

Management of Adults with Chronic Hepatitis B in Primary Care

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Contents

Background.....	4
Acknowledgement.....	5
 Chapter 1 Background of HBV infection	 6
1.1 HBV infection in Hong Kong	6
1.2 Virology.....	6
1.3 Natural history	7
 Chapter 2 Stratification of care for people with CHB	 9
 Chapter 3 Identification and management of people with CHB.....	 10
3.1 Who to test and how to test for CHB	10
3.2 Initial assessment of HBsAg-positive individuals	11
3.3 Counselling.....	14
3.4 Antiviral treatment.....	15
3.5 Monitoring.....	18
3.6 HCC surveillance	21
3.7 Subgroups of people with CHB requiring specialist care	22
 Chapter 4 Bidirectional referral between primary care and hepatology	 25
4.1 Criteria for referral from primary care to hepatology	25
4.2 Criteria for referral from hepatology to primary care	27
4.3 Experience sharing between hepatology and primary care	27
 Abbreviations.....	 28
References	30
Annex I: Government Subsidised Services under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme)	31
Annex II: Clinical Workflow under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme).....	32
Annex III: Investigation Services under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme).....	36

Background

To enhance prevention-oriented primary healthcare services, the Government launched the Chronic Disease Co-Care Pilot Scheme (CDCC Pilot Scheme) in November 2023. The Scheme provides subsidised diabetes mellitus (DM) and hypertension (HT) screening services in the private healthcare sector to Hong Kong residents aged 45 or above with no known medical history of DM or HT, with a view to encouraging citizens to receive early screening, so as to achieve the goals of “early prevention, early identification and early treatment”. In March 2025, the Scheme was expanded to include blood lipid testing, thus achieving full coverage of the “three highs”. In addition to covering the “three highs”, the service scope of the CDCC Pilot Scheme will further be expanded to provide risk-based chronic hepatitis B screening and management as the Hepatitis B Co-care Scheme.

This Guideline provides support to the implementation of risk-based chronic hepatitis B screening and management under the Hepatitis B Co-care Scheme. It covers the assessment, monitoring, and management of adults with chronic hepatitis B in primary care; and the bidirectional referral criteria between primary care and secondary care.

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Chapter 1 Background of HBV infection

1.1 HBV infection in Hong Kong

- 1.1.1** CHB remains prevalent in Hong Kong and accounts for the majority of liver-related morbidity and mortality despite universal newborn vaccination since 1988. Based on findings from the Population Health Survey 2020-22 conducted by the DH, the seroprevalence of hepatitis B surface antigen (HBsAg) in Hong Kong is about 5.6%, corresponding to around 410,000 individuals.
- 1.1.2** 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 people with CHB acquired the infection during the perinatal period or childhood. Over 90% of infants infected before the age of one will develop chronic infection. Complications of chronic HBV infection include hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC).
- 1.1.3** 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 yet to be diagnosed and linked to care, placing considerable strain on the management capacity of secondary care.
- 1.1.4** 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 guidance to facilitate the management of adults with CHB in primary care settings.

1.2 Virology

- 1.2.1** 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 large, middle, and small hepatitis B surface antigen (HBsAg). HBeAg and HBsAg are commonly used as serologic markers of HBV infection.
- 1.2.2** 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 explains the persistence of HBV infection despite low or undetectable circulating virus.

1.3 Natural history

- 1.3.1** Acute HBV infection in infants and young children is generally asymptomatic, whereas in some adults it may cause symptoms such as nausea, upper abdominal discomfort, and tea-coloured urine.
- 1.3.2** In rare cases, acute HBV infection in adults can progress to fulminant hepatitis and liver failure.
- 1.3.3** The risk of developing chronic HBV infection is inversely related to age at the time of infection. Over 90% of infants infected before one year of age will develop chronic infection, compared to less than 5% of those infected in adulthood.
- 1.3.4** CHB is defined by the persistence of serum HBsAg beyond six months.
- 1.3.5** The interpretation of hepatitis B serology is shown in **Table 1**.
- 1.3.6** 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

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

- 1.3.7** 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 Phases of chronic HBV infection (adapted from the EASL guidelines)

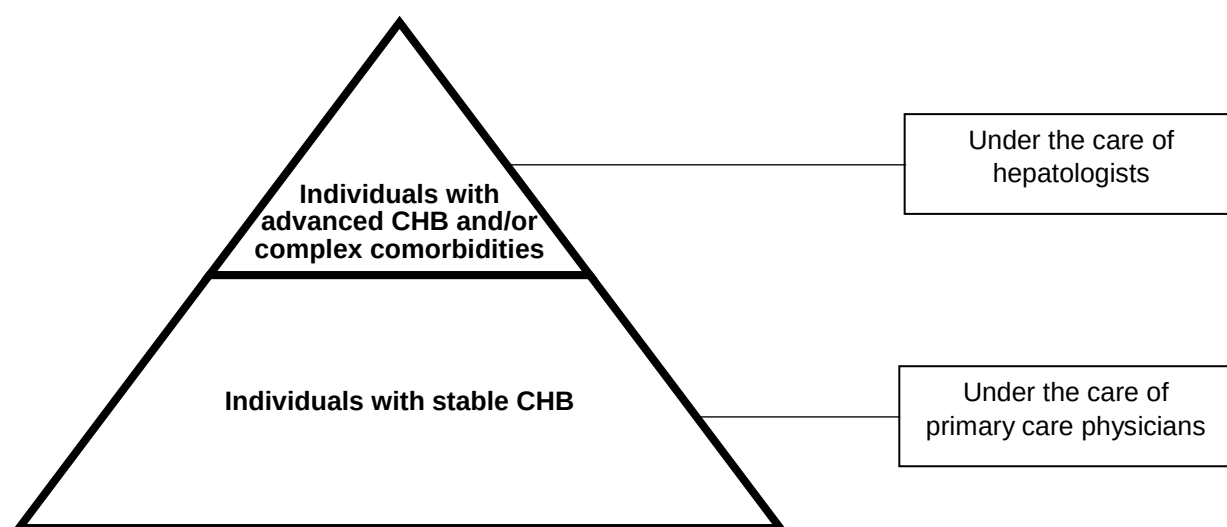
Phases	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBV DNA	High, usually $\geq 10^7$ IU/ml	Moderate to high, usually 10^{4-7} IU/ml	Usually < 2000 IU/ml	Usually > 2000 IU/ml
ALT	Normal	Elevated	Normal	Elevated
Liver disease progression (if untreated)	None / minimal	Moderate to severe	None	Mild to severe

- 1.3.8** Perinatal exposure to HBV leads to immune tolerance of the host to the virus. Most people 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.
- 1.3.9** 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 HBeAg-positive chronic hepatitis 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 individuals 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 HBeAg-negative chronic infection phase. About 30% of these individuals will develop reactivation of HBV, with a rise in HBV DNA and serum ALT.
- 1.3.10** In untreated individuals, repeated viral reactivation and immune-mediated hepatitis lead to fibrosis, cirrhosis, and end-stage liver failure. Many 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.
- 1.3.11** HCC is another dreaded complication of CHB. HCC can develop in patients with or without cirrhosis. The lifetime risk of HCC in people with HBV infection is 10–25 times greater than in those without the infection. In contrast, HCC associated with other liver diseases, such as alcohol-related liver disease or hepatitis C virus (HCV) infection, develops mainly in cirrhotic livers.
- 1.3.12** 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 direct effect on the cccDNA, a virologic cure is currently not possible, and viral relapse is frequent after treatment cessation. Most individuals who begin treatment will require long-term therapy.

Chapter 2 Stratification of care for people with CHB

- 2.1** Facilitating care for the large local population with CHB necessitates stratification to ensure appropriate care. Most individuals with stable CHB who are either treatment-naïve or on treatment can be appropriately managed in primary care settings. This guidance will focus on the management of individuals with stable CHB (**Figure 1**).
- 2.2** In contrast, those with advanced disease or complex conditions require management by hepatologists. They should be referred to specialists for further care. Detailed management in these situations is beyond the scope of this guidance.

Figure 1 Stratification of care for people with chronic hepatitis B



Chapter 3 Identification and management of people with CHB

3.1 Who to test and how to test for CHB

- 3.1.1** Given that the seroprevalence of HBsAg in Hong Kong is $\geq 5\%$, the WHO recommends that all adults should have access to HBsAg serological testing and be linked to prevention, care, and treatment services. In addition, targeted testing is recommended for all pregnant women, blood donors, health care workers, and individuals suspected of having chronic viral hepatitis.
- 3.1.2** Recognising variations in resource availability across local settings, a phased approach is proposed to improve access to hepatitis B testing and subsequent care in Hong Kong, prioritising high-risk populations. The priority groups include people who inject drugs, people with HIV, men who have sex with men, sex workers, people in prisons, and family members or sexual partners of those with HBV infection.
- 3.1.3** A serological assay (either a rapid diagnostic test (RDT) or a laboratory-based immunoassay) is recommended for detecting HBsAg. Laboratory-based immunoassays are preferred in settings where facilities are available, while RDTs play an important role in expanding access to testing. A protocol-driven approach is recommended for the use of RDT to detect HBsAg in primary care setting. For individuals who test positive for HBsAg using RDT, a laboratory-based immunoassay should be performed to confirm the diagnosis. Persistence of HBsAg for six months or more confirms the chronicity of HBV infection.

3.2 Initial assessment of HBsAg-positive individuals

3.2.1 Individuals with stable, uncomplicated CHB can be assessed and managed in primary care settings with clinical and laboratory monitoring, antiviral treatment and HCC surveillance when indicated. The algorithm for the management of individuals with CHB in primary care settings is summarised in **Figure 2**. The criteria for specialist referral of individuals with advanced disease or complex conditions are outlined in Sections 3.7 and 4.1.

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, steatotic liver disease, 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 women of child-bearing age
- Hepatitis A vaccination history
- Marital status and cohabitants
- Sexual history

Physical examination

- Stigmata of chronic liver disease, e.g. jaundice, ascites
- 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
- Individuals with CHB who are indicated for antiviral treatment should be considered for anti-HIV testing because of the potential development of drug resistance in cases of undiagnosed HIV infection.

Other investigations

- Consider ultrasonography (USG) of the liver
- Non-invasive tests to assess liver fibrosis
 - Serum biomarkers, e.g. APRI, FIB-4
 - Transient elastography: recommended if APRI >1.0 or FIB-4 >3.25; consider assessment where available, as detailed below

AST-to-platelet ratio index (APRI)

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

APRI has been validated for the diagnosis of both significant fibrosis and cirrhosis. The WHO recommended APRI as the preferred non-invasive test for assessing the presence of significant fibrosis or cirrhosis in resource-limited settings. An APRI score of >1.0 predicts the presence of cirrhosis and warrants further evaluation, preferably with transient elastography using a validated device, such as FibroScan. An APRI score of >0.5 predicts the presence of significant fibrosis. For individuals with an APRI score of >0.5 and ≤1.0, transient elastography can be considered if available, or if repeat testing confirms persistent elevation.

Fibrosis-4 index (FIB-4)

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

FIB-4 is an alternative non-invasive test used to assess liver fibrosis. A FIB-4 score of >3.25 predicts advanced fibrosis and warrants further evaluation, preferably with transient elastography using a validated device, such as FibroScan. For individuals with a FIB-4 score in the indeterminate range of 1.45 to 3.25, transient elastography

can be considered if available, or if repeat testing confirms persistent elevation.

Transient elastography

Transient elastography is a non-invasive method used to measure liver stiffness. The threshold values for liver stiffness measurements (LSM) are defined as follows: >7 kPa (significant fibrosis), >8 kPa (advanced fibrosis), and >11 kPa (cirrhosis). Repeat evaluation by transient elastography can be considered every two to three years to detect fibrosis progression in individuals with elevated APRI or FIB-4 who are not on antiviral treatment, or those with a LSM of >7 kPa.

3.3 Counselling

3.3.1 Individuals 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 quit smoking
- Maintain a balanced diet
- Engage in regular physical activity and maintain an optimal 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
- Use 1:4 diluted household bleach (mixing 1 part of 5.25% bleach with 4 parts of water) for surfaces or articles contaminated with blood spillage

3.4 Antiviral treatment

3.4.1 The main goal of therapy for people with CHB 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.

3.4.2 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.

3.4.3 Indications for treatment

- People with CHB who have significant fibrosis (LSM >7 kPa, or APRI >0.5 if transient elastography is unavailable), cirrhosis, decompensated liver disease, or HCC; and detectable HBV DNA; or
- People with CHB who have elevated ALT (>ULN) and HBV DNA >2000 IU/ml; or
- Pre-emptive treatment for patients on anti-cancer chemotherapy or immunosuppressive therapy at risk of hepatitis B reactivation; or
- Transplant patients with hepatitis B infection; or
- 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)

3.4.3.1 Besides the above indications, antiviral treatment can be considered in individuals at increased risk of complications, e.g. family history of cirrhosis or HCC, comorbidities such as diabetes or metabolic dysfunction-associated steatotic liver disease, or people over the age of 40 with persistently high HBV DNA levels. Personalised assessment and shared decision-making are key to ensuring a person-centred approach to treatment initiation, balancing individual preferences with the need for strict adherence to long-term treatment.

3.4.4 Antiviral agents

3.4.4.1 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 people with CHB 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.

3.4.4.2 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 eGFR¹ <50 ml/min - Avoid in patients with a history of lamivudine or telbivudine resistance - Switch to tenofovir in pregnant patients or women planning pregnancy - 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 - Switch to ETV or TAF in patients with or at risk for renal or bone disease (e.g. osteoporosis) - Consider bone density study at baseline and during therapy in patients with a 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

¹ eGFR: estimated glomerular filtration rate

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

3.4.5 When to stop treatment

3.4.5.1 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 individuals 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.

3.4.5.2 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 6 months in patients without cirrhosis, provided there are no coexisting risk factors and close monitoring for reactivation is guaranteed. Non-cirrhotic patients with confirmed HBsAg loss while on therapy should be referred to hepatologists for consideration of treatment discontinuation and monitoring.

3.5 Monitoring

3.5.1 Regular monitoring is necessary for all people 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)
- Perform 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 3.6 HCC surveillance)
- Review the need for specialist referral

3.5.2 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.

3.5.3 Individuals not receiving antiviral treatment

- LFT and AFP every 6 months
- HBV DNA every 6-12 months
- APRI and/or FIB-4 annually

Where available:

- (For HBeAg-positive individuals) HBeAg and anti-HBe annually
- (For HBeAg-negative individuals) HBsAg annually

3.5.3.1 More frequent monitoring may be required for people with abnormal ALT and/or HBV DNA >2000 IU/ml but not yet on treatment.

3.5.4 Individuals receiving antiviral treatment

- LFT and AFP every 6 months
- HBV DNA every 6 months during the first year of treatment, then annually
- RFT every 6 months (with serum phosphate if on tenofovir)
- APRI and/or FIB-4 annually

Where available:

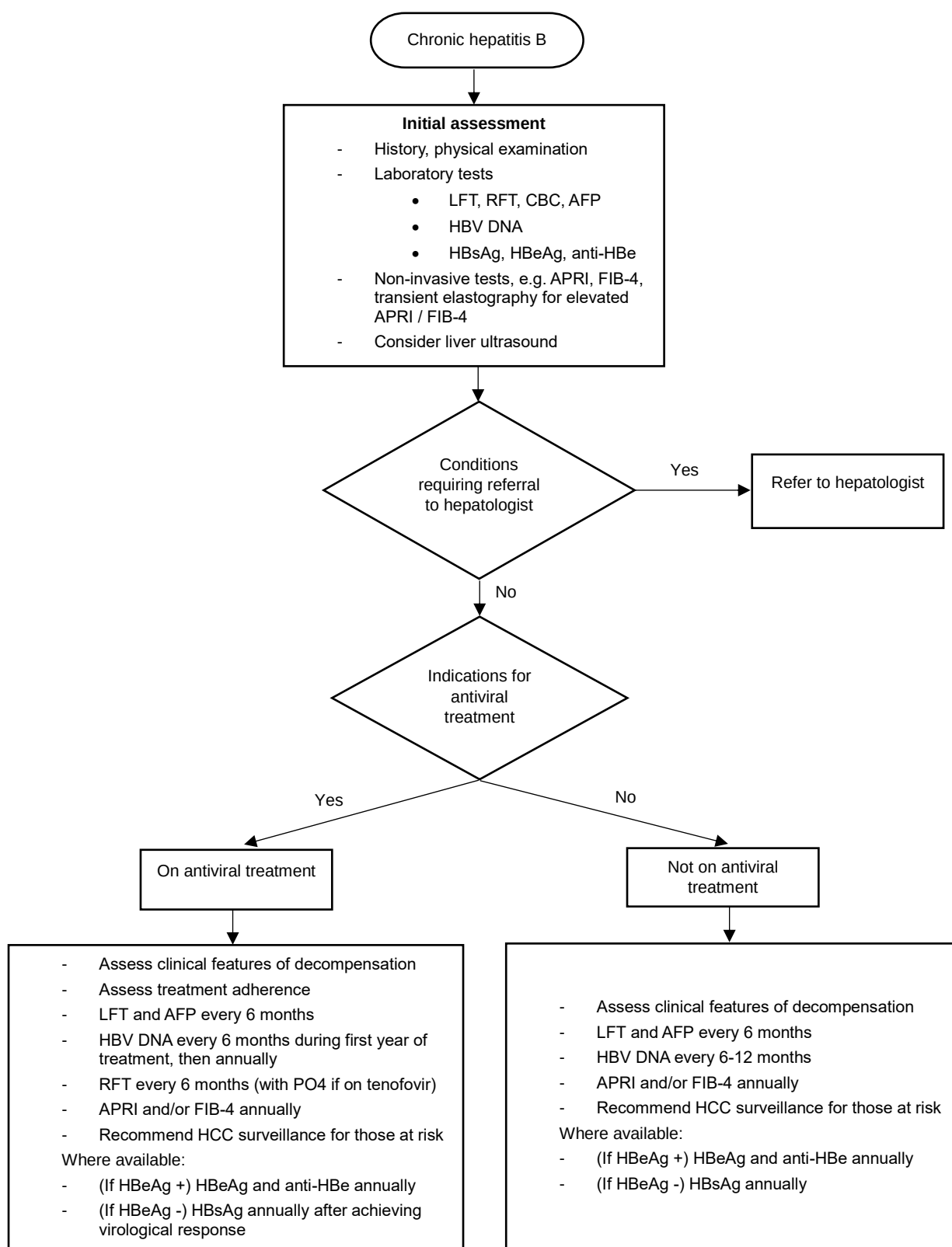
- (For HBeAg-positive individuals) HBeAg and anti-HBe annually
- (For HBeAg-negative individuals) HBsAg annually after HBV virological response is achieved, i.e. HBV DNA is <20 IU/mL.

3.5.4.1 More frequent monitoring (LFT every 3-6 months for the first year) may be required at treatment initiation to assess treatment response, especially in people with abnormal ALT; or where treatment adherence is a concern.

3.5.4.2 In adherent individuals receiving antiviral therapy, treatment response can be categorised as follows:

- Complete virological response: undetectable HBV DNA measured using a sensitive assay (<20 IU/ml)
- Partial virological response: HBV DNA does not decline steadily and remains >2,000 IU/ml
- Virological non-response: a decline of <1 log₁₀ IU/ml in HBV DNA at 6 months of treatment
- Virological resistance: assumed if HBV DNA increases to ≥1 log₁₀ IU/ml above nadir

Figure 2 Algorithm for management of individuals with CHB in primary care settings



Note:

- More frequent monitoring may be required at treatment initiation, in those with abnormal ALT and/or HBV DNA >2000 IU/ml but not yet on treatment, or where treatment adherence is a concern.
- 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.

3.6 HCC surveillance

3.6.1 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. Regular surveillance for HCC facilitates the detection of malignancy at an earlier stage, enabling the consideration of more curative treatment modalities. 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.

3.6.2 Indications

3.6.2.1 HCC surveillance is recommended for people with CHB who have the following risk factors:

- People with cirrhosis (high priority)
- People with a family history of HCC (high priority)
- Males over 40 years of age
- Females over 50 years of age

3.6.2.2 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 approach for surveillance. Determining the appropriate surveillance approach for individuals with additional risk factors requires personalised assessment and shared decision-making.

3.6.3 Modalities

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

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

3.6.3.2 The combination of AFP and novel biomarkers, such as protein induced by vitamin K absence-II (PIVKA-II), could further enhance the sensitivity of HCC detection. The use of PIVKA-II in addition to standard surveillance modalities may be considered in specific patient populations, especially those with cirrhosis.

3.7 Subgroups of people with CHB requiring specialist care

Subgroups of people with CHB requiring specialist care:

- Patients with or at risk for complications from CHB
- Patients with concurrent liver diseases
- Patients with liver lesions
- Special populations
 - Co-infection with HCV or HIV
 - Pregnant women with high viral load (HBV DNA >200,000 IU/ml)
 - Patients on immunosuppressive therapy at risk of hepatitis B reactivation

3.7.1 Patients with or at risk for complications from CHB

3.7.1.1 Cirrhosis and HCC are the two major long-term complications of CHB. Patients with cirrhosis and HCC require close monitoring and may sometimes need inpatient care with multidisciplinary management. For instance, patients with cirrhosis may require endoscopic screening for varices, admissions for abdominal paracentesis or treatment of hepatic encephalopathy. A LSM of >15 kPa is highly suggestive of compensated advanced chronic liver disease (cACLD). Endoscopy for variceal screening should be considered if LSM is ≥ 20 kPa or platelet count is $\leq 150 \times 10^9/L$. Individuals with cACLD or signs of hepatic decompensation (e.g. ascites) should be referred to hepatologists for further management. Patients with HCC often require multi-disciplinary care involving physicians, surgeons, oncologists, and radiologists to formulate the best treatment strategy.

3.7.1.2 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.

3.7.2 Patients with concurrent liver diseases

3.7.2.1 People with CHB may have concurrent liver diseases, e.g. steatotic liver disease, autoimmune hepatitis, and primary biliary cholangitis. Steatotic liver disease is increasingly common in the general population and among people with CHB. Up to 40% of people with CHB have concurrent steatotic liver disease. Management of steatotic liver disease 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. Pharmacologic therapy for metabolic dysfunction-associated steatotic liver disease is generally not indicated for individuals without significant fibrosis. People with CHB and steatotic liver disease 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. for liver biopsy and treatment.

3.7.3 Patients with liver lesions

- 3.7.3.1 Incidental finding of liver lesions is common in people 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 to a hepatologist can be considered for individuals with focal nodular hyperplasia, hepatocellular adenoma, and other suspicious or indeterminate lesions on imaging. Referral to a surgeon as well as a hepatologist should be considered if imaging findings suggest hepatocellular carcinoma.

3.7.4 Special populations

- 3.7.4.1 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 individuals can continue monitoring in primary care after delivery.

Management of CHB in pregnant women without cirrhosis is similar to that of non-pregnant individuals with CHB. 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) or tenofovir alafenamide (TAF) are the recommended antiviral agents in pregnant women with CHB. Pregnant women who are already on tenofovir can be monitored in

primary care, with appropriate specialist input as necessary. Pregnant women who are on other antiviral agents are advised to switch to tenofovir, a conversion that can be managed by primary care physicians.

Criteria for referral of pregnant women with CHB to hepatologists:

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

Pregnant women who do not meet the criteria for specialist referral can be managed in primary care. Breastfeeding should not be discouraged if tenofovir is continued after delivery.

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.

Chapter 4 Bidirectional referral between primary care and hepatology

Some individuals with CHB 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

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

Criteria for referral from primary care to hepatology:

- Unexplained deranged liver function
- Severe acute hepatitis or acute-on-chronic liver failure
- Virological breakthrough in patients receiving antiviral treatment
- Abnormal AFP

4.1.2 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

- 4.1.2.1 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 steatotic liver disease is the most common cause. Further assessment is needed to identify alternative causes of abnormal liver function, such as drug-induced liver injury, alcohol use, co-infections (e.g. HCV), or other liver diseases (e.g. metabolic). Transient elastography with measurement of the controlled attenuation parameter can be used to assess hepatic steatosis. Additional investigation may be warranted if no apparent cause of the deranged liver function is identified.

4.1.3 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

4.1.3.1 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.

4.1.4 Virological breakthrough in patients receiving antiviral treatment

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

4.1.4.1 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.

4.1.4.2 After confirming treatment adherence, the following adjustments are recommended in cases of partial virological response, virological non-response, or virological resistance:

- Switch to tenofovir if entecavir was previously used
- Switch to or add on entecavir if tenofovir was previously used

4.1.4.3 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.

4.1.5 Abnormal AFP

- Rising or persistently elevated AFP ($> \text{ULN}$) despite normal ALT and liver imaging

4.1.5.1 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

- 4.2.1 Most people with stable CHB can be appropriately managed in primary care, while those with advanced disease should receive timely care from hepatologists.
- 4.2.2 People with CHB and 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 ($<3\times$ ULN) after the exclusion of other causes, and
 - No change in antiviral medication, and
 - Absence of advanced fibrosis (LSM <8 kPa) with fibrosis assessment within three years
- 4.2.3 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

- 4.3.1 As non-hepatologists are involved in the care continuum of people with CHB, knowledge and experience sharing are vital to support the management of people with CHB 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.

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
cACLD	Compensated advanced chronic liver disease
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
LSM	Liver stiffness measurement

MCHC	Maternal and Child Health Centre
MTCT	Mother-to-child transmission
PO4	Phosphate
RDT	Rapid diagnostic test
RFT	Renal function test
RNA	Ribonucleic acid
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
ULN	Upper limit of normal
USG	Ultrasonography
WHO	World Health Organization

References

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6. Hepatitis B (chronic): diagnosis and management. NICE Clinical Guideline [CG165]. 2013 June (updated 2017 October).
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Annex I: Government Subsidised Services under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme)

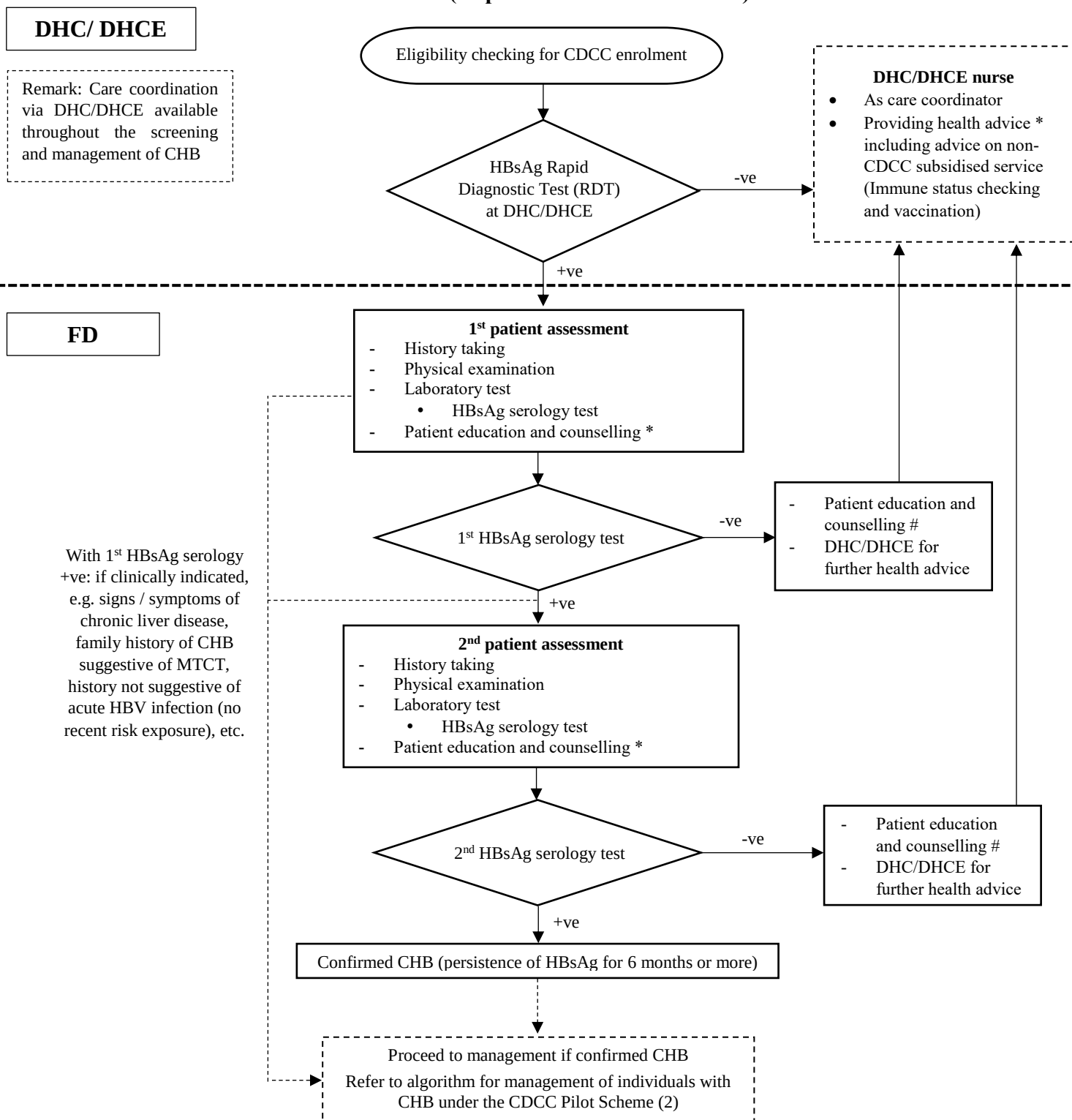
Through the CDCC Pilot Scheme, the Government aims to establish a family doctor regime and position District Health Centres and District Health Centre Express as hubs to foster expansion of the community healthcare network.

For service locations of the District Health Centres (DHC) and District Health Centre Express (DHC Express), please refer to the DHC website (<https://www.dhc.gov.hk/en/dhc.html>) and DHC Express website (https://www.dhc.gov.hk/en/dhc_express.html) for more information.

For service information of the preventive screening and care services for the underprivileged groups provided in designated pilot sites of Hospital Authority's Family Medicine Clinics (FMCs), please refer to the website of the CDCC Pilot Scheme (<https://www.primaryhealthcare.gov.hk/cdcc/en/gp/introduction.html>) for more information.

Annex II: Clinical Workflow under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme)

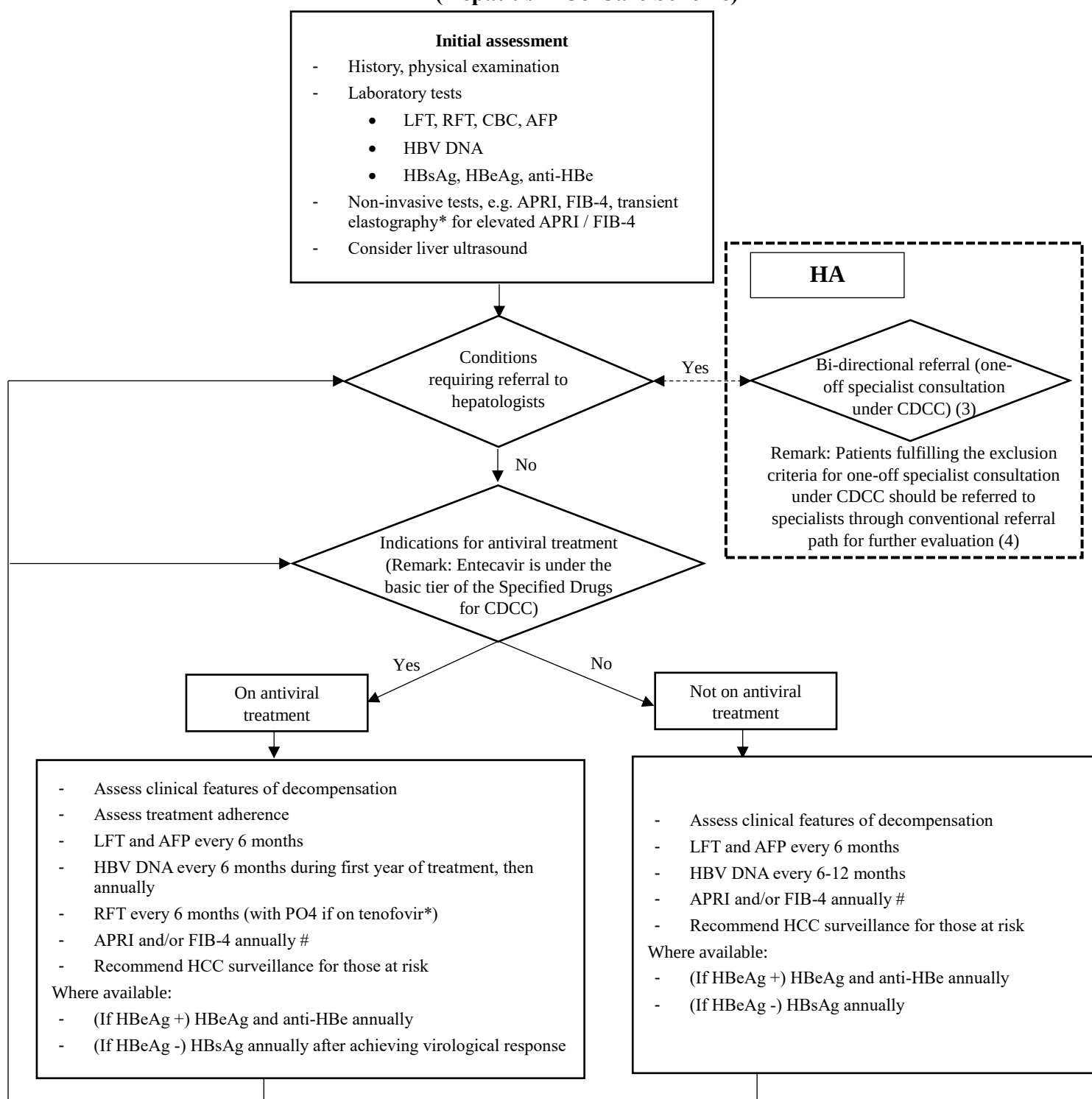
(1) Algorithm for Chronic Hepatitis B (CHB) Screening under the CDCC Pilot Scheme (Hepatitis B Co-Care Scheme)



*Health education materials will be provided to DHC/DHCE and FD for supporting patient education and counselling.

#Including advice on immune status checking and vaccination if susceptible (non-CDCC subsidised service that can be offered by FD)

(2) Algorithm for Management of Individuals with CHB under the CDCC Pilot Scheme (Hepatitis B Co-Care Scheme)



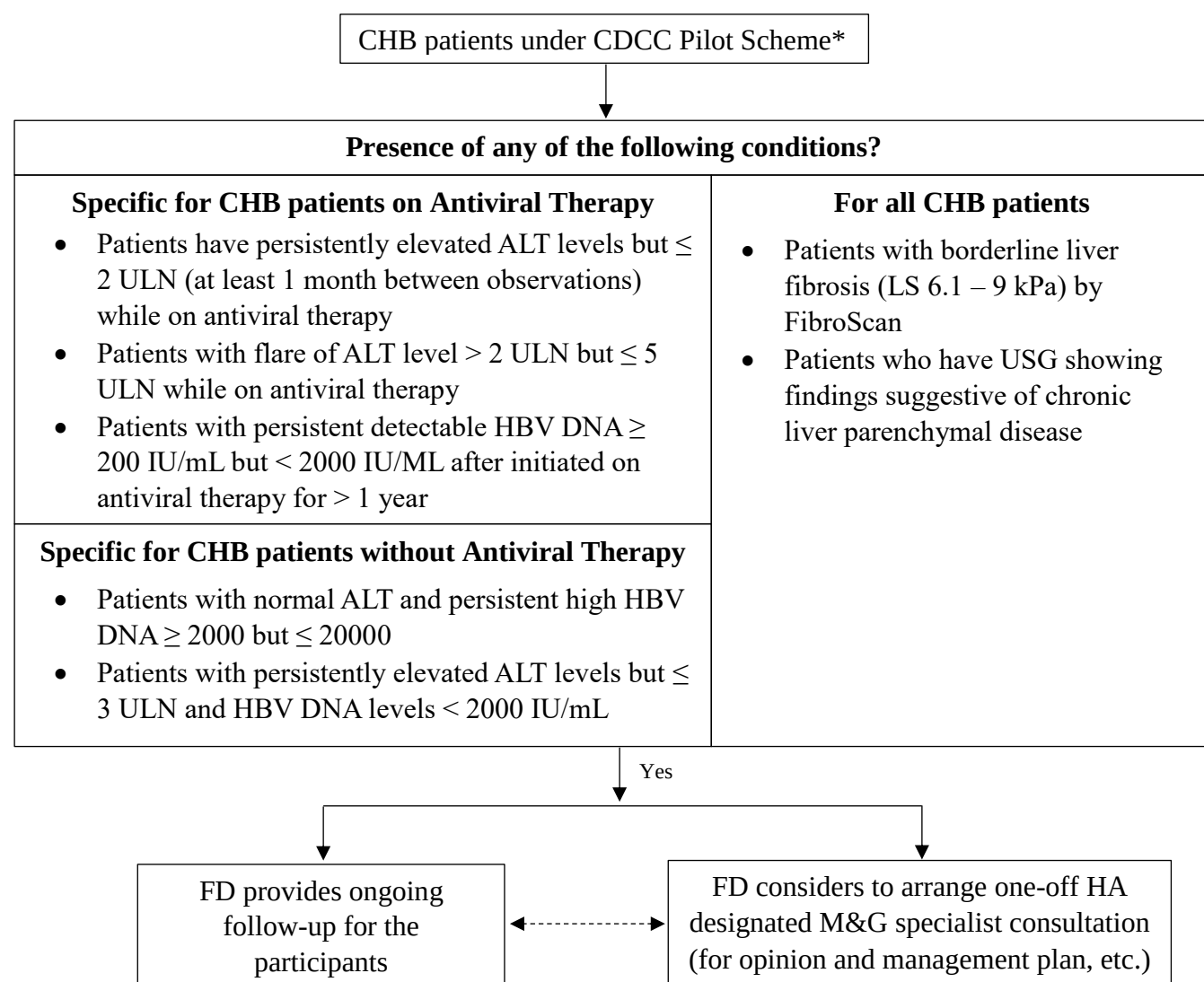
Note:

- More frequent monitoring may be required at treatment initiation, in those with abnormal ALT and/or HBV DNA >2000 IU/ml but not yet on treatment, or where treatment adherence is a concern.
- 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.

Consider transient elastography* where available, as detailed in the Hong Kong Primary Healthcare Reference Framework – Management of Adults with Chronic Hepatitis B in Primary Care

* Non-subsidised item under CDCC Pilot Scheme

(3) Criteria for One-off Specialist Consultation under the CDCC Pilot Scheme (Hepatitis B Co-Care Scheme) for CHB patients



*If none of the conditions required for One-off Specialist Consultation under CDCC Pilot Scheme is present, but specialist consultation is nonetheless clinically indicated, FDs may make the necessary referral(s) to specialists for the Scheme Participant through conventional referral path.

(4) Exclusion Criteria for One-off Specialist Consultation under the CDCC Pilot Scheme (Hepatitis B Co-Care Scheme) for CHB Patients

(Scheme Participants fulfilling the exclusion criteria should be referred to specialists through conventional referral path for further evaluation and management)

Specific for CHB patients on Antiviral Therapy

- Patients with ALT level > 5 ULN
- Patients have persistently elevated ALT levels (at least 1 month between observations) > 2 ULN and further investigations, assessment or treatment by physicians / hepatologists are indicated
- Patients with persistent detectable HBV DNA ≥ 2000 after initiated on antiviral therapy for > 1 year
- Patients are suspected to have treatment failure or drug resistance (e.g. rising HBV DNA > 1 log while on antiviral therapy)
- Patients have unexplained rising trend ALT despite low HBV DNA levels
- Patients have seroconversion of HBsAg from positive to negative while on antiviral therapy and are under consideration of stopping anti-viral treatment

Specific for CHB patients without Antiviral Therapy

- Patients are clinically indicated for antiviral therapy but the family doctors cannot provide antiviral therapy
- Patients have persistently elevated ALT levels > 3 ULN but HBV DNA levels < 2000 IU/mL
- Patients with normal ALT and persistent high HBV DNA > 20000

For all CHB patients

- Patients developed symptoms and signs of decompensated liver disease
- Patients with radiological (USG / CT / MRI) evidence of severe fibrosis or any severity of liver cirrhosis or probable advanced liver fibrosis / liver cirrhosis (LS > 9 kPa) by FibroScan
- Patients with radiologically (USG / CT / MRI) suspected or confirmed HCC or other hepatobiliary malignant lesions
- Patients are found to have co-infection with HCV or HIV
- Patients have concurrent serious chronic liver disease such as autoimmune hepatitis, primary biliary cholangitis
- Patients on immunosuppressive treatment
- Patients with elevated AFP or PIVKA-II
- Patients are pregnant
- Patients with other abnormal liver function tests which require further assessment by medical specialists

Annex III: Investigation Services under Chronic Disease Co-Care Pilot Scheme (Hepatitis B Co-Care Scheme)

Investigation Services

(I) Laboratory Items

Programme Package - Screening	
Hepatitis B Screening (1st blood-taking) Hepatitis B Surface Antigen (HBsAg)	Hepatitis B Screening (2nd blood-taking) HBsAg
Programme Package - Management	
<u>Chronic Hepatitis B (CHB) Initial Assessment</u> - Complete Blood Count (CBC) - Liver Function Test (LFT) with Aspartate Aminotransferase (AST) & Gamma-Glutamyl Transferase (GGT) - Renal Function Test (RFT) - Hepatitis B e Antigen (HBeAg) - Hepatitis B e Antibody (Anti-HBe) - Hepatitis B Virus DNA (HBV DNA) - Alpha Fetoprotein (AFP) - AST-to-platelet ratio index (APRI)	
<u>Not on antiviral (at 6 month interval)</u> - LFT - AFP - HBV DNA if clinically indicated	<u>On antiviral (at 6 month interval)</u> - LFT - RFT - AFP - HBV DNA if clinically indicated
<u>Not on antiviral, if HBeAg +ve (at 12 month interval)</u> - LFT - AFP - HBV DNA - HBeAg - Anti-HBe - APRI	<u>Not on antiviral, if HBeAg -ve (at 12 month interval)</u> - LFT - AFP - HBV DNA - HBsAg - APRI
<u>On antiviral, if HBeAg +ve (at 12 month interval)</u> - LFT - RFT - AFP - HBeAg - Anti-HBe	<u>On antiviral, if HBeAg -ve (at 12 month interval)</u> - LFT - RFT - AFP - HBV DNA - HBsAg

• HBV DNA • APRI	• APRI
Individual Laboratory Items	
Haematology	
CBC CBC (with differential count) Erythrocyte Sedimentation Rate (ESR)	
Chemical Pathology	
HbA1c Glucose, Fasting / FPG Oral Glucose Tolerance Test (OGTT) 2 hours Full Lipid Profile RFT RFT with eGFR LFT LFT with AST and GGT APRI	Urate Thyroid Stimulating Hormone (TSH) Free Thyroxine (fT4) Calcium (Ca), Phosphate (PO4) AFP Urine Protein / Creatinine Ratio (PCR) Spot Urine Albumin: Creatinine Ratio (ACR) Protein Induced by Vitamin K Absence-II (PIVKA-II)
Microbiology	
HBV DNA HBsAg HBeAg Anti-HBe Hepatitis B Surface Antibody (Anti-HBs) Hepatitis B Core Antibody (Anti-HBc)	MSU: Routine / Microscopy MSU: Microscopy & Bacterial Culture Sputum: Microscopy & Bacterial Culture Sputum: Acid Fast Bacilli (Smear) Sputum: Acid Fast Bacilli (Culture)

(II) Imaging Items

- **Liver Ultrasonography Service (USG liver)**