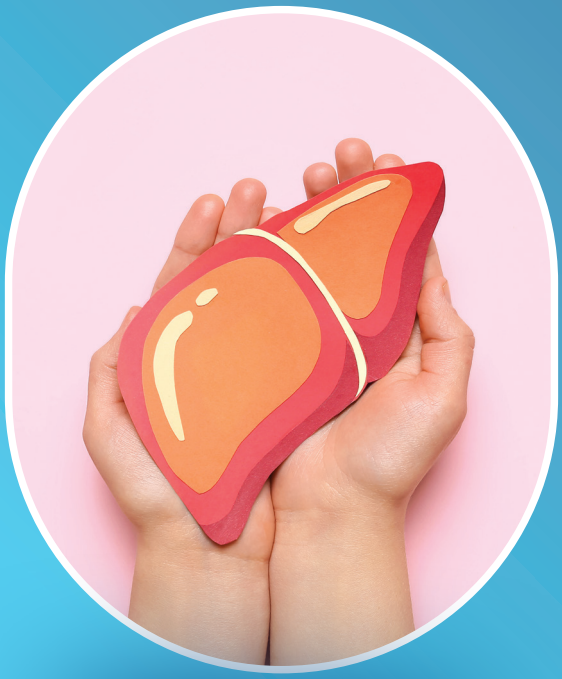
The Management of Hepatitis B

A Guide for Health Professionals



The Hepatitis Foundation of New Zealand

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The Hepatitis Foundation of New Zealand

The Hepatitis Foundation of New Zealand (HFNZ) is a charitable trust, contracted to Health New Zealand to provide a health monitoring programme that supports people living with hepatitis B.

What do we deliver?

Our free, lifelong, national monitoring programme is for all people living with hepatitis B in New Zealand to help improve health outcomes. People enrolled in this programme receive regular monitoring, education, support and referral to secondary care (if required).

We work in partnership with GP clinics and other health providers to support the ongoing care of their patients living with hepatitis B.

How do we deliver this?

HFNZ keep GPs informed of patient management, through letters and copies of results. We ask that you copy us into any investigations or results relating to the management of hepatitis B; LFT's, hepatitis serology, AFP, liver ultrasounds that you might request.

We provide enrolled patients with

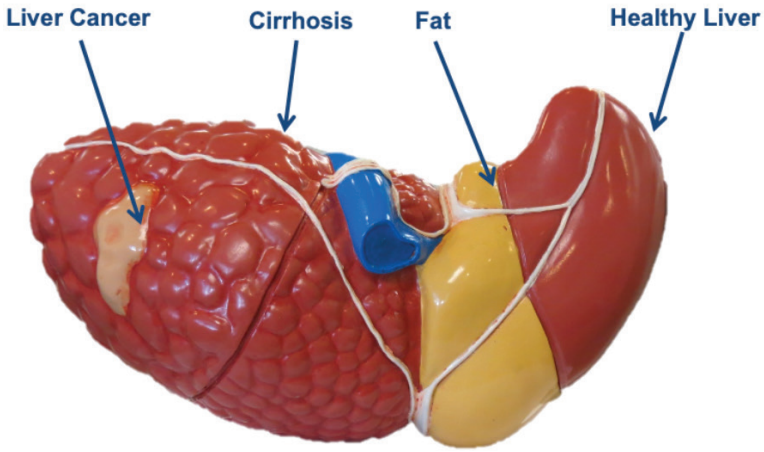
- Blood tests six-monthly (or as required)
- Clinical oversight
- Education
- Support
- Home visits if required
- Free testing of other family members

Hepatitis is one of the world's most common Infectious diseases

About 350 million people worldwide have the virus. Every year between 500,000 to one million people die of hepatitis B (HBV) related chronic hepatitis (CHB), cirrhosis or liver cancer (HCC).

In New Zealand almost 94,000 people are estimated to have HBV. New Zealand is one of the 196 countries participating in the World Health Organisation's initiative to eliminate viral hepatitis by 2030.

Long-term, six-monthly blood test monitoring of people infected with CHB pick up early signs of liver disease such as cirrhosis and HCC, reducing morbidity and mortality.



World Health Organisation Elimination Targets

- Reducing new infections by 90%
- Diagnosing 90% of people with viral hepatitis
- Reducing mortality by 65%
- Treating 80% of eligible people

Screening for Hepatitis B

High-risk groups include:

- Anyone over 35 years of age
- Especially Māori, Pasifika or Asian ethnicity
- Born outside New Zealand, from a high risk country
- Have a mother or close family member with hepatitis B
- Live with someone who has hepatitis B
- Had unprotected sex with a person living with hepatitis B
- Have ever injected drugs
- Have received a tattoo using unsterilised equipment

Chronic hepatitis B can be hard to detect as many people with the virus have no symptoms until the liver is damaged. This is why regular blood tests are so important, even for patients who feel well.

As a part of the HFNZ services, our specialist nurses triage patients with abnormal blood test results and our Clinical Specialists will refer patients to secondary care for further investigations and/or commence treatment when deemed necessary. **GPs can also commence treatment** (read through this booklet for more information).

Key Terms

- Hepatitis B virus (HBV): Acute or Chronic
- Chronic hepatitis B virus (CHB): HBV present >6 months
- Fibrosis: Scarring of the liver
- Cirrhosis: Extreme scarring of the liver
- Hepatocellular carcinoma (HCC): Primary Liver cancer
- Steatosis: Fatty Liver

Screening tests for Hepatitis B

- **HBsAg** tests whether someone is currently infected with HBV
- **Anti-HBc** indicates current/past infection
- **Anti-HBs** indicates immunity >10 and HBsAg is negative.
- **HBeAg** indicates a high level of infectivity

Initially a positive **HBsAg** test simply reveals the presence of HBV in the blood. In order to consider an individual to have CHB, a further confirmatory test six months later is required.

HBsAg, **Anti-HBs** and **Anti-HBc** testing should be offered to household and sexual contacts of people with HBV and vaccination should be offered via GP to those who are susceptible to the virus. This is free of charge on the immunisation schedule to people under 18, sexual partners, household contacts, and other groups.

Hepatitis B Testing

Who to test:

- Anyone over 35 years of age
- Especially Māori, Pasifika or Asian ethnicity
- Born outside New Zealand from a high risk country
- Have a mother or close family member with hepatitis B
- Live with someone who has hepatitis B
- Had unprotected sex with a person living with hepatitis B
- Have ever injected drugs
- Have received a tattoo using unsterilised equipment.

Diagnostic serology tests

1. **HBsAg** Hepatitis B surface Antigen
2. **Anti-HBs or HBsAb** Hepatitis B surface Antibody
3. **Anti-HBc or HBcAb** Hepatitis B core Antibody

If surface antigen is negative and antibody positive, the patient is immune and no further action is needed.

HBsAg Positive

Refer to The Hepatitis Foundation with results of: HBsAg (+), HBeAg (+/-), LFT's (Incl AST), AFP, HBV DNA, FBC and Patient Consent.

HBsAg Negative

Anti-HBs and Anti-HBc (-) consider HBV vaccination.
If Anti-HBc (+) and HBsAg (-), indicates past infection/exposure therefore natural immunity.
NO Vaccination required.

HFNZ will organise:

- Additional blood tests and investigations
- Liver ultrasound (if required)
- Long term monitoring with The Hepatitis Foundation
- Referral to secondary care where appropriate. GP's/Midwives can still refer to secondary care when necessary. Refer to your 'Regional Health Pathway' for more information.

Patient Management
HFNZ Monitoring Programmme

Under the hepatitis B monitoring programme, people living with hepatitis B are offered regular blood tests to check whether they are still infected with the virus. HFNZ will keep GPs informed of patients regular blood test results.

Research shows six-monthly monitoring of chronic hepatitis B patients is the gold standard of care to help reduce the risk of liver disease (including HCC)[1]. Blood tests can detect early signs of liver disease, HCC and cirrhosis.

HFNZ Long-term monitoring includes:

- New patient education, HBV assessment following HBV diagnosis and letter to GP.
- HBV education and support for patients and healthcare providers.
- Six-monthly blood tests - results of which are copied to GP's:
  - **HBsAg** hepatitis B surface antigen
  - **HBeAg** hepatitis B e antigen
  - **LFT** Liver function tests (All LFT's including AST)
  - **AFP** alpha-fetoprotein tests
  - **FBC** Full Blood Count
  - **HBV DNA** Hepatitis B Viral Load (when required)
- **Referrals for six-monthly liver ultrasound scans for patients with an increased risk of liver cancer (HCC),** e.g:
  - History of HCC in first degree relatives
  - Cirrhosis
  - Reach B>5% risk of HCC in ten years
- Referrals to secondary care and/or HFNZ specialist assessment where appropriate.
- Arranging liver Elastography/Fibroscan (when required).
- Copies to GP's of all relevant correspondence including referrals and electronic blood test results.
- May refer to GP for long-term antiviral treatment.

Blood Tests

HBsAg

Hepatitis B surface antigen

A positive or reactive HBsAg test result means the patient is infected with hepatitis B and is HBV positive therefore at risk of liver damage. HBV is a blood borne virus. Further testing is needed to determine if this is a new (acute) or a long-standing (chronic) hepatitis B infection.

Anti-HBs or HBsAb

Hepatitis B surface antibody

A positive or reactive HBsAb test result indicates the immune system is active against the virus. A positive HBsAg and HBsAb can occur at the same time and still has active infection with HBV.

Anti-HBc or HBcAb

Hepatitis B core antibody

A positive or reactive HBcAb test result indicates a past or current hepatitis B infection. If HBsAg negative and HBcAb positive this person has natural immunity regardless of HBsAb level.

HBeAg

Hepatitis B e antigen

This checks the status of the infection. A positive or reactive result indicates the virus is in the more active form. The e-antigen is a protein from the hepatitis B virus that circulates in infected blood when the virus is actively replicating. Being HBeAg positive means the patient is likely to have a high level of virus present, which is related to increased risk or transmission.

AFP

Alpha-fetoprotein

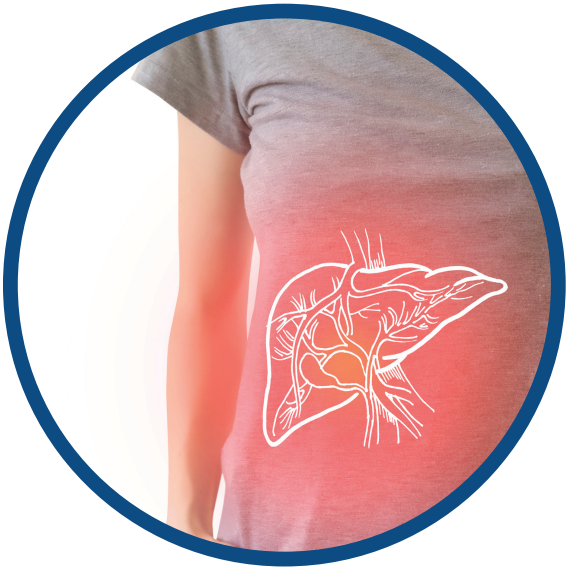
This biomarker is primarily an indicator for HCC. AFP >20 Ug/L will pick up approx. 40% of early stage HCC (liver ultra sound scans pick up approximately 60% of early HCC and are added in high-risk cases). Screen for AFP six-monthly. If AFP is elevated seek advice. Request HBV DNA if AFP is raised.

NOTE: AFP is raised in pregnancy.

Request HBV DNA if AFP is raised.

HBV DNA (Hepatitis B Viral Load)

- HBV DNA at least every three years >30yrs or six-monthly when on Anti Viral Treatment (HFNZ Guidelines).
- Request HBV DNA if ALT/AST is abnormal. Deranged LFT can indicate Liver inflammation, HBV flare or HCC and may need investigation of other causes.
- Depending on HBV DNA result consider Anti-Viral treatment.



Interpretation of hepatitis B blood tests

HBsAg	Anti-HBc	Anti-HBs	IgM Anti-HBc	Result	Action Required
Negative	Negative	Negative	N/A	Susceptible	Vaccinate if exposed to hepatitis B risk factors unless previous full vaccina-tion course completed
Negative	Positive	Positive	N/A	Immune due to natural infection	No action required
Negative	Negative	Positive	N/A	Immune due to hep B Vaccination	No action required
Positive	Positive	Negative	Positive	Acutely Infected	Retest in six months. Notify Public Health.
Positive	Positive	Negative	Negative	Chronically Infected	Refer to HFNZ
Negative	Positive	Negative	N/A	Previous Natural Infection	No action required
Positive	Positive	Positive	Negative	Chronic infection (even though antibodies are present)	Refer to HFNZ

Hepatocellular carcinoma (HCC)

Chronic hepatitis B leads to an increased risk of death from liver cirrhosis and liver cancer. Primary liver cancer is the seventh most common type of cancer globally (fifth for men) and the fourth leading cause of annual cancer deaths worldwide (second for men).

Men develop liver cancer more than twice as frequently as women. In settings with limited resources and a high burden of hepatitis B, people are often diagnosed with Hepatitis B at an advanced stage of disease (decompensated cirrhosis or HCC).

Although 80–90% of people with hepatitis B associated HCC already have cirrhosis when diagnosed, HCC may occur without cirrhosis. A further challenge is that HCC is usually asymptomatic until it is at a clinically advanced stage.

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 tumours and underlying liver function and is improved if treatment can begin at an early stage of the disease, when the tumour is small.

Treatments would include microwave ablation, radio frequency ablation or percutaneous ethanol injection of small tumours. Current surveillance is with ultrasound and AFP measurement but with a consensus that people with Chronic Hepatitis B (CHB) should be monitored for HCC every six months.

HCC rates secondary to HBV in New Zealand are rising despite infant vaccination due to aging population and immigration from endemic areas, currently more than 80 cases per year.

Ref: (Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024. Licence: CC BYNC-SA 3.0 IGO).

Treatment

Hepatitis B Virus management - What is the current state of the Art?

NZ Doctor - May 2024
Dr Chris Moyes, Medical Director HFNZ

Hepatitis B Virus is endemic in New Zealand and many parts of the world including the Pacific, South-East Asia, the Middle East, and Africa. Although universal vaccination of infants has been the policy in New Zealand for over 30 years, there is still a substantial reservoir of chronic infection in older adults and in immigrants of all ages from many countries. In some cases, HBV infection is aggravated by hepatitis D (delta), which is prevalent in Samoa and Kiribati and only found in people with HBV. Consequently, the complications of active hepatitis, cirrhosis, and HCC continues to increase, with several hundred deaths a year from HCC alone.

What are current treatments?

Recommended medications for most patients in NZ are either entecavir 0.5mg daily or tenofovir disoproxil 245mg daily, both of which can be prescribed by family practitioners.

Both are extremely effective at suppressing HBV and reduce liver damage and HCC risk with very few side effects and no interaction with other medications, but need to be continued long-term.

Tenofovir disoproxil is considered to be safest for pregnancy and is the first choice for women of reproductive age. It can aggravate renal failure and very occasionally causes renal tubular problems so

creatinine, calcium, and phosphorus levels should be monitored, along with periodic liver function and viral load (HBV DNA quantification).

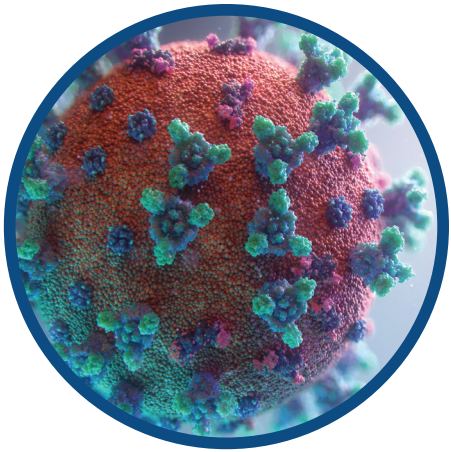
Who should be treated?

International guidelines vary but all agree that:

- Patients with persistently raised ALT levels and HBV DNA above 20,000 IU/mL should be treated.
- Patients under 30 yrs who are HBeAg positive with high HBV DNA (often many millions of units) but normal ALT (immune tolerance stage) do not usually need treatment.

This leaves a 'grey' area consisting of many patients where recommendations vary, but at HFNZ we have chosen to use a risk-based approach as endorsed by the Asia Pacific Association for the Study of the Liver[2].

REACH-B is a score that predicts risk of HCC (on the free MDCalc App). **At present we refer for possible treatment, all patients with a risk above 2% in ten years (this includes many patients with normal ALT.**



Treatment reduces subsequent HCC by around ¾ but does not eliminate risk.

However, many experts now consider that earlier treatment may further reduce long-term risks of HCC by reducing integration of HBV into the liver cell genome, and recommend offering anti-virals to any patients over thirty years of age with an HBV DNA > 2000 or HBeAg positive[3].

This is included in current BPAC guidelines, and is suitable for primary care management. Secondary care referral can be restricted to those with evidence of severe fibrosis/cirrhosis or co-morbidities.

How long should treatment last?

All patients with chronic HBV once commenced on Anti-Viral treatment will need it lifelong, unless otherwise advised and further assessed under a Specialist.

Chronic HBV patients also need regular lifelong monitoring for any possible hepatocellular carcinoma and/or progression to cirrhosis.

Detection of Hepatocellular Carcinoma

Patients with chronic HBV infection are at much increased risk of HCC, increasing with age, male gender, and especially with cirrhosis (those with cirrhosis should be under secondary care). Preclinical detection of HCC is essential for any prospect of cure.

We include AFP in our six-monthly blood tests, but this detects less than half of tumours at a very early stage (Barcelona 0/A who have high cure rates)[4-6]. Six-monthly ultrasounds are more sensitive, at around 58%[6], but are not logistically practical for all of the 20,000 patients we supervise, and a pragmatic approach is to confine this to patients with REACH-B score 10 yr risk of >5 per cent or family history of HCC.

We are currently piloting the use of a more sensitive marker (protein induced by vitamin K absence or antagonist II; PIVKA II) in combination with AFP and a weighting for age and gender (GAAD) which is reported to be 73 per cent sensitive for early stage HCC[6], and this may become the standard of care.

Anti-viral Medications

Entecavir is an oral tablet used in adults who have active virus and liver damage. Entecavir is funded as a first-line therapy for patients with chronic hepatitis B. Almost all patients achieve viral suppression (undetectable HBV DNA) and biochemical response (ALT below the upper limit of normal). Entecavir resistance is rare at less than one percent after six years.

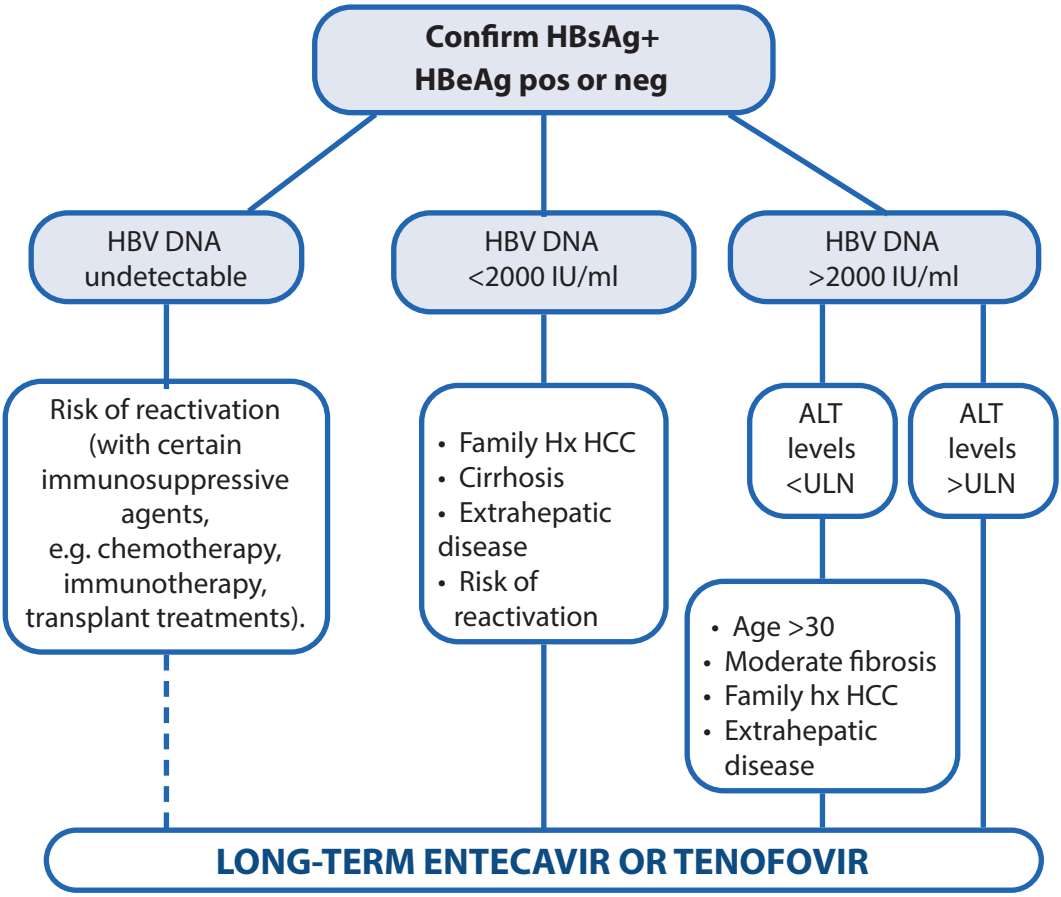
Tenofovir is also an oral tablet. It has replaced Adefovir in New Zealand as the first-line therapy for Lamivudine-resistant hepatitis B infection. It is the preferred treatment during pregnancy and breastfeeding and dramatically reduced the risk of vertical transmission.

No resistance to Tenofovir has been observed after five years of therapy. Renal function (creatinine, calcium, and phosphorus) should be assessed before commencement of Tenofovir and periodically while on treatment.

Pegylated Interferon (Pegasys) boosts the body's immune system and changes the virus' ability to multiply. It is a synthetic version of a protein naturally produced by the body (interferon). In select individuals it may be recommended as treatment. Pegasys is injected under the skin once a week for 48 weeks. The goal of therapy is to put the virus into an inactive state. The virus may be cured in a very small proportion of people treated.

The hepatitis B virus cannot usually be cured and in most cases, anti-viral therapy needs to be lifelong. In select cases therapy may be discontinued but only under close supervision by a specialist. Pegylated Interferon (Pegasys) is not widely used in NZ due to effective Anti-Viral treatment available.

Recommendations for HBV Therapy



Seroconversion of hepatitis B surface antigen

HBsAg seroconversion when a patient has cleared the Hepatitis B Virus (HBV) from their blood. (**HBsAg** is negative or not detected).

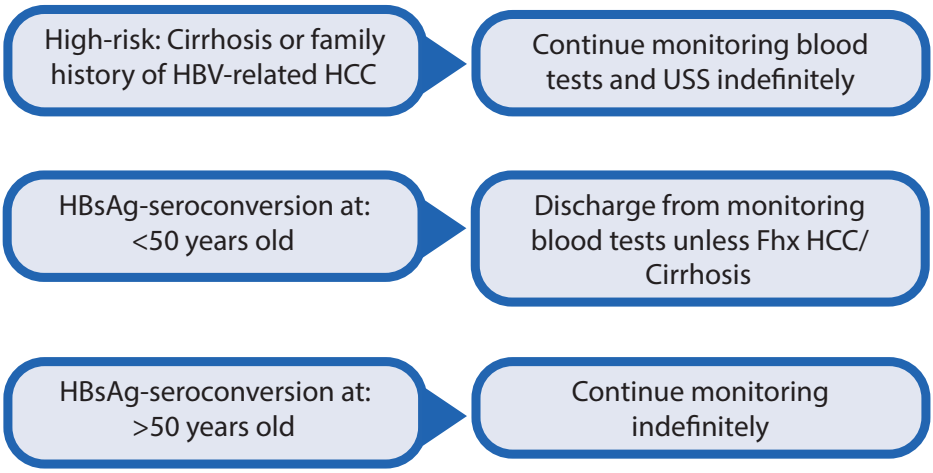
About one percent of people with hepatitis B will spontaneously lose **HBsAg** per year. Following seroconversion from HBsAg + to HBsAg - the HBV infection is usually no longer active and they are immune from further infection, but can still be at risk of HCC.

HBV reactivation can occur with potent immunosuppressive therapy and may need cover with prophylactic antiviral treatment.

People who seroconvert >50 years old may still be at risk of hepatocellular carcinoma (HCC), although this risk is reduced compared to being HBsAg positive. The Hepatitis Foundation will monitor these people indefinitely.

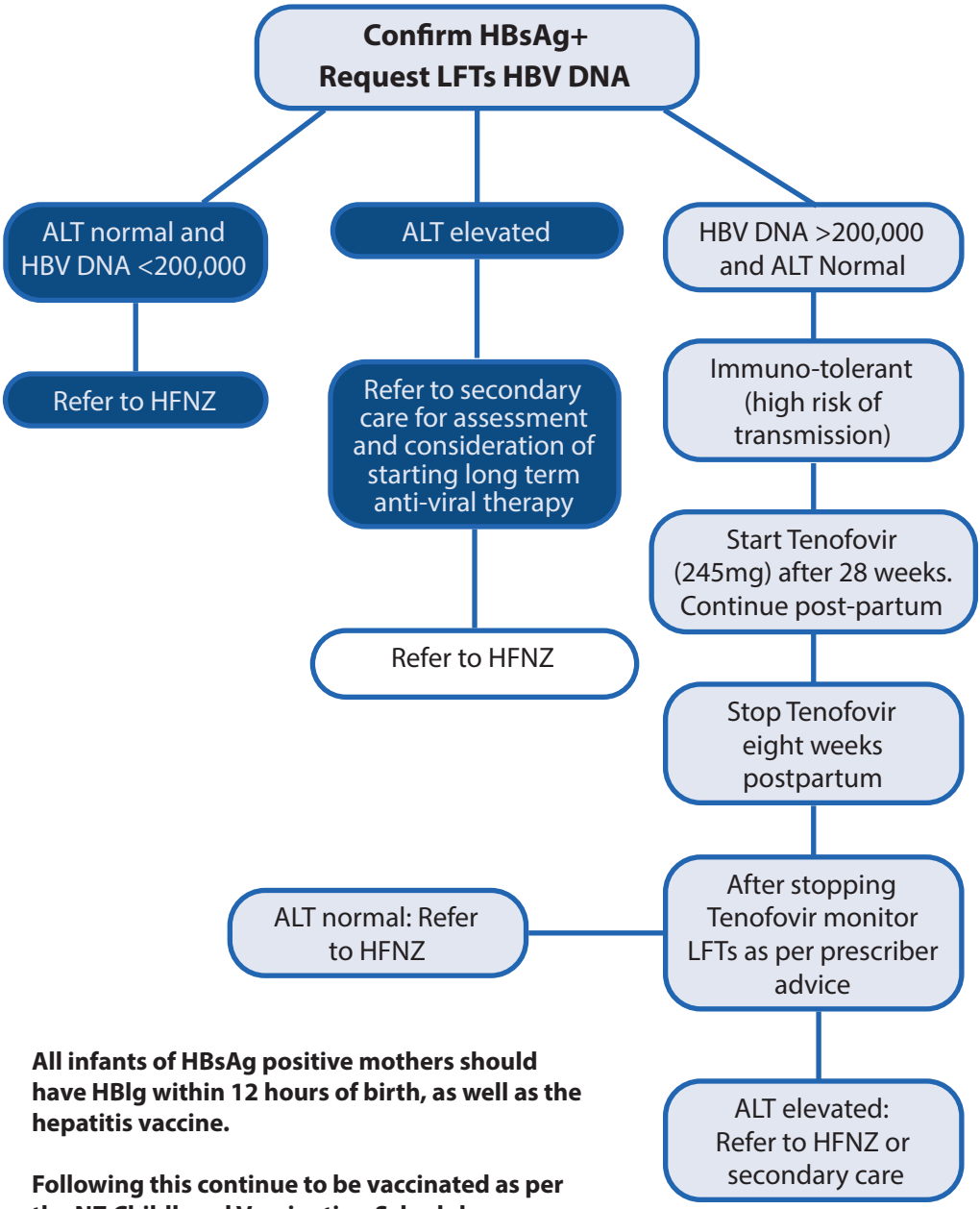
Patients with close family history for HCC and/or cirrhosis will require 6 monthly liver ultrasound scans in addition to these 6 monthly bloods indefinitely. Cirrhotic Patients should be monitored under Secondary Care Gastroenterology indefinitely and be registered with HFNZ.

HBsAg becomes negative



Six-monthly liver function tests (LFTs) and alpha-fetoprotein (AFP)
12-monthly full blood count (FBC)

Antenatal Screening



All infants of HBsAg positive mothers should have HBIg within 12 hours of birth, as well as the hepatitis vaccine.

Following this continue to be vaccinated as per the NZ Childhood Vaccination Schedule.

Referrals to The Hepatitis Foundation

We encourage you to refer hepatitis B patients to The Foundation for our free monitoring programme.

Verbal consent for referral is required.

We receive referrals through **Healthlink (CareSelect)** (Our EDI is nzhepfnd), **Best Practice, ERMS or Medtech Outbox.**

We also receive referrals by downloading our enrolment form at **www.hepatitisfoundation.org.nz** and emailing to **hepteam@hfnz.nz** or call **0800 33 20 10**

Ideally include in referral:

- Blood test results must include a positive HBsAg (hepatitis B surface antigen). Other relevant tests are: LFT, AFP, HBeAg, HBV DNA and FBC.
- The patient must be a New Zealand resident or eligible for free health care in NZ. If on Healthlink please provide proof of residency or eligibility of health care (see next page for more details on non resident/immigration patients).
- If under hospital care for hepatitis B, include ultrasound reports and clinic letters.

Referral Process

A registered nurse will be in contact with your patient to answer all questions on CHB; a thorough education and assessment can be provided in-person, virtually or over the phone, and, if required, testing of family members.

The patient must be a New Zealand resident or be eligible for free healthcare in NZ. If they are resident on Healthlink, please provide proof of residency or eligibility of health care.

If they are under hospital care for hepatitis B, please include ultrasound reports and clinic letters.

Once referral is received, we'll send you an acknowledgment letter, advising we have received the referral.

A welcome pack will be sent to your patient, including a result letter, hepatitis B pamphlets and a consent form, if not already signed.

Note: We can accept referrals for non-resident or immigration patients but please advise them they may have to pay for other health services if they don't meet eligibility requirements for free care.

Useful Links

The Hepatitis Foundation of New Zealand
www.hepatitisfoundation.org.nz/health-professionals

Information for Health Professionals, MD Calc App - REACH-B Score,
www.mdcalc.com

Immunisation Handbook
www.tewhatuora.govt.nz/for-health-professionals/clinical-guidance/immunisation-handbook

University of Liverpool – Drug Interactions
www.hep-druginteractions.org

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6. Terrault NZ, et al. Hepatology, vol 67, no. 4, 2018 Lampertico P, et al. Journal of Hepatology. 2017, vol 67, 370-398.

Get in Touch

If you would like one of our Community Hepatitis Nurses to visit your practice to provide education on chronic hepatitis B for you and your staff, you can contact us and we will connect with you.

Our hepatitis nurse will provide you with hepatitis B resources, flyers, posters etc for your clinic.

Or you can request Hepatitis B resources from
The Hepatitis Foundation of New Zealand anytime by contacting the team below.

The Hepatitis Foundation of New Zealand

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0800 33 20 10
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