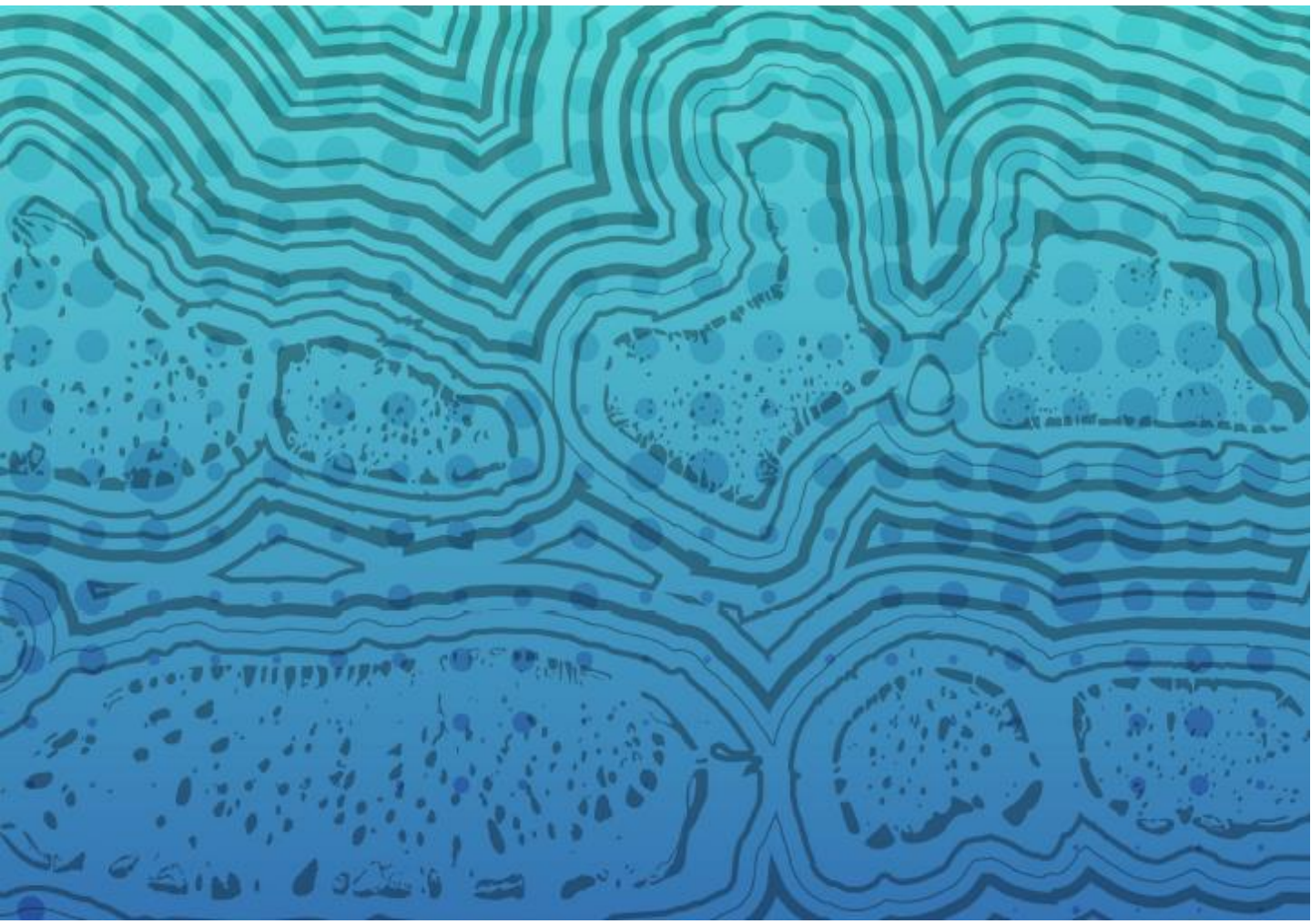
NATIONAL GUIDELINE FOR THE
DIAGNOSIS AND MANAGEMENT OF
HEPATITIS B



Ministry of Health
Republic of Maldives

Health Protection Agency

World Health Organization
Maldives

National Guideline | 2021

Contents

Abbreviations

AASLD	American Association for the study of Liver disease
ACIP	Advisory Committee on Immunization Practices
ADV	Adevfovir dipivoxil
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti-HBc	Antibody to hepatitis B core antigen
Anti-Hbe	Antibody to hepatitis B envelope antigen
Anti-HBs	Antibody to hepatitis B surface antigen
APRI	Aspartate aminotransferase-to-platelet ratio index
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
cccDNA	Covalently closed circular DNA
CDC	Centers for disease control
CHB	Chronic hepatitis B
DAA	Direct-acting antiviral
DNA	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ETV	Fibrosis-4 score
FIB-4	Gamma-glutamyl transferase
GGT	Hepatitis B surface antigen
HBeAg	Hepatitis B envelop antigen
HBIG	Hepatitis B immune globulin

Abbreviations

HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Health care personnel
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HIV	Human Immunodeficiency virus
INR	International normalized ratio
LAM	Lamivudine
MSM	Men who have sex with men
NA	Nucleos(t)ide analogue
PegINF-a	Pegylated interferon alpha
PWID	Persons who inject drugs
RDT	Rapid diagnostic test
STI	Sexually transmitted infection
TAF	Tenofovir alafenamide
TDF	Tenofovir disproxil fumarate
TDV	Telbivudine
WHO	World Health Organization

1 Introduction

Worldwide, viral hepatitis caused 1.34 million deaths in 2015, which was comparable to that of HIV, tuberculosis and Malaria (1). Most viral hepatitis deaths were due to chronic liver disease and primary liver cancer. WHO estimated that in 2015, worldwide, 257 million persons, or 3.5% of the population, were living with chronic HBV infection. 2.7 million persons were coinfected with HBV and HIV. In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis, which proposes to eliminate viral hepatitis as a public health threat by 2030 (1).

Hepatitis B immunization including the birth dose was introduced in Maldives in the year 1993, and at present all districts in Maldives have more than 95% childhood hepatitis B immunization coverage. Screening for HIV and viral hepatitis is mandatory for all pregnant women and for all foreigners during the pre-employment medical evaluation. A sizeable number of high-risk groups exist in the country as revealed by the 2008 behavioral and biological survey on HIV/AIDs (2). Hepatitis B and Hepatitis C has been detected in these risk groups. Unsafe practices among these risk groups poses risks of wider transmission.

At present, rapid diagnostic test for HBsAg is available in the majority of the islands. Laboratory based immunoassay for HBsAg testing is available in tertiary hospitals in the capital and some regional hospitals. Additional hepatitis B serology such as HBe antigen testing, anti- HBe, anti- HBs and anti- HBc is available only in the tertiary centres in the capital. Hepatitis B DNA viral load testing is going to commence soon at Indira Gandhi Memorial Hospital, the main tertiary hospital in Maldives. Ultrasound scan facilities are available only in regional hospitals and some atoll hospitals in addition to hospitals in the capital.

In line with the viral hepatitis elimination target, the WHO country office provided technical support to the HPA, Ministry of Health to develop national guidelines for the diagnosis and management of Hepatitis B and Hepatitis C and a national action plan for viral hepatitis. Taking in to consideration the local context and challenges to health care delivery, the guideline development group drafted a practical, feasible and evidence-based treatment approach based on the most current global guidelines for management of Hepatitis B such as WHO, AASLD and EASL guidelines.

The guideline was reviewed by a panel of internal reviewers and the final draft was reviewed by WHO SEARO technical unit.

With the establishment of the national treatment guideline, first line anti-viral drugs for treatment of hepatitis B will be made available in the country.

This document will be periodically updated as per new evidence and updates in the international guidelines on management of hepatitis B.

2 Background

2.1 Epidemiology and Burden

Hepatitis B virus (HBV) infection is one of the leading public health problems globally. HBV related morbidity and mortality remains one of the challenges we face in our daily clinical practice. It is estimated that about one –third of the global population is infected with HBV and 5 % of them become chronic carriers (3). One-fourth of these chronic carriers ultimately develop disease complications like cirrhosis and hepatocellular carcinoma (HCC) (3). HBV related mortality rate has increased over the years, with an estimated increase of 33% from 1990 to 2013 (4).

Viral hepatitis screening data from IGMH, the main tertiary referral center in Maldives, for the period March 2017 to August 2019 showed that a total of 910 out of 43,773 Maldivian patients screened (2%) were positive for HBV infection (HbsAg positive). Out of a total of 466 children below the age of 5 years tested during this period, 1 child (0.2%) was positive for HBV infection. Out of 9862 individuals of age group 5 to 26 years of age tested, 7 were HbsAg positive (0.07%). The rest of the positive cases (99% of the total HBsAg positive results) were in individuals older than 26 years reflecting persons born prior to introduction of the childhood Hepatitis B immunization in Maldives. In the 2008 behavioral and biological survey (BBS) on HIV/AIDS, Hepatitis B was found in 6% of the MSM in Addu and 1% of MSM in Male', 4% of the seafarers, 2% among resort workers and 0.8% among IDUs in Addu (2).

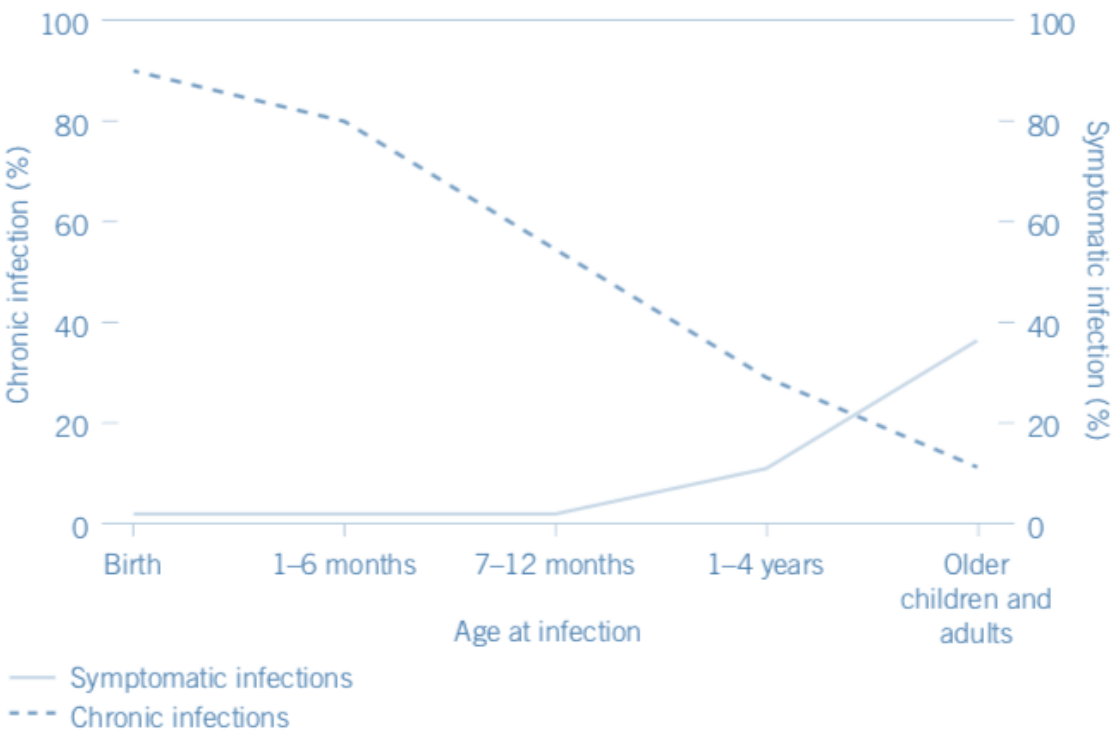
2.2 Virology

HBV is a double-stranded DNA virus belonging to the family of hepadnaviruses. It is primarily a hepatotropic virus, which replicates and assembles exclusively in the hepatocytes. The injury that occurs to the liver are through the immune-mediated damage to the infected hepatocytes. HBV is also an oncogenic virus that leads to development of HCC. At least ten genotypes (A to J) and several sub-genotypes have been identified on the basis of the differences in their genomic sequences (5). HBV vaccine and anti-viral therapy are effective against all HBV genotypes.

2.3 Transmission

HBV is transmitted by exposure to infected blood and various body fluids (6). Mode of transmission of HBV varies depending on the endemicity of the region. Perinatal transmission is the predominant mode in high- prevalence areas, while horizontal transmission accounts predominantly for intermediate prevalence areas and intravenous drug use and unprotected sexual intercourse are the major routes transmission in the low-prevalence areas (7-9).

Acute HBV infection is usually a self-limited disease, with spontaneous recovery in more than 95% of immunocompetent adults, with a very low mortality rate (11). Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg) for more than 6 months in the blood. Age of infection is the primary determinant of chronicity of infection. The risk of chronic HBV may be as high as 90% in infants born to HBeAg positive mothers to as low as less than 5% in people who get infected as adults (11). (Figure 1)



Source: Guidelines for the prevention, care and treatment of persons with hepatitis B infection. Geneva: WHO; 2015 (11).

▲ Figure 1: Natural History of Hepatitis B infection

Chronic HBV is a complex and dynamic disease with various phases that progress non-linearly. Patients may transition from different phases of the disease depending on the level of ALT, HBV DNA and HBV antigens. Different phases may not always be sequential and are varied in their duration.

2.4 Phases of chronic hepatitis B

Phase 1: HBeAg-positive chronic HBV infection, previously termed ''immune tolerant'' phase

Characterized by detectable serum HBeAg, very high levels of HBV DNA (usually more than 1,000,000 IU/mL) and ALT persistently within the normal range or minimally raised. In the liver, there is minimal inflammation or no fibrosis. More common and prolonged in Children and young adults infected perinatally or early childhood. The rate of spontaneous HBeAg loss is very low and patients have higher potential for HBV transmission.

Phase 2: HBeAg-positive chronic hepatitis B (immune-active phase)

This phase is characterized by detectable serum HBeAg, high levels of HBV DNA and raised ALT. It may show moderate or severe liver necroinflammation and with or without fibrosis. More frequently and rapidly reached in patients who are infected during adulthood. Majority of patients become HBeAg seroconverted and reach HBeAg-negative infection phase with HBV DNA suppression.

Phase 3: HBeAg-negative chronic HBV infection (Immune control phase, inactive carrier)

This phase is characterized by negative HBeAg and presence of antibodies to HBeAg (Anti-HBe) undetectable or low HBV DNA levels (< 2,000 IU/mL) with normal ALT. Liver biopsy shows absence of significant necroinflammation and low fibrosis. The risk of progression to cirrhosis and HCC is usually low if patient remain in this phase.

Phase 4: HBeAg-negative chronic hepatitis B

This phase is characterized by negative HBeAg and presence of anti-HBe, fluctuating moderate to high HBV DNA levels and fluctuating or persistently raised ALT. Liver biopsy shows necroinflammation and fibrosis with more rapid progression to cirrhosis and low rate of spontaneous remission.

Phase 5: HBsAg-negative phase

This phase is characterized by negative HBsAg, positive antibodies to HBcAg (Anti-HBc) with or without detectable anti-HBs. Also known as occult HBV infection. This phase is characterized by normal ALT with usually undetectable HBV DNA levels. Loss of HBsAg prior to development of cirrhosis is associated with low risk of cirrhosis and HCC. However, if the loss of HBsAg occurs after development of cirrhosis, the patient is at risk of HCC. Patients in this phase are at risk of reactivation with immunosuppression.

Phases of Chronic Hepatitis B		
Phases	**HBeAg/ serological status**	**Characteristics**
PHASE 1 (HBeAg-positive chronic HBV infection)	HBeAg positive	• Very high levels of HBV DNA; > 1,000,000 IU/ml • ALT: normal, • Liver histology: minimal inflammation or no fibrosis
PHASE 2 (HBeAg-positive chronic hepatitis B)	HBeAg positive	• High levels of HBV DNA • ALT: raised • Liver histology: moderate or severe liver necroinflammation and with or without fibrosis
PHASE 3 (HBeAg-negative chronic HBV infection)	HBeAg- negative, anti-Hbe positive,	• Undetectable or low HBV DNA; < 2,000 IU/mL • ALT: normal • Liver histology: absence of significant necroinflammation and low fibrosis
PHASE 4 (HBeAg-negative chornic hepatitis B)	HbeAg-negative, anti-HBe positive.	• Fluctuating moderate to high HBV DNA levels; > 2,000IU/mL • ALT: fluctuating or persistently raised • Liver histology: necroinflammation and fibrosis
PHASE 5 (HBsAg-negative phase)	Negative HBsAg with or without detectable anti-HBs and positive antibodies to HBcAg,	• HBV DNA: usually undetectable serum HBV DNA • ALT: Normal

▲ Table 1: Phases of chronic hepatitis B

3 Screening and Assessment

3.1 Screening

Hepatitis B screening is recommended for the following groups of people. (Table 2)

Screening Population	Screening Tests
Persons with history of injecting drugs, tattooing Men who have sex with men (MSM) Needle-sharing & sexual contacts of HBsAg-positive persons Persons with multiple sexual partners Any person seeking evaluation for sexually transmitted infections (STI) Staff and inmates of correctional facilities Family and close household contacts of HBsAg-positive persons Health care personnel Residents & staff of facilities for developmentally disabled persons	HBsAg with Anti-Hbs (where available)
All pregnant women during the first antenatal visit Pre-employment medical evaluation of all expatriate workers Persons diagnosed as Chronic Kidney disease (stage IV and V) [12] Public safety workers such as police, fire fighters Unvaccinated persons with diabetes Persons with family history of Hepatocellular carcinoma HBV screening prior to surgical procedures Persons without any high risk features who voluntarily request screening	HBsAg only
Persons planned to undergo anti-cancer or other immunosuppressive therapies Persons with HIV/AIDS Persons diagnosed with Hepatitis C (prior to starting DAAs) Donors of blood, plasma, organs and tissues Persons being evaluated for chronic liver disease Persons on renal dialysis	HBsAg with Anti-HBs and Anti-HBc

3.1.1 Screening tests

Hepatitis B screening should be performed with a quality assured serological diagnostic test i.e. either laboratory-based immunoassay [Enzyme immunoassay or Chemiluminescence immunoassay] or rapid diagnostic test (RDT) to detect HBsAg. A positive HBsAg result is compatible with HBV infection. A positive screening test should be confirmed with a laboratory based HBsAg **confirmatory** immunoassay. All persons with a positive HBsAg confirmatory immunoassay should be notified to the Health Protection Agency and should undergo further evaluation (see section 3.2).

Where available, Anti-HBs should be sent in addition, for persons who have a high likelihood of previous exposure. See table 3 for interpretation of screening tests.

Anti-HBc is done in addition, in patients who are HIV positive or on renal dialysis as they may have negative Anti-Hbs despite previous exposure. Anti-HBc should also be done in patients who are planned for anti-cancer or other immunosuppressive therapies and HCV patients who are planned for treatment with directly acting anti-viral drugs (DAAs) as such treatment may lead to reactivation of previously resolved HBV infection. Donor screening prior to blood or organ donation should also include Anti- HBc in order to rule out possibility of occult HBV infection.

All persons who are HbsAg negative and non-immune should be recommended for hepatitis B immunization.

3.1.2 Interpretation of screening test results

HBsAg	Anti-HBc	Anti-HBs	Interpretation	Management	Vaccinate?
+	+	-	Chronic hepatitis B	Evaluation for chronic HBV infection	No
-	+	+	Past HBV infection, resolved	No further testing	No
-	+	-	Past HBV infection, resolved or false positive	No further testing	No
-	-	+	Immune due to prior vaccination	No further testing	No
-	-	-	Uninfected & not immune	No further testing	Yes

▲ Table 3: Interpretation of Hepatitis B screening test

3.2 Evaluation of patients with HBV infection

If patient is found to be HBsAg positive, detailed history taking, clinical examination and investigations should be done to determine the management of the patient. If the required investigations are not available at the island health facility, patient should be referred to atoll hospital/regional hospital or tertiary center where such evaluation is possible.

3.2.1 History and clinical examination

Patients with acute Hepatitis B present with malaise, nausea, vomiting and a serum sickness-like prodrome of fever, arthralgia or arthritis and rash (maculopapular or urticarial). These features usually abate before the manifestations of liver disease and peak serum aminotransferase elevations are observed. Icterus is found in only about 30% of patients (10). Clinical symptoms disappear after 1-3 months. Acute liver failure is rare, but usually present within 4 weeks of onset of symptoms and may present with coagulopathy, encephalopathy and multiorgan dysfunction, and is associated with high mortality.

In patients with chronic HBV infection, history of acute or symptomatic hepatitis is often lacking. Patients may even remain asymptomatic during periods of reactivated hepatitis. In some cases, particularly when superimposed on cirrhosis, reactivation of HBV infection may be associated with frank jaundice and signs of liver failure.

It is also important to take history regarding the mode of transmission and weather the patient has any high-risk factors mentioned in section 3.1 (Screening). Family history of chronic HBV infection and presence of HCC should also be noted.

Physical examination may be normal in most of the cases. However, hepatosplenomegaly may be seen in some patients. In decompensated cirrhosis, spider telangiectasias, jaundice, ascites, and peripheral edema are often present. (Table 4)

Extrahepatic manifestations are rare but can occur with acute or, more commonly with chronic HBV infection. It is important to recognize manifestations as they may occur without clinically apparent liver disease and can be mistaken for independent disease processes in other organ systems. Extrahepatic manifestations include arthritis-dermatitis, polyarteritis nodosa, glomerulonephritis and cryoglobulinemia.

Skin, Nails and Hands

- Spider naevi – small telangiectatic superficial blood vessels with a central feeding vessel
- Clubbing of the hands
- Leuconychia – expansion of the paler half-moon at the base of the nail
- Palmar erythema – seen on the thenar and hypothenar eminence – often with blotchy appearance
- Bruising
- Dupuytren's contracture
- Scratch marks – particularly in cholestatic liver disease

Endocrine

- Gynaecomastia
- Testicular atrophy
- Loss of axillary and pubic hair

Others

- Parotid swelling – particularly in alcohol-related liver disease
- Hepatic foetor – characteristic sweet-smelling breath
- Hepatic flap – a sign of encephalopathy and advanced disease

▲Table 4: Peripheral stigma of chronic liver disease.

3.2.2 Investigations for the initial workup of HBV infection

Investigations comprise of serological markers of HBV infection (HBeAg, anti-HBe), markers to determine liver inflammation (AST, ALT), Quantification of HBV DNA levels and assessment of liver fibrosis (invasive or non-invasive tests) and other routine investigations.

3.2.2.1 Serological Tests

HBeAg: HBeAg positivity in a patient with chronic HBV infection indicates presence of active HBV replication and high infectivity.
Anti-HBe: HBeAg seroconversion (defined as HBeAg-negative and anti-HBe-positive) indicates decline in HBV replication, low infectivity and is associated with normalization of aminotransferases.

Some HBeAg-negative patients may still have active viral DNA replication due to the presence of HBV variants or pre-core mutants.

Anti HBc (IgM/IgG): Anti-HBc testing can be done in some circumstances such as suspected acute HBV infection, exacerbations of chronic hepatitis B (hepatitis B flair) or reactivation of chronic hepatitis B. Anti HBc IgM is usually present in acute HBV infection, flair or reactivation. Anti-HBc IgG indicates prior exposure to HBV.

3.2.2.2 Markers of liver inflammation

An upper limit of normal (ULN) of 40 U/L for ALT should be used for males and females (14).

AST and ALT can be used to determine the presence of liver inflammation. ALT is more liver specific and is usually higher than AST levels. However, with the progression of disease the AST/ALT ratio may be reversed.

ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Persistently abnormal may be defined as three ALT determinations above the upper limit of normal, made at unspecified intervals during a 6–12-month period or predefined intervals during a 12-month period (11). Persistent elevation of ALT should also prompt an evaluation for causes other than HBV infection.

3.2.2.3 Viral load quantification

Serum HBV DNA concentrations correlate with disease activity and are used to differentiate HBeAg-negative chronic hepatitis B from HBeAg negative chronic HBV infection (inactive chronic carriers). This level can also detect the response to antiviral therapy and emergence of antiviral resistance.

Patients with inactive disease generally have HBV-DNA levels <2,000 IU/mL. HBeAg-negative chronic hepatitis B (HBeAg negative immune-active chronic hepatitis B) usually have HBV DNA levels in between 2000 to 20,000 IU/mL. Patients with HBeAg-positive chronic hepatitis B (HBeAg-positive immune-active chronic hepatitis B) generally have HBV DNA levels > 20,000 IU/mL.

3.2.2.4 Assessment of liver fibrosis

Liver Biopsy is the gold standard to ascertain the degree of necroinflammation and fibrosis, and to help guide the decisions to treat. Table 5 shows the METAVIR liver-biopsy scoring system to determine the level of fibrosis. However, as liver biopsy is invasive, associated with risks of complications and due to unavailability, non-invasive tests (NITs) are recommended to determine liver fibrosis in patients with chronic HBV infection.

METAVIR STAGE	F0	F1	F2	F3	F4
Definition	No Fibrosis	Portal fibrosis without septa	Portal fibrosis few thin septa	Numerous septa without cirrhosis	Cirrhosis

▲ Table 5: METAVIR liver-biopsy scoring system

There are numerous NITs for liver fibrosis that have been validated in adults. These include tests that uses blood and serum markers for fibrosis such as APRI, FIB-4 scores and FibroTest (commercially available blood markers).

Transient elastography (FibroScan) is an ultrasound based technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver.

APRI Score is easy to calculate using readily available laboratory investigations. Using the formula below APRI score can be calculated easily.

$$\text{APRI} = \frac{\dfrac{\text{AST level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9 / \text{L})} \times 100$$

There are no validated exact cut-offs for specific stages of fibrosis with FibroScan. Table 6 shows the most commonly used cut-offs for F4 and ≥ F2 stages of fibrosis in CHB.

	APRI (Low cut-off)	APRI (High cut-off)	Transient Elastography (FibroScan)
Cirrhosis (METAVIR F4)	1.0	2.0	> 11-14 kPa
Significant Fibrosis (METAVIR ≥ F2)	0.5	1.5	> 7 – 8.5 kPa

▲ Table 6: Commonly used cut-off values for detection of significant fibrosis and cirrhosis

FibroScan is the recommended NIT where available to assess the degree of liver fibrosis. However, in places where FibroScan is not available APRI should be used.

APRI score > 2 or liver stiffness mean cut-off of 12.5 kPa (on FibroScan) can be used to diagnose cirrhosis (11).

APRI score > 1.5 or liver stiffness of > 7 kPa (on FibroScan) can be used to diagnose significant fibrosis (11).

For diagnosis of cirrhosis, Fibroscan has a better sensitivity (86%) than the APRI low or high cut-off (65% and 35%, respectively). FibroScan has similar specificity (87%) to the APRI high cut-off (89%). For diagnosis of fibrosis stage ≥ F2, sensitivities of APRI (low cut-off) and FibroScan was 78% and 76% respectively, while specificities of APRI (low cut-off), APRI (high cut-off) and FIbroScan were 60%, 92% and 82%, respectively (11).

3.2.2.5 Other tests for evaluation of patients newly diagnosed with HBV infection

Complete blood count (CBC)

Prothrombin time / International normalized ratio (PT/INR)

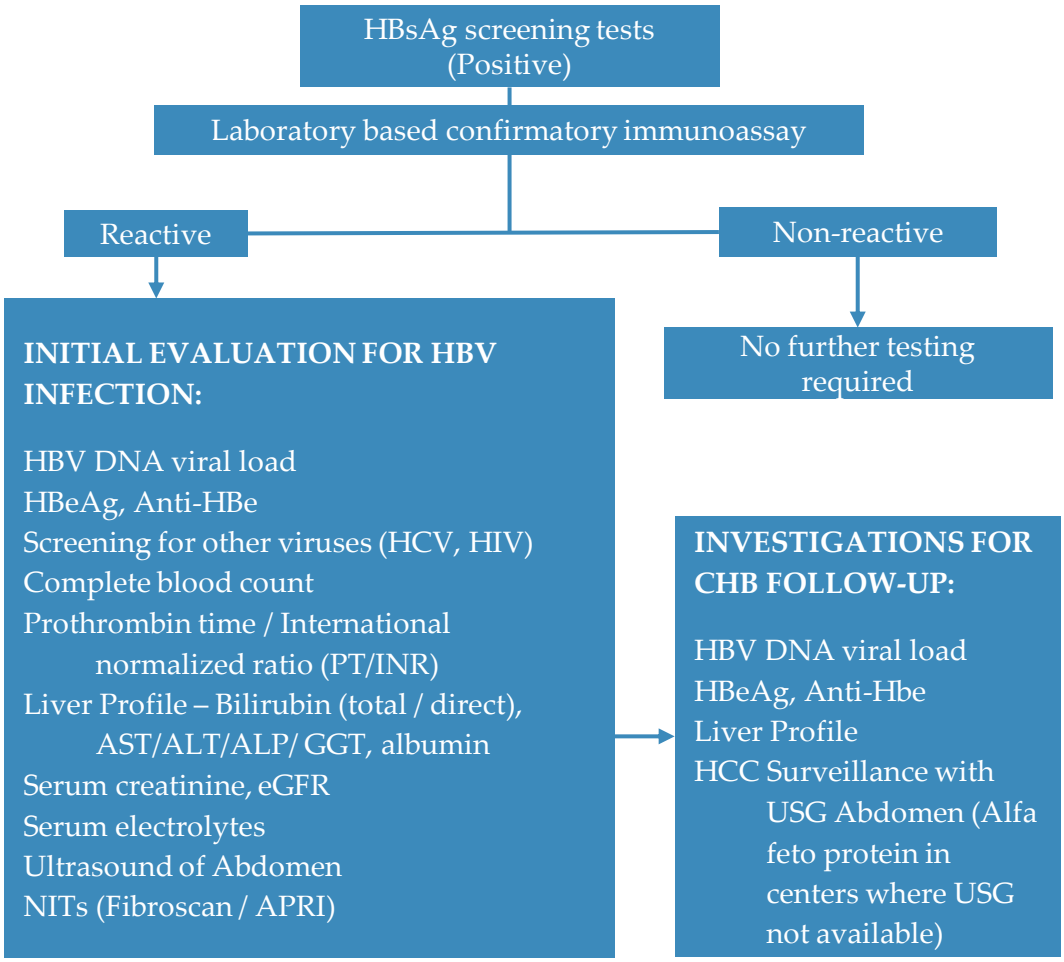
Liver Profile – Bilirubin (total /direct), AST/ALT/ALP/ GGT, serum albumin

Renal function tests – Serum creatinine, eGFR

Serum electrolytes

Screening for other viruses (HCV and HIV in all cases)

Ultrasound of abdomen



NOTE: If the required investigations are not available at the island health facility, patient should be referred to atoll hospital/regional hospital or tertiary center where such evaluation is possible.

▲ Figure 2: Algorithm for investigating patients with suspected HBV infection

4 Treatment

The main goal of therapy for patients with chronic hepatitis B (CHB) is to improve survival and quality of life by preventing disease progression, and consequently development of HCC.

Anti-viral treatment with nucleos(t)ide analogues (NA)s suppresses viral replication with reduction in liver cell inflammation and leads to normalization of ALT levels. Inhibition of viral replication has been shown to achieve regression of fibrosis and cirrhosis and reduce the risk of development of HCC (15).

Although NAs are potent inhibitors of HBV DNA replication, they do not result in cure, because NA therapy does not eliminate the replicative template cccDNA in the nucleus.

HBsAg loss is considered to be the optimal goal of antiviral therapy, and a marker of sustained treatment response in both HBe-Ag-positive and HBe-Ag-negative persons. However, it occurs only in a minority of HBe-Ag- positive patients (10-15% after 5 years) and rarely in those who are HBe-Ag negative. Treatment induced HBe-Ag loss and seroconversion to Anti-HBe achieves a partial immune control leading to a low replicative phase. After stopping treatment, this response maybe sustained or patients may develop HBeAg sero reversion or develop HBeAg negative CHB.

In treatment of CHB, antiviral therapy is generally given to the active phases of CHB where the risks of disease progression (fibrosis) is greatest.

The indications for treatment in CHB are based mainly on a combination of the following factors:

- Serum ALT levels
- Serum HBV DNA levels
- HBe-Ag status
- Severity of liver disease

4.1 Which patients to treat or not to treat

4.1.1 Indications of treatment

The following patients should be treated:

All adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis should be treated, regardless of ALT levels, HBe-Ag status or HBV DNA levels (NIT such as APRI score or Fibroscan can be used to assess presence of liver cirrhosis) (11, 14 16).

HBe-Ag positive chronic hepatitis B (HBV DNA above 20,000 IU/ml AND either ALT ≥ 2 times ULN, OR moderate necro-inflammation/fibrosis on NIT or liver biopsy) (11, 14, 16).

HBe-Ag negative chronic hepatitis B (HBV DNA above 2,000 IU/ml AND either ALT ≥ 2 times ULN, OR moderate necro-inflammation/fibrosis on NIT or liver biopsy) (14, 16).

4.1.2 Patients not requiring treatment but to be monitored

The following patients should be not be treated but should be monitored:

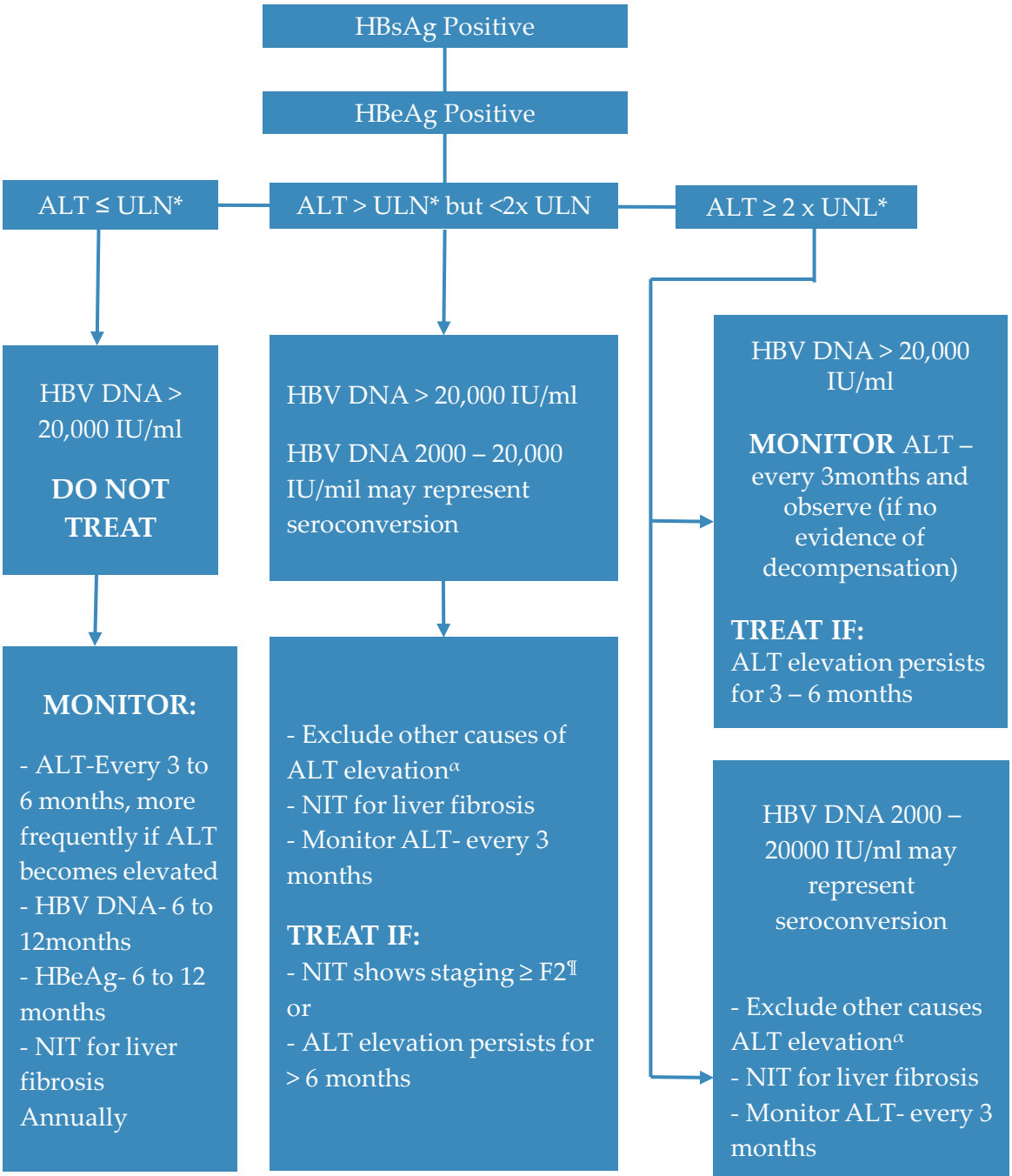
Antiviral therapy is not recommended and can be deferred in persons without clinical evidence of cirrhosis (or evidence of cirrhosis based on NIT), and with persistently normal ALT levels and low levels of HBV DNA replication (HBV DNA <2000 IU/mL), regardless of HBeAg status or age. (11, 14, 16).

Persons without cirrhosis aged 30 years or less, with HBV DNA levels >20 000 IU/ mL but persistently normal ALT (11, 14, 16).

Continued monitoring is necessary in all persons with chronic HBV infection, but in particular those who do not currently fulfill the indications for treatment, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease. (Figure 3 and Figure 4)

4.1.3 Counselling prior to starting treatment

Patient should be assessed regarding history of alcohol intake and advised on lifestyle modification including alcohol reduction, diet and physical activity. Patient should be counselled about indications for treatment, including benefits and adverse effects of drugs, the need for regular follow up and monitoring and the need for strict adherence to treatment to minimize the chances of developing drug resistance.

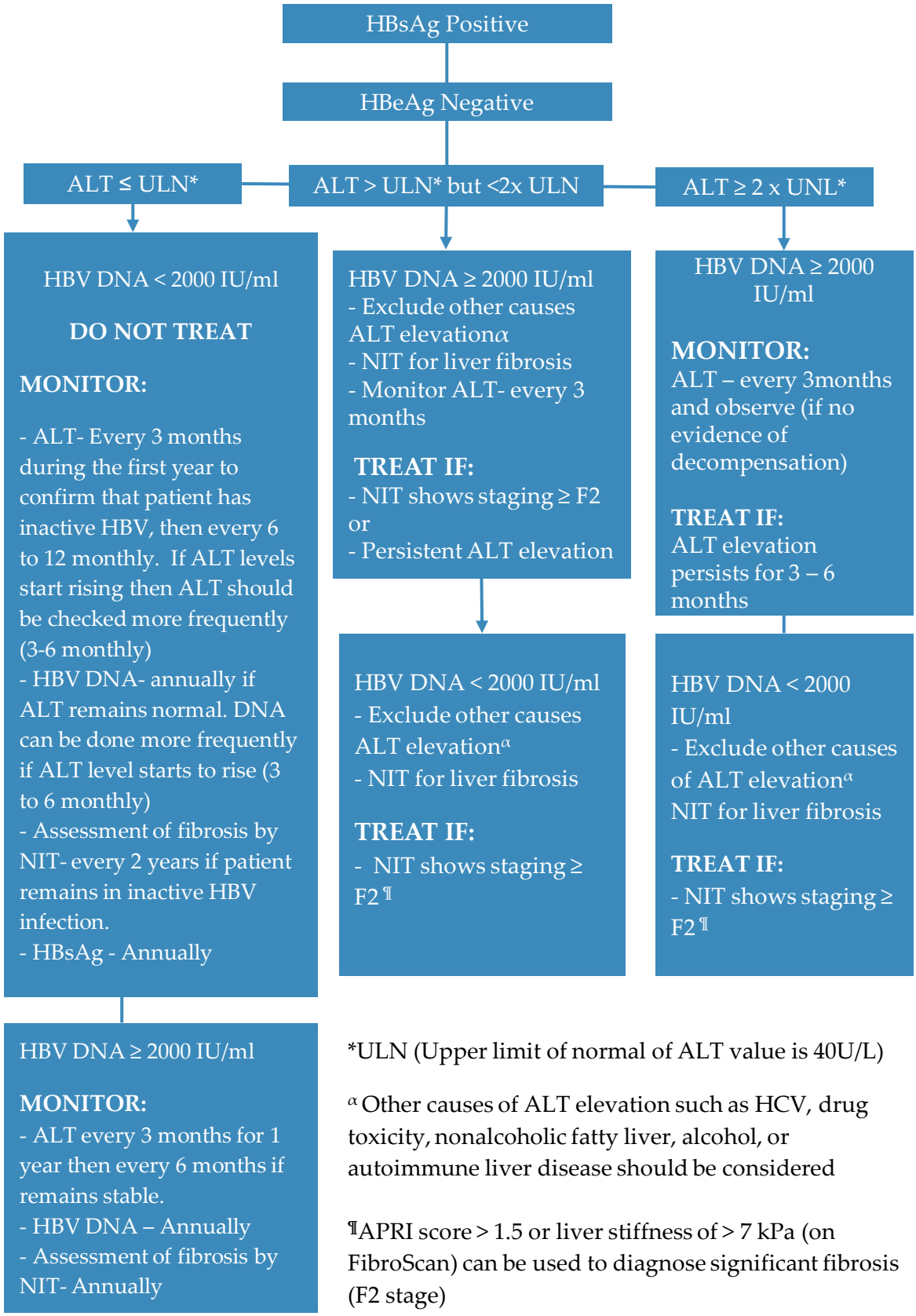


*ULN (Upper limit of normal of ALT value is 40U/L)

α Other causes of ALT elevation such as HCV, drug toxicity, non-alcoholic fatty liver, alcohol, or autoimmune liver disease should be considered

¶APRI score > 1.5 or liver stiffness of > 7 kPa (on FibroScan) can be used to diagnose significant fibrosis (F2 stage)

▲ **Figure 3: Algorithm for management of HBsAg-positive persons without cirrhosis who are HBeAg-positive (Adapted from AASLD 2018 Hepatitis B Guidance - Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B)**



*ULN (Upper limit of normal of ALT value is 40U/L)

α Other causes of ALT elevation such as HCV, drug toxicity, nonalcoholic fatty liver, alcohol, or autoimmune liver disease should be considered

¶APRI score > 1.5 or liver stiffness of > 7 kPa (on FibroScan) can be used to diagnose significant fibrosis (F2 stage)

▲ **Figure 4: Algorithm for management of HBsAg-positive persons without cirrhosis who are HBeAg-negative** ***(Adapted from AASLD 2018 Hepatitis B Guidance - Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B)***

4.2 First Line Antiviral therapies for Chronic Hepatitis B

4.2.1 First Line Antiviral therapies for Chronic Hepatitis B:

In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended (11, 14, 16)**.**

Entecavir is recommended in children aged 2–11 years (11, 14, 16)**.**

NAs with a low barrier to resistance such as Lamivudine, Telbivudine and Adefovir are not recommended (11, 14, 16)**.**

Currently, there are two main classes of antiviral drugs for treatment of chronic hepatitis B: Nucleos(t)ide analogues (NAs) and pegylated interferon alpha (PegIFN-a). NAs recommended for use in CHB are those with a high barrier to viral resistance such as Entecavir (ETV), Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide Fumarate (TAF).

TAF is a nucleotide analogue and a pro-drug of TDF which is more stable than TDF in plasma and delivers the active metabolite to hepatocytes more efficiently, allowing a lower dose to be used with similar antiviral activity, less systemic exposure, and thus decreased renal and bone toxicity (16).

The main advantages of PegIFN-a over NAs are the absence of resistance and achievement of higher rates of HBeAg and HBsAg loss and finite duration of treatment. However, the disadvantages of PegIFN-a are low efficacy (less than 50% of persons treated will respond), high cost, need to administer by injection, frequent adverse effects and several contraindications.

The main advantages of treatment with a potent NA with high barrier to resistance is its high long-term antiviral efficacy leading to undetectable HBV DNA levels in the vast majority of patients who are complaint to treatment, its favorable safety profile and cheaper cost. NAs are also appropriate for use in decompensated liver cirrhosis. Table 7 shows the doses and adverse effects of the recommended first line NAs.

Among the preferred NA therapies ETV, TDF and TAF have very low rates of drug resistance in NA naive patients. Entecavir has a high rate of resistance in patients who have developed resistance to Lamivudine due to prior exposure and should not be used in patients with Lamivudine resistance. TDF, and TAF have very low rates of drug resistance even in NA-experienced patients.

Drug	Dose in Adults	Use in children	Pregnancy category	Potential side effects
Tenofovir disproxil fumarate (TDF)	300 mg once daily	≥ 12 years	B	Nephropathy, Fanconi syndrome, Osteomalacia, lactic acidosis in decompensated liver disease
Tenofovir Alafenamide (TAF)	25 mg daily	-	Insufficient data	Lactic acidosis (in decompensated liver disease)
Entecavir	0.5mg once daily. 1 mg daily in decompensated liver disease	≥2 years dose: weight-based to 10-30 kg; above 30 kg: 0.5 mg daily	C	Lactic acidosis (in decompensated liver disease)

▲ Table 7: Recommended NAs for treatment of CHB, doses and adverse effects in adults

Acute renal failure, hypophosphatemia and cases of Fanconi syndrome have been reported in TDF-treated persons. ETV or TAF may be used in preference to TDF for patients older than 60 years, CKD with eGFR <60 ml/min/1.73m2 or history of osteoporosis or fragility fractures (14).

Measurement of baseline renal function and assessment of baseline risk for renal dysfunction should be considered in all persons prior to starting antiviral therapy. Renal function should be monitored in all persons on long-term tenofovir or entecavir therapy and appropriate renal dose adjustments should be made (Table 8). In cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or entecavir (after considering any previous known drug resistance)

Drug	Recommended dose adjustment of NAs for renal function			
	CrCl (ml/min)			
	> 50	30- 49	10- 29	< 10, HD or CAPD
Tenofovir disproxil fumarate (TDF)	300 mg once daily	300 every 48 hours	300 mg every 72–96 hours	Every 7 days or 300 mg following completion of approximately every 12 hours of dialysis
Tenofovir Alafenamide (TAF)	No dosage adjustment is required in patients with eGFR ≥15 mL per minute, or in patients with eGFR <15 mL per minute who are on hemodialysis. Not recommended in patients with ESRD who are not on hemodialysis			
Entecavir	0.5 mg once daily	0.25 mg once daily OR 0.5 mg every 48 hours	0.15 mg once daily OR 0.5 mg every 72 hours	0.05 mg once daily OR 0.5 mg every 7 days
Entecavir (Decompensated liver disease)	1 mg once daily	0.5 mg once daily OR 1 mg every 48 hours	0.3 mg once daily OR 1 mg every 72 hours	0.1 mg once daily OR 1 mg every 7 days

Note: For Entecavir doses less than 0.5 mg, oral solution is recommended.

▲Table 8: Recommended dose adjustment of NAs for renal function

4.3 Treatment of patients with virological failure on NA therapy

Type of response	Definition
Virological response	During NA treatment, undetectable HBV DNA by a sensitive PCR assay
Primary nonresponse	Less than one $\log_{10}$ (10-fold) decrease of serum HBV DNA after 3 months of therapy.
Partial virological response	A decrease in HBV DNA of more than 1 $\log_{10}$ IU/ml (10-fold) but detectable HBV DNA after at least 12 months of therapy in compliant patients.
Virological breakthrough	Confirmed increase in HBV DNA level of more than 1 $\log_{10}$ IU/ml (10-fold) compared to the nadir (lowest value) HBV DNA level on-therapy
Biochemical response	Normalization of ALT levels based on the traditional ULN

▲Table 9: Definitions of types of response to treatment

- The most common reason for primary non response, partial response or virological breakthrough is poor compliance to treatment.
- Primary non-response is rare in persons initiating and adherent to entecavir or tenofovir treatment.
- Elevation in ALT level tends to occur late and is a relatively poor predictive marker of resistance.
- While on NA treatment, regular counselling should be given on importance of compliance to treatment.
- Treatment adherence should be reinforced in all persons with confirmed or suspected antiviral failure.
- Partial virological response may be seen even in treatment complaint patients on ETV, TDF or TAF who have very high pre-treatment viral loads and it is not the result of a lack of drug efficacy. In such patients with a partial virological response at week 48, the HBV DNA level and its trend must be taken into account. Patients with declining trend of serum HBV DNA levels may continue treatment with the same agent.
- The AASLD suggests that patients with persistent low-level viremia on ETV or TDF/TAF monotherapy with HBV DNA < 2000 IU/ml with plateau in the decline of HBV DNA and/or failure to achieve an undetectable HBV DNA level after 96 weeks of therapy should continue the same agent.
- Virological breakthrough in treatment compliant patients is mainly related to the development of HBV drug resistance.
- In persons with confirmed or suspected antiviral resistance, to lamivudine, entecavir, adefovir or telbivudine, a switch to tenofovir is recommended.
- Entecavir should not be used in patients with lamivudine or telbivudine resistance, because the risk of subsequent entecavir resistance is high.
- Entecavir should be used in patients with tenofovir-resistant HBV, though confirmed cases of tenofovir resistance are extremely rare (16).

4.4 Decompensated Cirrhosis

HBsAg positive persons with decompensated cirrhosis should be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease risk of worsening liver-related complications

Antiviral therapy has been shown to improve outcomes in decompensated cirrhosis, especially with early treatment initiation (17). Both improved liver function and increased transplant free survival have been demonstrated (17, 18). Despite successful treatment with antivirals the risk for development of HCC is high and should continue long-term HCC surveillance.

4.5 When to stop treatment

4.5.1 Lifelong NA therapy

All persons with cirrhosis based on clinical evidence or NIT should be given lifelong treatment with nucleos(t)ide analogues. They should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury (11, 14, 16).

Indefinite NA therapy is advised for HBeAg-negative CHB patients unless they achieve HbsAg loss (11, 14, 16).

4.5.2 Discontinuation of treatment

NA therapy may be discontinued in patients with no clinical evidence of cirrhosis, with evidence of HBeAg loss and seroconversion to anti-Hbe and after completion of at least one additional year of treatment with persistently normal ALT levels and persistently undetectable HBV DNA levels during this period and who can be followed long term for reactivation (11, 14, 16).

NAs cans be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (11, 14, 16).

5 Monitoring

5.1 Monitoring of patients who are not started on antiviral treatment

The goal of monitoring a patient who is not on treatment, is to determine the need for treatment at the earliest, as chronic HBV infection is a dynamic disease. (See Figure 2 and Figure 3 for treatment algorithm for monitoring of patients who are not started on anti-viral treatment.)

Immune- tolerant HBV (HBeAg positive with high HBV DNA with Normal ALT) not on treatment.

- Require monitoring every 3 - 6 monthly.
- Monitor ALT, AST (for APRI score calculation), HBsAg, HBeAg, HBV DNA levels.
- HBV DNA quantification can be done annually.
- Patients monitored for 3 – 6 months whose, ALT levels are more than 2 times Upper Normal Limit and with HBV DNA greater than 20,000 should be considered for treatment.
- Liver Biopsy can be considered in patients older than 40 years, who were infected at a younger age, with persistent borderline normal or slightly elevated ALT levels
- Noninvasive tests can be used as a substitute for liver biopsy.

Inactive Chronic HBV Infection (HBeAg negative, Anti-HBe positive, Normal ALT with HBV DNA < 2000)

- Require ALT monitoring every 3months for the 1st year to make sure that patient is in inactive stage. If ALT remains normal monitoring can be reduced to every 6 months.
- HBV DNA levels can be done annually if ALT levels are normal. DNA can be done more frequently if ALT levels starts to rise (3 to 6 monthly).
- Assessment of fibrosis by NIT can be done every 2 years if patient remains in inactive HBV infection.
- These patients should be assessed for HBsAg loss annually.

5.2 Monitoring during treatment

All patients on anti-viral treatment should be monitored periodically for:

- **Assessment of treatment adherence**
- **Viral suppression**
- **Liver function and progression of liver disease**
- **Adverse effects of drugs**

Adherence to anti-viral treatment should be monitored regularly at each visit. In addition, the following biochemical monitoring is required (Table 10).

Parameter	Frequency of monitoring
LFT	Every 3 months during first year and every 6 months thereafter
HBV DNA	Every 3 months during first year and every 6 -12 months thereafter
HbeAg	Annually
APRI score/Fibro scan	Annually for patients without cirrhosis at baseline
Renal Parameters • **urine dipsticks for proteinuria and glycosuria** • **serum creatinine (eGFR)** • **serum phosphate,** • **Urine P/C ratio**	Every 3 months during the first year and every 6 months thereafter, if no deterioration Closer renal monitoring is required in persons with CrCl <50 mL/min.
HbsAg	Annually if HBV DNA remains undetectable
Anti Hbs	Patients who clear HbsAg should be tested for Anti- Hbs

▲Table 10: Monitoring of CHB patients on NA treatment

5.3 Monitoring for drug toxicity

Measure baseline renal function before starting tenofovir and entecavir.

Monitoring for renal toxicity should be done every 3 months during the first year and every 6 months thereafter, if no deterioration. Monitor serum creatine, eGFR, Urine PC ratio, urine for proteinuria/glycosuria, serum phosphate.

Make appropriate renal dose adjustments for all patients on NAs (Table 8).

Do not use tenofovir along with other nephrotoxic drugs like aminoglycosides, amphotericin B, acyclovir, vancomycin.

5.4 Monitoring after stopping anti-viral treatment

After stopping treatment, long-term monitoring is required.

ALT and HBV DNA should be monitored every 3 months for at least 1 year to look for recurrent viremia, ALT flares and clinical decompensation. Thereafter ALT, HBV DNA level, HBsAg, HBeAg and Anti-HBe should be monitored annually.

Retreatment is recommended if there are signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again).

Risk of developing HCC persists despite loss of HBsAg.

For patients who achieve sustained HBsAg sero-clearance, routine monitoring with ALT and HBV-DNA is not required.

HCC surveillance should be continued even after HBsAg clearance in patients who are older than 40 years, patients who have cirrhosis or a history of HCC in a first-degree family member.

All HBsAg-positive patients with cirrhosis should be screened with ultrasound examination with or without AFP every 6 months.

All HBsAg-positive adults without clinical evidence of cirrhosis but aged > 40 years or with a first-degree family member with a history of HCC should be screened with US examination with or without AFP every 6 months.

Chronic HBV infection leads to an increased risk of death from liver cirrhosis and liver cancer, with an estimated 650 000 annual deaths from HCC (19).

HCC may be asymptomatic and rapidly progressive until it presents clinically at an advanced stage. Risk factors for development of HCC In CHB are the presence of cirrhosis, HBeAg positivity, persistently high HBV DNA levels, family history of HCC, age >40 years HIV and HCV coinfection.

Treatment options for advanced HCC are limited and overall survival is extremely poor. The prognosis of HCC is affected by the size and number of tumors, and the underlying liver function. The prognosis is better if treatment can be started at an early stage of the disease when the tumor is small. Surveillance is therefore required to detect HCC at an early stage (tumor size <3 cm in diameter) and increase the chances of effective treatment.

6 Special circumstances

6.1 HBV/HIV Co-infection

The risk of HBV infection is higher in HIV infected adults. All persons newly diagnosed with HIV should be screened for HBsAg and anti-HBs to identify patients with HIV/HBV co-infection. Patients who are non-immune for HBV should be vaccinated.

HIV coinfection has been shown to cause more rapid progression to cirrhosis and HCC, decreased treatment response and higher liver-related mortality.

Other issues include cross-resistance between HIV and HBV drugs.

HIV/HBV-coinfected persons should be simultaneously treated for both HIV and HBV infection. The ARVT regimen should include 2 drugs with activity against HBV. A tenofovir-based regimen is recommended, which should include tenofovir/lamivudine, or tenofovir/ emtricitabine (provided there is no contraindication to tenofovir), together with a third drug efavirenz, to prevent the selection of HIV-resistant mutants (14, 16).

6.2 HBV /HDV Co-infection

HBV/HDV co-infection is uncommon. The incidences of cirrhosis and HCC are higher in patients with HBV/HDV coinfection than in those with HBV mono-infection. Patients at high risk of HDV/HBV co infection include persons who inject drugs, MSM, individuals infected with HCV or HIV and persons who have multiple sexual partners. HDV infection can be diagnosed by detecting anti-HDV antibody (IgM or IgG) and HDV RNA in the serum, however, HDV diagnostics are not widely available. PEG-IFN is the only drug effective against HDV infection. Antiviral NAs have no or limited effect on HDV replication. PegIFNa for at least 48 weeks is the current treatment of choice in HDV-HBV co-infected patients with compensated liver disease (16). The overall rate of sustained virological response remains low.

6.3 HBV/HCV Co-infection

In patients with chronic HBV infection, HCV co-infection accelerates liver disease progression and increases the risk of HCC.

HBsAg-positive patients are at risk of HBVDNA and ALT flares during HCV DAA therapy.

If HCV RNA is detectable, HCV should be treated with directly acting anti-viral agents (DAAs).

In those HBV-HCV–coinfected patients with cirrhosis or those meeting recommended criteria for HBV treatment, HBV antiviral therapy should be started concurrently with DAA therapy.

In those who do not meet treatment criteria for HBV treatment, AST, ALT can be done at 3 monthly intervals from the start of DAA treatment until 3 months after completion of treatment. HBV DNA viral load should be done at the time of doing HCV viral load to assess SVR 12.

HBsAg-negative, anti-HBc–positive patients with HCV are at very low risk of reactivation with HCV-DAA therapy but they should be monitored for reactivation of hepatitis B.

6.4 Pregnant women

Indications for treatment in adults with CHB also apply to pregnant women. Based on safety and resistance profile, Tenofovir (TDF) is the preferred antiviral. The safety of entecavir in pregnancy is not known.

Infants of all HBsAg-positive women should receive Hepatitis B immunoglobulin and Hepatitis B active immunization at birth (see section on HBV prevention).

Breastfeeding is not contraindicated in patients not on treatment or receiving Tenofovir.

Antiviral therapy is recommended to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with an HBV- DN A level >200,000 IU/mL (14,16). Anti-viral should be started at 24–28 weeks of gestation and continued up to 12 weeks post-partum (14, 16). After stopping treatment ALT monitoring should be continued for 1 year at 3 monthly intervals.

6.5 Patients who receive immunosuppressive or cytotoxic therapy

Several immunosuppressive and immunomodulating drugs have been associated with HBV reactivation. Studies had shown that HBV reactivation from anti-cancer therapies occurred in 41%-53% (20) of HBsAg-positive, anti-HBc–positive patients and 8% - 18% (21) of HBsAg-negative, anti-HBc–positive patients.

The criteria for HBV reactivation include a rise in HBV DNA compared to baseline (or an absolute level of HBV DNA when a baseline is unavailable) and reverse seroconversion (sero-reversion) from HBsAg negative to HBsAg positive for HBsAg-negative, anti-HBc–positive patients (16).

Following HBV reactivation, a hepatitis flare and hepatic failure can occur. A hepatitis flare is defined as an ALT increase to 3 times the baseline level and >100 U/L (16).

Before initiation of immunosuppressive therapy, both the HBsAg and anti-HBc (total or immunoglobulin G) tests should be used for HBV screening.

HBsAg-positive patients are at high risk of HBV reactivation, especially if their HBV-DNA levels are elevated and they should receive anti-HBV prophylaxis before the initiation of immunosuppressive or cytotoxic therapy (16).

HBsAg-negative, anti-HBc–positive patients are at lower risk of HBV reactivation than HBsAg positive patients. They could be monitored with ALT, HBV DNA, and HBsAg with a view to treat if any evidence of HBV reactivation, except patients receiving anti-CD20 antibody therapy (e.g., rituximab) or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended (16). When indicated, prophylaxis is given with ETV, TDF or TAF.

6.6 Extrahepatic manifestations

HBV related extrahepatic manifestations include vasculitis, skin manifestations (purpura), polyarteritis nodosa, arthralgias, peripheral neuropathy and glomerulonephritis. HBsAg-positive patients with extrahepatic manifestations and active HBV replication should receive antiviral treatment with NA (11, 14, 16).

7 Chronic HBV infection in children

Mother-to-child transmission accounts for more than 50% of chronic infections in highly endemic areas. After exposure, the risk of chronicity is higher for newborns (90%), infants and children younger than 5 years (25–30%) than for adolescents or adults (<5%).

Chronic HBV infection is a mild disease in childhood and tends to run a benign course during childhood and adolescence. Most infected children are asymptomatic, with a normal growth and a normal physical examination. The great majority of perinatally infected subjects are HBeAg-positive, with high serum levels of HBV DNA and normal serum alanine aminotransferases (immunotolerant phase). About 3–5% and 0.01–0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC), respectively, before adulthood (22,23).

Over time, HBV DNA levels fluctuate and ALT levels can rise along with histologic finding of necroinflammation of liver parenchyma. This phase of active hepatitis leads to seroconversion to anti-HBe antibodies in 60–95% of patients on long-term follow-up. ALT levels may remain elevated for 6–12 months after seroconversion.

Most HBsAg positive, HBeAg negative, and anti-HBe positive patients (i.e. those who undergo HBeAg seroconversion) are defined as inactive carriers. They have absent or low viral replication (HBV DNA <2000 IU/ml) and usually inactive liver histology, with normal ALT levels. seroconversion to anti-HBs is a rare event in childhood (0.6–1% per year) and if it happens, indicates resolution of HBV infection. Even in these patients who sero convert to anti- HBs, cccDNA persists indefinitely in hepatocytes, and low-level viral replication or reactivation upon immunosuppression is possible.

A subgroup of HBeAg negative, anti-HBe positive subjects have active viral replication with abnormal ALT levels and histologically active hepatitis (HBeAg negative chronic hepatitis). HBeAg negative hepatitis affects about 10% of pediatric patients. This is associated with disease progression and have a higher incidence of HCC than HBeAg negative patients in sustained remission (24).

7.1 Monitoring and treatment of Chronic HBV in Children

The clinical approach to HBV infected children is still evolving. Our recommendations for monitoring and treatment are based on the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGAN) (25) clinical practice guideline on management of chronic hepatitis B in childhood.

Children with chronic HBV infection should undergo physical examination and measurement of serum ALT and HBeAg, anti-HBe levels every 6 months. The need for treatment should be evaluated at each follow-up visit, in order to initiate antiviral drugs at the earliest signs of liver damage.

The upper limit of normal (ULN) for ALT levels in pediatric age has not been established yet. A patient should be considered for antiviral treatment if ALT levels are more than 1.5 times the laboratory ULN or more than 60 IU/L, whichever is lower (25).

In HBeAg positive patients with persistently elevated ALT, their levels should be monitored every 3 months for at least one year before considering for antiviral treatment. This is done in order to avoid treating patients who are undergoing spontaneous HBeAg seroconversion.

In HBeAg negative patients, ALT and HBV DNA levels should be measured 4-monthly within the first year to rule out HBeAg negative hepatitis. After confirmation of the inactive carrier status (normal ALT and HBV DNA <2000 IU/ml), patients should be monitored every 6 months. If ALT is persistently normal, ALT alone can be monitored.

In the presence of high ALT levels, assessment of serum HBV DNA levels is important, as high HBV DNA values warrant antiviral treatment, whereas low levels should prompt investigations to exclude other causes of liver disease.

Non-invasive tests (NITs) to assess the degree of hepatic fibrosis, such as APRI and Fibro Scan are not validated for use in children at present. At present, NITs cannot substitute for liver biopsy in the decision to treat a child or an adolescent with chronic hepatitis B.

Patients with persistently abnormal ALT levels with elevated HBV DNA levels (> 2000 IU/ml) and evidence of moderate to severe inflammation or fibrosis on liver biopsy should be started on antiviral treatment. Table 11 shows the recommended NAs for the treatment of CHB in children and their doses.

HCC surveillance with liver ultrasound should be done every 6–12 months, depending on the stage of fibrosis

In children and adolescents in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended. (11, 14, 16)

Entecavir can be used in children aged 2 years and above. Tenofovir can be used in children 12 years and above. (11, 14, 16)

NAs with a low barrier to resistance such as Lamivudine, Telbivudine and Adefovir are not recommended. (11, 14, 16)

Drug	Dose	
Tenofovir (in children ≥ 12 years old and weighing at least 35 kgs)	300 mg once daily	
Entecavir (in children 2 years of age and weighing at least 10 kgs. Oral solution should be given to children with a body weight up to 30 kgs) • **Entecavir syrup contains 0.05 mg Entecavir/ml**	Recommended once daily dose of oral solution (ml) in treatment naive persons	
	Body weight (Kgs)	Dose (ml)
	10 – 11 kgs	3
	> 11 to 14	4
	> 14 to 17	5
	> 17 to 20	6
	> 20 to 23	7
	> 23 to 26	8
	> 26 to 30	9
	> 30	10

▲ Table 11: Recommended NAs for the treatment of CHB in children and their doses

7.2 Duration of Treatment

7.2.1 Indefinite, long term NA therapy

The following patients require indefinite, long term NA therapy:

- **Cirrhotic patients**
- **Patients who do not undergo HBeAg seroconversion on treatment**
- **HBeAg negative chronic hepatitis (unless they achieve HBsAg loss)**

7.2.1 Discontinuation of treatment

Discontinuation of NA therapy can be considered in patients with no clinical evidence of cirrhosis, with evidence of HBeAg loss and seroconversion to anti-Hbe and after completion of at least one additional year of treatment with persistently normal ALT levels and persistently undetectable HBV DNA levels during this period and who can be followed long term for reactivation.

7.3 Immunocompromised children

All children who are planned for chemotherapy or immunosuppressive therapy should be screened for HBsAg, anti-HBs, and anti-HBc, and seronegative patients should be vaccinated.

Prophylactic treatment with NAs should be considered for inactive carriers requiring immunosuppressive therapy in order to prevent HBV reactivation.

NA treatment should be continued until 12 months after cessation of the immunosuppressive therapy

8 Prevention of HBV infection

Perinatal transmission is the predominant mode of hepatitis B transmission in high-prevalence regions. Other common modes of transmission word wide are unprotected sexual intercourse and intravenous drug use. Measures to prevent perinatal transmission, universal vaccination of infants and vaccination of adults particularly those at risk for HBV infection are the main preventive strategies against prevention of hepatitis B transmission.

For infants and children, the two primary sources of HBV infection are vertical transmission from infected mothers during pregnancy, and horizontal transmission from infected household contacts after birth. Newborns are most commonly infected with HBV via exposure to infected maternal blood at the time of delivery. With hepatitis B immunization, hepatitis B infection is a highly preventable condition in infants and children. The risk of perinatal HBV infection in an infant from an HBsAg positive mother is less than 10 percent if the mother's HBeAg status is negative, but is 70 to 90 percent if her HBeAg status is positive. If infected at birth, an infant has approximately a 90 percent chance of becoming a chronic HBV carrier and, when chronically infected, has a 15 to 25 percent risk of dying in adulthood from cirrhosis or liver cancer. However, the combination of hepatitis B vaccine and hepatitis B immune globulin is 85 to 95 percent effective in reducing HBV infection from vertical transmission when given within 12 hours of birth (13, 26).

8.1 Prevention of Perinatal HBV transmission

- All pregnant women should be screened for HBsAg at first prenatal visit (Test HbsAg).
- All HbsAg positive pregnant women should be tested for HbeAg and HBV DNA.
- Anti-viral therapy is recommended for pregnant women with HBV DNA >200,000 IU/mL. Anti-viral should be started at 24–28 weeks of gestation and continued up to 12 weeks post-partum (14, 16).
- Women with CHB who meet standard indications for HBV treatment should be treated regardless of gestational age.

- Newborns of all HBsAg positive mothers should receive HBIG and HBV vaccine as soon as possible after birth within 12 hours and complete the vaccination series with post vaccination testing at 9 to 12 months.
- Pregnant women who are HbsAg negative and who have not received Hepatitis B immunization before, should receive the Hepatitis B vaccine series during pregnancy.
- No evidence exists that caesarean delivery provides additional protection against transmission.
- Women with HBV infection should be counselled that breastfeeding does not increase the likelihood of infection in their children.

8.2 Management of infants born to women who are HBsAg-positive

- Newborns of all HBsAg positive mothers should receive HBIG and HBV vaccine as soon as possible after birth within 12 hours.
- HBIG is administered in a dose of 200 IU intramuscular to the opposite thigh (to other thigh that HBV vaccine was given to).
- Infants who are born to HBsAg-positive mothers and receive HBIG and HBV vaccine at birth may be breastfed beginning immediately after birth
- The HBV vaccine series should be completed
- Infants should have follow-up serology (HBsAg and anti-HBs) between 9 and 12 months of age, after completing the HBV vaccine series, to assess response to vaccination and to rule out perinatal infection.
- Testing should not be performed before the age of 9 months as anti-HBs related to HBIG administration could be present, affecting the interpretation of results.
- HBsAg-negative infants with anti-HBs levels ≥10 mIU/ mL are protected and need no further medical management.
- HbsAg negative infants with anti-HBs levels less than 10 mIU per mL should be revaccinated with a single dose of HBV vaccine and receive post vaccination serological testing 1-2 months later. Infants whose anti-HBs remains <10 mIU/ml following single dose revaccination should receive two additional doses of HBV vaccine to complete the second series, followed by postvaccination serological testing 1-2 months after the final dose.

- There is no role of giving additional doses of HBV vaccine to infants who have not attained anti-HBs ≥10 mIU/mL following receipt of two complete HBV vaccine series.
- Infants who test positive for HBsAg and remain HbsAg positive for more than 6 months need to be followed and treated as chronic hepatitis B infection.

8.3 Universal vaccinations of infants

First dose of hepatitis B vaccine must be given to all newborn babies in Maldives as soon as possible after birth within 24 hours, irrespective of baby's weight and gestational age. This is the birth dose of hepatitis B vaccine. If birth dose is missed for any reason this dose should be given as soon as possible up to 1 month of age. It is given intra muscular to the thigh muscle. There are additional 3 more doses of hepatitis B vaccine. These doses are given as part of Pentavalent vaccine which is given at 8 weekly intervals at child's 2nd, 4th and 6th month of life.

8.4 Prevention of hepatitis B transmission from Hepatitis B patients

All HbsAg-positive persons should be counselled regarding transmission to others (Table 12)

Persons Who Are HbsAg Positive Should
• Have household members and sexual partners vaccinated if they test negative for serological markers of HBV infection • Use barrier protection during sexual intercourse if partner is not vaccinated or is not naturally immune • Sexual partners who have not been tested or have not completed the full immunization series, should use barrier protection methods • Not share toothbrushes or razors • Not share injection equipment • Not share glucose testing equipment • Cover open cuts and scratches • Clean blood spills with bleach solution • Not donate blood, organs
Children and Adults Who Are HbsAg Positive
• Can participate in all activities, including contact sports • Should not be excluded from daycare or school participation and should not be isolated from other children • Should not be isolated from others at institutionalized settings • Can share food and utensils and kiss others

▲ Table 12: Recommendations for prevention of HBV transmission from infected persons

8.5 Hepatitis B vaccination in adolescents and adults

Hepatitis B vaccination is recommended for all unvaccinated adolescents and adults at risk for HBV infection (27) (Table14) and for all adults requesting protection from HBV infection.

Primary vaccination for adolescents and adults generally consists of three intramuscular doses administered on a 0-, 1-, and 6-month schedule (27) (Table 13).

For all ages, if the Hep B vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose should be administered as soon as possible, and the second and third doses should be separated by an interval of at least 8 weeks. If only the third dose has been delayed, it should be administered as soon as possible. The final dose of vaccine must be administered at least 8 weeks after the second dose and should follow the first dose by at least 16 weeks; the minimum interval between the first and second doses is 4 weeks.

Category		Schedule (Engerix B)*	Dose (Engerix B)*
Adolescents (11 to 19 years)		0, 1, and 6 months	10µg (0.5 ml)
Adults (≥ 20 years)		0, 1, and 6 months	20µg (1 ml)
Haemodialysis patients and other immuno-compromised persons	<20 yrs	0, 1, and 6 months	10µg (0.5 ml)
	≥20 yrs	0, 1, 2, and 6 months	40 µg (Two 1.0-mL doses administered at one site)

* Engerix B is the currently available single antigen hepatitis B vaccine approved by MFDA

Note: all doses must be administered in the deltoid by the intramuscular route

▲ Table13: Recommended dose and schedule for Hepatitis B vaccine in adults and adolescents

All infants
Unvaccinated children aged <19 years
Persons at risk for infection by sexual exposure – Sex partners of hepatitis B surface antigen (HBsAg)–positive persons – History of multiple sexual partners – Persons seeking evaluation or treatment for a sexually transmitted infection – Men who have sex with men
Persons at risk for infection by percutaneous or mucosal exposure to blood – Current or recent injection-drug users – Household contacts of HBsAg-positive persons – Residents and staff of facilities for developmentally disabled persons – Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids – Hemodialysis patients, peritoneal dialysis patients – Persons with diabetes
Others – Persons with hepatitis C virus infection – Persons with chronic liver disease – Persons with HIV infection – Incarcerated persons – All other persons seeking protection from HBV infection

▲ Table 14: Persons recommended to receive hepatitis B vaccination

8.6 Pre-vaccination testing

In persons who have a high likelihood of previous HBV infection, pre-vaccination testing helps to identify persons who may already be immune or who already may be having HBV infection. These individuals will not require immunization.

Pre-vaccination testing consists of testing for HbsAg and antiHBs. Anti-HBc should be done in some circumstances such as in HIV positive patients and dialysis patients.

Serologic testing should not be a barrier to vaccination of susceptible persons, especially where testing is not available.

Pre-vaccination testing is recommended for the following persons (27) (Table 15) .

Household, sexual, or needle-sharing contacts of HBsAg-positive persons
HIV-positive persons
Persons with elevated alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) of unknown etiology
Hemodialysis patients
Past or current injection-drug users.
Men who have sex with men
Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterological disorders
Donors of blood, plasma, organs, tissues, or semen

▲ Table 15: Persons recommended to receive serologic testing prior to vaccination

8.7 Postvaccination serologic testing

Serologic testing for immunity is not necessary after routine vaccination of infants, children, or adults.

Testing for anti-HBs after vaccination is recommended for persons with increased risk of exposure, whose clinical management or prophylaxis after a exposure depends on knowledge of their immune status (27). (Table 16)

Testing should be performed 1–2 months after administration of the final dose of the vaccine series.

Postvaccination serologic testing for persons other than infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of testing anti-HBs level.

Postvaccination serologic testing for infants born to HBsAg-positive (or HBsAg-unknown) mothers consists of testing HBsAg and anti-HBs level.

Persons found to have anti-HBs concentrations of ≥10 mIU/mL after the primary vaccine series are considered to be immune.

Immunocompetent persons have long-term protection and do not need further periodic testing to assess anti-HBs levels.

Immunocompromised persons might need annual testing to assess anti-HBs concentrations, if they are at risk for persistent exposure such as patients undergoing hemodialysis.

Infants born to hepatitis B surface antigen (HBsAg)– positive mothers or mothers whose HBsAg status remains unknown
Health care personnel and public safety workers
Pre-dialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
HIV-infected persons
Other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy)
Sexual partners of HBsAg-positive persons

▲ Table 16: Persons recommended to receive postvaccination serologic testing following a complete series of Hepatitis B vaccination

8.8 Revaccination

Persons who are recommended for post vaccination testing and found to have anti-HBs level of <10 mIU/mL after the primary vaccine series, should be revaccinated. They should receive a second complete series of Hep B vaccination, followed by anti-HBs testing 1–2 months after the final dose.

Persons who have anti-HBs level of <10 mIU/mL after revaccination should be tested for HBsAg. If HbsAg is positive the patient should receive appropriate management.

HbsAg negative persons who have an anti- HBs titre of < 10 mIU/ml after revaccination should be considered a vaccine non responder and is considered susceptible to HBV infection. They should be counselled about precautions to prevent HBV infection and the need to obtain HBIG postexposure prophylaxis in case of any exposure to an HBsAg-positive source.

Additional Hep B vaccine doses are not recommended for those who do not respond to the second series.

Hemodialysis patients who responded to vaccination should be checked annually for anti-HBs titer. If anti-HBs declines to <10 mIU/mL, administer a booster dose of hepatitis B vaccine and continue annual testing of anti-HBs (28).

For other immunocompromised persons (e.g., HIV-infected persons, hematopoietic stem-cell transplant recipients, and persons receiving chemotherapy), the need for booster doses has not been determined. Annual anti-HBs testing and booster doses should be considered for persons with an ongoing risk for exposure (27).

8.9 Post-exposure management of health care personnel following a possible occupational exposure to HBV

Health care personnels (HCPs) should take standard precautions during the care of all patients. These precautions include hand hygiene, wearing gloves when touching blood, body fluids and contaminated items and wearing mask, gown, and eye protection during procedures that are likely to cause splashes and sprays of blood, body fluids and excretions.

HBV is highly infectious. The risk of transmission depends upon the HBsAg and HBeAg status of the source. The risk of developing serologic evidence of HBV infection after a percutaneous injury ranges from 37 to 62 percent if the source patient is both HBsAg positive and HBeAg positive, and ranges from 23 to 37 percent if the source is HBsAg positive but HBeAg negative (29). HBV remains infectious on environmental surfaces for at least 7 days (30).

Blood is the most important source of HBV and HCV transmission in HCP. Other body fluids, such as CSF, synovial fluid, pleural fluid, peritoneal fluid, and amniotic fluid are considered potentially infectious. Urine, faeces, vomitus, sputum, and sweat are not considered infectious, unless they contain visible blood.

The main occupational risk for acquiring hepatitis B is via a percutaneous sharps injury with a contaminated object or mucous membrane exposure to blood or other potentially infectious materials.

8.9.1 Wound care

Wounds and skin sites of the HCP that have been in contact with blood or body fluids should be washed with soap and water, and mucous membranes should be flushed with water. Using antiseptics such as 2%–4% chlorhexidine or expressing fluid by squeezing the wound have not been shown to reduce the risk for HBV transmission.

8.9.2 Obtaining information from HCP and source and testing

Relevant information is obtained from the HCP to determine the immune status of the HCP and information regarding the source is obtained if available to determine the risks following the exposure and to decide on investigations. (Table 17 & Table 18)

When required, testing the source patient and the HCP should occur simultaneously. Testing the HCP should not be delayed while awaiting investigations in the source and vice versa.

Obtain the following information of the HCP, Source and Exposure		
HCP	Source	Exposure
• **Dates of Hep B immunization** • **Post-immunization anti-HBs titre (if known)** • **Previous testing (if available) for HBV and HCV** • **Underlying medical conditions that might influence use of/response to vaccination**	• HBsAg and HCV status of the source patient should be assessed (if known)	• Date and time of incident • Nature of the exposure (i.e. nonintact skin, mucosal, percutaneous, human bite etc) • Type of fluid (ie, blood, or other blood contaminated or potentially infectious fluid) • A description of the percutaneous injury

▲ Table 17: Assessment of HCP and source after occupational exposure of HCP

Send the following Investigations in HCP and Source	
HCP	Source
• HBsAg • Anti-HBs • Anti-HBc - If the HCP has a written documentation of a complete Hep B vaccine series with post vaccination anti-HBs ≥10 mIU/mL, testing the HCP is unnecessary. - If HCP is a documented vaccine non responder anti-HBs testing is unnecessary.	• HBsAg (unless source is known to be HbsAg positive) • HCV RNA (unless source is known to be HCV positive) • HIV

▲ Table 18: Testing of HCP and source after occupational exposure of HCP

8.9.3 Post exposure prophylaxis

Our recommendations for management following occupational exposure to a likely source of Hep B is based upon the recommendation of ACIP, CDC (27). Post-exposure management of HCP with a possible exposure to HBV depends first upon the immune status of the HCP and second upon the HBsAg status of the source patient.

If the HBsAg status of a source patient cannot be determined, the HCP should be managed as if the source patient is HBsAg positive.

HCP may have evidence of immunity based upon past HBV infection (i.e. Hbs Ag negative, anti-HBc and anti-HBs positive). They are considered protected against HBV infection.

For HCP without evidence of prior HBV infection, the risk of infection and management depends upon their vaccine status. (Table 19).

Providers should only accept written, dated records as evidence of HBV vaccination. If such documentation is not available, HCP should be treated as an unvaccinated person.

<table>
<tr><th>Source HBV status</th><th colspan="2">HCP unvaccinated/ No documentation of vaccination</th><th>HCP not fully vaccinated (<3doses received)</th><th>HCP fully vaccinated but Anti HBs status unknown ł</th><th>HCP documented vaccine non responder ¶</th><th>HCP vaccinated and documented vaccine responder α</th></tr>
<tr><td>HBsAg Positive
HBsAg Status unknown or not available for testing</td><td colspan="3">Administer one dose of HBIG and the first dose of the HBV vaccine series* and complete the HBV vaccine series. Check anti-HBs titer 1 to 2 months after completing the vaccine series. If anti-HBs is ≥ 10 mIU/ml after receipt of primary vaccine series, HCP is considered immune. If anti-HBs is < 10mIU/ml, HPC should be revaccinated with 3 dose series followed by repeat anti-HBs testing.</td><td>Test anti-HBs titer of HCP: If Anti-HBs Titer < 10mIU/ml, Give HBIG 1dose and HBV vaccine 1 dose stat*. HCP should then receive two more doses of the hepatitis B vaccine to complete the series. ¥

If Anti-HBs is ≥ 10 mIU/ml, no post-exposure management is required.

If anti-HBs testing not available **</td><td>Administer HBIG stat and repeat the dose of HBIG after 1month (total of 2 doses to be given). Do not give HBV vaccine.</td><td rowspan="2">Post exposure Hepatitis B prophylaxis not required</td></tr>
<tr><td>HBsAg Negative</td><td>HCP should start the hepatitis B vaccine series and be tested for anti-HBs titer after completion of vaccination.</td><td colspan="2">HCP should complete the hepatitis B vaccine series and be tested for anti-HBs titer after completion of vaccination</td><td>If anti-HBs titer is < 10, give one dose of HBV vaccine. Test anti-HBs titer 1-2months later. If anti-HBs remains < 10 mIU/mL, HCP should complete two more doses of vaccine series followed by repeat anti-HBs testing.</td><td>Post exposure of Hepatitis B prophylaxis not required.</td></tr>
</table>

α If the anti-HBs level after completing a Hepatitis B vaccine series is ≥10mIU/ml the individual is considered a vaccine responder protected against HBV.

¶ If the anti-HBs remains < 10 mIU/mL after completing a hepatitis B vaccine series on two separate occasions, the individual is a vaccine non-responder

* HBIG and 1st dose of HBV vaccine should be given simultaneously but at different injection sites.

¥ Anti- HBs Level should be tested one to two months after the last dose of hepatitis B vaccine series and at least 6months after HBIG was administered

** If anti-HBs testing is not available in island health facility and cannot be arranged within 24 hours, HCP should be given 1 dose of HBV vaccine. Anti-HBs testing should be done from a center where it is available as soon as possible. Further management will depend on Anti-HBs titer.
ł If Hepatitis B vaccine was completed, but post-vaccination serological testing was not performed, the individual has an unknown vaccine response.
NOTE: The standard adult dose of HBIG is 0.06ml/Kg and should be given intramuscularly. It should ideally be given within 24hours of exposure, but if this is not possible it must be given within seven days.

▲ Table 19: Post exposure prophylaxis for Hepatitis B in occupational setting

8.9.4 Follow-up testing of HCP after exposure

If the source patient was HBsAg positive or if the status could not be obtained, HCP should undergo follow-up testing with anti-HBc and HBsAg six months after the exposure to assess for HBV transmission to the HCP.

During this six-month period, HCP should refrain from donating blood, plasma or organs. However, they can resume their normal health care duties.

8.10 Post-exposure management of possible non-occupational exposure to HBV

Most adults who acquire hepatitis B virus (HBV) do so through percutaneous exposure (e.g. bite or needlestick) or mucosal exposure to blood or infectious secretions (e.g. semen or body fluids that contain blood)

Post-exposure prophylaxis should be administered to patients without previously documented HBV immunity who are exposed to blood or body fluids from a source who is HBsAg-positive or whose HBV status is unknown.

The following groups of patients does not require post-exposure prophylaxis (regardless of the HBV status of the source):

- Patients with a known history of recovery from HBV infection (anti-HBs and anti-HBc-positive).
- Patients previously vaccinated and are known to have responded to vaccine (ie, a post-vaccination anti-HBs ≥10 mIU/mL). These patients are considered to be immune.
- Patients with chronic HBV infection (HBsAg-positive).

8.10.1 Wound care

After a percutaneous (e.g. bite or needlestick) or mucosal exposure to blood or infectious secretions (e.g. semen or body fluids that contain blood), it is important that any wounds be cleaned (see section 7.9.1 above)

8.10.2 Laboratory testing

Laboratory testing should include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs) and hepatitis B core antibody (anti-HBc) of exposed person and source (where available).

8.10.3 Post exposure prophylaxis

Post exposure prophylaxis depends primarily upon the vaccination history of the exposed person and the HBV status of the source. (Table 20)

8.10.4 Follow-up testing of exposed person

For patients who receive post-exposure prophylaxis for HBV, Anti-HBc and HBsAg testing should be done after six months from the time of exposure to rule out HBV acquisition.

Vaccination and /or antibody response status of exposed person	Treatment depending on HbsAg status of source	
	Source is HBsAg-positive/source unknown or not available for testing	Source HBsAg-negative
Unvaccinated/non-immune	Give 1 dose of HBIG* and the first dose of HBV vaccine simultaneously at different sites, as soon as possible after exposure, preferably within 24 hours. Subsequently the HBV vaccine series should be completed.	Initiate HBV vaccine series
Previously vaccinated [α], known responder[¶]	No treatment needed.	No treatment needed
Previously vaccinated [α], known non-responder to first series[β]	Give 1 dose of HBIG* and initiate revaccination and complete the second series OR give HBIG 1 dose stat and repeat another dose after 1 month (2 doses in total)	No treatment needed
Previously vaccinated [α], antibody response unknown	Give HBV vaccine 1 dose as soon as possible after exposure, preferably within 24 hours. Further management depends on results of anti-HBs of exposed person as follows: • If anti-HBs titre ≥ 10 mIU/ml, no further action needed. • If anti-HBs titre < 10 mIU/ml and patient had previously received 1 series of HBV vaccine: Give HBIG and complete the second series of HBV vaccine with post vaccination anti HBS testing 1 month after completing the HBV vaccine. • If anti-HBs titre < 10mIU/ml and patient had previously received 2 series of HBV vaccine: No role of further HBV vaccine doses. Give HBIG 1 dose and repeat one more dose of HBIG after 1 month.	No treatment needed
Incomplete vaccination (primary 3 dose series not completed)	Give 1 dose of HBIG* and complete the vaccine series (not necessary to restart the series)	Complete the series

*HBIG should ideally be administered within 24 hours, but if that is not possible it can be given up to 7 days from time of exposure

α Completed 3 doses of Hep B vaccine series

¶ Previously documented anti-HBs level of ≥10mIU/ml after completing a vaccination series

β Previously documented anti-Hbs titre of <10 mIU/ml after completing one vaccination series

▲ Table 20: Post-exposure prophylaxis for hepatitis B virus after a non-occupational exposure

Acknowledgements

Guideline development team

Dr Ahmed Shaheed, MIntMed, Consultant in Internal Medicine, IGMH

Dr Abdullah Isneen Hilmy, MD Consultant in Internal Medicine, IGMH

Dr Muaz Moosa, DrIntMed, Consultant in Internal Medicine, IGMH

Dr Ahmed Faisal, MPaed, Consultant in Pediatrics, IGMH

Guideline Reviewers

Internal Reviewers

Dr. Ali Latheef MD, Senior consultant in Internal Medicine and Head of Department of Internal Medicine, IGMH

Dr. Mohan Khadka, MD, DM, Consultant in Gastroenterology, ADK hospital

Dr. Rajib Kumar Dey, MD, MRCP Consultant in Internal Medicine, IGMH

Dr. Nazla Musthafa Luthfee, MD Consultant in Pediatrics, IGMH

Dr. Mohamed Faisham, MD Consultant in Internal Medicine, IGMH

External Reviewers

Dr. B B Rewari, Scientist, HIV/STI/Hepatitis, WHO South-East Asia Regional Office

Dr. Amit Goel, Additional Professor, Sanajay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India (WHO collaborating Centre)

References

1. Global hepatitis report, 2017. Geneva: World Health Organization; 2017
2. 2008 Biological and Behavioral Survey on HIV/AIDS (UNDP, 2008)
3. Jefferies M, Rauff B, Rashid H, Lam T, Rafiq S. Update on global epidemiology of viral hepaitis and preventive strategies. World journal of clinical cases. 2018 Nov 6;6(13):589.
4. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, Abu-Raddad LJ, Assadi R, Bhala N, Cowie B, Forouzanfour MH. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. The Lancet. 2016 Sep 10;388(10049):1081-8.
5. Arauz-Ruiz P, Norder H, Robertson BH, Magnius LO. Genotype H: a new Amerindian genotype of hepatitis B virus revealed in Central America. Journal of general virology. 2002 Aug 1;83(8):2059-73.
6. Mast EE, Alter MJ, Margolis HS. Strategies to prevent and control hepatitis B and C virus infections: a global perspective. Vaccine. 1999 Jan 1;17(13-14):1730-3.
7. Alter MJ, Hadler SC, Margolis HS, Alexander WJ, Hu PY, Judson FN, Mares A, Miller JK, Moyer LA. The changing epidemiology of hepatitis B in the United States: need for alternative vaccination strategies. Jama. 1990 Mar 2;263(9):1218-22.
8. Beasley RP, Hwang LY, Lin CC, Leu ML, Stevens CE, Szmuness W, Chen KP. Incidence of hepatitis B virus infections in preschool children in Taiwan. The Journal of infectious diseases. 1982 Aug 1;146(2):198-204.
9. Kim WR, Ishitani MR, Dickson ER. Rising burden of Hepatitis B in the United States should'the other'virus be forgotten?. InHepatology 2002 Oct 1 (Vol. 36, No. 4, pp. 222A-222A). INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399 USA: WB SAUNDERS CO.
10. Weisiger RA, Bilhartz LE. Sleisenger and Fordtrans: gastrointestinal and liver disease: review and assesment. vol. 1. 10th ed. Pg 1317: Philadelphia: W.B. Saunders; 1999.
11. World Health Organization. Guidelines for the Prevention Care and Treatment of Persons with Chronic Hepatitis B Infection: Mar-15. World Health Organization; 2015 Aug 5.

12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney international. Supplement. 2009 Aug(113):S1.
13. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents [published corrections appear in MMWR Morb Mortal Wkly Rep. 2006;55(6):158–159 and MMWR Morb Mortal Wkly Rep. 2007;56(48):1267]. MMWR Recomm Rep. 2005;54(RR-16):1–31
14. European Association For The Study Of The Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of hepatology. 2017 Aug 1;67(2):370-98.
15. G. Treatment of HBeAg positive chronic hepatitis B: interferon or nucleoside analogues. Liver Int. 2013;33 (Suppl 1):137–50.
16. Norah A. Terrault, Anna S.F. Lok, Brian J. McMahon, Kyong-Mi Chang, Jessica P. Hwang, Maureen M. Jonas: Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance HEPATOLOGY, VOL. 67, NO. 4, 2018
17. Jang JW, Choi JY, Kim YS, Woo HY, Choi SK, Lee CH, et al. Long-term effect of antiviral therapy on disease course after decompensation in patients with hepatitis B virus-related cirrhosis. HEPATOLOGY 2015;61:1809-1820.
18. Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. J Hepatol 2012;57:442-450.
19. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
20. Lau GK, Yiu HH, Fong DY, Cheng HC, Au WY, Lai LS, et al. Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 2003;125:1742-1749
21. Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, Yang MH, Tzeng CH, Lee PC, Lin HC, Lee SD. Randomized controlled trial of entecavir prophylaxis for rituximabassociated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013;31:2765-2772.

22. Chang M, Hsu H, Hsu H, Ni Y, Chen J, Chen D. The significance of spontaneous hepatitis B e antigen seroconversion in childhood: with special emphasis on the clearance of hepatitis B e antigen before 3 years of age. Hepatology 1995;22:1387–1392.

23. Chang MH. Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: the effect and problems. Clin Cancer Res 2005;11:7953–7957.

24. Hsu Y-S, Chien R-N, Yeh C-T, Sheen I-S, Chiou H-Y, Chu C-M, et al. Longterm outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. Hepatology 2002;35:1522–1527.

25. Sokal EM, Paganelli M, Wirth S, Socha P, Vajro P, Lacaille F, et al. Management of chronic hepatitis in childhood : ESPGHAN clinical practice guidelines : consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol 2013;59:814–829.

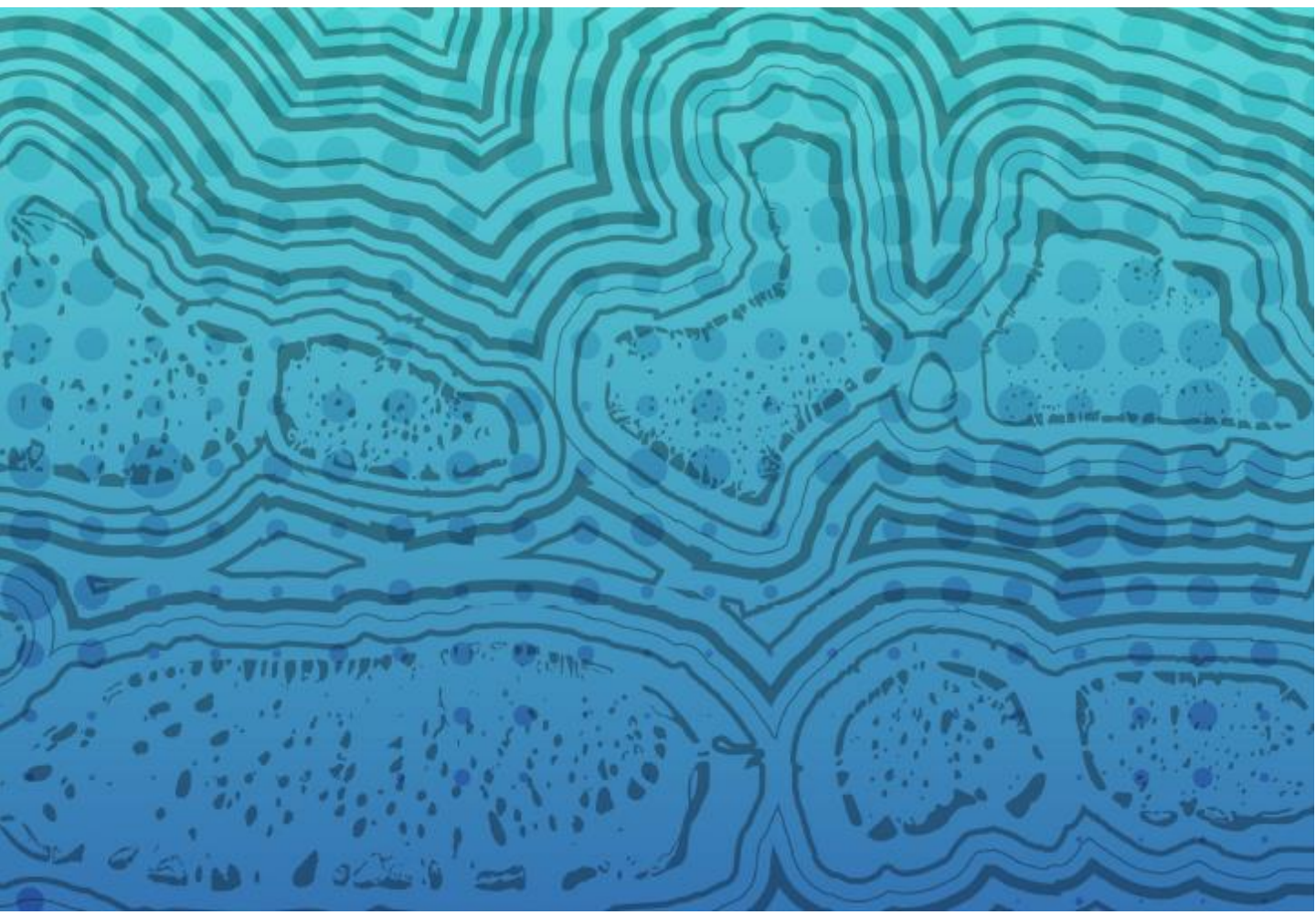
26. Centers for Disease Control and Prevention (CDC). Implementation of newborn hepatitis B vaccination—worldwide, 2006. MMWR Morb Mortal Wkly Rep. 2008;57(46):1249–1252.

27. Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices.Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW, Nelson NP MMWR Recomm Rep. 2018;67(1):1. Epub 2018 Jan 12

28. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep 2001;50(No. RR-5):1–43)

29. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. U.S. Public Health Service MMWR Recomm Rep. 2001;50(RR-11):1.

30. Bond WW, Favero MS, Petersen NJ, Gravelle CR, Ebert JW, Maynard JE. Survival of hepatitis B virus after drying and storage for one week. Lancet 1981;317:550–1. https://doi.org/10.1016/S0140-6736(81)92877-4



Ministry of Health
Republic of Maldives

Health Protection Agency

World Health Organization
Maldives