Recommendations for Hepatitis B Virus Screening and Management

R1. Screening for cancer patients prior to immunosuppressive treatment

- Test all cancer patients who are starting immunosuppressive treatment (or have already started but have not been screened previously) with 3 tests: 1) hepatitis B surface antigen (HBsAg), 2) hepatitis B core antibody (anti-HBc) (total immunoglobulin (Ig) or IgG), and 3) antibody to hepatitis B surface antigen (anti-HBs) – prior to, or sometime within, the first cycle. *(Type of recommendation: Evidence based; benefits outweigh harms; Strength of recommendation: Strong*).
    - **Patient Education Resource** available in **Appendix A** to support clinical discussion.
    - Some patients with hematologic malignancy may have impaired antibody responses and may test negative for anti-HBc and anti-HBs despite past exposure to HBV. Physicians are advised to consider HBVr if hepatitis occurs during/post systemic cancer treatment in such patients despite negative serologies at baseline.

- In most cases it is not necessary to delay cancer treatment while awaiting results of screening HBV tests (except for patients awaiting a bone marrow transplant and/or patients with unexplained hepatitis). *(Type of recommendation: Evidence based; benefits outweigh harms; Strength of recommendation: Strong).*

- Consider retesting for HBV markers (HBsAg, HBcAb, HBsAb) when a new line of cancer treatment is planned/started. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Moderate).*
    - Special considerations: recent travel to an endemic country, ongoing risk factors (e.g., hemodialysis, IV drug use) and/or unexplained changes in liver enzymes.
    - It may be reasonable to defer HBV testing in the absence of on-going risk factors if there is a result available in the past 12 months.

R2. Management for patients with chronic HBV (HBsAg+)

Initial Management:

- Order HBV DNA. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Public Health Labs: In addition to the local lab requestion, complete the HBV DNA Test Requisition available on the Public Health Ontario website and indicate the reason for the test Failure to do so may result in an auto-rejection if there is a test on file within the last 6 months. Hospital Labs: Indicate the reason in clinic notes**.**

- Refer to a clinician experienced in HBV management (e.g., Hepatologist, Infectious Diseases Specialist, Gastroenterologist) *(Type: Consensus based, benefits outweigh harms; Strength of recommendation: Strong).*
- While awaiting HBV Specialist consultation, start entecavir 0.5 mg po daily (1st line) (LU code 508) or tenofovir 300 mg po daily (if past HBV treatment) (LU code 521). Continue antiviral therapy during and for at least 12 months after the cessation of systemic treatment and/or as recommended by HBV expert clinician. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Both antivirals are well-tolerated.
    - Entecavir and tenofovir disoproxil are funded in Ontario.
    - Avoid Entecavir for Lamivudine-resistant HBV or in pregnant patients.
    - Avoid Tenofovir, if possible, in patients with renal impairment or patients receiving concurrent nephrotoxic therapy.
    - For HIV co-infected patients, consult HIV Specialist. HBV antiviral therapy (typically Tenofovir) can often be incorporated into the HIV treatment regimen.
    - Refer to **Clinical Considerations** in **Appendix B** for more information.

Monitoring recommendations during antiviral therapy:

- Check ALT and HBV DNA level every 6 months during antiviral therapy. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

Monitoring recommendations after the cessation of antiviral therapy:

- Monitor ALT and HBV DNA monthly for the first 3 months after stopping antivirals then four additional times at 6, 12, 18 and 24 months. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

R3. Management for patients with clinically resolved HBV (HBsAg-/Anti-HBc+)

3a. Immunosuppressive cancer treatments associated with a high risk of HBVr

Cancer treatments associated with an established high risk of HBVr include B-cell depleting including anti-CD20 drugs (e.g., rituximab, obinutuzumab, ofatumumab), anti-CD38 drugs (e.g., daratumumab, isatuximab), BTK Inhibitors (e.g., ibrutinib, acalabrutinib, zanubrutinib), STC (allogenic and autologous), and CAR T-cell therapy. PD-1/PD-L1 inhibitors (e.g., pembrolizumab, nivolumab) and patients treated with transarterial chemoembolization (TACE) may have an increased risk of HBVr. There may be other agents that carry a risk of reactivation, and the clinician is advised to consider the risk as literature evolves for newer agents, and to err on the side of caution when new immunosuppressive agents are introduced to the treatment plan.

Antiviral therapy:

- Start entecavir 0.5 mg po daily (1st line) (LU code 508) or tenofovir 300 mg po daily (if past treatment) (LU code 521). Continue antiviral therapy during and for at least 12 months after the cessation of systemic treatment. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Both antivirals are well-tolerated.
    - Refer to **Clinical Considerations** in **Appendix B** for more information.

Monitoring recommendations during antiviral therapy:

- Check HBsAg and ALT every 6 months during antiviral therapy. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

Monitoring recommendations after the cessation of antiviral therapy

- Check HBsAg and ALT levels at 1 month, 3 months, and 6 months, after stopping antiviral therapy. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

At the earliest sign of HBV reactivation (HBsAg converts to positive):

- Order HBV DNA. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Public Health Labs: In addition to the local lab requisition, complete the HBV DNA Test Requisition Form available on the Public Health Ontario website and indicate the reason for the test (i.e., pre-treatment, post-treatment). Failure to do so may result in an auto-rejection if there is a test on file within the last 6 months.
- Refer urgently to a clinician experienced in HBV management (e.g., Hepatologist, Infectious Diseases Specialist, Gastroenterologist). *(Type: Consensus, benefits outweigh harms; Strength of recommendation: Strong).*
- Consider starting entecavir 0.5 mg po daily (1st line) (LU code 508) or tenofovir 300 mg po daily (if past HBV treatment) (LU code 521) if you anticipate a delay in HBV Specialist consultation. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Both antivirals are well-tolerated.
    - Refer to **Clinical Considerations** in **Appendix B** for more information.

3b. Immunosuppressive cancer treatments not associated with a high risk of HBVr

Monitoring recommendations during cancer treatment:

- Check HBsAg and ALT testing every 3 months during systemic treatment. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

Monitoring recommendations after cancer treatment:

- Check HBsAg and ALT at 3 months and 6 months after completion of systemic treatment. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*

At the earliest sign of HBVr (HBsAg converts to positive):

- Order HBV DNA. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Public Health Labs: In addition to the local lab requestion, complete the HBV DNA Test Requisition Form available on the Public Health Ontario website and indicate the reason for the test (i.e., pre-treatment, post-treatment). Failure to do so may result in an auto-rejection if there is a test on file within the last 6 months. Hospital Labs: Indicate reason in clinic notes.
- Refer to clinician experienced in HBV management (e.g., Hepatologist, Infectious Disease Specialist, Gastroenterologist) urgently. *(Type: Consensus, benefits outweigh harms; Strength of recommendation: Strong).*
- Consider starting entecavir 0.5 mg po daily (1st line) (LU code 508) or tenofovir 300 mg po daily (if past treatment) (LU code 521) if you anticipate a delay in HBV Specialist consultation. *(Type: Consensus based; benefits outweigh harms; Strength of recommendation: Strong).*
    - Both antivirals are well-tolerated.
    - Refer to **Clinical Considerations** in **Appendix B** for more information.

Appendix A: Patient Education Resource

Hepatitis B and Cancer Medications - What you need to know

What is Hepatitis B?

Hepatitis B is a serious liver infection caused by a virus. Your liver is an organ that helps your body process nutrients, filter your blood and fight infections.
Hepatitis B may cause:

- No signs or symptoms. Many people who get the hepatitis B never feel sick and get better. They may not even know they have the infection.
- Illness for a few weeks (acute infection). An acute infection can make you feel tired and less hungry. Your skin and/or eyes may also turn yellow (jaundice).
- A serious life-long illness (chronic hepatitis B). Untreated chronic hepatitis B can lead to liver scarring (cirrhosis), liver cancer, and death. Chronic hepatitis B is known as a 'silent' disease because you can have it for many years before it causes any problems in your body.

How does Hepatitis B spread from person to person?

Hepatitis B spreads through **contact with blood and other body fluids** of an infected person. Since people can have the infection and not know it, they can also spread it to others without knowing it.
Most people who get hepatitis B get it from the following situations:

- Sexual contact with someone who is infected with hepatitis B
- A mother with hepatitis B spreading it to their baby during childbirth
- People with hepatitis B spreading it to children and other members of their household
- People who are exposed to blood or body fluids while at work (e.g., health care workers)
- Travel to parts of the world where hepatitis B is more common
- Getting tattoos, piercings, pedicures, manicures, or medical procedures with unclean equipment

Hepatitis B **cannot** be spread through touching objects, sneezing, coughing, hugging, or eating meals with someone who has hepatitis B.

How do I know if I have Hepatitis B?

Hepatitis B can only be diagnosed by a blood test.
The blood tests will show if you:

- Had hepatitis B and got better
- Have hepatitis B now
- Have never had hepatitis B

If you have had the hepatitis B vaccine it is likely that you are protected against the infection for life.

People receiving cancer medications will be tested for hepatitis B before treatment begins. This includes those who have been vaccinated for hepatitis B.

If you have hepatitis B it can cause problems such as liver damage or liver failure during your treatment. Your cancer care team will need to plan your care so that the hepatitis does not cause any health problems for you during treatment.

How will my hepatitis B be managed during cancer treatment?

Your cancer care team will use your blood test results to plan how to care for your hepatitis B during your treatment. Your health care team may:

- Monitor your hepatitis B and your liver health through blood tests every 3 to 6 months
- Prescribe medicine to keep your liver healthy. You will take the medicine during your cancer treatment, and for up to 12 months after your cancer treatment ends.
- Refer you to a doctor that specializes in liver health to help look after your hepatitis B.

Talk to a member of your cancer care team for more information about your care and treatment.

Appendix B: Clinical Considerations for Entecavir and Tenofovir

	Entecavir	Tenofovir
Advantages	• Low rate of resistance in treatment naïve patients • Can be used for patients on dialysis	• Can be used in patients who have had resistance to other drugs
Disadvantages	• Lack of safety data in pregnancy • Can cause increased ALT, lactic acidosis, and hepatomegaly	• Can cause nephrotoxicity, decreased bone mineral density, lactic acidosis, and hepatomegaly
Preferred For	Treatment of naïve patients, especially: • Patients with decompensated cirrhosis • Patients with renal impairment or those receiving concomitant therapy that may reduce renal function (with caution – monitor closely)	• Patients who have had prior antiviral treatment • Patients who are pregnant • For HIV co-infected patients, consult HIV Specialist. HBV antiviral therapy (typically tenofovir) can often be incorporated into the HIV treatment regimen
Do Not Use For	• HIV co-infected patients (consult with HIV Specialist) • Lamivudine-resistant HBV • Patients who are pregnant	• If possible: patients with renal impairment or patients receiving concurrent or recent nephrotoxic therapy
Dose Adjustments	Use with caution and decrease dose if reduced kidney function - consider: • CrCl 30-49 mL/min: full dose every other day (q 48hrs) • CrCl 10-29 mL/min: full dose every 72 hours • CrCl < 10 mL/min or dialysis: full dose every 7 days No dose adjustment required for hepatic impairment	Use with caution and decrease dose if reduced kidney function - consider: • CrCl 30-49 mL/min: full dose every other day (q 48hrs) • CrCl 10-29 mL/min: full dose every 72 to 96 hours • hemodialysis: full dose every 7 days • No data on use if CrCl < 10 mL/min No dose adjustment required for hepatic impairment