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LE SAVOIR PREND FORME

Screening for latent infections before initiating immunosuppressive therapy for cancer

August 24, 2026

TARGETED USERS

Healthcare professionals, pharmacists and nurses working in oncology.

OBJECTIVE

To harmonize clinical practices and promote the appropriate use of screening tests for latent infections in oncology.

TARGET POPULATION

Adults who are candidates for initiation of immunosuppressive cancer treatment.

EXCLUSIONS

- Pediatric patients
- Individuals with a known active infection from one of the pathogens targeted by the screening
- Hematopoietic stem cell transplantation
- CAR T-cell therapy

This clinical tool is provided for information purposes only and is not a substitute for the clinician's judgment in the performance of activities reserved for clinicians by law or regulation.

This tool is not intended to provide guidance on the management of each of the latent infections covered. It addresses decision-making regarding screening for latent infections before initiating treatment, as well as key elements of monitoring and indications for referral to a specialist.

The **legal aspects** of certain infections covered by this tool, such as notifiable diseases, are not addressed.

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Click here to consult all the scientific publications on this subject.

APPROPRIATE USE OF SCREENING TESTS

Screening for latent infections before initiating immunosuppressive cancer therapy, with an emphasis on the appropriate use of screening tests for the following infections:

- human immunodeficiency virus (HIV)
- hepatitis B virus (HBV)
- hepatitis C virus (HCV)
- herpes simplex virus (HSV)
- varicella-zoster virus (VZV)
- cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)
- tuberculosis (TB)
- strongyloidiasis (STRNG)

→ For some infections (HIV, HBV, HCV), screening is routinely recommended. For others, the need for screening may vary depending on the type of immunosuppressive cancer treatment or the presence of risk factors.

→ It is appropriate to screen for varicella-zoster virus, herpes simplex virus, cytomegalovirus, Epstein-Barr virus, tuberculosis and strongyloidiasis only when there are risk factors for infection and/or clinically significant reactivation risk.

→ Conducting screening in the absence of a risk of infection or reactivation risk generates many clinically insignificant results that may, in turn, lead to unnecessary tests or treatments with significant economic and organizational implications.

→ If a previous **negative** screening result is available, repeat screening is not necessary unless there have been risk factors for infection since the previous test.

→ Screening tests performed during immunosuppressive treatment may yield false-negative results. A prior history of infection should take precedence over a negative test result.

Québec

SUMMARY OF SCREENING RECOMMENDATIONS

Treatment with a combination of agents
Perform screening when recommended for at least one of the combined immunosuppressive agents.

Screening recommendations by type of cancer treatment

Targets	Type of treatment	HIV	HBV	HCV	HSV	VZV	CMV	EBV	TB	STRNG
BLOOD CELLS										
B and T lymphocytes	Anti-CD52	✓	✓	✓	✓	✓	✓	✗	!	!
	Anti-CD38						✗ a			
B lymphocytes	Bispecific antibodies	✓	✓	✓	✓	✓	✓	✓	!	!
	Anti-BCMA				✗	✗	✗	✗		
	Anti-CD19									
	Anti-CD20									
	Immunomodulatory agents					✓				
T lymphocytes	CCR4 inhibitors	✓	✓	✓	✓	✓	✓	✗	!	!
	JAK inhibitors				✗		✗		✓ b	
	CTLA-4 inhibitors					✗			!	
	LAG-3 inhibitors									
	PD-1/ PD-L1 receptor inhibitors									
SIGNALING PATHWAYS										
mTOR	mTOR inhibitors	✓	✓	✓	✗	✗	✗	✗	!	!
	PI3K inhibitors						✓			
Tyrosine kinases	BCR::ABL inhibitors	✓	✓	✓	✗	✗	✗	✗	!	!
	Bruton's tyrosine kinase inhibitors									
Proteasome	Proteasome inhibitors	✓	✓	✓	✓	✓	✗	✗	!	!
Histone deacetylases	Histone deacetylase inhibitors	✓	✓	✓	✗	✗	✗	✗	!	!
DNA replication	Topoisomerase inhibitors	✓	✓	✓	✗ c	✗ c	✗	✗	!	!
	Antimetabolites						✓ d			
	Alkylating agents								✓ e	
	Other						✗		!	
Microtubules function	Antimitotic agents	✓	✓	✓	✗	✗	✗	✗	!	!
Glucocorticoid receptors	Glucocorticoids	✓	✓	✓	✓ f	✓ f	✗	✗	✓ g	!

LEGEND
✓ Recommended ! May be recommended depending on risk factors ✗ Not recommended

a: CMV screening is not recommended for daratumumab.
b: TB screening is recommended for ruxolitinib.
c: VZV and HSV screening is not recommended during chemotherapy for a solid tumor. Screening is recommended during induction treatment for acute myeloid leukemia and during treatment for hematological malignancies involving the lymphoid lineage: e.g., lymphoma, myeloma, and lymphocytic leukemia.
d: CMV screening is recommended for fludarabine and bendamustine.
e: TB screening is recommended for bendamustine.
f: HSV and VZV screening is recommended for patients receiving high-dose corticosteroids (prednisone ≥ 30 mg/day or equivalent for 3 weeks or longer).
g: TB screening is recommended for patients receiving high-dose corticosteroids (prednisone ≥ 15 mg/day or equivalent for ≥ 1 month or longer).

LATENT INFECTIONS REQUIRING SCREENING

HUMAN IMMUNODEFICIENCY VIRUS

✅ HIV screening is recommended for all treatments.

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• HIV serology (anti-HIV 1 and 2 antibodies)	For individuals with a newly positive HIV serology result, urgent specialist consultation is recommended before initiating immunosuppressive treatment. For individuals with known HIV infection, consult treating physician to adjust antiretroviral therapy based on the anticancer treatment regimen.

HEPATITIS B

✅ Hepatitis B screening is recommended for all treatments.

SCREENING TESTS TO PERFORM	ADDITIONAL TESTING FOLLOWING POSITIVE SCREENING RESULT
• HBs antigen (HBsAg) • Anti-HBc antibodies • Anti-HBs antibodies	When HBsAg and/or anti-HBc antibodies are positive, perform HBV DNA testing.

FOLLOW-UP AFTER SCREENING

- Individuals with a positive HBsAg or HBV DNA test should be assessed by a specialist.
- Individuals with resolved HBV infection (positive anti-HBc, negative HBsAg, negative HBV DNA, with or without positive anti-HBs) should undergo an assessment of their risk of reactivation and either monitoring or prophylaxis should be considered, depending on the clinical situation.
  - **Monitoring** of individuals with resolved HBV infection involves testing alanine aminotransferase (ALT) and HBV DNA every 3 to 6 months during treatment.
  - Consultation with an infectious disease or hepatology specialist should be considered to determine the appropriate antiviral **prophylaxis** for patients at moderate to high risk of hepatitis B reactivation.

LIMITATIONS

Intravenous immunoglobulin (IVIG) therapy **may** render false positive anti-HBs or anti-HBc test results.



VACCINATION

When all three serologic markers are negative (HBs-Ag-, anti-HBc-, anti-HBs-), hepatitis B vaccination should be recommended, ideally before initiating immunosuppressive treatment. In some cases, it may be appropriate to delay treatment.

HEPATITIS C

✅ Hepatitis C testing is recommended for all treatments.

SCREENING TESTS TO PERFORM	ADDITIONAL TESTING FOLLOWING POSITIVE SCREENING RESULT
• Anti-HCV antibody serology. • **Do not repeat serologic testing** in individuals who have previously had a positive serological test. Instead, perform an HCV RNA test if the infection has never been treated or if it was previously treated but there are ongoing risk factors for exposure.	When the anti-HCV antibody test is positive or indeterminate, perform an HCV RNA test to distinguish between active and resolved infection.

FOLLOW-UP AFTER SCREENING

In individuals who test positive for HCV RNA, antiviral treatment should be considered under the supervision of a specialist.

HERPES SIMPLEX VIRUS

⚠ Do not screen individuals with a documented history of oral or genital herpes. They should be considered seropositive regardless of the test result.

✅ Screening for **herpes simplex virus** is recommended **only for the following treatments**:

- anti-CD52 agents, anti-CD38 agents, bispecific antibodies, CCR4 inhibitors, proteasome inhibitors, induction treatment for acute myeloid leukemia, treatment of hematological malignancies involving the lymphoid lineage, and high-dose corticosteroids.

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• Total HSV antibodies or HSV-1 and HSV-2 antibodies	• HSV prophylaxis should be considered for individuals with positive serology or a history of HSV infection. • Repeat HSV serology is not recommended during prophylaxis.

VARICELLA-ZOSTER VIRUS

⚠ Do not screen individuals with a documented history of varicella vaccination, chickenpox or shingles. They should be considered seropositive regardless of the test result.

✅ Screening for **varicella-zoster virus** is recommended **only for the following treatments**:

- anti-CD52 agents, anti-CD38 agents, bispecific antibodies, immunomodulatory agents, CCR4 inhibitors, JAK inhibitors, proteasome inhibitors, induction therapy for acute myeloid leukemia, treatment of hematological malignancies involving the lymphoid lineage, and high-dose corticosteroids.

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• VZV antibody serology	• VZV prophylaxis should be considered for individuals with positive serology or a history of VZV infection. • Repeat VZV antibody serology is not recommended during prophylaxis.



VACCINATION

- Recommend inactivated varicella-zoster vaccination to all individuals who have never been vaccinated, as soon as immunosuppressive therapy is being planned.
- Administration of the **live-attenuated varicella vaccine** is **contraindicated** in individuals receiving immunosuppressive therapy.

CYTOMEGALOVIRUS

✅ Screening for **cytomegalovirus** is recommended for the following treatments:

- bispecific antibodies, anti-CD52 agents, CCR4 inhibitors, PI3K inhibitors, fludarabine (antimetabolites) and bendamustine (alkylating agents).

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• CMV IgG antibodies	In symptomatic individuals who are CMV-positive, consider performing regular nucleic acid amplification testing (NAAT) for plasma CMV DNA during immunosuppressive therapy.

EPSTEIN-BARR VIRUS

✅ Screening for **Epstein-Barr virus** is recommended only for treatment with bispecific antibodies.

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• EBNA IgG antibodies • VCA IgG antibodies	Routine monitoring of EBV DNA is not recommended in the absence of symptoms.

TUBERCULOSIS INFECTION

Screening for tuberculosis infection is recommended:

- in all individuals receiving the following treatments[1]:
  - ruxolitinib;
  - bendamustine;
  - glucocorticoids;
- in the presence of a risk factor for TB **exposure**, for all other treatments.

RISK FACTORS FOR TUBERCULOSIS EXPOSURE*
• Contact with a person with active tuberculosis • Immigrants from countries with a high incidence of tuberculosis (> 50 TB cases per 100,000 population; see box) • Individuals from the Canadian far north • Individuals who use injection or inhaled drugs • Residence or travel abroad for 3 months or more in certain circumstances (e.g., prolonged stays, likely contact with people with tuberculosis, or a high prevalence of tuberculosis in the destination; see box) • Incarceration • Homelessness

* Healthcare professionals are considered to have a risk factor for exposure only in the event of documented contact.

To determine whether a country has an incidence rate above the threshold of 50 tuberculosis cases per 100,000 population, consult the WHO tool.

This tool is provided for guidance only and does not replace clinical judgment. The epidemiology of tuberculosis infection at the time of immigration should be taken into consideration.

For individuals born in Quebec before 1960, the epidemiology of tuberculosis at the time of birth should also be taken into consideration.

SCREENING TESTS TO PERFORM	ADDITIONAL TESTS FOLLOWING THE POSITIVE SCREENING
• Tuberculin skin test (TST) **or** interferon-gamma release assay (IGRA) when there is a risk factor for exposure. • Perform sequential testing (TST **and** IGRA) when the individual has a high risk factor for exposure and progression to active tuberculosis, depending on the type of immunosuppressive therapy. If the first test is positive, the second test is not necessary.	Clinical assessment and chest x-ray to rule out active tuberculosis before initiating preventive treatment.
FOLLOW-UP AFTER SCREENING	
Consult a specialist to determine the appropriate preventive treatment for individuals with a positive screening result, after active tuberculosis has been ruled out.	
LIMITATIONS	
• Screening tests may have lower sensitivity in immunosuppressed individuals. • IGRA testing is preferred for individuals who: 1. received Bacillus Calmette-Guérin (BCG) vaccination after one year of age; 2. are unable or unlikely to return for TST reading at 48-72 hours.	

1. Clinical practice guidelines and the product monographs for immunosuppressive agents recommend TB screening for all individuals receiving these treatments.

STRONGYLOIDIASIS

Screening is recommended **based on the risk of exposure** to strongyloidiasis.

RISK FACTORS FOR EXPOSURE TO STRONGYLOIDIASIS
Birth, residence, or long-term travel totaling 6 cumulative months in an endemic country: • High risk of exposure: Southeast Asia, Oceania, Sub-Saharan Africa, South America, and the Caribbean. • Moderate risk of exposure: Mediterranean countries, the Middle East, North Africa, the Indian subcontinent, Asia and other tropical or subtropical regions.

SCREENING TESTS TO PERFORM	FOLLOW-UP AFTER SCREENING
• Anti-*S. stercoralis* IgG antibody serology **and/or** • Stool testing including detection of *S. stercoralis* eggs and larvae by microscopy of fresh or preserved stool specimen, as well as *S.stercoralis* culture.	In the event of a positive test result, refer the individual to a specialist for management and treatment of the infection.

LIMITATIONS
• Serology has good sensitivity, whereas stool testing is highly specific. • False-positive serologic results may occur due to other helminth infections, particularly nematode infections.

In individuals at very high risk of exposure, empiric treatment may be indicated before serologic results are available. Consultation with an infectious disease specialist is recommended.

This document was developed based on the guidelines established by INESSS through a systematic process drawing on the scientific literature as well as the knowledge and experience of Quebec clinicians and experts. For further details, see inesss.qc.ca.

For more details, including references, please refer to the **report associated** with this clinical tool.

For any questions relating to clinical tools, write to **info-outils.cliniques@inesss.qc.ca**.

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APPENDIX

Screening recommendations were classified by treatment type according to the targets of immunosuppressive treatments. The table below provides a list of medications available in Quebec for each type of immunosuppressive treatment.

TARGET	TYPE OF TREATMENT	MEDICATION
Blood cells		
B and T lymphocytes	**Anti-CD52**	Alemtuzumab
	Anti-CD38	Daratumumab, isatuximab
B lymphocytes	**Bispecific antibodies**	Elranatamab, teclistamab, blinatumomab, epcoritamab, glofitamab, talquetamab, tarlatamab, tebentafusp and others
	Anti-BCMA	Belantamab mafodotin
	Anti-CD19	Tafasitamab
	Anti-CD20	Obinutuzumab, rituximab, ibritumomab tiuxetan
	Immunomodulatory agents	Thalidomide, lenalidomide, pomalidomide
T lymphocytes	**CCR4 inhibitors**	Mogamulizumab
	JAK inhibitors	Fedratinib, ruxolitinib
	CTLA-4 inhibitors	Ipilimumab, tremelimumab
	LAG-3 inhibitors	Relatlimab (combined with nivolumab)
	PD-1/PD-L1 receptor inhibitors	Atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, pembrolizumab, toripalimab, tislelizumab
Signaling pathways		
mTOR	**mTOR inhibitors**	Everolimus, temsirolimus
	PI3K inhibitors	Alpelisib, idelalisib
Tyrosine kinases	**BCR::ABL inhibitors**	Asciminib, bosutinib, dasatinib, imatinib, nilotinib, ponatinib
	Bruton's tyrosine kinase inhibitors	Acalabrutinib, ibrutinib, zanubrutinib
Proteasome	**Proteasome inhibitors**	Bortezomib, carfilzomib, ixazomib
Histone deacetylases	**Histone deacetylase inhibitors**	Vorinostat, romidepsin
DNA replication	**Topoisomerase inhibitors**	Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone, irinotecan, topotecan, etoposide
	Antimetabolites	Methotrexate, 6-mercaptopurine, fluradabine, fluorouracil, gemcitabine, cladribine, clofarabine, cytarabine, nelarabine, azacitidine, capecitabine, pemetrexed, pralatrexate, decitabine
	Alkylating agents	Busulfan, carmustine, cyclophosphamide, chlorambucil, melphalan, ifosphamide, thiotepa, mitomycin C, lomustine, carboplatin, cisplatin, oxaliplatin, trabectedin, bendamustine
	Other	Bleomycin
Microtubule function	**Antimitotic agents**	Paclitaxel, docetaxel, eribulin, vinblastine, vincristine, vinorelbine
Glucocorticoid receptors	**Glucocorticoids**	Dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone

Given the rapid evolution of available treatments, the list may not be exhaustive.