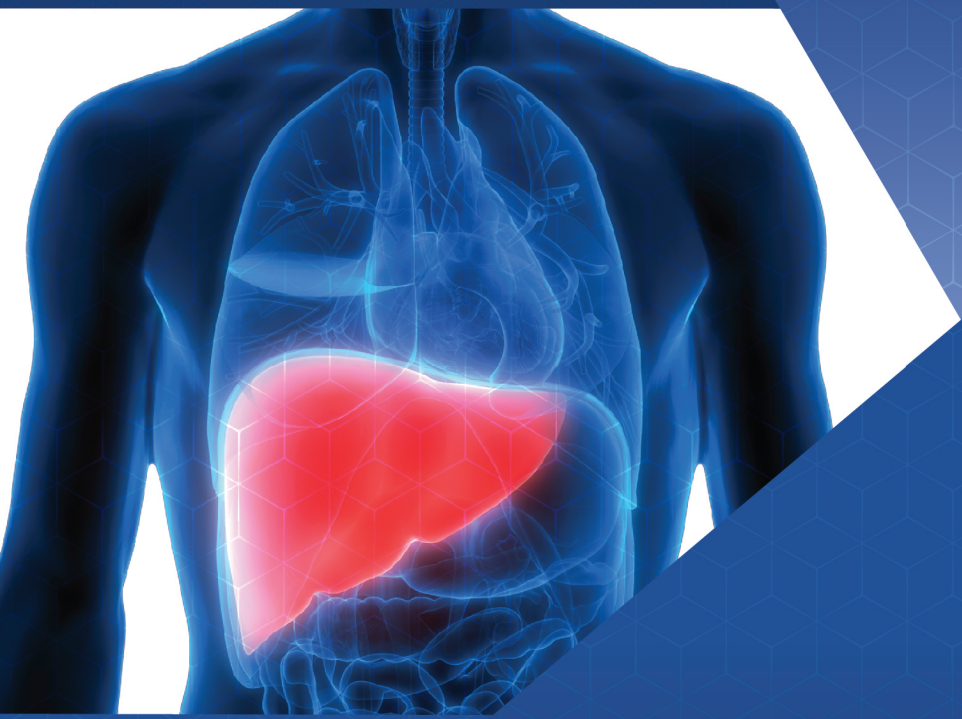
2022 MOH/P/PAK/502.22(GU)-e

# CLINICAL PRACTICE GUIDELINES



# MANAGEMENT OF CHRONIC HEPATITIS B IN ADULTS

Ministry of Health Malaysia

Academy of Medicine Malaysia

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Also available as an app for Android and IOS platforms: MyMaHTAS

**STATEMENT OF INTENT**

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

## UPDATING THE CPG

These guidelines were issued in 2022 and will be reviewed in a minimum period of four years (2026) or sooner if there is a need to do so. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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**LEVELS OF EVIDENCE**

| Level | Study design |
|---|---|
| I | Evidence from at least one properly randomised controlled trial |
| II-1 | Evidence obtained from well-designed controlled trials without randomisation |
| II-2 | Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group |
| II-3 | Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence |
| III | Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees |

***SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001***

## FORMULATION OF RECOMMENDATION

In line with current development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size is carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harms
- values and preferences
- resource implications
- equity, feasibility and acceptability

## KEY RECOMMENDATIONS

The following recommendations were highlighted by the CPG Development Group (DG) as the key clinical recommendations that should be recognised for implementation.

## SCREENING AND DIAGNOSIS

- Targeted screening for hepatitis B virus (HBV) infection should be done in the following groups of people:
  - family members of hepatitis B surface antigen (HBsAg)-positive persons
  - household contacts of HBsAg-positive persons
  - blood donors
  - healthcare workers
  - people who inject drugs participating in harm reduction programmes
  - foreign workers
  - pregnant women
- Other high-risk groups should be offered to screen for HBV infection.
- Screening of HBV infection should be done using either a rapid diagnostic test or laboratory-based immunoassay.
- HBV infection should be notified under the Prevention and Control on Infectious Disease Act 1988 within seven days of diagnosis.
- Hepatitis B virus deoxyribonucleic acid (DNA) should be ideally done before initiation of treatment and for assessment of its response.

## TREATMENT

- Initial assessment of patients with chronic hepatitis B (CHB) should include:
  - phase of infection
  - degree of liver fibrosis or cirrhosis
  - presence of co-infection
- Nucleos(t)ide analogues with high genetic barrier resistance should be used as first-line therapy in CHB i.e.
  - entecavir (ETV)
  - tenofovir disoproxil fumarate (TDF)
  - tenofovir alafenamide (TAF)
- ETV or TAF is preferred in CHB patients with age >60 years, bone disease or impaired renal function.
- Treatment should be initiated in patients with:
  - non-cirrhotic liver
    - hepatitis B e antigen (HBeAg)-positive with HBV DNA >20,000 IU/ml and alanine transaminase (ALT) twice the upper limit of normal (ULN)

- HBeAg-negative with HBV DNA >2,000 IU/ml and ALT twice ULN
- cirrhotic liver
  - any detectable level of HBV DNA regardless of ALT and HBeAg status

## SPECIAL GROUPS

- Human Immunodeficiency virus (HIV)/HBV co-infected patients should be treated simultaneously with dual active HBV treatment (tenofovir in combination with lamivudine or emtricitabine) plus another third agent of antiretroviral therapy.
- All patients with hepatitis B/hepatitis C virus co-infection should be treated as per indication of hepatitis B and hepatitis C mono-infection.
- Antiviral agents should be considered in pregnant CHB women with TDF with high viral load (>200,000 IU/ml) as the preferred choice.
- All candidates for chemotherapy and immunosuppressive treatment should be tested for HBV markers prior to immunosuppression e.g. HBsAg. If HBsAg-negative, antibody to hepatitis B core antigen should be tested.
- Antiviral dose should be adjusted according to the estimated glomerular filtration rate of CHB patients with chronic kidney disease.

## MONITORING

- CHB patients who are not on treatment should be monitored for:
  - ALT
  - HBV DNA
  - liver fibrosis or cirrhosis

## PREVENTION

- First dose hepatitis B vaccination should be given to all newborns within 24 hours of life.
- Hepatitis B immunoglobulin should be given to all newborns of CHB mothers within 12 hours of life.
- Antiviral prophylaxis should be initiated at 28 - 32 weeks of gestation in HBeAg-positive mothers with viral load >200,000 IU/ml.

## GUIDELINES DEVELOPMENT AND OBJECTIVES

### GUIDELINES DEVELOPMENT

The members of the DG for these CPG were from the Ministry of Health (MoH) and the Ministry of Higher Education. There was active involvement of a multidisciplinary Review Committee during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and Embase. Refer to **Appendix 1** for **Example of Search Strategy**. The inclusion criteria are all adults at risk and with hepatitis B infection regardless of study design. The first search was limited to literature published in the last 10 years (2010 - 2020) for majority of the clinical questions and on adults aged 19 to 44 years old and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field were contacted to identify relevant studies. All searches were conducted from 24 July 2020 to 30 September 2020. The literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 July 2022 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines on chronic hepatitis B in adults as listed below:

- EASL 2017 Clinical Practice Guidelines on The Management of Hepatitis B Virus Infection
- Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance
- Asian-Pacific Clinical Practice Guidelines on The Management of Hepatitis B: A 2015 Update

A total of 17 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 24 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and recommendations formulated after that were agreed upon by both the DG and review committee (RC). Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion are resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literatures used in these guidelines were graded using the US/ Canadian Preventive Services Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE (refer to the preceding page). The writing of the CPG follows strictly the requirement of Appraisal of Guidelines for Research and Evaluation (AGREE II).

On completion, the draft CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from **Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines** published in 2015 (available at https://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf

## OBJECTIVES

The objectives of the CPG are to provide evidence-based recommendations on the management of chronic hepatitis B in adults on the following aspects:

- diagnosis
- treatment
- monitoring & follow-up
- prevention
- referral

## CLINICAL QUESTIONS

Refer to **Appendix 2**.

## TARGET POPULATION

Inclusion Criteria

- Adults at risk and with hepatitis B infection

## TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in primary and secondary/tertiary care of the management of chronic hepatitis B in adults including:

- doctors
- allied health professionals
- trainees and medical students
- policymakers
- patients and their advocates
- professional societies

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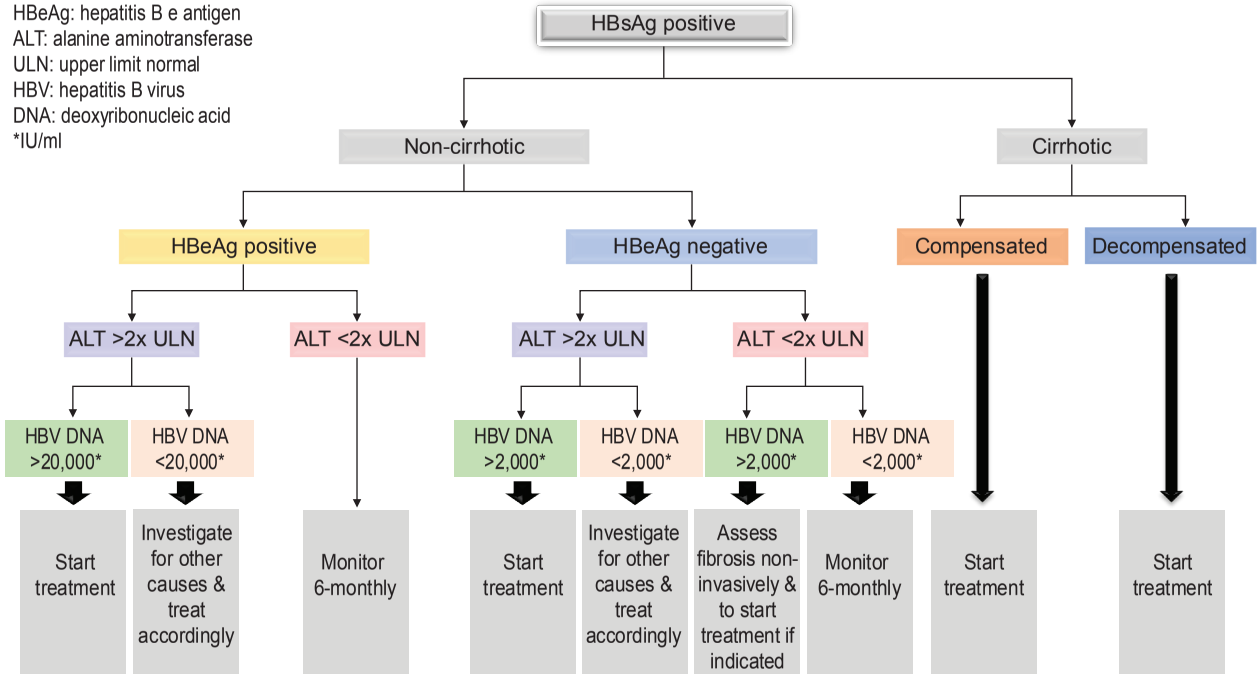
## ALGORITHM ON MANAGEMENT OF CHRONIC HEPATITIS B IN ADULTS

HBsAg: hepatitis B surface antigen
HBeAg: hepatitis B e antigen
ALT: alanine aminotransferase
ULN: upper limit normal
HBV: hepatitis B virus
DNA: deoxyribonucleic acid
*IU/ml



## 1. INTRODUCTION

Chronic Hepatitis B (CHB) is defined by the presence of hepatitis B surface antigen (HBsAg) for at least six months.[1; 2, level III] It is a global public health problem. In Malaysia, the incidence rate is approximately 12.64 in 100,000 population.[3, level III] The prevalence is decreasing due to improvements in socioeconomic status, universal vaccination programs and perhaps effective antiviral treatments.

Hepatitis B virus (HBV) is transmitted by perinatal or horizontal transmission, percutaneous, and sexual exposure and exposure to infected blood and body fluids. HBV can progress to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Screening is important, especially for those at high risk.

Non-invasive methods to assess liver fibrosis and cirrhosis e.g. the use of aspartate aminotransferase to platelet ratio (APRI) and fibrosis-4 index (FIB-4) testing have been validated in hepatitis B and are easily performed.

The induction of long-term suppression of HBV replication represents the main endpoint of current treatment strategies. Functional cure of hepatitis B is an optimal endpoint which is defined as sustained undetectable circulating HBsAg and HBV deoxyribonucleic acid (DNA).

Additional indications for treatment include the prevention of mother-to-child transmission in pregnant women with high viremia and the prevention of HBV reactivation in patients requiring immunosuppression or chemotherapy.

The long-term administration of a potent nucleos(t)ide analogue (NA) with a high barrier to resistance, such as entecavir (ETV), tenofovir disoproxil (TDF) or tenofovir alafenamide (TAF), represents the treatment of choice.

In view of high disease burden, variation in practice and non-existence of local guidelines, as well as the aim of elimination of viral hepatitis by 2030 in line with World Health Organization's (WHO) goal, an evidence-based CPG is required to guide healthcare providers locally in the management of CHB in adults.

## 2. RISK FACTORS

The following groups of people below are listed as high-risk for HBV infection and thus should be screened for the infection: [1; 4 ; 5 - 6, level III]

- family members, household and sexual contacts of HBsAg-positive persons
- persons who have ever injected drugs
- men who have sex with men
- persons with human immunodeficiency virus (HIV)
- persons seeking evaluation or treatment for sexually-transmitted disease
- healthcare workers (HCW)
- persons in prison/correctional facilities
- indigenous populations
- sex workers
- transgenders
- individuals with elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of unknown aetiology
- infants born to HBsAg-positive mothers
- persons with chronic liver disease (CLD)
- persons with end-stage renal disease including those receiving haemodialysis
- persons with multiple sexual partners
- persons exposed in healthcare setting

Other groups of people that should be screened for HBV infection are:[1; 4; 5 - 6, level III]

- persons requiring immunosuppressive therapy
- donors of blood, plasma, organ, tissue or semen
- residents and staff of facilities for developmentally disabled persons
- pregnant women

Based on National Strategic Plan for Hepatitis B and C Malaysia, targeted screening is recommended for the following groups of people:[7, level III]

- blood donors
- HCW
- persons who inject drugs participating in harm reduction programmes
- foreign workers

In a local pilot study of four states in 2019, the incidence of hepatitis B during antenatal screening ranged from 0.40% to 0.47% in Pahang, Kedah and Terengganu, whereas it was 0.95% in Sabah.[8, level III]

A technology review by MaHTAS revealed that there was a high level of evidence on antenatal screening for HBV infection being effective and cost-effective in reducing perinatal transmission of HBV.[94]

**Recommendation 1**

- Targeted screening for hepatitis B virus (HBV) infection should be done in the following groups of people:
  - family members of hepatitis B surface antigen (HBsAg)-positive persons
  - household contacts of HBsAg-positive persons
  - blood donors
  - healthcare workers
  - people who inject drugs participating in harm reduction programmes
  - foreign workers
  - pregnant women
- Other high-risk groups should be offered to screen for HBV infection*.

*Refer to the preceding text.

## 3. LABORATORY DIAGNOSIS

### 3.1 Screening Test

Screening for HBV infection in adults, adolescents and children (>12 months of age) is by detection of HBsAg using either rapid diagnostic test (RDT) or laboratory-based immunoassays. CHB is defined as persistent HBV infection (the presence of detectable HBsAg in the blood for ≥6 months).[1; 2, level III] In Malaysia, HBV infection is a notifiable disease under Prevention and Control on Infectious Disease Act 1988 and should be notified within seven days of diagnosis.[9, level III] For those in high-risk group who are HBsAg-negative are advised to check for antibody to hepatitis B surface protein (anti-HBs) and considered for vaccination if anti-HBs is negative.

Quality-assured RDT for HBsAg is recommended in settings where there is limited access to laboratory testing and/or in populations where access to rapid testing would facilitate care and treatment. A meta-analysis on the diagnostic accuracy of tests in HBsAg detection demonstrated that RDT had pooled sensitivity of 90% (95% CI 89 to 91) and specificity of 99% (95% CI 99 to 100) with enzyme immunoassays (EIA) as the reference standard. The sensitivity varies widely overall and within brands of RDT and it was lower (72.3%, 95% CI 67.9 to 76.4) in HIV-positive individuals.[10, level III]

Screening tests should meet the minimum acceptance criteria of WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use.[1] Test kits should be in the WHO list of prequalified in vitro diagnostic tests and the Malaysian medical device authority register.

- RDT of HBsAg
  - accurate and affordable point-of-care testing
- Laboratory-based Immunoassays
  - high throughput testing using an automated analyser and normally available in the hospital
  - include EIA, chemoluminescence immunoassay and electrochemoluminescence assay

**Recommendation 2**
- Screening of hepatitis B virus (HBV) infection with hepatitis B surface antigen should be done using either a rapid diagnostic test or laboratory-based immunoassay.
- HBV infection should be notified under the Prevention and Control on Infectious Disease Act 1988 within seven days of diagnosis.

### 3.2 Serological Markers

Diagnosis of HBV infection is accomplished by HBsAg. It can be further categorised by a series of serological markers.

Serological tests are used to distinguish acute from chronic HBV infections and to monitor vaccine-induced immunity. Molecular testing for HBV DNA is increasingly being used to quantify HBV viral load and monitor treatment response. Test selection should be based on the person's risk factors, vaccination history and findings of previous tests.[2, level III] **Table 1** shows various diagnostics and monitoring panels for hepatitis B interpretation.

**Table 1. Tests to Diagnose and Monitor Hepatitis B Virus Infection**

| HBsAg | Anti-HBc | IgM anti-HBc | Anti-HBs | HBeAg | HBeAb | HBV DNA | Interpretation |
|---|---|---|---|---|---|---|---|
| - | - | - | - | - | - | - | Not infected nor protected, suggest vaccination |
| + | - | - | - | - | - | - | Transient (up to 52 days) after vaccination |
| + | - | - | - | - | - | ± | Early acute infection |
| + | + | + | - | + | - | + | Acute infection |
| - | + | + | ± | - | ± | ± | Acute resolving infection |
| - | + | - | + | - | ± | - | Recovered from past infection and immune |
| + | + | - | - | ± | ± | + | Chronic infection |
| - | + | - | - | - | - | ± | False-positive; past infection; 'low level' chronic infection; or passive transfer of anti-HBc to an infant born to HBsAg-positive mother |
| - | - | - | + | - | - | - | Immune if the anti-HBs concentration is ≥10 IU/ml after vaccine series completion; passive transfer after hepatitis B immune globulin administration |

HBsAg = Hepatitis B surface antigen; Anti-HBc = Antibody to hepatitis B core antigen; IgM anti-HBc = Immunoglobulin M antibody to hepatitis B core antigen; Anti-HBs = Antibody to hepatitis B surface protein; HBeAg = Hepatitis B e antigen; HBeAb = Hepatitis B e antibody; HBV DNA = Hepatitis B virus deoxyribonucleic acid
+ implies positive; - implies negative; ± may be positive or negative

**Adapted**:

1. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. Can J Infect Dis Med Microbiol. 2005 Mar;16(2):65-72.
2. Centers for Disease Control and Prevention. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices (Available at: https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm#T1_down).

**Figure 1** represents a typical serology course of hepatitis B progression from acute to chronic overtime

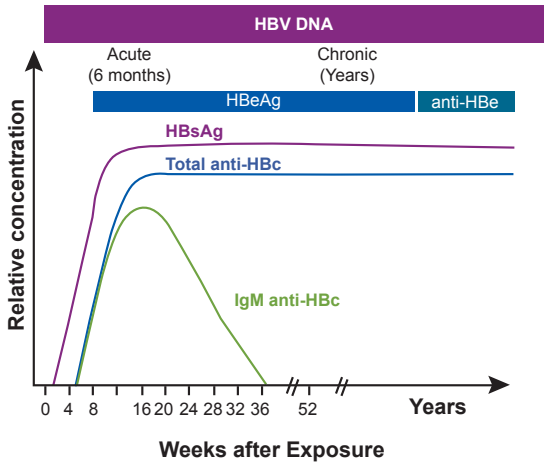



**Figure 1. Progression to Chronic HBV Infection - Typical Serology Course**

**Source**: Centers for Disease Control and Prevention. Recommendations for Identification and Public Health Management of Persons with Chronic Hepatitis B Virus Infection (Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm)

- **HBV DNA molecular test**

HBV DNA molecular test is used to detect the presence of the virus which reflects the level of viral replication and correlates with disease progression.[1]

Quantitative molecular (viral load) test for detection of HBV DNA following a reactive HBsAg serological test is an essential component in:[1; 5, level III]

- evaluation for the need of treatment
- assessment of the effectiveness of antiviral treatment

A real-time polymerase chain reaction has become the standard assay to detect and quantify HBV DNA due to its ability in detection of low viral loads (10 - 15 IU/ml) and highest up to $1.0x10^9$ IU/ml.[11]

Advance serological and molecular markers e.g. HBsAg quantification and HBV genotype can be considered to assess the prognosis of CHB and treatment selection.[12, level III] However, these are not widely available in Malaysia.

Refer to **Appendix 3** on **Laboratory Workflow for Diagnosis of Chronic Hepatitis B Infection**.

**Recommendation 3**

- Quantitative hepatitis B virus deoxyribonucleic acid should be ideally done before initiation of treatment and for assessment of its response.

## 4. INITIAL ASSESSMENT

### 4.1 Clinical Assessment

All patients diagnosed with HBV infection should be assessed for:[5, level III; 13 - 14]

- detailed history
- physical examination for stigmata of CLD

### 4.2 Biochemical Assessment

The natural course of HBV infection consists of four phases as shown in **Table 2**.

**Table 2. Natural History and Assessment of Patients with Chronic Hepatitis B Virus Infection**

| Investigation/ Terminology | HBeAg-positive | | HBeAg-negative | |
|---|---|---|---|---|
| | Chronic infection | Chronic hepatitis | Chronic infection | Chronic hepatitis |
| HBsAg | High | High/intermediate | Low | Intermediate |
| HBeAg | Positive | Positive | Negative | Negative |
| HBV DNA | >$10^7$ IU/ml | $10^4$ - $10^7$ IU/ml | <2,000 IU/ml | >2,000 IU/ml |
| ALT | Normal | Elevated | Normal | Elevated |
| Liver disease | None/minimal | Moderate/severe | None | Moderate/severe |
| Old terminology | Immune tolerant | Immune reactive HBeAg-positive | Inactive carrier | HBeAg-negative chronic hepatitis |

**Source**: European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.

The following investigations may be helpful in the assessment of CHB patients:[5, level III; 13 - 14]

- hepatitis B e antigen (HBeAg) and hepatitis B e antibody (HBeAb)
- biochemical markers, including AST and ALT, alkaline phosphatase, bilirubin and serum creatinine (Cr)
- serum albumin
- full blood count (FBC) and prothrombin time/international normalisation ratio (INR)
- HBV DNA detection and level measurement
- co-infections with HIV and hepatitis C
- co-morbidities and other liver-related diseases based on clinical judgement

For those with cirrhosis, assessment for compensated and decompensated cirrhosis is done using Child-Turcotte-Pugh Score (CPS) as shown below.

**Table 3. Child-Turcotte-Pugh Score for Grading Severity of Liver Disease**

| Variable | Score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | None | Mild/ on diuretics | Moderate/ severe |
| Encephalopathy | None | Grade I - II* | Grade III - IV* |
| Bilirubin (mmol/L) | <34 | 34 - 50 | >50 |
| Albumin (g/L) | >35 | 28 - 35 | <28 |
| Prothrombin time<br>• seconds over normal<br>• INR | <br><4<br><1.7 | <br>4 - 6<br>1.7 - 2.3 | <br>>6<br>>2.3 |

*Grade I: alteration of sleep pattern, Grade II: asterixis, Grade III: somnolence, Grade IV: coma

**Modified**: Ministry of Health Malaysia, Clinical Practice Guidelines Management of Chronic Hepatitis C in Adults. Putrajaya: MoH; 2019.

- A total Child-Turcotte-Pugh Score (CPS) of:
  - 5 - 6 is class A
  - 7 - 9 is class B
  - 10 - 15 is class C
- CPS classes B and C are considered decompensated stages.

Model for End-Stage Liver Disease (MELD) score is a scoring system ranging from 6 - 40 to evaluate the severity of liver disease. Incorporation of serum sodium into MELD (MELD-Na) may further increase its prognostic ability. It uses values e.g. bilirubin, serum Cr, INR and serum sodium. The higher score indicates a poorer prognosis and warrant for tertiary care.

**Formula**

- MELD score = 3.8 [Ln serum bilirubin (mg/dL)] + 11.2 [Ln INR] + 9.6 [Ln serum creatinine (mg/dL)] + 6.4
- MELD-Na score = MELD + 1.32 x (137 - Na) - [0.033 x MELD*(137- Na)]

**Table 4. Interpretation of MELD-Na Score**

| Score | Mortality (%) |
|---|---|
| MELD-Na score ≥40 | 71.3 |
| MELD-Na score 30 - 39 | 52.6 |
| MELD-Na score 20 - 29 | 19.6 |
| MELD-Na score 10 - 19 | 6.0 |
| MELD-Na score ≤9 | 1.9 |

Accurate assessments on the severity of liver fibrosis are prudent for prognostication and planning the management of HBV patients. Non-invasive methods of assessing fibrosis have been developed to reduce the need for liver biopsy which is deemed risky and may lead to complications.

### 4.3 Fibrosis Assessment in Patients with Chronic Hepatitis B

#### i. Non-invasive methods

- **Aspartate aminotransferase to platelet ratio (APRI) score**

This is a simple test whereby it uses two cut-off points for diagnosing specific fibrosis stages. Reported cut-off values for APRI for the detection of significant fibrosis and cirrhosis are as follows:[13]

- for significant fibrosis, low and high cut-offs for APRI are 0.5 and 1.5
- for cirrhosis, low and high cut-offs for APRI are 1.0 and 2.0

- **Fibrosis-4 index**

FIB-4 is a non-invasive tool with good diagnostic accuracy. In a diagnostic study on hepatitis C, a FIB-4 index <1.45 had a negative predictive value (NPV) of 94.7% to exclude advanced fibrosis or cirrhosis (F3 - F4) while a FIB-4 index >3.25 had a PPV of 82.1% to confirm the existence of advanced fibrosis or cirrhosis (F3 - F4). The FIB-4 index efficiently identified cirrhosis with an area under the curve (AUC) of 0.91 (95% CI 0.86 to 0.95).[15, level III] The CPG DG opines that the results of this study can be extrapolated on hepatitis B patients.

**Formula**

- APRI score = $\frac{\text{AST (IU/L) / AST (upper limit of normal) (IU/L)} \times 100}{\text{platelet } (10^9 \text{ /L})}$

- FIB-4 index = $\frac{\text{age [(year) x AST (IU/L)]}}{\text{platelet } (10^9 \text{ /L}) \times \sqrt{\text{ALT (IU/L)}}}$

- **Imaging**

Cirrhosis is a high-risk factor for developing HCC and other complications caused by portal hypertension, therefore early detection of cirrhosis can help identify high-risk patients earlier. Besides laboratory testing, imaging e.g. ultrasonography (US), computed tomography and magnetic resonance imaging can be used to look for evidence of cirrhosis.

In a diagnostic study, transient elastography (TE) was superior to US in assessing liver cirrhosis in patients with CHB. TE has significantly increased the accuracy of detecting cirrhosis compared with US with an AUC of 0.96 vs 0.71.[16, level III]

Another diagnostic study showed that magnetic resonance elastography (MRE) was superior to TE and point shear-wave elastography in the detection of early stages of liver fibrosis with a high AUC of 0.88.[17, level III]

Although MRE and TE have shown high accuracy, US is an acceptable option for liver cirrhosis assessment in a local setting due to its wide availability.

Assessment of liver cirrhosis/fibrosis using an APRI, FIB-4 and TE is shown in the following table.

**Table 5. Evaluation of APRI, FIB-4 and TE**

| Test | Non-cirrhotic/fibrosis liver | Cirrhotic liver APRI |
|---|---|---|
| low cut-off | 0.5 | 1.0 |
| APRI high cut-off | 1.0 | 2.0 |
| FIB-4 | <3.25 | ≥3.25 |
| TE | <8.0 | ≥12.5 |

Treatment decisions can be based on non-invasive tests of significant fibrosis (e.g. APRI ≥1.5, FIB-4 ≥3.25, liver stiffness ≥8 kPa by TE).[18, level III]

**ii. Invasive method**

Liver biopsy place a central role in treatment algorithm in hepatitis B and remains the gold standard for evaluation of hepatic pathology and should be considered when non-invasive assessments are inconclusive.

**Recommendation 4**

- Initial assessment of patients with chronic hepatitis B should include:
  - phase of infection
  - degree of liver fibrosis or cirrhosis
  - presence of co-infection

# 5. TREATMENT

## 5.1 Non-pharmacological Treatment

*Phyllanthus* (dukung anak) has long been used in Chinese medicine to treat CLD.

In two Cochrane systematic reviews, many clinical trials were done on Phyllanthus with no consensus on its effectiveness and safety. Phyllanthus was:

- not effective in HBsAg seroconversion compared with placebo[19, level I]
- showed no difference in HBsAg clearance or HBV DNA level compared with antiviral alone[19 - 20, level I]
- more effective in HBV DNA clearance when combined with antiviral compared with antiviral alone (RR=0.69, 95% CI 0.52 to 0.91)[19, level I]

There was no significant difference in adverse events (AEs) between Phyllanthus and placebo.[19, level I]

As all primary papers in both reviews had a high risk of bias, there was insufficient evidence to support the use of Phyllanthus in the treatment of CHB.[19 - 20, level I]

In another Cochrane systematic review, selenium was not effective in preventing primary liver cancer in CHB patients. However, vitamin E supplements showed a sustained biochemical and virological response at end of treatment (RR=0.55, 95 % CI 0.34 to 0.87 and RR=0.55, 95% CI 0.34 to 0.86 respectively). The quality of primary papers was highly biased due to significant role of chance.[21, level I]

- There is insufficient evidence to support the use of traditional and complementary medicine in the treatment of CHB.

## 5.2 Pharmacological Treatment

The mainstay of CHB treatment consists of immunomodulators and NA. The NAs can be classified according to HBV resistance barrier as shown below.

**Table 6. Pharmacological Treatment**

| Type | Drug Name | Route of Administration | HBV Resistance Barrier |
|---|---|---|---|
| Immunomodulators | Standard interferon | Subcutaneous Injection | - |
| | Pegylated interferon alpha | Subcutaneous Injection | - |
| Nucleoside analogues | Lamivudine | Oral | Low |
| | Telbivudine* | Oral | Intermediate |
| | Entecavir | Oral | High |
| Nucleotide analogues | Adefovir# | Oral | Intermediate |
| | Tenofovir disoproxil fumarate | Oral | High |
| | Tenofovir alafenamide | Oral | High |

*deregistered in Malaysia in 2022
#discontinued worldwide in 2020 (important for drug-resistance assessment in view of preferred antiviral choice)

In a large, multi-centre randomised controlled trial (RCT), both ETV and TDF were equally effective in HBV DNA suppression (p=0.807) and a comparable side effect profile among NA-naive CHB patients at long-term follow-up of 144 weeks.[22, level I]

Another large, multi-centre RCT showed TAF was non-inferior to TDF in HBV suppression (<29 IU/ml) among HBeAg-negative CHB patients at week 48. TAF had a significantly smaller reduction in bone mineral density and estimated glomerular filtration rate (eGFR) compared with TDF. Apart from that, most AEs were mild to moderate in severity in the two treatment groups.[23, level I]

In a prospective cohort study on both treatment-naïve and treatment-experienced CHB patients, TDF and TAF were equally effective in the reduction of HBV DNA and HBsAg levels. Apart from that, switching from TDF to TAF therapy contributed to the maintenance of the antiviral effect and significant recovery of renal dysfunction.[24, level II-2]

Treatment with TAF was also associated with significant improvement in the renal and bone safety profiles.[25, level I]

In a meta-analysis on CHB, interferon (IFN) monotherapy or combined with NA was compared with NA monotherapy. The regimen using IFN had a small but significant increase in HBsAg loss over NA monotherapy:[26, level I]

- combination vs NA monotherapy with RD of 5% (95% CI 3 to 7)
- IFN monotherapy vs NA monotherapy with RD of 3% (95% CI 2 to 5)

The impact of IFN could be modulated by its discontinuation rate due to AEs at 5.9%.

Long-term administration of a potent NA with a high barrier to resistance is the treatment of choice regardless of the severity of liver disease in CHB.[13] The preferred first-line therapies are TDF, ETV and TAF.[5, level III; 13 - 14]

ETV or TAF is preferred over TDF in:[13]

- age >60 years
- bone disease
- renal impairment

Treatment options and the recommended doses are featured in **Appendix 4**.

**Recommendation 5**

- Nucleos(t)ide analogues with high genetic barrier resistance should be used as first-line therapy in chronic hepatitis B (CHB) i.e.
  - entecavir (ETV)
  - tenofovir disoproxil fumarate
  - tenofovir alafenamide (TAF)
- ETV or TAF is preferred in CHB patients with age >60 years, bone disease or impaired renal function*.

*TAF is not recommended in patients with eGFR <15 ml/min/$m^2$.

- **Treatment initiation**

Not all CHB patients require antiviral treatment. Treatment is generally recommended for individuals at a high risk of disease progression i.e. those with high ALT levels, active viral replication and advanced fibrosis or cirrhosis.[27, level III]

A review of four important CPGs for CHB; European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), Asia Pacific Association for the Study of the Liver (APASL) and WHO summarised treatment initiation as shown in the table below:[27, level III]

**Table 7. Comparison of Different Guidelines in Initiation of Hepatitis B Treatment**

| | EASL 2017 | | AASLD 2016 | | APASL 2015 | | WHO 2015 | |
|---|---|---|---|---|---|---|---|---|
| **Non-cirrhotic** | | | | | | | | |
| **HBeAg** | Positive | Negative | Positive | Negative | Positive | Negative | Positive | Negative |
| HBV DNA (IU/ml) | >2,000 | | >20,000 | >2,000 | >20,000 | >2,000 | >20,000 | |
| ALT (U/L) | >ULN | | 2x ULN | | 2x ULN | | Abnormal | |
| Histological changes | Moderate liver necroinflammation /fibrosis | | Moderate-to-severe liver necroinflammation/fibrosis | | | | - | |
| **Compensated Cirrhosis** | | | | | | | | |
| HBV DNA (IU/ml) | Any detectable level | | | | >2,000 | | Any detectable level | |
| ALT (U/L) | Any level | | | | | | | |
| **Decompensated Cirrhosis** | | | | | | | | |
| HBV DNA (IU/ml) | Any detectable level | | | | | | | |
| ALT (U/L) | Any level | | | | | | | |

The four existing CPGs for CHB on treatment initiation criteria for non-cirrhotic HBeAg-positive and negative individuals and cirrhotic individuals are almost similar in their recommendations, with minor differences. Other predictors of advanced disease should be considered for treatment initiation including gender, age, hepatitis B genotype and family history.[18, level III; 27, level III]

The management of CHB in adults is summarised in the **Algorithm** on **Management of Chronic Hepatitis B in Adults** (page x).

- Hepatitis B patients should be considered for antiviral treatment if they meet treatment indications based on three main parameters as stated below:[27, level III]
  - HBV DNA level should be above a designated threshold
  - ALT levels should be elevated and/or
  - evidence of significant fibrosis

**Recommendation 6**

- Treatment should be initiated in patients with:
  - non-cirrhotic liver
    - hepatitis B e antigen (HBeAg)-positive with hepatitis B virus deoxyribonucleic acid (HBV DNA) >20,000 IU/ml and alanine transaminase (ALT) twice upper limit normal (ULN)
    - HBeAg-negative with HBV DNA >2,000 IU/ml and ALT twice ULN
  - cirrhotic liver
    - any detectable level of HBV DNA regardless of ALT and HBeAg status

## 6. SPECIAL GROUPS

### 6.1 Acute Hepatitis B

Acute hepatitis B is a short-term illness that occurs within the first six months after exposure to HBV. The diagnosis of acute HBV infection is based upon the detection of HBsAg and immunoglobulin M antibody to hepatitis B core antigen (IgM anti-HBc).

- More than 95% of adults with acute HBV hepatitis do not require specific treatment as they will fully recover spontaneously unless in severe infection.[13]
- Only patients with severe acute hepatitis B should be treated with NAs and considered for liver transplantation.[13]
- Characteristics of severe acute hepatitis B are:[13]
  - coagulopathy INR >1.5
  - protracted course i.e. persistent symptoms or marked jaundice >4 weeks
  - sign(s) of acute liver failure

In a meta-analysis of pharmacological interventions for acute hepatitis B infection, the risk of progression to chronic HBV infection was higher in lamivudine (3TC) group compared with placebo or no intervention group (OR=1.99, 95% CI 1.05 to 3.77) and ETV group (OR=3.64, 95% CI 1.31 to 10.13). However, there was no difference in the risk between ETV and no intervention groups. The rate of seroconversion was higher in ETV compared with 3TC (OR=0.15, 95% CI 0.05 to 0.48) although there was no significant difference in the time taken.[28, level I]

Apart from that, there was no difference in short-term mortality (<1 year) in any of the comparisons between hepatitis B immunoglobulin (HBIG) vs placebo, 3TC vs placebo or no intervention, 3TC vs ETV and ETV vs no intervention. The proportion of people with AEs was higher in interferon group than placebo group but there was no difference between 3TC and placebo or no intervention groups. No serious AEs were reported in all groups. None of the trials reported progression to fulminant HBV infection. The quality of primary papers used in the meta-analysis was generally low.[28, level I]

In a small retrospective cohort study involving 32 patients with fulminant acute hepatitis B who started on NAs; transaminases, bilirubin and INR values returned to normal range within three months. The therapy was well tolerated with no observed side effects. Of the 32 patients, the remaining 22 (68.8%) who were followed further lost their HBsAg in a median of 108 days (range 40 - 366) and 72.7% of them experienced a seroconversion to anti-HBs in a median of 137 days. None of the

patients developed CHB. The risk of not achieving seroconversion was independent of transaminases, bilirubin, INR, antiviral drug and days from diagnosis to treatment initiation. The patients who developed seroconversion lost their HBsAg earlier than those who did not (median 97.5 days vs 229.5 days; p=0.0219).[29, level II-2]

### 6.2 Acute Liver Failure/Acute-on-chronic Liver Failure

Acute liver failure (ALF) is a medical emergency. It is defined as severe liver injury, leading to coagulopathy (usually with an INR ≥1.5) and any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease. On the other hand, acute-on-chronic liver failure applies to any patient who has an underlying chronic liver disease with superimposed acute insult which leads to a poorer outcome.[30, level III]

Treating all hepatitis B patients with ALF is indicated given its safety and the ultimate need for liver transplantation in many of them. Lowering HBV DNA levels are important to reduce the risk of recurrent hepatitis B after a liver transplant.

- Antiviral treatment is indicated only for those patients with acute hepatitis B who have ALF or who have a protracted, severe course, as indicated by total bilirubin >3 mg/dL (or direct bilirubin >1.5 mg/dL), INR >1.5, encephalopathy or ascites.[5, level III]
  - ETV, TDF or TAF are the preferred antiviral drugs.

### 6.3 Hepatitis B Flare

Hepatitis B flare, defined as an event with an abrupt rise of ALT levels to >5 times the upper limit of normal (ULN) in CHB, is considered to be the result of a human leukocyte antigen-I restricted, cytotoxic T-lymphocyte-mediated immune response against HBV and its downstream mechanisms. It may occur spontaneously, during or after antiviral treatment and in the setting of immunosuppression and/or chemotherapy.

The clinical spectrum of hepatitis B flares varies from asymptomatic to symptomatic and typical overt acute hepatitis, even with hepatic decompensation or failure. Flares may also occur in viraemic cirrhotic patients with a higher incidence of decompensation/mortality compared with those without cirrhosis, hence requiring immediate antiviral treatment for prevention or rescue.[31, level III]

- While flares in cirrhotic patients always require immediate antiviral treatment, those occurring in non-cirrhotic patients with decreasing HBV DNA may be followed by HBV and/or HBeAg loss with remission, and therefore may be observed for 3 - 6 months for real indication of antiviral treatment.[31, level III]

### 6.4 Co-infection with Human Immunodeficiency Virus (HIV)

Prevalence of HBV co-infection among people living with HIV was found to be 13% in a study on tertiary care hospitals in Malaysia.[32, level III] TREAT Asia HIV Observational Database (TAHOD) study from Asia-Pacific Region reported 10.4% of subjects were HBsAg-positive, 15.2% were positive for antibody to hepatitis C virus (anti-HCV) while 1.8% were positive for both markers.[33, level II-2] Thus, all hepatitis B patients should be screened for HIV and hepatitis C virus (HCV).[13]

A cohort study showed the hazard ratio (HR) for an acquired immunodeficiency syndrome (AIDS) or death event was almost double for those with HIV/HBV co-infected compared with HIV mono-infected patients (adjusted-HR=1.80, 95% CI 1.20 to 2.69).[34, level II-2] In another multicentre cohort study showed that HIV/HBV co-infected patients, especially those with low cluster of differentiation 4 (CD4) nadir count, were at increased risk for liver-related mortality.[35, level II-2] HIV/HBV co-infected patients may have faster progression of hepatic fibrosis and higher risk of cirrhosis, end-stage liver disease and HCC than HBV-mono-infected persons.[13 - 14] Hence, antiretroviral therapy (ART) should be initiated in HIV/HBV co-infected patients irrespective of CD4 cell count.[5, level III; 13 - 14]

An RCT in African HIV/HBV co-infected adults with high HBV replication showed that they remained at heightened risk of mortality in the early ART era. The 60-month probability of death was 11.8% (95% CI 5.4 to 24.5) in co-infected patients with HBV DNA ≥2000 IU/ml, 4.4% (95% CI 1.9 to 10.4) in co-infected patients with HBV DNA <2000 IU/ml and 4.2% (95% CI 3.3 to 5.4) in HIV mono-infected patients. Mortality risk-adjusted for ART strategy (immediate vs deferred) was higher in co-infected patients with HBV DNA ≥2,000 IU/ml in comparison with HIV mono-infected patients (HR=2.74, 95% CI 1.26 to 5.97).[36, level I]

- HIV/HBV co-infected patients should be treated simultaneously for both HIV and HBV with TDF in combination with 3TC or emtricitabine (FTC) plus another third agent that is active against HIV in the form of lifelong ART.[5, level III; 13 - 14]
- Entecavir is an alternative treatment for HBV in patients who have contraindications to tenofovir. However, due to weak activity against HIV, it must be administered in conjunction with a fully active HIV ART regimen.[13]
- When antiretroviral therapy regimens are altered (e.g., due to HIV resistance or intolerance), drugs that are effective against HBV should not be discontinued unless it is substituted with another drug that has activity against HBV.[37, level III]

A meta-analysis showed that 3TC plus TDF combination therapy was more effective than 3TC monotherapy in HBV/HIV co-infected patients, in terms of rate of undetectable HBV DNA (RR=1.57, 95% CI 1.23 to 2.00) and undetectable HIV ribonucleic acid (RNA) (RR=1.26, 95% CI 1.11 to 1.42).[38, level I]

In a small open labelled RCT, TDF/FTC combination therapy compared with FTC monotherapy in antiretroviral-naive HIV/HBV co-infected patients at 48 weeks resulted in:[39, level I]

- a greater decrease in median HBV DNA level [-5.32 log10 copies/ml (IQR -6.19, -5.13) vs -3.25 log10 copies/ml (IQR -5.43, -2.66); p=0.03]
- a greater proportion of patients with undetectable HBV DNA i.e. <30 IU/ml (90% vs 33%; p=0.036)

A retrospective cohort study revealed that TDF in combination with 3TC or FTC was more effective than 3TC alone in durable HBV viral suppression among HIV/HBV co-infected patients (HR=2.635, 95% CI 1.720 to 4.037). HBeAg positivity at baseline was associated with failure to achieve HBV suppression despite long-term TDF-containing ART (HR=0.293, 95% CI 0.178 to 0.482).[40, level II-2]

Another cohort study also supported the effectiveness of TDF-based dual HBV-active ART compared with mono HBV-active (3TC or FTC) ART in achieving HBV DNA <200 IU/ml at 144 weeks (p=0.02) when adjusted for baseline HBV DNA and HBeAg among HIV/HBV co-infected patients. However, the effectiveness was not at short-term review (24 weeks). The failures in the monotherapy group to maintain durability of HBV DNA suppression were primarily seen in those with HBV DNA >20,000 IU/ml. This study also showed that pre-treatment HBeAg status demonstrated that a greater proportion of HBeAg-negative subjects achieved HBV DNA <200 IU/ml at week 24 than HBeAg-positive subjects, with difference increased over time (p=0.04).[35, level II-2]

Limited data from a multicentre observational study supported the switch of TDF to TAF in HIV/HBV co-infected patients with renal impairment. After one year of switching, there were improvements in eGFR of 3.2 ml/min/1.73 $m^2$ (95% CI 1.2 to 5.2) and 6.2 ml/min/1.73 $m^2$ (95% CI 2.4 to 10.0) in individuals with eGFR of 60 - 89 ml/min/1.73 $m^2$ and <60 ml/min/1.73 $m^2$, respectively. Apart from that, there was a reduction in urine protein-to-creatinine ratio of -6.3 mg/mmol (95% CI -10.0 to -2) for the whole group.[41, level II-3]

**Recommendation 7**

- All hepatitis B patients should be screened for human immunodeficiency virus (HIV) and hepatitis C virus.
- HIV/hepatitis B virus (HBV) co-infected patients should be treated simultaneously with dual active HBV treatment (tenofovir in combination with lamivudine or emtricitabine) plus another third agent of lifelong antiretroviral therapy (ART).
- Pre-treatment hepatitis B e antigen and/or HBV deoxyribonucleic acid (DNA) viral load should be used for prognosis markers of sustained HBV DNA suppression with ART in co-infected patients.

### 6.5 Co-infection with Hepatitis C Virus

Patients with HBV/HCV co-infection have accelerated liver progression to cirrhosis and decompensation, and have an increased risk of HCC i.e. 45% in HBV/HCV co-infected patients compared with 16% in HBV and 28% in HCV mono-infected patients.[42, level III]

In HBV/HCV co-infected patients, the virus responsible for liver disease should be determined by measuring HBV DNA and HCV RNA. With effective direct-acting antivirals (DAAs) therapy, sustained virological response rates for HCV in HBV and HCV co-infected patients are comparable with those in HCV mono-infected patients. There is a potential risk of HBV reactivation during DAAs therapy or after clearance of HCV.[13] However, there is no known drug-drug interaction between DAAs and preferred hepatitis B therapy.

Patients with HBV/HCV co-infection who fulfil the indication for HBV treatment should receive NA treatment. Those with HCV treated with DAA are at risk of HBV DNA and ALT flares. Monitoring of HBV DNA levels during treatment and for three months post-treatment is indicated in those who do not meet treatment criteria for mono-infected patients. In patients with HBsAg-negative and antibody to hepatitis B core antigen (anti-HBc)-positive, the risk of HBV reactivation is low. ALT monitoring should be done at baseline, end of treatment and during follow-up. HBV DNA and HBsAg are testing reserved for those whose ALT levels increase or fail to normalise during treatment or post-treatment.[13]

**Recommendation 8**
- All patients with hepatitis B/hepatitis C virus co-infection should be treated as per indication of hepatitis B and hepatitis C mono-infection*.

*Refer to **Algorithm** on **Management of Chronic Hepatitis B in Adults** (page x)

### 6.6 Pregnancy and Lactation

Screening for HBsAg at the first antenatal visit is prudent to identify pregnant mothers at high-risk of transmitting the virus to their babies perinatally. This is further discussed in **Subchapter 8.1**. Antiviral agents e.g. 3TC, telbivudine (LdT), TDF or TAF have been used to reduce high viraemia in CHB mothers during the second and third trimesters of pregnancy. Breastfeeding is generally safe as the common use TDF has minimal bioavailability in breast milk.

In a cohort study, TAF and TDF were effective in reducing viral load at delivery compared with baseline. The mean decreases in serum HBV DNA levels in TAF-treated and TDF-treated mothers were 4.3 (±0.6) and 4.4 (±0.7) $\log^{10}$ IU/ml, leading to mean viral loads of 3.5 (±0.9) and 3.4 (±1.0) $\log^{10}$ IU/ml at delivery respectively. Upon delivery, all mothers achieved HBV DNA levels <200,000 IU/ml in both treatment groups. Generally, both antiviral agents were well tolerated and safe during the second and third trimesters of pregnancy. They were also safe in their infants at seven months of follow-up.[43, level II-2]

A meta-analysis showed that TDF was more effective than control (3TC, LdT and no treatment) in reducing maternal HBV DNA level (WMD=2.33 $\log^{10}$ IU/ml, 95% CI 1.01 to 3.64) and infant HBsAg positivity (RR=0.15, 95% CI 0.07 to 0.31). Maternal and infant safety profiles, including ALT, creatine kinase (CK) and Cr, were comparable between TDF and other treatment groups. The quality of included cohort studies was moderate to high.[44, level I]

Studies have shown that there was no association between breastfeeding and CHB in vaccinated infants. In a meta-analysis, breastfeeding was not associated with an additional risk of infantile CHB infection compared with formula feeding.[45, level I] Two cohort studies showed no significant difference in CHB between breastfed and formula-fed children.[46 - 47, level II-2]

Indication of treatment in pregnant CHB is similar to the normal CHB population (refer to **Algorithm** on **Management of Chronic Hepatitis B in Adults**). A summary of prophylaxis and treatment in pregnant CHB patients can be seen in **Appendix 5**.

**Recommendation 9**
- Antiviral agents should be considered in pregnant women with chronic hepatitis B (CHB) with high viral load (>200,000 IU/ml).
  - Tenofovir disoproxil fumarate is the preferred choice.
- Breastfeeding may be continued in women with CHB.

### 6.7 Immunosuppression or Cytotoxic Therapy

- All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression.[13]

- **HBsAg-positive patients**

All HBsAg-positive patients should receive either ETV, TDF or TAF for treatment or prophylaxis. The prophylaxis should continue for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment.[13]

Liver function test (LFT) and HBV DNA should be tested every 3 - 6 months during prophylaxis and for at least 12 months after NA withdrawal as a large proportion of HBV reactivation (HBV-R) develops after NA discontinuation.[13]

- **HBsAg-negative, anti-HBc-positive patients**

A meta-analysis showed that HBV-R occurred in 6.5% of HBsAg-negative, anti-HBc-total-positive patients who were receiving immunosuppressive therapy. The risk of HBV-R was higher but non-significant in rituximab-containing regimens compared with rituximab-free regimens. Further analysis also showed HBV-R rate in the rituximab-free regimen was higher in patients with detectable HBV DNA compared with those without (RR=12.67, 95% CI 2.39 to 67.04). Apart from that, HBV-R risk was lower in anti-HBs-positive vs anti-HBs-negative at baseline in all patient subgroups:[48, level I]
  - hematological diseases (RR=0.29, 95% CI 0.19 to 0.46)
  - non-haematological diseases (RR=0.28, 95% CI 0.11 to 0.76)
  - rituximab-containing regimens (RR=0.32, 95% CI 0.15 to 0.69)
  - rituximab-free regimens (RR=0.36, 95% CI 0.14 to 0.96)

After cessation of immunosuppression, HBV-R developed in 42% of the rituximab-containing regimens group and 32% of rituximab-free regimens group.

In another meta-analysis, the median time for HBV-R from the last rituximab dose was three months; it was at one month in anti-HBc-positive and five months in HBsAg-positive (p=0.021). Apart from that, 55% of patients experienced fulminant liver failure.[49, level III]

In HBsAg-negative, anti-HBc-positive subjects, the risk of HBV-R can be classified as high (>10%), moderate (1 - 10%) or low (<1%). Patients are classified based on their immunosuppression risk of reactivation as shown in **Table 8**.[50]

**Table 8. Types and duration of prophylaxis according to risk of reactivation**

| | High-risk group | Moderate-risk group | Low-risk group |
|---|---|---|---|
| Immunosuppressive treatment | • B-cell depleting agents (e.g. rituximab, ofatumumab) | • Tumour necrosis factor-α inhibitors (e.g. etanercept, adalimumab, certolizumab, infliximab)<br>• Other cytokine or integrin inhibitors (e.g. abatacept, ustekinumab, natalizumab, vedolizumab)<br>• Tyrosine kinase inhibitors (e.g. imatinib, nilotinib)<br>• >10 mg prednisolone daily or equivalent for >4 weeks<br>• Anthracycline derivatives (e.g. doxorubicin, epirubicin | • Traditional immunosuppressive agents (e.g. azathioprine, 6-mercaptopurine, methotrexate)<br>• Intra-articular corticosteroids<br>• Any dose of oral corticosteroids daily for <1 week<br>• Low dose (<10 mg prednisolone or equivalent) corticosteroids for >4 weeks |
| Duration of prophylaxis | 18 months | 6 - 12 months | Monitoring HBsAg and/ or HBV DNA every 1 - 3 months |
| Monitoring after cessation of prophylaxis | 12 months | 12 months | |

**Source**:

1. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.
2. Reddy KR, Beavers KL, Hammond SP et al. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015 Jan;148(1):215-9; quiz e16-7.
3. Hwang JP, Feld JJ, Hammond SP et al. Hepatitis B Virus Screening and Management for Patients with Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update. J Clin Oncol. 2020 Nov 1;38(31):3698-3715.

Refer to **Appendix 6** on **Antiviral Prophylaxis Before Immunosuppression**.

**Recommendation 10**

- All candidates for chemotherapy and immunosuppressive treatment should be tested for HBV markers prior to immunosuppression e.g. hepatitis B surface antigen (HBsAg). If HBsAg-negative, antibody to hepatitis B core antigen (anti-HBc) should be tested.
- All HBsAg-positive patients should receive either entecavir, tenofovir disoproxil fumarate or tenofovir alafenamide as treatment or prophylaxis.
- In HBsAg-positive patients, prophylaxis should be continued for at least 12 months (18 months for rituximab-based regimens) after cessation of the immunosuppressive treatment.
- In HBsAg-negative patients, anti-HBc-positive patients should receive anti-HBV prophylaxis if they are at high-risk. Prophylaxis should be continued for at least 18 months after stopping immunosuppression and close monitoring for at least 12 months after prophylaxis withdrawal.
- In HBsAg-negative, anti-HBc-positive patients should receive anti-HBV prophylaxis if they are at moderate risk. Prophylaxis should be continued for 6 - 12 months after discontinuation of immunosuppressive treatment.

### 6.8 Renal Diseases

HBV infection in patients with chronic kidney disease (CKD) are prone to increase liver-related complications, accelerated progression to end-stage renal disease, and risk of increased mortality and morbidity.

In a cohort study, TDF-treated CHB patients had a higher risk of CKD progression compared with ETV-treated and untreated patients. The 5-year cumulative incidences of CKD progression were:[51, level II-2]

- 48% (95 % CI 45 to 51) in TDF-treated group
- 43% (95% CI 40 to 46) in ETV-treated group
- 43% (95% CI 39 to 47) in untreated group

There was a reduction in eGFR >20% in TDF-treated group compared with ETV-treated and untreated groups (p=0.023).

Another cohort study showed that both LdT and ETV significantly improved eGFR while TDF significantly worsened it among NA-naive CHB patients with impaired renal function.[52, level II-2]

- Renal safety monitoring with serum Cr, phosphorus, and urine glucose and protein should be assessed before treatment initiation and periodically thereafter (e.g. at least annually and more frequently if the patient is at high risk for renal dysfunction or has a pre-existing renal dysfunction) for CHB patients on TDF.[5, level III]

In dialysis patients with HBsAg-positive, ETV or TAF is recommended for treatment.[13] WHO mentions that TAF is not recommended if eGFR is <15ml/min.[64] Dose reduction or interval for NAs can be elicited in the table below.

**Table 9. Recommended Dose Reduction or Dosing Interval for Tenofovir and Entecavir**

| Drug | eGFR (ml/min) | | | |
|---|---|---|---|---|
| | ≥50 | 30 - 49 | 10 - 29 | <10, HD/CAPD |
| TDF | 300 mg once daily | 300 mg every 48 hours | 300 mg every 72 hours | Every seven days or one 300 mg tablet following completion of approximately every 12 hours of dialysis |
| TAF | 25 mg once daily | | | Not recommended if eGFR <15 ml/min |
| ETV | 0.5 mg once daily | 0.5 mg every 48 hours | 0.5 mg every 72 hours | 0.5 mg every 7 days |

eGFR: estimated glomerular filtration rate; HD: haemodialysis; CAPD: Continuous Ambulatory Peritoneal Dialysis

**Source**: World Health Organization. Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. WHO; Geneva: 2015

The incidence of HBV-related glomerulonephritis is from 0.1 to 25 % and may present clinically in three forms, i.e., membranous, membranoproliferative, and IgA nephropathy. Membranous glomerulonephritis (MGN) is the most common type, especially in areas endemic for HBV infection, and usually presents as nephrotic syndrome, with proteinuria, oedema and hypertension. Remission of clinical and laboratory manifestations of nephropathy with successful antiviral treatment has been demonstrated.[14, level III]

A meta-analysis showed that remission of the nephrotic syndrome is accompanied by clearance of HBV replication, supporting the role of the virus in the pathogenesis of the disease hence the need for treatment for those in this group.[53, level III]

**Recommendation 11**

- All dialysis and renal transplant patients should be screened for hepatitis B virus infection.
- Antiviral dose should be adjusted according to the estimated glomerular filtration rate of a chronic hepatitis B with chronic kidney disease patients.
  - Renal function should be monitored during antiviral treatment.

### 6.9 Solid Organ Transplant

TDF therapy was safe and effective in HBV-positive organ transplant patients in a cross-sectional study as there was no occurrence of rejection during treatment. The HBV DNA viral load decreased significantly at different time points within a year post-TDF initiation. However, there were no differences:[54, level III]

- in creatinine, eGFR, serum phosphorus and daily microalbuminuria levels compared with baseline
- in AST, ALT, ALP and GGT levels compared with baseline

In a cohort study with a median 26 months follow-up, ETV monotherapy was effective in suppressing HBV after liver transplantation:[55, level II-2]

- 91% of patients had loss HBsAg after two years of follow-up
- 98.8% of patients achieved undetectable HBV DNA levels
- HBsAg seroclearance was 86% and 91% after the first and second years respectively
- relapse rate after initial HBsAg seroclearance was:
  - 8.6% at six months
  - 11.6% at one year
  - 13.7% at second and third year

There was no significant difference in baseline HBV DNA levels between patients with or without HBV recurrence/persistence.

- Long-term antiviral therapy use is safe in patients with organ transplants.

### 6.10 Occult Hepatitis B

Occult HBV infection (OBI) is defined as the presence of HBV DNA in the blood of people who tested negative for HBsAg. It can be divided into:[56, level III]

- seropositive OBI - anti-HBc and/or anti-HBs-positive
- seronegative OBI - anti-HBc and anti-HBs-negative

There are a few scenarios in which OBI is of clinical importance i.e:[57, level III]

- after acute hepatitis B
- blood donation
- organ transplantation
- immunosuppression
- cryptogenic CLD
- HCC

The initiation of HBV antiviral therapy prior to chemotherapy in patients with OBI (especially in the absence of anti-HBs) is a prudent therapeutic approach. Refer to **Table 8** on the recommended treatment.

### 6.11 Healthcare Workers

The risk of transmission from patients with CHB to a susceptible individual following a single hollow bore needle stick injury is high, around 30 - 62% in HBeAg-positive and 6 - 37% in HBeAg-negative patients.

- The Malaysia Medical Council (MMC) guideline recommends:[58, level III]
  - HBV-infected HCW is to be treated with effective antiviral regardless of HBeAg status if the HCW intends to perform exposure-prone procedures (EPPs)
  - criteria for the HBV-infected HCW to perform EPPs -
    - HBV DNA viral load undetectable or very low (<50 IU/ml)
    - regular HBV DNA monitoring every 12 - 24 weeks
    - the HCW agrees to inform MMC if there is any change in the work scope

Refer to the MMC guideline document for details of description and definition of the EPPs.[58, level III]

## 7. MONITORING AND FOLLOW-UP

### 7.1 Monitoring

#### i. CHB patients not on treatment

CHB patients with HBeAg-positive chronic infection (immune tolerance) or HBeAg-negative chronic infection (inactive carrier) do not need pharmacological treatment. However, they are at risk of developing complications and thus require regular monitoring.

In a small prospective cohort study on patients with CHB in immune tolerance phase, 15.8% developed elevated serum ALT and these patients were significantly more likely to have disease progression on follow-up liver biopsy.[59, level II-2]

A prospective cohort study of 283 CHB patients with nine years of follow-up and well-documented spontaneous HBeAg seroconversion to HBeAb showed that:[60, level II-2]

- 66.8% remained in sustained remission while 33.2% developed hepatitis (elevated ALT)
- 7.8% developed cirrhosis with an annual incidence of 0.9%; the cumulative incidence was highest in the HBeAg reversion, followed by HBeAg-negative hepatitis and sustained remission groups ($p=0.0129$)
- 2.2% developed HCC with an annual risk of 0.2%; the cumulative incidence was higher in patients with HBeAg-negative hepatitis than those with sustained remission ($p<0.005$)
- 4.8% achieved sustained remission in HBsAg seroclearance of which 4.4% are those with HBeAg-negative

The aim of monitoring patients with CHB is to identify those who need intervention to reduce their risk of progression to liver cirrhosis and HCC.

- In a large prospective cohort of CHB patients, liver-related mortality increased proportionally with elevated serum ALT. The best cut-off serum ALT level for identification of patients with CHB at risk of mortality was estimated at 34 U/L in men (AUC=0.691, $p<0.0001$) and 30 U/L in women (AUC=0.783, $p<0.0001$).[61, level II-2]
- A cohort study on long-term outcomes in CHB patients showed that the risk of liver cirrhosis and HCC increased with elevated HBV DNA levels.[62, level II-2]
- A cross-sectional study showed that both APRI and FIB-4 index was useful non-invasive methods to evaluate the severity of hepatic fibrosis and cirrhosis in CHB patients.[63, level III]

For recommendations on monitoring, refer to **Algorithm** on **Management of Chronic Hepatitis B in Adults** (page x).

### ii. CHB patients on treatment

Monitoring CHB patients while on treatment are required to assess adherence, viral suppression and progression of liver disease. It is also important to review indications for discontinuation of treatment.[64]

The following parameters are recommended to monitor patients with hepatitis B who were started on treatment:[5, level III; 65]

- FBC
- LFT
- renal profile (RP)
- thyroid function tests (only for pegylated interferon)
- HBsAg
- HBeAg
- HBV DNA
- phosphate level (only for TDF)

These tests are recommended to be tested before the commencement of treatment and the frequency of testing would depend on the antiviral treatment started as per **Table 10**.

**Table 10. Recommended Frequency of Laboratory Monitoring in Patients with Hepatitis B on Treatment**

| Treatment / Investigation | Pegylated interferon | Lamivudine | Entecavir | Tenofovir disoproxil | Tenofovir alafenamide |
|---|---|---|---|---|---|
| | Frequency of testing | | | | |
| Full Blood Count | 2, 4, 12, 24, 36 and 48 weeks[1] | 4 weeks after starting and then every 24 weeks | | | |
| Liver Function Test | | 4 weeks after starting and then every 12 weeks[1] during first year and subsequently every 24 weeks[4] | | | |
| Renal Profile | | | | | |
| Thyroid Function Test | Every 12 weeks | - | | | |
| HBeAg | 24 - 48 weeks[3, 5] | 12 and 24 weeks of therapy and then every 12 - 24 weeks[3] | 24 - 48 weeks[3, 5] | 24 - 48 weeks[3, 5] | 24 - 48 weeks[3, 5] |
| HBV DNA | | | | | |
| HBsAg | Ideally once a year, preferably after HBeAg seroconversion | | | | |
| Others | - | - | - | Phosphate level every 12 weeks[3] | - |

**Modified**:

1. National Institute for Health and Care Excellence. Hepatitis B (chronic): diagnosis and management. United Kingdom: NICE; 2013
2. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-1599.

3. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98.
4. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.
5. World Health Organization. Guidelines on Hepatitis B and C Testing. Geneva: WHO; 2017

For CHB patients with HBeAg-negative status taking 3TC for ≥5 years, it is recommended to monitor HBV DNA levels every 12 weeks.[65]

For patients who are decompensated, it is recommended to monitor FBC, LFT, RP, coagulation profile, HBsAg, HBeAg and HBV DNA level before and during treatment at a more frequent basis to assess treatment response and adverse reactions. Additional phosphate monitoring is needed for those on TDF. When the person is no longer decompensated, the recommended frequency of testing would be as per **Table 10**.[65]

### 7.2 Complications

Liver cirrhosis and HCC are the main complications of CHB. Liver cirrhosis causes portal hypertension which can lead to ascites, varices and hepatic encephalopathy. Furthermore, liver cirrhosis will significantly increase the risk of HCC development.

In a cohort study on cirrhosis-related complications in CHB, 5.3% of the patients developed at least one complication i.e.:[66, level II-2]

- ascites
- spontaneous bacterial peritonitis
- oesophageal varices
- hepatic encephalopathy
- hepatoma

Factors that increased the risk of complications were:

- older age
- ALT at entry 1 - 2x ULN and at follow-up 1 - 2x ULN
- low albumin
- peak alpha-fetoprotein (AFP) >100 ng/ml during or after exacerbation

Among patients with complications, 29% of them had HBV DNA level of <200 copies/ml. There was no significant difference in cumulative risk of liver-related complications between HBeAg-positive and negative patients.

Patients with liver stiffness by TE (20 - 25 kPa) alone or combined with platelets and spleen size, or imaging showing collateral circulation are at risk of having endoscopic signs of portal hypertension, should undergo screening esophagogastroduodenoscopy. Patients with a liver stiffness <20 kPa and platelet count of >150,000 $10^9$/L have a very low

risk of having varices requiring treatment and can avoid the screening endoscopy. These patients can be followed-up with yearly TE and platelet count.[67, level III]

Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B (REACH-B) study developed and validated a predictive score for the risk of development of HCC in 3,584 non-cirrhotic chronic HBV patients and validated it in a cohort with 1,050 patients with chronic HBV. The 17-point risk score was composed of five predictors of HCC which were male sex, age, serum ALT level, HBeAg status and serum HBV DNA level. The risk score could precisely estimate the risk of HCC development at three, five and ten years of follow-up.[68, level II-2]

Regular surveillance of CHB patients with US and AFP analysis every six months are recommended and show a low HCC detection failure rate (0.8% per person or 0.1% per test). Significant predictors of HCC detection failure are liver cirrhosis, AFP level >9 ng/ml and diabetes mellitus.[69, level II-2]

Surveillance for HCC with US ± AFP every six months should be done in the following group of HBsAg-positive patients with:[5, level III; 70]

- liver cirrhosis
- high-risk for HCC (men over 40 years and women over 50 years of age)
- first-degree family member with a history of HCC
- hepatitis D virus

In a diagnostic study, magnetic resonance imaging had better accuracy compared with computed tomography with higher sensitivity (78.82% vs 62.35%) and specificity (78.46% vs 73.85%) in the diagnosis of small HCC among CHB patients.[71, level III]

**Recommendation 12**

- Surveillance for hepatocellular carcinoma (HCC) with ultrasound and alpha-fetoprotein every six months should be done in the following group of hepatitis B surface antigen-positive patients with:
  - liver cirrhosis
  - high-risk for HCC (men over 40 years and women over 50 years of age)
  - first-degree family member with a history of HCC

### 7.3 Treatment Discontinuation

Hepatitis B patients who are receiving antiviral treatment routinely continue their treatment indefinitely to ensure sustained viral suppression and improve clinical outcomes. However, prolonged

antiviral treatment raises concerns about increased treatment cost and, risks of treatment non-adherence and AEs e.g. renal impairment, bone loss and virological resistance. In recent years, many studies have shown that antiviral treatment discontinuation may lead to a functional cure but contradicting results are seen in the following recent evidence. In an open-label RCT, NA discontinuation before HBsAg loss was shown to have limited benefits, especially for pre-treatment HBeAg-positive patients. HBV DNA <2000 IU/ml at week 48 was observed in 27% NA discontinuation group vs 95% continuation group (p<0.005). Similarly, sustained disease remission was observed in 29% NA discontinuation group vs 82% continuation group. In NA discontinuation group, 33% had a virological or biochemical relapse and 38% required re-treatment. Re-treatment was higher in pre-treatment HBeAg-positive than HBeAg-negative (61% vs 22%; p=0.01). HBeAg-positive at start of treatment was the only independent predictor of relapse (OR=7.4, 95% CI 1.3 to 42.6).[72, level I]

A systematic review showed that cessation of long-term NAs therapy before HBsAg seroclearance in Asian patients with CHB was a feasible alternative to indefinite treatment. At ≥12 months off-therapy regardless of HBeAg status, the virological and clinical relapse rate was lower when HBsAg <100 IU/ml at the end of treatment (EoT) compared with HBsAg >100 IU/ml (9.1% - 19.2% vs 31.4% - 86.8% and 15.4% - 29.4% vs 48.1% - 63.6% respectively). For HBsAg loss at ≥39 months off-therapy in HBeAg-negative patients, a higher rate was found with HBsAg <100 IU/ml at EoT compared with HBsAg >100 IU/ml (21.1% - 58.8% vs 3.3% - 7.4%).[73, level II-2]

In a cohort study, TDF cessation group had higher HBV relapse rates and earlier median time of relapse (p<0.001) than ETV cessation group in non-cirrhotic patients regardless of HBeAg status. The TDF group also had significantly higher cumulative virological and clinical relapse rates at each follow-up interval irrespective of HBeAg status. TDF cessation was an independent factor of virological (HR=2.04, 95% CI 1.49 to 2.80) and clinical relapse (HR=1.72, 95% CI 1.22 to 2.43) in patients with total bilirubin <2 mg/dL. There was no difference in HBsAg loss for both TDF and ETV cessation groups after 24- to 36-month follow-up. TDF cessation group had a higher rate of re-treatment than the ETV cessation group in HBeAg-positive patients (p=0.001). Overall, TDF cessation showed sooner and more severe HBV relapse than after ETV cessation.[74, level II-2]

A multicentre cohort that looked into association between serum level of HBsAg at end of ETV therapy and risk of relapse in HBeAg-negative patients showed no clinical hepatitis relapse in those with EoT HBsAg <10 IU/ml but 29.4% relapses occurred in those with HBsAg 10 - 100 IU/ml, 28.4% in those with HBsAg 100 - 1000 IU/ml and 49.7% in those

with HBsAg >1000 IU/ml. Virological relapse rates were 9.5%, 63.2%, 81.1% and 93.1% with HBsAg <10 IU/ml, 10 - 100 IU/ml,100 - 1000 IU/ml and 1000 IU/ml respectively. All individuals with HBsAg <10 IU/ml maintained clinical remission through follow-up.[75, level II-2]

Various international practice guidelines show that treatment may be discontinued in selected CHB patients with close monitoring. A review paper on treatment discontinuation based on the guidelines are summarised in **Table 11**.[76, level III]

**Table 11. Patients Selection Criteria for Treatment Discontinuation**

| Guidelines | HBeAg-positive | HBeAg-negative |
|---|---|---|
| APASL Guidance, 2021 | HBeAg seroconversion (HBeAg-negative and anti-HBe-positive for at least two consecutive measurements at least six months apart) + undetectable HBV DNA (two consecutive measurements at least six months apart) + treatment duration of at least three years. Not recommended in cirrhosis. | Undetectable HBV DNA (two consecutive measurements at least six months apart) + treatment duration of at least three years. Not recommended in cirrhosis. |
| AASLD, 2018 | HBeAg seroconversion + undetectable HBV DNA + normal ALT for ≥12 months. Not recommended in cirrhosis. | HBsAg clearance. Not recommended in cirrhosis. |
| EASL, 2017 | HBeAg seroconversion + undetectable HBV DNA for ≥12 months. Not recommended in cirrhosis. | HBsAg clearance. Or selected non-cirrhotic with undetectable HBV DNA ≥3 years. Not recommended in cirrhosis. |

**Adapted**:

1. Kaewdech A, Sripongpun P. Challenges in the discontinuation of chronic hepatitis B antiviral agents. World J Hepatol. 2021 Sep 27;13(9):1042-1057.
2. Kao JH, Jeng WJ, Ning Q et al. APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients. Hepatol Int. 2021 Aug;15(4):833-851.

In local setting, based on the above evidence, the CPG DG opines that HBV antiviral treatment may be considered for discontinuation when HBsAg loss occurs and is sustained for at least one-year duration. Monitoring with HBV DNA and LFT should be more frequent once treatment is discontinued.

**Recommendation 13**

- In cirrhotic patients, hepatitis B antiviral treatment should be continued indefinitely.
- In non-cirrhotic patients, hepatitis B antiviral treatment may be discontinued when the optimal endpoint of hepatitis B surface antigen loss consolidated over 12 months is achieved.

### 7.4 Treatment Options for Virological Failure

In circumstances where patients with hepatitis B show inadequate treatment response in terms of virological, biochemical or serological failure to antiviral treatment, the patient's compliance towards antiviral treatment and/or possible viral resistance emergence should be investigated. Rescue treatment needs to be carefully selected based on the pre-existing choice of antiviral treatment, type of viral resistance and patient's underlying co-morbidities.

**i. Lamivudine-resistance**

In an RCT, TDF monotherapy was effective and well tolerated in 3TC-resistance CHB patients compared with baseline for up to 240 weeks. There was no significant difference between TDF monotherapy and combination therapy of emtricitabine/tenofovir (FTC/TDF) in terms of:[77, level I]

- virological response (HBV DNA <69 IU/ml)
- biochemical response (rates of normal ALT and normalised ALT)
- serological response (HBeAg loss and seroconversion)
- resistance surveillance - no development of resistance
- safety
  - overall incidence of adverse events was similar
  - overall renal events were mild and infrequent (8.6%)
  - overall mean change in bone mineral density was 0.98% and 2.54% at the spine and hip respectively

In another multicentre non-inferiority trial, stable switching to TDF monotherapy yielded non-inferior results at 96 weeks compared with 3TC+adefovir (ADV) combination therapy in CHB patients with 3TC-resistant and undetectable HBV DNA.[78, level I]

- Viral reactivation - 6.8% 3TC+ADV vs 4.5% TDF by using ITT analysis (percentage difference of -2.3%, 95% CI -9.84 to 5.24)
- No significant differences in serological (HBsAg seroconversion, HBeAg loss and HBeAg seroconversion) and biochemical responses (ALT, serum bilirubin, albumin, Cr and INR)
- Safety -
  - eGFR at week 96 significantly decreased in the TDF group (87.93 vs 84.47 ml/min/1.73 $m^2$, p=0.008) and a higher percentage in those with cirrhosis (85.22 vs 79.83 ml/min/1.73 $m^2$; p=0.000)
  - no difference in serious adverse reactions (SAR)
  - no difference in number of HCC cases

**ii. Entecavir-resistance**

In a retrospective cohort study, four rescue therapies (TDF, 0.5 mg ETV+ADV, 1 mg ETV, 0.5 mg ETV+TDF) were compared in patients with ETV-resistance mutation:[79, level II-2]

- Virological response -

- reduction in serum HBV DNA in all four groups (p=0.011)
- undetectable HBV DNA rate at week 48 was highest in 0.5 mg ETV+TDF (78.57%), followed by TDF (76.19%), 0.5 mg ETV+ADV (63.16%) and 1 mg ETV (18.18%)

- Biochemical and serological response -
  - higher percentages of ALT normalisation from baseline to week 48 were detected in TDF, ETV+TDF and ETV+ADV groups compared with 1 mg ETV group (p=0.039)
  - no difference in HBeAg seroclearance and seroconversion
  - none of the treated patients achieved HBsAg loss or seroconversion
- Safety - no SAR and deterioration of renal function

**iii. Multidrug-resistance**

In a retrospective cohort study, rescue therapy with ETV+TDF combination was safe and effective in patients with multidrug-resistant (MDR) HBV strains (e.g. 3TC/ETV-R, 3TC/ADV-R, and 3TC/ETV/ADV-R):[80, level II-2]

- Virological response -
  - 79.6% had complete virologic suppression in all groups
  - median time of 4.5 months to reach undetectable HBV DNA (95% CI 3 to 6)
- Biochemical response
  - 65.5% achieved biochemical response
  - lower baseline HBV DNA level was independently associated with complete virological suppression (HR=0.565, 95% CI 0.461 to 0.692)
- Safety - no renal dysfunction

A recent RCT showed that TAF was non-inferior to TDF in HBV DNA suppression (<60 IU/ml) among CHB patients with drug resistance to 3TC, ETV and/or ADV at week 48. Treatment with TAF was also associated with significant improvement in the renal and bone safety profiles.[25, level I]

The management of treatment failure should be based on cross-resistance data as shown in **Table 12**.

**Table 12. Cross-Resistance Data for The Most Frequent Nucleos(t)ide Analogues-Resistant Hepatitis B Virus Variants**

| HBV variant | 3TC | Ldt | ETV | ADV | TDF/TAF* |
|---|---|---|---|---|---|
| Wild-type | S | S | S | S | S |
| M204V | R | S | I | I | S |
| M204I | R | R | I | I | S |
| L180M + M204V | R | R | I | I | S |
| A181T/V | I | I | S | R | I |
| N236T | S | S | S | R | I |
| L180M+M204V/ I±I169T±V173L±M250V | R | R | R | S | S |
| L180M+M204V/ I±T184G±S202I/G | R | R | R | S | S |

*In vitro data for tenofovir, in vivo data for TDF, no clinical data for TAF
The amino acid substitution profiles are shown in the left column and the level of susceptibility is given for each drug: S (sensitive), I (intermediate/reduced susceptibility), R (resistant) 3TC - lamivudine; LdT - telbivudine; ETV - entecavir; ADV - adefovir; TDF - tenofovir disoproxil fumarate; TAF - tenofovir alafenamide

**Source:** European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.

Recommended rescue treatments for patients who developed antiviral treatment resistance are summarised in **Table 13**.

**Table 13. Management of Patients Who Developed Antiviral Treatment Resistance**

| Resistance Pattern | Recommended Rescue Strategies |
|---|---|
| 3TC-resistance | Switch to TDF or TAF |
| LdT-resistance | Switch to TDF or TAF |
| ETV-resistance | Switch to TDF or TAF |
| ADV-resistance | • If 3TC-naïve: switch to ETV or TDF or TAF<br>• If 3TC-resistance: switch to TDF or TAF<br>• If HBV DNA plateaus: add ETV*** or switch to ETV |
| TDF/TAF-resistance** | • If 3TC-naïve: switch to ETV<br>• If 3TC-resistance: add ETV* |
| MDR | Switch to ETV plus TDF or TAF combination |

3TC - lamivudine; LdT - telbivudine; ETV - entecavir; ADV - adefovir; TDF - tenofovir disoproxil fumarate; TAF - tenofovir alafenamide; MDR - multidrug-resistance
*Long-term safety of these combinations is unknown.
**Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine cross-resistance profile.
***Especially in patients with ADV-resistant mutations (rA181T/V and/or rN236T) and high viral load, response to TDF can be protracted.

**Source**: European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-398.

## 8. PREVENTION

### 8.1 Mother-to-Child Transmission

Mother-to-child transmission (MTCT) of HBV is the commonest mode of transmission worldwide; it may occur either in utero or perinatally. MTCT of HBV is associated with a very high rate of chronicity.

In a meta-analysis on the effect of hepatitis B immunisation in newborn infants of HBsAg-positive mothers, hepatitis B vaccination and/or HBIG were effective in the prevention of MTCT:[81, level I]

- hepatitis B vaccination vs placebo or no intervention (RR=0.28, 95% CI 0.20 to 0.40)
- HBIG alone vs placebo or no intervention (RR=0.50, 95% CI 0.41 to 0.60)
- vaccination (plasma-derived or recombinant) plus HBIG vs vaccination alone (RR=0.54, 95% CI 0.41 to 0.73)
- plasma-derived vaccine (PDV) plus HBIG vs placebo or no intervention (RR=0.08, 95% CI 0.03 to 0.17)

There were no differences in AEs between the infants in vaccination and control groups. The quality of included RCTs was low to moderate.

In a meta-analysis on peripartum antiviral prophylaxis among HBeAg-positive CHB mothers, all three antivirals were more effective than control in the prevention of MTCT:[82, level I]

- TDF (OR=0.16, 95% CI 0.09 to 0.25)
- 3TC (OR=0.17, 95% CI 0.13 to 0.22)
- LdT (OR=0.10, 95% CI 0.08 to 0.13)

There were no significant differences in effectiveness at different times of antiviral prophylaxis initiation (i.e. <28 weeks, 28 weeks or >28 weeks) or maternal viral load at baseline. The quality of primary papers was moderate to high.

In another meta-analysis, 3TC treatment was more effective than comparator (placebo or no intervention or HBIG) in preventing MTCT among HBeAg-positive mothers if:[83, level I]

- at baseline maternal HBV DNA of $10^6$ - $10^8$ copies/ml, the risk of HBsAg-positive in infants reduced by 70% (RR=0.30, 95% CI 0.15 to 0.57)
- after treatment maternal HBV DNA $<10^6$ copies/ml, the risk of HBsAg-positive in infants was reduced by 67% (RR=0.33, 95% CI 0.21 to 0.53)
- initiation of treatment at week 28 of gestation compared with week 32 (RR=0.34, 95% CI 0.22 to 0.52)

There were no differences in the AEs reported among mothers and only one related-to-drug with symptoms of jaundice in a newborn. The quality of the primary papers was low to moderate.

In a cohort study, antiviral prophylaxis with TAF and TDF reduced the MTCT rate to 0% in combination with standard immunoprophylaxis. Infants' blood at seven months showed:[43, level II-2]

- HBsAg: not detected in both groups
- anti-HBs: TAF (98.3%) vs TDF (99.1%)

In the third meta-analysis on HBeAg-positive pregnant women with high viral load, additional antiviral treatment (3TC, LdT or TDF) in second or third trimester of pregnancy was more effective than HBIG alone in preventing MTCT at 6 - 12 months post-hepatitis vaccination given at birth:[84, level I]

- RR of infant HBsAg seropositivity=0.3, 95% CI 0.2 to 0.4
- RR of infant HBV DNA positivity=0.3, 95% CI 0.2 to 0.5
- no significant difference in reduction in infant HBsAg seropositivity between antivirals

There were no safety issues for maternal (postpartum haemorrhage, caesarean section and elevated CK) or foetal outcomes (congenital malformation, prematurity and Apgar scores) reported. The quality of primary papers was however low.

In a multicentre non-randomised study, initiation of TDF at 30 - 32 weeks of pregnancy until one-month post-partum in high viral load HBeAg-positive pregnant women was more effective than standard care in decreasing infant HBsAg positivity at six months (p=0.0481). In terms of safety, TDF had less incidence of:[85, level II-1]

- maternal ALT level >5 x ULN at two months post-partum (p=0.0135)
- maternal ALT level >2 x ULN for ≥3 months (p=0.0455)

There were no significant differences in maternal Cr and CK levels, rates of congenital anomaly, premature birth and growth parameters of infants in both TDF with standard of care and standard of care alone.

In a multicentre, open-label, RCT, MTCT rate at post-partum week 28 for those who received TDF was lower than those without for HBeAg-positive mothers with an HBV DNA level of >200,000 IU/ml during the third trimester [ITT analysis (p=0.007)]. The maternal and infant safety profiles were similar between TDF and control groups. After the discontinuation of TDF (four weeks post-partum), ALT elevations above the normal range occurred more frequently in mothers in TDF group than in those in control group (p=0.03).[86, level I]

In a meta-analysis of 66 studies, the optimal threshold of maternal HBV DNA causing MTCT was ≥5.30 $\log^{10}$ IU/ml (≥200,000 IU/ml). HBeAg was an accurate marker to identify women with HBV DNA levels above this threshold with a pooled sensitivity of 88.25% (95% CI 83.91 to 91.53). In predicting MTCT, the pooled sensitivity of HBeAg testing was 99.5% (95% CI 91.7 to 100). Thus, in healthcare facilities where HBV

DNA assays were unavailable, HBeAg can be used as an alternative to assess eligibility for antiviral prophylaxis.[87, level III]

According to Malaysian National Immunisation Programme (NIP), first dose hepatitis B vaccination should be given to all newborns within 24 hours of life.[88] In addition, HBIG is given to all newborns of CHB mothers within 12 hours of life.[4]

A summary of prophylaxis and treatment of mother-to-child HBV transmission can be seen in **Appendix 5**.

**Recommendation 14**
- First dose hepatitis B vaccination should be given to all newborns within 24 hours of life.
- Hepatitis B immunoglobulin should be given to all newborns of chronic hepatitis B mothers within 12 hours of life.
- Antiviral prophylaxis should be initiated at 28 - 32 weeks of gestation in hepatitis B e antigen-positive mothers or viral load >200,000 IU/ml.
  - Tenofovir disoproxil fumarate is the preferred antiviral.

### 8.2 Post-Exposure Prophylaxis

This subchapter on post-exposure prophylaxis (PEP) is adapted from guidelines on Occupational Exposures to HIV, HBV, HCV and Recommendations for PEP[89, level III] and CDC Guidance for Evaluating Health-Care Personnel for HBV Protection and for Administering Post Exposure Management.[90, level III] PEP management of healthcare provider (HCP) with possible exposure to HBV depends on the immune status of the HCP and HBsAg status of the source patient. Serological markers, i.e. baseline anti-HBs and HBsAg, are important in deciding the requirement for PEP.

The PEP management is as follows:

i. **Evidence of prior HBV infection**
   No PEP management is required because the HCP is protected against HBV infection.

**ii. Vaccine responders (anti-HBs level ≥10 mIU/ml)**
   No PEP management is required if the HCP has received and adequately responded to the three-dose hepatitis B vaccine series.

**iii. Vaccine non-responders (anti-HBs level <10 mIU/ml)**
   Non-responder is defined as a person who failed to respond after completing two vaccination series. The source patient should be tested for HBsAg. If the HBsAg is positive or if it cannot be obtained, the HCP should receive two doses of HBIG. The first dose should be administered as soon as possible within seven days after the exposure, and the second dose should be administered one month later.

**iv. Unknown vaccine response**

The source patient should be tested for HBsAg and the HCP should be tested for anti-HBs. These tests should be done as soon as possible after the exposure and done simultaneously:

- if the anti-HBs titer is ≥10 mIU/ml, no PEP management is needed
- if the anti-HBs titer is <10 mIU/ml, PEP management depends upon the HBsAg status of the source patient:
  - if the source patient is HBsAg-positive or cannot be obtained -
  - the HCP should receive one dose of HBIG and a dose of hepatitis B vaccine given simultaneously but at different injection sites, the HCP should then complete two more doses of hepatitis B vaccine.
  - to determine immunity, the HCP should have anti-HBs testing performed one to two months after the last dose of the hepatitis B vaccine series
  - if the source patient is HBsAg-negative -
  - the HCP should receive one dose of the hepatitis B vaccine followed by repeat anti-HBs testing one to two months later; if the anti-HBs remain <10 mIU/ml, then the HCP should complete the vaccine series followed by anti-HBs testing one to two months after the last dose

**v. Follow-up testing after exposure**

If the source patient is HBsAg-positive or unknown status, the HCP should have follow-up testing with anti-HBc and HBsAg six months after the exposure to assess for HBV transmission.

Refer to **Appendix 7** on **Post-Exposure Prophylaxis Workflow**.

**Recommendation 15**

- If the hepatitis B virus status of the healthcare provider (HCP) is unknown, baseline antibody to hepatitis B surface protein and hepatitis B surface antigen (HBsAg) status should be obtained before determining post-exposure prophylaxis (PEP) management to the HCP.
- If the HBsAg status of a source patient is unknown, the HCP should have PEP management as if the source is HBsAg-positive.

### 8.3 Healthcare Workers

Occupational exposure of HBV infection to HCW can occur through accidental sharp injury, mucocutaneous contact or blood contact with non-intact skin.

In a Cochrane systematic review, hepatitis B vaccination in HCW showed:[91, level I]

- PDV was effective in reducing hepatitis B events (RR=0.51, 95% CI 0.35 to 0.71)

- recombinant vaccine (RV) was as effective as PDV in terms of protective anti-HBs level and AEs

In terms of protective anti-HBs level, vaccine administration:

- intramuscular (IM) injection was more effective than intradermal injection for both PDV and RV [RR=2.33 (95% CI 1.47 to 3.68) and 1.41 (95% CI 1.13 to 1.76) respectively]
- IM deltoid was more effective than IM gluteal injection (RR=1.13, 95% CI 2.91 to 153.32)
- standard vaccination schedule (0, 1 and 6 months) was more effective than rapid vaccination schedule (0, 1 and 2 months) (RR=3.45, 95% CI 1.47 to 8.07)
- in non-responder, there was no difference in protective anti-HBs level between low-dose and high-dose vaccines

### 8.4 Contact Tracing

At present, limited data exists on the safe and effective strategies for contact tracing for hepatitis B. Household and/or sexually closed contacts should be traced and tested. They may either be referred for follow-up if tested hepatitis B positive or vaccinated if tested negative but not immunised before for hepatitis B.

A prospective cohort study showed that nurse-delivered home Dry Blood Spot service was more effective than conventional primary care follow-up (control) in household contact tracing of hepatitis B-infected pregnant women in terms of:[92, level II-2]

- more identified contacts (100% vs 55.7%; p<0.001)
- improved in HBV screening (96.6% vs 39.4%; p<0.001)
- increased in vaccination rate of non-infected household closed contact (74.1% vs 36.4%; p<0.001)

A study showed that nurse-led enhanced management improved contact tracing of CHB patients.[93, level II-3]

- identification: 86% (pre-intervention) vs 99.7% (post-intervention)
- testing: 34% (pre-intervention) vs 94% (post-intervention)
- vaccination rate of at least three doses: 77% (pre-intervention) vs 93% (post-intervention)

This evidence showed that paramedics can be trained for dedicated tasks to improve current contact tracing policies, e.g. home visits and household contact tracing for HBV-infected post-partum women. A similar strategy can be expanded to all HBV-infected patients later once the programme is more established.

**Recommendation 16**
- Household contacts of hepatitis B virus (HBV) infected patients should be identified and screened.

### 8.5 Vaccination

Hepatitis B vaccination is advised to all adults who are high-risk, immunocompromised or seeking protection from HBV infection. The latest adult immunisation guidelines can be used as a reference.

### 8.6 Counselling

Medical providers should counsel patients regarding:[5, level III]
- risk for HBV transmission
- need for evaluation of family members, sexual contacts and household members for HBV
- need for barrier protection when sexual partners have not been fully vaccinated
- not sharing of toothbrushes or razors
- covering open cuts and scratches
- cleaning any blood spills with bleach solution

In contrast, the sharing of food and utensils, as well as close physical contact, including kissing, is not contraindicated.

## 9. REFERRAL

There is no retrievable evidence on referral criteria for patients with HBV. Based on the consensus of CPG DG, patients with the following features should be referred to centres with Gastroenterologists and Hepatologists for further management:

- decompensated cirrhosis
- transplant candidates
- hepatitis B resistance
- pregnancy with indication for antiviral treatment
- immunosuppression
- hepatitis B flare
- discontinuation of antiviral treatment

## 10. IMPLEMENTING THE GUIDELINES

Hepatitis B is an infectious disease and the infected patients may need life-long treatment. It is important to implement this CPG as guidance in providing quality healthcare services based on the best and latest evidence and expertise suited for local scenarios.

### 10.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:

i. availability of CPG to healthcare providers (hardcopies and softcopies)
ii. conferences and updates on the management of hepatitis B which may involve professional societies e.g. Malaysian Society of Gastroenterology & Hepatology, Malaysian Association of HIV Medicine, Obstetrical & Gynaecological Society of Malaysia, Malaysian Family Medicine Specialist Association, Malaysian Pharmaceutical Society, etc.
iii. hepatitis B programmes by MoH e.g. Elimination of Mother-to-Child Transmission (EMTCT) programme
iv. public awareness hepatitis campaign which may involve other government agencies and non-governmental organisations e.g. World Hepatitis Day

Limiting factors in the CPG implementation include:

i. limited awareness and knowledge in the management of hepatitis B among healthcare providers
ii. different levels of hepatitis B care due to expertise, drugs, laboratory and radiology facilities
iii. challenges in managing hepatitis B patients with/in:
    - renal failure
    - immunosuppression

- on-going risk factors
- antiviral resistance

iv. lack of surveillance programmes which includes a national registry, etc.

### 10.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:

i. ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
ii. reinforce training of healthcare providers via regular seminars and workshops
iii. involve multidisciplinary teams at all levels of healthcare
iv. improve the diagnostic and therapeutic facilities
v. train more experts in the field of hepatitis B
vi. strengthen the hepatitis B registry

The Regional Framework for Triple EMTCT of HIV, HBV and Syphilis in Asia and the Pacific 2018-30 was endorsed by the Regional Committee of WHO Western Pacific in October 2017. It involves an integrated and coordinated approach to achieve elimination in an efficient, coordinated and sustainable manner. Malaysia has been certified as the first country in the region in EMTCT of HIV and syphilis. This is possible due to universal screening among pregnant mothers.

The CPG recommends pregnant mothers in a high-risk group be screened for hepatitis B. It also addresses the treatment of CHB mothers to prevent MTCT. Thus, in order to achieve triple elimination in EMTCT, it is important to screen universally pregnant mothers and treat them accordingly as recommended in the CPG. This would cause resource implications in the health service but it has to be strongly considered to achieve the aim of EMTCT by 2030.

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:

- Percentage of pregnant mothers being screened for HBV within a year* $= \frac{\text{Number of pregnant mothers being screened within a year}}{\text{Total number of pregnant mothers in the same year}} \times 100\%$

*Target ≥70%

Implementation strategies will be developed following the approval of the CPG by MoH which include Quick Reference and Training Module (Available at: https://www.moh.gov.my/index.php/pages/view/3962?mid=1570).

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## APPENDIX 1

## EXAMPLE OF SEARCH STRATEGY

**Clinical Question**: What are the safe and effective pharmacological treatments for hepatitis B infection?

1. HEPATITIS B/
2. hepatitis b.tw.
3. hepatitis b virus infection.tw.
4. 1 or 2 or 3
5. DRUG THERAPY/
6. chemotherap*.tw.
7. (drug adj1 therap*).tw.
8. pharmacotherap*.tw.
9. THERAPEUTICS/
10. therap*.tw.
11. treatment*.tw.
12. PHARMACEUTICAL PREPARATIONS/
13. drug*.tw.
14. pharmaceutical*.tw.
15. (pharmaceutic* adj1 (preparation* or product*)).tw.
16. ANTIVIRAL AGENTS/
17. (antiviral adj1 (agent* or drug*)).tw.
18. antiviral*.tw.
19. entecavir.tw.
20. baraclude.tw.
21. TENOFOVIR/
22. (tenofovir adj2 disoproxil fumarate).tw.
23. (tenofovir adj1 disoproxil).tw.
24. tenofovir.tw.
25. viread.tw.
26. LAMIVUDINE/
27. lamivudine.tw.
28. TELBIVUDINE/
29. telbivudin*.tw.
30. adefovir.tw.
31. tenofovir alafenamide.tw.
32. INTERFERONS/
33. interferon*.tw.
34. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 4 and 34
36. limit 35 to (english language and humans and “adult (19 to 44 years)” and last 10 years)
37. limit 36 to randomized controlled trial (396)

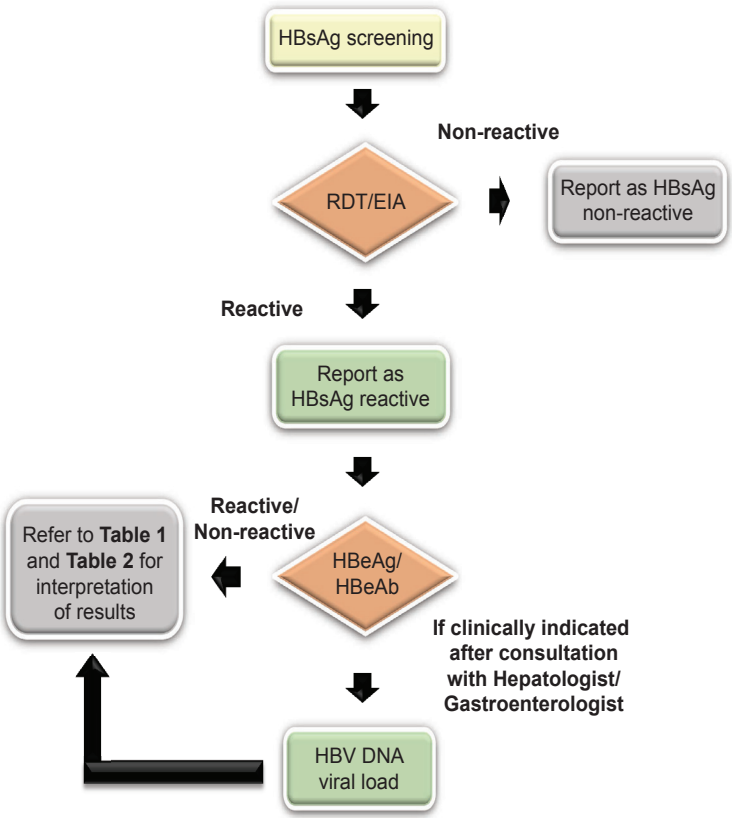
## APPENDIX 2

## CLINICAL QUESTIONS

1. What are the risk factors for hepatitis B infection?
2. What are the accurate screening tools for diagnosing hepatitis B infection?
3. What are the accurate serological markers for hepatitis B patients?
4. What are the safe and effective tools for pre-treatment assessment in patients with hepatitis B infection?
5. What are the safe and effective imaging modalities for pre-treatment assessment in patients with hepatitis B infection?
6. What is the safe and effective non-pharmacological management of hepatitis B infection? (education)
7. What are the safe and effective pharmacological treatments for hepatitis B infection?
8. When is the appropriate time to initiate treatment in patients with hepatitis B infection?
9. What are the safe and effective treatments in special populations with hepatitis b?
    - acute hepatitis B
    - acute liver failure/chronic liver failure
    - hepatitis B flare
    - co-infection with HIV
    - co-infection with HCV
    - pregnancy and lactation
    - immunosuppression or cytotoxic therapy
    - renal diseases
    - solid organ transplant
    - occult hepatitis B (anti-Hep B core positive)
    - healthcare workers
10. What are the parameters to be monitored in patients with hepatitis B?
11. What are the parameters to be monitored in patients with hepatitis B on treatment?
12. What are the treatment options for virological failure in patients with hepatitis B?
13. What are the complications of hepatitis B?
14. What is the effective hepatocellular carcinoma (HCC) surveillance in patients with hepatitis B?
15. What are the criteria for treatment discontinuation in patients with hepatitis B?
16. What are the criteria to refer patients with hepatitis B?
17. What are the safe and effective prevention strategies for hepatitis B?
    - Mother-to-child transmission
    - Post-exposure prophylaxis
    - Healthcare workers
    - Contact tracing

## APPENDIX 3

## LABORATORY WORKFLOW FOR DIAGNOSIS OF CHRONIC HEPATITIS B INFECTION




HBsAg: hepatitis B surface antigen; RDT: rapid diagnostic test; EIA: enzyme immunoassays; HBeAg: hepatitis B e antigen; HBeAb: hepatitis B e antibody; HBV: hepatitis B virus; DNA: deoxyribonucleic acid

## DOSAGE FORM, ADMINISTRATION AND COMMON SIDE EFFECTS OF HEPATITIS B ANTIVIRAL IN MALAYSIA

| Drug | Standard dosage | Administration | Renal Adjustment (based on Creatinine Clearance, CrCl)* (ml/min) | | | Potential Side effects |
|---|---|---|---|---|---|---|
| | | | 30 - <50 | 10 - <30 | <10/ Hemodialysis (HD) | |
| **Preferred (high barrier to HBV resistance)** | | | | | | |
| Pegylated Interferon-α 2a | 180 mcg once weekly | Subcutaneous Injection | No dosage adjustment | 135 mcg once weekly | 90 - 135 mcg once weekly | Flu-like symptoms, fatigue, mood disturbances, cytopenia, autoimmune disorders |
| Entecavir[a] | 0.5 mg once daily | Oral tablet, take on empty stomach, 2 hours apart from food | 50% of usual dose **OR** 0.5 mg every 48 hours | 30% of usual dose **OR** 0.5 mg every 72 hours | 10% of usual dose **OR** 0.5 mg every 7 days | Lactic acidosis |
| Tenofovir Disoproxil Fumarate | 300 mg once daily | Oral tablet, take with or without food | 300 mg every 48 hours | 300 mg every 72 to 96 hours | Avoid use. If no alternative, 300 mg every 7 days | Nephropathy, Fanconi syndrome osteomalacia, lactic acidosis |
| Tenofovir Alafenamide | 25 mg once daily | Oral tablet, after food | **CrCl >15 ml/min**: No dose adjustment<br>**CrCl <15 ml/min**: Use is not recommended | | | Lactic acidosis |

| Drug | Standard dosage | Administration | Renal Adjustment (based on Creatinine Clearance, CrCl)* (ml/min) | | | Potential Side effects |
|---|---|---|---|---|---|---|
| | | | 30 - <50 | 10 - <30 | <10/ Hemodialysis (HD) | |
| **Non-Preferred (low barrier to HBV resistance)** | | | | | | |
| Lamivudine | 100 mg once daily | Oral tablet, take with or without food | **CrCl 30 - ≤50 ml/min:** 50 mg once daily<br>**CrCl <5 - <15 ml/min:** 15 mg once daily<br>**CrCl <5 ml/min:** 10 mg once daily | | | Pancreatitis, lactic acidosis |
| Adefovir[b] Dipivoxil | 10 mg once daily | Oral tablet, take with or without food | 10 mg every 48 hours | 10 mg every 72 hours | Non-HD: No data<br>HD: 10 mg every day | Acute renal failure, Fanconi syndrome, lactic acidosis |
| Telbivudine[c] | 600 mg once daily | Oral tablet, take with or without food | 600 mg every 48 hours | 600 mg every 72 hours | 600 mg every 96 hours | Creatine kinase elevations and myopathy, peripheral neuropathy, lactic acidosis |

*Creatinine clearance (CrCl) calculated by Cockcroft-Gault formula
[a]Entecavir dose is 1 mg once daily if the patient has decompensated cirrhosis
[b]Product discontinued
[c]Deregistered in Malaysia in 2022

**Source**:

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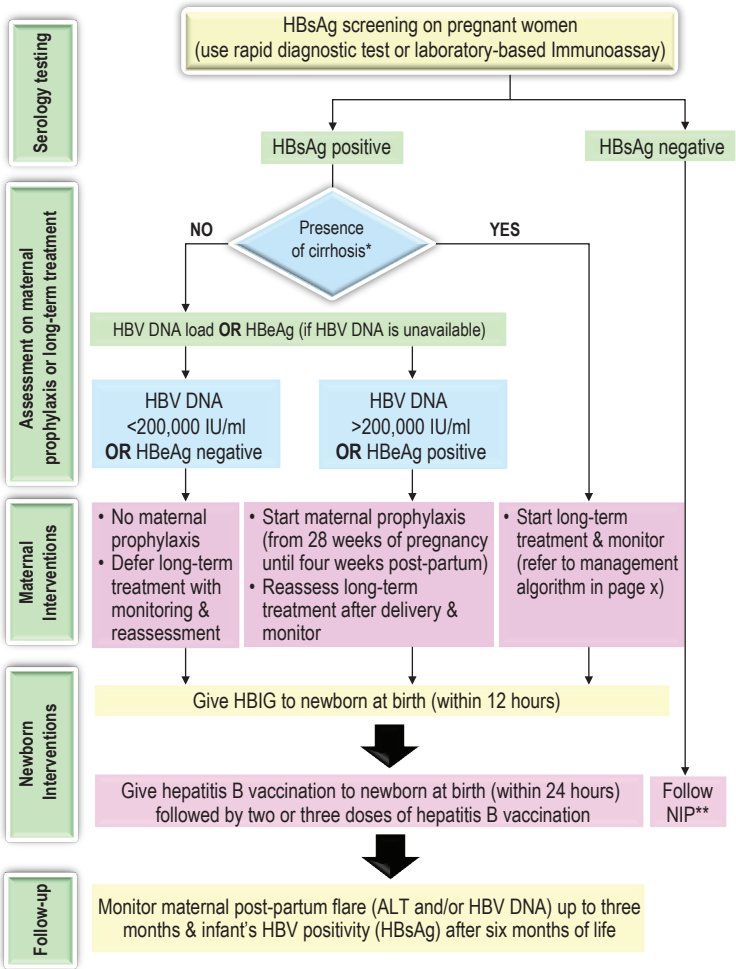
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017 Aug;67(2):370-398.
3. Product inserts of the respective antiviral.

## APPENDIX 5

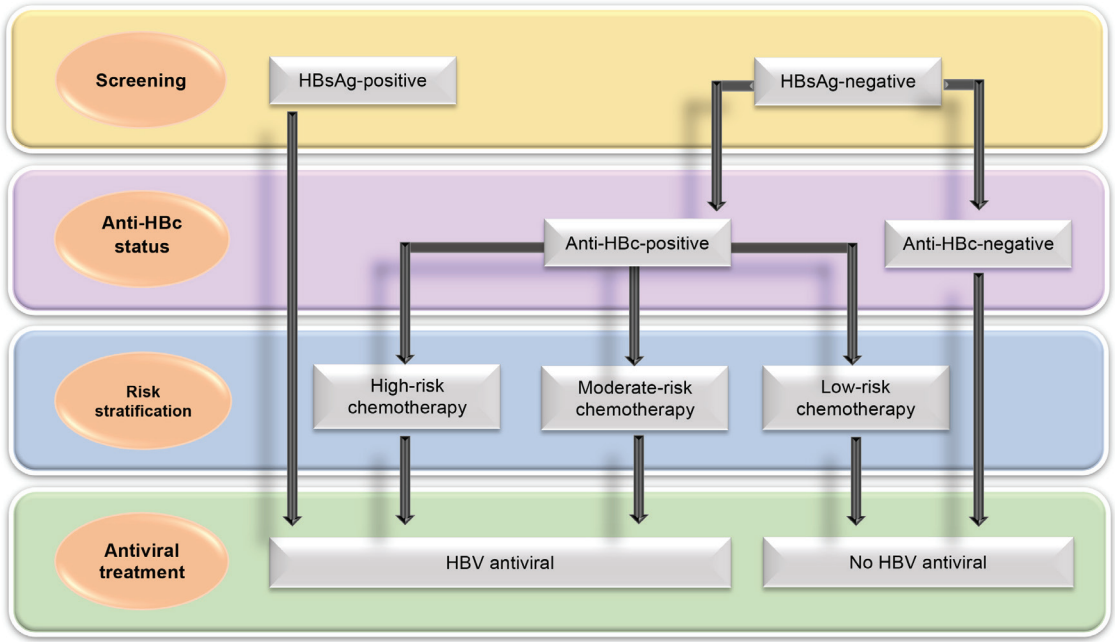
## PROPHYLAXIS AND TREATMENT OF MOTHER-TO-CHILD HEPATITIS B VIRUS TRANSMISSION




*Based on recommended methods of assessment for fibrosis in CPG

ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; IU/ml; international unit/millilitre; RDT: rapid diagnostic test; NIP: National Immunisation Programme

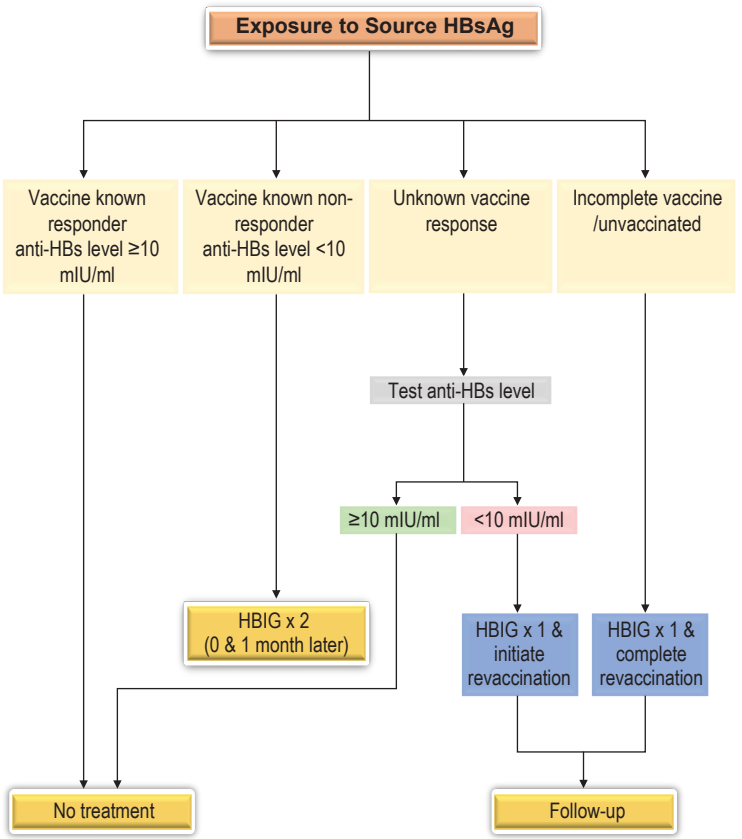
## ANTIVIRAL PROPHYLAXIS BEFORE IMMUNOSUPPRESSION




HBsAg: hepatitis B surface antigen; anti-HBc: antibody to hepatitis B core antigen; HBV: hepatitis B virus

## APPENDIX 7

### POST-EXPOSURE PROPHYLAXIS WORKFLOW



## LIST OF ABBREVIATIONS

| | |
|---|---|
| AASLD | American Association for the Study of Liver Diseases |
| ADV | adefovir |
| AE (s) | adverse event (s) |
| AFP | alpha-fetoprotein |
| AIDS | acquired immunodeficiency syndrome |
| ALF | acute liver failure |
| ALT | alanine transaminase |
| Anti-HBc | antibody to hepatitis B core antigen |
| Anti-HBc-total | antibody to hepatitis B core total protein |
| Anti-HBs | antibody to hepatitis B surface protein |
| Anti-HCV | antibody to hepatitis C virus |
| APASL | Asia Pacific Association for the Study of the Liver |
| APRI | aspartate aminotransferase to platelet ratio |
| ART | antiretroviral therapy |
| AST | aspartate transaminase |
| AUC | area under curve |
| CAPD | Continuous Ambulatory Peritoneal Dialysis |
| CHB | chronic hepatitis B |
| CK | creatine kinase |
| CKD | chronic kidney disease |
| CLD | chronic liver disease |
| CPG | clinical practice guidelines |
| CPS | Child-Turcotte-Pugh Score |
| Cr | creatinine |
| DAA (s) | direct-acting antiviral (s) |
| dL | decilitre |
| DNA | deoxyribonucleic acid |
| DG | Development Group |
| EASL | European Association for the Study of the Liver |
| ECG | electrocardiogramme |
| eGFR | estimated glomerular filtration rate |
| EIA | enzyme immunoassays |
| EMTCT | Elimination of Mother-to-Child Transmission |
| EoT | end of treatment |
| EPP (s) | exposure prone procedure (s) |
| ETV | entecavir |
| FBC | full blood count |
| FIB-4 | Fibrosis-4 |
| FTC | emtricitabine |
| GGT | gamma-glutamyl transpeptidase |
| GRADE | Grading Recommendations, Assessment, Development and Evaluation |
| Hb | haemoglobin |
| HBeAb | hepatitis B e antibody |
| HBeAg | hepatitis B e antigen |
| HBIG | hepatitis B immunoglobulin |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HBV-R | HBV-reactivation |
| HCC | hepatocellular carcinoma |
| HCP | healthcare provider |
| HCV | hepatitis C virus |
| HCW | healthcare workers |

| | |
|---|---|
| HD | hemodialysis |
| HIV | Human Immunodeficiency Virus |
| HR | hazard ratio |
| IFN | interferon |
| IgG | immunoglobulin G |
| IgM | immunoglobulin M |
| IgM anti-HBc | immunoglobulin M antibody to hepatitis B core antigen |
| IM | intramuscular |
| INR | international normalisation ratio |
| IU | international unit |
| IV | intravenous |
| IVD (s) | in vitro diagnostic (s) |
| LdT | telbivudine |
| LFT | liver function test |
| MaHTAS | Malaysia Health Technology Assessment Section |
| mcg | microgramme |
| MDR | multidrug-resistant |
| mg | milligramme |
| min | minutes |
| mIU | milli-international unit |
| ml | millilitre |
| MMC | Malaysia Medical Council |
| mmol | millimoles |
| MoH | Ministry of Health |
| mosmol | milliosmole |
| MRE | magnetic resonance elastography |
| MTCT | mother-to-child transmission |
| NA | nucleos(t)ide analogue |
| ng | nanogramme |
| NPV | negative predictive value |
| OBI | occult hepatitis B virus infection |
| PDV | plasma-derived vaccine |
| PEP | post-exposure prophylaxis |
| PPV | positive predictive value |
| RC | Review Committee |
| RD | risk difference |
| RDT | rapid diagnostic test |
| RNA | ribonucleic acid |
| RP | renal profile |
| RV | recombinant vaccine |
| RCT(s) | randomised controlled trial(s) |
| RN | registered number |
| SAR | serious adverse reactions |
| TAF | tenofovir alafenamide |
| TAHOD | TREAT Asia HIV Observational Database |
| TDF | tenofovir disoproxil fumarate |
| TE | transient elastography |
| ULN | upper limit of normal |
| US | ultrasonography |
| WHO | World Health Organization |
| 3TC | lamivudine |
| µmol | micromoles |
| WMD | Weighted Mean Difference |

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