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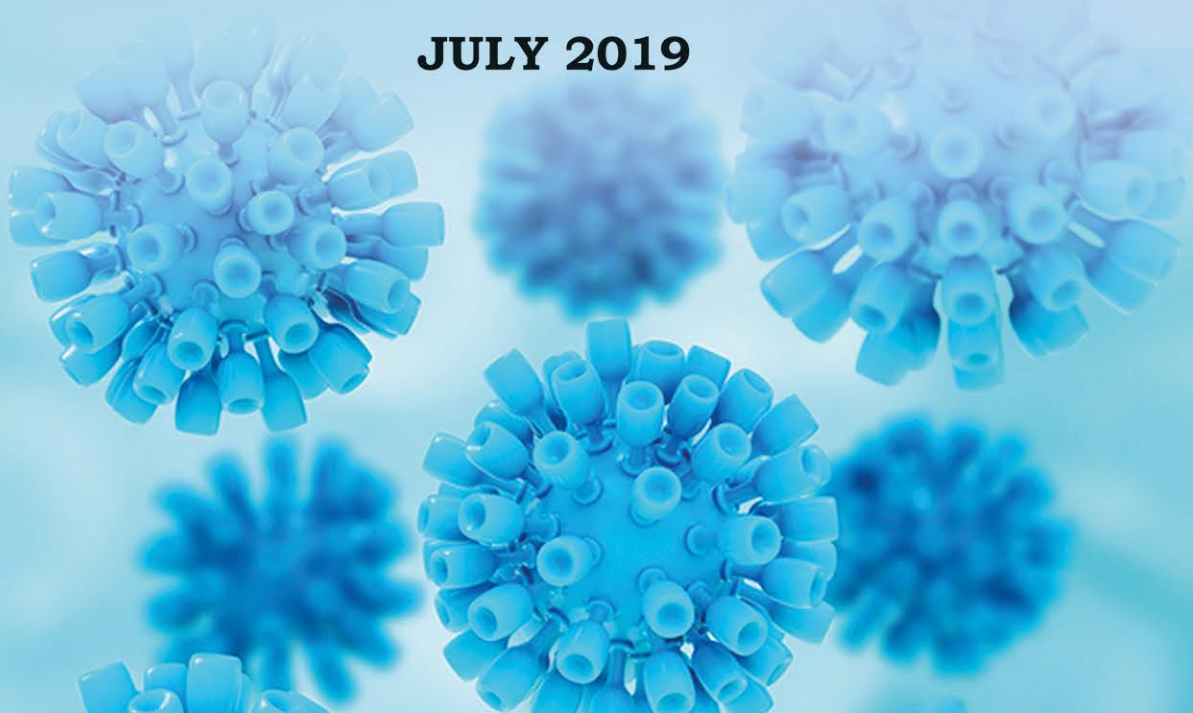
NATIONAL SIMPLIFIED TREATMENT GUIDELINES OF VIRAL HEPATITIS B INFECTION

NATIONAL HEPATITIS CONTROL PROGRAM

MINISTRY OF HEALTH AND SPORTS
MYANMAR

JULY 2019



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FOREWORD

Viral hepatitis (A, B, C, D, E) is recognized as a global public health concern. Globally estimated that viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining. Most viral hepatitis deaths in 2015 were due to chronic liver disease (720 000 deaths due to cirrhosis) and primary liver cancer (470 000 deaths due to hepatocellular carcinoma).

It is estimated in 2015 that worldwide 257 million people or 3.5% of the population, were living with chronic HBV infection, and 71 million people with chronic HCV infection which was 1% of world's population. Hepatitis B is a potentially life-threatening liver infection and a major global health problem.[1]

In 2013, clinical practice guidelines for treatment of viral hepatitis B was developed by Myanmar Gastrointestine and Liver Society (MGLS) in collaboration with the Internal Medicine Society of Myanmar Medical Association to help the clinicians for better management of patients with acute and chronic hepatitis B.

In 2019, the National Hepatitis Control Program (NHCP) developed this hepatitis B treatment guidelines in collaboration with the Department of Medical Services (DMS), Departments of Hepatology, World Health Organization (WHO) and Clinton Health Access Initiative (CHAI) and Myanmar Gastrointestine and Liver Society (MGLS). It is intended to update the physicians and other health care professionals in the clinical decision-making process, by describing the current optimal management of viral hepatitis B. These recommendations apply to the diagnoses and treatments approved by the Ministry of Health and Sports, Myanmar at the time of publication.

1 WHO fact sheet. (2018, July 18). Retrieved from https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.

ACRONYMS AND ABBREVIATIONS

AASLD	American Association for the Study of Liver Disease
ALT	Alanine Aminotransferase
Anti-HBs	Hepatitis B Surface Antibody
APASL	Asian Pacific Association for the Study of the Liver
APRI	AST to Platelet Ratio Index
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
CHB	Chronic Hepatitis B
CSW	Commercial Sex Worker
Cr	Creatinine
CrCl	Creatinine Clearance (ml/min)
DMR	Department of Medical Research
DNA	Deoxyribonucleic Acid
EASL	European Association for the Study of the Liver
ETV	Entecavir
EPI	Expanded Program for Immunization
GFR	Glomerular Filtration Rate (ml/min)
HBIG	Hepatitis B Immune Globulin
HBeAg	Hepatitis B e Antigen
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCC	Hepatocellular Carcinoma
HepB-BD	Hepatitis B Birth Dose Vaccination

HIV	Human Immunodeficiency Virus
IDU	Injecting Drug Users
IHC	Integrated HIV Care
LMIC	Lower-middle-income Country
MSM	Men Who Have Sex with Men
NAs	Nucleos(t)ide Analogues
NBC	National Blood Center
NHL	National Health Laboratory
NITs	Non Invasive Tests
PEG IFN	Pegylated Interferon
PHL	Public Health Laboratory
PLHIV	People Living with HIV
PWID	People Who Inject Drugs
RDT	Rapid Diagnostic Test
STI	Sexually-transmitted Infection
TAF	Tenofovir Alafenamide
TDF	Tenofovir Disoproxil Fumarate
WHO	World Health Organization

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We would also like to express genuine thanks to Professor Christian Ramers, Senior Clinical Advisor, Dr Hlaing Thazin Aung, Dr Yee Mon Kyaw, Clinton Health Access Initiative, for his technical updates. We would also like to thank Dr. Aye Myat Soe and Dr Fabio Mesquita, World Health Organization, for initiating this work and Dr Rewari and Dr Amit Goel for reviewing the draft and for their valuable comments. In addition, we would like to thank Clinton Health Access Initiative and staff from World Health Organization for their technical and logistical support for the development of Myanmar's Simplified Guidelines for the Treatment of Hepatitis B Infection.

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1. INTRODUCTION AND EPIDEMIOLOGY

Hepatitis B viral infection is a global public health problem with approximately 257 million chronically infected people.[1] HBV causes inflammation of the liver, and if left untreated can lead to liver cirrhosis, hepatocellular carcinoma (HCC) and death. Approximately 20% to 30% of persons with chronic HBV will develop cirrhosis or HCC.[2] In Myanmar, HBV is estimated to cause 60% of HCC cases.[3] Globally, more than 887,000 people are estimated to die with HBV-related liver disease each year.[2]

To date, at least 9 different genotypes of HBV have been identified. It is well known that genotype C HBV infection is an independent risk factor for HCC development in addition to liver cirrhosis.[3] In Myanmar, genotype C is most prevalent, with one study estimating 77% of HBV-infected patients in Yangon to have genotype C infection.[4]

HBV is endemic in Myanmar. According to 2015 National Prevalence Survey for Hepatitis B and C carried out by the Department of Medical Research (DMR), prevalence of the hepatitis B surface antigen (HBsAg) among the general population is 6.5%. The study, which was conducted from May to November 2015 across 18 facilities covering all States and Regions, showed varying prevalence of HBsAg based on different geographies and demographics. Prevalence within the male and female populations screened was found to be 9.0% and 5.5% respectively. Geographically, the highest prevalence was seen in Yangon, Pathein, and Mawlamyine, with a prevalence of 12.3%, 9.2%, and 7.8% respectively. The prevalence of Hepatitis B in the general population was 6.5%--8.95% in males and 5.47% in females. The highest prevalence was seen in Yangon with 12.29%. Among blood donors, the highest prevalence was seen in Bago, Rakhine, and Tanintharyi with prevalence rates of 4.0%, 4.8% and 5.0% respectively.[4] Myanmar has a national policy for hepatitis B (HBV) prevention with birth dose and pentavalent hepatitis B vaccination scheme. Pentavalent vaccination as a part of the EPI program was initiated in 2013 but birth dose hepatitis B vaccination is limited to the hospital deliveries since 2010. Due to the lack of regular support for the birth dose vaccination program, it was reported only 7% of hospital deliveries

1 WHO. (2017). Guidelines on Hepatitis B and C Testing.

2 WHO. (2015). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection.

3 Win NN, Nakamoto S, Sein MM, Moriyama M, et al. (2018, March). Hepatitis B Virus Genotype C is Predominant in Myanmar. Disease. 6(1):3.

4 National Blood Center. (2016). Annual Report on Blood Transfusions Services.

have been covered in 2018.[5]

The antiviral treatment for HBV can be categorized into 2 groups: interferons and nucleos(t)ide analogues (NAs). The injectable forms of pegylated interferon alfa (alfa 2a or alfa 2b) are available for HBV therapy. However, its use is limited by cost and adverse effects which includes cytopenia, exacerbation of neuropsychiatric symptoms and induction of autoantibodies. So close monitoring by the attending physician is necessary. Interferon is contraindicated in patients with mental health disorders,[6] pregnancy, autoimmune disease and decompensated cirrhosis7. Moreover, overall responses to pegylated interferon for 48 weeks remain unsatisfactory. The oral NAs are becoming more popular with low cost, ease of administration, once daily regimen, excellent adverse effects profile, high efficacy and have been shown to slow the progression of cirrhosis and reduce the incidence of death from liver cancer and other liver related diseases.[7]

In 2013, the Myanmar Gastrointestinal and Liver Society developed the Treatment Guidelines for the Chronic Hepatitis B Infection with considerations for availability and drug resistance over time.[6,8]

This national guideline for hepatitis B treatment is developed to provide information to healthcare providers in Myanmar for the testing and treatment of chronic hepatitis B infection. In this guideline, oral nucleos(t)ide- analog treatment is the preferred first line treatment.

The development of the guidelines included a formal review of the following recent publications:

- European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection
- Asian Pacific Association for the Study of the Liver (APASL) Clinical Practice Guidelines on the Management of Hepatitis B: 2015 Update
- American Association for the Study of Liver Disease (AASLD) Guidelines for Treatment of Chronic Hepatitis B 2018

5 EPI unit. WHO Myanmar. (2019).

6 WHO. (2015). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection.

7 WHO. (2015). Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection.

8 WHO. (2017). Global Hepatitis Report.

- WHO Guidelines on Hepatitis B and C Testing 2017
- WHO Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection 2015
- WHO Global Hepatitis Report 2017
- WHO Progress Report on Access to Hepatitis C Treatment 2018

The guideline was discussed at a national consultation meeting with Professor Dr Khin Maung Win, Professor Win Naing, Professor Naomi Khaing Than Hlaing and Professor Win Win Swe and also peer-reviewed by the core group which is led by National Hepatitis Control Program (NHCP), National Health Laboratory (NHL), World Health Organization (WHO) and Clinton Health Access Initiative (CHAI).

2. TRANSMISSION AND PREVENTION

2.1 Transmission of hepatitis B infection

HBV is transmitted through percutaneous, mucosal, or non-intact skin exposure to infected blood or body fluids. HBV infection is regarded as a highly infectious disease as it is known to survive outside of the body for at least 7 days.[9] HBV transmission can occur if an unvaccinated person becomes exposed to the virus. In high prevalence areas like Myanmar, perinatal transmission (mother-to-child transmission during pregnancy, delivery, or soon after)[10] is the most common mode of HBV transmission.

In infants and children:

- 80–90% of infants infected during the first year of life develop chronic infections
- 30–50% of children infected before the age of 6 years develop chronic infections

In adults:

- Less than 5% of otherwise healthy persons who are infected as adults will develop chronic infection

9 Centers for Disease Control and Prevention. (2018). Hepatitis B Questions and Answers for the Public. https://www.cdc.gov/hepatitis/hbv/bfaq.htm.

10 WHO. (2018, July 18). Fact sheet Hepatitis B. Retrieved from https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b.

- 20–30% of adults who are chronically infected will develop cirrhosis and/or liver cancer.

HBV is also commonly transmitted through percutaneous or mucosal exposure to infected blood and body fluids, including saliva and menstrual, vaginal and seminal fluids. Amongst adults, HBV is primarily transmitted through percutaneous exposure to infected blood or unsafe sexual intercourse. Studies of needlestick injuries in healthcare workers have shown HBV to be 10-100-fold more infectious than HIV. Exposure to infectious blood most commonly occurs through the sharing of needles and syringes, razor blades, and other injecting equipment. It may also occur through healthcare-associated practices, such as transfusions of HBV-infected blood and blood products and contaminated injections during medical procedures, or through use of multi-dose vials of medications or vaccines. Adults and older children who are exposed through percutaneous or sexual exposure have a 1% to 10% risk of progressing to chronic infection. The risk of chronic infection becomes significantly higher in adults with impaired immunity, e.g., persons with HIV infection.[11]

2.2 Prioritized populations [12]

In Myanmar, if possible, everybody should be tested for hepatitis B infection. However, the following are high-risk groups with respect to HBV and have shown a higher prevalence than the general population. They should be prioritized for HBV testing and vaccinated if non-immune and HBsAg negative.

- Infants born to infected mothers
- People who inject drugs (PWID)
- Persons living with HIV and / or other sexually transmitted infections (STIs)
- People who frequently require blood or blood products
- Dialysis patients
- Recipients of organ transplantations

11 Sarah Schillie S, Vellozzi C, Reingold A, et al. (2018, January 12). Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Centers for Disease Control and Preventions. 67(1);1–31. Retrieved from https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm.

12 WHO. (2017). Guidelines on Hepatitis B and C Testing.

- People with sexual and/or close household contact with those chronically-infected
- Men who have sex with men (MSM)
- Sex workers (SW)
- People with multiple sex partners
- Healthcare workers and others who may be exposed to blood and blood products through their work
- People in prisons and closed settings
- Mobile or migrant populations
- Indigenous populations
- Persons exposed via other invasive procedures

2.3 Prevention of hepatitis B infection

2.3.1 HBV prevention through vaccination

The strategy for the vaccination of all unvaccinated persons should be adopted irrespective of the presence or absence of risk factors if the resources are available.

Vaccines against HBV are widely available, and vaccination is a critical component of preventing transmission and new infections. The primary HBV immunization series typically consists of three doses of the vaccine.

Vaccination for Infants

The WHO recommends universal hepatitis B birth dose (HepB-BD) vaccination for all infants, and recommends administration of birth dose as soon as possible after birth, preferably within 24 hours. [1] The HBV birth dose consists of a single dose monovalent vaccination and must be administered within 12 hours of birth in order to achieve maximum efficacy for prevention of mother to child transmission (PMTCT). Birth dose combined with at least two other doses of the HepB vaccine, induces protective antibody concentrations in more than 95% of infants.[13] Infants exposed to HBV are significantly more likely to become infected when the birth dose is delayed, as the effectiveness of the vaccine decreases

13 WHO. (2017, July). Hepatitis B vaccines: WHO position paper. *Weekly Epidemiological Record*. No27: 92;369-392.

with time.[14,15] This makes timely HepB-BD administration critical in reducing the number of mother-to-child HBV transmissions.[16] However, at this point of time the HepB-BD nationwide coverage is unsatisfactory and all out efforts should be put in to increase the HepB-BD coverage rate.

In Myanmar, HBV birth dose is recommended for all infants followed by three doses of the pentavalent vaccine. These vaccines are to be administered at week 8, week 16 and week 24 of life (Table 1). The dosage for newborn is 10 µg regardless of the birth weight.

Catch-up and Adult Vaccinations

In addition to infants, other populations with a high risk of transmission should be targeted for catch-up vaccination as well as other preventive strategies. These populations include unvaccinated children and adolescents, as well as adults at risk for HBV infection as described in the "section 2.2: high risk groups", including household and sexual contacts of persons who are HBsAg-positive, people who inject drugs (PWID), people living with HIV (PLHIV), men who have sex with men (MSM), sex workers, persons with multiple sexual partners, persons who are incarcerated, hemodialysis patients, persons who receive frequent transfusions, healthcare workers, people with HIV, indigenous and migrant populations, and persons exposed via invasive procedures.

Prior to vaccination, patients are recommended to first be screened for the presence of HBsAg, as the vaccination will not be effective in those already infected. Those who are determined to be HBsAg positive should undergo confirmatory test. If the positivity is confirmed, the patient should be referred for clinical evaluation and possible treatment initiation, while those who are determined to be negative will be eligible for a vaccination at month 0, month 1, month 2, (Table 1). The usual dosage for adults is 20 mcg for immunocompetent patients and may be increased to 40 mcg for people living with HIV or hemodialysis or immunocompromised patients.

14 WHO. (2012). Practices to improve coverage of the hepatitis B birth dose vaccine. p 1.

15 Bongomin Bodo and Oliver Ombeva Malande. (2017). Delayed introduction of the birth dose of Hepatitis B vaccine in EPI programs in East Africa: a missed opportunity for combating vertical transmission of Hepatitis B. Pan Afr Am J. (27 Suppl 3): 19. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5745935/.

16 WHO. (n.d.). A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination.

Table 1: HBV Vaccine Schedule for Myanmar

	Group	Dose 1	Dose 2	Dose 3	Dose 4
Timing	Standard regimen	Month 0	Month 1	Month 6	
	Newborn	Within first 24 hours after birth	Week 8	Week 16	Week 24
	Child/Adult	Month 0	Month 1	Month 2	Month 12
	People who inject drugs[1]	Day 1	Day 7	Day 21	
	People living with HIV[2]	Month 0	Month 1	Month 2	Month 12
	Hemodialysis Patients[3]	Month 0	Month 1	Month 2	

2.3.2 Prevention of mother to child transmission of HBV infection

Perinatal transmission (mother-to-child transmission delivery, or soon after) is the most common mode of HBV transmission in high-prevalence areas. In the clinical setting where HBV vaccine alone is used for the prevention of mother-to-infant transmission without the NAs administration to the mothers and without the HBIG injection to the baby within 12 hours after delivery[17], exposed infants who do not receive birth dose vaccine (HepB-BD) have up to a 70% to 90% chance of HBV acquisition depending on maternal clinical factors.[18] Once exposed, approximately 90% of the unvaccinated infants will develop chronic HBV infection[19],[20], with an ensuing 25% at risk of premature death in USA.[21] In contrast, most of those who acquire hepatitis B in adulthood do not develop chronic active

17 WHO. Immunization, vaccines, and biological. 24 January 2018. https://www.who.int/immunization/diseases/hepatitisB/en/.

18 Gentile I and Borgia G. (2014). Vertical transmission of hepatitis B virus: challenges and solutions. *International Journal of Women's Health*.6:605-611. doi:10.2147/IJWH.S51138.

19 Nelson NP, Easterbrook PJ and McMahon BJ. (2016, November) Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. *Clin Liver Dis*.; 20(4): 607–628. doi: 10.1016/j.cld.2016.06.006.

20 Edmunds WJ, Medley GF, Nokes DJ, Hall AJ, Whittle HC. The influence of age on the development of the hepatitis B carrier state. *ProcBiol Sci*. 1993;253(1337):197-201.

21 Hepatitis B foundation/hep B united Philadelphia. Hepatitis B. (2017, May). Issue Brief Vol. 1 Issue 1 Retrieved from www.hepb.org/assets/Uploads/Hepatitis-B-Policy-Brief.pdf.

infections, underscoring the importance of prevention in the perinatal period.[22, 23, 25] As noted above, timely administration of HepB-BD vaccine within 12 hours after delivery, followed by completion of the hepatitis B vaccine 3- or 4-dose schedule is recommended to reduce mother-to-child transmissions. In addition, mother-to-child transmission can further be reduced with comprehensive case management programs, which include the administration of hepatitis B immune globulin (HBIG) and anti-viral treatment for pregnant women with very high HBV DNA levels (e.g. >200,000 IU/ml).

However, in real-life situation in Myanmar, HBIG is prohibitively expensive and HBV DNA determination in the general population at large will not be feasible. Therefore, for practical purposes the administration of oral NAs particularly tenofovir disoproxil fumarate (TDF) 300 mg once a day should be administered starting from week 28 of pregnancy to 3 months after delivery.

The following are recommended for the prevention of mother-to-child transmission:

- All pregnant women should be tested for HBsAg during a prenatal visit in the first trimester of their pregnancy. The result of HBsAg testing should be informed to the patient. A copy of laboratory report indicating the patient's status should be sent to the hospital or birthing facility where possible[24]
- All HBsAg negative pregnant women should be vaccinated for hepatitis B. Hepatitis B vaccination is safe in any trimester of pregnancy[25]
- Pregnant women with positive HBsAg should have an HBV DNA test when available to assess whether they would have maximal benefit from anti-viral therapy

22 Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. (1983). Prevention of perinatally transmitted Hepatitis B virus infections with Hepatitis B virus infections with Hepatitis B immune globulin and Hepatitis B vaccine. *The Lancet*. 2(8359):1099-102.

23 Acute vs. Chronic Infection. (n.d). Hepatitis B Foundation. http://www.hepb.org/what-is-hepatitis-b/what-is-hepb/acute-vs-chronic/.

24 Centers for Disease Control and Preventions. (2018). Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. (https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm).

25 Centers for Disease Control and Preventions. (2006). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 2: immunization of adults. *MMWR*. 55 (No. RR-16): 13.

- Pregnant women with positive HBsAg who are not on antiviral therapy as well as those who stop antiviral at or early after delivery should be monitored closely for up to 6 months after delivery for hepatitis flares and seroconversion[26]
- Counseling involving the potential use of antiviral therapy and importance of prophylaxis for their infant should be provided for all HBsAg-positive pregnant women[2]
- Birth dose HBV vaccine should be given to all infants as soon as possible after delivery, preferably within 12 hours.
- For infants born to HBsAg positive mothers, HBIG should also be administered intramuscularly in combination with the HBV-BD vaccine but at a separate injection site from HBV-BD vaccine within 12 hours of birth.

2.3.3 Prevention of HBV in Community Settings

Household contacts of individuals with chronic HBV should be tested for HBsAg and if negative, should be prioritized for HBV vaccine.

All individuals, particularly those with known HBV-infections, should

- Avoid unsafe medical or traditional practices (e.g., cosmetic, scarification, tattoos, and circumcision procedures, as well as traditional healing practices)
- Follow safe household practices (avoid sharing toothbrush, razors, practice hand washing, blood contact)
- Adopt correct and consistent condom use during sexual intercourse

2.3.4 Prevention of HBV Infection among People Who Inject Drugs

The following are recommended to prevent HBV transmission and infection among PWID:

- HBV vaccination, with incentives to increase uptake and complete the vaccination schedule
- Distribution of sterile injection equipment including needles and

26 Terrault NA, Lok A, McMahon BJ., et al. (2018). Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: Hepatitis B Guidance. *AASLD.*

syringes with low dead-space, possibly through needle and syringe exchange programs

- Peer-based behavioral interventions, which involve peers (current or ex PWID) in service delivery to enhance engagement and improve acceptability of services and programs
- Provision of opioid substitution therapy and other drug-dependence treatment and integration of therapies with medical services for hepatitis
- Targeted provision of information, education and communication for PWID and their sexual partners [2]

2.3.5 Prevention of sexual transmission of HBV infection

The following are recommended to prevent sexual transmission of HBV:

- Testing of sexual partners and vaccination if HBsAg negative
- Promotion of correct and consistent condom use
- Education around seeking regular screening and treatment for STIs
- Targeted and routine screening of sex workers

2.3.6 Prevention of HBV Infection in Healthcare Settings

The following are recommended to prevent the transmission of HBV in healthcare settings: [2]

- Hand hygiene including surgical hand-washing and use of gloves
- Safe handling and disposal of sharps and waste
- Safe cleaning of equipment
- Testing of donors, donated blood and blood products
- Improved access to safe blood
- Vaccination of healthcare workers
- Training of healthcare personnel in Universal Precautions

2.3.7 Injection Safety

The following injection safety practices should be implemented across facilities.

- General safety practices including hand hygiene, gloves where

appropriate, other single-use personal protective equipment, and skin preparation and disinfection[27]

- Auto-disable syringes should be used for intramuscular, intra-dermal and subcutaneous injections
- Facilities should have a sufficient supply of quality-assured syringes and matching quantities of safety boxes
- Unsafe practices include
    - Reusing syringes and / or needles without sterilization
    - Recapping of used needles
    - Using multi-dose vials without sterile needle & syringe each time
    - Handling of infected sharps before and after disposal, and general unsafe handling of sharps resulting in needle-stick injuries
    - Administering injections where oral formulations are available and recommended as the first-line treatment
    - Inappropriate sharps waste management

2.3.8 HBV Post Exposure Prophylaxis

After mucosal, non-intact skin or percutaneous exposure to blood or other body substances, the following are recommended as soon as possible:

- Wounds should be washed with soap and water and mucous membranes (e.g., mouth, eyes) should be flushed or rinsed with water
- Contaminated clothing should be removed and wearer should shower with soap
- Where water is not available, use of non-water cleanser or antiseptic should replace the use of soap and water for washing cuts or punctures of the skin or intact skin
- Source should be screened for HBsAg, HIV, and HCV antibodies
- Baseline evaluation and testing (if source is not infected, baseline testing is not required; if HBV positive source, test exposed person for HBsAg)

27 WHO. (2017, February). Guidelines on hepatitis B and C testing.

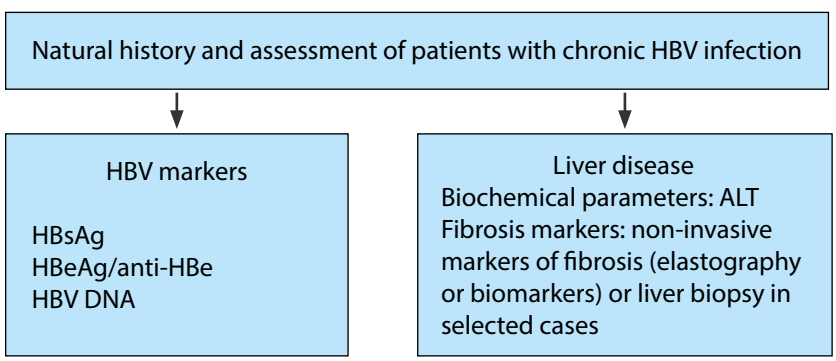
- If source is positive or if status is unknown, HBIG (0.06 ml/kg or 500 IU) should be administered intramuscularly simultaneously but at separate injection site from the first dose of the vaccine

3. NATURAL HISTORY OF HBV INFECTION

3.1 Natural History of HBV Infection

The natural history of chronic HBV is complex and progresses non-linearly through five phases. The phases are HBeAg positive chronic infection (formerly 'Immune Tolerant'), HBeAg positive chronic hepatitis (formerly 'Immune Active'), HBeAg negative chronic infection (formerly 'Immune Control' or 'Inactive Carrier') and HBeAg negative chronic hepatitis (formerly 'Reactivation' or 'Immune Escape') and HBsAg negative (Occult HBV) chronic infection[28] as shown in figure 1.

Figure 1. Natural history and assessment of patients with chronic HBV infection



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

28 European Association for the Study of the Liver. (2017). EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of hepatology*. vol. 67: j 370–398.

Hepatitis B virus causes both acute and chronic infection, which can range from asymptomatic infection or mild disease to severe hepatitis. Acute hepatitis B is identified within the first 6 months of exposure. During this period, some of those infected are able to clear the infection on their own, while the remaining will go on to develop a persistent chronic hepatitis B infection (CHB), defined as the presence of detectable HBsAg in the blood or serum for longer than six months. The age of infection acquired is the most important factor in determining the risk progressing to chronic infection. 90% of exposed infants will develop chronic infection, 20-60% of children exposed before the age of five will develop chronic infection, while this figure is less than 5% for those who acquire the infection in adulthood.[29] The severity of liver disease in persons with CHB ranges from minimal fibrosis to cirrhosis to HCC.

After many years of chronic infection an estimated 20% of patients will develop cirrhosis, which may progress to decompensated cirrhosis and development of portal hypertension. Then, there will be potentially life-threatening complications such as ascites, spontaneous bacterial peritonitis, oesophageal varices and bleeding, hepatic encephalopathy, coagulopathy, sepsis and renal failure. HCC can develop after many years of chronic infection and may occur even without cirrhosis. Persons with advanced fibrosis and cirrhosis require antiviral therapy in order to prevent further disease progression. HBV is vaccine-preventable, but without a cure, most infected people require long term treatment to prevent disease progression.

3.2 Interpretation of Serological Markers of HBV infection

A range of HBV markers namely HBsAg, anti-HBc (total), anti-HBc IgM, HBeAg, anti-HBe, anti-HBs and HBV DNA can be used to characterize the course of HBV infection (see Table 2). In Myanmar, further assessment of HBsAg-positive persons is needed to guide management and indicate the need for treatment. In Myanmar, this includes measuring alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels to help determine liver inflammation, complete blood count (CBC) to assess for thrombocytopenia, a sign of cirrhosis, and quantification of HBV DNA levels. An assessment of the stage of liver fibrosis must be conducted using clinical history an examination as well as by non-invasive tests such as AST-to-platelet ratio index (APRI).

29 WHO. (2017, February). WHO Guidelines on Hepatitis B and C Testing.

The appearance of HBsAg in the blood is followed by that of HBeAg, which is a marker of high levels of viral replication. In acute HBV infection that resolves by itself, HBeAg seroconverts relatively early to anti-HBe with the disappearance of HBsAg and HBeAg. But in chronic HBV infection, seroconversion to anti-HBe may be delayed for many years. Antibodies to hepatitis B core antigen (anti-HBc) may occur relatively early in the infection, often within a week or two after the appearance of HBsAg, and is typified by a profound immunoglobulin (Ig) M anti-HBc response that wanes approximately 6 months later, yielding to the more persistent IgG Anti-HBc. Because the core antigen is not present in the HBV vaccine, antibodies to this antigen (anti-HBc) are only present in persons who have been exposed to natural HBV (as opposed to vaccination).

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

The stage of disease can be further characterized by HBeAg-positive or HBeAg-negative status. These will require serial measurement as the condition may change over time. In persons with CHB, a positive HBeAg result suggests more recent infection, usually with high-level HBV replication and high infectivity. Spontaneous improvement may occur following HBeAg-positive seroconversion (loss of HBeAg and development of anti- HBe), with a decline in HBV replication, and normalization of alanine aminotransferase (ALT) levels. This confers a good prognosis and indicates some host immune response to HBV.

Table 2. Seromarkers of hepatitis B infection

HBsAg	Total anti-HBc	Anti-HBc IgM	Anti-HBs	HBV DNA	Interpretation
-	-	-	-	-	Never infected
+	-	-	-	-	Transient (up to 18 days) after vaccination
+	-	-	-	+	Early acute infection
+	+	+	-	+	Acute infection
-	+	+	+ or -	+ or -	Acute resolving infection
-	+	-	+	-	Recovered from past infection and immune
+	+	-	-	+	Chronic infection
-	+	-	-	+ or -	False-positive (i.e., susceptible); past infection; "low-level" chronic infection; or passive transfer of anti-HBc to infant born to HBsAg-positive mother
-	-	-	+	-	Immune if anti-HBs concentration is ≥10mIU/ml after vaccine series completion; passive transfer after hepatitis B immune globulin administration

Abbreviations: - =negative; + = positive; anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; IgM = immunoglobulin class M.

Figure 2. Acute HBV infection with Recovery

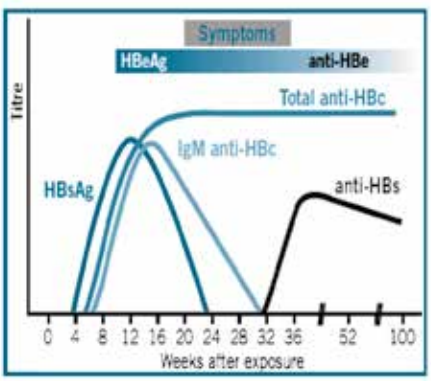
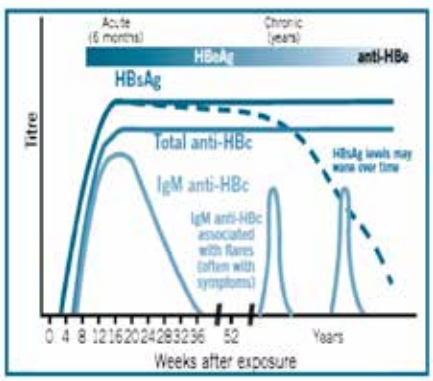


Figure 3. Chronic HBV infection[31]



4. DIAGNOSIS AND TREATMENT ELIGIBILITY

4.1 Simplified Algorithm for Testing and Treatment of HBV

Everybody should be screened for HBsAg to detect HBV infection. Hepatitis B infection is diagnosed by presence of HBsAg. All people with positive HBsAg for more than 6 months are considered to have a chronic infection, but not all those with chronic infection need to be initiated on treatment immediately unless the patient has the criteria for treatment indications. This is because some stages of chronic HBV infection are associated with little to no progression of fibrosis and therefore the balance between risks and benefits of therapy favors monitoring rather than immediate treatment.

Once confirmed HBsAg positive, all patients should have an assessment of the severity of liver disease. Physical examination together with serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, alphafetoprotein (AFP), complete blood count (CBC), serum creatinine and eGFR must be done. Anti-HIV and anti-HCV testing should also be done as necessary.

The staging of liver fibrosis and cirrhosis needs to be assessed by using the aspartate aminotransferase (AST)-to-platelet ratio index (APRI). Fibroscan needs to be done where available. Every patient needs to undergo ultrasonography of the liver which can detect liver cirrhosis as well as HCC.

HBV DNA testing should be done in all HBsAg positive patients. However, HBV DNA level will not always be included in the consideration of treatment initiation

due to limited access to the test for all patients.

All cirrhotic patients should be initiated on antiviral therapy to decrease likelihood of hepatic decompensation irrespective of HBV DNA level. For non-cirrhotic patients, HBV DNA testing may be required to further assess eligibility for treatment.

4.2 Who Should Be Tested

In Myanmar, screening should be conducted for:

- Preferably all patients attending hospital services either as an out-patient or in-patient for any reason
- In resource limited settings, all patients admitted to hospitals with signs and symptoms of liver disease (i.e., jaundice, abdominal pain, fatigue, nausea, vomiting, or abnormal liver function tests or ultrasound), other patients at the discretion of the attending doctor
- Routine opt-out testing should be conducted for pregnant women
- Focused screening should be offered to high-risk groups described in **Section 2**, particularly PLHIV, PWID, MSM, patients with chronic Hepatitis C infection, repeated transfusion recipients, institutionalized populations, sexual partners and those with close household contacts with infected individuals, and healthcare workers
- Screening of blood and organ donors is mandatory
- Linkage to care, counseling and treatment should be offered to those who are HBsAg test positive[30]

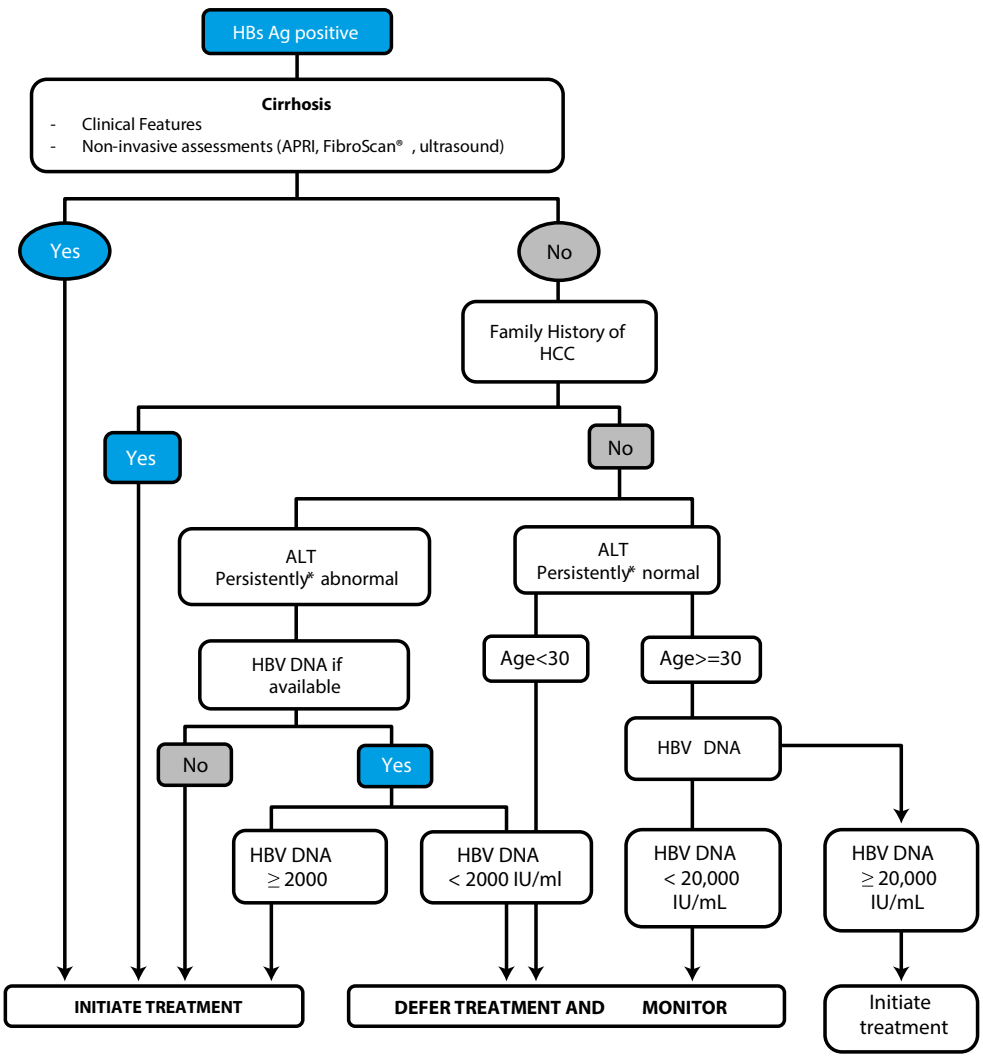
4.3 Diagnosis of HBV

The diagnosis of hepatitis B in adults, adolescents and children should be conducted by assessing the presence of HBsAg using a rapid diagnostic test (RDT) or laboratory-based immunoassay. In Myanmar, RDTs are recommended given ease of use, cost, infrastructure, and access considerations. RDTs which meet minimum safety, quality, and performance standards, as defined by the WHO, should be prioritized for use in the program. HBsAg positive with 6 months apart is indicative of chronicity and patients should be recommended for additional testing to determine treatment eligibility. In cases of suspected acute infection,

30 WHO Guidelines on Hepatitis B and C Testing. Geneva: World Health Organization; 2017.

one may consider reassessing with repeat markers in 6 months to see if infection clears or is established as a chronic infection, however, identifying acute HBV infection is rare.

Figure 4. Treatment algorithm



*Monitor ALT on 2 separate occasions 3 months apart for 6 months. If elevated, exclude other causes of ALT elevation.

4.4 Counseling and Education on HBV infection and Treatment

4.4.1 Pre-test counseling and Education about HBV

Prior to testing, healthcare workers, professional counsellors, social workers, or trained providers should:

- Encourage the individuals for screening test
- Clarify information about HBV, including transmission risks and progression
- Explain the value and benefits of testing, as well as negative consequences in settings where high-risk activities are stigmatized or criminalized
- Facilitate a discussion on ways to cope with this information
- Assure confidentiality of test results and all information shared

Patients in Myanmar will likely have access to their test results within the same day.

4.4.2 Post-test Counseling on Chronic HBV and Treatment

For those who test HBsAg positive, healthcare workers, professional counselors, social workers, or trained providers should:

- Explain test results and diagnosis
- Provide clear information on further tests required.
- Explain the potential long-term health implications of chronic HBV infection, such as liver failure, cirrhosis, and liver cancer, and that the chronic nature of the disease warrants long term monitoring and treatment
- Provide information on preventing transmission to others, including the use of condoms to interrupt sexual transmission and clean needles or opioid substitution to prevent percutaneous transmission
- Encourage and offer HBV testing for spouse(s), children, household contacts, close relatives, and sexual partners
- Discuss possible disclosure of the result including the risks and benefits of disclosure to those around the client who are at risk of infection
- Provide lifestyle counseling including the avoidance of alcohol, herbal

concoctions, multiple sexual partners, tattooing, scarification marks, etc.

- Provide additional information and referrals for counseling, support and other services where applicable (e.g., HIV testing, HCV testing, etc.)

For individuals in high-risk groups who test HBsAg positive, post-test counseling should be combined with additional sessions of counseling by community health workers to strengthen linkage to care and treatment. Other services including HIV and HCV-testing should also be offered.

For those HBsAg positive and eligible for treatment, in addition to information above, the following should be explained and discussed

- Objectives and likely outcomes of treatment
- Financial implications of treatment
- Potential adverse effects of treatment (see **Section 5.4**)

Given that treatment is only recommended in certain stages of chronic HBV, individuals who are screened positive but who are ineligible for treatment should be encouraged to return in 3-6 months for further monitoring.

For those who test HBsAg negative, healthcare workers, professional counselors, social workers, or trained providers should briefly

- Explain test results
- Offer 3 doses of HBV vaccination
- Provide educational materials on prevention and transmission of the virus
- Encourage the individual to return for repeat testing if there is a risk of ongoing exposure or when test results are inconclusive

4.5 Evaluation of Patients with Chronic Hepatitis B for Treatment

4.5.1 Pre-treatment Assessments

Once confirmed HBsAg positive, all patients should have an assessment of the severity of liver disease to identify patients with impaired liver function and advanced liver cirrhosis, which must be prioritized for treatment. If the patient has decompensated cirrhosis or HCC, referral to specialist center with liver transplant facility will be necessary.

- Formal clinical assessment
    - History
        - ✓ Duration of HBsAg positivity
        - ✓ Family history of HCC and other liver diseases
        - ✓ Social History to identify household contacts (for testing), risk of transmission (sexual partners or PWID)
        - ✓ Assessment and counseling on alcohol and drug use, smoking, betel chewing
        - ✓ Presence of comorbid conditions such as Diabetes Mellitus, HCV, HIV infection
    - Physical Examination
        - Signs of chronic liver insufficiency such as spider naevi, palmar erythema, gynecomastia, white nails, muscle wasting (sarcopenia)
        - Complications of cirrhosis and portal hypertension such as hepatic encephalopathy, leg edema, jaundice, ascites, oesophagogastric varices

- Laboratory investigation
    - Blood tests
        - ✓ Alanine aminotransferase (ALT)
        - ✓ Aspartate aminotransferase (AST)
        - ✓ Alphafetoprotein (AFP)
        - ✓ Complete blood count (CBC)
        - ✓ Serum creatinine and eGFR
        - ✓ Serum total bilirubin (optional)
        - ✓ Serum albumin (optional)
        - ✓ Prothrombin time/ INR (optional)

    - Calculation for liver fibrosis staging: APRI
      (Aspartate aminotransferase to platelet ratio index)

The APRI score correlates with METAVIR scores to indicate the degree of liver fibrosis:

Table 3. METAVIR Liver Biopsy Scoring System 31

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

Table 4. Aminotransferase/Platelets Ratio Index (APRI)

Non-invasive test	Components assessed	Lower cut off	Upper cut off
APRI	AST and platelet count	0.5	1.5

The APRI score is calculated using a ratio of AST levels and platelet count.

Formula: APRI = [{AST (IU/L)/ AST_ULN (IU/L)} ×100]/platelet count (10^9/L)

AST - Aspartate aminotransferase

IU- International Unit

ULN- Upper Limit of Normal of the Lab (often 40 IU/ml)

APRI Calculation Example.

AST Level (IU/L) = 60
AST Upper Limit of Normal (IU/L) = 40
Platelet Count (10^9/L) = 133,000/mm^3 (Ref: 150,000-400,000/mm^3) = 13
3

APRI = [{60/40} x 100] / 133
APRI = [1.5 x 100] / 133
APRI = 150/133
APRI = 1.128

31 WHO. (2015, March). Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. P 26.

Table 5. APRI Score Interpretation

APRI score	Interpretation
> 1.5	Cirrhosis
0.5 - 1.5	Moderate Fibrosis, risk of cirrhosis
< 0.5	No Fibrosis

All cirrhotic patients (APRI > 1.5) should be initiated on treatment.

- Imaging
    - Ultrasound abdomen
    - Fibroscan
- Liver biopsy
    - No longer recommended as a routine assessment for liver fibrosis in Myanmar.

4.6 Treatment Eligibility

Treatment Recommended

- HBsAg positive patients with cirrhosis
- HBsAg positive patients with a family history of HCC[32]
- HBsAg positive patients above 30 years of age
- Patients with persistently abnormal ALT and HBV DNA > 2,000 IU/ml
- Patients with persistently abnormal ALT (if HBV DNA is not available)
- Patients above 30 years of age with persistently normal ALT and HBV DNA > 20,000 IU/ml
- Patients with HIV/HBV co-infection should begin anti-retroviral therapy with a regimen that contains activity against HBV regardless of liver staging, ALT levels, or HBV DNA

Treatment Deferred

- Patients under 30 years of age with persistently normal ALT
- Patients with persistently abnormal ALT and HBV DNA <2,000 IU/ml

32 EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection.

Adults with CHB who do not meet treatment criteria should be monitored at regular intervals (3 - 6 months) for serum ALT and liver fibrosis severity to determine if antiviral therapy may be indicated in future to prevent liver disease progression.

Timing and frequency of follow-up may differ in patients, based on the presence or absence of cirrhosis of liver.

- If cirrhosis, every 3-6 months
- If no cirrhosis, every 6 months

5. TREATMENT

5.1 Goals of Therapy

The main goal of treatment for CHB is the prevention of cirrhosis and HCC. In cirrhotic patients, it is to prevent liver decompensation and portal hypertension.

5.2 Pre-treatment Counseling

Ahead of initiation on treatment, patients should receive comprehensive counseling on:

- Indications for treatment
- Benefits of the treatment
    - Treatment can prevent development of liver cirrhosis and decompensation.
    - Benefits of treatment outweighs the concomitant cost implications in the long term.
- Need and willingness to commit to potential long-term treatment (drug adherence)
    - Abrupt cessation of treatment may result in an acute rebound hepatitis flare.
    - Failure to stick adherence can cause drug resistance.
- Follow-up monitoring both on and off therapy
- Advice on lifestyle changes, including alcohol, smoking, diet and physical activity

- Side-effects of treatment

5.3 Recommended Treatment Strategies and Dosing

Available Treatment Options

Currently, two main treatment options are available for patients with CHB:

1. ***Nucleos(t)ide Analogues (NAs)***

   Several NAs are approved and licensed for treatment: Lamivudine (LAM), Adefovir Dipivoxil (ADV), Entecavir (ETV), Telbivudine (TBV), Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF).

   Lamivudine, Adefovir and Telbivudine are not recommended for treatment because they can cause high risk of resistance.

   In all adults, adolescents and children, who meet the treatment criteria, a NA with the high genetic barrier to resistance is recommended:

   Recommendations for Treatment

   - Tenofovir Disoproxil Fumarate (TDF)
   - Tenofovir Alafenamide (TAF)
   - Entecavir (ETV)

2. ***Pegylated Interferon (PegIFN)***

   There are benefits and disadvantages of use of pegIFN in patients with CHB. However, it is not recommended for the National Hepatitis Control Program in Myanmar.

Table 6. Dosing for Recommended HBV Treatment Regimens for Adults

Regimen	Dosage per Tablet	Frequency and Dosing
Tenofovir Disoproxil Fumarate (TDF)	300 mg Tablet	▪ Once Daily
Tenofovir Alafenamide (TAF)	25 mg Tablet	▪ Once Daily

Regimen	Dosage per Tablet	Frequency and Dosing
Entecavir (ETV)	0.5 mg* or 1mg	▪ Patients with fibrosis or compensated cirrhosis: *0.5 mg once daily* ▪ Lamivudine-*experienced patients: 1 mg once daily* ▪ Patients with decompensated Liver Disease: *1 mg once daily*

*Children with body weight more than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily.

5.4 Adverse effects and Drug Interactions

Table 7. Adverse Effects of Recommended HBV Treatment Regimens

Drug	Most Common Adverse Effects
Tenofovir Disoproxil Fumarate (TDF)	Nausea, abdominal pain, diarrhea, headache, dizziness, fatigue
Tenofovir Alafenamide (TAF)	Headache, Abdominal Pain, Fatigue, Cough, Nausea, Back Pain
Entecavir (ETV)	Headache, Fatigue, Dizziness, Nausea

Drug to Drug Interactions of Recommended HBV Treatment Regimens

Drug interactions result from a change in plasma concentration due to effects of another drug on liver or kidney systems of drug processing or elimination. Drug-drug interactions (DDIs) can delay, enhance or decrease the absorption metabolism or elimination of either drug and potentially cause adverse effects. The concomitant use of multiple medications is common in patients being managed for CHB, so the potential for drug-drug interaction is significant.

Table 8. Drug-Drug Interactions Between HBV Drugs Co-administered with HCV or HIV Treatment

	TDF	ETV	TAF
HCV Therapy			
Sofosbuvir	■	■	■
Daclatasvir	■	■	■
Ledipasvir/Sofosbuvir	✸	■	■
Sofosbuvir/Velpatasvir	✸	■	■
Ribavirin	■	■	■
HIV Antivirals			
NRTIs			
Abacavir (ABC)	■	■	■
Lamivudine (3TC)	■	■	■
Zidovudine (AZT)	■	■	■
NNRTIs			
Efavirenz (EFV)	■	■	■
Nevirapine (NVP)	■	■	■
Protease Inhibitors			
Atazanavir (ATV/r)	✸	■	✸
Lopinavir	✸	■	✸
Ritonavir	✸	■	✸

✸ Potential interaction, consider increased monitoring
■ No clinical significant interaction expected

Table 9. Potentially Significant Drug-Drug Interactions of Tenofovir Disoproxil Fumarate (TDF)

Concomitant Drug Class/Name	Effect on ARV and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Cytomegalovirus : Adefovir Ganciclovir Valganciclovir	No data	**Do not coadminister with Adefovir.** Serum concentrations of TDF and/or other renally eliminated drugs may be increased. When co-administering with ganciclovir, Serum concentrations of these drugs and/or TDF may increase. Monitor for dose-related toxicities. For co-administration with valganciclovir, there is a potential for increase in hematologic toxicities.
PIs (HIV): ATV (unboosted), ATV/c, ATV/r DRV/c DRV/r LPV/r	↑Tenofovir Disoproxil Fumarate	Avoid concomitant use without RTV or COBI. Dose: ATV 300 mg daily+ (RTV 100 mg or COBI 150 mg) daily when coadministered with TDF 300 mg daily. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg daily + (RTV 100 mg or COBI 150 mg) daily Monitor for TDF-associated toxicity. When co-administered with DRV/c, DRV/r, or LPV/r, monitor for TDF toxicity.

Concomitant Drug Class/Name	Effect on ARV and/or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Didanosine (HIV)	↑Didanosine	Coadministration increases didanosine concentrations. Use with caution and monitor for evidence of didanosine toxicity (e.g., pancreatitis, neuropathy). Consider dose reductions or discontinuations of didanosine if warranted.

Potentially Significant Drug-Drug Interactions of Entecavir

Entecavir is not a substrate, inhibitor, or inducer of the Cytochrome P450 system (CYP450). Therefore, the pharmacokinetics are unlikely to be affected by coadministration with agents that are either metabolized, or inhibit the CYP450 system. Likewise, the pharmacokinetics of known CYP450 substrates are unlikely to be affected by the coadministration of Entecavir. After oral administration, no oxidative or acetylated metabolites are observed, and only minimal glucoronidated or sulfate conjugated metabolites can be detected. Entecavir is predominantly eliminated by the kidney in an unchanged form and urinary recovery of unchanged drug occurs at 62-73% of the administered dose. Coadministration of drugs that reduce renal function or compete for active tubular secretion may increase serum concentrations of Entecavir.

Table 10. Potentially Significant Drug-Drug Interactions of Tenofovir Alafenamide

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Anticonvulsants: carbamazepinec* oxcarbazepine* phenobarbital* phenytoin*	↓ Tenofovir Alafenamide	When coadministered with carbamazepine, the tenofovir alafenamide dose should be increased to two tablets once daily. Coadministration of tenofovir alafenamide with oxcarbazepine, phenobarbital, or phenytoin is not recommended.
Antimycobacterial: Rifabutin* Rifampin* Rifapentine*	↓ Tenofovir Alafenamide	Coadministration of tenofoviralafenamide with rifabutin, rifampin or rifapentine is not recommended.
Herbal Products: St. John's wort* (Hypericumperforatum)	↓ Tenofovir Alafenamide	Coadministration of tenofoviralafenamide with St. John's wort is not recommended.

For a full listing of significant drug-drug interactions, please see www.hep-druginteractions.org or consult the package insert.

5.5 Treatment Monitoring

For Patients Indicated and Initiated on Treatment

All patients who are initiated on treatment with NAs should undergo periodic monitoring. Success of a patient's therapy is dependent on appropriate baseline investigations and patient monitoring for desirable clinical outcomes and reduced risk of harm to the patient. The objective of monitoring during treatment is to assess the effectiveness of the treatment, treatment adherence, adverse effects, progression of liver disease and development of liver cancer and the potential for treatment discontinuation.

Table 11. Baseline Testing and Treatment Monitoring for CHB Patients on NA Therapy

	Baseline Week 0	Week 12	Week 24	6 monthly
History and Physical Examination	X	X	X	X
HBsAg	X		X	X
HBV DNA	X			
ALT	X	X	X	X
AST	X			
AFP	X		X	X
Serum creatinine	X	X	X	X
CBC	X			
Bilirubin (optional)	X			
Albumin (optional)	X			
Prothrombin time (optional)	X			
APRI	X			
Anti-HCV	X			
Anti-HIV	X			
Ultrasound	X		X	X
Fibroscan	X			

Note that:

- Patients at risk of renal disease (Eg: Diabetic nephropathy) treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodic renal monitoring including serum Creatinine and serum phosphate levels (if available)
- Patients with renal failure/ dysfunction should be referred to the specialist center.

- Patients on TDF at risk of development and/or with underlying renal or bone disease should be considered for a switch to ETV or TAF, depending on previous LAM exposure with TAF preferred in those with prior LAM exposure.

Treatment Endpoint

Long term monotherapy with TDF, TAF or ETV has been shown to halt progression of liver disease and can also result in significant improvement of hepatic necroinflammation or fibrosis.

But NA therapy does not usually achieve HBV eradication and rarely results in HBsAg loss. Consequently, a majority of CHB patients will remain on long term therapy.[33]

6. SPECIAL POPULATIONS

6.1 Pregnant Women

In HBV mono-infected pregnant women, the indications for treatment are the same as for other adults. All the pregnant women who do not meet the criteria for treatment indications should receive tenofovir disoproxil fumarate (TDF) 300 mg once a day from 28 week of pregnancy until 3 months after delivery.

Based on available safety data, TDF is the preferred antiviral in pregnant women, because it has a better resistance profile and more extensive safety data in HBV positive pregnant women. As the safety of TAF and ETV in pregnancy is not known, these drugs should not be used in pregnancy. Pregnant women already on the other antivirals should be switched to TDF. IFN-based therapy is contraindicated.

In HIV-infected pregnant and breastfeeding women (including pregnant women in the first trimester of pregnancy and women of childbearing age), a once-daily fixed-dose combination of tenofovir + lamivudine (or emtricitabine) + efavirenz is recommended as first-line ART.

6.2 Children

Although 70–90% of children who are exposed perinatally will become chronically infected, HBV-related morbidity is low during childhood as they are generally in the immune-tolerant phase and typically will maintain normal ALT through childhood until moving into the 'immune active' phase. Given the low curative rates of treatment and concerns of safety and drug resistance from long-term use, the initiation of antiviral therapy should be based on evidence of severe ongoing necroinflammation and significant fibrosis and cirrhosis.

While most children will not require antiviral therapy, early identification and monitoring of children to determine if therapy may be indicated in the future to prevent progressive liver disease is critical. TDF is approved for use in adolescents and children above the age of 12 years for HBV treatment, and ETV above 2 years of age.

For children initiated on treatment, the following is regimens and dosages are recommended:

Regimen	Dosage per Tablet	Frequency and Dosing
Tenofovir Disoproxil Fumarate (TDF)	300 mg	Once Daily *(in children 12 years of age and older, and weighing at least 35 kg)*
Entecavir (ETV)	0.5 mg	*In children 2 years of age or older and weighing at least 10 kg up to 30 kg.* Children with body weight more than 30 kg should receive 0.5 mg once daily. *Dosing dependent on body weight (see table below*)*

* Recommended once-daily dose of oral solution of Entecavir (ml)	
Body weight (kg)	**Treatment-naive persons**
10 to 11	3
>11 to 14	4
>14 to 17	5
>17 to 20	6
>20 to 23	7
>23 to 26	8
>26 to 30	9
>30	10

6.3 HBV/HCV Co-infected Persons

Persons with HBV/HCV co-infection are at a greater risk of progression to cirrhosis and HCC. In this population, treatment indications for HBV are the same as in mono-infected patients. HBV/HCV co-infected patients should be first assessed for whether they meet HBV treatment criteria and if they do, then should be started on HBV treatment prior to initiating HCV treatment.

If a decision is made not to start HBV treatment first, evidence of HBV flare should be closely monitored during or after HCV treatment. Cases of clinically significant HBV reactivation have been reported during HCV treatment, including severe cases involving liver decompensation, need for liver transplant, and even death. If the close monitoring is not feasible for HBV flare, concomitant NA treatment should be started until week 12 post HCV treatment.

6.4 HIV/HBV Co-infected Persons

Persons who are HIV/HBV co-infected are more adversely affected by their HBV infection as compared to the HBV mono-infected population. HIV/HBV co-infected patients face higher rates of conversation to chronicity after acute HBV infection, higher levels of HBV replication, a greater risk of progression to cirrhosis and HCC, and lower treatment response rates, leading to higher liver-related mortality. In HBV/HIV co-infected persons, ART that includes TDF should be initiated regardless of stage of liver disease.

6.5 Decompensated Cirrhosis

Patients with decompensated cirrhosis should be immediately treated with recommended NAs (TDF or ETV) irrespective of ALT and HBV DNA level. Then the patients need to be referred to specialist center preferably with liver transplant facility.

6.6 Dialysis and Renal Transplant Patients

Patients with end-stage renal disease (ESRD) should be screened for HBV infection. All HBsAg positive patients with ESRD should be referred to a specialist for liver disease severity assessment.

ETV is recommended for NA naïve patients with ESRD. TAF could be used in both NA naïve or experienced patient. Doses of ETV should be adjusted according to eGFR values. TAF does not need dose adjustment if the patient has eGFR > 15 ml/min. If eGFR is < 15 ml/min, TAF is not recommended.

Annex 1. HBV Markers[33]

Marker	Characteristics
HBsAg	• First serological marker of HBV infection to appear
	• Window period between HBV infection and detection of HBsAg estimated to be around 38 days, but depends on analytical sensitivity of assay • Occult HBV infection has been observed, i.e. HBsAg is undetectable but HBV DNA can be detected in individuals not in the window period • Quantification of HBsAg is a potential alternative marker of viremia and to monitor response to antiviral treatment
	• High levels present during acute infection but may remain detectable for up to 6 months • Used to differentiate between acute and chronic HBV infection, but its reappearance during "flares" in chronic HBV infection make it an unreliable indicator of recent primary HBV infection
Anti-HBc (total)	• Develop around 3 months after infection and most constant marker of infection • Together with anti-HBs, indicates resolved infection • Anti-HBc, with or without anti-HBs, also indicates individuals who may reactivate in the context of immunosuppression
HBeAg	• Present when the virus is actively replicating in the liver • Associated with high levels of HBV viremia and is therefore a marker of "high infectivity" • Associated with progressive liver disease

33 WHO. (2017, February). Guidelines on Hepatitis B and C Testing. p 22-23.

Marker	Characteristics
Anti-HBe	• Represents host response to HBeAg and usually indicates decreasing HBV DNA and therefor infectivity • Present in the immune-control and immune-escape phases • May coexist with HBeAg during the period of seroconversion from e antigen to e antibody at the end of immune-tolerance phase
Anti-HBs	• Neutralizing antibody that confers protection from infection • Present following spontaneous HBsAg clearance (with anti-HBc IgG) • Generated by immunization and used to monitor post-immunization responses (anti-HBc absent) • May coexist with HBsAg so presence cannot be used to exclude current infection
HBV DNA	• Use as a more direct and accurate measure of active HBV viral replication, which correlates with disease progression • Serum HBV DNA is measured in international unit (IU/ml) as the recognized international standard or copies/ml by nucleic acid testing (NAT) technologies • Used to also monitor response to therapy (a rise may indicate inadequate adherence or the emergence of resistant variants) and as a marker of infectivity • May be detectable in early infection before HBsAg, and therefore useful in early diagnosis of at-risk individuals before HBsAg appears, but depends on sensitivity of the assay • Also present at low levels in the absence of HBsAg in the context of occult infection

Annex 2. Main concepts and features of current treatment strategies of chronic hepatitis B[34]

	ETV, TDF, TAF
Route of Administration	Oral
Treatment Duration	Long-term until HBsAg loss (stopping NA after some years might be considered in selected cases)
Tolerability	High
Long-term safety concerns	Probably not (uncertainties regarding kidney function, bone diseases for some NA)
Contraindications	None (dose adjustment according to eGFR)
Strategy	Stopping hepatitis and disease progression by inhibiting viral replication
Level of viral suppression	Universally high
Effect on HBeAg loss	Low in the first year, increases to moderate during long-term treatment
Effect on HBsAg levels	Low: slowly increases with treatment time in HBeAg-positive patients; usually very low in HBeAg-negative patients
Risk of relapse after treatment cessation	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Stopping Rules	No
Risks of viral resistance	Minimal to None

34 WHO. (2017, February). Guidelines on Hepatitis B and C Testing. p 22-23.