Hepatitis B Virus Reactivation with Immunosuppression

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Table 1 Interpretation of results from triple screening of hepatitis B [5••]

Testing results			Interpretation
HBsAg	Anti-HBs	Anti-HBc*	
-	-	-	Non-immune, vaccinate
-	+	+	Immune-control
-	+	-	Immune-protected
+	-	+	Infected
-	-	+	Exposed

Table 2 Definitions of HBV reactivation and hepatitis flare [7]

	AASLD	APASL	EASL
HBV reactivation	-HBV DNA elevation compared to baseline, or any increase if no baseline available -Previously HBsAg-negative and anti-HBc-positive persons with seroconversion to HBsAg positivity	-HBV DNA ≥ 2 log increase, or newly appearing HBV DNA to a level ≥ 100 IU/mL in previously stable or undetectable persons -HBV DNA at a level ≥ 20,000 IU/mL in a person with no previous baseline level	Not clearly defined
Hepatitis flare	Elevation of ALT 3 times greater than the baseline and at a level > 100 U/L	Elevation of aminotransferase levels > 5 times the upper limit of normal and twice the value at baseline	Not clearly defined

CHRONIC HEPATITIS B INFECTION (HBsAg +)*							
	HBsAg	**Anti-HBc**	**Anti-HBs**	**HBV Viral Load**	**Liver Enzymes**	**Synthetic function**	**Symptoms**
Pre-treatment	Positive	Positive	Negative	Baseline	Normal	Normal	Absent
Increased Viral Replication	Positive	Positive	Negative	**INCREASED**	Normal	Normal	Absent
HBVr-associated hepatitis	Positive	Positive	Negative	**INCREASED**	**INCREASED**	Normal	**May be present**
HBVr-associated liver failure	Positive	Positive	Negative	**INCREASED**	**INCREASED**	**ABNORMAL**	**PRESENT**
Recovery	Positive	Positive	Negative	Return to baseline	**Improved**	Normal	Normal
PAST HEPATITIS B INFECTION (HBsAg -)							
Pre-treatment	Negative	Positive	May be positive or negative	Negative	Normal	Normal	Absent
Increased Viral Replication	**May become positive****	Positive	May be positive or negative	**Positive**	Normal	Normal	Absent
HBVr-associated hepatitis	Positive	Positive	May be positive or negative	**INCREASED**	**INCREASED**	Normal	**May be present**
HBVr-associated liver failure	Positive	Positive	May be positive or negative	**INCREASED**	**INCREASED**	**ABNORMAL**	**PRESENT**
Recovery	Variable+	Positive	May be positive or negative	Variable+	Improved	Normal	Normal

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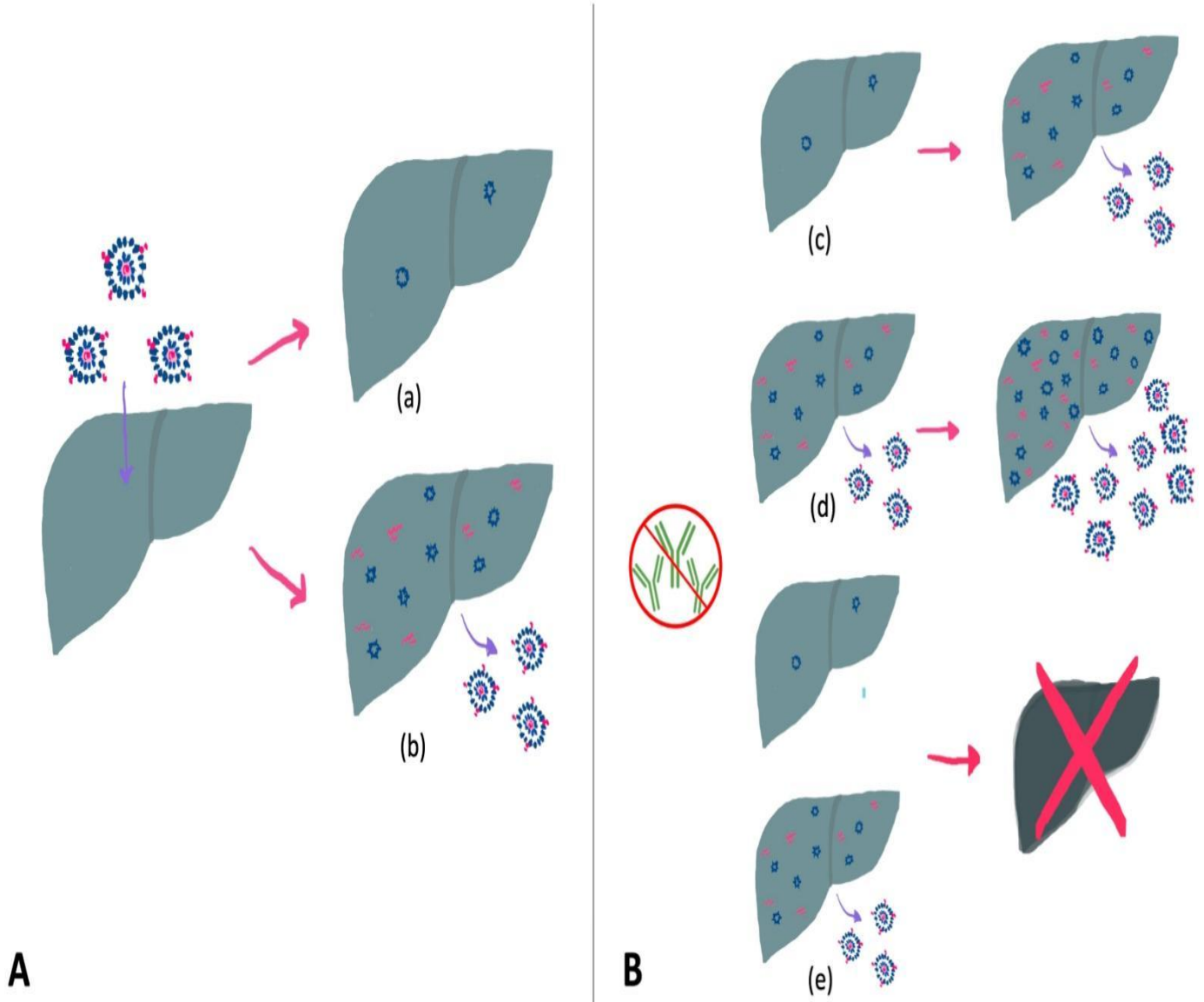
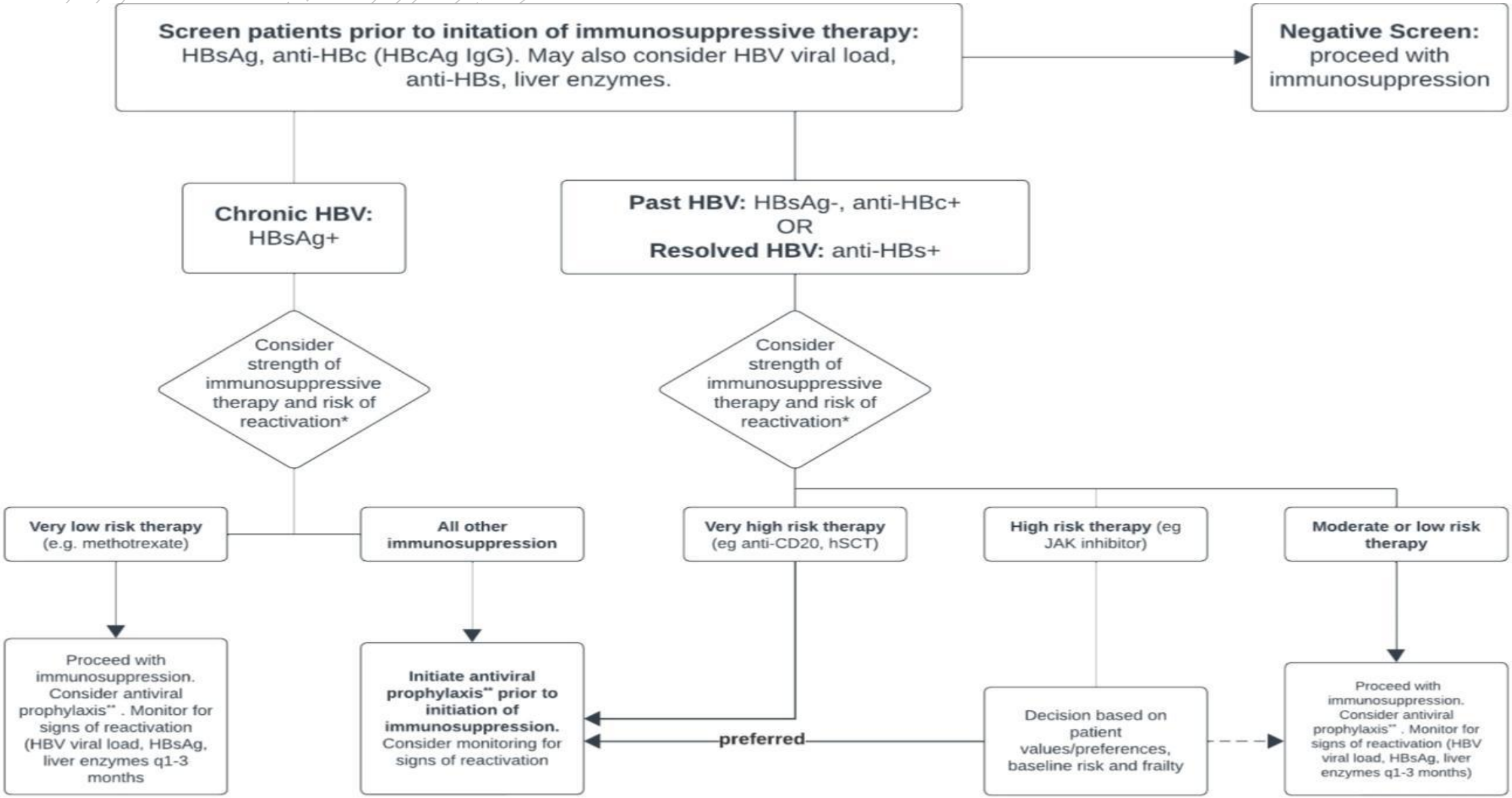


Risk of Reactivation	HBsAg Positive (Chronic HBV)	HbsAg Negative, anti-HBc Positive (Past HBV)
High (>10%)	Anti-CD20 * Hematopoietic stem cell transplant Immune checkpoint inhibitors Cytokine inhibitors Tyrosine kinase inhibitors CAR-T cell immunotherapy Corticosteroids (≥20 mg/day for ≥4 weeks) Alkylating agents Anti-proliferative agents Calcineurin inhibitors mTOR inhibitors Janus kinase (JAK) inhibitors	Janus Kinase (JAK) inhibitors
Moderate (1–10%)	T-cell-depleting agents Anti-TNF (without steroids) + Anti-rejection (without steroids)	Anti-CD20 **,+ Cytokine inhibitors CAR-T cell immunotherapy Corticosteroids (≥20 mg/day for ≥4 weeks) Calcineurin inhibitors Hematopoietic stem cell transplant +
Low (<1%)	Methotrexate Azathioprine	Anti-TNF agents ++ Immune checkpoint inhibitors Tyrosine kinase inhibitors T-cell-depleting agents Alkylating agents
Rare		Methotrexate Azathioprine Cytotoxic chemotherapy without steroids
Unknown		mTOR inhibitors


Screen patients prior to initation of immunosuppressive therapy: HBsAg, anti-HBc (HBcAg IgG). May also consider HBV viral load, anti-HBs, liver enzymes.
Negative Screen: proceed with immunosuppression
Chronic HBV: HBsAg+
Past HBV: HBsAg-, anti-HBc+ OR **Resolved HBV:** anti-HBs+
Consider strength of immunosuppressive therapy and risk of reactivation*
Consider strength of immunosuppressive therapy and risk of reactivation*
Very low risk therapy (e.g. methotrexate)
All other immunosuppression
Very high risk therapy (eg anti-CD20, hSCT)
High risk therapy (eg JAK inhibitor)
Moderate or low risk therapy
Proceed with immunosuppression. Consider antiviral prophylaxis** . Monitor for signs of reactivation (HBV viral load, HBsAg, liver enzymes q1-3 months
Initiate antiviral prophylaxis prior to initiation of immunosuppression.** Consider monitoring for signs of reactivation
preferred
Decision based on patient values/preferences, baseline risk and frailty
Proceed with immunosuppression. Consider antiviral prophylaxis** . Monitor for signs of reactivation (HBV viral load, HBsAg, liver enzymes q1-3 months)

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
B-cell-depleting agents Humanized antibodies	Rituximab, alemtuzumab, obinutuzumab, ocrelizumab, ofatumumab	Commonly prescribed for active RA and is a key component of B-cell non-Hodgkin lymphoma treatment regimens	Target CD20 sites on B lymphocyte cells, suppressing humoral immunity that controls HBV by generating neutralizing antibodies against circulating viruses	High risk; use prophylaxis	High risk; use prophylaxis
T-cell activation blocking agents Monoclonal antibody	Belatacept, abatacept, secukinumab, mogamulizumab	Belatacept is used in combination with other agents as prophylaxis for kidney transplant rejection. Abatacept is used for different autoimmune arthritic conditions, including RA, psoriatic arthritis, and juvenile idiopathic arthritis	These agents hinder CD2-mediated T-cell co-stimulation. Belatacept blocks T-cell activation by inhibiting the CD80/CD86 binding costimulatory signal. In contrast, alefacept disrupts CD2-mediated T cell co-stimulation, resulting in T cell depletion involving natural killer cells [17] Secukinumab impedes the IL-17 pathway of pro-inflammatory cytokines released from immune cells, including T-helper cells. Mogamulizumab targets the C–C chemokine receptor 4 used for the treatment of relapse/refractory adult T cell leukemia/lymphoma [73] Mechanism of HBVr remains unclear	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis. In a recent study of patients with a kidney transplant receiving belatacept, 16.7% of 32 anti-HBc-positive patients encountered HBVr [18]

Immune checkpoint inhibitors	Durvalumab, atezolizumab, nivolumab, pembrolizumab, ipilimumab, tremelimumab, camrelizumab	Durvalumab and atezolizumab primarily treat NSCLC but may be used in treating other malignancies like HCC and melanomas, often in combination with other drugs. Nivolumab and pembrolizumab primarily treat melanomas and NSCLC. Ipilimumab is primarily used for melanomas. Tremelimumab combined with durvalumab or camrelizumab combined with apatinib can be used to treat HCC	Activate cytotoxic T cells by inhibiting immune-suppressive molecules like PD-1, PD-L1, and CTLA-4. Mechanism of HBVr remains unclear	Low risk when treated with concurrent HBV prophylaxis and/or treatment [19]	N/A

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
TKIs	Imatinib, nilotinib, erlotinib, dasatinib, ibrutinib	Used in hematologic malignancies such as chronic lymphocytic leukemia, mantle cell lymphoma, and Waldenstrom macroglobulinemia	Competitively inhibit ATP at the catalytic binding site of tyrosine kinase, potentially affecting HBV-specific immune control by disrupting kinase signaling pathways and lymphocyte proliferation crucial for immune activation [11••]	Moderate risk; use prophylaxis. In a retrospective study, it was estimated that 9.36% of HBsAg (+) patients had HBVr [20••]	Moderate risk; use prophylaxis
TNF-α inhibitors	Adalimumab, etanercept, certolizumab, infliximab	Used in the treatment of immune-related diseases such as IBD, RA, spondylarthritis, and psoriasis	Inhibit TNF, which triggers various pro-inflammatory signaling pathways. They can result in reduced cytokine cascade involved in HBV clearance, decreased lymphocyte clearance and apoptosis, and insufficient T-cell response [11••]. TNF may also activate a unique host antiviral pathway that can cause regulate cccDNA, so blocking it with these agents can predispose one to HBVr [11••]	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis

			HBVr [11••]		
Proteasome inhibitors. Small molecule inhibitor	Bortezomib, carfilzomib, ixazomib	Used for the treatment of multiple myeloma and mantle cell lymphoma	Block proteasomes, potentially preventing the breakdown of pro-apoptotic factors and triggering programmed cell death in cancerous cells. They are believed to disrupt pathways essential for the proliferation of vital B and plasma cells that play a key role in HBV immune control [11••]	Moderate risk; use prophylaxis	Moderate risk; use prophylaxis
Anthracyclines Intercalating agent	Doxorubicin, epirubicin, daunorubicin	Used for the treatment of neoplastic conditions, including metastatic breast cancer, acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma	DNA intercalating agents and topoisomerase II inhibitors. Mechanism of HBVr remains unclear	High risk; Use prophylaxis. A prospective study found that 41% of HBsAg-positive patients treated with doxorubicin had HBVr [10]	Moderate risk; Use prophylaxis

Drug class	Drug examples	Drug indication	Mechanism of action	Risk and prophylaxis in HBsAg + patients	Risk and prophylaxis in HBsAg-/anti-HBc + patients
Corticosteroids	Prednisone, prednisolone, methylprednisolone, dexamethasone	Used for a variety of conditions: RA, IBD, asthma, and chronic obstructive pulmonary disease	These agents work primarily by binding to the glucocorticoid receptor, which leads to inhibition of pro-inflammatory signals and promotion of anti-inflammatory signals. Mechanism of HBVr involves suppression of cell-mediated immunity by inhibiting interleukin production, which are in turn important for T and B-cell production [11••]	High risk *For intra-articular steroids in any dose* ≤ 1 week: low risk; no prophylaxis; monitor HBV DNA and ALT every 3 months ≥ 10 mg/day for ≥ 4 weeks: high risk; use prophylaxis ≤ 10 mg/day for ≥ 4 weeks: moderate risk; use prophylaxis	Intermediate risk *For intra-articular steroids in any dose* ≤ 1 week: low risk; no prophylaxis; monitor HBsAg, HBV DNA, and ALT every 3 months ≥ 10 mg/day for ≥ 4 weeks: moderate risk; use prophylaxis

			[11••]		
Other immunosuppressive agents	Azathioprine, 6-mercaptopurine, methotrexate	Used for a variety of conditions: transplant anti-rejection medication, multiple sclerosis, IBD, RA	Azathioprine works as a purine metabolism antagonist, resulting in inhibition of DNA and RNA synthesis. 6-mercaptopurine works as a phosphoribosyl pyrophosphate amidotransferase inhibitor, inhibiting the synthesis of DNA and RNA [9] Methotrexate inhibits dihydrofolate reductase, which ultimately results in purine and thymidylate deficiencies and consequently, reduction in DNA synthesis [21]	Low risk; no prophylaxis needed. Monitor HBV DNA and ALT every 3 months	Low risk; no prophylaxis needed Monitor HBsAg, HBV DNA, and ALT every 3 months

Hepatitis B Virus Reactivation with Immunosuppression

- CDC recommends a triple-panel screening (HBsAg, anti-HBc, and anti-HBs) for all high-risk individuals .
- Recent systematic review suggested that higher anti-HBs titers (>100 IU/L) may be protective against HBV reactivation, while low or negative titers may be associated with reverse seroconversion

Checkpoint Inhibitors, Tyrosine Kinase Inhibitors, and mTOR Inhibitors

- anti-HBV prophylaxis may be recommended in patients with positive HBsAg, though it is unlikely to be necessary in patients with negative HBsAg and positive anti-HBc.

solid-organ transplant recipients

- Current AASLD guidelines recommend solid-organ transplant recipients with positive HBsAg receive lifelong anti-HBV therapy starting at the time of transplant surgery; though the evidence is less clear in patients with negative HBsAg and positive anti-HBc; a limited period of anti-HBV therapy is reasonable

Liver Transplant Recipients

- In liver transplantations involving recipients and/or donors who test positive for anti-HBc, providing lifelong HBV prophylaxis to recipients in conjunction with their immunosuppression is recommended.
- TAF and ETV stand as the preferred HBV prophylactic agents, and their administration is recommended for patients at the time of transplantation

Anti-TNF Agents (Infliximab, Adalimumab, Certolizumab, and Etanercept)

- There is also a different risk of reactivation associated with higher-potency agents in patients with positive HBsAg (e.g., infliximab, 12–39%) compared to lower potency agents (e.g., etanercept, 1–5%)
- Overall, most experts agree that prophylaxis is warranted in patients with positive HBsAg, whereas those with negative HBsAg and positive anti-HBc may be evaluated on a case-by-case basis.

Antiviral Prophylaxis: Choice of Agent and Duration of Therapy

- Current guidelines recommend the use of prophylactic first-line nucleot(s)ide analogues (NAs), such as entecavir, tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF), due to their high resistance barrier and potency
- Pegylated interferon is not recommended.
- In patients with chronic hepatitis B (HBsAg positive), most studies recommend the initiation of NAs 7 days before the initiation of immunosuppressive therapy and continuation for at least 6–12 months after the discontinuation of therapy .
- A longer duration of therapy may be warranted in patients receiving anti-CD20 therapy, these patients often require a prolonged course of prophylaxis, though there is no consensus on the exact duration—the European Association for Study of the Liver (EASL) recommends 18 months of prophylaxis . whereas the American Society of Clinical Oncology (ASCO) and the American Gastroenterological Association (AGA) suggest a shorter course of 6–12 months.

Prophylaxis and Suggested Monitoring

- EASL also suggests monitoring HBsAg due to the high risks of acute hepatitis in patients who undergo HBsAg reverse seroconversion
- Therefore, for patients in whom NA prophylaxis is not started (low or intermediate risk), HBV DNA, HBsAg, and ALT levels should be obtained every 1–3 months.
- In the event of HBsAg reverse seroconversion, NA therapy should be started

- **Thank you for your attention!**