

## Hepatitis B reactivation and screening

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### 1. What is Hepatitis B and Hepatitis B reactivation?<sup>1,2</sup>

Hepatitis B is the liver infection caused by Hepatitis B Virus (HBV), a DNA virus that can result in chronic liver disease. It is transmitted mainly by infected blood or body fluids primarily through perinatal, percutaneous or sexual exposure. Household contacts are considered at increased risk, as well as individuals born in intermediate/high HBV endemic regions. Chronic HBV infection is the leading cause of liver cancer and liver transplantation in Canada.

The clinical presentation of HBV can vary from asymptomatic hepatitis to potentially fatal fulminant hepatic failure. Less than 10% of children and approximately 30-50% of adults with acute infection experience symptoms. Elevated liver chemistry and presence of serologic HBV markers are still detected in asymptomatic individuals. These markers include HBV antigens, antibodies to the antigens and HBV DNA (HBV viral load).

About 95% of infected immune competent adults clear the virus within 6 months and become Hepatitis B surface antigen (HBsAg) negative but develop antibodies to the surface antigen (HBsAb positive). Adults who cannot clear the virus, will remain HBsAg positive and will be a chronic carrier. These adults are typically immunocompromised and/or have other viral co-infections such as HIV, Hepatitis C or Hepatitis D. All individuals who have had or are carrying HBV, test positive for Hepatitis B core antibodies (HBcoreAb). Of note, latent HBV remains in the liver, even after cleared infection, placing anyone with a history of HBV infection at risk of HBV “reactivation”.

Hepatitis B reactivation is the increase in HBV replication in individuals with a chronic or resolved HBV infection. Risk factors include certain host factors (male, advanced age, cirrhosis and type of cancer), degree and type of immunosuppressive therapy, and status of the hepatitis B infection or co-infection. HBV replication is sometimes described as a two-phase process:

- 1) If the immune system is suppressed (e.g., initiation of immunosuppressive therapy):
  - host immunity against HBV is decreased
  - HBV replication and hepatocyte HBV-antigen expression are increased
- 2) When the immune system recovers (e.g., withdrawal of immunosuppressive therapy):
  - host immunity against HBV is increased
  - immunocompetent cells attack the hepatocytes that had become HBV antigen-laden, resulting in elevation of ALT (ALT “flare”) and liver injury

Hepatitis B reactivation may occur spontaneously or whenever an individual with past or chronic HBV infection becomes immunosuppressed, receives treatment with or completes immunosuppressive therapy, recovers from immunosuppression, or completes antiviral therapy. It is usually associated with increasing or fluctuating ALT and HBV DNA (HBV viral load) levels.

## 2. Why are cancer patients screened for Hepatitis B Virus (HBV)?<sup>1,3,4</sup>

Cancer patients may be unaware of past asymptomatic HBV infection and are at increased risk of HBV reactivation depending on their type of cancer, choice of anticancer therapy (including radiation therapy and transarterial chemoembolization) and extent of immunosuppression. HBV reactivation can be prevented by screening and appropriate antiviral prophylaxis or monitoring.

HBV reactivation has been well documented in HBV patients with hematologic malignancy. The risk of reactivation for these patients is about 48% with chronic HBV and about 18% with past HBV. The HBV reactivation risk is less for HBV patients with solid tumours and has been less studied.

The risk of HBV reactivation with cancer medication is usually classified as low (< 1%), moderate (1-10%), and high (> 10%), although there are a group of these patients that are in a very high risk group.

Patients receiving **B-cell depleting therapy** are at **very high risk** for HBV reactivation of their chronic HBV or past HBV. The BC Cancer [Protocol Summary for Hepatitis B Virus Reactivation Prophylaxis \(SCHBV\)](#) lists examples of B-Cell depleting cancer therapies. These therapies include various anti-B-cell or plasma cell monoclonal antibodies (e.g., daratumumab, rituximab), bi-specific antibodies (e.g., blinatumomab), bruton’s tyrosine kinase (BTK) inhibitors (e.g., ibrutinib, acalabrutinib) and chimeric antigen receptor T-cell (CAR T-cell) therapy.

All patients receiving **autologous or allogeneic hematopoietic stem cell transplant** are considered at **high risk** for HBV reactivation of their chronic HBV or past HBV.

Patients receiving **anthracyclines** or **high-dose corticosteroids** (prednisone equivalent  $\geq 20$  mg/day for  $\geq 4$  weeks) who have chronic HBV (HBsAg positive) are considered at **high risk** for HBV reactivation, while patients receiving these therapies who had past HBV (HBsAg negative, HBcoreAb positive) are considered at **moderate risk**.

### 3. Who should be screened?<sup>3,4</sup>

HBV screening is recommended for any cancer patient at increased risk of HBV reactivation prior to receiving immunosuppressive therapy. A new BC Cancer (Nov 2024) [Hepatitis B Reactivation and Cancer Medication Patient Handout](#) is available for patients. The handout discusses the importance of testing for past or chronic Hepatitis B infection prior to patients starting cancer treatment.

Patients with hematologic malignancies are at a particularly high risk for reactivation due to their exposure to the immunosuppressive effects of both cancer treatment and their disease. BC Cancer has incorporated routine HBV screening in the relevant hematologic protocols found in the [Lymphoma, Myeloma](#) and [Leukemia](#) protocol summaries. As described above, assessment of HBV reactivation risk in individuals with chronic or previous HBV infection is based on treatment regimen risk. Hormonal therapy is unlikely to increase the risk of HBV reactivation risk. HBV serology testing is used to identify patients at risk for reactivation.

### 4. How do you interpret the results of the Hepatitis B screening tests?<sup>2,4,6,7</sup>

Hepatitis B serology testing can be used to identify patients at risk for HBV reactivation by measuring serum concentrations of HBV-specific antigens and antibodies (see Table 1). Different combinations of serology markers are used to determine the clinical status of the hepatitis B infection (see Table 2).

HBsAg, HBcoreAb (Anti-HBc) and HBsAb (Anti-HBs) are hepatitis B screening tests required at baseline for select [Lymphoma, Myeloma](#) and [Leukemia](#) protocols. Patients that test positive for HBsAg and/or HBcoreAb will also require a baseline HBV DNA (HBV viral load) test.

## Hepatitis B Screening

**Table 1. Common Hepatitis B Serology Markers**

Marker	Definition	Note
HBsAg	Hepatitis B surface antigen	<ul style="list-style-type: none"> <li>▪ <b>General marker of Hepatitis B infection</b></li> <li>▪ Usually disappears in 4 to 6 months after acute infection</li> <li>▪ Persistence for &gt; 6 months suggests chronic infection</li> </ul>
HBcoreAb or Anti-HBc <ul style="list-style-type: none"> <li>▪ IgM anti-HBc</li> <li>▪ IgG anti-HBc</li> </ul>	Hepatitis B core antibody	<ul style="list-style-type: none"> <li>▪ <b>Confirmed prior exposure to HBV</b> (resolved, acute or chronic infection)</li> <li>▪ IgM anti-HBc: Acute Hepatitis B infection (usually disappears within 6 months)*</li> <li>▪ IgG anti-HBc: Resolved or chronic Hepatitis B infection</li> </ul>
HBsAb or Anti-HBs	Hepatitis B surface antibody	<ul style="list-style-type: none"> <li>▪ Immunity to Hepatitis B from resolved infection or from vaccination</li> </ul>
HBV DNA	Hepatitis B DNA Viral load	<ul style="list-style-type: none"> <li>▪ Therapeutic monitoring of chronic HBV infection</li> <li>▪ Magnitude of HBV replication and risk of disease progression</li> <li>▪ Predictor of cirrhosis and hepatocellular carcinoma</li> </ul>

\* IgM anti-HBc can remain positive for many years in some chronically infected patients or in chronically infected patients during HBV reactivation

**Table 2. Interpretation of Hepatitis B Serology Test Results**

Tests	Results	Interpretation	At Risk For Reactivation
HBsAg	–	Susceptible to future hepatitis infection	No
Anti-HBc	–		
Anti-HBs	–		
HBsAg	–	Immune due to natural infection	Yes
<b>Anti-HBc</b>	+		
Anti-HBs	+		
HBsAg	–	Immune due to hepatitis B vaccination	No
Anti-HBc	–		
Anti-HBs	+		
<b>HBsAg</b>	+	Acutely infected	Yes
<b>Anti-HBc</b>	+		
IgM anti-HBc	+		
Anti-HBs	–		
<b>HBsAg</b>	+	Chronically infected	Yes
<b>Anti-HBc</b>	+		
IgM anti-HBc	–		
Anti-HBs	–		
HBsAg	–	<b>Four Possible Interpretations:</b> 1. Resolved infection <sup>a</sup> (most common) 2. False positive anti-HBc, thus susceptible 3. ‘Low level’ chronic infection <sup>b</sup> 4. Resolving acute infection <sup>c</sup>	Yes
<b>Anti-HBc</b>	+		
Anti-HBs	–		

a After many years of acute hepatitis B recovery, anti HBs may fall to undetectable levels

b After many years of chronic hepatitis B infection, HBsAg may fall to undetectable levels

c May occur in patients with fulminant hepatitis B where virus clearance tends to be more rapid. During this window, HBsAg may disappear while anti-HBs is still not detected. The sole marker that indicates acute hepatitis B infection is the presence of IgM anti-HBc.

## 5. How do you minimize the risk for Hepatitis B reactivation?<sup>2,4,7,8,9</sup>

The [SCHBV](#) protocol outlines the current baseline tests, reactivation risk assessment, antiviral prophylaxis and monitoring for patients undergoing systemic therapy for lymphoid, plasma cell and myeloid malignancies. The BC Cancer [Lymphoma, Myeloma](#) and [Leukemia](#) protocols reference [SCHBV](#) in a number of sections of their protocols.

See the ***Appendix: Risk of hepatitis B reactivation with immunosuppressive therapy*** in the [SCHBV](#) protocol. The prescribed cancer treatment regimen is used to determine reactivation risk and whether monitoring alone or added antiviral prophylaxis is recommended. Level of risk also determines how long the prophylactic antiviral and/or monitoring will continue after cancer therapy has been completed.

### Monitoring

The **Tests** section of the SCHBV protocol outlines the hepatitis B screening tests recommended at baseline for select protocols: HBsAg, HBcoreAb (Anti-HBc) and HBsAb (Anti-HBs). Patients who test positive for either HBsAg or HBcoreAb during baseline testing, also require a baseline HBV DNA (HBV viral load) test.

A positive HBsAg result (**HBsAg reactive**) usually indicates active HBV infection, and ongoing monitoring of HBV DNA (HBV viral load) and ALT every 3 months and for at least 12 months after stopping antivirals is recommended. HBV DNA reflects viral load and ALT is a liver enzyme that can indicate liver inflammation although it does not always correlate with disease severity.

Individuals with past HBV that has resolved may test negative for HBsAg but positive for HBcoreAb (**HBsAg nonreactive, HBcoreAb reactive**). They will require monitoring of HBsAg, along with HBV DNA (HBV viral load) and ALT as above, for possibility of change to HBsAg positive status.

A hepatology specialist should be consulted for co-managing patients with liver fibrosis or cirrhosis, when monitoring is challenging, if HBV DNA (HBV viral load) level rises or if a HBsAg negative patient becomes positive.

### Antiviral prophylaxis

The antivirals recommended for HBV prophylaxis are entecavir and tenofovir. Entecavir 0.5 mg PO daily is preferred; it requires dose modifications for altered kidney function. An alternative to entecavir is tenofovir disoproxil fumarate (Viread®-type) 300 mg PO daily, which can cause renal toxicity and also requires dose modifications for altered kidney function. Antiviral prophylaxis will continue during and from 6 to 18 months after completion of cancer treatment, depending on cancer treatment regimen.

Entecavir and tenofovir are PharmaCare benefits requiring exceptional [Special Authority](#) approval when antiviral prophylaxis is recommended. The new BC Cancer guidelines in the [SCHBV](#) protocol have been developed after discussion with PharmaCare.

## References:

1. Lau G, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. *Hepatol Int* 2021;15:1031-1048.
2. BC Centre for Disease Control Communicable Disease Control Hepatitis B. Vancouver, British Columbia: BCCDC. April 2021; Available from: [http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/BCCDC%20HBV%20Guideline%20FINAL%20April\\_2021.pdf](http://www.bccdc.ca/resource-gallery/Documents/Guidelines%20and%20Forms/Guidelines%20and%20Manuals/Epid/CD%20Manual/Chapter%201%20-%20CDC/BCCDC%20HBV%20Guideline%20FINAL%20April_2021.pdf)
3. Hwang J, Feld J, Hammond S, et al. Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update. *J Clin Oncol* 2020 38:31, 3698-3715.
4. BC Cancer Chemotherapy Protocols. Vancouver, British Columbia: BC Cancer; [updated continuously;cited 2025 Jan 14]; Available from: <http://www.bccancer.bc.ca/health-professionals/clinical-resources/chemotherapy-protocols>.
5. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. *Can J Infect Dis Med Microbiol* 2005; 16(2):65-72.
6. Kao JH. Diagnosis of Hepatitis B virus infection through serological and virological markers. *Expert Rev Gastroenterol Hepatol* 2008 Aug; 2(4):553-562
7. De Lemos, M, Savage K, Gerrie A. BC Cancer Provincial Pharmacy and Lymphoma and Myeloma Tumour Group Briefing Note: Changes in Antiviral Prophylaxis for Hepatitis B Virus Reactivation in Lymphoma/Myeloma Patients. BC Cancer communication.18 August 2023.
8. Government of British Columbia [Internet]. Victoria BC: Government of British Columbia; 2022. Special Authority; [updated 2024 Nov 19;cited 2025 Jan 14]; Available from: <https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/programs/special-authority>