Pacific Islands and Territories Hepatitis B Treatment and Care guidelines

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Adapted from WHO guidelines for the Prevention, Care and Treatment of persons with Chronic Hepatitis B infection, March 2015, WHO guidelines on Prevention of Mother to Child transmission of hepatitis B, 2020 and Kiribati, Kingdom of Tonga, Vanuatu and Fiji Treatment and Care Guidelines (Hepatitis B Free Organisation).

Acknowledgments and authorship

The original guidelines were prepared, revised and edited by Hepatitis B Free team including Alice Lee, David Hilmers, Caroline Lee, Robert Batey, Adrian Clayton and Aidan Foy.

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Amendment record

Version	Date of issue	Summary of main changes
ABG_EX_001_Ver 1	14/3/24	This document was prepared as a reference version for the PNG Antibiotic Guidelines 2024 by Dr John Ferguson (john.ferguson@health.nsw.gov.au) Review to take place when the original guidance has been updated (also contingent on new guidance from WHO).

Executive Summary

Chronic hepatitis B is a major public health burden in the Pacific islands Countries and Territories (PICT) contributing to unnecessary suffering from liver failure and liver cancer leading to loss of life. Treatment is highly effective, safe, and affordable.

Simplified treatment algorithms along with access to cheaper diagnostics and antiviral therapy has provided a pathway for the expansion of treatment to the PICT.

Screening is recommended for all patients, but where resources are limited, high priority groups should be screened. This includes persons presenting with liver disease (advanced liver disease or liver test abnormalities), family history (or contact) of hepatitis B positive patient, health care workers, pregnant women, persons undergoing immunosuppressive therapy, and those with other significant medical comorbidities.

In addition to supporting birth dose vaccination for hepatitis B followed by EPI, ongoing attention to improve vaccination coverage for those at risk should be prioritised.

Patient with positive HBsAg results based on point of care (WHO prequalified tests where possible) or ELISA (if available) should be linked to care where liver disease assessment is undertaken by trained personnel. Baseline Cr, ALT, AST and FBC is recommended. Where available, HBeAg and HBV viral load testing can support treatment decision but are not essential.

Priority treatment is indicated in patients with advanced liver disease based on clinical, APRI, FIB-4, imaging or transient elastography findings; health care workers undertaking exposure prone procedures (EPP) with positive viral load (>200 IU/ml), pregnant women (viral load >200 000 IU/ml or HBeAg if available), and those undergoing immunosuppressive therapy. Treatment guidelines should be individualised in each country pending resources available. Where appropriate, a test and treat approach should be explored.

Treatment is lifelong for those with cirrhosis. Non cirrhotic patients can be considered for treatment cessation after achieving biochemical, serological and virological response and are able to be monitored for flares post treatment cessation.

Younger patients with normal liver function tests, minimal liver fibrosis and negative family history can be monitored with 6 monthly blood tests and ultrasound.

Where possible, care of patients with advanced liver disease should be undertaken at referral centres by trained physicians (or remotely supported). Liver cancer screening with ultrasound and AFP (if available) should be integrated into the service when possible.

Programmatic support through data/medical record systems, laboratory systems support, medicine procurement pathway, evaluation, and translational research as well as education and training are required. Where possible, consideration for centralised and even regional cooperation could be explored.

Abbreviations and acronyms

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
DAA	direct acting antivirals
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EPP*	exposure prone procedures
ETV	entecavir
FIB-4	Fibrosis-4
eGFR	estimated glomerular filtration rate
gGT	gamma glutamyl transpeptidase
HBcAb	hepatitis B core antibody
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma

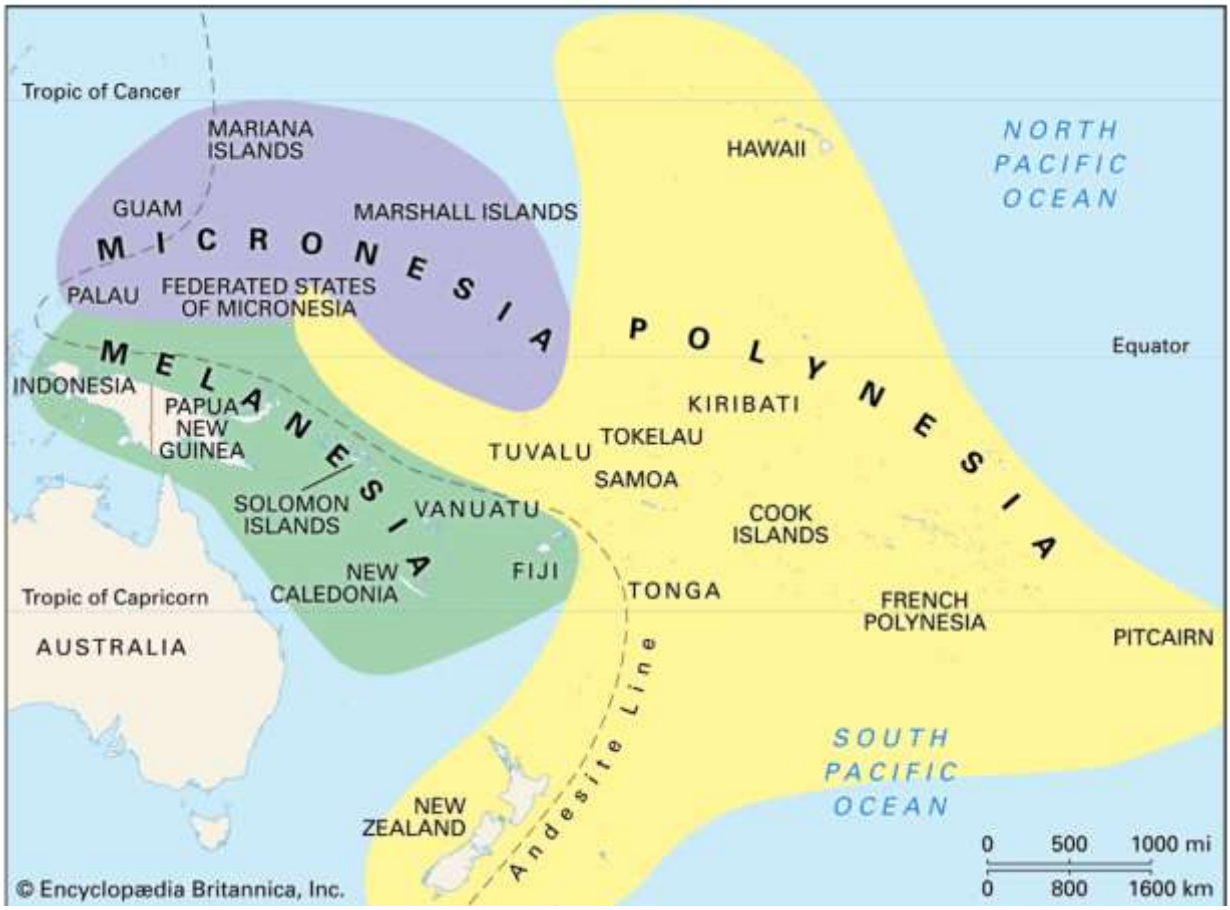
HCV	hepatitis C virus
HDV	hepatitis D virus
HCW	Health care worker
HIV	human immunodeficiency virus
INR	international normalized ratio
IST	immune suppressive therapy
NAT	nucleic acid testing
NIT	non-invasive test
PCR	polymerase chain reaction
PICT	Pacific Islands and its Territories
RDT	Rapid diagnostic test
RNA	ribonucleic acid
STD	sexually transmitted disease
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal
VIDRL	Victorian Infectious Disease Reference Laboratory
WHO	World Health Organization

*****Exposure prone procedures (EPPs) are procedures where there is a risk of injury to the HCW resulting in exposure of the patient's open tissues to the blood of the HCW. These procedures include those where the HCW's hands (whether gloved or not) may be in contact with sharp instruments, needle tips or sharp tissues (spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hands or fingertips may not be completely visible at all times.

1. Background

Over one third of the world's population has been exposed to hepatitis B infection, leading to up to 750 000 deaths per year from liver failure and liver cancer. Global prevalence varies with some of the highest rates of hepatitis B prevalence reported the Asia Pacific, Sub Saharan Africa, and Amazon basin of South America, especially in areas where resources are limited.

Pacific Islands and its Territories (PICT) are widely diverse communities that cover an expansive oceanic area over thousands of islands and atolls. Ranging from urban centres in Fiji to remote sparsely populated rural atolls, PICT encompasses diverse geographic, sociocultural, and economic communities. Divided into three regions (Melanesia, Micronesia, and Polynesia), there are 22 countries, and most are classified as low or middle income.



West, Francis James and Foster, Sophie. "Pacific Islands". *Encyclopedia Britannica*, 17 Nov. 2020, https://www.britannica.com/place/Pacific-Islands. Accessed 24 January 2021.

Introducing a new program in a setting with already stretched resources is a significant challenge. For many in this region, food security, access to permanent homes and clean water is not consistent. Competing medical needs include high rates of infections such as malaria and tuberculosis, and non-communicable diseases such as malnutrition, alcohol use disorders and

metabolic syndrome. Sociocultural, linguistic, and ethnic diversity is extensive and complex due to significant movements between the islands and to neighbouring countries.

Access to health care is variable. (For example, antenatal care is often accessed only late in pregnancy). High rates of mobility, often no fixed addresses, uncertain date of birth and identification are additional challenges in continuity of care. Health care resources, laboratory supplies, procurement pathways, access to essential medicines and adequate human resources are restrictive. Health care workers remain in low supply with many competing needs and movement so that staff turnover is high and leads to interruption in program implementation.

In recent years, the high morbidity and mortality from hepatitis B and need to integrate hepatitis services is garnering increasing attention. The burden of hepatitis B is high, yet unaddressed in many places, often lacking in current local data. In comparison, blood bank serosurveys and antenatal screening indicate low rates of hepatitis C. Recent progress with the support of the governmental agencies, clinicians, donors and WHO has seen significant progress in hepatitis B related advocacy with introduction of treatment and care guidelines in many PICT. As per WHO recommendations, antiviral therapy (tenofovir) has been added to the essential drug list in Fiji, Vanuatu, Tonga, Solomon Islands and Kiribati.

This document provides technical advice for the care and management of patients with hepatitis B with a special focus on the local context and the unique challenges of the PICT. Antiviral therapy, monitoring and care of special populations are addressed in detail. There are additional detailed guidelines for the care of special populations including health care workers, pregnant women, and children.

Despite every effort being made to integrate these newer services into the current health systems, the added economic and health system burden remains an additional barrier. Newer models such as private/public partnerships, funding from invested international partners with a social responsibility as well as larger philanthropic and government agencies all require exploration and engagement. No one solution will fit for the various nations.

Remote geographic location and vast distances and small populations increase cost of transport and shipping and can lead to interruptions in supply of medicines, laboratory consumables, and access to treatment and clinic services. Health systems strengthening remains a significant challenge, particularly in the more remote areas where novel and creative solutions need to be actively sought with local partnerships.

Systematic universal medical record keeping remains a challenge even in the well-resourced settings. These challenges are amplified in resource poor settings from lack of hardware, skills, internet bandwidth, let alone systems that are workable across many sectors (including laboratory, pharmacy, outpatient and inpatient care). For now, simple, and easy systems are being implemented using readily available Microsoft software, but as the programs expand, complex data systems are required to provide streamlined data entry as well as data extraction system to

complement monitoring key indicators and improving patient outcome as well as optimising efficiency. This too will need carefully considered investment.

Many lessons have been learnt early on in program roll out. Health literacy and communicating with the affected communities require sensitivity. Even in those patients who have advanced disease, where treatment need may be obvious, a reluctance to take up treatment, associated with high rates of discontinuation and failure to return needs to be better understood. None of this should distract from the ongoing needs to support other equally urgent priorities preventative care, as well as attention to poverty, high rates of tuberculosis, malaria and HIV.

Understanding local context, not just the barriers, but the burden of disease (local prevalence rates, impact of coinfection with HDV or HCV), including significant comorbidities whether it be coinfection with hepatitis D, HIV, tuberculosis or metabolic syndrome is needed. Hence, support for all elements of hepatitis programs from prevention with vaccination, introduction of prevention of mother to child transmission, harm minimisation (including long standing cultural practices such as scarification), therapy and monitoring are required.

Local context support by local champions is essential, but an overarching regional system to minimize cost and avoid duplication could be implemented. Where possible, sharing resources, from simple training to centralising procurement pathways, laboratory systems support, as well as development of regional referral pathways could be considered. Cooperation within the region both clinically and in translational research will further advocate for the injection of much needed support.

2. Summary of current programs in PICT

Hepatitis programs are an all-encompassing program from prevention, screening, linkage to care, treatment, monitoring and follow up of patients with liver disease. All PICT have endorsed birth dose hepatitis B vaccine followed by an additional 3 doses of hepatitis B vaccine as part of the expanded program of immunisation (EPI). Although rates of three dose vaccination are high in many places, there are ongoing challenges in delivery timely birth dose hepatitis B vaccine.

Universal antenatal screening presents another opportunity for case finding and provide linkage to care as well as implement preventative strategies by ensuring timely birth dose vaccination and follow up of both infants and positive mothers. More recently, the recommended use of tenofovir as prevention of mother to child transmission (PMTCT) in some PICT has added a further level of protection for babies at risk of infection during delivery. Work to ensure higher rates of antenatal screening in a timely manner by promoting presentation earlier in pregnancy (if at all) and availing HBsAg testing and thereafter linkage to care requires ongoing attention.

Health care work force remains a highly valued resource with health care delivery often provided by a very small number of medical doctors, supported by nursing staff, and allied health. In many parts of the PICT, much of primary care is provided by a small army of health care workers who have received variable amount of training from village health assistants, to birthing assistants, traditional healers in addition to those who have completed tertiary studies. They are critical to the program delivery and require training from prevention, screening, monitoring, as well as identifying those to refer for treatment commencement. Appropriate curriculum is required to support this network of health providers.

Patients identified through blood bank screening require linkage to care as well as those who have been identified as part of screening for chronic illnesses such as tuberculosis, renal failure, HIV or HCV or when receiving immunosuppressive therapy. As hepatitis B treatment programs expand, a clear linkage pathway (often requiring multisectoral participation and with the oversight from hepatitis task force) should be established to ensure all positive cases are followed up.

Screening activities through awareness programs as well as in routine practice has been rolled out as resources permit. In Niue, a program to ‘çure a country’ has been completed with the support of Global Health New Zealand where all persons have been screened for viral hepatitis and positive cases linked to care.

Laboratory systems strengthening and support is required ranging from purchase of analysers, reagents, RDT or viral load cartridges to upskilling laboratory technicians. Viral load testing has been made available through VIDRL who are also supporting local testing with hepatitis B GeneXpert cartridges. Treatment algorithm with or without access to viral load testing has been developed.

All patients who are identified with positive HBsAg should be linked to care for assessment of eligibility for antiviral therapy.

All cirrhotic patients should be started on antiviral therapy. Clinical assessment with history and physical findings of decompensation such as ascites, encephalopathy, and variceal haemorrhage are indicators for treatment. Diagnosis of cirrhosis can also be made based on APRI > 2, and liver stiffness measurement (LSM) >11kPa.

Other priority groups for antiviral therapy include patients at risk for disease progression (older patients with elevated ALT and positive viral load (> 20 000 IU/ml) – if available).

Special groups for treatment consideration include health care workers performing exposure prone procedures, pregnant women with high viral load (>200 000 IU/ml), patients undergoing significant immunosuppressive therapy, and those with a family history of hepatitis B related complications including liver cancer and liver failure.

Serum creatinine for an estimation of glomerular filtration rate is required for dosing and ongoing monitoring. Viral load testing if available can be used to support treatment decisions. For those not requiring antiviral therapy, lifelong monitoring is warranted. This includes at least annual clinical assessment and ALT. For those at risk of liver cancer, monitoring with 6 monthly ultrasound and ALT is recommended.

Treatment with tenofovir disoproxil fumarate 300 mg once daily is recommended for all adults with normal renal function. Monitoring should occur every 6 months with ALT, AST, creatinine and FBC for the first year and annually thereafter in non-cirrhotic patients. Patients with cirrhosis should be reviewed every 6 months with ALT and Cr. They should be counselled to undertake lifestyle modifications such as minimizing alcohol intake and improving measures of metabolic syndrome to reduce their risk of further liver injury. Tenofovir alafenamide with no renal dosing requirements would be an ideal alternative if affordable.

Patients with cirrhosis require life-long therapy.

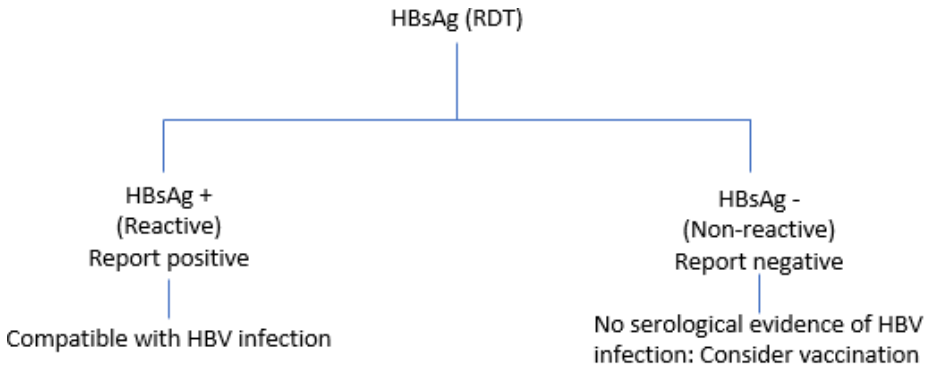
Treatment can be discontinued in selected patients without cirrhosis who achieve a loss of HBsAg (and who are treated 12 months thereafter), after completion of chemoprophylaxis in immunocompromised individuals, or after delivery in prevention of mother to child transmission. Monitoring after cessation of treatment is required to assess for flares every 3 months for the first 12 months. Even after cessation of antiviral therapy, liver cancer screening with 6 monthly ultrasounds should be considered for all patients with cirrhosis, family history of liver cancer who are over the age of 40 years.

Compliance, confidentiality, and avoidance of stigma should be considered as part of a complete counselling process during all stages of the care pathway.

3. Algorithms for the management of persons with chronic hepatitis B infection

All persons in the PICT should be considered for hepatitis B screening using WHO prequalified RDT. Priority groups include those who present with liver disease, antenatal screening, blood bank, those who present to STI clinics, health care workers, those receiving immunosuppressive therapy, patients with HCV, HIV or tuberculosis. Vaccination should be considered in negative patients who have not had prior vaccination and remain at risk (including partners and household members).

3.1 Screening



Consider vaccination for HBsAg negative patients at risk of infection.

3.2 Assessment for treatment

*Treat older patients with raised ALT and positive HBV DNA >2000 IU/ml (if available, if HBV DNA unavailable -treat based on ALT alone)

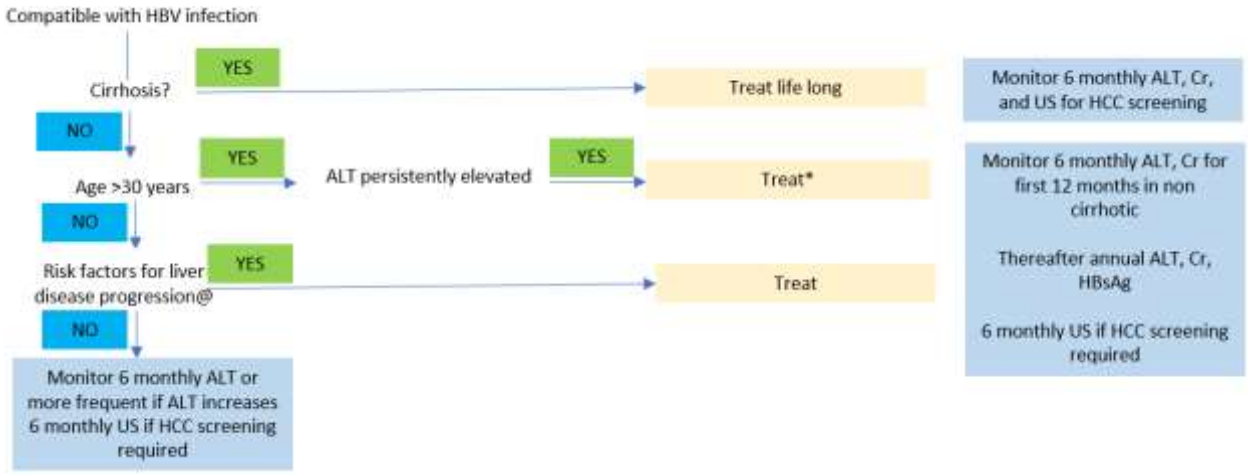
@ Treat patients with first degree relative with HCC or cirrhosis, or extrahepatic manifestations of hepatitis B.

Chronic hepatitis B is a dynamic disease. All patients should be considered as potential candidates for antiviral therapy and regular monitoring is required. History, physical examination, baseline bloods (AST, ALT, Cr and FBC) and ultrasound should be completed.

Liver cancer screening with 6 monthly ultrasounds should be considered where available.

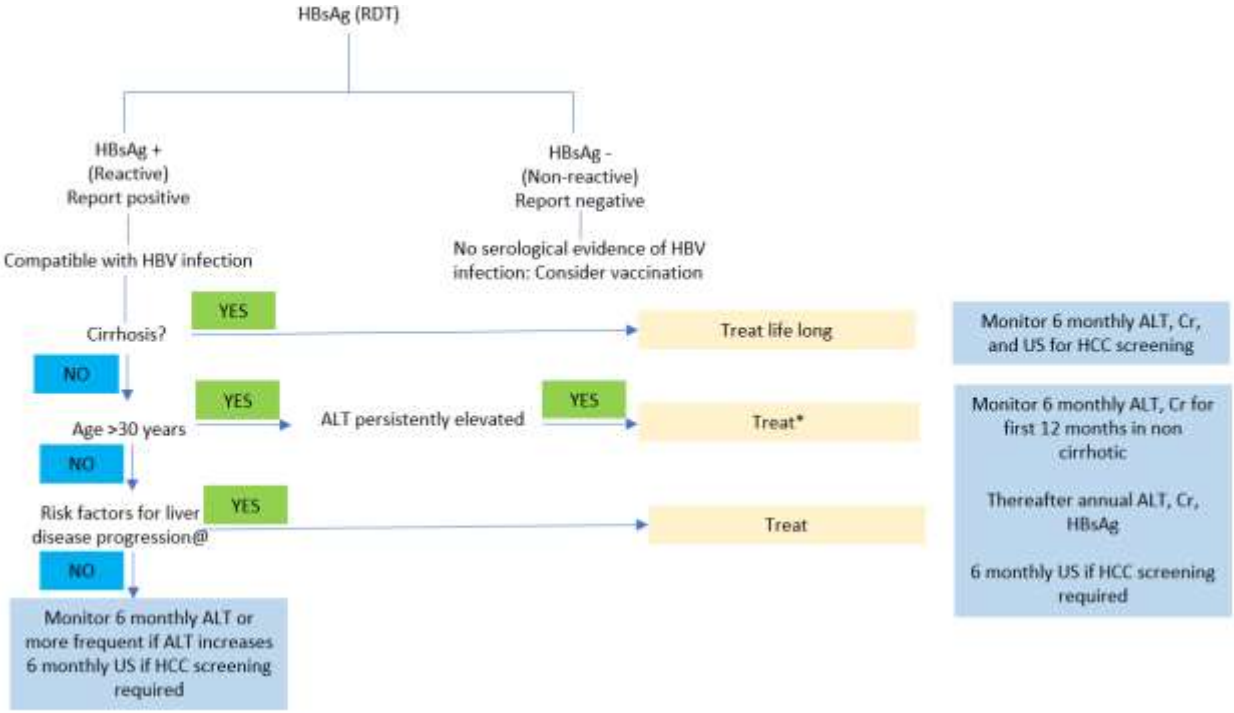
Treat all patients with cirrhosis irrespective of ALT or viral load.

3.3 Monitoring



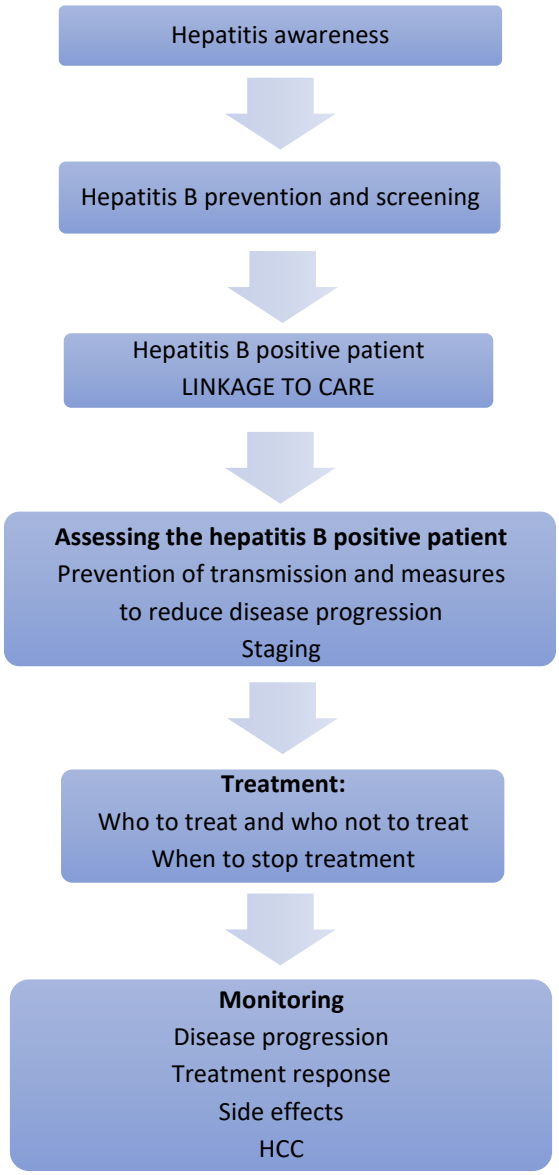
Lifelong monitoring is required for all patients with CHB infection, whether on treatment or not. Liver cancer screening should be integrated into hepatitis programs.

3.4 Summary



The above algorithm is based on WHO Rx and care guidelines and the Asian consensus recommendations on optimising the diagnosis and initiation of treatment of hepatitis B virus infection in resource-limited settings. (1,2)

4 Overview of hepatitis B care



4.1 Hepatitis B awareness

Despite reported high rates of hepatitis B in the PICT, awareness of its impact remains patchy even amongst the health care workers. Even if recognised as a significant issue, lack of resources as well as training leave health care workers with limited ability to respond to the needs of the patients.

Work done to date clearly demonstrates the role of advocacy supported by WHO with national action plans (Kiribati and Vanuatu) developed. These documents provide an investment case to the Policy makers as well as funders, whilst outlining the key priority areas. Sharing progress made is also critical through publications as well as presentations at international meetings, particularly with view to support set up of programs in other islands.

Persons and families affected by CHB remain at the core of engagement and activities such as World hepatitis Day celebrations using locally effective and appropriate awareness programs. Where possible, integration of appropriately tiered training modules at all types of educational opportunities should be considered, from high schools to health care worker training, to tertiary settings (both under and postgraduate).

4.2 Hepatitis B prevention and Screening

All persons in the PICT should know their hepatitis B status. The following groups should be prioritized.

- Persons presenting with liver disease including liver failure and cirrhosis
- Persons presenting with deranged liver tests
- Household and sexual contacts of persons with CHB infection
- Health care workers and trainees
- Blood donors
- Pregnant women and babies born to positive mothers
- People undergoing immunosuppressive therapy
- People with tuberculosis undergoing treatment
- People presenting to STD clinics
- HIV infected persons
- HCV infected persons
- Persons who inject drugs
- Men who have sex with men
- Sex workers
- Incarcerated persons

Other groups for consideration include police, military, security and prison officers, patients with chronic illnesses, immune deficiency or having frequent transfusions. Opportunistic HBsAg screening at any medical encounter should be undertaken where possible.

Screening should be done using WHO prequalified rapid diagnostic test kits (3). Opportunities for awareness should be linked to provision of testing with appropriate pre and post testing counselling provided by trained personnel. At all times, confidentiality and potential for stigma and discrimination should be considered.

All health care facilities including health posts in remote settings should have access to RDT and HCW trained and encouraged to screen. Where ELISA testing is available, full serology testing including HBeAg, HBcAb is recommended. Where vaccination is provided to high risk groups and ELISA available, HBsAb titre pre and post vaccination is recommended.

Collection and recording appropriate data including total screened, number of positive cases and outcome including linkage to care, treatment commencement, monitoring and development of HCC and liver failure is required. Resources including soft and hardware should be supported.

All babies should be given a timely birth dose followed by completion of the hepatitis B vaccination via EPI. Vaccination of infants and, in particular, delivery of hepatitis B vaccine within 24 hours of birth is 90–95% effective in preventing infection with HBV as well as decreasing HBV transmission if followed by 2 or 3 further doses. A proportion of vaccinated children (5–10%) have a poor response to vaccination and will remain susceptible as adults to acquisition of HBV infection.

Vertical transmission remains an important and significant source of new infection in the PICT. All pregnant women should be screened for hepatitis B at the first antenatal visit. All positive mothers should be linked to care. Babies born to positive mothers should be screened as per protocol (PICT guidelines on the PMTCT).

All healthcare workers should be screened and vaccinated as indicated. HBsAg positive healthcare worker should be linked to care. All close contacts of positive patients should be screened and vaccinated. All patients undergoing significant immunosuppressive therapy should be screened for HBsAg and linked to care for consideration of immunoprophylaxis.

Blood donations should be screened for HBV, HCV, and HIV. Positive patients should be linked to care.

Better understanding of local prevalence rates of HCV and HDV should be supported by routine surveillance testing. HIV testing as per local guidelines.

Test results should be linked to hospital systems and medical records. All should receive pre-test counselling including access to written material if available.

All positive HBsAg cases should be offered post-test counselling, advice on prevention of transmission (including not share razors, toothbrushes, not donate blood and follow standard universal precautions with open cuts or bleeding).

Excess alcohol (>20 g/day in women and >30 g/day in men) can accelerate the progression of HBV related cirrhosis. Non-alcoholic fatty liver disease, obesity and metabolic syndrome are also potential contributors to liver disease. Patients should be advised about dangers of excess alcohol intake, value in maintaining healthy weight, diet, exercise, and healthy lifestyle.

Clearly defined referral pathways should be established for positive patients. Data systems to ensure secure recording of positive cases, track referral and outcome should be developed. All patients should be assessed by a trained health care worker. Ongoing follow up with decision to treat as appropriate. Linkage to care may require supporting health care workers in remote health posts via telehealth after initial assessment at a outreach service. Various models of health care delivery will need to be explored in local context. All patients with CHB infection, whether on treatment or not should be monitored. All should be considered as potential candidates for antiviral therapy in the future.

5 Hepatitis B positive patient: Linkage to care

5.1 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 is defined as persistence of hepatitis B surface antigen (HBsAg) for six months. 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. Factors that accelerate disease includes alcohol, metabolic syndrome, family history of HBV related complications, coinfection with HCV, HDV, HIV, high viral load, longer duration of infection, and liver inflammation (indicated by raised ALT level).

The majority of people are unaware of their HBV infection, and therefore often present for the first time with advanced disease. Patients may be made aware of their diagnosis as part of screening for high-risk groups as outlined above, or present with advanced disease due to liver cirrhosis or liver cancer. Most patients remain asymptomatic with some reporting anorexia, nausea, fatigue and episodes of jaundice which may be related to previous episodes of hepatitis flares. Physical examination findings can be normal in a non cirrhotic. Patients with decompensated liver disease can present with muscle wasting, jaundice, bruising, scratch marks, ascites, peripheral oedema and encephalopathy.

Antiviral agents including tenofovir have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. Currently available treatments fail to eradicate the virus in most of those treated, necessitating long-term therapy which should be lifelong for patients with HBV-related cirrhosis. In non cirrhotic patients, loss of HBsAg on treatment is considered as functional cure and an indication for treatment cessation. Tenofovir is safe and highly effective in reducing viral load. Hence, it is recommended for preventing mother to child transmission in pregnant women with high viral load.

5.2 Assessment for treatment eligibility

5.2.1 Staging the patient

Assessing liver disease severity (including staging- a scoring system to determine liver scarring or fibrosis) should be done by a health care provider trained in history taking, physical examination (including presence of hepatomegaly or splenomegaly and stigmata of chronic liver disease), and interpretation of lab test results.

Staging of HBV-related liver disease is the key next step in the clinical assessment for HBV treatment. The METAVIR (4) system of staging liver fibrosis based on liver biopsy findings is widely recognized and shown in figure 3.

Figure 3: METAVIR liver fibrosis staging system

METAVIR stage	F0	F1	F2	F3	F4
Definition	No fibrosis	Portal fibrosis without septa	Portal fibrosis with septa	Numerous septa without cirrhosis	Cirrhosis

Several non-invasive fibrosis tests (NIT) based on blood or serum indices or ultrasound are now available and used for staging liver fibrosis. Baseline blood tests should include a FBC (in particular platelet count), ALT and AST. Using these, an APRI and FIB-4 score can be calculated. A baseline creatinine should also be done as tenofovir disoproxil requires dose adjustment in patients with renal dysfunction. Transient elastography, ultrasound as well as other forms of imaging as available can also support the diagnosis of cirrhosis.

Where available, further hepatitis B serology including HBeAg and viral load testing (HBV DNA) should be done. However, treatment decisions can be made without these tests.

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.

FIB-4 score = age x AST / platelet count (10^9/L) x √ALT

These online calculators can be accessed for APRI and FIB-4 scores:

- https://www.mdcalc.com/calc/3094/ast-platelet-ratio-index-apri
- https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis

Transient elastography is a non-invasive method to assess liver stiffness, measured in kilopascals (kPa). It measures the speed at which elastic waves travel through the liver, directly correlating to

the degree of liver fibrosis. This provides a simple, non-invasive way to assess liver fibrosis staging, is quick to do, provide immediate results, and can be done at the bedside in the clinic setting.

Liver stiffness measurements (LSM) have been validated in a number of liver conditions including HBV. The results range from 2.5-75 (kPa). A score of >11-14 kPa is considered consistent with cirrhosis and a score of >7-8 kPa consistent with significant fibrosis. Current high costs of the equipment pose barrier to access.

A liver biopsy is not routinely done to assess hepatitis B patients, but can be considered where resources permit and where there are discrepancies in staging modalities or other concurrent diagnosis require exclusion.

Any patients presenting with clinical features of advanced liver disease such as ascites, variceal bleed or encephalopathy should be treated with antivirals as a matter of urgency based on a positive HBsAg on a RDT.

In HBV:

Significant fibrosis (Metavir > or =F2) is defined as APRI >1.5, FIB-4 >3.25 or LSM >7-8.5kPa.

Cirrhosis (Metavir 4) is defined as APRI score >2 in adults, or LSM >11–14 kPa.

It is critical to determine whether the patient is cirrhotic or not.

The decision to start a patient on therapy with tenofovir can be simple. In patients with clear clinical features of advanced liver disease, therapy should not be deferred. However, there are many instances where the decision to start treatment can be much more complex. Careful consideration with consultation with the local expert should be undertaken. Where possible, all patients should undergo a full review by a medical practitioner prior to starting treatment. Where this may be impractical, the health care worker who is in direct contact should be supported by the remote health care model and have access to a local expert for case discussion.

Prior to treatment initiation patients should be counselled about treatment indications, likely benefits and potential side-effects, the need for long-term treatment and monitoring. Importance of adherence to treatment require emphasis. When available, culturally, and linguistically appropriate written information should also be provided with ample time for counselling (patient information booklets developed in partnership with local experts are available).

Baseline renal function and assessment of renal dysfunction should be undertaken in all patients prior to starting antiviral therapy with tenofovir disoproxil. BSL and urine analysis is also recommended in patients where available. Serum Cr levels (eGFR) can be calculated using the Cockcroft-Gault (CG) or modification of diet in renal disease formulas.

https://www.mdcalc.com/creatinine-clearance-cockcroft-gault-equation

Risk factors for renal dysfunction includes decompensated cirrhosis, CrCL <50 mL/min, older age, BMI <18.5/m2 (or body weight < 50kg), poorly controlled hypertension, proteinuria, uncontrolled

diabetes, active glomerulonephritis and concomitant use of nephrotoxic drugs or boosted protease inhibitor for HIV.

5.2.2 Who to treat

All cirrhotic patients:

Adults and adolescents with CHB and clinical evidence of compensated or decompensated cirrhosis, or cirrhosis based on APRI score of > 2, FIB-4 >3.25 or transient elastography (liver stiffness measurement LSM) reading of > 11 kPa, irrespective of ALT or HBV viral load should be treated.

Non cirrhotic patients:

- Older patients (>30 years of age) and persistently raised ALT (normal in male, female) and have evidence of viral load > 2000 (if HBeAg not available) or >20 000 if HBeAg positive should be treated.
- Younger patients (<30 years of age) as above but with evidence of significant fibrosis (based on APRI >1.5, FIB-4 >3.25).
- Patients with family history of HCC or cirrhosis and viral load as above (if available) should be treated.
- Health care workers performing exposure prone procedures.
- Pregnant women with viral load > 200 000 IU/ml for PMTCT.
- Patients undergoing high risk immunosuppressive therapy.
- Patients with extrahepatic manifestations of CHB such as glomerulonephritis or vasculitis.

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 the HBV DNA level is low or undetectable. 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. 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) are at an increased risk of HCC and liver cirrhosis and hence candidates for therapy. Younger patients should also be considered for therapy based on APRI and family history to determine risk of disease progression. If viral load testing is available, it can be used according to the following algorithm.

Local normal ALT range should be established. Suggested ULN values for ALT and AST are 30 IU/ml (men) and 19 IU/ml (women).

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 taken into account.

Special populations are discussed in Section 6.

5.2.3 Recommended antiviral therapy

In all adults, adolescents and children aged 12 years (>35 kg) or older in whom antiviral therapy is indicated, the nucleos(t)ide analogue with high barrier to drug resistance and high potency tenofovir disoproxil (245 mg) once daily is recommended. Tenofovir disoproxil is approved for use in children by EMA from aged 2, FDA from aged 12 years. Tenofovir alafenamide is approved for use from aged 12 by EMA.

Tenofovir is a potent inhibitor of HBV replication, and is an effective antiviral therapy, achieves undetectable HBV DNA levels and normalization of ALT levels, reducing liver inflammation and preventing disease progression. There is a high genetic barrier to resistance, with case reports of drug resistance over long-term follow up. They have low rates of side effects and can both be administered orally once daily with no food restrictions.

There is extensive safety data on the use of tenofovir disoproxil which now extends to well over 15 years. They are also safe in patients with decompensate cirrhosis.

Major toxicity concerns with tenofovir disoproxil (principally eliminated via the kidney) have included renal toxicity with renal tubular injury which are rare. High risk patients include those with hypertension, chronic kidney disease and diabetes mellitus (5). Reduced bone density and hypophosphatemia are also reported with tenofovir disoproxil. Other risk factors for renal dysfunction includes decompensated cirrhosis, older age, lower BMI, uncontrolled diabetes, HIV, concomitant renal disease, lower baseline CrCl and use of nephrotoxic drugs. Rare cases of lactic acidosis, a rare side effect of nucleus(t)ide analogues is reported. There is increased risk in with those with decompensation. (6)

At baseline and during treatment, consider dose reduction of tenofovir disoproxil if the estimated glomerular filtration rate (eGFR) is <50 mL/min.

Dosage adjustments for tenofovir disoproxil in renal impairment are as follows:

CrCl >50 ml/min	one tablet a day
30-49	one tablet every 2 days
10-29	one table every 3 days
<10	one table 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)]

Tenofovir alafenamide (25mg) is a prodrug of tenofovir disoproxil and has been documented to have similar antiviral efficacy as tenofovir disoproxil and is associated with smaller decrease in glomerular filtration decline in bone mineral densitometry and is preferred if available. Dose adjustments are not required to eGFR of 15 ml/min.

5.2.4 Who not to treat and can be monitored

Treatment can be deferred for persons without clinical evidence of cirrhosis (or APRI score ≤2 in adults), no family history of HCC and with persistently normal ALT levels and low levels of HBV replication (HBV DNA <2000 IU/mL, where DNA testing is available), regardless of HBeAg status or age.

Persistently normal ALT is defined as three ALT tests below the upper limit of normal, made during a 6 to 12–month period.

Despite meeting criteria for treatment, initiating antiviral treatment may not be appropriate in the presence of a concomitant medical or social situation that would make it difficult for the patient to adhere to treatment or return for follow up. These decisions should be made by clinicians on a case by case basis in discussion with the patient and their family. Continued monitoring is necessary in all persons with CHB, including those that do not meet the criteria for treatment, to determine if antiviral therapy may be indicated in the future to prevent progressive liver disease.

5.2.5 Monitoring

All patients whether on treatment or not, should be monitored on a regular basis.

Monitoring includes assessment for progression and complications of disease such as hepatocellular carcinoma (HCC), treatment adherence, response, and adverse effects.

The following should be monitored at least annually regardless of whether a patient is commenced on treatment:

- ALT, AST and FBC, HBsAg, (*HBeAg and HBV DNA if available and if results will support clinical management of patient*)
- Non-invasive test for cirrhosis, APRI and FIB-4 (or transient elastography if available)

The following should be monitored in patients commenced on treatment:

- Creatinine annually
- Adherence to treatment ***at every visit.***

More frequent monitoring is recommended in these situations:

- for patients not yet on treatment with intermittently abnormal ALT who may be candidate for Rx.
- for patients on treatment with cirrhosis, if there are adherence concerns, renal impairment, HIV coinfection, or those discontinuing treatment. Testing frequency for these patients should be every three months for the first year. Additional review for those who require support to improve adherence to therapy.
- for patients not yet on treatment with intermittently abnormal ALT who may be candidate for Rx.

Monitoring for HCC

- Is recommended for patients with cirrhosis regardless of age or other risk factors
- Is recommended for those with a family history of HCC
- Is recommended for persons aged over 40 years
- Comprises 6 monthly liver ultrasound +/- *serum alpha-fetoprotein (if available)*

Monitoring for liver disease progression and decompensation

Treatment of the cirrhotic patient does not always result in resolution of disease progression. Hence, progression from compensated cirrhosis to decompensation may occur. Regular clinical assessment for signs of new onset ascites, hepatic encephalopathy (manifest with personality changes or sleep pattern changes), jaundice or loss of weight due to reduction in muscle mass should be monitored.

Screen and manage for other complications such as oesophageal varices if available.

Consider other medical therapies for the care of the patient with cirrhosis.

Optimise diet (high protein and low salt) and reduce risks (avoid nephrotoxins and hepatotoxins). This should be undertaken by appropriately trained personnel.

5.2.6 Stopping Treatment

Cessation of therapy (either due to non-adherence or interruption in drug supply) is likely to result in virological rebound and potential hepatic flare. Hepatic flare in persons with underlying cirrhosis may result in significant morbidity, hepatic decompensation, and in some cases can result in death (7).

All persons with chronic hepatitis B **cirrhosis** should be continued on lifelong antiviral therapy and must NOT stop treatment for any reasons and should be counselled on the risk of treatment interruption.

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

1. **No** evidence of cirrhosis and APRI < 2
2. **Persistent loss of HBsAg** and completion of at least one additional year of treatment (functional cure)
3. **and** persistently normal ALT
4. **and** persistently undetectable HBV DNA *(if available)*
5. **and** able to attend for post cessation of therapy monitoring.

Where funding is limited, consideration for treatment cessation before achieving all of the end points could be considered on a case by case basis. Careful discussion about the pros and cons of stopping treatment in those who are NON CIRRHOTIC, remain HBsAg positive but achieved all of the other end points could be considered after a minimal treatment period of 3 years. This recommendation is based on increasing data to support the findings that HBsAg loss is possible after stopping Rx with upto 19% losing HBsAg as compared with 0% seroconversion in those who continued on Rx (8). This may be related to T cell function restoration.

In any patient where therapy is discontinued, liver function should be monitored closely, as severe acute exacerbations of hepatitis have been reported on discontinuation of therapy, and resumption of antiviral therapy may be required. This should include measurement of ALT 3 monthly for the first 12 months and 6 monthly thereafter. In the event of a flare, hepatitis serology (HBsAg) should be repeated, and consideration given to restarting treatment.

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

Stop treatment in non-cirrhotic patients if one of these criteria is met:

- HBsAg loss associated with normal liver function tests AND able to monitor after stopping treatment
- HBsAg positive, 3 years of treatment with normal ALT and undetected viral load for 12 months (if available) AND able to monitor after stopping treatment
- Where HBeAg testing is available and positive at baseline, stop Rx once HBeAg becomes negative and HBV DNA has been undetected for 12 months AND able to monitor after stopping treatment

5.2.7 Monitoring after stopping Rx and when to restart Rx

Monitor with ALT at 1 months and thereafter every 3 months for the first 12 months. If ALT up, repeat within 1 month.

Retreat if ALT <5-10 x ULN on more than 2 occasions than two times.

Retreat if ALT >10 x ULN.

After 12 months off Rx, retreat if fit criteria for Rx.

After 12 months off Rx, and no retreatment required, monitor every 6 months. Consider HCC screening if indicated and available.

5.2.8 Summary of Treatment recommendations

Cirrhotic patients:

Treat with tenofovir (TDF- renal dose adjust), monitor 3 monthly for the first 6 months, thereafter 6 monthly with ALT and Cr. NO role of routine viral load testing. Lifelong treatment recommended.

Non cirrhotic patients:

Patients with persistently raised ALT, and or other risk factors for liver disease progression (higher staging score, older, family history, comorbidities), treat with renal dose adjusted tenofovir. Monitor 6 monthly ALT and Cr for 12 months and thereafter annually. After 2 years of Rx, if viral load available, and Rx cessation indicated, consider viral load testing. If viral load is negative, repeat at 3 years and stop Rx. Monitor after stopping. If longer Rx indicted, stop after HBsAg loss.

6 Special populations

6.1 Patients with decompensated cirrhosis

Patients with chronic hepatitis B virus (HBV) can develop progressive fibrosis, cirrhosis and hepatocellular carcinoma. Those with cirrhosis are at risk of decompensation with high mortality rates without intervention. Treatment can reduce risk of decompensation in patients with well compensated cirrhosis.

Decompensation can manifest with symptoms and signs such as weight loss, weakness, wasting, oedema, dark urine, and jaundice, ascites, hepatomegaly, spontaneous bacterial peritonitis, oesophageal varices, encephalopathy, renal failure and sepsis. They are potentially life-threatening. Laboratory tests can become progressively more abnormal. There is generally an increase in the ratio of AST:ALT; a low platelet count (suggesting the development of portal hypertension); an increase in ALP and GGT, a fall in serum albumin, and prolongation of prothrombin time with worsening hepatocellular function. Hyperbilirubinaemia with depressed albumin and prolonged prothrombin time are poor prognostic findings in CHB and associated with an increased risk of liver-related death. Referral to specialised centres is recommended.

All persons with decompensated cirrhosis should be considered for urgent antiviral therapy with tenofovir, irrespective of the ALT or HBV DNA level. Treatment should be continued indefinitely. Tenofovir disoproxil is well tolerated in patients with decompensated cirrhosis demonstrating improved liver function, increased transplant free survival and improved Model for End-Stage Liver Disease and Child-Turcotte-Pugh scores. (9, 10,11)

Survival depended on antiviral response and is better in responders. Indefinite therapy is recommended in those with decompensated cirrhosis. Despite successful treatment with antivirals, this group remains at high risk for HCC and should continue long-term HCC surveillance (12).

In addition to improving outcomes, treatment prevents flares or reactivation which in patients with decompensated cirrhosis can lead to death.

Management of complications such as ascites, variceal bleed, sepsis, renal dysfunction and hepatic encephalopathy require expert supervision. Nutrition and preventative care require particular attention.

6.2 Care for women of child bearing age

Women of childbearing age should be considered for antiviral therapy and if pregnancy occurs whilst on treatment, patients should be advised to continue therapy. Particular attention should be paid to women with advanced disease who are at risk of complications. Counselling prior to pregnancy, the effects of hepatitis B on pregnancy as well as the effects of pregnancy on hepatitis B should be considered. There is extensive data on the safety of tenofovir for women throughout all stages of pregnancy with no significant adverse outcome on pregnancy or infant outcome. Breast

feeding should be encouraged with small amounts of tenofovir detected in breast milk without any significant adverse effects on babies reported. **(See Pacific guidelines on the prevention of mother to child transmission of hepatitis B).**

6.3 Pregnant women/prevention of mother to child transmission

All pregnant women should be screened for HBsAg at the first antenatal visit. All positive patients should be linked to care where a full assessment is undertaken as above. Pregnant women who are eligible for treatment should be offered antiviral therapy with tenofovir at any stage of pregnancy. If treatment is not indicated for the patient, treatment for the purpose of prevention of mother to child transmission should be considered.

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, preferably within 24 hours followed by at least two timely subsequent doses as per national EPI program. HBIG is currently not available in most PICT. Babies born to positive mothers should have follow up in the paediatric service with testing done after 9 months of age. Positive infants should be offered linkage to care.

Even with implementation of the above strategies, babies born to HBsAg positive women with high viral load remain at risk of vertical transmission. Hence, for mothers who have HBV DNA viral loads >200 000 IU/ml or HepBeAg positive, tenofovir disoproxil taken from week 24-28 is recommended to reduces viral load and transmission to the infant (13). Where viral load and HBeAg is not available, decisions to use tenofovir should be made on a case by case after discussion with the patient.

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.

There is no additional transmission risk with breast feeding the baby.

Breast feeding is not contraindicated whether the mother is on Rx or not.

6.4 Care of infants born to HBsAg positive mothers

Acute hepatitis B virus (HBV) infection in a pregnant woman poses a serious risk to her infant at birth. Without post exposure immunoprophylaxis, approximately 40% of infants born to acute HBV infected mothers will develop chronic-HBV infection, approximately one fourth of whom will eventually die from chronic liver disease.

Perinatal HBV transmission can be prevented by identifying HBV-infected (i.e. Hepatitis B surface antigen [HBsAg]-positive) pregnant women and providing hepatitis B immunoglobulin and (if

available) hepatitis B vaccine to their infants within 12 hours of birth. Tenofovir for high viral load mothers can further reduce risk of transmission.

Preventing perinatal HBV transmission is an integral part of the national strategy to eliminate hepatitis B, National guidelines call for the following:

- Universal screening of pregnant women for HBsAg during each pregnancy
- Case management of HBsAg-positive mothers and their infants
- Hep B birth dose vaccine as soon as possible (*HBIG if available*)
- Completion of hepatitis B vaccine series as part of EPI
- Breast feeding recommended for babies born to positive mothers (on treatment or not on Rx)
- Test babies at least 3 months after completion of three dose of hepatitis B vaccine – birth dose followed by EPI scheduling (at least after 9 months of age – in the paediatric clinic)

6.5 Care of children with chronic hepatitis B infection

All children in the Pacific Islands should know their hepatitis B status. All children should have confirmation of vaccination status and if not done or not known, test for HBs Ab and if not available (or negative), full course of hepatitis B vaccination provided. Detailed guidelines on the care of children with hepatitis B are available on a separate document.

Priority groups for testing are:

children born to hepatitis B positive mothers irrespective of vaccination or PMTCT program status,

children with household members diagnosed with CHB,

children presenting with liver disease,

children receiving immunosuppressive therapy,

children with HIV, tuberculosis and

Children subject to child trafficking or sexual abuse.

CHB is usually benign and asymptomatic in children, there are low curative response rates with long term antiviral treatment requirements. Hence, a conservative approach to treatment is generally indicated, unless there is cirrhosis. Although the majority of children will not require antiviral therapy, early identification and monitoring of children at risk for progression of liver disease is important. The use of NITs and identification of appropriate cut-offs have not yet been defined in children.

Hepatitis BsAg positive children should be linked to care and assessed for treatment eligibility. All children with cirrhosis should be prioritized for treatment with tenofovir or entecavir (if available). Children with advanced fibrosis and at risk factors should be considered for Rx. Children without cirrhosis but raised ALT, should be monitored with repeat ALT at least 6 monthly. Those with normal ALT should be monitored 6-12 monthly.

Prevention of hepatitis reactivation should be evaluated in all children receiving immunosuppressive therapy.

Adult stopping rules for antiviral therapy should be applied for children also. Detailed guidelines are available in the Pacific Islands and Territories guidelines in the treatment of hepatitis B in children.

6.6 Health care workers

All health care workers should be offered screening and vaccination if HBsAg negative. Those who are HBsAg positive should be linked to care and treated if indicated. Those who undertake exposure prone procedures should be considered a priority group for antiviral therapy with tenofovir to reduce risk of transmission to others. If available, a viral load should confirm reduction in viral load after 12 months of therapy, and thereafter monitor for compliance.

Exposure Prone Procedures (EPPs) are procedures where there is an increased likelihood of injury to the healthcare worker, which can mean that the healthcare worker's blood can then reach the patient's blood. These procedures are ones where the healthcare worker's hands may be in contact with sharp instruments, needle tips or sharp spikes of bone or teeth while inside the patient's body and the hands or fingertips may not be clearly seen at all times.

In addition to the above, the following general recommendations are advised to reduce transmission in the health care setting: screening for donated blood, safe handling and disposal of sharps and waste, safe cleaning of equipment, hand hygiene and training of health personnel.

Hepatitis B infection does not disqualify a health care worker from surgery, dentistry or any other aspects of health care service.

For detailed guidelines for health care workers, see Pacific islands and Territories guidelines on the treatment and care of health care workers.

6.7 Persons receiving immunosuppressive therapy

Patient receiving immune suppressive therapy are at risk of hepatitis B reactivation. In severe cases, reactivation can lead to liver failure and death.

Risk of reactivation is associated with three factors:

- Patient: male sex, older age, presence of cirrhosis, and type of disease treated with immune suppressive therapy (IST) (such as bone marrow transplant or solid-organ transplantation);
- Viral: HBsAg seropositivity, high baseline HBV DNA levels, positive HBeAg, and absence of anti-HBs among patients with resolved HBV infection, or co-infection with HCV, HDV, or HIV; and
- Potency of IST.

All patients undergoing IST should be screened for hepatitis B with HBsAg (and HBcAb and HBsAB if available). HBV DNA in HBsAg positive patients when available. In patients with positive HBsAg, assessment for antiviral therapy and treatment started if indicated. For those who are not candidates for hepatitis B treatment (no fibrosis, normal ALT and no increased risk factor for liver disease progression), antiviral therapy for the purpose of immunoprophlyaxis should be considered for those considered to be at risk for hepatitis B reactivation.

High risk immunosuppressive therapy includes B cell depleting agents (eg Rituximab), high dose steroids (prednisone) ≥20 mg/day for ≥4 weeks, anti-TNF agents with high potency (Adalimumab, Infliximab, Golimumab, Certolizumab), anthracyclines (including when used for transarterial chemoembolization), haematopoietic stem cell transplantation (both allogeneic and autologous), Immune checkpoint inhibitors (Anti-PD-1: nivolumab, pembrolizumab), Anti-PD-L1 (atezolizumab), Anti-CTLA-4 (ipilimumab) and tyrosine kinase inhibitors.

Moderate risk immune suppressive therapy includes chemotherapy (except anthracyclines), anti-TNF agents with lower potency (etanercept), lower dose steroids (prednisone 10–20 mg/day) for≥4 weeks and proteasome inhibitors (eg Ustekinumab). Antiviral therapy for prevention of hepatitis B reactivation is recommended for this cohort in those who are HBsAg positive and HBcAb positive (if available).

The following are considered low risk immune suppressive therapy: methotrexate, azathioprine and low dose steroids. Antiviral therapy is not recommended for the purpose of immunoprophlyaxis in HBsAg positive patients. Monitor ALT every three months and start antiviral therapy if ALT >2 times ULN.

Where HBcAb is unavailable, all patients on moderate to high risk IST should have routine ALT every three months. If the ALT >2 x ULN, repeat HBsAg and commence treatment with antivirals if HBsAg positive.

Reactivation of hepatitis B can occur following hepatitis C or hepatitis D treatment. This is likely due to virus-virus interaction with the inhibition of replication of one virus of the other, mostly often

with hepatitis B being the non dominant virus. Antiviral therapy for the dominant virus (HCV/HDV) can lead to down regulation of the immune system so that HBV replication increases. In coinfected patients, antiviral Rx for HBsAg positive patients should be considered (see later section).

Antiviral therapy should be initiated at the time of IST and continued for at least 6-12 months post cessation of IST.

These recommendations were based on APASL guidelines (14).

6.8 Coinfection with HCV, HDV and/or HIV

HBV and HCV coinfection

Coinfection with both HBV and HCV is not an uncommon occurrence in many populations as the risk factors for acquiring both overlap significantly. World-wide data suggest coinfection rates of 1-15% in different countries. It is important to note, however that in populations where HBV has been endemic for generations and where injecting drug use is uncommon, the majority will have infection with one virus (HBV) only. Unfortunately, injection drug use is increasing in many populations and if this occurs without attention given to the minimisation of BBV transmission, coinfection of HBV individuals with HCV and/or HIV will become more common. As both HBV and HCV are spread by exposure to infected body fluids (blood being the most common), coinfection may occur at the same time or the second virus may be acquired as a superinfection at some later time. Acquiring both viruses at the same time increases the risk of the affected individual experiencing a severe or even fulminant hepatitis.

Coinfection with HBV and HCV results in significant consequences:

1. Liver disease in the coinfected population tends to be more active, to progress more rapidly to chronic and fibrotic liver disease and to HCC. Risk for HCC may be increased 3-5 fold in the coinfected.
2. Active infection with HCV may suppress replication of HBV in the clinical setting and this may lead to confusing serological results for HBV. Occult HBV (HBsAg negative) may be present in a patient with active HCV and full HBV serological testing (HBcAb and HBsAb) of all HCV positive patients is recommended.
3. Treatment of HCV with DAA's in the presence of an active HBV infection may result in a flare of the HBV. This demands specific assessment protocols to ensure HBV is identified and managed before HCV DAA's are commenced.

Treatment of hepatitis B in the coinfected:

Adhere to all guidelines in relation to CHB infection and its management.

Screen patients for HCV where the risk of infection is significant (local context).

Where coinfection with HBV and HCV is evident, assume the HCV is driving the inflammatory liver disease in most and consider HCV treatment having evaluated the need for HBV treatment first.

If HBV DNA available and high low, start antiviral therapy for hepatitis B.

If HBV DNA unavailable or low, monitor ALT and start antiviral therapy for hepatitis B if ALT > 2x.

If the patient is already on HBV treatment tenofovir, and HCV infection detected (irrespective of the ALT), treat the active HCV infection with DAA's if available.

Once HCV is cured, continue HBV medications or monitoring as per guidelines. HCC screening as indicated.

HBV and HDV coinfection.

There is a growing interest in HBV/HDV coinfection as the consequences of this clinical situation are recognised to be serious for many patients. Testing for HDV has been variable and not routinely done or easily accessible. Prevalence rates vary widely (0.8 to 14.5%) with pockets of high prevalence throughout the PICT (15). Much of this has been done through the support of VIDRL. Better understanding of local disease burden remains a priority so as to draft appropriate recommendations in testing and management.

Coinfection or superinfection with HDV increases disease severity and increases the risk and rate of development of end stage liver disease, cirrhosis and HCC. Management of both infections is necessary and at present is driven by availability and efficacy of antiviral agents for HBV and HDV.

Initial management focuses on HBV treatment utilising the available antiviral agents. If control of HBV fails to normalise ALT/AST and if HDV RNA levels are high, it can be assumed (in the absence of NAFLD or other causes of liver disease) that the HDV is the driver of liver injury. Pegylated interferon has been the only recommended treatment is the standard treatment for HDV until recently. Newer agents (bulevirtide) are approved in Europe but access to any form of therapy for HDV remains challenging for the resource poor setting.

All patients require monitoring for disease progression and for HCC where identification of these complications will lead to active interventions.

All CHB patients with coinfection should be considered candidates for hepatitis B antiviral therapy.

HBV and HIV coinfection.

As with HCV and HDV coinfection, HIV coinfection increases the severity of the clinical illness in patients with HBV. In those with active HIV, HBV related liver damage may be decreased as it is normally immune driven. Restoration of immune function through the use of anti retrovirals can lead to an activation of liver damage in some patients.

Management of HBV/HIV coinfection is best undertaken by clinicians who are skilled in both infections or with close consultation between HBV and HIV experts.

Tenofovir is a component of Truvada, used as Pre exposure prophylaxis, post exposure prophylaxis and in the treatment of HIV.

In considering management of HIV risk exposure and HIV, the use of tenofovir containing agents is most appropriate as the drug will cover HBV infection. If the HIV medication is ceased (in patients receiving Truvada for prophylaxis) then tenofovir can be continued as a single agent for the HBV.

6.9 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 which affect the liver including dengue fever, leptospirosis, malaria, 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 HBcAb (IgM, if available) indicating recent hepatitis B infection. Many acute cases are undiagnosed with diagnosed at later date, but those who are diagnosed with acute hepatitis B should have follow up serology after 6 months to assess for chronicity. 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 (see appendix on natural history of hepatitis B). Persons with fulminant or severe acute hepatitis may benefit from antiviral therapy with tenofovir 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 HBsAb. 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.

6.10 Metabolic syndrome, alcohol and hepatitis B

Metabolic syndrome describes a cluster of risk factors including obesity, hypertension and an adverse lipid profile, that increases the risk of developing type II diabetes, cardiovascular disease, and non-alcoholic fatty liver disease (NAFLD). NAFLD is now recognized as the most common liver

disease worldwide with a global prevalence of 25%-33% (16). The Oceania region has a high incidence of metabolic syndrome, (>50%) and with growing rates of obesity, this is set to increase.

Excessive alcohol consumption has long been known to be associated with the development of chronic liver disease, and causes a very similar pattern of liver disease to NAFLD, with steatosis, steatohepatitis, fibrosis and cirrhosis. It is also known to compound the effects of metabolic syndrome. There is good evidence that consumption of greater than 40g alcohol (male) or 20g (female) per day in patients with chronic hepatitis B, is associated with an increased risk of advanced liver disease including hepatocellular carcinoma. There is variability in excess alcohol intake throughout the Pacific, but is thought to be generally low.

Lifestyle factors should be addressed in a wholistic way when treating patients with liver disease and coexisting metabolic syndrome, including limiting carbohydrate, particularly in the form of refined sugar, promoting exercise, and advice around reducing alcohol consumption.

Chronic HBV infection and NAFLD is likely to co-exist in many patients. Like HBV, NAFLD and insulin resistance are risk factors for the development of HCC. As a result, it would not be surprising if the co-existence of these two liver disorders was associated with a high risk of HCC. There is growing data that shows higher risk (by 3-7 fold) of developing HCC in patients with NAFLD and chronic HBV infection compared with chronic HBV infection alone (17, 18).

Hence, if ALT fails to decline to normal ranges after antiviral therapy has been initiated (and compliance confirmed), another co-existent liver disease is probably present and additional tests should be performed to determine the aetiology of this liver disease. If the co-existent liver disease cannot be effectively treated, the patient remains at high risk of developing progressive liver injury with potential to hepatic decompensation.

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