NHS LOTHIAN CHRONIC HEPATITIS B MANAGEMENT AND TREATMENT GUIDELINE

The following guideline outlines the management of individuals diagnosed with chronic hepatitis B. These patients are managed by either the Regional Infectious Disease Unit, Western General Hospital (WGH) or Hepatology service, Royal Infirmary of Edinburgh (RIE). Referrals to named individuals within the units are recommended on the laboratory result issued by the Department of Virology, RIE.

The shared care agreement (SCA) is in place to enable GP support with prescribing of treatment. Overall clinical responsibility remains with the managing unit.

Background Information

Chronic hepatitis B infection is defined as testing Hepatitis B surface antigen positive for greater than 6 months.

In NHS Lothian the vast majority of new cases of chronic hepatitis B virus (HBV) infection are in patients born outside the UK. Prevalence of HBV is highest in the Pacific islands, sub-Saharan Africa and East Asia regions. Europe is considered a low-prevalence region (<2%) HBV - in general, prevalence is intermediate in eastern and southern-eastern Europe.

Approximately 20-25% of people with untreated chronic HBV infection develop progressive liver disease, which can lead to cirrhosis and increased risk of HCC.

The natural history of chronic hepatitis B is in 4 phases with individuals varying in their progression through the phases. The table below, taken from the European Association for the Study of the Liver (EASL) guideline (2025) outlines the separate phases and the expected laboratory results for each phase.

HBV functional cure defined as hepatitis B surface antigen (HBsAg) loss and undetectable serum HBV DNA is associated with improved clinical outcomes in patients with chronic HBV infection. However, spontaneous loss of HBsAg is rare and occurs in only 1% of all HBsAg-positive individuals annually. Confirmation of sero-conversion at 12 months is recommended.

Table 4. Phase of chronic HBV infection, modified based on.[5]

	Phase 1	Phase 2	Phase 3	Phase 4
	HBeAg-positive chronic infection	HBeAg-positive chronic hepatitis	HBeAg-negative chronic infection	HBeAg-negative chronic hepatitis
HBsAg	High	Intermediate to high	Low, usually <1,000 IU/ml	Intermediate, usually >1,000 IU/ml
HBV DNA	High, usually $\geq 10^7$ IU/ml	Moderate to high, usually 10^4-10^7 IU/ml	Usually <2,000 IU/ml	Usually, >2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease progression (if untreated)	None/minimal	Moderate to severe	None	Mild to severe

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
*Either persistently or intermittently.

Initial Assessment

At the patient's first clinic visit establish:

1. Possible route of transmission (often not clear and can be assumed to have occurred early in life if born in area of high prevalence)
2. Any previous treatment for HBV (lamivudine/3TC use influences future treatment choice)
3. Any co-factors that may affect fibrosis progression e.g. alcohol history, metabolic risk factors (obesity, hypertension, type 2 DM, dyslipidaemia), co-infection (HIV, HCV)
4. Family history - HBV, cirrhosis, HCC
5. Any household/sexual contacts
6. Baseline ultrasound

Clinical assessment is largely based around establishing stage of fibrosis:

- Fibro scan and APRI score (+/-hyaluronic acid)
- HBV DNA PCR (viral load)
- HBeAg status. If HBeAg negative, then no further eAg tests are routinely required.
- Appendix 1 outlines the suggested blood tests at this visit.

Patient understanding of hepatitis B infection may be limited. Signpost patients to online information on the NHS inform Scotland website (leaflets may be available in clinic) or British Liver Trust:

- British Liver Trust, HBV just diagnosed, English
- Translations
- British Liver Trust, HBV tests and treatments, English

Contact Tracing

Public Health will follow up contacts of the patient. Where possible complete the details of those living in the same household on the Notification to Health Protection of contacts of Chronic Hepatitis B cases form, Appendix 2.

(if not available, as a minimum document names, relationship, GP and DOB).

Treatment of Chronic HBV Infection

The clinical goal of treating chronic HBV infection is to reduce morbidity (cirrhosis, hepatic decompensation, liver failure, HCC) and improve survival. Treatment decisions are based on ALT, HBV DNA, liver fibrosis stage and additional risk factors for poor liver outcomes.

Treatment should be offered to patients fulfilling any of the following criteria:

e-antigen positive	e-antigen negative
•Fibroscan >7kPa •ALT >40 persisting for >3 months •Over 30 years of age •Family history of HCC (first-degree relative) •Extra-hepatic manifestations of HBV (rare)	•Cirrhosis regardless of HBV DNA level (Fibroscan >11kPa) •HBV DNA >2000 **and** ALT >40 or Fibroscan >7kPa •HBV DNA >2000 **and** family history of HCC •Co-infection with Delta virus regardless of HBV DNA •Extra-hepatic manifestations of HBV (rare)

Drug Treatments:

Drug	Dose	Indication	Monitoring
Tenofovir disoproxil (TDF)	245mg once daily	**First line treatment** Caution in: - >60yrs - Diabetes - Osteoporosis - Renal impairment (CrCl 50-60 ml/min). Dose reduction may be required in <50ml/min Contraindicated in: - CrCl <30ml/min	HBV DNA, LFTs, renal function, phosphate on 3 occasions (2, 6 and 12 months) in first 12 months and then annually (or 6 monthly until HBV DNA<10) protein:creatinine ratio is also advised; If evidence of renal impairment, switch to entecavir.
Entecavir	*0.5mg once daily	Recommended for pts in whom TDF is not suitable or tolerated. Caution in women of reproductive age. Contraindicated in pregnancy. *If lamivudine experienced consider 1mg OD. Seek specialist advice	HBV DNA, LFTs, renal function on 3 occasions (2, 6 and 12 months) in first 12 months and then annually (or 6 monthly until HBV DNA<10).
Tenofovir Alafenamide (TAF)	Is currently non-SMC approved, available via IPTR. It should be considered where both entecavir and tenofovir are inappropriate. Seek specialist advice.		

On-treatment Monitoring

Both anti-virals are tolerated well with minimal side effects reported. Most commonly reported side-effects are GI disorders, dizziness, headache, fatigue.

The follow-up of patients on therapy is initially to confirm response and adherence and thereafter to monitor renal function and maintain adherence.

Fibrosis assessment is recommended 12-24 monthly with either fibroscan or APRI score (AST-platelet ratio). If discordant values are obtained, then treatment decisions may be deferred for confirmation of fibroscan result at subsequent appointment e.g. fibroscan of 7.1 kPa and APRI 0.3.

Both antivirals should be initially prescribed from the hospital for 3 months. GPs may then take over the prescribing of the antivirals under the shared care agreement. Clinical responsibility remains with the specialist clinical team, and it is not anticipated that routine monitoring blood tests will be necessary in primary care.

Pegylated interferon can be considered but is rarely used due to lack of response and tolerability.

Stopping treatment

Patients with on-treatment HBeAg seroconversion (i.e. loss of HBeAg and development of anti-HBe antibodies) can consider stopping therapy after a minimum of 12 months consolidation in non-cirrhotic patients, if HBV DNA is not detected and ALT normal. However, this is not recommended as a sustained response is observed in around 50% of patients and frequent monitoring for relapse is required (2 monthly HBV DNA and LFTs for 12 months).

Stopping therapy in patients treated for HBeAg negative hepatitis results in frequent relapses and should only be considered if there is a significant chance of HBsAg loss. This can be considered in non-cirrhotic patients if HBV DNA not detected on therapy for at least 3 years and quantitative HBsAg levels are <100 iu/ml in Asian patients and <1000 iu/ml in non-Asian patients. The testing of quantitative HBsAg requires contacting virology (brown serology tube from clinic). Patients will require to be committed to regular HBV DNA and LFTs (monthly for 3 months and then every 2 months) in the first 12 months off therapy.

Patients who are persistently HBV DNA negative (not detected) should have annual HBsAg testing and if HBsAg loss occurs with confirmation at 6-12 months then treatment can be stopped (development of anti-HBs is not required unless evidence of cirrhosis). If HBsAg loss is confirmed patients not under HCC surveillance can be discharged.

Monitoring Patients not on Drug Treatment

Patients who do not fulfil treatment criteria or who do not wish to commence therapy should be followed up in clinic according to viral load. If HBeAg positive or HBeAg negative with HBV DNA >2000 IU then 6 monthly review is recommended with measurement of U and E, LFTs, FBC, HBV DNA. Fibrosis assessment is recommended annually with either fibroscan or APRI score (AST-platelet ratio), unless fibroscan between 6-7kPa when annual fibroscan is recommended.

Annual review of HBeAg negative patients with viral load consistently <2000 is recommended with fibrosis assessment every 2-3 years.

Lifestyle advice with respect to ethanol intake, weight gain, smoking cessation and high-risk activity should be re-enforced. Super-infection with HDV is an unusual occurrence in the UK but should be considered if there is a persistent rise in ALT (consider repeating autoantibodies, HCV, steatosis risk).

In patients with persistently HBV DNA negative (not detected) results then annual HBsAg assessment is recommended. Patients with spontaneous HBsAg loss confirmed at 12 months from initially testing negative, can be discharged from follow up if there is no evidence of cirrhosis. These individuals, similar to all individuals who have been infected with hepatitis B, are at risk of reactivation (see separate section).

HCC surveillance

The risk of developing hepatocellular carcinoma in chronic HBV is significantly elevated in people with cirrhosis (over 90% of HCC related to HBV).

In those individuals without cirrhosis, family history (first-degree relative) is the most significant risk factor.

Other risk factors include smoking, diabetes, male sex and viral load.

Historically guidelines have suggested commencing HCC surveillance at an early age in African males. Recent evidence from Europe (Patmore et al, Kamal et al) suggests that HCC occurs in advanced fibrosis and at an older age in Africans following emigration and the influence of ethnicity on risk is now questioned (EASL 2025). The WHO guidelines recommend surveillance in cirrhosis and in individuals with a family history of HCC, whereas other international guidelines include other groups. The recent EASL guideline (2025) has recommended the use of risk scores for stratifying risk.

NHSL recommended surveillance is 6 monthly Ultrasound and AFP in patients with acceptable performance status:

- Cirrhosis (decompensation or clinical features e.g. nodular liver, splenomegaly, platelets <100,000)
- Advanced fibrosis – fibroscan > 8kPa (accurate scan on 2 separate occasions)
- Co-infection with HDV
- Family history of HCC (first degree-relative)
- PAGE B > 10 in patients on treatment for chronic HBV

Special Treatment Groups

Pregnancy

Treatment of expectant mothers with high viral load reduces the risk of transmission from mother to infant. Treatment with tenofovir 245mg once daily is recommended for all mothers with a viral load over 200,000 IU at week 28. Treatment initiation can be considered earlier in pregnancy for mothers

with particularly high viral loads (>10^7). Mothers with chronic HBV are reviewed in a specialised ante-natal clinic by Consultant Obstetrician with an interest in HBV.

All mothers are screened for HBsAg at booking and, if positive, referred to hepatology. A separate Blood-Borne Virus Protocol in Pregnancy is available on the Lothian intranet.

HDV co-infection

There is reflex testing for HDV antibody in all new (to Lothian) positive HBsAg patients. HDV RNA testing is recommended in all antibody positive individuals and if positive these individuals are regarded as co-infected. Treatment with oral anti-virals for HBV is recommended in all co-infected patients.

HDV co-infection may respond to prolonged therapy (at least 48 weeks) with pegylated interferon (IFN) although a sustained response is uncommon. It is recommended that IFN is offered to patients who do not have evidence of cirrhosis.

SMC have recently approved Bulevirtide for use in NHS Scotland, recommended for treatment of HDV infection in patients with significant fibrosis with inadequate response to IFN or who are ineligible to receive interferon-based therapy due to intolerance or contra-indication. Bulevirtide is administered as a 2mg once-daily subcutaneous injection.

Assessment of response to therapy requires assessment of HDV RNA at 12 weeks, 6 months and 12 months. Long-term therapy is likely if well-tolerated, unless HBsAg seroconversion is achieved when treatment can be stopped. Annual monitoring of HBsAg and 6 monthly HDV RNA is recommended.

HBV/HIV co-infection

In Lothian the management of HIV infection is established in both the Regional Infectious Diseases Unit at WGH, and the Department of Sexual Health at the Chalmers Centre.

Co-infection of HBV with HIV is an indication for treatment of chronic hepatitis B. Tenofovir containing regimens of anti-viral therapy for HIV are recommended.

If the HIV therapy requires to be changed to a non-tenofovir containing regimen then entecavir (no activity against HIV) should be added.

Fibrosis assessment and HCC surveillance should be performed as per mono-infection with HBV.

Individuals managed at Chalmers are referred to either RIDU (combined HIV/HBV care) or Hepatology (HBV only) depending on patient preference.

HBV/HCV co-infection (see NHSL Hepatitis C Treatment Guideline for further information)

- HBsAg +ve pts should be treated prophylactically with a nucleotide analogue
- HBV exposed (HBsAg –ve, anti-HBc +ve pts):
    - Repeat LFTs at end of treatment
    - If ongoing/worsening ALT elevation – further tests should include HBV DNA