Management of Adult Patients with Chronic Hepatitis B in Primary Care

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Purpose

Hepatitis B virus (HBV) infection is a significant health issue globally and locally. To meet the goal set by the World Health Organization (WHO) to eliminate viral hepatitis as a public health threat by 2030, the Government of the Hong Kong Special Administrative Region launched the *Hong Kong Viral Hepatitis Action Plan 2020 - 2024* (the Action Plan) in October 2020, setting out a comprehensive strategy with specific actions by the Department of Health (DH), the Hospital Authority (HA) and other stakeholders to reduce transmission of viral hepatitis, as well as related morbidity and mortality. Early identification and management of people with chronic hepatitis B (CHB) is one of the focus areas of the Action Plan.

This guidance is an effort to enhance the management capacity of hepatitis B infection in our health care system. It covers the assessment, monitoring, and management of adult patients with CHB in primary care; and the bidirectional referral criteria between primary care and hepatology.

This document provides guidance for primary care physicians, hepatologists, and other health care providers on managing patients with CHB in primary care settings. It draws upon the valuable experience gained from the pilot programme conducted in the HA. The current version has been finalised upon incorporation of comments from various relevant stakeholders. For the detailed management of other manifestations of HBV infection or special patient populations, clinicians are advised to refer to the recommendations published by international liver societies in the reference list.

1. Background of HBV infection

1.1 HBV infection in Hong Kong

HBV infection remains prevalent in Hong Kong and accounts for the majority of liver-related morbidity and mortality despite universal newborn vaccination since 1988. The Population Health Survey 2020-22 conducted by the DH gauged a prevalence of hepatitis B surface antigen (HBsAg) at 6.2% among the population aged 15 to 84 in Hong Kong.

Transmission of HBV occurs through contact with blood or body fluid, which can happen through mother-to-child / vertical transmission (MTCT) during birth, sexual contact, or parenteral exposure. In Hong Kong and areas of moderate-to-high prevalence, most patients with chronic hepatitis B (CHB) acquired the infection during the perinatal period or childhood. Over 90% of infants infected before the age of one will become chronic carriers. Complications of chronic HBV infection include hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC).

Despite the availability of effective antiviral treatment, the diagnosis and treatment rates of chronic HBV infection in Hong Kong remain suboptimal. Many of the infected population are undiagnosed or not linked to care. The management capacity of specialist outpatient clinics (SOPC) is limited, given the large number of patients yet to be diagnosed and linked to care.

To achieve the WHO target of eliminating HBV infection as a public health threat by 2030, it is pivotal to augment the management capacity for CHB. Collaboration between hepatologists and family physicians is key to ensuring a sustainable care continuum of CHB in our community. This document provides recommendations to facilitate the management of patients with CHB in primary care settings.

1.2 Virology

HBV is a partially double-stranded DNA virus with 3200 base pairs. It belongs to the family of Hepadnaviridae. There are four viral genes, namely the core, surface, polymerase, and X genes, with overlapping open reading frames. The core gene consists of the pre-core and core regions, which encode the hepatitis B e antigen (HBeAg) and core protein. The surface gene comprises the pre-S1, pre-S2, and S regions, generating the small, middle, and large hepatitis B surface antigen (HBsAg). HBeAg and HBsAg are commonly used as serologic markers of HBV infection.

HBV enters the host hepatocytes by binding to the sodium taurocholate co-transporting polypeptide receptor. The HBV genome then enters the hepatocyte nuclei, followed by its incorporation into the host genome (HBV integration) and formation of the transcription template, the covalently closed circular (ccc) DNA. Maintenance of cccDNA inside the hepatocyte genome explains the persistence of HBV infection despite low or undetectable circulating virus.

1.3 Natural history

CHB is defined by the persistence of serum HBsAg beyond six months. The interpretation of hepatitis B serology is shown in Table 1. The natural course of CHB is characterised by fluctuations in viral load and degree of hepatic necro-inflammation, which can be stratified by HBeAg status (Table 2).

Table 1 Interpretation of serology tests for HBV infection[1]

HBsAg	Anti-HBc	Anti-HBs	Interpretation	Suggested action
+	+	-	HBV infection	Repeat testing: chronic hepatitis B confirmed if HBsAg remains positive after 6 months
-	+	+/-	Past HBV infection, resolved	No further management unless cirrhotic, immunocompromised or undergoing immunosuppressive therapy
-	-	+	Not infected; immune to HBV	No further testing
-	-	-	Not infected; non-immune to HBV	Vaccination

[1] HBsAg is the hallmark of current HBV infection. Anti-HBc may be checked in selected patients requiring potent immunosuppression, whereas the role of anti-HBs is largely reserved for selecting uninfected people for vaccination.

Table 2 Stages of chronic HBV infection (adapted from the EASL guidelines)

Stages of chronic hepatitis	HBeAg positive		HBeAg negative	
	Chronic infection	**Chronic hepatitis**	**Chronic infection**	**Chronic hepatitis**
Alternative terminology	Immune tolerant	Immune active HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis
HBV DNA	$>10^7$ IU/ml	10^{4-7} IU/ml	<2000 IU/ml	>2000 IU/ml
ALT	Normal	Elevated	Normal	Elevated
Liver disease	None / minimal	Moderate / Severe	None	Moderate / Severe
Need for antiviral treatment	No	Yes	No	Yes

Perinatal exposure to HBV leads to immune tolerance of the host to the virus. Most patients acquiring HBV infection during the neonatal period or early childhood enter the HBeAg-positive chronic infection phase with a normal serum alanine aminotransferase (ALT), positive HBeAg, high HBV DNA and HBsAg levels, and minimal hepatic inflammation or fibrosis.

Loss of immune tolerance with activation of the immune system targeting infected hepatocytes typically occurs after 20 – 40 years of perinatal HBV infection compared to earlier immune clearance in adults with horizontal transmission. As HBV is a non-cytopathic virus, it induces liver damage by a complex immune-mediated response. The immune-active phase is characterised by a rise in ALT, decreased HBV DNA and HBsAg levels, with variable degrees of necroinflammation and fibrosis. HBeAg seroconversion follows in 10-20% of patients per year, defined as the loss of HBeAg and the development of anti-HBe. Those with HBeAg seroconversion, suppression of viral replication, and normalisation of serum ALT enter the inactive carrier phase. About 30% of inactive carriers will develop reactivation of HBV, with a rise in HBV DNA and serum ALT.

In untreated patients, repeated viral reactivation and immune-mediated hepatitis lead to fibrosis, cirrhosis, and end-stage liver failure. Patients often remain asymptomatic despite their underlying advanced liver disease. Development of symptoms, such as jaundice or ascites, usually indicates decompensation, which is irreversible despite treatment. Cirrhosis and the associated complications typically present in the fifth decade of life. Acute hepatitis flare may be potentially fulminant, resulting in acute liver failure or acute-on-chronic liver failure (ACLF) in younger patients.

HCC is another dreaded complication of CHB. HCC can develop in patients with or without cirrhosis. The lifetime risk of HCC in HBV carriers is 10–25 times greater than in non-carriers. In contrast, HCC associated with other liver diseases, such as alcoholic liver disease or hepatitis C virus (HCV) infection, develops mainly in cirrhotic livers.

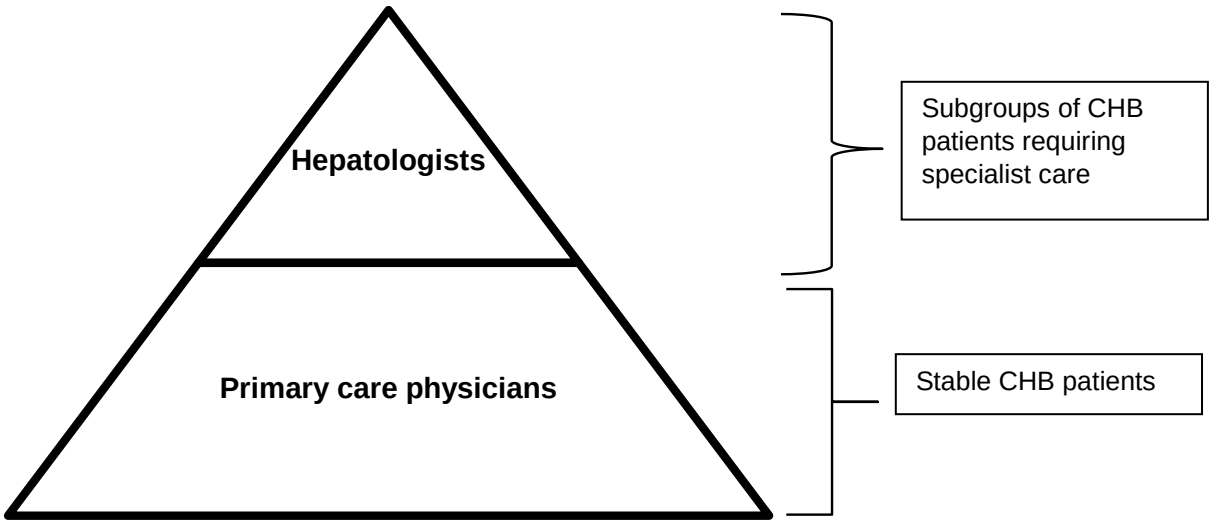
Nucleoside/nucleotide analogues act by inhibiting the reverse transcription of the pregenomic RNA into HBV DNA, thereby suppressing viral replication. Long-term antiviral therapy can reduce the risk of cirrhosis and HCC. Since antiviral drugs have no effect on the cccDNA, a virologic cure is currently not possible, and viral relapse is frequent after treatment cessation. Most patients started on treatment will require long-term therapy.

2. Stratification of patients for appropriate care

Facilitating care for the large population of local CHB patients necessitates the stratification of patients for appropriate care. Most of the stable CHB patients who are either treatment-naïve or on treatment can be safely managed in primary care settings. This guidance will focus on the management of stable CHB patients (Figure 1).

On the other hand, some patients require management by hepatologists for disease complications or concurrent conditions. These patients should be referred to specialists for further care. The detailed management of patients requiring specialist care is outside the scope of this guidance.

Figure 1 Stratification of CHB patients



3. Management of stable CHB patients

Stable CHB patients without complications can be assessed and managed in primary care settings with clinical and laboratory monitoring, antiviral treatment and HCC surveillance in indicated patients. The algorithm for the management of CHB patients without cirrhosis is summarised in Figure 2.

3.1 Initial assessment of HBsAg-positive patient

Aims

- Establish the diagnosis of chronic hepatitis B
- Detect complications and assess the need for hepatology care
- Counsel patient
- Identify the need for antiviral treatment and HCC surveillance

History

- Symptoms of decompensated liver disease
- Alcohol consumption and smoking history
- Co-morbidities, e.g. obesity, diabetes mellitus, metabolic syndrome, fatty liver, co-infections with HCV or HIV, and other chronic liver diseases
- Medications, e.g. previous antiviral treatment, over-the-counter drugs, herbs, immunosuppressants
- Family history of HBV infection, cirrhosis, HCC, and other liver diseases
- Pregnancy planning in female patients
- Hepatitis A vaccination history
- Marital status and cohabitants

Physical examination

- Stigmata of chronic liver disease
- Hepatomegaly, splenomegaly, liver masses

Laboratory investigations

- Complete blood count (CBC)
- Liver function test (LFT), including ALT and AST
- Renal function test (RFT)
- Alpha-fetoprotein (AFP)
- HBsAg (to confirm chronic infection if there is no repeat HBsAg 6 months after the first positive test)
- HBeAg and anti-HBe
- HBV DNA
- (If clinically indicated) Anti-HAV IgG, anti-HCV, anti-HIV, fasting glucose, HbA1c, lipid profile

Other investigations

- Consider ultrasonography (USG) of the liver
- Non-invasive tests to assess liver fibrosis
  - Serum biomarkers, e.g. APRI, FIB-4
  - Transient elastography (if available; and consider if APRI > 1)

AST-to-platelet ratio index (APRI)

$$\text{APRI} = \frac{\frac{\text{AST level (U/L)}}{\text{AST (ULN)(U/L)}}}{\text{Platelet count } (10^9/\text{L})} \; x \; 100$$

APRI has been validated for the diagnosis of both significant fibrosis and cirrhosis. WHO recommended APRI as the preferred non-invasive test to assess the presence of cirrhosis in resource-limited settings. A cut-off value of 1 is recommended to identify patients for further assessment, i.e. by transient elastography. Patients with advanced fibrosis (liver stiffness > 9 kPa) on transient elastography or other means of fibrosis measurement should be referred for specialist assessment. Patients without advanced fibrosis can be managed in primary care. Repeat evaluation by transient elastography can be considered every three years to detect fibrosis progression in patients with elevated APRI who are not on antiviral treatment.

Fibrosis-4 index (FIB-4)

$$\text{FIB-4} = \frac{\text{Age (years) x AST level (U/L)}}{\text{Platelet count } (10^9/\text{L}) \text{ x } \sqrt{\text{ALT (U/L)}}}$$

FIB-4 is an alternative non-invasive test used to assess liver fibrosis.

3.2 Counselling

Patients diagnosed with CHB should receive counselling on lifestyle modifications, prevention of transmission, and the importance of lifelong monitoring.

Reinforce the importance of lifelong monitoring

- Attend regular follow-up appointments to monitor disease progression, even in the absence of symptoms
- Follow doctor's instructions regarding blood tests, HCC surveillance, and medication adherence (if prescribed)
- Inform healthcare providers of their CHB status, particularly before initiating a new medication

Promote a healthy diet and lifestyle

- Avoid alcohol consumption and cigarette smoking
- Maintain a balanced diet
- Engage in regular exercise and maintain a healthy body weight

Advise on preventive measures against HBV transmission

- Encourage household members and sexual partners to undergo HBV testing and recommend vaccination if they are not immune and not infected with HBV
- Use barrier protection during sexual intercourse if partner is not vaccinated or is not naturally immune
- Avoid sharing personal care products that could potentially be contaminated with blood, such as razors, toothbrushes, injection equipment, and glucose testing equipment
- Cover open cuts and scratches with a bandage
- Clean blood spills with bleach solution

3.3 Antiviral treatment

The main goal of therapy for patients with HBV infection is to improve survival by preventing disease progression, acute hepatitis, and HCC development. The indications for treatment depend on the severity of the underlying liver disease, serum ALT and HBV DNA level.

To provide guidance for managing CHB, it is recommended to use an upper limit of normal (ULN) for ALT of 35 U/L for males and 25 U/L for females.

3.3.1 Indications for treatment

- CHB patients with advanced fibrosis (liver stiffness > 9 kPa), cirrhosis, decompensated liver disease, or HCC; and detectable HBV DNA
- HBeAg-positive or HBeAg-negative CHB patients with elevated ALT (> ULN) and HBV DNA > 2000 IU/ml
- Pre-emptive treatment for patients on anti-cancer chemotherapy or immunosuppressive therapy at risk of hepatitis B reactivation
- Transplant patients with hepatitis B infection
- Pregnant women with HBV DNA > 200,000 IU/ml (start at week 24-28 of gestation and continue for up to 12 weeks after delivery)

Besides the above indications, antiviral treatment can be considered in patients at increased risk of complications, e.g. family history of cirrhosis or HCC, and patients over the age of 40 with persistently high HBV DNA levels.

3.3.2 Antiviral agents

The long-term administration of a potent nucleos(t)ide analogue with a high barrier to resistance is the treatment of choice. Entecavir and tenofovir are the preferred oral antiviral agents in primary care settings because of their ease of administration, high potency, and favourable safety profile. The older generation of oral antiviral agents (e.g. lamivudine,

adefovir, telbivudine) is not recommended due to the lower barrier to viral resistance. Current first-line agents can be used in patients previously treated with another antiviral agent unless there is a history of drug resistance. Most CHB patients on antiviral therapy will require lifelong treatment. Counselling patients about antiviral medication adherence before the initiation of treatment is important. Details of the antiviral agents and dosage adjustments for renal impairment are shown in Table 3 and Table 4, respectively.

Pegylated interferon is an alternative treatment for chronic hepatitis B. Given the need for regular injection and the significant side effects of treatment, those requesting interferon-based treatment should be referred to hepatologists for assessment and counselling.

Table 3 Preferred oral antiviral agents for chronic hepatitis B

Drug	Dosage	Side effects	Cautions
Entecavir (ETV)	0.5 mg daily	Nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, insomnia, dizziness Lactic acidosis (reported in a small number of patients with decompensated cirrhosis)	- Adjust dose if eGFR[2] < 50 ml/min - Avoid in patients with a history of lamivudine or telbivudine resistance - Switch to TDF in pregnant patients - Note a drug resistance rate of 1.2% in 5 years
Tenofovir disoproxil fumarate (TDF)	300 mg daily	Abdominal distention, diarrhoea, vomiting, nausea, headache, dizziness, osteomalacia, nephropathy, Fanconi syndrome, hypophosphataemia, lactic acidosis	- Adjust dose if eGFR < 50 ml/min - Monitor RFT, eGFR, and serum phosphate (PO4) at baseline and during therapy - Consider switching to ETV or TAF in patients

[2] eGFR: estimated glomerular filtration rate

Drug	Dosage	Side effects	Cautions
			with or at risk for renal or bone disease - Consider bone density study at baseline and during therapy in patients with history of fracture or risks for osteopenia
Tenofovir alafenamide (TAF)	25 mg daily	Abdominal distention, diarrhoea, nausea, headache, arthralgia, cough, renal impairment, laboratory parameter abnormalities (ALT, AST, LDL-cholesterol, glycosuria, creatine kinase, serum amylase), lactic acidosis	- Not recommended in patients with eGFR < 15 ml/min who are not receiving haemodialysis - Monitor RFT and serum phosphate at baseline and during therapy

Table 4 Recommended dosage of antiviral agents for patients with renal impairment

Creatinine clearance (ml/min)	Entecavir	Tenofovir disoproxil fumarate	Tenofovir alafenamide
CrCl $\geq$ 50	0.5mg daily	300mg daily	25mg daily
CrCl 30-49	0.5mg Q48H	300mg Q48H	25mg daily
CrCl 20-29	0.5mg Q72H	300mg Q72H	25mg daily
CrCl 10-19	0.5mg Q72H	300mg Q96H	**
CrCl <10	0.5mg once weekly	300mg once weekly*	**
Hemodialysis (after HD)	0.5mg once weekly	300mg once weekly	25mg daily

*: The dosage has not been studied. If there is no alternative therapy, may consider 300mg weekly

**: CrCl <15 ml/min: use is not recommended

3.3.3 When to stop treatment

The long-term suppression of HBV DNA levels is the main endpoint of treatment. Reactivation may occur after stopping therapy with nucleos(t)ide analogues. Therefore, most patients who are indicated for treatment require long-term therapy. Patients with cirrhosis should not discontinue antiviral therapy due to the risk of reactivation and decompensation.

HBsAg loss, with or without anti-HBs seroconversion, is an optimal treatment endpoint (termed ‘functional cure’), although it is rarely achieved with the current antiviral treatment. Nucleos(t)ide analogues may be discontinued after persistent HBsAg loss for 1 year in patients without cirrhosis, who can be monitored closely for reactivation. Non-cirrhotic patients with confirmed HBsAg loss while on therapy should be referred to hepatologists for consideration of treatment discontinuation and monitoring.

3.4 Monitoring

Regular monitoring is necessary for all patients with CHB, which consists of the following:

- Assess clinical features of decompensated cirrhosis, e.g. jaundice, ascites
- Monitor adherence at each visit if on treatment
- Perform laboratory investigations (as outlined below)
- Consider periodic non-invasive tests to assess liver fibrosis
- Evaluate the need for antiviral therapy if not yet on treatment
- Recommend HCC surveillance in patients at increased risk (section 3.4 HCC surveillance)
- Review the need for specialist referral

The suggested frequency of monitoring serves as a general reference. Clinicians may adapt their approach based on individual patients' needs, patient acceptance, and resource availability.

3.4.1 Patients not receiving antiviral treatment

HBeAg-positive

- LFT every 3-6 months
- AFP every 6 months
- HBV DNA every 6-12 months
- APRI yearly
- HBeAg and anti-HBe yearly until HBeAg seroconversion
- More frequent monitoring is required for patients with abnormal ALT and HBV DNA >2000 IU/ml but not yet on treatment

HBeAg-negative

- LFT and AFP every 6 months
- HBV DNA every 6-12 months
- APRI yearly
- HBsAg yearly
- More frequent monitoring is required for patients with abnormal ALT and HBV DNA >2000 IU/ml but not yet on treatment

3.4.2 Patients receiving antiviral treatment

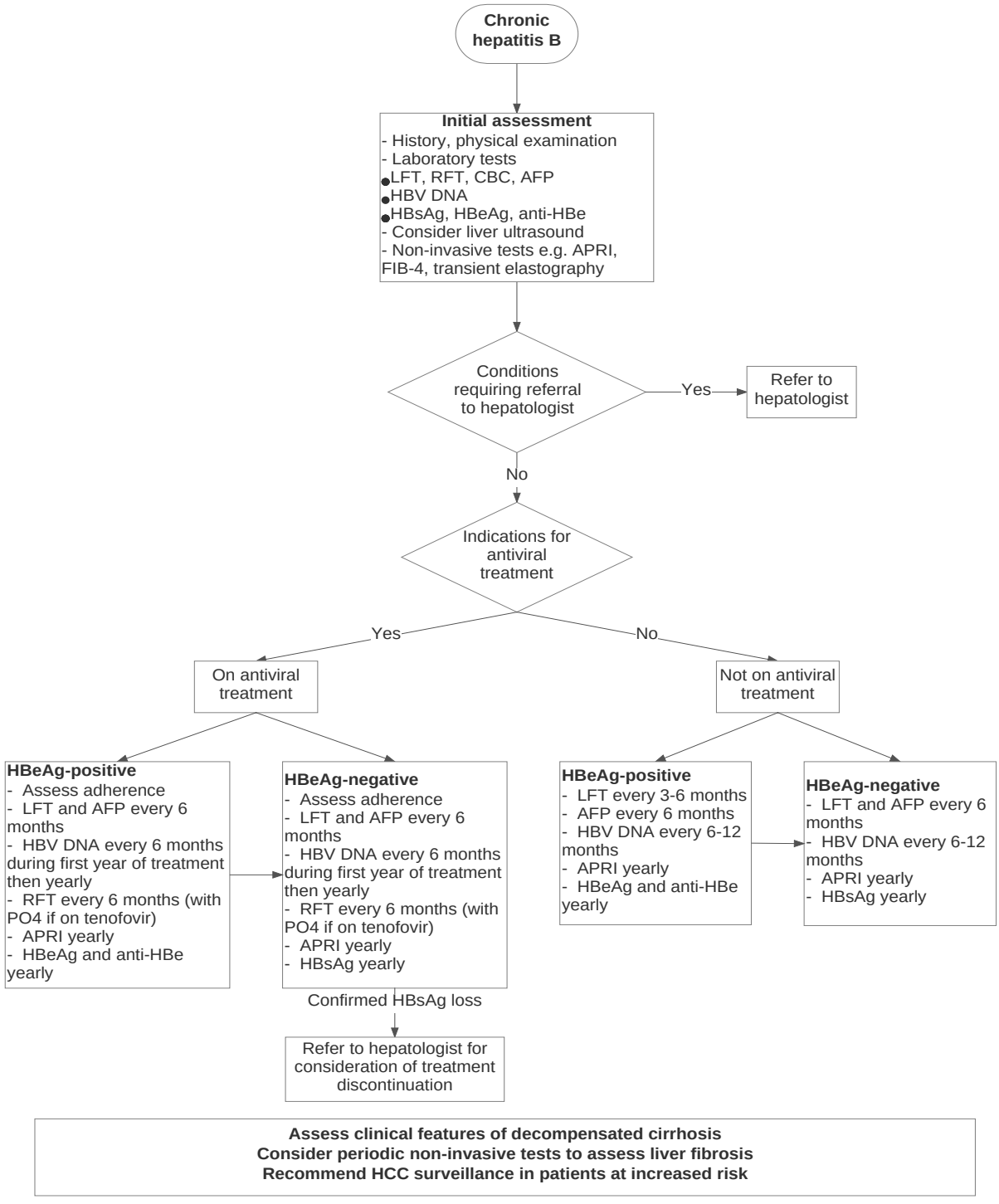
HBeAg-positive

- LFT and AFP every 6 months
- HBV DNA every 6 months during the first year of treatment, then yearly
- RFT every 6 months (with serum phosphate if on tenofovir)
- APRI yearly
- HBeAg and anti-HBe yearly until HBeAg seroconversion
- More frequent monitoring is required at treatment initiation to assess treatment response, especially in patients with abnormal ALT

HBeAg-negative

- LFT and AFP every 6 months
- HBV DNA every 6 months during the first year of treatment, then yearly
- RFT every 6 months (with serum phosphate if on tenofovir)
- APRI yearly
- HBsAg yearly
- More frequent monitoring is required at treatment initiation to assess treatment response, especially in patients with abnormal ALT

Figure 2 Algorithm for management of CHB patients without cirrhosis



Note:

- More frequent monitoring is required at treatment initiation, and in those with abnormal ALT and HBV DNA >2000 IU/ml but not yet on treatment.
- The suggested frequency of monitoring serves as a general reference. Clinicians may adapt their approach based on individual patients' needs, patient acceptance, and resource availability.

3.5 HCC surveillance

Chronic HBV infection is a risk factor for developing HCC, even in the absence of cirrhosis. In Hong Kong, CHB accounts for 80% of incident HCC. Antiviral therapy does not completely eliminate the risk for HCC. Therefore, surveillance for HCC is crucial in reducing the morbidity and mortality of HBV infection. HCC may still develop even after spontaneous HBsAg loss, but the risk is lower if HBsAg loss is achieved at a younger age and in the absence of significant fibrosis.

Indications

HCC surveillance is recommended for CHB patients with the following risk factors:

- Patients with cirrhosis
- Men over 40 years of age
- Women over 50 years of age
- Patients with a family history of HCC

Apart from assessing the above risk factors, the use of validated HCC risk scores can be considered to identify patients at risk of developing HCC and guide the need for surveillance.

Modalities

- Alpha-fetoprotein (AFP) should be performed every six months; and
- USG of the liver, preferably every six months, should be recommended

Patient participation plays a pivotal role in the success of HCC surveillance. Patients are encouraged to take responsibility and proactively engage in arranging relevant investigations to ensure they receive appropriate care.

3.6 Subgroups of CHB patients requiring hepatology care

3.6.1 Patients with complications of CHB

Cirrhosis and HCC are the two major long-term complications of CHB. Patients with cirrhosis and HCC require close follow-up and sometimes inpatient care with multi-disciplinary management. For instance, patients with cirrhosis may require endoscopic screening for varices, admissions for abdominal paracentesis or treatment of hepatic encephalopathy. Patients with HCC often require multi-disciplinary care involving physicians, surgeons, oncologists, and radiologists to formulate the best treatment strategy.

It is noteworthy that ultrasound findings of coarsened hepatic echotexture may be subjective and operator-dependent. In such cases, transient elastography can be a valuable tool for measuring liver stiffness.

3.6.2 Patients with concurrent liver diseases

Patients with CHB may have concurrent liver diseases, e.g. fatty liver, autoimmune hepatitis, and primary biliary cholangitis. Fatty liver is increasingly common in the general population and among patients with CHB. Up to 40% of CHB patients have concurrent fatty liver. Management of fatty liver includes the exclusion of harmful alcohol use and steatogenic medications (such as corticosteroids and tamoxifen), assessment of associated metabolic syndrome, and lifestyle modification, especially weight reduction. Currently, there is no specific pharmacologic agent for metabolic dysfunction-associated steatotic liver disease. Patients with CHB and fatty liver can be managed in primary care settings if the liver function is stable and they have no significant fibrosis. Referrals should be made for other liver conditions requiring hepatologist assessment, e.g. liver biopsy and treatment.

3.6.3 Patients with liver lesions

Incidental finding of liver lesions is common in patients with CHB, discovered through imaging for surveillance or investigation of abnormal liver function. Asymptomatic, benign liver lesions do not require further intervention or treatment. These lesions include simple liver cysts,

haemangioma, and calcified granuloma. Referral can be considered for patients with focal nodular hyperplasia, hepatocellular adenoma, and other suspicious or indeterminate lesions on imaging.

3.6.4 Special populations

The following patient populations have special needs and indications for antiviral treatment. They should be managed or co-managed by relevant specialists.

a) Co-infection with HCV or HIV

The risk of long-term complications increases in patients co-infected with HCV or human immunodeficiency virus (HIV). Reactivation of HBV infection is possible during direct-acting antiviral (DAA) therapy for HCV infection, where patients should be monitored closely and considered for antiviral prophylaxis. CHB patients with HIV co-infection should receive highly active antiretroviral therapy (HAART), which includes an agent with antiviral activity against HBV.

b) Pregnant women with high viral load

Pregnant women receiving antenatal care at Maternal and Child Health Centres (MCHCs) of the DH or obstetric units of the HA are screened for HBV infection. HBsAg-positive pregnant women with high viral load are referred to hepatologists for counselling and consideration for antiviral prophylaxis. Most patients can continue monitoring in primary care after delivery.

Management of pregnant CHB women without cirrhosis is similar to that of non-pregnant CHB patients. In addition to the usual indications for antiviral treatment, pregnant women with high viral load (HBV DNA > 200,000 IU/ml) should be offered antiviral prophylaxis to prevent mother-to-child transmission (MTCT) of HBV. The antiviral prophylaxis should be initiated at week 24-28 of gestation and continued for up to 12 weeks after delivery. Tenofovir disoproxil fumarate (TDF) is the recommended antiviral agent in pregnant CHB patients. Pregnant women who are already on TDF can be safely monitored in primary care, with appropriate specialist input as necessary. Pregnant women who are on other antiviral agents are advised to switch to TDF, a conversion that can be safely managed by primary care physicians.

Criteria for referral of pregnant CHB patients to hepatologists:

- Abnormal ALT, or
- HBV DNA > 200,000 IU/ml, or
- Patients on antiviral agents other than TDF

Pregnant women who do not meet the criteria for specialist referral can be safely managed in primary care.

c) Patients on immunosuppressive therapy at risk of hepatitis B reactivation

Patients with cancer, immune-mediated conditions, and transplant recipients receiving immunosuppressive therapy are at risk of HBV reactivation. These patients require close monitoring of liver function and hepatitis serology, and consideration for pre-emptive antiviral therapy by the treating physicians.

4. Bidirectional referral between primary care and hepatology

Some CHB patients may develop hepatitis or other conditions requiring assessment and management by hepatologists. When the liver condition becomes stable, with a clear diagnosis and management plan formulated after review by hepatologists, some of these patients can be referred to primary care for ongoing monitoring.

4.1 Criteria for referral from primary care to hepatology

Besides the subgroups of CHB patients requiring specialist care, early assessment by hepatologists should be offered to the following patients.

4.1.1 Unexplained deranged liver function

- Persistently elevated ALT (> 2x ULN) despite low viral load (HBV DNA < 2000 IU/ml), or
- Persistently elevated ALT (> 2x ULN) despite antiviral treatment and decreasing HBV DNA

Most cases of hepatitis flare due to viral reactivation are reflected by a rise in ALT and a high viral load. The ALT should normalise after antiviral treatment with concurrent suppression of HBV DNA. Persistently elevated liver enzymes despite a low or suppressed viral load require further investigation, in which fatty liver is the most common cause. Further assessment includes history taking, physical examination, blood tests, USG, and transient elastography to identify alternative causes of abnormal liver function and to assess hepatic steatosis.

4.1.2 Severe acute hepatitis or acute-on-chronic liver failure (ACLF)

- ALT > 5x ULN, regardless of aetiology, or
- Urgent referral to the Accident and Emergency Department if symptoms and signs of acute liver failure (hepatic encephalopathy, jaundice) or INR ≥ 1.5

Most cases of hepatitis flare associated with viral reactivation present as a self-limiting elevation of liver enzymes. However, ACLF may develop, which can be life-threatening. Markedly raised ALT, especially when associated with derangement of synthetic (clotting profile) or metabolic (bilirubin) functions of the liver, requires urgent assessment to rule out other causes of liver injury, close monitoring, and timely initiation of antiviral treatment. Some patients with severe flares may require liver transplantation.

4.1.3 Virological breakthrough in patients receiving antiviral treatment

- Virological breakthrough: > 1 $\log_{10}$ (10-fold) IU/ml increase in HBV DNA from nadir (lowest value) on-therapy after initial response

Most cases of virological breakthrough are due to treatment non-adherence rather than viral resistance. Reinforcement of drug adherence with close monitoring of HBV DNA level and liver biochemistry can be considered. Patients should be referred to a hepatologist if they experience virological breakthrough despite maintaining good drug adherence or if there is evidence of biochemical breakthrough.

4.1.4 Abnormal AFP

- Rising or persistently elevated AFP (> ULN) despite normal ALT and liver imaging

HCC is the most important diagnosis to rule out in patients with elevated AFP. However, the accuracy of AFP in diagnosing HCC is limited. Elevated AFP may be seen in other conditions, such as acute hepatitis, pregnancy, gonadal neoplasms (both germ cell and non-germ cell), and gastric cancer. USG of the liver or preferably cross-sectional imaging (triphasic contrast-enhanced computed tomography or magnetic resonance imaging) should be performed in patients with newly elevated AFP. Some patients have an elevated AFP at baseline, which can be observed after investigation.

4.2 Criteria for referral from hepatology to primary care

Most CHB patients with stable conditions can be safely managed in primary care, while patients with advanced disease can receive timely management by hepatologists.

CHB patients with stable liver conditions over the past year may be referred to primary care for monitoring:

- Absence of symptoms and signs suggestive of advanced liver disease, and
- Normal ALT and AFP, or stably elevated ALT (< 3x ULN) after the exclusion of other causes, and
- No change in antiviral medication, and
- Absence of advanced fibrosis (liver stiffness < 9 kPa) with fibrosis assessment within three years

The above criteria should be evaluated based on individual patient conditions. It is important for hepatologists to maintain open communication with primary care physicians, especially in cases of abnormal test results.

4.3 Experience sharing between hepatology and primary care

As non-hepatologists are involved in the care continuum of CHB patients, knowledge and experience sharing are vital to support the management of CHB patients in primary care settings. In parallel with the above referral mechanism, communication channels between hepatology and primary care can facilitate case discussion and management. Consultation platforms for the discussion of selected cases and formulation of management plans can reduce unnecessary referrals and expedite patient care. Co-management of patients recently referred from hepatology to primary care can be considered to aid the transition of care.

5. Abbreviations

ACLF	Acute-on-chronic liver failure
AFP	Alpha-fetoprotein
ALT	Alanine aminotransferase
Anti-HBc	Antibody against hepatitis B core antigen
Anti-HBe	Antibody against hepatitis B e antigen
Anti-HBs	Antibody against hepatitis B surface antigen
APRI	AST-to-platelet ratio index
AST	Aspartate aminotransferase
CBC	Complete blood count
cccDNA	Covalently closed circular DNA
CHB	Chronic hepatitis B
CrCl	Creatinine clearance
DAA	Direct-acting antiviral
DH	Department of Health
DNA	Deoxyribonucleic acid
eGFR	Estimated glomerular filtration rate
ETV	Entecavir
FIB-4	Fibrosis-4 index
HA	Hospital Authority
HAART	Highly active antiretroviral therapy
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HD	Haemodialysis

HIV	Human immunodeficiency virus
LFT	Liver function test
MCHC	Maternal and Child Health Centre
MTCT	Mother-to-child transmission
PO4	Phosphate
RFT	Renal function test
RNA	Ribonucleic acid
SOPC	Specialist outpatient clinic
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
USG	Ultrasonography
WHO	World Health Organization

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