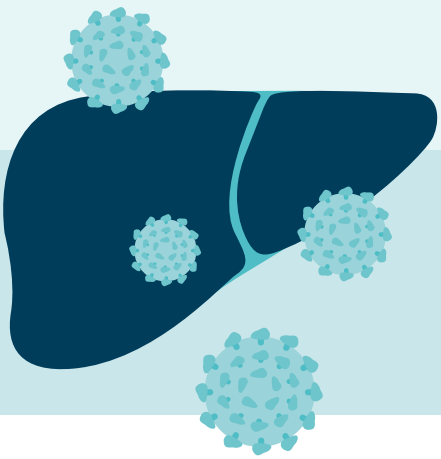
Reactivation of hepatitis B virus (HBV)

This guide provides a summary of the updated recommendations for the optimal prophylactic, therapeutic and clinical management of HBV reactivation in children undergoing immune suppressive, cytotoxic or biological modifier therapies, or with acquired immunodeficiencies.[1] HBV vaccine represents the most effective way to prevent HBV infection.

What is reactivation of HBV?

Reactivation of HBV is a known complication of immune suppressive, cytotoxic and biological modifier therapies,[2,3] irrespective of alanine aminotransferase level and of HBsAg reverse seroconversion, resulting in a sudden and rapid increase in HBV DNA level or the *de novo* detection of HBV DNA viremia. Reactivation occurs whenever the dynamic balance between HBV and the host's immune system changes causing a reduction in the host's immune control.

- Reactivation of HBV is an increasingly recognised but often lately diagnosed and misdiagnosed clinical problem
- The clinical course of HBV reactivation is unpredictable and ranges from mild hepatitis to death or need for liver transplantation
- There is a lack of systematic approach to the care of patients with, or at risk of, HBV reactivation
- Reactivation of HBV is preventable or receptive to treatment with the appropriate use of antiviral drugs
- Enhanced awareness of the risk of reactivation of HBV is crucial for its correct therapeutic management
- All patients at moderate or high-risk of HBV reactivation should receive prophylaxis
- Entecavir or tenofovir are the drugs of choice for prophylaxis or pre-emptive therapy of HBV reactivation



Clinical and therapeutic management of HBV reactivation in children

Clinical Question	Recommendation
Should children planned for immune suppressive, cytotoxic or biological modifier therapies be screened for HBV infection before starting treatment and which test(s) should be done for screening?	Routine HBV screening amongst all children who are at risk of HBV reactivation should be done by HBsAg, anti-HBs and anti-HBc testing.
Should HBV vaccination be done and when?	HBV vaccine represents the most effective way to prevent HBV infection.[4,5] All children and adolescents who are negative for HBsAg, anti-HBc and anti-HBs should be vaccinated against HBV as soon as possible before starting immune suppressive, cytotoxic or biological modifier therapies.
How can the risk of HBV reactivation be stratified for children?	Due to the lack of paediatric data the risk of HBV reactivation in children and adolescents should be extrapolated from adult studies and can be divided broadly into high risk (if the rate of HBV reactivation is >10%), moderate risk (if the rate of reactivation is between 1%–10%), and low risk (if the rate of reactivation is <1%). Patients undergoing bone marrow or haematologic stem cell transplant or solid organ transplant are at high risk of HBV reactivation.
When should antiviral prophylaxis be initiated?	For children and adolescents at a high or moderate risk of reactivation – it should be initiated before starting immune suppressive, cytotoxic or biologic modifier therapy
When should watchful monitoring and pre-emptive therapy be suggested?	Watchful monitoring of HBV DNA and aminotransferases levels, and prompt pre-emptive therapy are recommended for children and adolescents when the risk of HBV reactivation is low (<1%).
Which are the preferred drugs?	Antiviral drugs with a high barrier to resistance (entecavir or tenofovir) are recommended over lamivudine for prophylaxis, pre-emptive treatment and for treatment of HBV reactivation in patients undergoing immune suppressive, cytotoxic and biological modifier therapy.
How long should the antiviral prophylaxis last?	The duration is at least 6 months after discontinuation of immune suppressive, cytotoxic and biological modifier therapy. The duration of antiviral prophylaxis should be extended to 12 months when high risk treatments such as B cell-depleting agents are used and in patients undergoing bone marrow or haematologic stem cell transplant.

Anti-HBV drugs

None of the anti-HBV drugs currently available can be considered curative or eradicative for HBV. Two different classes of anti-HBV drugs are available: immune-modulators and nucleos(t)ide analogues (NA).[6]

Interferon (IFN) α and pegylated (PEG) IFN α act as immune-modulators and can be administered for a predefined duration with the aim of inducing an immune-mediated control of HBV infection to achieve long-lasting suppression of viral replication off-treatment[6]. NA have been characterised as carrying low (lamivudine, adefovir, telbivudine) or high (tenofovir and entecavir) genetic barriers to resistance.

Tenofovir and entecavir have no significant drug-drug interactions and excellent safety records,[7,8] which makes them suitable for long-term use.

Risk of HBV reactivation based on the type of therapy stratified by the characteristics of the patient

Therapeutic class	HBsAg positive and anti-HBc positive	HBsAg negative and anti-HBc positive with or without anti-HBs
B cell-depleting agents	high risk	high risk
Anthracycline derivatives	high risk	moderate risk
Corticosteroids	from extremely low to high risk*	moderate and low risk*
Tumour necrosis α inhibitors (more potent)	high risk	moderate risk
Tumour necrosis α inhibitors (less potent)	moderate risk	low
Other cytokine or integrin inhibitors	moderate risk	moderate risk
Tyrosine kinase inhibitors	moderate risk	moderate risk
Proteasome inhibitors	moderate risk	moderate
Other traditional immune suppressive agents	low risk	low risk
Histone deacetylase inhibitors	moderate risk	moderate risk
Immunophilin inhibitors	moderate risk	moderate risk
Systemic chemotherapy	moderate risk	moderate

* depending on dose and treatment duration

Management of specific cases

Recommendations for managing HBV reactivation in liver transplant recipients:

- HBsAg-positive liver transplant recipients with detectable serum HBV DNA should start antiviral therapy as soon as possible before transplant with the aim of achieving an undetectable HBV DNA level at the time of transplant.
- HBsAg-positive liver transplant recipients should be treated after liver transplant with the combination of HBIg and lifelong entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide for the prevention of HBV recurrence. HBIg could be discontinued (5-7 days) shortly after transplant in patients at low risk of recurrence.
- Anti-HBc positive and HBsAg negative liver transplant recipients should be treated with lifelong entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide.
- HBsAg-negative patients receiving livers from anti-HBc positive donors should receive lifelong antiviral prophylaxis with entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide.
- Anti-HBc and HBsAg negative recipients from anti-HBc positive donors should be vaccinated or given a booster dose when anti-HBs titre if <10 mIU/mL, in addition to antivirals.

Managing HBV reactivation in children undergoing haematologic stem cell transplantation

Such patients should be considered at high risk of HBV reactivation.[9] It is recommended that antiviral prophylaxis is initiated in:

- anti-HBc positive haematologic stem cell transplantation recipients regardless of their HBsAg status (positive and negative)
- HBsAg and anti-HBs negative patients receiving allo-haematologic stem cell transplantation with anti-HBc-positive donors.

Recommendations for managing HBV reactivation in non-liver solid organ transplant recipients:

- HBsAg-positive non-liver solid transplant recipients should receive lifelong antiviral therapy with entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide.
- Anti-HBc positive and HBsAg negative non-liver solid transplant recipients should be treated with entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide for 6-12 months after transplant and during periods of intensified immunosuppression.
- Anti-HBc and anti-HBs negative children receiving non-liver solid transplant from anti-HBc positive, HBsAg negative donors should be treated with entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide for 6-12 months.
- Vaccination of anti-HBc and HBsAg negative recipients or a booster dose when anti-HBs titre is <10 mIU/mL is recommended.

Managing HBV reactivation in children with acquired immunodeficiencies

Adults and children who are HIV-HBV co-infected are at increased risk of liver fibrosis progression, cirrhosis and hepatocellular carcinoma. It is recommended that:

- all HIV-positive children with HBV co-infection should start antiretroviral therapy irrespective of CD_4 cell count
- HIV-HBV co-infected children should be treated with a tenofovir disoproxil fumarate or tenofovir alafenamide-based antiretroviral regimen

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