1. Introduction and who guideline applies to

Hepatitis B virus (HBV) is an enveloped, hepatotropic, partially double- stranded DNA virus that can cause both acute and chronic hepatitis[1]. Chronic hepatitis B (CHB) infection remains a significant global health problem, with an estimated 296 million individuals infected worldwide[2]. Many of those infected are asymptomatic and, over time, may progress to chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC). Approximately three quarters of CHB carriers live in Asia and the Western Pacific, with most cases in such endemic areas acquired via perinatal transmission[3,4]. Factors such as maternal prenatal blood borne virus screening and access to vaccination and healthcare significantly reduce the risk of transmission.

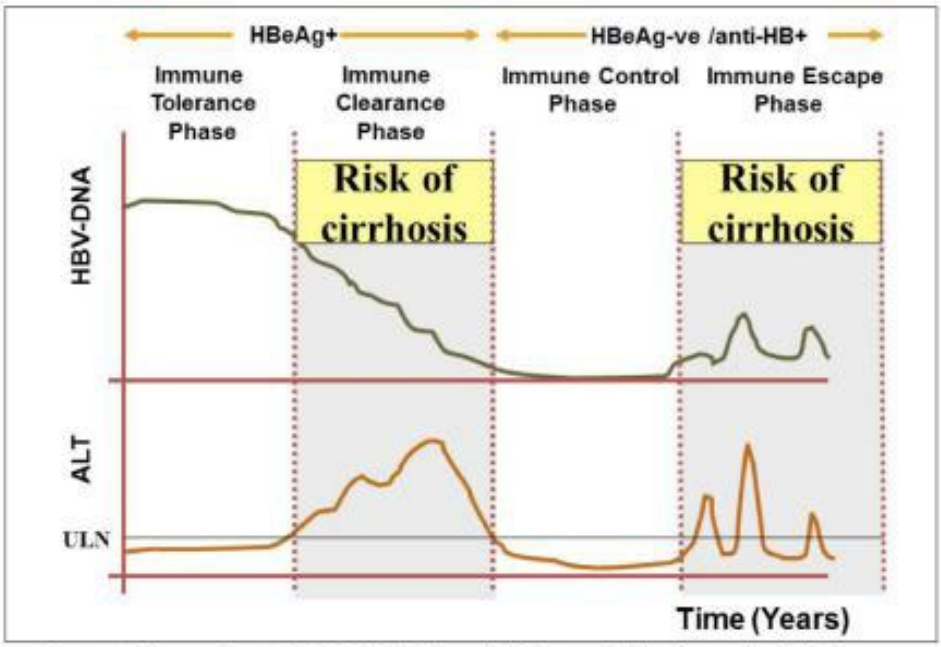
The natural course of CHB can be separated into four phases (terminology can vary and stages will not necessarily follow in sequence)[5]:

(1) Immune tolerance phase

(2) Immune clearance / immune reactive phase

(3) Immune control phase / inactive infection

(4) Immune escape / reactivation phase



After Chu et al, Hepatology 1985;5:431-34 ULN: upper limit of normal of ALT

The rate of viral replication, and thus HBV DNA level, varies according to the viral phase (see Table 1). Similarly, liver enzymes (e.g. ALT) will also vary according to phase, with elevated levels indicating an increased immune response to the virus and a subsequent cytotoxic T-lymphocyte mediated necro-inflammatory process within the liver hepatocytes[5]. There are eight well- known genotypes, which may have an impact on treatment response (especially pegylated interferon)[6].

Hepatitis B surface antigen (HBsAg) is used as the screening test for active hepatitis B; if you require advice with regards to testing or results please discuss with ID/virology/microbiology. This guideline updates the previous (2008) UHL guidelines on the diagnosis and outpatient management of CHB, and incorporates current NICE (2013)[7] and EASL (2017) guidance[8].

2. Guideline Standards and Procedures

1. Drug Treatment Options for Chronic Hepatitis B

Two classes of drugs are currently licensed for the treatment of CHB:

- Pegylated Interferon Alfa-2a **(**PEG-IFN)
- nucleoside/nucleotide analogues (NAs)

(i) Pegylated Interferon Alfa-2a

PEG-IFN is administered as a once-weekly subcutaneous injection of 180 micrograms. It is a cytokine with a dual antiviral and immunomodulatory activity, offering the potential for an immune-mediated control of HBV infection. This provides the opportunity to obtain a sustained virological response following a defined/finite treatment course, usually of 48 weeks maximum, without concerns for viral resistance. It may also induce HBsAg loss in patients who achieve and maintain undetectable HBV DNA. The aims of treatment are[9-12]:

- suppression of serum HBV DNA
- normalisation of liver enzymes and decrease in necro-inflammatory activity
- loss of HBeAg (in those that are HBeAg positive) – *occurs in 20-30% of patients; may take over 12 months to achieve*
- loss of HBsAg – *3-4% of patients at 6 months following treatment*

Success rates are variable and dependent on a number of factors. Sustained suppression/disappearance of HBV DNA in serum is only likely in those who clear both HBeAg and HBsAg. In addition, there is lower tolerability when compared to NAs. Side effects include flu-like symptoms (these usually lessen after the first few weeks of treatment), fatigue, injection site reactions, anorexia, nausea, leukopenia and thrombocytopenia.

PEG-IFN is contraindicated in pregnancy and in patients with decompensated liver disease or autoimmune disease. PEG-IFN is most likely to benefit those with replicative infection and immune response. Pre-treatment predictors of good response include[9,12]:

- ALT ≥ 2 x ULN
- Low baseline HBV DNA
- Genotype A or B (respond best to PEG-IFN (30-40%) compared to other genotypes (5%)

(ii) Nucleoside/nucleotide analogues (NAs)

The NAs are oral antiviral agents that work mainly by inhibiting HBV DNA polymerase activity and thus suppress HBV replication[13]. Although effective at reducing HBV DNA to undetectable levels, they have no effect on cccDNA within infected hepatocytes; therefore, treatment is long-term and, usually, lifelong. However, they are well tolerated and have a low

side effect profile, making them the current mainstay of treatment of chronic HBV infection. Treatments currently recommended for use in the UK:

- tenofovir disoproxil fumarate (TDF) – *nucleotide analogue*
- entecavir (ETV) – *nucleoside analogue*
- lamivudine (3TC) – *nucleoside analogue*

Adefovir and telbivudine are no longer recommended by NICE.
Tenofovir alafenamide fumarate (TAF), a pro- drug of tenofovir, is FDA approved for CHB treatment and is an appropriate choice for selected patients. Its use is likely to be recommended by NICE in the future, although Gilead have not as yet submitted evidence.

2. Liver biopsy and Transient Elastography

Non-invasive methods for the assessment of liver damage, such as transient elastography (TE) by FibroScan® have replaced liver biopsy as gold standard. TE is now widely available, easy (can be performed in clinic) and is a sensitive method for assessing liver stiffness and fibrosis[1].Advanced fibrosis is associated with greater risk of liver related events such as decompensation and HCC. Liver biopsy should only be considered, after MDT discussion, where dual pathology is suspected and if this is likely to alter management.

3. Initial Clinic Assessment

1) 1st appointment in Hepatitis Clinic:

   - History/Exam (including psychiatric history, alcohol and recreational drug use, review of social circumstances, previous hepatitis treatment, presence of peripheral stigmata of chronic liver disease).
   - Review risk factors for acquisition of HBV, and risk factors for disease progression (including family history of CHB and HCC).
   - Explanation of risk factors for transmission, and transmission avoidance (e.g. household contacts; medical/dental treatment; donation of blood or tissue; condom use for sex until partner tested/vaccinated; avoid sharing toothbrushes and razors; clean-up of blood spillage)
   - Family screening and vaccination (inform GP to help facilitate; contacts can be screened in clinic if present). If the patient is high risk then they should be referred to GU Medicine for an STI screen and contact tracing.
   - Signposting to patient information leaflets /websites (see Appendix 4)

   - Investigations:
     i. FBC, INR, U&E, LFT.
     ii. Patients with abnormal LFTs should have: immunoglobulins, autoantibodies, ferritin, α-1-antitrypsin, lipid profile, glucose, HbA1c (plus caeruloplasmin if less than 30 years old with elevated ALT.)
     iii. Full HBV serology if not already known and HBV DNA
     iv. Consider checking for pre-core mutant in patients who are HBeAg negative and who have HBV DNA greater than 2000iu/ml
     v. Serology for HAV (IgG), HCV, HDV, HIV and syphilis (white top bottle).
     vi. Assessment/surveillance for HCC with baseline alfa-foetoprotein (AFP) & liver ultrasound scan (USS)

2) Perform FibroScan® (in clinic if trained staff/portable scanner available, or complete referral form) (see Appendix 1)**.** Document result/fibrosis score in notes.
3) Follow-up within 2-3 months of initial appointment.

4. Management

The decision to a) offer treatment and b) choose type of treatment will depend on a number of factors, including the patient's age, HBV DNA, HBeAg status, genotype, ALT and any additional risk factors for development of HCC.

For those found to have compensated liver disease:

- Refer to hepatology for baseline review +/- long-term follow-up
- OGD at baseline and every 3 years thereafter
- DEXA scan at baseline
- HCC surveillance (see below)

Offer antiviral treatment to the following groups of patients:

- Any age with HBV DNA >20,000 IU/ml and abnormal ALT (≥30 IU/L in males and ≥ 19IU/L in females) on 2 consecutive tests conducted 3 months apart regardless of extent of liver disease.
- Aged ≥30 years with HBV DNA >2000 IU/ml and abnormal ALT (≥30 IU/L in males and ≥ 19IU/L in females) on 2 consecutive tests conducted 3 months apart.
- Aged <30 years with HBV DNA >2000 IU/ml and abnormal ALT (≥30 IU/L in males and ≥ 19IU/L) in females on 2 consecutive tests conducted 3 months apart **AND** evidence of necroinflammation or fibrosis on liver biopsy **OR** TE score of > 6kPa.
- Any age with cirrhosis and detectable HBV DNA regardless of HBeAg status, HBV DNA and ALT levels.

Consider treatment in those with HBV DNA >2000 IU/ml and evidence of necroinflammation or fibrosis on liver biopsy.

(i) Treatment options for either HBeAg-positive or HBeAg-negative individuals

- Entecavir (500 micrograms OD if no previous treatment with nucleoside analogues; 1mg OD if previous lamivudine failure/ lamivudine resistance)
- Tenofovir disoproxil (245mg OD). Including those with HIV and HBV co-infection (must form part of anti retroviral regime; see (v) below)
- Tenofovir alafenamide fumarate (TAF), is FDA approved for CHB treatment and is an appropriate choice for selected patients especially those who are already taking it as part of their HIV regime.
- PEG-IFN is an option for the initial treatment within its licensed indications (compensated liver disease, evidence of viral replication, increased ALT and histologically verified liver inflammation and/or fibrosis) particularly in HBeAg-positive individuals.

(ii) Treatment sequences

(a) HBeAg-positive chronic hepatitis B and compensated liver disease

1. Consider 48 week course of PEG-IFN

2. Consider stopping PEG-IFN at 24 weeks if HBV DNA level has decreased by less than 2 $\log_{10}$ IU/ml and/or HBsAg > 20,000 IU/ml and offer second line treatment as below.
3. Offer Tenofovir as second-line treatment in those who do not undergo HBeAg seroconversion or who revert their HBeAg positive following seroconversion with PEG-IFN.
4. Offer Entecavir as an alternative second-line agent in those who can not tolerate Tenofovir or in whom it is contraindicated.

Review adherence and offer support in patients taking Tenofovir who have a detectable HBV DNA at 48 weeks. If HBV DNA remains detectable at 96 weeks consider adding entecavir to tenofovir.

Consider stopping treatment 12 months after HBeAg seroconversion only in those **without** cirrhosis.

(b) HBeAg-negative chronic hepatitis B and compensated liver disease

1. Offer either entecavir or tenofovir
2. Consider adding tenofovir to entecavir or entecavir to tenofovir as a second line regime in those with detectable HBV DNA at 48 weeks of treatment.

Consider stopping treatment 12 months after achieving undetectable HBV DNA and HBsAg seroconversion in those **without** cirrhosis.

(c) Adults with decompensated liver disease

1. All patients should be managed by a Hepatologist long-term and if appropriate, refer to transplant centre
2. **Do not** offer PEG-IFN
3. Entecavir as 1st line (1mg OD) unless prior history of lamivudine resistance. In the latter case, tenofovir should be used.

(iii) Monitoring of patients on treatment

(a) <u>Patients treated with PEG-IFN:</u>

- Treatment overseen / monitored by specialist Hepatitis nurses (in conjunction with dedicated ID SpR)
- Routine monitoring as per treatment for chronic Hepatitis C (including regular blood tests, monitoring for development of neutropaenia, etc)
- Check HBV DNA and quantitative HBsAg levels at baseline and then at 12, 24 and 48 weeks after starting treatment. Repeat at 6 months and 12 months post treatment completion (see section **5(vii)**).
- In addition to the above, in HBeAg positive patients check HBeAg and anti-HBe at 12, 24 and 48 weeks after starting treatment. Repeat at 6 and 12 months post treatment completion

(b) Patients taking oral antivirals (NAs):

- See 1-2 months after commencing treatment then 4-6 monthly for first year. May be seen 6-monthly thereafter if stable on treatment
- Check ALT and HBV DNA at each appointment
- For HBeAg positive patients, check HBeAg annually to look for anti-HBe seroconversion.
- For patients with undetectable HBV DNA check HBsAg annually. If HBsAg becomes negative (may occur in a minority of HBsAg / HBeAg positive patients) then check anti-HBs
- In patients taking tenofovir ensure close monitoring of renal function. Check eGFR and serum phosphate
- If HBV not suppressed by $1\log_{10}$ at 3 months check compliance
- For patients who do not suppress HBV DNA on NA treatment:
    - If slow continual fall in HBV DNA, and non-cirrhotic, a 'watch & wait' approach may be used
    - If non-response or partial response check adherence and facilitate measures to improve this.
    - If detectable viral load despite above measures, consider resistance testing and switching agent eg. tenofovir to entecavir
    - If virological breakthrough, combination therapy with tenofovir and entecavir may be used.

(iv) Monitoring of patients who seroconvert following treatment

(a) Anti-HBe seroconversion after antiviral treatment:

- Monitor HBeAg, anti-HBe, HBV DNA level and liver function at 4, 12 and 24 weeks after Anti-HBe seroconversion, and every 6 months thereafter.

(b) HBsAg seroconversion after antiviral treatment:

- Monitor HBsAg and anti-HBs annually
- If appropriate, consider discharging patients who are anti-HBs positive on 2 consecutive tests

(vii) Monitoring of patients not eligible for treatment

(a) HBeAg-positive and normal ALT

- Monitor ALT and HBV DNA levels every 6 months
- Monitor ALT every 3 months on at least 3 consecutive occasions if there is an increase in ALT levels

(b) HBeAg-negative and normal ALT

- Monitor ALT and HBV DNA annually

5. SPECIAL SCENARIOS

(i) Pregnancy

Diagnosis of HBV infection at antenatal screening is a common route of referral for new patients to hepatitis clinic. In most cases the disease will run the same course in pregnant women as those in the general adult population; however, alterations in the maternal immune system during pregnancy may lead to a depressed immune response and consequent rise in HBV DNA levels, with a reduction in ALT[14]. After birth the opposite may occur, leading to a "flare" and jump in ALT levels.

For details on the assessment and treatment of pregnant women with HBsAg positive see Appendix 2

Further information available via the Royal College of Obstetrics & Gynaecology guideline on the management of viral hepatitis in pregnancy.

(ii) Hepatocellular carcinoma (HCC) surveillance

NICE recommend enhanced surveillance (six monthly AFP and liver USS) in patients:

- With significant fibrosis or cirrhosis
- Family History of HCC

There is also a higher associated risk of HCC in certain ethnic groups and enhanced surveillance should also be offered to those in the following groups:

- Asian male >40y
- Asian female >50y
- All African hepatitis B carriers >20 years

(iii) Treatment and prophylaxis during immunosuppressive therapy

All patients HBsAg positive due to undergo immunosuppressive therapy should be discussed with Infectious Diseases before starting treatment.

All patients HBsAg negative and anti-HBc positive (regardless of anti-HBs status) should be discussed with Infectious Diseases before starting treatment.

Refer to appendix 3 (UK Chemotherapy Board position statement) to assist with risk assessment and treatment options for these patients.

(iv) Hepatitis D co-infection

Hepatitis D virus causes an aggressive viral hepatitis, with rapid progression to cirrhosis and hepatic decompensation, and relies on hepatitis B co-infection for its pathogenesis and propagation[15].

Recently Bulevirtide is recommended for treating chronic hepatitis D in adults with **compensated liver disease** only[16] if:

- there is evidence of significant fibrosis and
- their hepatitis has not responded to PEG-IFN or they cannot have interferon-based therapy.

Those on Buleviritide will require regular monitoring in the hepatitis clinic initially every 6 weeks.

PEG- IFN is an alternative option for those with significant fibrosis but it is not licensed for this use[17]. Eradication of HBV will eliminate HDV. Patients should be treated following the steps listed above.

The decision to treat Hepatitis D co-infection should be undertaken with MDT approval from the hepatitis MDT and prescriptions for Buleviritide should be undertaken by hepatitis specialists and procured nationally via commercial arrangement with the drug company (via blueteq system).

(v) HIV co-infection:

- According to current guidance[18], where possible all HIV infected patients should start antiretroviral (ARV) therapy regardless of CD4+ count.
- Tenofovir should form part of ARV regime. If there are concerns regarding renal toxicity then a TAF-based regimen may be used
- Where TDF or TAF is contraindicated, add entecavir to non-tenofovir-based ARV regimen
- Should be managed by an Infectious Diseases consultant and refer to hepatology if cirrhotic

(vi) Hepatitis C co-infection

- In patients co-infected with both hepatitis B and C, reduced levels of HBV DNA may be seen and may lead to earlier anti-HBs seroconverison
- However, treatment of hepatitis C with directly acting agents (DAA) may lead to flares in HBV DNA levels or reactivation of HBV in HBsAg negative patients[19]
- For those that meet the criteria for Hep B treatment, start prior to or at the same time as Hep C treatment

For those who do not meet the criteria for Hep B treatment, monitor HBV DNA closely during, and up to 12 weeks after, DAA treatment.

3. Education and Training

No additional education or training is required

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
The viral hepatitis MDT meeting will discuss patients with complex or uncertain treatment decisions	Retrospective/review	Dr George Hills	Annual	Hepatitis MDT

5. Supporting References (maximum of 3)

For full reference list see Appendix 5

6. Key Words

Hepatitis B, HBV, viral hepatitis, hepatitis, interferon

CONTACT AND REVIEW DETAILS	
Guideline Lead (Name and Title) Professor Martin Wiselka	**Executive Lead** Dr Andrew Furlong, Medical Director
Contributing Authors Dr Benedict Rogers and Dr Caroline Williams (ID/Microbiology SpR) Dr Julian Tang (Virology consultant) Joanne Dey (ID Specialist Pharmacist)	**Ratified by** Antimicrobial Working Party – 13 November 2018 Policy and Guideline Committee – 15 March 2019
Details of Changes made during review: Updates made to the following areas: • Treatment guidelines • Hep D co-infection • Hep in Pregnancy	

Appendix 1

FIBROSCAN REFERRAL FORM

FIBROSCAN REFERRAL FORM
INFECTIOUS DISEASES - SPECIALIST LIVER NURSES

Hospital No:	Name of Referrer: .....
Name of Patient:	Job Title / Dept: .....
DOB:	Site: .....
Address:	Tel No: .....
.....	Email: .....
Postcode:	Date: .....
Tel No:	Signature: .....

Urgent <4w ☐ Routine ☐

Indication for Fibroscan

HCV ☐ NAFLD ☐ ALD ☐ Albumin .....

HBV ☐ Chronic Cholestatic Liver disease ☐ Platelets .....

HIV ☐ Other (please specify) ☐ ..... Splenomegaly Y/N

Male ☐ Female ☐ Pregnant ☐ Diabetes Y/N

Height ..... Weight ..... BMI .....

Cross infection risk Y/N MRSA ☐ CDT ☐ VRE ☐

ALT .....

Previous Fibroscan Result ..... Year .....

Fibroscan Result

Fibroscan ..... kPa (F score.....) CAP ..... (S score.....)

IQR ..... IQR/Med .....

Probe used: Medium ☐ Large ☐

Date ..... Performed By: .....

Please post/email referral to: Specialist Liver Nurses, Ground Floor, Victoria Building, LRI.
LiverNurses@uhl-tr.nhs.uk

Mother HBsAg positive in pregnancy

Specialist Midwives review and repeat HBV DNA/Liver function tests: In first trimester
At 22 weeks gestation
At 34 weeks gestation

Appendix 2. Preventing Mother to Child Transmission of Hepatitis B

Table 1. Management of mother and infant according to serology and HBV DNA levels during pregnancy *

Maternal serology	Maternal HBV DNA IU/ml	Maternal Tenofovir disoproxil (TDF) from 24 weeks gestation	Infant HBIG See Table 2	Infant vaccination See Table 3
HBsAg positive; irrespective of eAg/Ab status	Any single level greater than 10^6 during pregnancy	YES	YES	YES
HBeAg positive	Greater than 200,000	YES	YES	YES
HBeAg positive	Less than 200,000	X	YES	YES
HBeAg negative AND Anti-HBe (HBeAb) negative/equivocal	Greater than 200,000	YES	YES	YES
HBeAg negative AND Anti-HBe (HBeAb) negative/equivocal	Less than 200,000	X	YES	YES
HBeAg negative AND Anti-HBe (HBeAb) positive	Greater than 200,000	YES	X	YES
HBeAg negative AND Anti-HBe (HBeAb) positive	Less than 200,000	X	X	YES

Table 2 NEONATE HBIG schedule

Hepatitis B Immunoglobulin 250 IU at birth[1,2]
PLUS
Hepatitis B vaccination[1,2] in opposite limb at birth and further vaccinations as per Table 3

Table 3 NEONATE Hepatitis B vaccination schedule

Monovalent Hepatitis B Vaccine at:	Birth 1 month
Infanrix Hexa® routine childhood vaccination at:	2 months 3 months 4 months
Monovalent Hepatitis B booster at:	12 months
Dried Blood Spot Test also at:	12 months

***Any woman who has previously given birth to a baby who was subsequently found to be infected with Hepatitis B should also be considered for tenofovir disoproxil (TDF) therapy and their infant considered for Hepatitis B Immunoglobulin at birth[1].**

***Infants born to mothers who had acute Hepatitis B infection during pregnancy, or those born weighing less than 1500g should also receive Hepatitis B Immunoglobulin at birth, irrespective of the viral load or HBeAg of the mother[2].**

In the above circumstances please contact phe.hepatitisbabies@nhs.net during office hours call 0330 128 1020-option 2. Out of hours Sat-Sun and bank holidays contact the Duty Doctor on 0208 327 7471

Clinical advice is available from Infectious Diseases or Hepatology or Virology. Out of hours there is an Infectious Diseases consultant on call – contact main hospital switchboard.

Management of women prescribed anti-viral treatment for prevention of vertical transmission of Hepatitis B infection[1,3]

Women who have conceived on anti-viral therapy should continue anti-viral treatment throughout pregnancy and beyond[1].

Women who have conceived on entecavir should be offered the option to switch to tenofovir disoproxil (TDF) during pregnancy as this is the preferred treatment option during pregnancy[1]. Additionally, entecavir studies in animals have shown reproductive toxicity at high doses and the manufacturer recommends avoiding during pregnancy as the potential risk for humans is unknown.

Women who have conceived on tenofovir alafenamide (TAF) should be discussed directly with Infectious diseases or Hepatology for further advice as the use of this drug in pregnancy is not currently advised during the first trimester. Further data is required.

For women commencing TDF during pregnancy:

1. Start treatment at 24 weeks gestation and check HBV DNA at least once to ensure falling viraemia
2. Monitor renal function (in line with TDF SPC guidance[3])
3. Aim to discontinue TDF by 12 weeks post-partum but ALT monitoring may be required to detect postnatal HBV flare

Safety in pregnancy[1,4]

There is a considerable body of safety data from the Antiretroviral Pregnancy Registry for the use of TDF in pregnancy. The FDA considers it a Category B drug. Safety advice is supported by the British Viral Hepatitis Group guidelines.

Breastfeeding advice[1,5]

TDF is excreted in breast milk but in tiny amounts, considered insignificant. There is no current evidence of teratogenicity from its use in hepatitis B treatment in pregnancy. Current advice from the UK Drugs in Breast Milk Advisory Service (based in Leicester) is that the benefits of breastfeeding outweigh any risks from TDF in this setting. This view is supported by the British Viral Hepatitis Group guidelines, provided that the infant is vaccinated from birth.

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Appendix 3

Table 1: Immunosuppressive therapy risk groups for HBsAg positive patients

Taken from the UKCB Position Statement on Hepatitis B virus Screening and Reactivation Prophylaxis for Patients Planned to Receive Immunosuppressive SACT.

Risk of reactivation	Immunosuppressive therapy	Prophylaxis
High risk	B-cell depleting agents including; rituximab, ocrelizumab, epratuzumab, ofatumumab,ibritumomab. Bone marrow transplant, Haemopoietic stem cell transplant or Solid organ transplant High risk cytokine modulators; Ustekinumab and JAK inhibitors including; baricitinib, tofacitinib. More potent TNF-α inhibitors including; infliximab, adalimumab, certolizumab, golimumab. High-dose corticosteroids (prednisolone>20mg OD for >4weeks). Anthracyclines including; doxorubicin, epirubicin. Local therapy for HCC including; TACE. Immunomodulatory drugs (IMiDs) such as lenolidamide	Anti-viral prophylaxis with tenofovir or entecavir
Moderate risk	Systemic chemotherapy Cladribine Moderate risk cytokine modulators; abatacept, ixekizumab, mogamulizumab, natalizumab, sarilumab, secukinumab, tocilizumab, vedolizumab Less potent TNF-α inhibitors including; etanercept. Immunophilin inhibitors including; cyclosporine. Tyrosine-kinase inhibitors including; imantnib, nilotinib. Proteasome inhibitors such as; bortezomib. Moderate-dose corticosteroids (prednisolone 10mg OD for >4 weeks).	Anti-viral prophylaxis with tenofovir or entecavir
Low risk	Antimetabolites including; azathioprine, 6-mercaptopurine, methotrexate. Fingolimod Short-term low dose corticosteroids. Intra-articular steroid injections (extremely low risk).	Anti-viral prophylaxis with tenofovir or entecavir Or Monitor HBsAg, HBV DNA and ALT every 3 months
Unknown risk	Immune checkpoint inhibitors such as; anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab).	Anti-viral prophylaxis with tenofovir or entecavir To prevent potential treatment interruption

Table 2: Immunosuppressive therapy risk groups for HBsAg negative, HBcAb positive patients

Taken from the UKCB Position Statement on Hepatitis B virus Screening and Reactivation Prophylaxis for Patients Planned to Receive Immunosuppressive SACT.

Risk of reactivation	Immunosuppressive therapy	Prophylaxis
High risk	B-cell depleting agents including; rituximab, ocrelizumab, epratuzumab, ofatumumab, alemtuzumab, ibritumomab. Bone marrow transplant, Haemopoietic stem cell transplant or Solid organ transplant. Immunomodulatory drugs (IMiDs); lenalidomide, pomalidomide, thalidomide	Anti-viral prophylaxis with tenofovir or entecavir
Moderate risk	High-dose corticosteroids (prednisolone>20mg OD for >4weeks). Anthracyclines including; doxorubicin, epirubicin. Local therapy for HCC including; TACE. Systemic chemotherapy Cladribine Cytokine modulators; abatacept, , ixekizumab, mogamulizumab, natalizumab, sarilumab, secukinumab, tocilizumab, ustekinumab, vedolizumab, TNF-α inhibitors including; infliximab, adalimumab, certolizumab, etanercept,golimumab. JAK inhibitors including;baricitinib, tofacitinib. Immunophilin inhibitors including; cyclosporine. Tyrosine-kinase inhibitors including; imatinib, nilotinib. Proteasome inhibitors such as; bortezomib.	Anti-viral prophylaxis with tenofovir or entecavir Or *Monitor HBsAg, HBV DNA and ALT every 3 months
Low risk	Moderate and low dose prednisone (10mg prednisolone OD for > 4 weeks or intra-articular steroid injections). Fingolimod Antimetabolites including; azathioprine, 6-mercaptopurine, methotrexate.	NA not required and monitoring not mandatory
Unknown risk	Immune checkpoint inhibitors such as; anti-PD-L1 (e.g. nivolumab), anti-PD-1 (e.g. pembrolizumab) and anti-CTLA4 (e.g. ipilimumab).	Anti-viral prophylaxis with tenofovir or entecavir To prevent potential interruption of treatment.

Appendix 4

Other useful resources:

1. Patient information:
   - British Liver Trust. https://www.britishlivertrust.org.uk/liver-information/liver-conditions/hepatitis-b/
   - British Liver Trust also provide translated information documents that may be downloaded in: Urdu, Bengali, Hindi, Traditional and Simplified Chinese, Gujarati, Punjabi and Polish: https://www.britishlivertrust.org.uk/publications/translations/
   - NHS Choices. http://www.nhs.uk/conditions/Hepatitis-B/Pages/Introduction.aspx

2. HIV & hepatitis B co-infection:
   - British HIV Association guideline. http://www.bhiva.org/HepBC2010.aspx

3. Hepatitis B in pregnancy:
   - Royal College of Obstetrics & Gynaecology. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/hepatitis-b-in-pregnancy---query-bank/

Appendix 5

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