Fiji Hepatitis B Care and Treatment Guidelines

MINISTRY OF HEALTH
& MEDICAL SERVICES

World Health Organization

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ACRONYMS AND ABBREVIATIONS

AFP	alpha-fetoprotein
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APRI	aspartate aminotransferase-to-platelet ratio index
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
anti-HBc	hepatitis B core antibody
anti-HBe	antibody to hepatitis B e antigen
anti-HBs	antibody to hepatitis B surface antigen
BMI	body mass index
CHB	chronic hepatitis B
CrCl	creatinine clearance
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETV	entecavir
FBC	full blood count
FIB4	fibrosis-4 score
GFR	glomerular filtration rate
gGT	gamma glutamyl transpeptidase
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immunoglobulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
INR	international normalized ratio
MDRD	modified diet renal disease
MSM	men who have sex with men
NAT	nucleic acid testing
NIT	non-invasive test
PCR	polymerase chain reaction
PLHIV	people living with HIV
PWID	people who inject drugs
RDT	rapid diagnostic test
RNA	ribonucleic acid
STI	sexually transmitted infection
SW	sex worker
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TG	transgender
ULN	upper limit of normal
WHO	World Health Organization

CONTENT

01

INTRODUCTION OF HEPATITIS B

SECTION 1: INTRODUCTION OF HEPATITIS B

1.1 EPIDEMIOLOGY

Available data show an intermediate adult prevalence of hepatitis B in Fiji – 2–3.8% in recent studies and laboratory records – with a large cohort of adults also potentially susceptible to infection. Awareness of hepatitis is high among healthcare workers but low in the general population. There is high infant hepatitis B immunization coverage including birth dose, and healthcare workers are immunized. No immunization of other adults is currently available. Immunization has resulted in very low hepatitis B prevalence in children. Transmission of hepatitis B has been predominantly mother to child and early childhood, but other potential mechanisms for transmission exist, including sexual transmission. Screening for hepatitis B is currently undertaken in blood donors, pregnant women, and patients at STI clinics.

These guidelines outline a framework for the key steps in screening and assessment, antiviral therapy, and monitoring of hepatitis B infection, including considerations in pregnancy and HIV/HBV co-infection.

1.2 BACKGROUND

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic, progressive disease. Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more – is a major public health problem. The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20% and 30% of those who become chronically infected will develop these complications.

Most people are unaware of their HBV infection, and therefore often present with advanced disease. Universal hepatitis B immunization programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction. Highly effective antiviral agents active against HBV are available, and have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. However, currently available treatments fail to eradicate the virus in most of those treated, necessitating long-term therapy and lifelong for people with HBV-related cirrhosis.

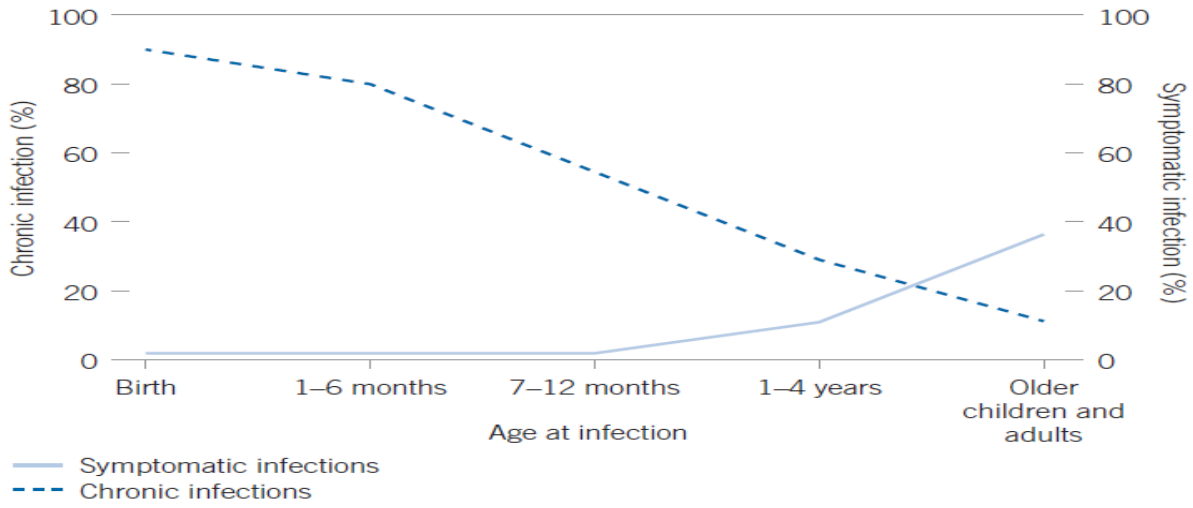
Progression of liver disease in chronic hepatitis B relates to several factors including the length of time since infection (indicated by age), liver inflammation (indicated by ALT level) and HBV DNA viral load level.

1.3 TRANSMISSION

HBV is primarily spread by percutaneous or mucosal exposure to infected blood and body fluids, including saliva, menstrual, vaginal, and seminal fluids. Sexual transmission of hepatitis B may occur. Transmission of the virus may also result from accidental inoculation of minute amounts of blood or fluid during medical, surgical, and dental procedures, or from razors and similar objects contaminated with infected blood; use of inadequately sterilized syringes and needles; intravenous and percutaneous drug abuse; tattooing; body piercing; and acupuncture. Infection in adulthood leads to chronic hepatitis in less than 5% of cases.

Perinatal transmission is the major route of HBV transmission in many parts of the world. In the absence of prophylaxis, a large proportion of viraemic mothers transmit the infection to their infants at the time of, or shortly after birth. Although HBV can infect the foetus in utero, this appears to be uncommon and is generally associated with antepartum haemorrhage and placental tears. The risk of developing a chronic infection is 90% following perinatal infection (up to 6 months of age) but decreases to 20–60% between the ages of 6 months and 5 years. (Figure 1)

Figure 1: Outcome of hepatitis B infection by age at infection

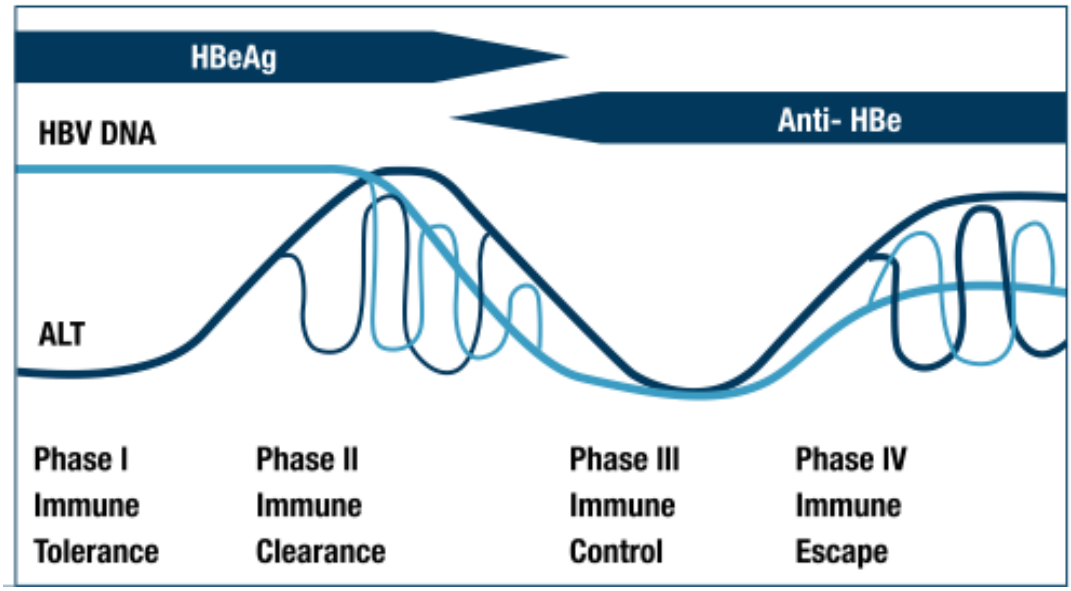


Horizontal transmission, including household, intrafamilial and especially child-to-child, is also important. At least 50% of infections in children cannot be accounted for by mother-to-infant transmission.

1.4 NATURAL HISTORY OF CHRONIC HEPATITIS B

The natural history of CHB is dynamic and complex, with a non-linear progression through several phases of disease defined by the immune response. Immune tolerant, immune active, immune control and immune escape are used to describe the different phases, but they are of variable duration, not all persons infected transition through all of the various phases, and do not always relate to indications for antiviral therapy. The phases are shown in figure 2, and further described in a table at appendix 1 (including alternative terminology).

Figure 2: Phases of Chronic Hepatitis B



02

PREVENTION

SECTION 2: PREVENTION

2.1 HEPATITIS B VIRUS (HBV)

Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth (preferably within 12 hours) is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by 3 further doses at 6,10, and 14 weeks of life according to EPI schedule for Fiji. WHO recommends universal hepatitis B vaccination for all infants, and that the first dose should be given as soon as possible after birth (ideally 24 hours, preferably 12 hours after birth). A proportion of vaccinated children (5–10%) have a poor response to vaccination and will remain susceptible as adults to the acquisition of HBV infection.

Universal infant vaccination will eventually result in high population coverage of protection; however, this may take several decades to come into effect. Other current high-risk groups for screening and vaccination include sex workers, people who inject drugs (PWID), prisoners, close household contacts of people living with HBV, those presenting to STI clinics, men who have sex with men (MSM), people with chronic illnesses, immune deficiency or having frequent transfusions, and people born in high-risk areas. In addition, screening is recommended for blood donors, health care workers, police, military, security, and prison officers, and if resources allow rolling out of adult vaccination should target those born before 1990 and any other adults who wish to be vaccinated.[1]

All blood donations should be screened for hepatitis A, B and C, and infection control activities in health care settings and other settings are also crucial. Please refer to Fiji Antibiotic Guidelines, Immunization Policy, Infection Control and Blood Safety policies for further information.

2.2 SPECIAL POPULATIONS

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION (MTCT)

Hepatitis B virus (HBV) infection in a pregnant woman poses a serious risk to her infant at birth. Without post-exposure immune-prophylaxis, approximately 40% of infants born to HBV-infected mothers will develop a chronic-HBV infection, approximately one-fourth of whom will eventually die from chronic liver disease. Preventing perinatal HBV transmission is an integral part of the Fiji national strategy to eliminate hepatitis B

- All pregnant women should be screened for HBsAg.
- HBsAg-positive pregnant women should have a case management plan established.
- Document details and fill in the notifiable report, referral to SRH Hub centre for contact tracing or from ANC setting if resources permit. A 6-month follow-up for a repeat screen to determine chronic disease may need to be scheduled at the MCH clinic to coincide with the baby`s clinic or at a health centre as this may fall out of the obstetric care period for the mother (42 days post-partum)
- Women who are identified and followed up for chronic hepatitis (without advanced liver disease) prior to pregnancy generally tolerate pregnancy well however need to be monitored for flares during pregnancy and in the post-partum period where decompensation can occur
- Ideally baseline investigations should include - HBeAg, Hepatitis B e antibody, HBV DNA and ALT
- Indications to start antiviral therapy include women with high HBV DNA levels >20,000IU/ml with a positive HBeAg, or HBV DNA levels > 2000 IU/ml with a negative HBeAg, an elevated ALT unlikely from any other foci (> 2 times the upper limit of normal). If these tests are available and satisfy the above criteria, the woman should be referred to the medical team for early initiation of antivirals.

[1] Draft Fiji National Hepatitis Action Plan, September 2016

- If HBeAg and HBV DNA levels are unavailable then clinical assessment and/or deranged LFTS (ALT, platelet count or coagulation profile) from no other foci may be used to assess the patient for discussion with the medical team to commence antiviral medications.
- If HBV DNA testing is available then commencement of antiviral therapy with tenofovir disoproxil fumarate (TDF) in the third trimester is advised to reduce the risk of perinatal transmission as transmission rates can be as high as 60% if acute infections occur near the time of delivery.
- Breastfeeding is not contraindicated however mothers with chronic hepatitis B should exercise care to prevent bleeding from cracked nipples.
- The first dose hepatitis B vaccine should be provided to all infants born to HBsAg-positive mothers within 24 hours (preferably 12 hours) of birth.
- Birth dose vaccine should be followed by a further two or three doses during early childhood as recommended by the national EPI schedule.
- Follow-up of HBsAg-positive child should be in conjunction with paediatric services.

PREVENTION OF TRANSMISSION IN THE HEALTH CARE SETTING/WORKER

All health care workers (HCW) should be screened for HBsAg, and HBV vaccination should be provided to those who are HBsAg negative. A serosurvey should be conducted to determine HCWs exposure to HBV. HBsAg positive HCW who are undertaking exposure prone procedures should be offered antiviral therapy to reduce HBV viral load to undetectable (or < 2,000 IU/ml) and reduce the risk of transmission to others. General recommendations to reduce HBV transmission in health care settings include:

- hand hygiene including surgical hand preparation, hand washing and use of gloves
- safe handling and disposal of sharps and waste
- safe cleaning of equipment
- testing of donated blood
- training of health personnel
- health care workers should be fully vaccinated with Hep B vaccine

PREVENTION OF REACTIVATION IN PEOPLE UNDERGOING CHEMOTHERAPY

Individuals with chronic HBV or past exposure to HBV infection are at risk of reactivation during immunosuppressive cancer chemotherapy. This reactivation may result in severe flare and occasionally may be fatal. All persons undergoing cancer treatment should be screened for hepatitis B. Those who are HBsAg positive should be commenced on antiviral prophylaxis for the duration of the immunosuppressive therapy and for up to 24 months thereafter depending on the therapy used (providing criteria for requiring treatment for hepatitis B irrespective are not met). International guidelines should be consulted for further recommendations.

2.3 PREVENTION OF ONWARD TRANSMISSION

HBsAg screening should be offered to all family members and sexual contacts of an HBsAg-positive person, followed by HBV vaccination of non-immune contacts.

Individuals who are HBsAg positive should be advised to adopt consistent condom use during sexual intercourse if the partner is neither HBV immune nor has been vaccinated; not share razors, toothbrushes, or other personal care items; not donate blood, organs, or sperm; and follow standard universal precautions with open cuts or bleeding.

Pregnant women with hepatitis B should be assessed and treated as per the recommendations in these guidelines. Their infants, as per the recommendation for all infants, should receive their first dose of the hepatitis B vaccine as soon as possible after birth, within 24 (and preferably within 12) hours, followed by two-three further doses according to the immunization schedule.

Hepatitis B-positive HCWs performing procedures with any potential of transmission should receive HBV treatment with TDF to result in an undetectable HBV viral load (or at least <2000 IU/ml) before resuming any exposure-prone procedures.

2.4 PREVENTION OF DISEASE PROGRESSION

Significant alcohol intake (>20 g/day in women and >30 g/day in men) can accelerate the progression of HBV-related cirrhosis. All HBsAg-positive individuals should receive an assessment of alcohol consumption, and advice on lifestyle, including an alcohol reduction diet. Since non-alcoholic steatohepatitis (NASH) is a co-factor in liver disease progression, obese individuals should be given diet and lifestyle advice to encourage weight reduction and recommendations on physical activity levels.

Hepatitis A vaccination should be offered if available. A Hepatitis A burden study as well as cost-benefit analysis should be conducted on Hepatitis A testing and vaccination.

Other co-factors for enhanced disease progression should be checked for including HIV and HCV, and where testing is available for hepatitis delta (HDV).

03

SCREENING AND DIAGNOSIS FOR HEPATITIS B

SECTION 3: SCREENING AND DIAGNOSIS FOR HEPATITIS B

3.1 INTRODUCTION

Hepatitis B screening is carried out by testing for the presence of HBsAg. HBsAg testing is performed through an ELISA test or a rapid diagnostic test (RDT). HBsAg testing is available in all divisional hospitals and sub-divisional hospitals on-site in Fiji.

> ***ELISA is only available in Divisional Hospitals (good for high volume testing)***

If a patient tests positive for HBsAg, they should receive post-test counselling including advice on prevention of transmission and measures to reduce disease progression and be referred to a divisional hospital medical department where they will undergo initial assessment/staging **(Section 2/3)**, be followed up, linked to care and support, and started on antiviral treatment where appropriate **(Section 4)**.

The linkage to care of patients who test positive for HBsAg is critically important. Many patients are lost at this stage in the care cascade and never receive appropriate assessment or therapy. A clear pathway after diagnosis should be established wherever testing is routinely carried out **(Figure 3)**

Those screened, identified as at risk and non-immune **SHOULD BE** offered hepatitis B vaccination/ consultation/ treatment.

3.2 WHO SHOULD BE TESTED/ SCREENING

Testing/Screening for hepatitis B should be carried out in **ALL** the following groups

- Blood and organ donors
- Antenatal patients and babies born to HBsAg-positive mothers
- People presenting to STI/SRH clinics
- People presenting with liver disease
- People undergoing treatment for cancer
- Healthcare workers or those in training to work in healthcare
- Household and sexual contact of persons with CHB
- People living with HIV (PLHIV)
- People who inject drugs (PWID)
- Men who have sex with men (MSM)
- Sex workers (SW)
- People who are incarcerated *(Risky behaviour)*
- Transgender people (TG)
- Other groups identified as priorities for HBV testing in Fiji include defence members, police, prison wardens, people with chronic illnesses, immune deficiency or having frequent transfusions, and people born in higher-risk areas. If possible, HBV screening should be extended to any other adults wanting to test, particularly those born before 1990.[Error! Bookmark not defined.]

Blood Donors:
If they test positive, the blood unit(s) is discarded, and the Donor Management is as per National Blood Services Guidelines with referral to the SRH Hubs

3.3 DESCRIPTION OF MARKERS OF DIAGNOSIS AND STAGING

Box 1: Diagnostic markers of Hepatitis B

Diagnosis of Hep B

Hep B Surface Antigen (HBsAg)
Hep B DNA Level (HBV Viral load)
Hep B Surface Anti-bodies (Titre) (Anti-HBs)
Hep B e-Antigen (HBeAg)

Hepatitis B Core antibody (upon special request)

Previous HBV infection is characterized by the presence of antibodies (anti-HBs and anti-HBc). Immunity to HBV infection after vaccination is characterized by the presence of only anti-HBs. CHB is defined as the persistence of HBsAg for more than 6 months. (**Table 2**)

A positive HBeAg result usually indicates the presence of active HBV replication and high infectivity. Spontaneous improvement may occur following HBeAg-positive sero-conversion (anti-HBe), with a decline in HBV replication, and normalization of ALT levels. This confers a good prognosis. However, some HBeAg negative persons have active HBV replication but are positive for anti-HBe and do not produce HBeAg due to the presence of HBV variants or pre-core mutants.

Serum HBV DNA concentrations quantified by real-time polymerase chain reaction (PCR) correlate with disease progression and are used to guide treatment decisions and subsequent monitoring.

Non-invasive tests (NITs) have replaced liver biopsy for assessing the stage of liver disease and have been validated in adults with CHB. Blood and serum markers for fibrosis, including APRI and FIB-4, as well as commercial markers such as FibroTest can be estimated, or transient elastography (FibroScan) performed to rule out advanced fibrosis.

Table 1: Phases of Acute Hepatitis B

HBsAg	HBeAg	IgM anti-HBC	Total anti-HBC*	Anti-HBs	Anti-HBe	HBV DNA	ALT	Interpretation
+	+	+	+			+++	Elevated	Early Phase
		+	+			+	Elevated	Window Phase
			+	+	+	+	Normal	Recovery Phase

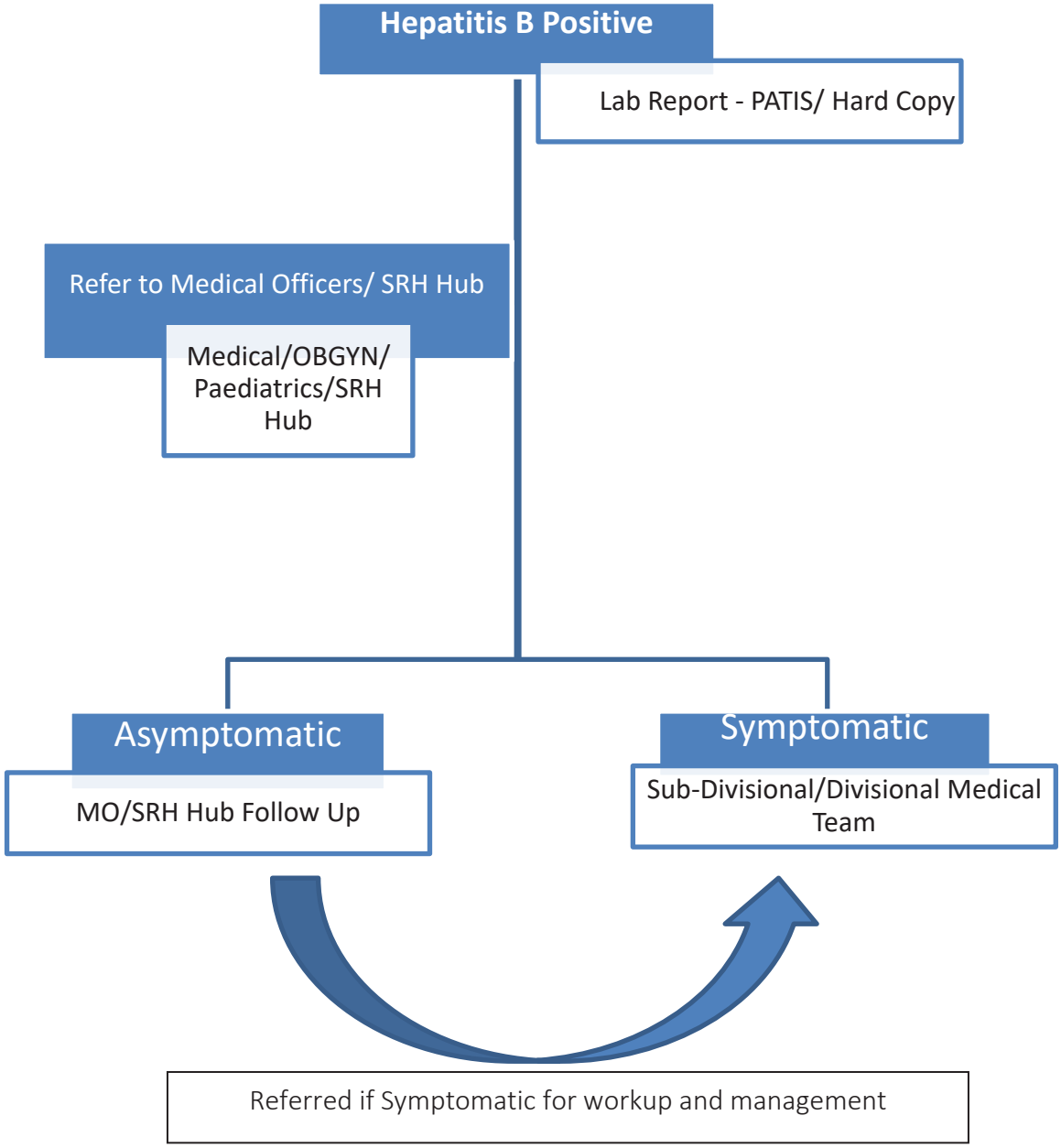
Table 2: Phases of Chronic Hepatitis B

Phase	Also referred to as:	HBeAg serological status	Pattern	Indications for treatment
Immune tolerant	HBeAg positive infection	HBeAg positive	• High levels of HBV replication (HBV DNA levels >200 000 IU/mL)) • Persistently normal ALT • Minimal histological disease	Treatment not generally indicated, but monitoring required
Immune active	HBeAg positive hepatitis	HBeAg positive; may develop anti-HBe	• Abnormal or intermittently abnormal ALT • High or fluctuating levels of HBV replication (HBV DNA levels >2000 IU/mL) • Histological necroinflammatory activity present • HBeAg to anti-HBe seroconversion possible	Treatment may be indicated
Immune control" (previously called inactive carrier)	HBeAg negative infection	HBeAg negative, anti-HBe positive	• Persistently normal ALT • Low or undetectable HBV DNA levels (<2000 IU/mL)	Treatment not generally indicated, but monitoring required for reactivation and HCC
Immune escape	HBeAg negative hepatitis	HBeAg negative with or without being anti-HBe positive	• HBeAg negative and anti-HBe positive • Abnormal ALT (persistent or intermittent) • Moderate to high levels of HBV replication (HBV DNA levels >20 000 IU/mL) • Older persons especially at risk for progressive disease (fibrosis/cirrhosis)	Treatment may be indicated
Reactivation or "acute-on chronic hepatitis"		HBeAg positive or negative	• Can occur spontaneously or be precipitated by immunosuppression from chemo– or immunosuppressive therapy, HIV infection or transplantation, development of antiviral resistance, or withdrawal of antiviral therapy • Abnormal ALT • Moderate to high levels of HBV replication • Seroreversion to HBeAg positivity can occur if HBeAg negative	Treatment indicated

			• High risk of decompensation in presence of cirrhosis	

***** Hep C and D Follows similar screening as Hep B**
***** Diagnosis of Hep C – Hep C Virus Anti-Bodies (HCV Ab) → ELISA/RDT (Span Signal) (referred to reference labs for RNA/genotype)**

Figure 3: Laboratory referral pathway



04

ASSESSMENT FOR HEPATITIS B TREATMENT

SECTION 4: ASSESSMENT FOR HEPATITIS B TREATMENT

4.1 ASSESSMENT OF HEPATITIS B POSITIVE PERSON

All HBsAg positive individuals should undergo assessment for the need for treatment. The initiation of treatment and subsequent monitoring should be undertaken at the medical services of the divisional hospitals Check scoping report.

Prior to treatment initiation patients should be counselled about why they need treatment, the likely benefits and side-effects, the need for long-term treatment and follow-up monitoring and the importance of full adherence for treatment. Baseline renal function[2] and baseline risk for renal dysfunction[3] should be assessed in all persons prior to initiation of antiviral therapy.

People with cirrhosis are at a much higher risk of developing life-threatening complications of liver disease (death, acute liver failure, flares [i.e. ALT flare with jaundice and/or coagulopathy]/reactivation and HCC) than persons without cirrhosis, and so should be treated to prevent further clinical events and stabilize disease, even if other markers of HBV disease are normal.

Antiviral therapy can halve disease progression and may also lead to regression of fibrosis and cirrhosis over the long term. Therefore, targeting treatment to persons with cirrhosis is an effective use of resources. Antiviral therapy can be safely administered to those with cirrhosis, even decompensated cirrhosis. Further information about cirrhosis and liver failure can be found in Section 7.

Those without cirrhosis aged above 30 years, with persistently abnormal ALT levels and evidence of ongoing HBV replication (based on HBV DNA level over 20 000 IU/mL if available) are at an increased risk of HCC and liver cirrhosis and are also recommended for treatment.

[2] serum creatinine levels, and calculation of estimated glomerular filtration rate (eGFR) using the Cockcroft–Gault (CG) or modification of diet in renal disease (MDRD) formulas. An online calculator is available at http://nephron.com/cgi-bin/CGSI.cgi.

[3] Factors associated with a higher risk of renal dysfunction include: decompensated cirrhosis, CrCl <50 mL/min, older age, body mass index (BMI) <18.5 kg/m^2 (or body weight <50 kg), poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV, and solid organ transplantation

Box 2: Key points in the assessment of the HBsAg positive person

Assessment of liver disease
- Medical history and examination (including hepatosplenomegaly)
- LFTs (ALT/AST/ALP/Bilirubin)
- FBC (including platelets and white blood cells)
- APRI (based on AST and platelet)
- Synthetic function (albumin and INR)

Assessment of treatment indication
- Repeated ALT measurements over 6-12 months
- HBV DNA quantification (where available)
- HBeAg and anti-HBe (where available)

Assessment for co-morbidities
- Co-infection with HIV, HCV or HDV
- Impaired glucose tolerance, dyslipidaemia, alcoholic and non-alcoholic fatty liver disease, iron overload, drug/toxin liver injury
- Family history of HCC
- Medication

Preventive measures
- Screen and vaccinate non-immune family members and sexual contacts

Lifestyle issues
- Alcohol reduction, diet and physical activity (WHO ASSIST package)
- Hepatitis A vaccination (if possible)

Treatment readiness
- Understanding indications for treatment, possible side effects, need for life long therapy and monitoring, adherence

Fitness for treatment
- Baseline renal function and risk for dysfunction

Assessment of the severity of liver disease should include a full review by a medical practitioner including a history and physical examination, including for the presence of hepatomegaly and splenomegaly and stigmata of chronic liver disease. Patients should also be questioned about the presence of liver-related symptoms, although it is recognized that even advanced disease may be asymptomatic. Blood tests including a reduced platelet count, low albumin and a reversed ALT: AST ratio may indicate the presence of portal hypertension and significant advanced disease and are important 'red flags' for patients at high risk of complications.

Box 3: RED FLAGS: Clinical and laboratory indicators of advanced liver disease

Ascites
Peripheral Oedema
Hepatosplenomegaly
Jaundice
Low platelet count
Low albumin
ALT:AST <1.0

Box 4: Summary of liver disease stage assessment for patients with hepatitis B

- History and physical examination
- Full blood count
- Liver function tests (ALT, AST, ALP and total bilirubin)
- Liver synthetic function (INR, Albumin)
- APRI score
- Fibro scan score (if available)

Patients with an APRI score of >2.0 should be prioritized for treatment

Most important in liver disease assessment is the identification of persons with cirrhosis who should be targeted for antiviral therapy as a priority. Although liver biopsy has previously been considered the gold standard in assessing liver fibrosis, it is no longer widely recommended due to its high cost, complication rate and sampling error.

WHO guidelines instead recommend two alternative forms of Non-Invasive Tests (NITs):

1. Biochemical algorithms including the APRI score (aspartate aminotransferase ratio index)
2. Transient elastography (Fibro scan)

Online calculators can be accessed for APRI at http://www.hepatitisc.uw.edu/page/clinical-calculators/apri
APRI has been validated for the diagnosis of both significant fibrosis and cirrhosis. An APRI score of >2.0 has high specificity 89% (although lower sensitivity 35%) for the diagnosis of cirrhosis and thus can be used to target patients who have a score > 2.0 for antiviral therapy. It is important to recognise that due to its lower sensitivity at this level, some patients will be missed who are indeed cirrhotic. A level of <1.0 has a high degree of accuracy for excluding cirrhosis. Patients with an APRI score of <1.0 and normal transaminases can have therapy deferred.

1. APRI score

The APRI score is a simple biochemical algorithm calculated from the AST and platelet count.

APRI score = (AST/ULN*) x 100) / platelet count (10^9/L)

*Upper limit of normal for AST in the laboratory where these investigations were undertaken.

Patients with APRI values between 1-2 have indeterminate results. Other factors such as ALT levels should be considered, and the patient re-evaluated every 1-2 years.

2. Transient elastography (Fibro scan)

Fibro scan is a non-invasive ultrasound-based method to assess liver stiffness (measured in kPa). It measures the speed at which elastic waves travel through the liver, directly correlating to the degree of liver damage. This provides a simple, non-invasive way to assess the liver, with a short procedure time, immediate results, and ability to be used at bedside and in outpatient clinics. Operator training is easy for all health care workers. Fibro scan has been validated for the diagnosis of fibrosis stage and cirrhosis for a variety of liver diseases including HBV. Fibro scan scores range between 0-75kPa. A score of >11-14kPa is considered consistent with cirrhosis and a score of >7-8.5kPa consistent with significant fibrosis.

Fibro scan machines are expensive to purchase and require regular maintenance thus they are not available in all settings. However, where large volumes of patients can be assessed regularly, they are cost effective and useful for the assessment of liver disease. Fibro scan has a significant failure rate in obese individuals and is not possible in pregnant women or those with ascites.

Table 3: Cut offs for fibrosis stage by non-invasive tests

FS score		APRI score	
>11-14kPa	Cirrhosis	>2.0	High likelihood of cirrhosis
8.5-11kPa	Moderate/indeterminate fibrosis	1-2	Indeterminate result. Take other measures into account and re-assess at later date
<7-8.5kPa	Absent or mild fibrosis	<1.0	Low likelihood of cirrhosis

* HBV DNA can be important for assessment of treatment eligibility (see Section 5) but does not correlate with liver disease stage

4.2 DISEASE PROGRESSION - DECOMPENSATED CIRRHOSIS

Liver failure and HCC are rarely seen less than 20 years after infection with HBV. Progression from compensated to decompensated cirrhosis may be suggested by the following:

Box 5: Clinical signs and laboratory findings of decompensated cirrhosis

Clinical signs	Laboratory findings
Progressive weight loss and weakness Jaundice/dark urine Ascites/Peripheral oedema Splenomegaly Bleeding from oesophageal varices Encephalopathy	Low platelet count (portal hypertension) Low albumin Increasing prothrombin time /INR ALT:AST ratio <1.0

Hyperbilirubinemia with depressed albumin and prolonged prothrombin time are poor prognostic findings in CHB and associated with an increased risk of liver-related death.

Regular clinical examination and monitoring (every 6–12 months) of serum bilirubin, albumin, international normalized ratio (INR) and liver ultrasound is a recommended part of the ongoing care of persons with HBV-related cirrhosis to detect further disease progression.

All persons with decompensated cirrhosis should be considered for urgent antiviral therapy with TDF, even if the HBV DNA level is low or undetectable, to improve clinical outcomes, and to prevent flares or reactivation.

Antiviral therapy should usually be continued indefinitely as should HCC surveillance.

Management of persons with decompensated cirrhosis should be performed by appropriately trained personnel.

05

HEPATITIS B TREATMENT

SECTION 5: HEPATITIS B TREATMENT

5.1 WHO TO TREAT

In all adults, adolescents and children aged 2 years or older in whom antiviral therapy is indicated, the nucleoside analogue Tenofovir disoproxil fumarate (TDF) is recommended as first line therapy.

The recommended dose of TDF is 300mg once daily for adults.

TDF is a potent inhibitor of HBV replication and is one of the most effective antiviral therapies to achieve undetectable HBV DNA levels and normalization of ALT levels. It reduces liver inflammation, prevents disease progression, and reduces the risk of hepatocellular carcinoma. TDF has a high genetic barrier to resistance, and HBV drug resistance over long-term follow up has not been described to date. TDF has very low rates of side effects and can be administered orally once daily with no food restrictions. The main toxicity of TDF is limited to renal and bone disease and has been predominantly described in HIV positive individuals.

Box 6: Treatment is recommended for:

As a priority:
ALL ADULTS, ADOLESCENT AND CHILDREN WITH: **CHORNIC HEPATITIS B AND** **EVIDENCE OF COMPENSATED OR DECOMPENSATED CIRRHOSIS** **OR** **CIRRHOSIS BASED ON APRI SCORE >2 IN ADULTS** **OR** **FIBROSCAN MEASUREMENT >11-14 kPa**

Treatment is recommended in adults with chronic hepatitis B who do not have clinical evidence of cirrhosis (or based on APRI score ≤2 in adults), but are:

- 30 years old AND
- Persistently have abnormal ALT levels (Persistently abnormal ALT level is defined as three ALT tests above the upper limit of normal, made during a 6 to 12-month period) OR
- Have evidence of high-level HBV replication (HBV DNA >20 000 IU/mL) (only if HBV DNA available)

This recommendation is regardless of HbeAg status.

It is recommended that all ADULT cases assessed for treatment outside the settings of Divisional Hospital be discussed with the Department of Internal Medicine. Occasionally patients may present with severe extra hepatic manifestations of hepatitis B disease (e.g. glomerulonephritis, vasculitis) and these situations would be considered as an indication for treatment regardless of ALL other measures.

Table 4: Upper limit of normal values for ALT

Recommended Upper Limit of Normal for ALT level (International)		Recommended Upper Limit of Normal for ALT level (Fiji)
Men	30 IU/ml	X 30 IU /ml
Women	19 IU/ml	X 19 IU/ml

When using ALT measurements alone to determine whether treatment will be initiated, other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidaemia and fatty liver should be excluded.

5.2 WHO NOT TO TREAT

- **Treatment is not recommended and can be deferred for** persons without clinical evidence of cirrhosis (or APRI score ≤2 in adults), and
- persistently normal ALT levels and
- low levels of HBV replication (HBV DNA <2000 IU/mL, where DNA testing is available)

This recommendation is regardless of HBeAg status or age.

Pregnant women who are Hepatitis B Positive should get a viral load testing close to 28 weeks and commenced on treatment if HBV DNA >200,000 IU/mL

TDF TREATMENT AND RENAL IMPAIRMENT

TDF is principally eliminated via the kidney and can cause a decline in renal function. Factors associated with a higher risk of renal dysfunction are given in Box 7. At baseline and during treatment, TDF dose should be reduced if the estimated glomerular filtration rate (eGFR) is <50 mL/min (Table 5). Alternatively, patients can be switched tenofovir alafenamide (TAF).

Box 7: Conditions in which TDF treatment is contraindicated

Decompensated cirrhosis
CrCl<50mlmin
Older age
Body mass index (BMI) <18.5kg/m2 (or body weight < 50kg)
Poorly controlled hypertension
Uncontrolled diabetes
Active glomerulonephritis
Concomitant use of nephrotoxic drugs or a boosted PI for HIV
Solid organ transplantation

Table 5: Recommended TDF dose adjustments in renal impairment

Creatinine clearance (mL/min)	TDF dose
≥50	One 300 mg tablet every 24 hours
30-49	One 300 mg tablet every 48 hours
10-29	One 300 mg tablet every 72-96 hours
<10	One 300 mg tablet every 7 days

Creatinine clearance can be calculated using the Cockcroft-Gault formula:

eGFR (creatinine clearance) = [(140-age) x wt. (in Kg) x 0.85 (if female)] / [72 x creat.(mg/dL)]

Alternative:

Modification of diet in renal disease (MDRD) formula = 186.3 x (Scr) $^{-1.154}$ x (age) $^{-0.203}$ x 0.742 (if female) x 1.210 (If African American)

5.3 SPECIAL POPULATIONS

ACUTE HEPATITIS B

Acute hepatitis B infection is generally asymptomatic but can manifest as an acute viral syndrome with symptoms including mild fevers, chills, headaches, fatigue, and malaise. It may also be associated with anorexia, nausea and vomiting with right upper quadrant discomfort and jaundice in more severe cases. Other diseases to be considered with this presentation include other hepatitis viruses (A, C and E), and other systemic infections that affect the liver including dengue fever, leptospirosis, EBV and CMV infection. Non-infectious causes of hepatitis including autoimmune disease, obstruction of the biliary system and drug induced liver disease should also be considered.

Diagnosis is based on clinical presentation and confirmation by laboratory findings of raised liver enzymes and positive HBV infection markers, with positive anti-HBc IgM indicating recent hepatitis B infection. Treatment is generally limited to supportive care, including fluid resuscitation, management of headache, nausea, and vomiting. Antiviral therapy is not necessary for uncomplicated symptomatic acute hepatitis B, as >95% of immunocompetent adults will spontaneously clear HBV infection. Persons with fulminant or severe acute hepatitis may benefit from antiviral therapy with TDF (or entecavir) to improve survival and reduce the risk of recurrent hepatitis B. The duration of treatment is not established, but continuation of antiviral therapy for at least 3 months after seroconversion to anti-HBs or at least 12 months after anti-HBe seroconversion without HBsAg loss is generally advised. Acute or subacute liver failure can be manifest by nausea and vomiting, progressive jaundice, development of ascites, haemorrhage from coagulopathy, severe infection, respiratory of circulatory collapse and changes in mental status including agitation, confusion and in loss of consciousness. This is uncommon with acute hepatitis B.

Note: Acute Hepatitis B infection presenting and diagnosed at primary health care facilities, e.g., GOPD, sub divisional hospitals should be reported in NNDSS and followed up for 6 months. Those who meet the criteria for chronic HBV should be referred to appropriate care pathway, e.g., medical clinic, hub centre.

CHILDREN AND ADOLESCENTS

All children in the Pacific Islands should know their hepatitis B status. Foetus and newborns exposed to HBV infection becomes chronic carriers >90% of the time. Although most children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease is important.

Testing in children:
1. All babies born to positive mothers and should be done at around 6-12 months of age or at least 1 month after the last dose of Hepatitis B vaccine. If antiHBs <10mIU/ml repeat the whole schedule of Hepatitis B vaccination and serological testing repeated at 1 month after the completion of repeat schedule.
2. Children who present with elevated LFTs
3. In areas of high prevalence, population screening and opportunistic screening
4. All positive cases should be linked to care
5. Ensure to check father/caregiver Hep B serological status

Indications for Treatment:
1. Any child with cirrhosis should be started on antiviral therapy
2. HBsAg positive children with persistently elevated ALT on 2 or 3 occasions 3-6 months apart.
If HBV DNA is available, it should be used to support decision to start therapy. Liver biopsy is not mandatory.

Table 6: Recommended TDF dosing for children >2 years of age or ≥17 kg body weight

Body weight (kg)	TDF dosing
≥17 - 22	150mg tablet orally daily
≥22 - 28	200mg tablet orally daily
≥28 – 35	250mg tablet orally daily
≥35	300mg tablet orally daily (adult dose)

Chronic Hepatitis B in children:
CHB is usually benign and asymptomatic in children, there are low curative response rates with antiviral treatment and concerns over long-term safety and risks of drug resistance, therefore a conservative approach to treatment is generally indicated, unless there is cirrhosis. Although most children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease is important. The use of nucleotide analogues and identification of appropriate cut-offs have not yet been defined in children. TDF is approved for use in adolescents and children above the age of 2 years for HBV, and entecavir is approved for children with CHB above 2 years of age. Children with normal ALT, 6 monthly ALT is recommended. Children with raised ALT, 3 monthly ALT is recommended and review at 6months whether treatment is to be initiated.

Children receiving immunosuppressive therapy:
- reactivation of hepatitis B in patients undergoing immunosuppressive therapy can lead to severe hepatitis.
- recent guidelines by ESPGHAN recommend that all children who are candidates for immunosuppressive therapy be screened for HBsAg and anti-HBc before starting immunosuppression.
- HBsAg negative children should be vaccinated as soon as possible before starting immunosuppressive treatment.
- HBsAg positive children are recommended to receive antiviral treatment with nucleoside analogues at start of immunosuppression and then for an additional 12 months after stopping immunosuppressive treatment.

PREGNANT WOMEN AND THEIR BABIES

All women should be screened for HBsAg early in pregnancy. Ensure to check positive mothers' sexual partners' Hep B serological status.

Indications for treatment in adults with CHB also apply to pregnant women. TDF is the preferred antiviral, because it has a better resistance profile and more extensive safety data in pregnant HBV-positive women. Indications for antiviral treatment are the same as non-pregnant women which are those women with high HBV DNA viral loads (defined as HBV DNA > 20000IU/mL in HBeAg positive mothers or > 2000 IU/mL in HBeAG negative mothers), persistently elevated ALT > 2 times the upper limit of normal and for those with non-decompensated Liver disease or Cirrhosis (high mortality rate)
There may be an additional benefit to commencing TDF in the third trimester to further reduce HBV vertical transmission. However, due to lack of widely available HBV viral load testing there is currently no official WHO recommendation on this policy. If a pregnant woman remains untreated or anti-HBV therapy is discontinued during pregnancy or early after delivery for any reason, close monitoring is necessary, as there is a risk of hepatic flares, especially after delivery.

For prevention of mother-to-child HBV transmission, the most important strategy is to deliver the first dose of hepatitis B vaccine as soon as possible after birth, within 24 (and preferably within 12hours) followed by

at least three timely subsequent doses per Fiji immunization schedule that is at weeks 6, 10 and 14. Babies of HBsAg positive mothers, should also receive HBIG 0.5mls IMI within 12hours after delivery (can be given up to 7 days after birth). Breastfeeding is not a contraindication if mom is HBsAg positive or a chronic carrier of the Hepatitis B virus. Infants born to HBsAg positive mothers should be tested for anti-HBsAg and HBsAg between 1month to <6 months after the last dose of HBV. If antiHBs <10 mlU/ml repeat the whole schedule of Hep B vaccination and serological testing repeated at 1 month after the completion of repeat schedule. Follow up in the neonatal clinic through the first year of life. Repeat HbsAg test at 1 year of age. If Negative discharge and if positive discuss with Paediatric Consultant.

HIV/HBV CO-INFECTION

Consequences of HIV infection on HBV include higher rates of chronicity after acute HBV infection, higher level of HBV replication, more rapid progression to cirrhosis and HCC, higher liver-related mortality, and decreased treatment response compared with persons without HIV coinfection.

All persons living with HIV/HBV co-infection infection should be commenced on ART regardless of CD4 count. The recommended ART regimen should include TDF (or tenofovir alafenamide (TAF) where available). Please refer to the Fiji HIV Care and Antiretroviral Therapy Guidelines for more information.

5.4 ALTERNATE ANTIVIRAL THERAPY

TDF is contra-indicated in children with significant renal impairment and in this case entecavir is recommended.

Entecavir is a nucleotide analogue with very high efficacy against HBV. It has an excellent safety profile and very low rates of resistance, except in the setting of prior lamivudine treatment failure.

Table 7: Recommended dosing for Entecavir

Population	Body weight (kg)	Recommended once daily dose of oral solution (mL)[1]	
		Treatment Naive	Treatment Experienced
Children 2 years of age or older and weighing at least 10 kg	10 to 11	3	6
	>11 to 14	4	8
	>14 to 17	5	10
	>17 to 20	6	12
	>20 to 23	7	14
	>23 to 26	8	16
	>26 to 30	9	18
	>30	10	20
Children with renal impairment	**Creatinine clearance (mL/min)**	**Recommended dose (mg)**	
	≥50	0.5 mg orally every 24 hours	
	30 to 49	0.5 mg orally every 48 hours	
	10 to 29	0.5 mg orally every 72 hours	
	<10	0.5 mg orally every 7 days	

[1] These dose calculations are based on an oral solution of strength 0.5mg/10mL. The oral solution should be given to children with a body weight up to 30 kg.
[2] Treatment naïve children with body weight more than 30 kg should receive one 0.5 mg tablet once daily.
[3] Treatment experienced children with body weight more than 30 kg should receive one 1 mg tablet once daily.

5.5 MONITORING

Patients commenced on treatment should be monitored for response, toxicity, and adherence. TDF is a highly potent well-tolerated agent, and most patients will suppress to low or undetectable levels of HBV DNA within 24-48 weeks.

Minimal **annual** monitoring consists of:

- ALT/AST/FBC (plus HBsAg, HBeAg, HBV DNA if available)
- Creatinine/eGFR
- APRI (or Fibro scan if available)
- Adherence to treatment

More frequent monitoring (**3-6 monthly**) is recommended in the following situations:

- during the first year of therapy
- patients with cirrhosis
- adherence concerns
- HIV-co infection
- renal impairment

5.6 DISCONTINUING

All persons with chronic hepatitis B cirrhosis should be continued on lifelong antiviral therapy.

Patients without cirrhosis can cease therapy if they fulfil ALL of the following criteria:

1. **No** evidence of cirrhosis and APRI < 2
2. **HBsAg loss and/or** HBeAg loss and seroconversion to anti-HBe with completion of at least one additional year of treatment
3. **and** persistently normal ALT
4. **and** persistently undetectable HBV DNA

OR

1. **No** evidence of cirrhosis and APRI < 2
2. Evidence of persistent HBsAg loss and completion of at least one additional year of treatment, regardless of prior HBeAg status (where HBV DNA is not available).

There is a significant risk of relapse after therapy is discontinued therefore this should only be considered in situations where the patient can be closely monitored after stopping, preferably with HBV DNA. ALT and HBV DNA should be measured monthly for the first three months after stopping and then 3 monthly for the first year. Severe acute exacerbations of hepatitis have been reported requiring the resumption of antiviral therapy. Stopping therapy is not advised in situations where HBV DNA testing is not available, but if essential then the same frequency of ALT/AST testing should be performed.

Patients should be advised of the potential adverse outcomes of premature cessation of therapy without medical supervision including antiviral resistance and flares.

Adherence and treatment failure

Adherence is a critical component to treatment success. The patient should be counselled both before and during treatment to ensure they understand the need and benefit to taking treatment. Adherence can be measured through:

- Direct self-report
- Pharmacy refill records
- Viral load monitoring (where available)

Primary non-response is defined as less than 10-fold drop in HBV DNA after 3 months of treatment and is very rare in persons initiating TDF therapy. In most resource limited settings (even if available) checking HBV DNA levels after 3 months is therefore NOT warranted.

Virological breakthrough is defined as rebound of HBV DNA more than 10-fold from nadir in a person who has had an initial response. If HBV DNA is not being measured it may be suspected through an increase in ALT/AST. The commonest reason for virological breakthrough whilst on TDF is non -adherence to therapy, or interruption in drug supply. Failure due to antiviral resistance is very uncommon. Treatment adherence and problems with drug access should be fully assessed.

Toxicity monitoring

The main toxicity of TDF is related to renal and bone disease, however this is rare in persons not co-infected with HIV.

In the setting of low eGFR (<50 ml/min) TDF dose reduction should be implemented **(Table 5)**. Monitoring should be performed annually using urine dipstick testing (proteinuria and glycosuria) and creatinine for eGFR. Patients with underlying renal disease, or at high risk for toxicity should be monitored more frequently (6 months or more)

All patients commencing therapy should have an assessment of baseline renal function and renal risk.

06

DISEASE PROGRESSION AND MONITORING FOR COMPLICATIONS

SECTION 6: DISEASE PROGRESSION AND MONITORING FOR COMPLICATIONS

6.1 FOLLOW UP ON CHRONIC HEPATITIS B PATIENTS NOT ON TREATMENT

Continued monitoring is necessary in all persons with CHB, including those who do not currently meet the criteria for treatment, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease.
The following should be monitored at least **annually** in patients who are not commenced on treatment:

- ALT, AST and FBC, (HBsAg, HBeAg and HBV DNA if available)
- Non-invasive test for cirrhosis, APRI (or Fibro scan if available)

More frequent monitoring (6 monthly):

- Is recommended for patients not yet on treatment with intermittently abnormal ALT, fluctuating HBV DNA between 2000 and 20,000 (where testing available) and HIV co-infection

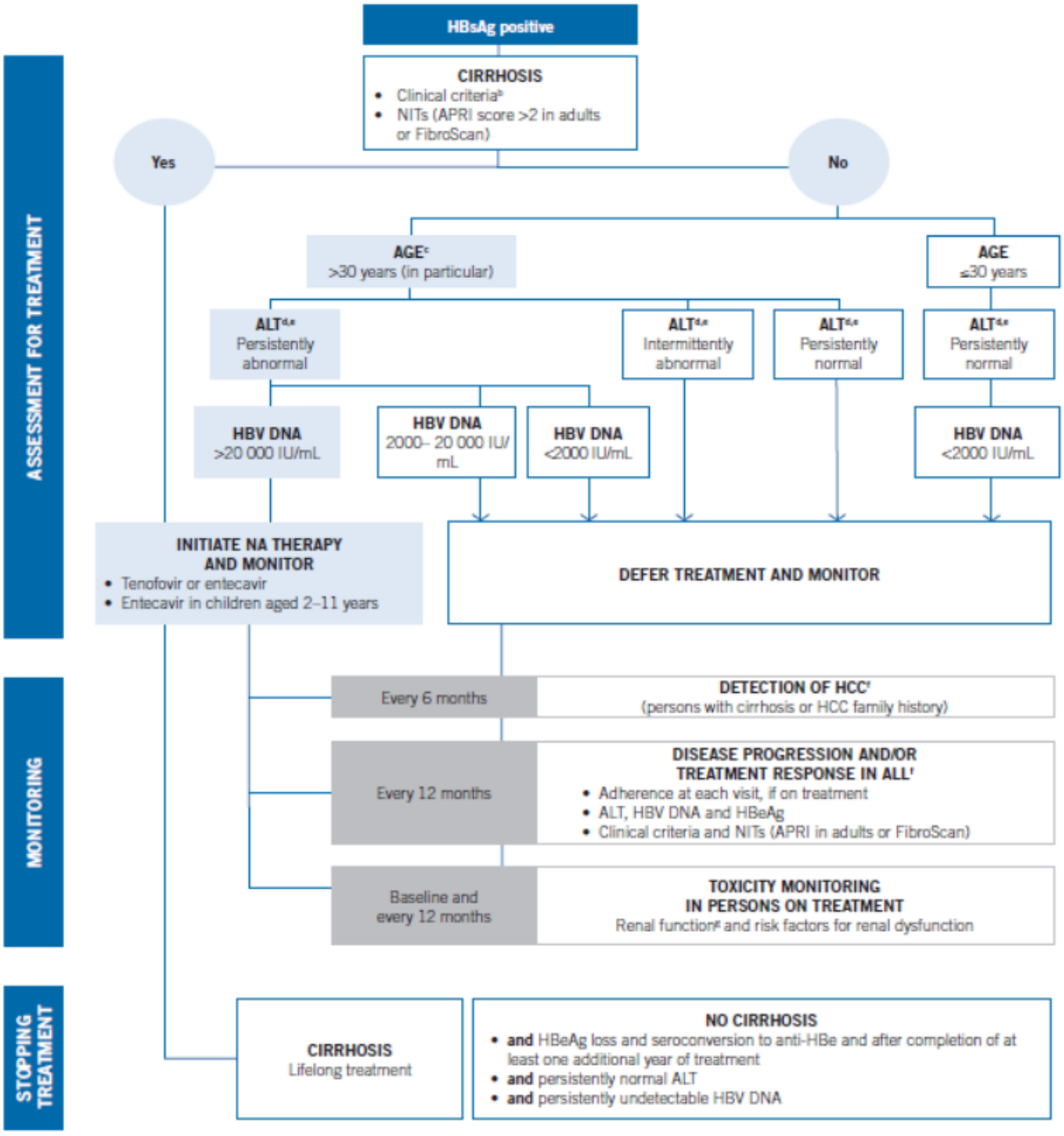
6.2 FOLLOW UP FOR CHRONIC HEPATITIS B PATIENTS ON TREATMENT (MONITORING FOR HCC)

Routine monitoring for HCC using 6 monthly ultrasound and alpha-fetoprotein testing is recommended for the following groups:

- All persons with cirrhosis regardless of age or other risk factors
- those with a family history of HCC
- persons aged over 40 years without clinical evidence of cirrhosis (or APRI score ≤2), and with HBV DNA level >2000 IU/mL (where HBV DNA testing is available)

However, it should be recognized that screening for HCC is only effective in terms of survival benefit if there is a suitable pathway for treatment of small HCC.

Figure 4: Algorithm of WHO Recommendations on the Management of Persons with Chronic Hepatitis B Infection[a].



NITs - non-invasive tests, ALT - alanine aminotransferase, APRI - aspartase aminotransferase-to-platelet ratio index

[a] Defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more. The algorithm does not capture all potential scenarios, but the main categories for treatment or monitoring. Recommendations for settings without access to HBV DNA testing are provided in the relevant chapters.

[b] Clinical features of decompensated cirrhosis: Portal hypertension (ascites, variceal hemorrhage and hepatic encephalopathy), coagulopathy, or liver insufficiency (jaundice). Other clinical features of advanced liver disease/cirrhosis may include hepatomegaly, splenomegaly, pruritus, fatigue, arthralgia, palmar erythema, and oedema.

[c] the age cut-off of >30 years is not absolute, and some persons with CHB less than 30 years may also meet criteria for antiviral treatment.

[d] ALT levels fluctuate in persons with chronic hepatitis B and require longitudinal monitoring to determine the trend. Upper limits for normal ALT have been defined as below 30 U/L for men and 19 U/L for women, though local laboratory normal ranges should be applied. Persistently normal/abnormal may be defined as three ALT

determinations below or above the upper limit of normal, made at unspecified intervals during a 6–12–month period or predefined intervals during 12-month period.

[e] Where HBV DNA testing is not available, treatment may be considered based on persistently abnormal ALT levels, but other common causes of persistently raised ALT levels such as impaired glucose tolerance, dyslipidemia and fatty liver should be excluded.

[f] All persons with CHB should be monitored regularly for disease activity/progression and detection of HCC, and after stopping treatment for evidence of reactivation. More frequent monitoring maybe required in those with more advanced liver disease, during the first year of treatment or where adherence is a concern, and in those with abnormal ALT and HBV DNA levels >2000 IU/mL, not yet on treatment.

[g] Before initiation, assessment should be done of renal function (serum creatinine level, estimated glomerular filtration rate, urine dipsticks for proteinuria and glycosuria, and risk factors for renal dysfunction (decompensated cirrhosis, CrCl <50 mL/min, poorly controlled hypertension, proteinuria, uncontrolled diabetes, active glomerulonephritis, concomitant nephrotoxic drugs, solid organ transplantation, older age, BMI <18.5 kg/m2 (or body weight <50 kg), concomitant use of nephrotoxic drugs or a boosted protease inhibitor (PI) for HIV). Monitoring should be more frequent in those at higher risk of renal dysfunction.

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REFERENCES

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