

Hepatitis B Reactivation in the Setting of Immunosuppression

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Background and Definitions

Background

Hepatitis B virus (HBV) reactivation is a well-described clinical entity characterized by a rise in HBV DNA and typically followed by a rise in aminotransferase levels.[1] Although HBV reactivation can occur spontaneously or in the setting of hepatitis C virus (HCV) treatment, it is most commonly triggered by immunosuppression.[2] In addition, in persons receiving treatment for HBV, reactivation almost always occurs following withdrawal of HBV antiviral therapy. Reactivation of HBV can lead to acute hepatitis and even liver failure; these complications, however, can be prevented with the use of antiviral therapy, when indicated.

Definitions

The following summarizes the American Association for the Study of Liver Diseases (AASLD) definitions related to HBV reactivation.[3]

- **Hepatitis B Reactivation:** Hepatitis B virus reactivation is the loss of HBV immune control in persons who are receiving immunosuppressive therapy for a concomitant medical condition and at baseline are either (1) hepatitis B surface antigen (HBsAg)-positive and anti-HBc-positive or (2) HBsAg-negative and anti-HBc-positive.
 - Among persons who are HBsAg-positive and anti-HBc-positive, the AASLD defines loss of immune control constituting reactivation as:
 - HBV DNA level that increases 100-fold (2-log) or greater compared to the baseline level;
 - HBV DNA level of 1,000 IU/mL or greater in a person with a previously undetectable level (given that HBV-DNA levels fluctuate); *or*
 - HBV DNA level of 10,000 IU/mL or greater if the baseline level is not available.
 - Among persons who are HBsAg-negative and anti-HBc-positive, the AASLD defines loss of immune control constituting reactivation as:
 - Detectable HBV DNA, *or*
 - Reversal of HBsAg seroconversion occurs (reappearance of HBsAg).
- **Hepatitis B Flare:** Typically, HBV flares accompany HBV reactivation and are defined as an alanine aminotransferase level (ALT) increase of at least 3 times baseline and reaching an absolute value greater than 100 U/L.

- **HBV-Associated Liver Failure:** HBV reactivation can result in liver failure, which the AASLD defines as at least one of the following:
 - Impaired synthetic function (total bilirubin greater than 3 mg /dL or an international normalized ratio [INR] greater than 1.5);
 - Ascites;
 - Encephalopathy;
 - Death following HBV-associated liver failure is attributed to HBV reactivation.

Pathophysiology of HBV Reactivation

Hepatitis B virus is a partially double-stranded DNA virus.[4] During an initial HBV infection, HBV viral particles enter hepatocytes, and genomic material is brought into the nucleus, where viral genomes are converted into covalently closed circular DNA (cccDNA) molecules (Figure 1).[4,5] These cccDNA molecules serve as the template for viral mRNA and, ultimately, viral replication.[2,5] Even in individuals who have resolution of their HBV infection, cccDNA persists within hepatocytes, serving as a molecular reservoir for potential future viral reactivation and replication. Similarly, current antiviral therapies that shut down HBV replication do not eliminate HBV cccDNA. Thus, even in persons with resolved or treated HBV, the cccDNA poses a permanent risk for reactivation, particularly in clinical settings associated with immunosuppression.[6]

Clinical Features of HBV Reactivation

The reactivation of HBV can result in manifestations that range in severity from silent reactivation, which is characterized by elevated HBV DNA but no overt signs of hepatitis; to HBV-associated hepatitis, with clinical, laboratory and histological evidence of hepatitis; and to fulminant liver failure, marked by synthetic dysfunction in conjunction with clinical symptoms, including ascites and encephalopathy.[2] These clinical and laboratory manifestations are not mutually exclusive but rather exist on a continuum, with the natural history of HBV reactivation typically progressing from increased viral replication, to clinically apparent disease activity and finally to either recovery or progression to fulminant liver failure ([Figure 2](#)).[1,7]

Risk Factors for HBV Reactivation

Persons with chronic HBV infection (HBsAg-positive), as well as those with resolved HBV infection (HBsAg-negative and anti-HBc-positive), are at risk for reactivation of HBV. The following outlines persons with resolved, treated, or active HBV who are at risk for HBV reactivation due to immunosuppressive therapy.

- **Persons Receiving Chemotherapy:** Receipt of chemotherapy for both solid and liquid tumors is a well-described risk factor for HBV reactivation.[[8,9,10](#)] Although the risk of reactivation depends on the individual's HBsAg status and the specific chemotherapy used, the risk of reactivation may be as high as 50 to 60% among HBsAg-positive persons who receive CD20-depleting agents without antiviral prophylaxis.[[10,11,12](#)]
- **Individuals Receiving Treatment for Autoimmune Disease:** Individuals receiving immunomodulatory medications for the treatment of autoimmune disease are also at risk for HBV reactivation. Hepatitis B reactivation and flares have been described following treatment with tumor necrosis factor (TNF)-alpha inhibitors, anti-CD20 agents, corticosteroids, and other cytokine and integrin inhibitors.[[13,14,15,16,17,18,19](#)] The reactivation risk is highly dependent on the baseline HBsAg status and the specific immunomodulatory medication used.[[10](#)]
- **Persons Undergoing Solid Organ or Bone Marrow Transplantation:** Hepatitis B reactivation has been well described among individuals who undergo solid organ or bone marrow transplantation, including among HBsAg-negative and anti-HBc-positive patients.[[20,21](#)] Hepatitis B reactivation has also been described among individuals who were previously negative for HBV but received a liver transplant from an anti-HBc positive donor.[[22,23](#)]
- **Persons Receiving Treatment for HCV:** Reactivation of HBV has been increasingly recognized as a potential adverse event associated with HCV direct-acting antiviral (DAA) therapy.[[24,25,26](#)] In this setting, HBV reactivation has been observed with multiple different DAA regimens.[[24,26](#)] Notably, some of the reactivation cases with DAA treatment have involved persons with isolated anti-HBc.[[24,26](#)] The mechanism for DAA treatment causing HBV reactivation remains unknown.

Assessing Risk for HBV Reactivation

When assessing the risk of HBV reactivation, it is important to consider both virologic factors and immunosuppressive factors, specifically hepatitis B serologic status and type of immunosuppression.

- **HBV Serologic Status:** There are two main serologic groups that indicate individuals at risk for HBV reactivation in the setting of immunosuppression: (1) HBsAg-positive and anti-HBc-positive or (2) HBsAg-negative and anti-HBc-positive.
 - **HBsAg-positive and anti-HBc-positive:** Studies indicate that anti-HBc-positive persons are up to 7 to 8 times more likely to experience HBV reactivation if they are HBsAg-positive than if they are HBsAg-negative.[[10,18,27](#)] As an example, prior studies with anti-HBc-positive participants showed that HBV reactivation following chemotherapy occurred in 41 to 53% of HBsAg-positive persons versus 8 to 18% of those who were HBsAg-negative, and following receipt of anti-rheumatic therapies HBV reaction occurred in 12.3% of HBsAg-positive persons versus 1.7% of those who were HBsAg-negative.[[3,28,29](#)] Persons who are HBsAg-positive and have a detectable baseline HBV DNA are at the highest risk for HBV reactivation and associated complications, based on studies performed in patients receiving cytotoxic chemotherapy and in the stem cell transplant population.[[30,31](#)]
 - **HBsAg-negative and anti-HBc-positive:** Although the risk of reactivation is lower in HBsAg-negative and anti-HBc-positive persons when compared to HBsAg-positive and anti-HBc-positive individuals, these patients remain at significant risk for HBV reactivation, particularly with the use of high-risk immunosuppressive drugs, such as CD20 inhibitors. In these settings, rates of reactivation up to 40% have been described among persons who are HBsAg-negative and anti-HBc-positive.[[32,33,34](#)] The presence of anti-HBs among persons who are HBsAg-negative and anti-HBc-positive has been shown to lower the risk of reactivation in some studies; however, data on anti-HBs titers (e.g., what titer of anti-HBs is needed to confer additional protection) is largely missing from the literature.[[31,32,35](#)] As such, professional society guidelines do not recommend basing antiviral prophylaxis decisions on the presence or absence of anti-HBs in persons who are HBsAg-negative and anti-HBc-positive.[[3,10](#)]
- **Immunosuppressive Factors:** In addition to HBsAg status, the risk of HBV reactivation depends on the immunosuppressive medication(s) received. Although many different immunosuppressive medications have been linked to HBV reactivation, it is challenging to discern the precise risk posed by specific drugs due to a lack of systematically collected data.[[3](#)]

Risk Categories for HBV Reactivation

Based on studies and reports in the literature, the American Association for the Study of Liver Disease (AASLD) and the American Gastroenterological Association (AGA) have categorized HBV serologic status and immunosuppressive medications by their level of risk for HBV reactivation. Risk categorizations differ slightly between AASLD and AGA guidelines, and both are outlined below.

The AGA Risk Categorization for HBV Reactivation

The American Gastroenterology Association (AGA) has generated the following specific risk categories for HBV reactivation.[\[10\]](#)

- **High Risk:** Persons with a greater than 10% risk of HBV reactivation are classified as high risk. These individuals include:
 - Persons who are HBsAg-positive and are receiving anti-CD20 therapy (e.g., rituximab, ofatumumab)
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving B cell-depleting agents (e.g., rituximab, ofatumumab)
 - Persons who are HBsAg-positive and are receiving anthracycline derivatives (e.g., doxorubicin, epirubicin)
 - HBsAg-positive patients receiving moderate-dose (10 to 20 mg prednisone per day) to high-dose (greater than 20 mg prednisone per day) corticosteroid therapy for 4 weeks or longer
- **Moderate Risk:** Patients with a 1 to 10% risk of HBV reactivation are classified as moderate risk. These patients include:
 - HBsAg-positive persons receiving TNF-alpha inhibitors (e.g., etanercept, adalimumab, certolizumab, infliximab)
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving TNF-alpha inhibitors (e.g., etanercept, adalimumab, certolizumab, infliximab)
 - HBsAg-positive persons receiving other cytokine inhibitors and integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, vedolizumab)
 - Persons who are HBsAg-negative and anti-HBc-positive and receiving other cytokine inhibitors and integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, vedolizumab)
 - HBsAg-positive persons receiving tyrosine kinase inhibitors (e.g., imatinib and nilotinib)
 - HBsAg-negative and anti-HBc-positive persons receiving tyrosine kinase inhibitors (e.g., imatinib, nilotinib)
 - HBsAg-positive persons receiving low-dose (less than 10 mg prednisone per day) corticosteroids for 4 weeks or longer
 - HBsAg-negative and anti-HBc-positive persons receiving moderate-dose (10 to 20 mg prednisone per day) to high-dose (20 mg prednisone/day) corticosteroids for 4 weeks or longer
 - HBsAg-negative and anti-HBc-positive persons receiving anthracycline derivatives (e.g., doxorubicin and epirubicin)
- **Low Risk:** Persons with a less than 1% risk of HBV reactivation are classified as low risk. These patients include:
 - HBsAg-positive persons receiving older immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, methotrexate)
 - Persons who are HBsAg-negative and anti-HBc-positive and receiving traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, methotrexate)
 - HBsAg-positive persons receiving intraarticular corticosteroids
 - HBsAg-negative and anti-HBc-positive persons receiving intraarticular corticosteroids
 - HBsAg-positive persons receiving corticosteroid therapy for 1 week or less
 - Persons who are HBsAg-negative and anti-HBc-positive and receiving corticosteroid therapy for 1 week or less
 - Persons who are HBsAg-negative and anti-HBc-positive and receiving low-dose corticosteroid

(less than 10 mg prednisone per day) therapy for 4 weeks or longer

AASLD Risk Categorization for HBV Reactivation

The AASLD has generated the following specific risk categories for HBV reactivation based on the HBV serologic status and the type of immunosuppression the individual is receiving.[36]

- **Very High Risk:** Persons with an estimated risk of HBV reactivation greater than 20% are deemed to be at very high risk. These persons include:
 - Persons who are HBsAg-positive and receiving anti-CD20 therapy (e.g. rituximab, ofatumumab)
 - Persons who are HBsAg-positive and undergoing hematopoietic stem cell transplantation.
- **High Risk:** Persons with an estimated 11 to 20% risk of HBV reactivation are deemed to be at high risk. These individuals include:
 - HBsAg-positive and receiving high-dose corticosteroids (doses equivalent to 20 mg or more of prednisone daily for at least 4 weeks)
 - HBsAg-positive and receiving other cytokine inhibitors other than anti-CD20 inhibitors (e.g., anti-CD52, ustekinumab).
- **Moderate Risk:** Persons with a 1 to 10% risk of HBV reactivation are considered to be at moderate risk, including:
 - HBsAg-positive and receiving combination cytotoxic chemotherapy without corticosteroids (e.g., cisplatin-based therapy for squamous cell carcinoma and CHOP for lymphoma)
 - HBsAg-positive and receiving anti-tumor necrosis factor agents
 - HBsAg-positive and receiving anti-rejection therapy for solid organ transplant recipients
 - HBsAg-negative and anti-HBc-positive and receiving anti-CD20 agents
 - HBsAg-negative and anti-HBc-positive and undergoing hematopoietic stem cell transplantation
- **Low Risk:** Persons with a less than 1% risk of HBV reactivation are considered low risk. This includes individuals who are:
 - HBsAg-positive and receiving methotrexate or azathioprine
 - HBsAg-negative and anti-HBc-positive and receiving high-dose corticosteroids (doses equivalent to 20 mg or greater of prednisone daily for at least 4 weeks)
 - HBsAg-negative and anti-HBc-positive and receiving other cytokine inhibitors (e.g., anti-CD52, ustekinumab).
- **Rare / Very Low Risk:** HBV reactivation is felt to be rare in the following groups:
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving combination cytotoxic chemotherapy without corticosteroids
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving anti-tumor necrosis factor agents
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving anti-rejection therapy for solid organ transplant recipients
 - Persons who are HBsAg-negative and anti-HBc-positive and are receiving methotrexate or azathioprine
- **No Known Effect:** There is no known risk of HBV reactivation associated with androgen deprivation therapy or estrogen and progesterone blockers for persons who are (1) HBsAg-positive and anti-HBc-positive or (2) HBsAg-negative and anti-HBc-positive.

HBV Screening Prior to Initiation of Immunosuppression

Given the risk for HBV reactivation among persons receiving immunosuppressive medications, several professional guidelines recommend routine HBV screening prior to the initiation of immunosuppressive therapy ([Table 1](#)).^[36] The Centers for Disease Control and Prevention (CDC) recommends screening for HBV in persons receiving or needing cytotoxic or immunosuppressive therapy, including chemotherapy for malignant diseases, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic and gastroenterologic disorders.^[37] In this population, the CDC recommends performing baseline HBV serologic testing, including evaluation for HBsAg, anti-HBc, and anti-HBs.^[37]

Data on Antiviral Therapy to Prevent HBV Reactivation

Several studies have shown that antiviral therapy can decrease the risk of HBV reactivation when initiated prior to or concurrently with immunosuppressive therapy.[[28,38,39,40,41](#)] Data from randomized clinical trials of HBsAg-positive patients undergoing chemotherapy indicate the risk of reactivation can be significantly decreased with the use of preemptive antiviral therapy.[[28,40,41](#)]

- **Delayed vs. Preemptive Antiviral Therapy to Prevent Reactivation:** In a small study of 30 HBsAg-positive persons undergoing treatment for lymphoma, investigators randomized adults to receive preemptive lamivudine 100 mg daily starting 1 week before chemotherapy versus no preemptive treatment.[[28](#)] Over the course of the study, 53% of the participants in the control arm versus 0% of those in the intervention arm experienced HBV reactivation.[[28](#)]
- **Reduced Risk of Reactivation Among Persons Receiving Antiviral Prophylaxis in HBsAg-positive Persons:** In a meta-analysis of 26 studies that included persons with chronic or resolved HBV who were receiving chemotherapy for a solid tumor, 13 studies compared reactivation risk among HBsAg-positive patients receiving antiviral prophylaxis versus no prophylaxis.[[9](#)] The pooled odds ratio for reactivation was 0.12 (95% CI: 0.06 - 0.22), suggesting a substantial reduction in HBV reactivation among those who received prophylactic antivirals.[[9](#)]
- **Entecavir in HBsAg-negative and anti-HBc-Positive Persons:** Clinical trial data similarly support the use of antiviral prophylaxis in patients with resolved HBV (HBsAg-negative and anti-HBc-positive) who are at high risk for HBV reactivation. In a randomized controlled trial of prophylactic entecavir versus no therapy among HBsAg-negative and anti-HBc-positive persons receiving chemotherapy for CD20+ lymphoma, the cumulative rate of HBV reactivation 18 months after chemotherapy was 25.9% in the control arm versus 4.3% in the entecavir arm.[[29](#)]
- **Lamivudine:** Lamivudine is the most extensively studied antiviral medication for the prevention of HBV reactivation.[[8,42,43,44,45](#)] The use of lamivudine, however, is associated with high rates of HBV drug resistance when treating chronic HBV, particularly when used for greater than 1 year.[[46,47,48,49](#)]

Professional Society Recommendations for HBV Prophylactic Antiviral Therapy

The American Association for the Study of Liver Disease (AASLD), the American Gastroenterological Association (AGA), and the American Society of Clinical Oncology (ASCO) have all released recommendations on the use of antiviral prophylaxis to prevent HBV reactivation during immunosuppressive therapy, which are summarized below.

AASLD Recommendations

The AASLD recommendations for antiviral prophylaxis to prevent HBV reactivation were published in 2015 and are based on the HBsAg and anti-HBc status of the individual under consideration and the type of immunosuppressive therapy.[36]

- **HBsAg-Positive and anti-HBc-Positive:** The AASLD recommends initiation of antiviral therapy in all HBsAg-positive patients prior to or at the initiation of chemotherapy, immunosuppressive therapy, hematopoietic stem cell transplant, or solid organ transplant.
- **HBsAg-Negative and anti-HBc-Positive:** The AASLD recommends routine antiviral prophylaxis for HBsAg-negative and anti-HBc-positive patients receiving anti-CD20 therapies and those undergoing hematopoietic stem cell transplantation. Monitoring of HBV DNA at 1- to 3-month intervals, with initiation of antiviral therapy if HBV DNA becomes detectable, is reasonable with HBsAg-negative and anti-HBc-positive patients with lesser degrees of immunosuppression.

AGA Recommendations

The AGA recommendations for prophylaxis to prevent HBV reactivation were published in 2015 and are based on a risk stratification rating (Figure 3).[10,50]

- **High Risk:** The AGA recommends antiviral prophylaxis for persons at high (greater than 10%) risk for HBV reactivation, including the following groups:
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive patients treated with B cell-depleting agents (e.g., rituximab and ofatumumab).
 - HBsAg-positive patients treated with anthracycline derivatives (e.g., doxorubicin, epirubicin)
 - HBsAg-positive patients treated with moderate-dose (10 to 20 mg prednisone/day) or high-dose (greater than 20 mg prednisone/day) corticosteroids daily for 4 weeks or longer
- **Moderate Risk:** The AGA suggests antiviral prophylaxis for patients at moderate (1% to 10%) risk for HBV reactivation. They qualify this suggestion by stating that “patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative) may reasonably select no prophylaxis over antiviral prophylaxis.”[50] The moderate risk group includes:
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive persons receiving tumor necrosis factor-alpha inhibitors (e.g., etanercept, adalimumab, certolizumab, and infliximab)
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive persons receiving other cytokine or integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, and vedolizumab)
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive persons receiving tyrosine kinase inhibitors (e.g., imatinib and nilotinib)
 - HBsAg-positive patients receiving low-dose (less than 10 mg prednisone/day) corticosteroids daily for 4 weeks or longer
 - HBsAg-negative and anti-HBc-positive patients receiving either moderate-dose (10 to 20 mg prednisone per day) or high-dose (greater than 20 mg prednisone per day) corticosteroids daily for 4 weeks or longer
 - HBsAg-negative and anti-HBc-positive patients receiving anthracycline derivatives (e.g., doxorubicin and epirubicin)

- **Low Risk:** The AGA recommends not using routine antiviral prophylaxis for patients at low risk (less than 1%) for HBV reactivation, including the following groups:
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive patients receiving traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, and methotrexate)
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive patients receiving intraarticular corticosteroids
 - HBsAg-positive OR HBsAg-negative and anti-HBc-positive patients receiving any dose of oral corticosteroids daily for 1 week or less
 - HBsAg-negative and anti-HBc-positive patients receiving low-dose (10 mg or less prednisone per day) corticosteroids for 4 weeks or more

ASCO Recommendations

The ASCO recommendations for preventing HBV reactivation with antiviral therapy were published in 2013 and include three categories based on the HBsAg and anti-HBc status and risk related to immunosuppression.[39]

- **HBsAg-Positive and anti-HBc-Positive:** The ASCO recommends initiation of antiviral therapy for all HBsAg-positive patients receiving any systemic anticancer therapy, with the exception of isolated hormonal therapy (e.g., without systemic anticancer therapy).
- **HBsAg-Negative and anti-HBc-Positive on High-Risk Immunosuppression:** The ASCO recommends initiation of antiviral therapy for HBsAg-negative and anti-HBc-positive patients receiving high-risk immunosuppressive therapies, including anti-CD20 monoclonal antibodies or stem-cell transplantation. An alternative option in this group is close monitoring with HBsAg and HBV DNA every 3 months, in patients who are able to adhere to frequent and consistent follow-up. with immediate initiation of antiviral therapy if reactivation occurs.
- **HBsAg-Negative and anti-HBc-Positive on Lower-Risk Immunosuppression:** The ASCO recommends HBsAg-negative and anti-HBc-positive patients on lower risk immunosuppression (e.g. regimens that do not include anti-CD20 agents or stem cell transplantation) be monitored with HBsAg and ALT testing every 3 months, with subsequent HBV DNA testing should a hepatitis flare occur. Individuals with emergent evidence of HBV reactivation should be started on antiviral therapy at that time.

Choice of Antiviral Agents for the Prevention of HBV Reactivation

The AASLD and AGA recommend using either entecavir or tenofovir, two drugs with high potency and a high barrier to resistance, for the prevention of HBV reactivation.[3,10] Note, for the use of tenofovir, these guidelines do not specify use of tenofovir DF versus tenofovir alafenamide. The use of lamivudine is not recommended due to the high rates of drug resistance that have been observed with lamivudine therapy for persons with chronic HBV. The recommendations for using entecavir or tenofovir to prevent HBV reactivation are supported by several meta-analyses and one randomized open-label trial of entecavir versus lamivudine for the prevention of HBV reactivation in persons undergoing treatment for diffuse large B-cell lymphoma.[10,39,51,52,53] In the randomized, open-label trial, investigators observed a lower incidence of HBV-related hepatitis, HBV reactivation, and chemotherapy interruption in those receiving entecavir when compared to those receiving lamivudine for HBV prophylaxis.[29] Although there are no trials that directly compare lamivudine with tenofovir for the prevention of HBV reactivation, expert opinion supports the use of tenofovir (both tenofovir DF and tenofovir alafenamide) for the prevention of HBV reactivation, owing to its high potency and high barrier to resistance.[3,10]

Duration of Antiviral Prophylaxis

The duration of antiviral prophylaxis for the prevention of HBV reactivation is not well studied. Experts agree that antiviral therapy should be continued for the duration of immunosuppressive therapy; however, there is

some uncertainty as to how long antiviral therapy should be continued after discontinuation of immunosuppression. In most studies, prophylactic therapy has been continued for 3 to 12 months following discontinuation of immunosuppressive therapy,[[36](#),[53](#),[54](#)] and reactivation has rarely been reported greater than 12 months following cessation of chemotherapy.[[55](#),[56](#)] The AASLD and AGA recommend continuing antiviral therapy for at least 6 months after completion of most immunosuppressive therapy.[[3](#),[50](#)] This recommendation is extended to 12 months for patients who received anti-CD20 therapy.[[3](#),[50](#)] Conversely, the ASCO recommends antiviral prophylaxis for at least 12 months following completion of all chemotherapy.[[57](#)]

Monitoring Low-Risk Patients Off Antiviral Therapy

Patients on immunomodulatory therapy who are at low risk for HBV reactivation and not initiated on prophylactic antivirals should be monitored routinely for HBV reactivation. In these patients, the AASLD recommends obtaining HBV DNA levels every 1 to 3 months.[[3](#)] The ASCO recommends monitoring HBsAg and ALT in these patients every 3 months while they are receiving chemotherapy.[[57](#)] How long to continue monitoring after the cessation of immunosuppressive therapy is not clear in this lower-risk group.

Special Populations to Consider for HBV Reactivation

Persons Receiving Treatment for Hepatitis C Virus Infection

Individuals with HBV and HCV coinfection are at elevated risk of HBV reactivation during HCV treatment with direct-acting antiviral (DAA) therapy.[[3](#),[24](#),[26](#),[58](#),[59](#)] In one meta-analysis, among HBsAg-positive individuals receiving DAA HCV therapy, the estimated risk of HBV reactivation was 14.1%, and the risk of clinical hepatitis was 12.2%.[[60](#)] In this same meta-analysis, the estimated incidence of clinical hepatitis due to HBV reactivation was 12.2% among persons receiving DAA therapy who were HBsAg-positive.[[60](#)] During HCV treatment, the risk of reactivation is highest among HBsAg-positive individuals, but rare cases have been described in HBsAg-negative and anti-HBc-positive patients.[[58](#),[61](#)] The AASLD recommends initiating HBV antiviral therapy concurrently with DAA therapy in persons with HBV-HCV coinfection who have cirrhosis and in those who otherwise meet AASLD guidelines for initiation of HBV antiviral therapy.[[3](#)] The AASLD states that HBsAg-positive patients who do not meet AASLD HBV treatment guideline criteria for the initiation of antiviral therapy may be monitored with HBV DNA levels every 4 to 8 weeks while on HCV DAA therapy and for 3 months post-HCV treatment.[[3](#)] Although not guideline-based, some experts choose to initiate HBV prophylaxis with entecavir or tenofovir concurrent with DAA therapy in all HBsAg-positive patients. Persons with chronic HCV infection who are HBsAg-negative and anti-HBc-positive have a very low risk of HBV reactivation during HCV treatment and can be monitored with ALT levels at baseline, at the end of HCV treatment, and at post-treatment follow-up.[[3](#)]

Persons with HIV

Progressive immunodeficiency from poorly controlled HIV can lead to reactivation of HBV in persons with chronic HBV infection and can even lead to reverse seroconversion in HBV patients who recovered from HBV infection (e.g., HBsAg-negative and anti-HBc-positive) through a gradual loss of anti-HBs and re-emergence of HBsAg with ALT elevation.[[1](#),[62](#),[63](#),[64](#),[65](#),[66](#)] In addition, many antiviral medications commonly used to treat or prevent HIV (tenofovir DF, tenofovir alafenamide, lamivudine, and emtricitabine) also have activity against HBV, and HBV flares can occur when these antiretroviral medications with HBV activity are discontinued.[[1](#),[67](#)]

Summary Points

- Reactivation of HBV most often occurs in persons with underlying immunosuppression or in those who initiate immunosuppressive medications; however, it has also been described in individuals receiving direct-acting antiviral therapy for HCV.
- HBV reactivation can result in manifestations that range from (1) silent reactivation to (2) HBV-associated hepatitis, to (3) fulminant liver failure.
- Persons with chronic HBV infection (HBsAg-positive), as well as those with resolved HBV infection (HBsAg-negative and anti-HBc positive), are at risk for reactivation of HBV, with risk depending both on an individual's HBV serologic status, and their type of immunosuppression.
- Persons who are HBsAg-positive and receiving anti-CD20 therapy (e.g., rituximab, ofatumumab), as well as persons who are HBsAg-positive and undergoing hematopoietic stem cell transplantation, are at highest risk for HBV reactivation.
- The CDC recommends screening for HBV in persons receiving or needing cytotoxic or immunosuppressive therapy, including chemotherapy for malignant diseases, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic and gastrointestinal disorders.
- Antiviral prophylaxis should generally be initiated in HBsAg-positive patients prior to or at the initiation of chemotherapy, many immunosuppressive therapies, hematopoietic stem cell transplant, or solid organ transplant.
- In general, HBsAg-negative and anti-HBc-positive patients receiving high-risk immunosuppression (e.g., anti-CD20 therapies, hematopoietic stem cell transplantation) should also be started in antiviral prophylaxis.
- Entecavir, tenofovir DF, or tenofovir alafenamide should be used if HBV prophylaxis is needed in the setting of immunosuppression.
- Antiviral therapy should be continued for the duration of immunosuppressive therapy, and in general, for 3 to 12 months following discontinuation of immunosuppressive therapy.
- Patients on immunomodulatory therapy who are at low risk for HBV reactivation and not initiated on prophylactic antivirals should be monitored routinely for HBV reactivation. In these patients, the AASLD recommends obtaining HBV DNA levels every 1 to 3 months.

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Figures

Figure 1 The Replication of HBV

Source: Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. *N Engl J Med.* 2004;350:1118-29. Reproduced with permission from the Massachusetts Medical Society. Copyright © 2004 Massachusetts Medical Society. All rights reserved.

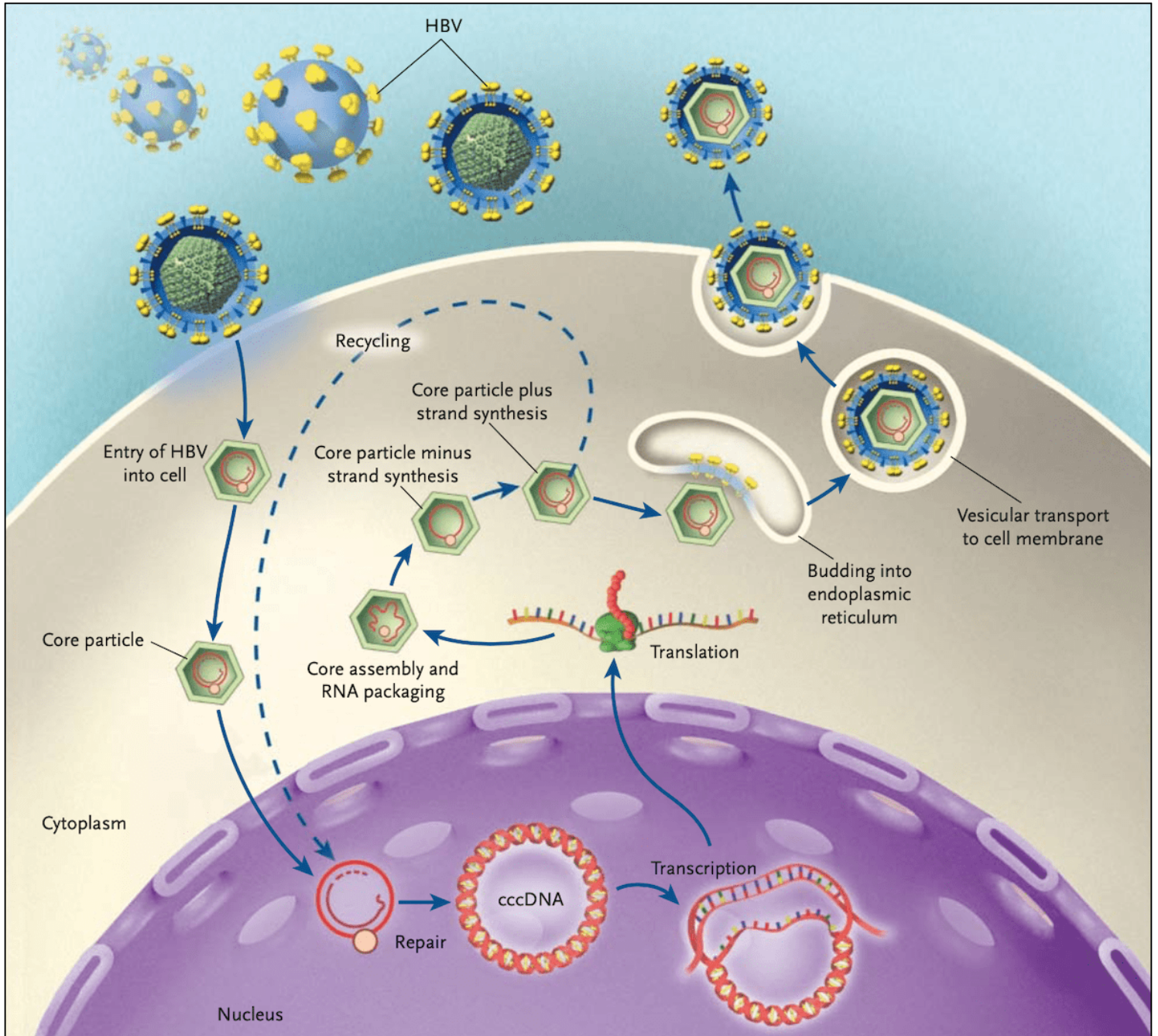


Figure 2 Course of HBV Reactivation after Receiving Immunosuppressive Therapy

Source: 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. Reprinted with permission from Elsevier. ©2017 Elsevier.

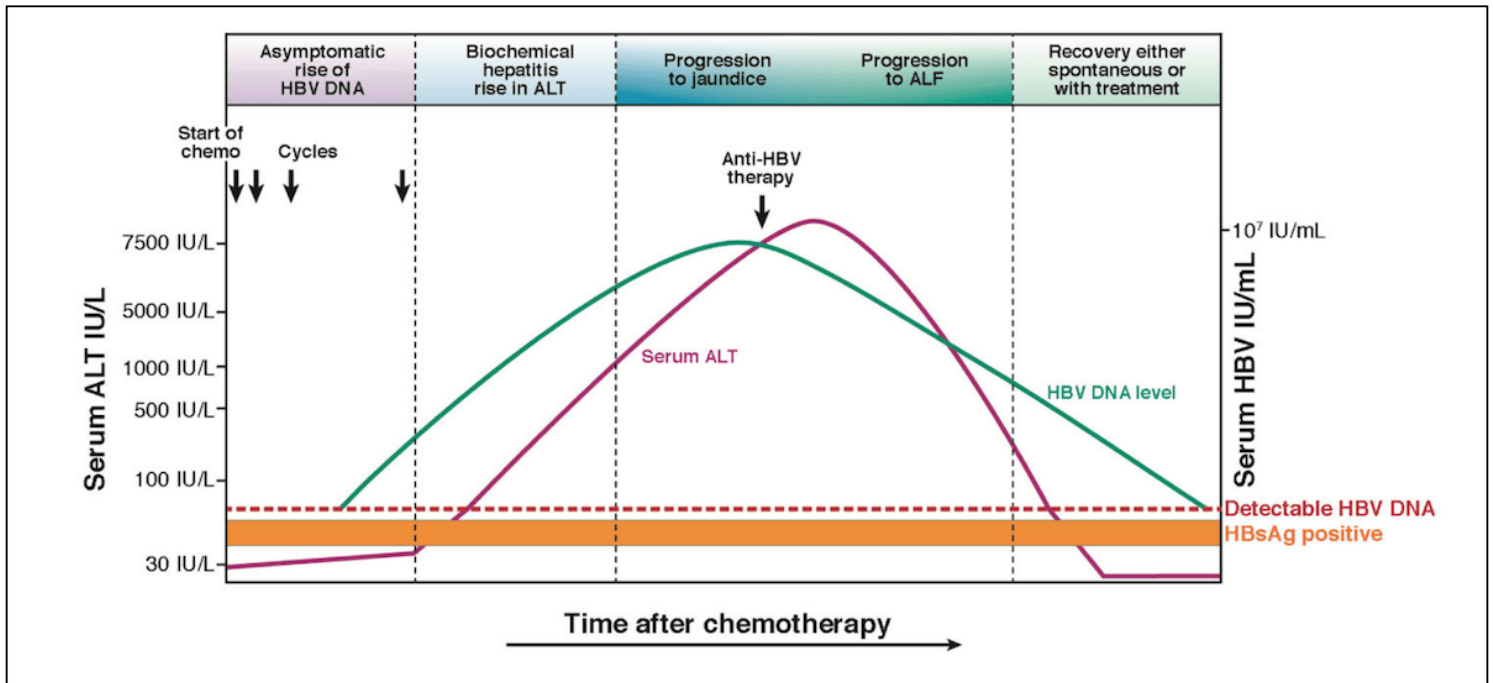


Figure 3 Hepatitis B Reactivation (HBVr): Clinical Decision Support Tool

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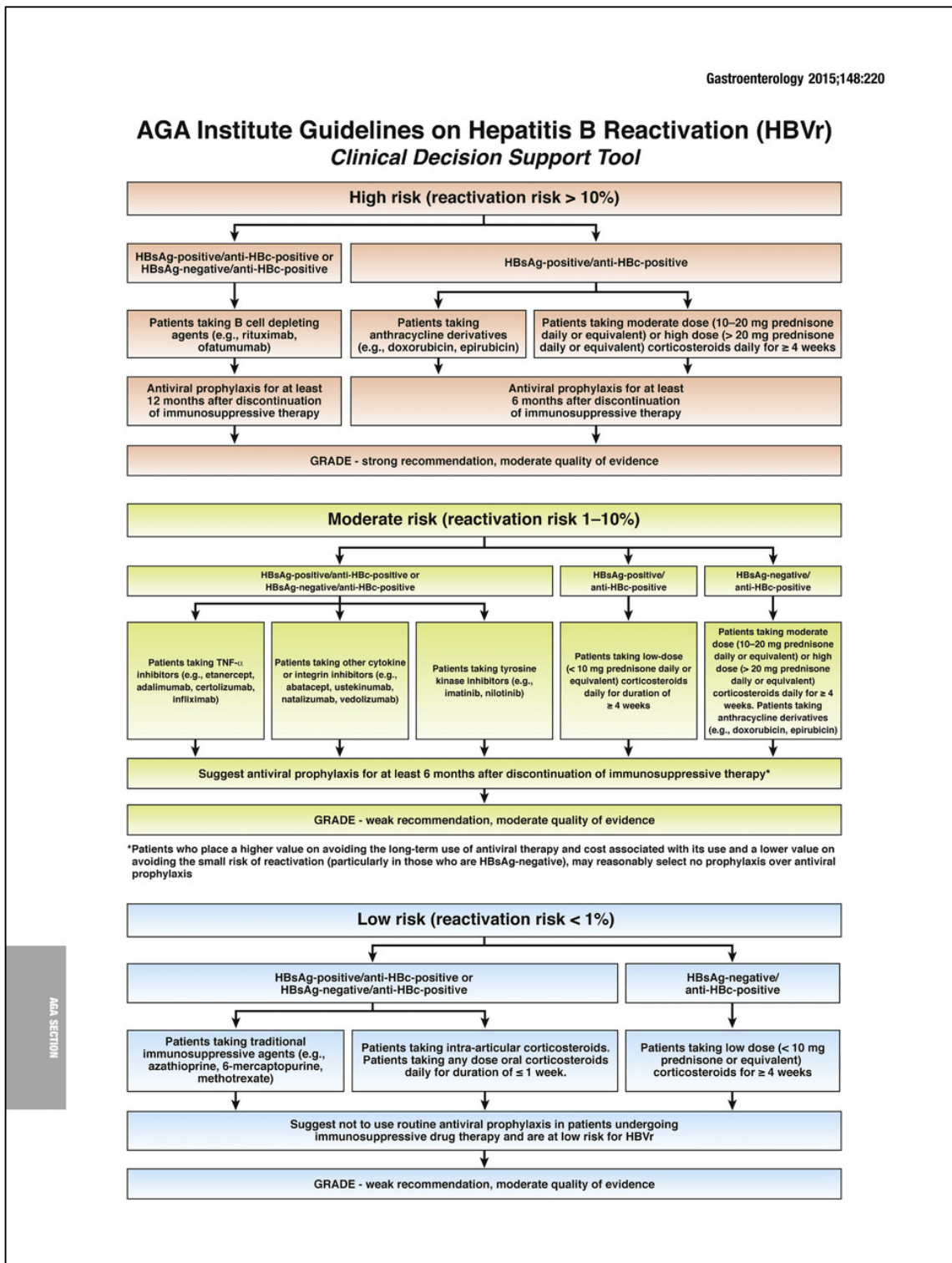


Table 1.

Recommended Screening for Hepatitis B to Mitigate the Risk of HBV Reactivation

| Organization | Recommendation | Tests to be Done |
|--|---|-----------------------------------|
| Centers for Disease Control and Prevention | Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders | HBsAg, anti-HBc, anti-HBs |
| American Academy of Dermatology | Hepatitis B reactivation after treatment with tumor necrosis factor inhibitors has been reported; in the appropriate clinical setting, patients should be screened for hepatitis B infection. | Not stated |
| American Association for the Study of Liver Diseases | All patients before beginning immunosuppressive therapy | HBsAg, anti-HBc |
| Asian Pacific Association for the Study of the Liver | Before receiving immunosuppression or chemotherapy, patients should be screened for HBsAg. Patients who are going to receive biologic agents such as anti-CD20 or anti-tumor necrosis factor- α should be screened for anti-HBc. | HBsAg, anti-HBc |
| European Association for the Study of the Liver | All candidates for chemotherapy and immunosuppressive therapy should be screened. | HBsAg, anti-HBc |
| American Society of Clinical Oncology | Physicians may consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy is recommended. | Consider HBsAg, consider anti-HBc |
| US Preventive Services Task Force | Screen persons who are immunosuppressed. | HBsAg |

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Source:

- 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;61:703-11. [[PubMed Abstract](#)]

