Nielsen T, Ueda E, Piper-Lepoutre H, Sellam G, Tobinai K. Risk of HBV reactivation in patients with B-cell lymphomas receiving obinutuzumab or rituximab immunochemotherapy. *Blood* 2019; **133**: 137-146 [PMID: 30341058 DOI: 10.1182/blood-2018-04-848044]

33 **Cholongitas E**, Haidich AB, Apostolidou-Kiouti F, Chalevas P, Papatheodoridis GV. Hepatitis B virus reactivation in HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy: a systematic review. *Ann Gastroenterol* 2018; **31**: 480-490 [PMID: 29991894 DOI: 10.20524/aog.2018.0266]

34 **Hsu C**, Hsiung CA, Su IJ, Hwang WS, Wang MC, Lin SF, Lin TH, Hsiao HH, Young JH, Chang MC, Liao YM, Li CC, Wu HB, Tien HF, Chao TY, Liu TW, Cheng AL, Chen PJ. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology* 2008; **47**: 844-853 [PMID: 18302293 DOI: 10.1002/hep.22106]

35 **Mya DH**, Han ST, Linn YC, Hwang WY, Goh YT, Tan DC. Risk of hepatitis B reactivation and the role of novel agents and stem-cell transplantation in multiple myeloma patients with hepatitis B virus (HBV) infection. *Ann Oncol* 2012; **23**: 421-426 [PMID: 21551005 DOI: 10.1093/annonc/mdr142]

36 **Lee JY**, Lim SH, Lee MY, Kim H, Sinn DH, Gwak GY, Choi MS, Lee JH, Jung CW, Jang JH, Kim WS, Kim SJ, Kim K. Hepatitis B reactivation in multiple myeloma patients with resolved hepatitis B undergoing chemotherapy. *Liver Int* 2015; **35**: 2363-2369 [PMID: 25832927 DOI: 10.1111/liv.12838]

37 **Li J**, Huang B, Li Y, Zheng D, Zhou Z, Liu J. Hepatitis B virus reactivation in patients with multiple myeloma receiving bortezomib-containing regimens followed by autologous stem cell transplant. *Leuk Lymphoma* 2015; **56**: 1710-1717 [PMID: 25098429 DOI: 10.3109/10428194.2014.941833]

38 **Feyler S**, Selby PJ, Cook G. Regulating the regulators in cancer-immunosuppression in multiple myeloma (MM). *Blood Rev* 2013; **27**: 155-164 [PMID: 23623928 DOI: 10.1016/j.blre.2013.04.004]

39 **Chen WC**, Cheng JS, Chiang PH, Tsay FW, Chan HH, Chang HW, Yu HC, Tsai WL, Lai KH, Hsu PI. A Comparison of Entecavir and Lamivudine for the Prophylaxis of Hepatitis B Virus Reactivation in Solid Tumor Patients Undergoing Systemic Cytotoxic Chemotherapy. *PLoS One* 2015; **10**: e0131545 [PMID: 26121480 DOI: 10.1371/journal.pone.0131545]

40 **Yun J**, Kim KH, Kang ES, Gwak GY, Choi MS, Lee JE, Nam SJ, Yang JH, Park YH, Ahn JS, Im YH. Prophylactic use of lamivudine for hepatitis B exacerbation in post-operative breast cancer patients receiving anthracycline-based adjuvant chemotherapy. *Br J Cancer* 2011; **104**: 559-563 [PMID: 21285992 DOI: 10.1038/bjc.2011.4]

41 **Yeo W**, Zee B, Zhong S, Chan PK, Wong WL, Ho WM, Lam KC, Johnson PJ. Comprehensive analysis of risk factors associating with Hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. *Br J Cancer* 2004; **90**: 1306-1311 [PMID: 15054446 DOI: 10.1038/sj.bjc.6601699]

42 **Jang JW**. Hepatitis B virus reactivation in patients with hepatocellular carcinoma undergoing anti-cancer therapy. *World J Gastroenterol* 2014; **20**: 7675-7685 [PMID: 24976705 DOI: 10.3748/wjg.v20.i24.7675]

43 **Jang JW**, Choi JY, Bae SH, Kim CW, Yoon SK, Cho SH, Yang JM, Ahn BM, Lee CD, Lee YS, Chung KW, Sun HS. Transarterial chemo-lipiodolization can reactivate hepatitis B virus replication in patients with hepatocellular carcinoma. *J Hepatol* 2004; **41**: 427-435 [PMID: 15336446 DOI: 10.1016/j.jhep.2004.05.014]

44 **Jang JW**, Kim YW, Lee SW, Kwon JH, Nam SW, Bae SH, Choi JY, Yoon SK, Chung KW. Reactivation of hepatitis B virus in HBsAg-negative patients with hepatocellular carcinoma. *PLoS One* 2015; **10**: e0122041 [PMID: 25894607 DOI: 10.1371/journal.pone.0122041]

45 **Locasciulli A**, Bruno B, Alessandrino EP, Meloni G, Arcese W, Bandini G, Cassibba V, Rotoli B, Morra E, Majolino I, Alberti A, Bacigalupo A; Italian Cooperative Group for Blood and Marrow Transplantation. Hepatitis reactivation and liver failure in haemopoietic stem cell transplants for hepatitis B virus (HBV)/hepatitis C virus (HCV) positive recipients: a retrospective study by the Italian group for blood and marrow transplantation. *Bone Marrow Transplant* 2003; **31**: 295-300 [PMID: 12621466 DOI: 10.1038/sj.bmt.1703826]

46 **Hammond SP**, Borchelt AM, Ukomadu C, Ho VT, Baden LR, Marty FM. Hepatitis B virus reactivation following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2009; **15**: 1049-1059 [PMID: 19660717 DOI: 10.1016/j.bbmt.2009.05.001]

47 **Lee YH**, Bae SC, Song GG. Hepatitis B virus reactivation in HBsAg-positive patients with rheumatic diseases undergoing anti-tumor necrosis factor therapy or DMARDs. *Int J Rheum Dis* 2013; **16**: 527-531 [PMID: 24164839 DOI: 10.1111/1756-185X.12154]

48 **Urata Y**, Uesato R, Tanaka D, Kowatari K, Nitobe T, Nakamura Y, Motomura S. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. *Mod Rheumatol* 2011; **21**: 16-23 [PMID: 20668905 DOI: 10.1007/s10165-010-0337-z]

49 **Perrillo RP**, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 221-244.e3 [PMID: 25447852 DOI: 10.1053/j.gastro.2014.10.038]

50 **Loras C**, Gisbert JP, Mínguez M, Merino O, Bujanda L, Saro C, Domenech E, Barrio J, Andreu M, Ordás I, Vida L, Bastida G, González-Huix F, Piqueras M, Ginard D, Calvet X, Gutiérrez A, Abad A, Torres M, Panés J, Chaparro M, Pascual I, Rodriguez-Carballeira M, Fernández-Bañares F, Viver JM, Esteve M; REPENTINA study; GETECCU (Grupo Español de Enfermedades de Crohn y Colitis Ulcerosa) Group. Liver dysfunction related to hepatitis B and C in patients with inflammatory bowel disease treated with immunosuppressive therapy. *Gut* 2010; **59**: 1340-1346 [PMID: 20577000 DOI: 10.1136/gut.2010.208413]

51 **Esteve M**, Saro C, González-Huix F, Suarez F, Forné M, Viver JM. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004; **53**: 1363-1365 [PMID: 15306601 DOI: 10.1136/gut.2004.040675]

52 **Loras C**, Gisbert JP, Saro MC, Piqueras M, Sánchez-Montes C, Barrio J, Ordás I, Montserrat A, Ferreiro R, Zabana Y, Chaparro M, Fernández-Bañares F, Esteve M; REPENTINA study, GETECCU group (Grupo Español de trabajo de Enfermedades de Crohn y Colitis Ulcerosa). Impact of surveillance of hepatitis b and hepatitis c in patients with inflammatory bowel disease under anti-TNF therapies: multicenter prospective observational study (REPENTINA 3). *J Crohns Colitis* 2014; **8**: 1529-1538 [PMID: 25052345 DOI: 10.1016/j.crohns.2014.06.009]

53 **Doo EC**, Hoofnagle JH, Rodgers GP. NIH consensus development conference: management of Hepatitis B. Introduction. *Hepatology* 2009; **49**: S1-S3 [PMID: 19399814 DOI: 10.1002/hep.22993]

54 **Reddy KR**, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT; American Gastroenterological Association Institute. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. *Gastroenterology* 2015; **148**: 215-9; quiz e16-7 [PMID: 25447850 DOI: 10.1053/j.gastro.2014.10.039]

55 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]

56 **Khokhar OS**, Farhadi A, McGrail L, Lewis JH. Oncologists and hepatitis B: a survey to determine current level of awareness and practice of antiviral prophylaxis to prevent reactivation. *Chemotherapy* 2009; **55**: 69-75 [PMID: 19077421 DOI: 10.1159/000183731]

57 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

58 **Ekpanyapong S**, Reddy KR. Hepatitis B Virus Reactivation: What Is the Issue, and How Should It Be Managed? *Clin Liver Dis* 2020; **24**: 317-333 [PMID: 32620274 DOI: 10.1016/j.cld.2020.04.002]

59 **Koffas A**, Dolman GE, Kennedy PT. Hepatitis B virus reactivation in patients treated with immunosuppressive drugs: a practical guide for clinicians. *Clin Med (Lond)* 2018; **18**: 212-218 [PMID: 29858430 DOI: 10.7861/clinmedicine.18-3-212]

60 **European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu.**; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]

61 **Arora A**, Anand AC, Kumar A, Singh SP, Aggarwal R, Dhiman RK, Aggarwal S, Alam S, Bhaumik P, Dixit VK, Goel A, Goswami B, Kumar A, Kumar M, Madan K, Murugan N, Nagral A, Puri AS, Rao PN, Saraf N, Saraswat VA, Sehgal S, Sharma P, Shenoy KT, Wadhawan M; Members of the INASL taskforce on Hepatitis B. INASL Guidelines on Management of Hepatitis B Virus Infection in Patients receiving Chemotherapy, Biologicals, Immunosupressants, or Corticosteroids. *J Clin Exp Hepatol* 2018; **8**: 403-431 [PMID: 30568345 DOI: 10.1016/j.jceh.2018.06.010]

62 **Lee R**, Vu K, Bell CM, Hicks LK. Screening for hepatitis B surface antigen before chemotherapy: current practice and opportunities for improvement. *Curr Oncol* 2010; **17**: 32-38 [PMID: 21151407 DOI: 10.3747/co.v17i6.653]

63 **Hwang JP**, Fisch MJ, Zhang H, Kallen MA, Routbort MJ, Lal LS, Vierling JM, Suarez-Almazor ME. Low rates of hepatitis B virus screening at the onset of chemotherapy. *J Oncol Pract* 2012; **8**: e32-e39 [PMID: 23180996 DOI: 10.1200/JOP.2011.000450]

64 **Wang Y**, Luo XM, Yang D, Zhang J, Zhuo HY, Zhang J, Jiang Y. Testing for hepatitis B infection in prospective chemotherapy patients: a retrospective study. *World J Gastroenterol* 2013; **19**: 923-930 [PMID: 23429298 DOI: 10.3748/wjg.v19.i6.923]

65 **Hsu PI**, Lai KH, Cheng JS, Kao SS, Li YR, Sun WC, Chen WC, Lin KH, Shin CA, Chiang PH, Li YD, Ou WT, Chen HC, Yu HC. Prevention of acute exacerbation of chronic hepatitis B infection in cancer patients receiving chemotherapy in a hepatitis B virus endemic area. *Hepatology* 2015; **62**: 387-396 [PMID: 26041578 DOI: 10.1002/hep.27843]

66 **Kohrt HE**, Ouyang DL, Keeffe EB. Systematic review: lamivudine prophylaxis for chemotherapy-induced reactivation of chronic hepatitis B virus infection. *Aliment Pharmacol Ther* 2006; **24**: 1003-1016 [PMID: 16984494 DOI: 10.1111/j.1365-2036.2006.03081.x]

67 **Huang H**, Li X, Zhu J, Ye S, Zhang H, Wang W, Wu X, Peng J, Xu B, Lin Y, Cao Y, Li H, Lin S, Liu Q, Lin T. Entecavir *vs* lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. *JAMA* 2014; **312**: 2521-2530 [PMID: 25514302 DOI: 10.1001/jama.2014.15704]

68 **Paul S**, Saxena A, Terrin N, Viveiros K, Balk EM, Wong JB. Hepatitis B Virus Reactivation and Prophylaxis During Solid Tumor Chemotherapy: A Systematic Review and Meta-analysis. *Ann Intern Med* 2016; **164**: 30-40 [PMID: 26595058 DOI: 10.7326/M15-1121]

69 **Zhang MY**, Zhu GQ, Shi KQ, Zheng JN, Cheng Z, Zou ZL, Huang HH, Chen FY, Zheng MH. Systematic review with network meta-analysis: Comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. *Oncotarget* 2016; **7**: 30642-30658 [PMID: 27121321 DOI: 10.18632/oncotarget.8907]

70 **Visram A**, Chan KK, McGee P, Boro J, Hicks LK, Feld JJ. Poor recognition of risk factors for hepatitis B by physicians prescribing immunosuppressive therapy: a call for universal rather than risk-based screening. *PLoS One* 2015; **10**: e0120749 [PMID: 25875198 DOI: 10.1371/journal.pone.0120749]

71 **Hwang JP**, Vierling JM, Zelenetz AD, Lackey SC, Loomba R. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. *Support Care Cancer* 2012; **20**: 2999-3008 [PMID: 22933131 DOI: 10.1007/s00520-012-1576-7]

72 **Su YC**, Lin PC, Yu HC, Wu CC. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. *Eur J Clin Pharmacol* 2018; **74**: 1111-1119 [PMID: 29845351 DOI: 10.1007/s00228-018-2487-4]

73 **Buti M**, Manzano ML, Morillas RM, García-Retortillo M, Martín L, Prieto M, Gutiérrez ML, Suárez E, Gómez Rubio M, López J, Castillo P, Rodríguez M, Zozaya JM, Simón MA, Morano LE, Calleja JL, Yébenes M, Esteban R. Randomized prospective study evaluating tenofovir disoproxil fumarate prophylaxis against hepatitis B virus reactivation in anti-HBc-positive patients with rituximab-based regimens to treat hematologic malignancies: The Preblin study. *PLoS One* 2017; **12**: e0184550 [PMID: 28898281 DOI: 10.1371/journal.pone.0184550]

74 **Hwang JP**, Somerfield MR, Alston-Johnson DE, Cryer DR, Feld JJ, Kramer BS, Sabichi AL, Wong SL, Artz AS. Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update. *J Clin Oncol* 2015; **33**: 2212-2220 [PMID: 25964247 DOI: 10.1200/JCO.2015.61.3745]

75 **Liang R**, Lau GK, Kwong YL. Chemotherapy and bone marrow transplantation for cancer patients who are also chronic hepatitis B carriers: a review of the problem. *J Clin Oncol* 1999; **17**: 394-398 [PMID: 10458258 DOI: 10.1200/JCO.1999.17.1.394]

**Footnotes**

**Conflict-of-interest statement:** The authors declare having no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** January 29, 2021

**First decision:** March 29, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Taiwan

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

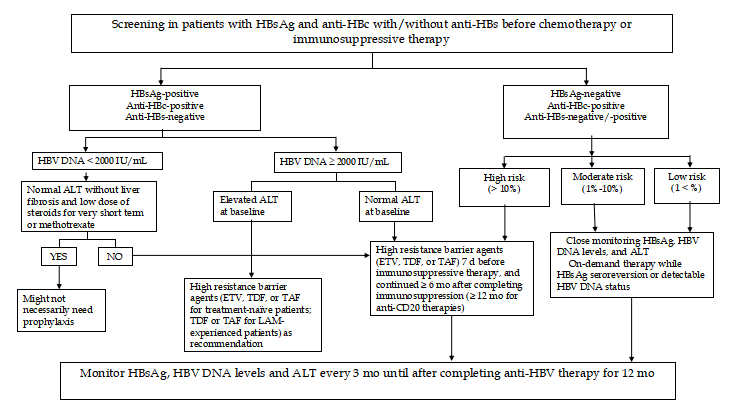
Grade C (Good): C, C, C

Grade D (Fair): 0

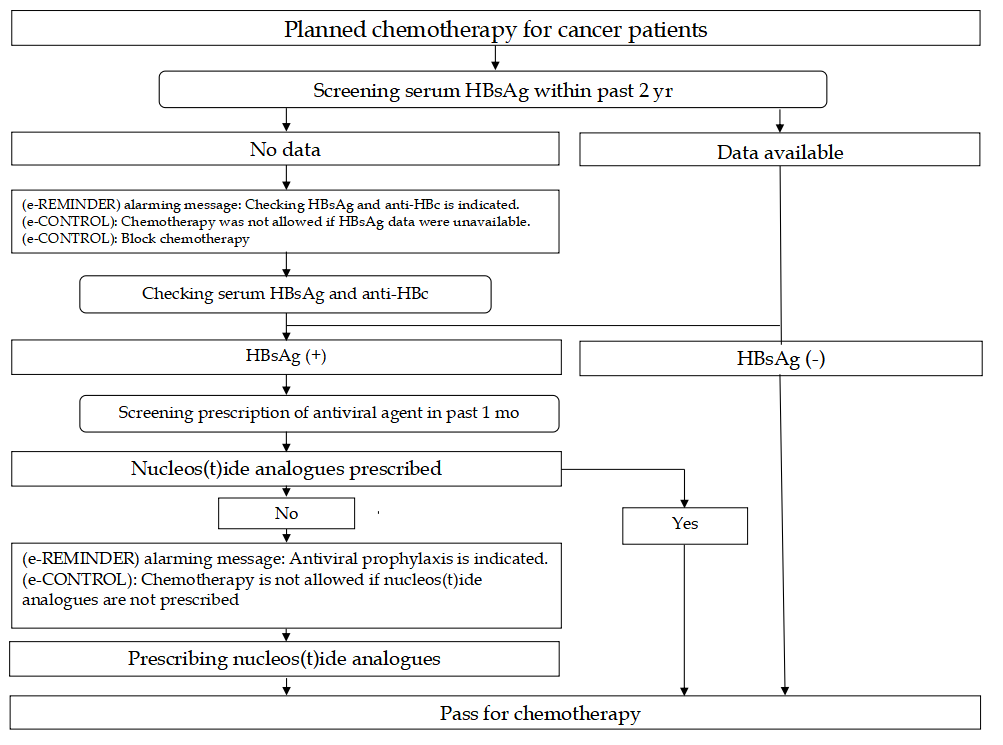
Grade E (Poor): 0

**P-Reviewer:** Hussaini T, Ko HH **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**Figure 1 Proposed algorithm for the screening and prevention of hepatitis B virus reactivation.** anti-HBc: Hepatitis B core antibodies; ALT: Alanine aminotransferase; ETV: Entecavir; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; LAM: Lamivudine; TAF: Tenofovir alafenamide; TDF: Tenofovirdisoproxil fumarate.



**Figure 2 Modified road map for hepatitis B virus screening before chemotherapy and prophylaxis in the order entry-based screening reminder (e-REMINDER) and therapeutic control (e-CONTROL) system (Courtesy of Professor Ping-I Hsu).** anti-HBc: Hepatitis B core antibodies; HBsAg: Hepatitis B surface antigen.

**Table 1 Immunosuppressive agent classes and corresponding risks of hepatitis B reactivation**

|  |  |  |
| --- | --- | --- |
| **Risk group** | **Seropositive for HBsAg and anti-HBc** | **Seronegative for HBsAg, seropositive for anti-HBc** |
| High risk (> 10%) | Anti-CD20 antibodies | Anti-CD20 antibodies |
| Anti-CD52 antibodies |
| Anthracycline derivatives |
| Costimulation inhibitors |
| JAK inhibitors |
| Moderate-high dose corticosteroid therapy1 for ≥ 4 wk |
| Moderate risk (1%-10%) | TNF-α inhibitors | Anthracycline derivatives |
| Integrin inhibitors | TNF-α inhibitors |
| IL-12 and IL-23 antibodies | Integrin inhibitors |
| Tyrosine kinase inhibitors | IL-12 and IL-23 antibodies |
| Low dose corticosteroid therapy1 for ≥ 4 wk | Tyrosine kinase inhibitors |
| Moderate-high dose corticosteroid therapy1 for ≥ 4 wk |
| Low risk (< 1%) | General immunosuppressive agents (azathioprine, 6-mercaptopurine and methotrexate) | General immunosuppressive agents (azathioprine, 6-mercaptopurine and methotrexate) |
| Corticosteroid therapy1 for ≤ 1 wk | Low dose corticosteroid therapy1 for ≥ 4 wk |
| Intra-articular corticosteroids | Corticosteroid therapy1 for ≤ 1 wk |
|  | Intra-articular corticosteroids |

1Corticosteroid therapy: Prednisone (or equivalent); low dose (< 10 mg), moderate dose (10-20 mg), high dose (> 20 mg). anti-HBc: Hepatitis B core antibodies; HBsAg: Hepatitis B surface antigen; IL: Interleukin; JAK: Janus kinase; TNF: Tumor necrosis factor.

**Table 2 Recommendations of international guidelines for treatment and follow-up in different clinical scenarios**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **AASLD 2018** | **EASL 2017** | **APASL 2016** | **AGA 2015** |
| Screening before chemotherapy/immunosuppressive therapy | HBsAg and anti-HBc | HBsAg, anti-HBc, and anti-HBs | HBsAg and anti-HBc | HBsAg and anti-HBc |
| HBV DNA if serology positive |
| Start antiviral prophylaxis before chemotherapy/immunosuppressive therapy | For HBsAg (+) patients | For HBsAg (+) patients | For HBsAg (+) patients | For HBsAg (+) patients |
| For HBsAg (-)/anti-HBc (+) patients: if at high risk of HBV reactivation | For HBsAg (-)/anti-HBc (+) patients: if detectable serum HBV DNA | For HBsAg (-)/anti-HBc (+) patients: if the chemotherapy is associated with high or moderate risk of HBV reactivation |
| Treatment duration of antiviral treatment after completing chemotherapy/immunosuppressive therapy | At least 6 mo | 12 mo | 12 mo | At least 6 mo |
| At least 12 mo for patients receiving anti-CD20 antibodies therapy | At least 12 mo for patient receiving anti-CD20 antibodies therapy |
| Antivirals of choice | TDF, TAF or ETV | TDF, TAF or ETV | TDF and ETV | TDF and ETV |

AASLD: American Association for the Study of Liver Diseases; AGA: American gastroenterology association; anti-HBc: Hepatitis B core antibodies; APASL: Asian paciﬁc association for the study of the liver; EASL: European association for the study of the liver; ETV: Entecavir; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; TAF: Tenofovir alafenamide; TDF: Tenofovirdisoproxil fumarate.