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Abbr.	Meaning
AALD	Alcohol-Associated Liver Diseases
AFP	Alpha Fetoprotein
Alb	Serum albumin
ALT	Alanine transaminase
ANA	Antinuclear Antibody
ANCA	Anti-neutrophil cytoplasmic antibody
Anti-GBM	Anti–glomerular basement membrane disease
Anti-HBc	Hepatitis B core Antibody
Anti-HBe	Hepatitis B e-antigen Antibody
Anti-HBs	Hepatitis B surface Antibody
Anti-HCV	HCV antibody
APTT	Partial thromboplastin time
AST	Aspartate aminotransferase
BJP	Bence-Jones Proteins
CHB	Chronic Hepatitis B
CVVHDF	Continuous Veno-Venous Hemodiafiltration
DEXA	Dual-Energy X-Ray Absorptiometry
DNA	Deoxyribonucleic Acid
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
FRAX	Fracture Risk Assessment Tool
HAV	Hepatitis A Virus
HB**c**Ag	Hepatitis B core Antigen
HB**e**Ag	Hepatitis B e-Antigen
HBIg	Hepatitis B Immunoglobulin
HB**s**Ag	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HBV DNA	HBV Viral Load
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HD	Haemodialysis
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HIV RNA	HIV Viral Load test
IgE	Immunoglobulin E
IgM	Immunoglobulin M
INR	International Normalised Ratio
LFT	Liver function tests
MASLD	Metabolic Dysfunction-Associated Steatotic Liver Disease
MTCT	Mother-to-child transmission
NICE	National Institute for Health and Care Excellence
PEG-IFN	Peginterferon alfa-2a
PT	Prothrombin Time
UE	Urea and Electrolytes
ULN	Upper limit of normal
WHO	World Health Organisation

Background

Hepatitis B virus (HBV) is contracted either sexually or by blood-to-blood transmission. The combined prevalence of HBV and HCV is just over 2% in the UK. More than 95% of immune competent patients clear HBV (loss of HBsAg with development of anti-HBs and anti-HBc), unless the disease is contracted in childhood, when 10% or less clear HBV. The patients who do not clear the virus develop a protracted relapsing/remitting chronic hepatitis. Untreated, up to 15% of adults with chronic HBV (CHB) develop cirrhosis and of those up to 1/3 develop HCC or decompensated cirrhosis; up to 25% of children with CHB eventually become cirrhotic and up to 20% of those develop HCC or decompensated cirrhosis.

Hepatitis B treatment centres in the Eastern Liver Network

Usually, patients should be referred to their nearest treatment centre. These are:

- Addenbrooke's Hospital / Cambridge University Hospitals
- Basildon Hospital
- Bedford Hospital
- Broomfield Hospital
- Ipswich Hospital
- King's Lynn Hospital
- Luton and Dunstable Hospital
- Norfolk and Norwich Hospital
- Peterborough Hospital
- Southend Hospital
- West Suffolk Hospital

Testing

Who to test

We recommend that the following groups are tested for hepatitis B infection:

- Household contacts and sexual partners of HBV-infected individuals
- Individuals born in geographic regions with high HBsAg prevalence (≥2%)
- Individuals infected with HIV
- Individuals who are the source of blood or body fluid exposures
- Individuals with elevated ALT/AST of unknown aetiology
- Individuals with selected medical conditions who require immunosuppressive therapy
- Infants born to HBsAg-positive mothers
- Intravenous drug users
- Men who have sex with men
- Pregnant women
- UK born Individuals not vaccinated as infants whose parents were born in geographic regions with a significant HBsAg prevalence

How to test, interpret and manage results

Workup for patients with evidence of chronic HBV infection:

- Basic blood testing (UE, LFT, FBC, PT, APTT)
- Viral serology

  - Hepatitis B and C screen
  - HBV DNA viral load (In Epic, order as: Hepatitis B virus PCR (quant))
  - HIV antigen/antibody
  - HAV total antibody (immunity)
- Autoimmune
  - Liver autoantibodies
  - Immunoglobulin profile
- Metabolic
  - alpha-1 antitrypsin level
  - AFP
  - caeruloplasmin (if < 50 y/o)
  - ferritin
  - HbA1c
  - lipid profile
- Liver ultrasound for disease staging. Preferably completed before referral to secondary care.

Table 1: HBV Blood Test Interpretation

Tests	Results	Interpretation	Management
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible	Vaccination recommended if at risk of infection
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune due to past, resolved natural infection	See "HBV reactivation" section if immunosuppressed in the future. No other action is required.
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune due to hepatitis B vaccination	There are some circumstances where checking anti-HBs titres and giving booster doses based on response is recommended. Further details can be found in the Green Book.
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected	See management below.
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Negative Positive Negative	Chronically infected	Full workup* and referral to hepatology in one of the hepatitis B treatment centres.
HBsAg anti-HBc anti-HBs	Negative Positive Negative	Reflects one of the following scenarios: 1. Past, resolved infection (most common) 2. False-positive anti-HBc, thus susceptible (can occur in the context of recent receipt of blood products) 3. Resolving acute infection	Repeat tests to include LFT and HBV DNA. If LFT normal and HBV DNA negative, vaccinate if susceptible. Otherwise for full workup and referral to hepatology in one of the hepatitis B treatment centres.

Acute hepatitis B

The serological profile of acute HBV infection is given above. Incubation period is 1 to 4 months to symptoms. Patients are infectious from several weeks before symptoms until clearance of the virus. Anti-HBc IgM develops around the time of symptoms, HBsAg and HBV DNA several weeks before symptoms.

Acute HBV leads to jaundice in about 30% of adults. Overall, 95% adults will clear the virus and have long term immunity, 5% will develop chronic hepatitis (with 15% developing cirrhosis and 5% developing liver cancer or failure in the future) and < 0.5% will develop acute liver failure.

Management of acute HBV is supportive. Jaundice and transaminitis can be managed as an outpatient. Liver impairment (elevated PT) as an inpatient, until the course of the infection is ascertained. It is reasonable to treat patients with liver impairment with tenofovir or entecavir, although there are no robust data to supporting this recommendation.

HBsAg loss occurs within six months in the majority of patients. Persistence beyond this usually indicates chronic infection. If therapy is given for acute HBV, this can be stopped on loss of HBsAg.

Chronic hepatitis B (CHB)

Phases of chronic hepatitis B

Patients with CHB go through the following disease phases. The combination of ALT, HBV DNA and serological profile characterizes which phase a patient is in. This guides management.

Phase 1: HBeAg positive chronic **infection** ("immune tolerant" disease).

Immune responses are poorly induced. Patients are highly infectious with a high viral load, but do not develop liver damage. Emergent data suggests that prolongation of this phase is associated with HCC risk. Phase 1 usually lasts until the age of between 20 and 40 for childhood CHB, but is not usually prolonged for adults who develop CHB.

Phase 2: HBeAg positive chronic **hepatitis** (immune clearance/reactive disease).

During this phase, which lasts for between several weeks and several years, the immune system becomes active as detected by the development of anti-HBe. Significant liver damage may occur and close monitoring of patients with *immune tolerant* disease should occur by means of 3 monthly ALT and 6 monthly HBV DNA levels to detect entry into the *immune reactive* phase. An increased ALT or HBV DNA > 2000 IU/ml usually indicates liver biopsy with liver damage necessitating treatment.

Phase 3: HBeAg negative chronic **infection** (immune control/inactive carrier state).

This is sometimes referred to as low risk CHB. However, immune escape (**phase 4:** HBeAg negative chronic **hepatitis**) may occur in this phase and at six to twelve monthly ALT and HBV DNA assessments should be made with flares of either necessitating further assessment by means of a biopsy. Interval elastography is useful in monitoring for development of fibrosis in this phase, with an elevated score being investigated with liver biopsy. This approach allows the detection of HBeAg negative CHB that often requires treatment.

Phase 5: HBsAg negative phase.

This is characterised by loss of HBsAg and development of anti-HBs. The disease has 'burnt out'. Anti-HBs often takes some time to develop after HBsAg loss. Anti-HBs is the neutralising antibody and indicates recovery from and immunity to HBV.

These phases are demonstrated graphically below.

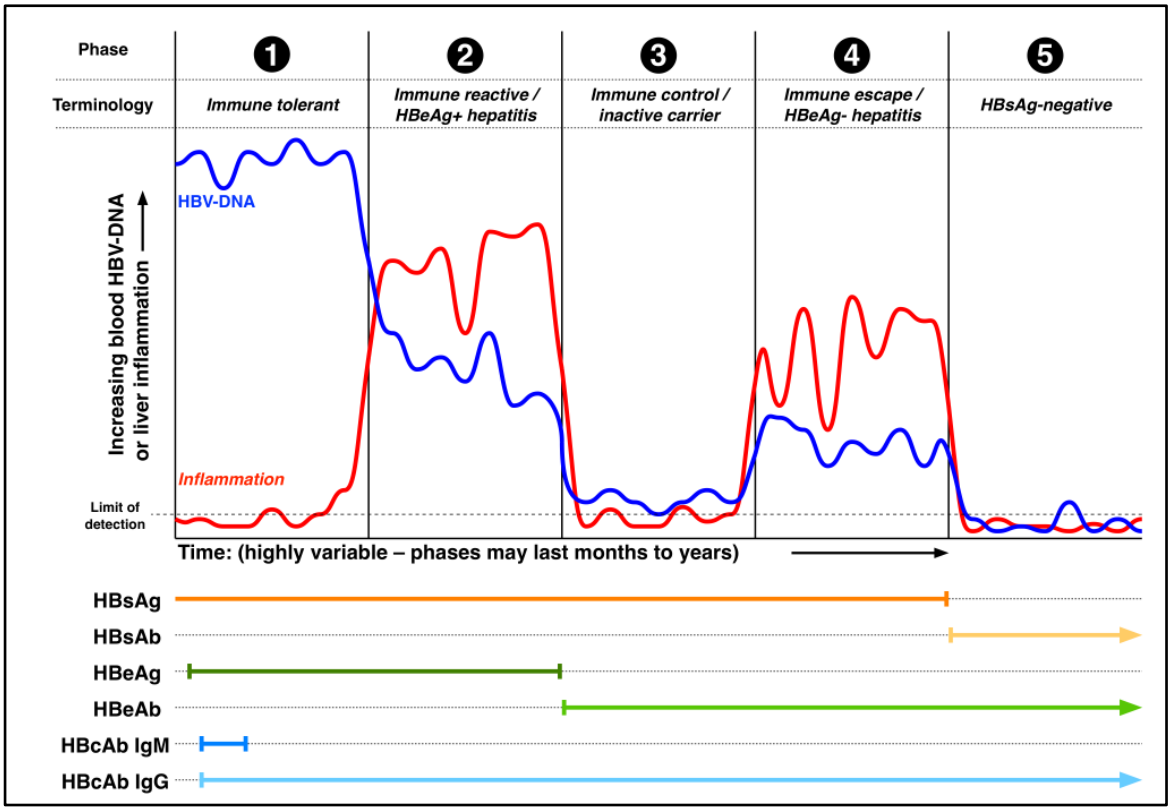


Figure 1: Phases of CHB

Treatment and Management

When to treat

Treatment usually follows full workup, including FibroScan and occasionally liver biopsy. EASL and WHO provide guidance, which together include:

- Significant inflammation or fibrosis (e.g. consistently or markedly elevated elastography values – WHO recommend a FibroScan score > 7 kPa)
- High or fluctuating viraemia with associated transaminitis (use EASL recommendations to guide - HBV DNA >20,000 IU/ml and ALT >2x ULN regardless of degree of fibrosis)
- Significant HCC risk (family history of HCC or high viral load/HBeAg positive > 30 yrs old, regardless of degree of fibrosis)
- Extrahepatic manifestations
- Family history of HBV related cirrhosis
- HIV coinfection
- Patients on immune suppression
- Extrahepatic manifestations
- Concurrent liver disease (e.g. MASLD, AALD)
- A “grey zone” has been established, which includes the following parameters and in which it is reasonable to treat:
  - Viral load log 3.3 (2,000 IU/mL) to 4.3 (20,000 IU/mL) on repeated measures, several months apart
  - Recurrent abnormal ALT over the course of several months
  - Mild inflammation

Choice of treatment and prophylaxis

First choice

- Entecavir 0.5/1 mg ONCE daily (dose dependent on clinical scenario), **or**
  - taken on an empty stomach (>2 hours before or after a meal)
- Tenofovir disoproxil fumarate 245 mg ONCE daily (First choice for pregnancy).

N.B. See Table 3 for dose adjustments in renal impairment and monitoring section for further details.

Once the decision to start treatment is made, patients should be counselled and provided patient information leaflets on side effects (usually asymptomatic, but the more common ones are GI disturbance and musculoskeletal pain; worrying ones are renal failure, lactic acidosis and pancreatitis).

Treatment should be considered long term/lifelong in most cases. It may be appropriate to trial treatment cessation for patients who achieve HBsAg titre < 100 IU/mL.

Failure to suppress HBV DNA should prompt mutational analysis, but resistance is rare/not described and so compliance should be investigated in this context.

Pegylated IFN (PEG-IFN)

Whilst NICE guidelines suggest PEG-IFN use first line, most clinicians recommend oral antiviral agents. If required, PEG-IFN is most likely to be successful in the following contexts:

- HBeAg positive
- High ALT
- Significant interface hepatitis
- Female gender
- Low HBV DNA levels

Dynamics of HBV DNA and HBsAg response to PEG-IFN are important in defining outcome of pegylated IFN treatment. After 24 weeks of therapy, if HBV DNA level has decreased by less than 2 $\log^{10}$ IU/ml and/or if HBsAg is greater than 20,000 IU/ml then treatment should be stopped and oral antiviral therapy considered. Otherwise, it should continue for 48 weeks with monitoring of ALT, HBeAg/ HBsAg status and HBV DNA thereafter. Persistent hepatitis at this stage necessitates oral antiviral therapy.

Use of elastography

Liver biopsy gives information regarding grade and stage of liver disease whereas elastography informs stage only. Elastography is often useful at initial assessment. Additionally, it may be useful when information regarding stage alone is required. Examples include follow up of patients with bland biopsies but continually abnormal ALT or high viral load. NICE guidelines recommend annual elastography for patients with HBeAg negative disease, which may be excessive. Interval elastography every few years is probably useful in this group.

Decision to biopsy

Biopsies are usually reserved for patients where there is diagnostic doubt as to the cause of abnormal chemistry or when elastography is equivocal. There may be some benefit in assessing inflammatory activity in patients where this will contribute to their treatment decision (e.g. use of PEG-IFN). All biopsies should be discussed.

Monitoring

Follow up interval guide

Phase 1: 3 - 6 monthly blood tests (LFT most important) and 6 monthly clinic/blood test visits.

Phase 2: depends on management strategy.

Phase 3: follow up to identify durability or progression to;

Phase 4:

- 3-6 monthly blood tests (LFT and HBV DNA)
- 6 monthly clinic/blood test visits for one year, then 6-12 monthly blood tests and annual clinic/blood test visits unless HCC surveillance is required.
- HBsAg/anti-HBs every two years.

Patients with active chronic hepatitis B should have a regular FibroScan®. Every two years is an appropriate interval.

Patients on hepatitis B antiviral therapy

- Baseline: LFT, HBV DNA, renal function, bone profile, vitamin D, urine dip and FRAX score
- Every 3-6 months: Clinic visit, clinical assessment, LFT, HBV DNA, and UE/renal function; bone profile if on tenofovir
    - Step down to every 6 months once established and stable on therapy
- Annual HBsAg titre
- Annual urine dip, vitamin D level and FRAX score if on tenofovir disoproxil

HCC surveillance

Offer to:

- All cirrhotic patients
- CHB patients (Male > 40 years old, Female > 50 years old) with MTCT of hepatitis B
- CHB patients with family history of HCC

Conduct surveillance every 6 months using ultrasound and AFP measurements.

It is reasonable to consider the use of HCC risk prediction scores to streamline HCC surveillance.

Analysis of data from our East of England chronic HBV cohort suggests that applying the modified REACH B (mREACH B) score showed excellent predictive performance for the development of HCC using a threshold score score of ≥ 10, whilst a score of <10 safely identified those at low risk of HCC and therefore not requiring surveillance. Where elastography is not available the aMAP (threshold score <50) and mPAGE B (threshold score ≤8) may be considered.

Table 2: HCC Risk Prediction Scores

	Modified REACH B score	Modified PAGE B score	aMAP score
Reference	Lee et al 2014	Kim et al 2018	Fan et al 2020
Score Parameters	Sum of: Age(years): 35-39 =1 point 40-44 =2 points 45-49 =3 points 50-54 =4 points 55-59 =5 points 60-65 =6 points Gender Male = 2 points ALT (U/L) 15-44 =1 point >45 =2 points Liver fibrosis measurements (kPa) <8kPa =0 points 8-13kPa =2 points ≥ 13=4 points HBeAg +ve =2 points	Sum of: Age (years) <30 =0 points 30-39 =3 points 40-49 =5 points 50-59 =7 points 60-69 =9 points >70 =11 points Gender Male = 2 points Platelet count(10*9/L) >250 =0 points 200-250 =2 points 150-200 =3 points 100-150 =4 points <100 =5 points Albumin 40 =0 points 35-40 =1 point 30-35 =2 points 30-35 =2 points <30 =3 points	Age (years) Gender Platelet count (10*9/L) ALBI score (bilirubin µmol/L, albumin in g/L aMAP Risk Score = ((0.06 x age + 0.89 x sex (Male: 1, Female: 0) + 0.48 x ((log10 bilirubin x 0.66) + (albumin x -0.085)) -0.01 x platelets) +7.4) /14.77 x 100
Optimal threshold score for low-risk patients	**<10**	**≤8**	**<50**

Patients travelling abroad

Patients with hepatitis B may wish to spend extended periods of time abroad to visit family or to work. The priority for patients on medication is to ensure that an adequate supply is available to cover the duration of the trip.

If monitoring blood tests can be obtained while overseas that is helpful, but patients clearly cannot be managed safely if they are not resident in the UK for the majority of the time. As such, a minimum requirement for all hepatitis B patients is that they should have blood tests in the UK at least annually.

Discharging patients

Generally, patients who are HBsAg positive should be offered lifelong follow up, unless other health conditions make this impractical or undesirable.

Patients with HBsAg loss on antivirals should receive a minimum of 12 months consolidation therapy. Following this they should be monitored for HBsAg, anti-HBs and HBV DNA six monthly for 1 year and can be discharged if HBsAg and HBV DNA remain undetectable, regardless of anti-HBs.

Patients with HBsAg seroclearance who are not on antivirals should be followed up for at least 12 months after the first negative HBsAg test with six monthly testing for HBsAg, Anti-HBs and HBV DNA. If HBsAg and HBV DNA remain undetectable then patients can be discharged, regardless of anti-HBs.

For all patients, ongoing follow up and HCC surveillance should be offered if there is significant fibrosis / cirrhosis, a secondary cause for liver disease or a history of HCC in a first degree relative. Patients with resolved hepatitis B should be advised of the risk of reactivation in the context of immunosuppression.

Common Clinical Issues

Renal impairment

Development of renal impairment on tenofovir should be investigated by a renal screen:

- blood tests [ANA, dsDNA, complement, ANCA, anti-GBM, paraprotein],
- urine dip with protein: creatinine and albumin: creatinine if positive
- urine BJP
- renal ultrasound scan

If that is negative and a dose reduction is necessary (i.e. eGFR < 50), then an alternative agent such as entecavir or cessation of therapy should be considered.

If the renal function fails to improve with this strategy, then a referral to nephrology should be made.

Table 3: HBV antivirals dosing recommendations in renal impairment

Renal function	Tenofovir disoproxil fumarate	Entecavir
eGFR >50 ml/min	245 mg daily	0.5-1 mg daily
eGFR 30 - 50 ml/min	245 mg every 2 days	0.5 mg every 2 days. 0.5mg daily in severe disease
eGFR 10 - 30 ml/min	245 mg every 3-4 days	0.5 mg every 3 days (usually twice a week) 0.5mg every 2 days in severe disease
eGFR < 10 ml/min	245 mg every 3-4 days	0.5mg every 5-7 days 0.5 mg every 3 days in severe disease
Renal Replacement Therapy	Haemodialysis (HD): Dialysed. 245 mg every 7 days. Give dose after dialysis session. CVVHDF: 245 mg every 3-4 days	HD and CVVHDF: Dose as per eGFR < 10 ml/min

*Please contact pharmacy for advice regarding historical treatments (e.g. adefovir and lamivudine)

Drug safety in pregnancy, breastfeeding and fertility

Pregnancy

Do not use PEG-IFN or entecavir as they are contraindicated in pregnancy.

Tenofovir disoproxil fumarate is the preferred drug. No cases of teratogenicity secondary to tenofovir beyond background risk have been reported. Significant liver disease is associated with miscarriage.

Breastfeeding

Safe for entecavir, tenofovir disoproxil fumarate and PEG-IFN.

We recommend temporary cessation if there is nipple bleeding and the mother is not on therapy. Please ensure that there is a birth plan in place and that this is accessible and agreed with the obstetric team.

Fertility

Entecavir, tenofovir and PEG-IFN do not affect fertility. PEG-IFN may prolong the menstrual cycle.

Proteinuria

Trace with normal renal function then repeat at next clinic visit with an assessment of blood pressure and other relevant co-morbidities/medications.

Recurrent trace or 1+/2+ then assess blood pressure, relevant co-morbidities/medications and manage as per renal impairment.

If proteinuria does not resolve on regimen change then referral to renal team is recommended.

Hypophosphatemia

For all cases, the investigations below should be performed. In terms of treatment:

- > 0.5 mmol/L: monitor
- 0.3 – 0.5 mmol/L: treat with oral supplementation, monitor closely
- < 0.3 mmol/L: admit for supplementation, investigation and management.

Assess for other causes: dietary, chronic diarrhoea, respiratory alkalosis, musculoskeletal symptoms, high alcohol intake, other drug causes, PTH, vitamin D, Mg, bicarbonate and renal function. If all normal, consider switch in antiviral regimen.

Elevated FRAX score

Investigate with DEXA scan.

If osteopenia: vitamin D/calcium supplements and consider switch from tenofovir disoproxil fumarate.

If osteoporotic: to commence bisphosphonate and consider switch from tenofovir disoproxil fumarate.

HIV/HBV co-infection

Staging and surveillance guidelines are as for chronic infection. The current recommendation from BHIVA is to treat any patient with HIV viraemia. Regimen choice should include an agent which also suppresses HBV (usually tenofovir) and HBV viraemia monitored during therapy.

HBV/HCV co-infection

Initial management is by assessing which disease is dominant. This should be treated first. If HCV is treated before HBV, then HBV activity should be closely monitored, as flares of hepatitis may occur once the suppressive activity of HCV is released.

Prevention of hepatitis B

Contact tracing

When patients are first seen, a recommendation should be made for screening of current/previous sexual and blood contacts. Those at risk of exposure from the patient (partners and children usually) should be screened and immunisation recommended. Barrier methods of contraception should be used until immunisation. The "Green Book" is available online and gives detailed advice regarding vaccination schedules.

Mother-to-Child Transmission (MTCT)

For patients who do not meet treatment eligibility criteria:

- Start prophylaxis with tenofovir disoproxil fumarate for all HBV positive (HBsAg positive) pregnant women with HBV DNA ≥200,000 IU/mL or positive HBeAg, from the second trimester (week 13) of pregnancy, until at least delivery or completion of the infant HBV vaccination series.
    - Please refer to the immunisation section below for vaccination advice.
- For women of childbearing age planning additional pregnancies, tenofovir prophylaxis can also be maintained after delivery and during subsequent pregnancies or reproductive years, or for lifelong treatment.

Immunisation

Patients with CHB who contract HAV are at risk of following a fulminant course. Vaccination of anti-HAV IgG negative patients should therefore be undertaken.

Hepatitis B vaccination schedules

The standard course of immunisation for adults is three injections at 0, 1 and 6 months. An accelerated course of 0, 1 and 2 months is possible - also for combined hepatitis A and B vaccines. Adults who need protection very quickly (e.g. within 48 hours of exposure) can have a schedule of 0, 7 and 21 days. After an accelerated course, a booster at one year is recommended. A booster is recommended at 5 years if continued exposure is likely. Anti-HBs titres are recommended for assessment of vaccination efficacy for healthcare workers and patients with renal failure.

Universal vaccination is now available as per the schedule below, taken from the Green Book, Chapter 18. For those born to HBsAg positive mothers, additional vaccination at 0 and 4 weeks is required with a hepatitis B screen at 12 months. Additional HBIg is given to low birthweight infants (< 1500 g), those born to HBsAg positive patients or those with an HBV DNA > 6 $\log^{10}$ IU/mL at any time during pregnancy. A booster vaccination is no longer recommended pre-school.

Age	Routine childhood programme		Babies born to hepatitis B infected mothers	
Birth	X*		✓	Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®) (with HBIG if indicated)
4 weeks	X		✓	Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®)
8 weeks	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)
12 weeks	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)
16 weeks	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)	✓	DTaP/IPV/Hib/HepB (Infanrix hexa®)
1 year	X		✓	Monovalent HepB (Engerix B® or HBvaxPRO Paediatric®) Test for HBsAg

*Newborn infants born to a hepatitis B negative woman but known to be going home to a household with another hepatitis B infected person may be at immediate risk of hepatitis B infection. In these situations, a monovalent dose of hepatitis B vaccine should be offered before discharge from hospital. They should then continue on the routine childhood schedule commencing at eight weeks.

Figure 2: Hepatitis B doses in the immunisation schedule for routine childhood and selective neonatal hepatitis B programmes

Transplant recipients

All prospective solid organ transplant recipients who are HBV naive should be vaccinated (time permitting) and response documented. However, transplantation should not be delayed to complete a vaccine course. We recommend following guidance set out by the British Transplant Society BTS_HepB_Guidelines_FINAL_09.03.18.pdf

Anti-HBc positive donor organs

Liver donation

Recipients should receive antiviral prophylaxis for at least one year after transplantation with 3 monthly monitoring of HBV DNA. At one year, prophylaxis could be stopped for Anti-HBs positive recipients with monitoring of HBV DNA thereafter (months 1, 3, 6, 9, 12 then at clinic visits). Otherwise, it should be continued long term.

Non-liver organ donation

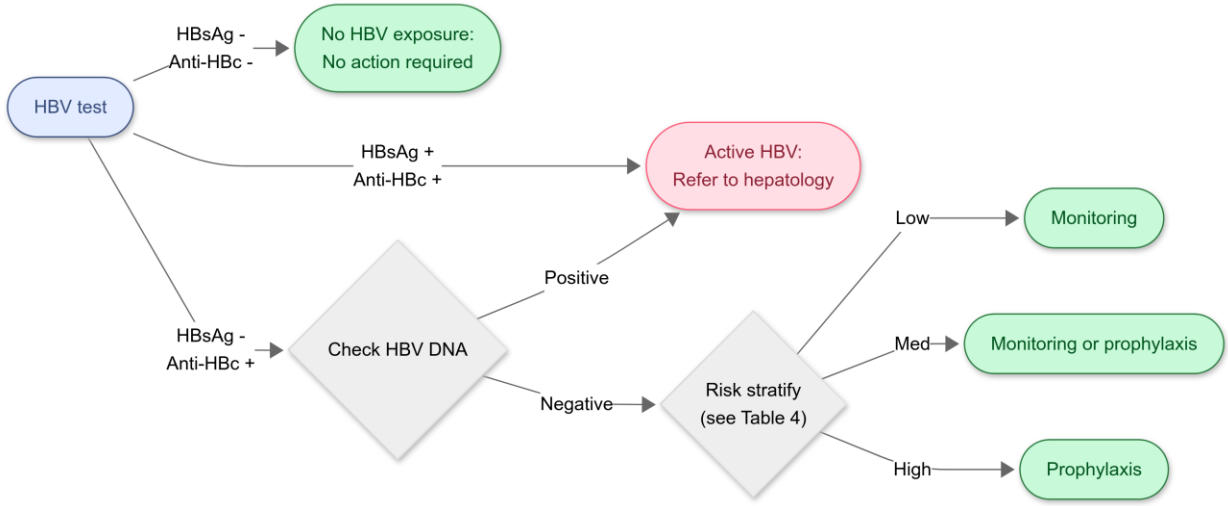
Anti-HBc negative, Anti-HBs negative recipients should receive antiviral prophylaxis for at least one year with three monthly monitoring of HBV DNA. At one year, prophylaxis could be stopped with monitoring of HBV DNA thereafter (months 1, 3, 6, 9, 12, then at each clinic visit).

Other recipients should have 3 monthly monitoring of HBV DNA with treatment if they become positive. An appropriate choice of antiviral is tenofovir disoproxil fumarate - dosed according to renal function.

HBV reactivation

Reactivation of HBV replication, an abrupt increase or reappearance of serum HBV DNA in a patient with chronic or past HBV infection, is a known complication of immunosuppression, or receiving drugs that affect the immune system, such as disease modifying drugs, immunosuppressants, biologics and chemotherapy.

All patients requiring these therapies should be screened for HBV prior to commencing treatment by testing, at minimum, Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (Anti-HBc). Please follow the algorithm below.



Monitoring:
- 3-monthly with ALT and HBV DNA
- Only refer to hepatitis service if patient becomes HBsAg or HBV DNA positive

Prophylaxis:
- Usually with entecavir 0.5 mg daily adjusted to renal function

HBV DNA can be requested as Hepatitis B PCR (quant) at CUH

Figure 3: HBV reactivation testing and management

The reactivation risk of immunosuppressive therapies are listed below in Table 4, along with management recommendations. If monitoring is problematic, then antiviral prophylaxis is reasonable.

Entecavir or tenofovir disoproxil fumarate are reasonable prophylactic antiviral choices and should be given until 12 months after cessation of immune suppression. Refer to 'Choice of treatment' section for detailed information.

Table 4: List of medications/ procedures and their HBV reactivation risk

Risk of Reactivation	Drug group/ procedure	Management
High	• B-cell depleting agents/ Anti-CD20: rituximab, ocrelizumab, epratuzumab, ofatumumab, alemtuzumab, ibritumomab, ublituximab etc. • Bone marrow transplant, Haemopoietic stem cell transplant or Solid organ transplant. • Immunomodulatory drugs (IMiDs): lenalidomide, pomalidomide, thalidomide	Start anti-viral prophylaxis with entecavir or tenofovir
Moderate	• Anthracyclines: doxorubicin, epirubicin, etc. • Calcineurin inhibitors (oral): ciclosporin, tacrolimus, voclosporin etc. • Cladribine • Cytokine modulators: abatacept, guselkumab, ixekizumab, mogamulizumab, mirikizumab, natalizumab, risankizumab, sarilumab, secukinumab, tocilizumab, ustekinumab, vedolizumab, etc. • High-dose corticosteroids (prednisolone >20mg OD for >4weeks). • Immune checkpoint inhibitors: anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab). • JAK inhibitors: baricitinib, tofacitinib, upadacitinib, ruxolitinib, filgotinib etc. • Local therapy for HCC including TACE. • mTOR inhibitor: sirolimus, everolimus etc. • Proteasome inhibitors: bortezomib etc. • Systemic chemotherapy • TNF-α inhibitors: infliximab, adalimumab, certolizumab, etanercept, golimumab etc. • Tyrosine-kinase inhibitors: imatinib, nilotinib etc.	3-monthly monitoring of ALT and HBV DNA. (Only refer to hepatitis services if patients become HBsAg / DNA positive) **Or** Antiviral prophylaxis with entecavir or tenofovir
Low	• Antimetabolites: azathioprine, 6-mercaptopurine, methotrexate. • Dimethyl fumarate • Diroximel fumarate • Glatiramer acetate • Leflunomide, Teriflunomide • Moderate and low dose prednisone (10mg prednisolone OD for > 4 weeks or intra-articular steroid injections). • Sphingosine-1-phosphate receptor modulators: etrasimod, fingolimod, siponimod, ponesimod, ozanimod etc.	Antiviral prophylaxis not required and monitoring not mandatory

Healthcare workers

Brief guidelines for vaccination of non-infected healthcare workers and healthcare workers with CHB are given above. Detailed guidance regarding patients chronically infected with HBV are given on the GOV.UK website.

Healthcare professionals with a viral load > 200 IU/mL cannot perform exposure prone procedures (EPPs). Individuals with HBV DNA < 200 IU/mL can perform EPPs and require annual testing. This applies for both patients on treatment, those who have natural suppression and those who are one year after completing treatment. Workplace recommendations should be made by the occupational health team.

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- SPC: Entecavir 0.5 mg Film-Coated Tablets https://www.medicines.org.uk/emc/product/213/smpc
- SPC: Pegasys 135 micrograms solution for injection in pre-filled syringe https://www.medicines.org.uk/emc/product/15748/smpc
- SPC: Tenofovir disoproxil 245 mg Film-Coated Tablets. https://www.medicines.org.uk/emc/product/8138/smpc#gref
- The Renal Drug Database https://www.renaldrugdatabase.com/s/
- UKHSA Guidance on the hepatitis B antenatal screening and selective neonatal immunisation pathway. https://www.gov.uk/government/publications/hepatitis-b-antenatal-screening-and-selective-neonatal-immunisation-pathway/guidance-on-the-hepatitis-b-antenatal-screening-and-selective-neonatal-immunisation-pathway--2
- What are the infectious risks with disease-modifying drugs for multiple sclerosis and how to reduce them? A review of literature https://www.sciencedirect.com/science/article/abs/pii/S0035378719309178?via%3Dihub
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