University Hospitals of Derby and Burton NHS Foundation Trust

Hepatitis B – Full Clinical Guideline

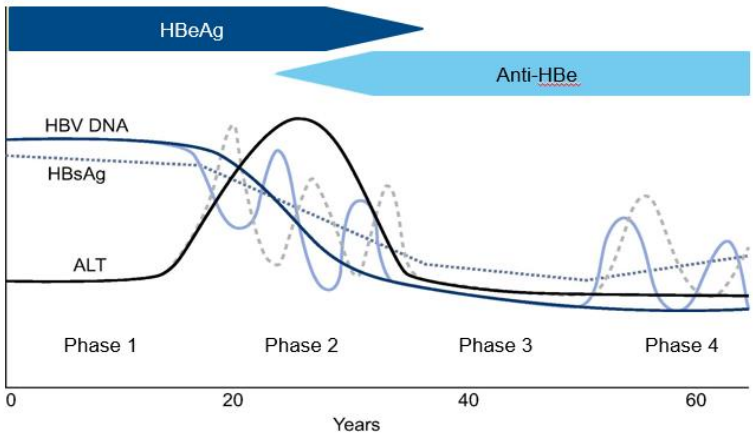
Reference no.: CG-GASTRO/2015/195

Phases of infection:

Chronic hepatitis B / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
EASL CPG HBV. J Hepatol 2017;67:370–98

EASL The Home of Hepatology



Clinic assessment:

- All HBsAg positive patients require follow-up in the liver clinic
- Patients with resolved HBV infection (follow-up not required, but need to ensure the patient is aware of the potential risk for reactivation with immunosuppressant /

chemotherapy)

Initial visit assessment:

- Initial evaluation should include a complete history, physical examination, assessment of liver disease activity and severity and markers of HBV infection.
- Elicit likely route of infection and assess risk of re-infection.
- Exclude co-morbid alcoholic, autoimmune, metabolic liver disease with steatosis or steatohepatitis as well as other liver disease such as viral co-infection.
- Check HIV, HCV, HDV, HAV IgG antibody status.
- Check HBeAg and HBeAb status to determine phase of chronic HBV infection.
- HBsAg quantification is useful in HBeAg negative patients in defining a low risk population requiring less frequent follow up (see below).
- Routine testing for genotype is not required (test when IFN being considered).
- Assess need for HCC screening (annual risk 2-5% if cirrhosis) – see HCC guidance
- Vaccination for HAV if IgG antibody negative
- Ensure appropriate testing/ vaccination of all 1st degree relatives and sexual partners.
- Undertake non-invasive assessment of liver stiffness using Fibroscan. The diagnostic accuracy of all non-invasive methods is better at excluding than confirming advanced fibrosis / cirrhosis. The result of transient elastography may be confounded by the presence of severe inflammation associated with high ALT levels.

Requirement for liver biopsy/ treatment (see algorithm):

A liver biopsy should be performed to determine disease activity and fibrosis assessment in cases where biochemical, HBV markers and non-invasive assessment of liver stiffness reveal inconclusive results and treatment indications are unclear.

The commonly applied ALT threshold of 40U/L may fail to identify some patients with significant liver disease. An ULN for a woman of 19U/L and for a man of 30U/L is an alternative threshold and should be considered in patients with a normal body mass index.

Consider antiviral therapy if moderate or severe necroinflammation and or Ishak fibrosis stage ≥2.

Indications for treatment according to 2017 EASL clinical practice guidelines:

- All patients with HBeAg-positive or negative chronic hepatitis B with a HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated.
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level regardless of the degree of ALT levels.
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis
- Patients with HBeAg-positive chronic HBV infection with a persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions.

- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extra-hepatic manifestations can be treated even if typical treatment indications are not fulfilled.

Treatment:

Options are a finite length of treatment with Pegylated interferon or potentially (remains an option to stop if treatment outcomes met) indefinite treatment with a nucleoside analogue (NA). HBeAg negative patients will almost always be treated with a NA. HBeAg positive patients requiring treatment may be considered for Pegylated interferon when favourable factors for treatment present.

Pegylated Interferon (48 weeks)

- Contraindicated in decompensated cirrhosis (use NA)
  Consider in HBeAg positive disease if favourable factors (low viral load < $2x10^6$IU/ml, Genotype A/B, ALT>2-5 ULN) or in HBeAg negative disease if there is a need for finite length of therapy.

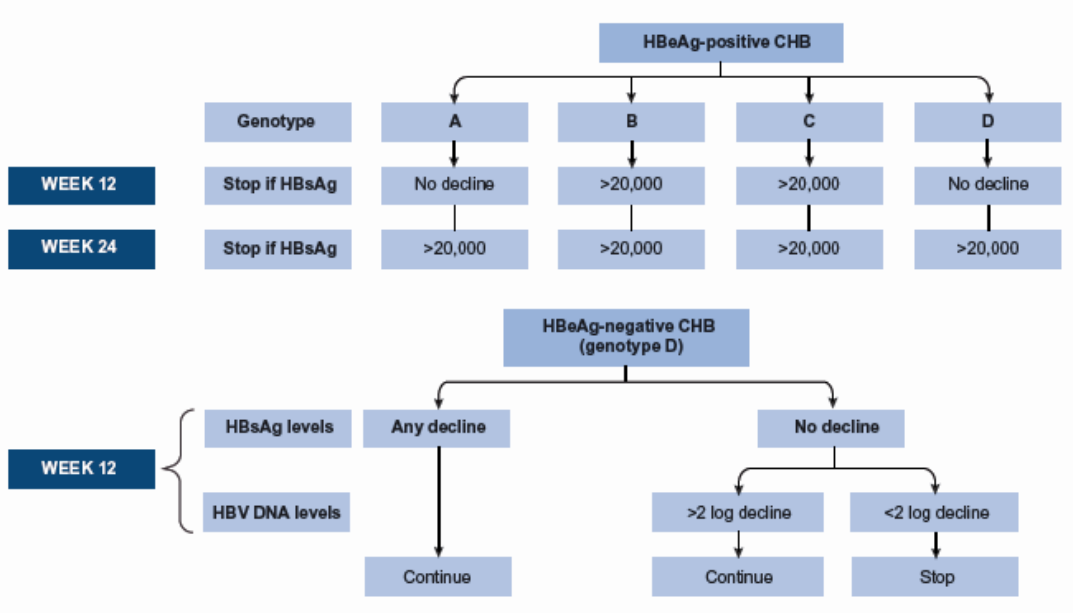
Outcome of treatment:

- Virological response (HBV DNA < 2000IU/ml at week 24): 25% (88% maintain at 5yrs)
- HBeAg seroconversion: 30%* (30% of those with HBeAg seroconversion have HBsAg loss @ 3yrs).* HBV DNA < 20,000 IU/ml at week 12 = 50% chance of HBeAg-seroconversion.
- Loss of HBsAg 3-7% at the end of treatment, 50% maintained in 5 years post treatment.

Monitoring (on IFN treatment)

- ALT and FBC every 4 weeks, TFTs every 3 months.
- HBV DNA - week 12, 24, 48.
- HBeAg and anti-HBe - week 24 and 48.

Stopping rules:



Reproduced from EASL 2017 practice guideline

- Monitoring (post treatment)
  - ALT every 3/12 for first year then 6-12/12.
  - HBV DNA at 3 and 6/12, then annual or if ALT ↑.
  - HBeAg - 6/12 then annual if HBeAg seroconversion (looking for reconversion).
  - If undetectable HBV DNA and HBeAg negative check annual HBsAg.

Nucleoside analogues (NA)

- Tenofovir disoproxil fumarate (TDF), Tenofovir Alafenamide (TAF) and Entecavir (ETV) are all potent inhibitors of HBV replication with a high barrier to resistance. Long-term monotherapy with TDF, TAF and ETV are considered preferred regimens.
- 51% of Lamivudine (LAM) refractory patients have ETV resistance at 5 years (use TDF or TAF).
- Both TDF and ETV require dose reduction if eGFR < 50ml/min.
- Patients on TDF at risk of development and/or with underlying renal disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure.
- NICE has been unable to recommend the use of Tenofavir Alafenamide for treating chronic HBV as no evidence was submitted to NICE by Gilead.

Outcome of treatment:

- Virological response (undetectable HBV DNA at week 48) for HBeAg positive patients: TDF 76%; ETV 67%; TAF 64%.
- HBeAg loss at 5 years: TDF 49% (40% with HBeAb); ETV 53%; TAF 22%.
- Virological response for HBeAg negative patients at week 48: TDF 93%; ETV 90%; TAF 94%.

- Loss at 5-years of HBsAg in patients who are HBeAg positive at commencement of treatment: TDF 10%; TAF 1%. (HBsAg loss at 5-years in patients who are HBeAg negative at commencement of treatment are approximately 1%).

Stopping treatment with NA therapy:

- Non-cirrhotic HBeAg positive patients who achieve HBeAg seroconversion can stop NA therapy after 12 months of consolidation therapy (90% maintain HBeAg seroconversion, 50% virological response)
- NA's can be stopped after confirmed (2 tests) HBsAg loss, with or without anti-HBs

Monitoring on patient on NA therapy

- U&Es (including eGFR), LFT's and serum phosphate at week 6 and then 3/12 for first year, then 6/12
- HBV DNA at week 12, 24, 48 and then 6-12 monthly
- HBeAg - 6/12 post undetectable HBV DNA then annual
- If undetectable HBV DNA and HBeAg negative check annual HBsAg.
- Failure to achieve a virological response should prompt a review of compliance, before considering resistance mutation analysis and a switch from ETV to TDF or TAF or vice versa, or the addition of one drug to the other. Virological breakthrough (increase in HBV DNA level of more than 1 $\log_{10}$ IU/ml compared to the lowest value on therapy) should prompt a similar response.

Monitoring in patients not requiring treatment:

- **HBeAg positive:** ALT 3 monthly for 12/12 then if normal every 6-12/12, HBV DNA 6-12/12, HBeAg 12/12, Fibroscan 12/12.
- **HBeAg negative with normal ALT and HBV DNA < 2000:**
  - Quantative HBsAg < 1000 iu/ml – ALT 12/12 and Quantative HBsAg/HBV DNA/ Fibroscan every 3 years
  - Quantative HBsAg ≥1000 iu/ml - ALT 6/12 and HBV DNA/ Fibroscan every 2 years
- **eAg negative with normal ALT and HBV DNA ≥ 2000:** ALT 3 monthly for 12/12 then if normal every 6-12/2, HBV DNA and Fibroscan 12/12

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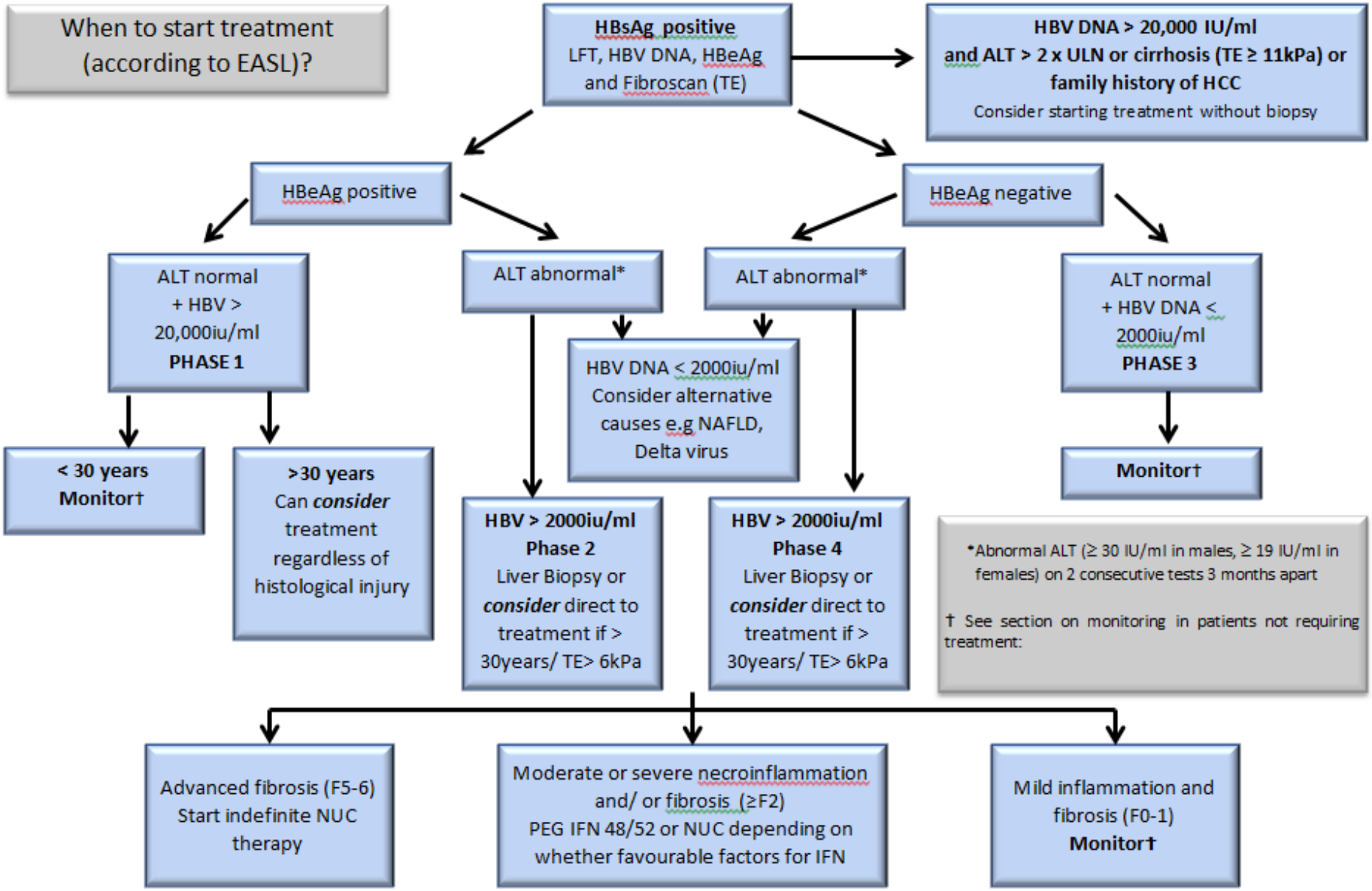
When to start treatment (according to EASL)?



HBV treatment in special patient groups

- **Patients co-infected with hepatitis D virus (HDV)**
  PegIFNα is currently the only available drug (though Bulvevitide – Hepcludex may receive a licence shortly) proven to have antiviral efficacy against chronic HDV infection (on treatment virological response 17-47%). HDV RNA negativity 24 weeks post treatment ≈ 25% and late relapses beyond 24 weeks occur in up to 50% of patients, hence long-term monitoring of HDV RNA is recommended. Treatment with PegIFNα for 48 weeks is the current treatment of choice and should be continued to its full length irrespective of on-treatment response. Concomitant nucleoside analogue (NA) treatment should be considered in patients with HBV DNA > 2000 iu/ml.

- **HCV co-infected patients**
  Treatment with direct acting antiviral agents (DAA) may cause reactivation of HBV. HBsAg positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until week 12 post DAA. HBsAg negative, anti-HBc positive patients should be monitored and tested for HBV reactivation in case of ALT elevation.

- **HIV co-infected patients**
  Initiation of antiretroviral therapy is imperative due to the high risk of liver fibrosis, cirrhosis and hepatocellular carcinoma. HIV-HBV co-infected patients should be treated with a TDF- or TAF-based regimen as guided by the GUM team.
  In patients with cirrhosis and low CD4 count careful biochemical surveillance is required in order to detect immune reconstitution syndrome and liver decompensation.

- **Patients having undergone liver transplantation or on the liver transplant waiting list**
  All patients on the liver transplant waiting list with HBV related liver disease should be treated with NA. Combination of hepatitis B immunoglobulin (HBIG) and a potent NA is recommended after liver transplantation for the prevention of HBV recurrence (risk <5%) until Anti-HBs levels are >50-100 IU/L. Patients with a low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with a potent NA. Lifelong combination therapy should be administered to patients who at high risk of HBV recurrence (HBV DNA positive at time of transplantation, HBeAg positive, have HCC, or are co-infected with HDV / HIV). HBsAg negative patients who receive organs from anti-HBc positive patients should receive lifelong prophylaxis with lamivudine.

- **Acute Hepatitis B**
  More than 95% of adults with acute HBV hepatitis do not require specific treatment, because they will fully recover spontaneously. Only patients with severe acute hepatitis B, characterised by coagulopathy (INR>1.5), protracted course (>4weeks) or signs of acute liver failure, should be treated with NA and considered for liver transplantation.

- **Renal dialysis**
  All dialysis and renal transplant recipients should be screened for HBV markers. HBsAg-positive dialysis patients who require treatment should receive ETV or TAF. All HBsAg-positive renal transplant recipients should receive ETV or TAF as prophylaxis or treatment. All HBsAg-negative, anti-HBc positive patients should be monitored for HBV reactivation after renal transplantation.

- **Extra-hepatic manifestations**
  Patients with replicative HBV infection and extra-hepatic manifestations should receive antiviral therapy with NA (PegIFNα is contraindicated).

Further reading:

EASL 2017 Clinical Practice guidelines on the management of hepatitis B virus infection. J Hepatol (2017)
NICE guidance CG165, last updated 10/2017

Documentation Controls **(these go at the end of the document but before any appendices)**

<table>
<tr><td>Reference Number

CG-GASTRO/2015/195</td><td colspan="2">Version:

3</td><td>Status

Final</td><td>Final</td></tr>
<tr><td rowspan="3">Version / Amendment History</td><td>Version</td><td>Date</td><td>Author</td><td colspan="2">Reason</td></tr>
<tr><td>3</td><td>2022</td><td>Liver Management Group</td><td colspan="2">Previous version of guideline expired</td></tr>
<tr><td></td><td></td><td></td><td colspan="2"></td></tr>
<tr><td colspan="5">Intended Recipients: All clinicians managing patients with liver disease</td></tr>
<tr><td colspan="5">Training and Dissemination: Forms part of liver handbook which is disseminated to all clinicians rotating through Hepatology</td></tr>
<tr><td colspan="5">Development of Guideline:
Job Title: Dr N Taylor and Dr A Lawson (Consultant Hepatologist)</td></tr>
<tr><td colspan="5">Consultation with: Liver management group</td></tr>
<tr><td colspan="5">Linked Documents: State the name(s) of any other relevant documents</td></tr>
<tr><td colspan="5">Keywords: Hepatitis B, Viral hepatitis</td></tr>
<tr><td colspan="3">Business Unit Sign Off</td><td colspan="2">Group:SMBU2
Date:24/3/2023</td></tr>
<tr><td colspan="3">Divisional Sign Off</td><td colspan="2">Group:Medicine Division
Date:24/3/2023</td></tr>
<tr><td colspan="3">Date of Upload</td><td colspan="2">March 2023</td></tr>
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<tr><td colspan="3">Contact for Review</td><td colspan="2">Hepatology Consultant A Lawson</td></tr>
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