Hepatitis A and B vaccination and prophylaxis against Hepatitis B reactivation in non-HIV immunosuppressed adults: Guidelines for clinicians
Acknowledgements

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Notes and disclaimer

The information contained in this brochure has been produced as a guide only and is not intended to replace specialist medical advice.

New vaccinations and related branding appear on the market regularly, so please refer to the Australian Technical Advisory Group on Immunisation for current information or visit www.immunise.health.gov.au for vaccine availability.

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Hepatitis A and B infections are preventable by vaccination and post-exposure prophylaxis. Hepatitis B virus can reactivate to cause hepatitis and liver failure in immunocompromised patients.
Hepatitis A and B vaccination and prophylaxis against Hepatitis B reactivation in non-HIV immunosuppressed adults

Introduction

Hepatitis B virus (HBV) persists in the body after serological recovery so reactivation can occur when an individual is immunosuppressed, with incidence as high as 65% in high risk patients. HBV reactivation is a sudden increase (e.g. \(>1 \log_{10}\)) in serum HBV DNA that can be associated with a HBV flare several weeks later. HBV flare is typically defined by three-fold elevation in serum aminotransferase levels from baseline values, and can lead to fulminant hepatic failure. There is a gradient of risk for HBV reactivation with immunosuppression, from high to low:

- HBsAg positive with high HBV viral load or HBeAg positive
- other HBsAg positive
- HBsAg negative and HBV DNA positive
- HBsAg negative and HBcAb positive and HBV DNA negative and HBsAb negative
- HBsAg negative and HBcAb positive and HBV DNA negative and HBsAb positive.

Flow diagram for the prevention of HBV reactivation in non-HIV immunosuppressed adults
Testing

Test HAV IgG, HBsAg, HBCAb and HBsAb.

If HBsAg or HBCAb test positive, order plasma HBV viral load, HBeAg and HBeAb.

Patients who are HBsAg negative and HBCAb positive with detectable plasma HBV DNA should be treated the same as HBsAg positive patients.

HAV and HBV vaccination

Indications

HBV vaccination is recommended for solid organ and haematopoietic stem cell transplants by Australian Immunisation Handbook (AIH) and the Infectious Diseases Society of America (IDSA).

Hepatitis B vaccination is suggested by the AIH for all other immunosuppressed adults, and by the IDSA for immunosuppressed adults at risk for acquiring Hepatitis B.

Hepatitis A vaccination is recommended by AIH and IDSA for liver transplant recipients, solid organ transplant recipients with chronic liver disease, and those immunosuppressed patients at risk for acquiring Hepatitis A.

The following define risk for acquiring hepatitis A or B:

- Intravenous drug users, inmates of correctional facilities, sex industry workers, men who have sex with men (risk for Hepatitis A and B).
- Aboriginal and Torres Strait Islanders (risk for Hepatitis A and B).
- Patients with chronic liver disease or chronic viral hepatitis (risk for Hepatitis A and B).
- Those with developmental disabilities or working with people who have developmental disabilities (risk for Hepatitis A and B).
- Those planning travel to endemic countries (risk for Hepatitis A or B depending on location).
- Those at occupational risk (risk for Hepatitis A or B depending on occupation).
- Recipients of blood products (risk for Hepatitis B).
- Patients on haemodialysis (risk for Hepatitis B).
- Patients who are close or sexual contacts of persons with hepatitis B (risk for Hepatitis B).
- Migrants from hepatitis B endemic countries (risk for Hepatitis B).

Given the high percentage of Australians travelling to countries endemic for hepatitis A and B (Asia, India, Africa), an argument could be made for Hepatitis A and B vaccination of all immunosuppressed Australian adults who lack immunity to these viruses.

It is preferable to administer HBV and HAV vaccines before immunosuppression for optimal efficacy but they are safe when administered while on immunosuppressants.
**HBV vaccination**

When only HBV vaccination is indicated, or HAV and HBV vaccination are indicated and the patient is Hepatitis A immune and Hepatitis B non-immune (HAV IgG positive and HBsAb<10IU/L):

- Hepatitis B vaccine 40mcg intramuscular (i.e. HBVax II Dialysis formulation 40mcg or 2x Engerix B 20mcg) given at 0, 1, 2 months.
- Accelerated Hepatitis B vaccination can be utilised where potent immunosuppression is required imminently. Give Hepatitis B vaccine (recombinant HBsAg 40mcg) on days 0, 7, 21.
- Check response by HBsAb level one month after the third dose. If HBsAb>10 IU/L give a final booster dose of 40mcg at six months after the first dose. If HBsAb<10 IU/L, give three further Hepatitis B vaccine 40mcg doses one month apart, again checking HBsAb one month after the last dose.
- If the patient remains with HBsAb<10 IU/L, refer to immunology for intradermal HBV vaccination.

**HAV vaccination**

When Hepatitis A vaccination is indicated and the patient is Hepatitis B immune and Hepatitis A non-immune (HAV IgG negative and HBsAb>10IU/L):

- Two doses of adult formulation Hepatitis A vaccine six months apart. Check HAV titre if there is a risk of exposure, such as planned travel to a high risk area.

**HAV and HBV vaccination**

When HAV and HBV are indicated and the patient is Hepatitis A and B non-immune (HAV IgG negative and HBsAb<10IU/L):

- Twinrix 720/20 (containing 720 ELISA units of HAV antigens and 20mcg recombinant HBsAg) plus additional Hepatitis B vaccine (Engerix B 20mcg), each given at 0, 1, 2 months.
- Accelerated combined HAV and HBV vaccination can be utilised where potent immunosuppression is required immediately. Use the same doses at days 0, 7, 21.
- Check response by HBsAb level one month after the third dose. If HBsAb>10 IU/L give final booster doses of Twinrix 720/20 and Engerix B 20mcg at six months after the first dose. If HBsAb<10 IU/L, give three further Hepatitis B vaccine 40mcg doses one month apart, again checking HBsAb one month after the last dose.
- If the patient remains with HBsAb<10 IU/L, refer to immunology for intradermal HBV vaccination.
- Check HAV titre if there is a risk of exposure, such as planned travel to a high risk area.
HBcAb positive (and HBsAg negative and HBV viral load negative)

These patients should be vaccinated the same as other patients according to the same indications. In particular for those that require it, a complete HBV vaccination course is recommended with serological follow up as described.

Post exposure prophylaxis

Immunosuppressed patients with no prior response to HBV vaccination should receive Hepatitis B Immunoglobulin 400 IU intramuscularly within 72 hours in the event of significant exposure (percutaneous, ocular, mucous membrane, sexual) to blood, blood-containing secretions or transplanted organ from an unidentified or HBV positive source. Those never vaccinated against HBV should additionally receive the first dose of a HBV vaccine course within seven days of exposure.

HAV non-immune (HAV IgG negative) immunosuppressed patients should receive normal human immunoglobulin 0.5mL/kg up to 15mL as a single IM injection within two weeks of exposure to HAV.

Risk of HBV reactivation

High risk (>10%)

HBsAg positive or HBV viral load positive: anti-CD20 therapy, haematopoietic stem cell transplantation, high dose steroids (>20mg/day prednisolone for > four weeks), solid organ transplant.

Moderate risk (1-10%)

HBsAg positive or HBV viral load positive: cytotoxic chemotherapy (including transarterial chemo-embolization), low dose steroids (<20mg/day prednisolone for >4 weeks), anti-TNF therapy, abatacept, integrin inhibitors, anti-CD52 therapy, tyrosine kinase inhibitors.

HBsAg negative and HBcAb positive and HBV viral load negative: anti-CD20 therapy or undergoing haematopoietic stem cell transplantation.

Low risk (<1%)

HBsAg positive or HBV viral load positive: azathioprine, 6-mercaptopurine, or methotrexate.

HBsAg negative and HBVcAb positive and HBV viral load negative: high dose steroids, cytotoxic chemotherapy, solid organ transplant recipients, anti-TNF therapy, abatacept, integrin inhibitors, anti-CD52 therapy, tyrosine kinase inhibitors.
Prophylaxis against HBV reactivation

Moderate or high risk

Antiviral prophylaxis:

- HBsAg positive or HBV viral load positive: entecavir 0.5mg daily*, or if contraindications use tenofovir 300mg daily*.
- HBsAg negative and HBcAb positive and HBV viral load negative: lamivudine 100mg daily*.
- Prophylaxis for a minimum six months after discontinuation of immunosuppressive therapy and minimum 12 months after anti-CD20 therapy. Perform three monthly LFTs and plasma HBV viral load during and until six months after ceasing antiviral therapy.

*Doses are for normal renal function.

Low risk

No antiviral prophylaxis:

- Perform three monthly LFTs, HBsAg and HBV viral load (and HBsAb level in those with baseline HBsAb>10 IU/L). Monthly testing can be considered at times of augmented immunosuppression (e.g. the first six months after solid organ transplantation, six months after therapy for solid organ rejection, use of multiple immunosuppressants).
References


5. Lok ASF, Bonis PAL. Hepatitis B virus reactivation associated with immunosuppressive therapy. UpToDate, last updated 11 Feb 2015.


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