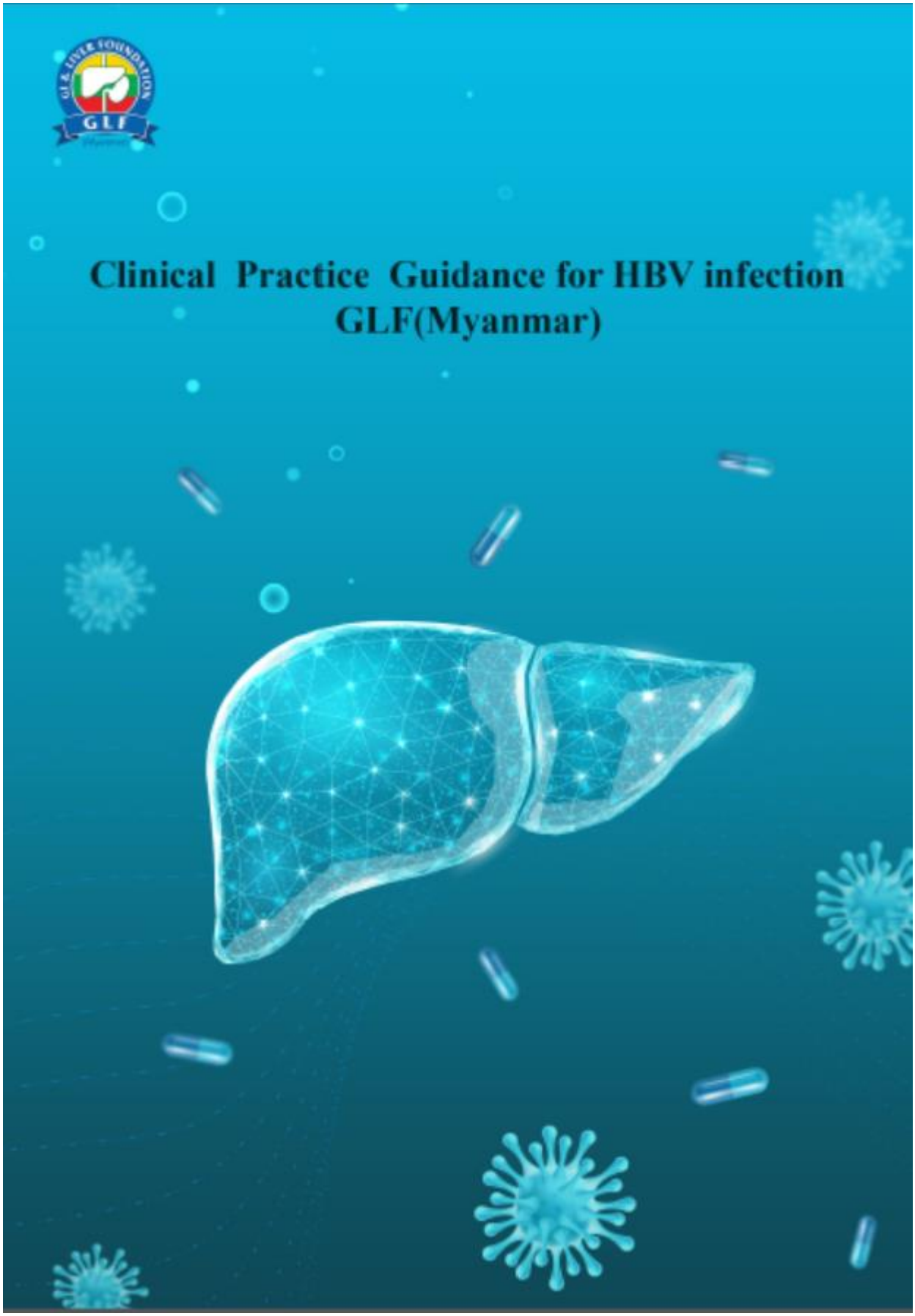
Clinical Practice Guidance for HBV infection
GLF(Myanmar)



Prevention, Diagnosis and Management of Chronic Hepatitis B Infection: 2024 Clinical Practice Guidance Recommendations by GI and Liver Foundation (Myanmar)

Preamble

GI and Liver Foundation (Myanmar) has produced clinical practice guidelines on Hepatitis B, Hepatitis C and Cirrhosis of the Liver to assist all the practicing doctors in the treatment of Liver Diseases.

However, AASLD has recently adopted a policy to differentiate between guidelines and guidance. AASLD published guidelines on some topics and guidance on some other diseases.

And therefore, it's time for GLF (Myanmar) to review the policy whether it should be clinical practice guidelines or guidance in future publications. For that purpose, GLF (Myanmar) decided to follow the AASLD policy.

According to the AASLD, practice guidelines use clinically relevant questions, which are then answered by systematic reviews of the literature and followed by data-supported recommendations. The guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system ("GRADE"). (AASLD Family of Websites:**AASLD.org**)

AASLD also publishes guidance on aspects of some topics. Practice guidances are based on a comprehensive review and analysis of relevant published data and put forward guidance statements to help clinicians understand and implement the most recent evidence. (AASLD Family of Websites:**AASLD.org**)

By AASLD policy mentioned above what GLF (Myanmar) has published are not practice guidelines but practice guidance. Therefore, future GLF (Myanmar) clinical practice publications will be labelled as "GLF (Myanmar) Clinical Practice Guidance".

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ABBREVIATIONS

AASLD	American association for the study of liver diseases
ADV	Adefovir Dipivoxil
AFP	Alpha fetoprotein
ALT	Alanine Transaminase
Anti-HBc	Antibodies to HBcAg
Anti-HBs	Antibodies to HBsAg
APASL	Asian Pacific Association for the Study of the Liver
AST	Aspartate transaminase
cccDNA	covalently closed circular DNA
CDC	Centers for Disease Control
CHB	Chronic Hepatitis B
CTP	Child-Turcotte-Pugh
DMR	Department of Medical Research
DNA	Deoxyribonucleic acid
DOPH	Department of Public Health
EASL	European Association for the Study of the Liver
EHLI	Evident histological liver injury
EPI	Expanded Program of Immunization
ETV	Entecavir
GAVI	Global Alliance for Vaccines Introduction
GGT	Gamma-glutamyl transpeptidase
GLF	GI and Liver Foundation
HBIG	Hepatitis B Immunoglobulin
HBcAb	Hepatitis B core Antibody
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCP	Health care personnel

HCV	Hepatitis C virus
HCWs	Health care workers
HIV	Human immunodeficiency virus
IBBS/PSE	Integrated Biological and Behavioral Surveillance Survey and Population Size Estimates
IFN	Interferon
IgM	Immunoglobulin M
INR	International normalized ratio
kPa	Kilopascal
LAM	Lamivudine
LdT	Telbivudine
LLV	Low-level viremia
LMICs	Low-income and middle-income countries
LSMs	Liver stiffness measurements
MRE	Magnetic resonance elastography
MSM	Men who have sex with men
MTCT	Mother to Child Transmission
NAs	Nucleos(t)ide Analogues
NHCP	National Hepatitis Control Program
Peg-IFN	Peg-interferon
RDT	Rapid Diagnostic Test
RT	Reverse Transcriptase
STDs	Sexually Transmitted Diseases
TAF	Tenofovir Alafenamide
TDF	Tenofovir Disoproxil Fumarate
TE	Transient elastography
TFV	Tenofovir
ULN	Upper limit of normal
USG	Ultrasound
WHO	World Health Organization

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Introduction

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus. HBV infection can be either acute or chronic and may range from asymptomatic infection or mild disease, to severe or rarely fulminant hepatitis. Acute hepatitis B is usually a self-limiting disease with a case fatality rate of 0.5–1%. Chronic hepatitis B (CHB) is defined by the presence of detectable HBsAg in the blood or serum for longer than six months and encompasses a spectrum of disease. Age of exposure is a key factor in determining the risk of chronic infection and chronicity is common following acquisition in childhood. [1] Once the infection becomes chronic, it is extremely refractory and is difficult to cure, despite recent developments of treatment measures.

HBV infection is an important global public health problem and cause of chronic liver disease that led to an estimated 820,000 deaths in 2019, mainly due to cirrhosis and liver cancer. In 2019, WHO estimated that at least two billion people, or one-third of the world's population, have been infected with HBV infection. Approximately 296 million people or about 6 % of the world's population were chronically infected and living with hepatitis B, with a disproportionately high burden in low- and middle-income countries according to WHO, 2024. Ultimately, around one third of the chronically infected HBV patients will eventually develop cirrhosis and hepatocellular carcinoma (HCC). In Myanmar, HBV is estimated to cause 60% of HCC cases. [2]

Overall, almost half of the global population lives in areas of high endemicity with a large regional variation of HBsAg positive patients between low (<2%) and high (>8%) endemicity levels [3,4], placing them at increased risk of developing cirrhosis, hepatic decompensation, and HCC. The WHO African region, together with the South-East Asia Region and Western Pacific Region account for 88% of the global burden. The prevalence is decreasing in several highly endemic countries due to improvements in the socioeconomic status, universal vaccination programs and perhaps effective antiviral treatments. [5] Myanmar is one of the countries for the high prevalence and transmission of HBV infection. 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%.

Due to its largely asymptomatic nature, viral hepatitis is a silent epidemic; most people are unaware of their infection. Since knowledge of the various risks and transmission routes is

central to preventing the spread of hepatitis, increasing awareness is another critical component of the global public health response.

Most of the global burden of Chronic Hepatitis B (CHB) can be attributed to mother-to-child transmission at the time of or shortly after birth, and such perinatal infections lead to a high rate of chronicity. Considerable progress has been made towards eliminating the perinatal transmission of HBV through universal infant HBV immunization, including the timely hepatitis B birth dose, which has been highly effective in reducing new infections among children. However, in 2022 hepatitis B birth-dose coverage was only 45% globally, with the lowest coverage (18%) in the WHO African Region according to WHO, 2024.

Myanmar has a national policy for Chronic Hepatitis B prevention with birth dose and pentavalent hepatitis B vaccination scheme. Pentavalent vaccination as a part of the Expanded Program of Immunization (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 have been covered in 2018. [6]

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, pregnancy, autoimmune disease and decompensated cirrhosis. Moreover, overall responses to PEGylated interferon for 48 weeks remain unsatisfactory. [7]

For people with chronic hepatitis B infection, nucleoside analogue treatment with currently recommended tenofovir and entecavir is low cost, ease of administration, once daily regimen, excellent adverse effects profile, highly efficacy and can delay the progression of cirrhosis, reduce the incidence of HCC and improve long-term survival. [7]

However, a major testing and treatment gap remains. In 2019, only 10% of the estimated 296 million people with CHB had been diagnosed and 2% had been treated. Scaling up testing and treatment towards the elimination goals will require a radical simplification of treatment criteria and care pathways to overcome barriers in access to Chronic Hepatitis B testing and treatment.

The global goal is to eliminate viral hepatitis as a public threat by 2030, with targets to reduce the incidence of chronic hepatitis infection from the current 6-10 million cases to 0.9 million and the annual deaths from chronic hepatitis from 1.4 million to less than 0.5 million by 2030. [8]

The 67th World Health Assembly in May 2014 approved a resolution to improve the prevention, diagnosis and treatment of viral hepatitis. In November 2014, Myanmar initiated the establishment of a National Hepatitis Control Program (NHCP) following the resolution set up by the WHO. [59]

At the 69th World Health Assembly, adopted the global health sector strategy on viral hepatitis (2016-2021) with a vision of a world in which viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable, and effective care and treatment. In April 2016, Regional Action Plan for Hepatitis in the South-East Asia Region was approved by Member States. Myanmar is taking a public health approach to the treatment and care of viral hepatitis, treating not only mono-infected patients but also those co-infected with HIV, in line with the WHO's strategic directions and the National Clinical Treatment Guidelines. Elimination can only be achieved through collaboration, coordination and cooperation among all stakeholders. [59]

GI and Liver Foundation (Myanmar) was actively participated in elimination of viral hepatitis since established, 2018. Nearly 50,000 of people were tested for HBV and HCV infection especially throughout the outreach area of Myanmar and all the people with HBsAg negative had been given the HBV vaccination.

The objective of the "Clinical Practice Guidance Recommendations by GI and Liver Foundation (Myanmar) 2024" is to provide updated evidence-informed recommendations on key priority topics. These include the use of non-invasive tests for staging of liver disease; considerations for availability and drug resistance over time; expanded and simplified treatment criteria for adults but now also for adolescents; "Testing", "Vaccination" and "Treat all" strategies for all adults (18 years); expanded eligibility for antiviral prophylaxis for pregnant women to prevent mother-to-child transmission of HBV infection.

1. Epidemiology of Chronic Hepatitis B in Myanmar

The prevalence of HBV infection is highly heterogeneous throughout the world; an estimated 296 million people are chronic carriers of HBsAg in worldwide. Age-specific HBsAg seroprevalence varies markedly by geographical region. Overall, almost half the global population lives in areas of high endemicity. with an intermediate to high prevalence in the Asia-Pacific region, representing three-quarters of chronic HBV-positive subjects worldwide. [9] In addition, the Western Pacific region (defined by the WHO as 37 countries including China, Japan, South Korea, Philippines, and Vietnam) accounts for nearly 50 % of all chronic HBV infection globally, although it has less than one-third of the world's population. [10] It is estimated that the South-East Asia Region has nearly 100 million people with chronic hepatitis B, and they account for more than 5.6% of the global population. More than 300 000 people are estimated to die each year in the Region as a result of the chronic consequences of hepatitis B, particularly cirrhosis and liver cancer. The data based on 2000-2010, a low prevalence of HBV infection less than 1% in two countries – Nepal and Sri Lanka; intermediate prevalence (2-6%) in seven countries – Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Thailand and Timor-Leste; and high prevalence (more than 10%) in two countries – Indonesia and Myanmar. [11]

In Myanmar, HBV prevalence in general population was 10-12%. [12] The prevalence of HBV infection in different regions or townships or different populations were found out by different research groups. [13] In the 2014 IBBS/PSE study (Integrated Biological and Behavioral Surveillance Survey and Population Size Estimates), among intravenous drug users in Myanmar, one of the sub-populations, HBV infection was 7.3%. The prevalence of HIV/HBV co-infection was found to be 2.2%, and HIV/HBV/HCV combined coinfection was 20.7%. [14]

The national prevalence survey for hepatitis B and C was conducted in Myanmar by the Department of Medical Research (DMR) and the Department of Public Health (DOPH) from May to November of 2015 in 18 study sites covering all States and Regions. Key preliminary results from the prevalence survey showed that the disease burden for hepatitis B in the general population was 6.51%. The HBV prevalence by urban rural populations was 6.1% (urban), 3.2% (rural) respectively. [15]

The highest HBV prevalence (7.4%) was found in 30-39 years of age group. Male had significantly higher prevalence than female gender (9:5.5) for HBV infection. The highest

occurrence of hepatitis B Surface Antigen (HBsAg) positivity was found in Yangon region (Hlinethaya Township) (12.3%), Pathein (9.15%), and Mawlamyine (7.84%) and the lowest was 3.3% in Magway Region. It may be due to urban population (population density) and floating population who are probably exposed to more risk factors of transmission, geography, economic level, lack of knowledge to risk factors of transmission. [15]

The risk factors associated with transmission of hepatitis B were male gender, history of liver disease or hepatitis and history of household contacts and no history of HBV vaccination. History of household contact, sharing razor and tooth brush were two times associated with HBV infection. [15]

2. Screening, Counseling and Prevention of Hepatitis B

2.1 Screening

The prevalence of HBsAg varies greatly across countries, with high prevalence of HBsAg-positive persons defined as ≥8%, intermediate as 2% to 7%, and low as <2%. [16,17] In developed countries, the prevalence is higher among those who immigrated from high- or intermediate-prevalence countries and in those with high-risk behaviors. [17,18] Myanmar is one of the countries for the high prevalence and transmission of HBV infection.

The impact of vaccination has been profound in reducing the global burden of HBV, particularly in children and young adults, but millions of chronic HBV-infected patients remain. In the interim, there is good established treatment for patients chronically infected with HBV that can reduce liver-related outcomes, although HBsAg clearance is still not a realistic goal.

The preventive measures, effective screening of those infections and early treatment are important to consider and perform to reduce transmission. Preventive measures include the screening and testing of blood, plasma, organ, and tissue donors, risk reduction counseling and services, implementation and maintenance of infection control practices, identification, counseling and testing of persons at risk, medical management of infected persons, health education, surveillance and research.

With the WHO resolution on viral hepatitis, the WHO has launched a number of initiatives, which include the Global Hepatitis Network and a Framework for Action, in order to tackle these issues. It is recognized that one of the major obstacles to action remains the large burden of undiagnosed cases of chronic HBV infection around the globe. Screening for hepatitis B infection is an important tool to discover new cases of chronic infection.

2.1.1 Risk factor for screening

HBV infection is regarded as a highly infectious disease as it is known to survive outside of the body for at least 7 days. [19] HBV is transmitted by perinatal, percutaneous, mucosal, sexual exposure and non-intact skin exposure to infected blood (presumably by open cuts and sores, especially among children in hyper-endemic areas) or body fluids (saliva, menstrual, vaginal and seminal). Amongst adults, HBV is primarily transmitted through percutaneous exposure to infected blood or unsafe sexual intercourse. Studies of needle-stick 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. In addition, immunosuppressed persons are more likely to develop chronic HBV infection after acute infection. [20]

In most countries where HBV is endemic, perinatal transmission remains the most important cause of chronic infection, mostly in children of HBV-infected mothers who do not receive appropriate HBV immunoprophylaxis at birth. The risk of developing chronic HBV infection after acute exposure ranges from 90% in newborns of HBeAg-positive mothers to 25%-30% in infants and children under 5 to less than 5% in adults. [21-25]

In countries with high endemicity, >90 % of new infections occurred among infants and young children as the result of perinatal or household transmission, while in countries of low endemicity (i.e., HBsAg prevalence of <2 %), the majority of new infections occur among adolescents and adults as a result of sexual and injection-drug use exposures. In countries of intermediate HBV endemicity, multiple modes of transmission operate, i.e., perinatal, household, sexual, injection-drug use, and health-care related. 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) is the most common mode of HBV transmission. [26]

There is a need for targeted screening for HBV infection in high-risk individuals because the infection remains asymptomatic in a vast majority of infected individuals, especially those who acquire infection at birth or during childhood. Screening of the general population may be cost effective in finding new cases in countries with high prevalence, but it is not in regions with low prevalence. In countries with intermediate prevalence, it would depend upon the socioeconomic status. However, it is worth doing screening of 'high-risk groups' irrespective of prevalence and socioeconomic status. WHO [27] and most other international guidelines [28-30] recommend that high-risk groups (Table 1**)** be screened for HBsAg and that those at risk and not immune should be offered hepatitis B vaccination. Population-based screening is also recommended for migrants from endemic countries. [31]

In Myanmar, if possible, everybody should be tested for hepatitis B infection. However, high-risk groups with respect to HBV (Table 1) have shown a higher prevalence than the general population. They should be prioritized for HBV testing and vaccinated if non-immune and HBsAg negative.

2.1.2 Screening tests

Screening tests are inexpensive and cost effective in populations at higher prevalence, as cost per case identified decreases, and they have the potential to reduce HBV-associated morbidity and mortality. Hepatitis B surface antigen (HBsAg) test is the primary way to definitively diagnose chronic HBV infection. WHO guidelines recommend using a single quality-assured serological in vitro diagnostic test {either a laboratory-based immunoassay; enzyme immunoassay or chemiluminescence immunoassay or rapid diagnostic test (RDT)} to detect HBsAg that meets minimum performance standards.

The total hepatitis B core antibody (HBcAb) test tells if a person has been previously exposed to HBV. Individuals with HIV infection or those about to undergo HCV or immunosuppressive therapy are at risk for potential reactivation if they have preexisting HBV and should be screened for anti-HBc. [32,33] Because of the risk for HBV transmission, screening for anti-HBc occurs routinely testing in organ donors. [32] The risk of infection after blood transfusion and transplantation of non-hepatic solid organs (kidneys, lungs, heart) from persons with isolated anti-HBc is low: 0–13 %. [34] The risk of infection after transplantation of liver from HBsAg-negative, anti-HBc-positive donors has been reported to be as high as 75 % and is related to the HBV immune status of the recipients. [35] If anti-HBc-positive donor organs are used for HBV seronegative recipients, antiviral therapy should be administered to prevent

de novo HBV infection. While the optimal duration of prophylactic therapy has not been determined, a limited duration, such as 6–12 months, may be sufficient for transplantation of non-hepatic solid organs. For transplantation of livers, lifelong antiviral therapy is recommended, but whether Hepatitis B Immunoglobulin (HBIG) is necessary is unclear. [36]

A large number of studies of epidemiology of chronic HBV infection only examine those who are detected to be HBsAg seropositive, but little is known of screening uptake (% of patients who agree to take the test), and of these, how many were referred and evaluated as requiring therapy. Consequently, screening to detect seropositive patients is insufficient as a management strategy, without proper linkage to care. Other recommended interventions to promote the uptake of hepatitis testing and linkage to care include peer and lay health worker support in community-based settings, clinician reminders in facilities and testing as part of integrated services within drug treatment and community-based harm-reduction services.

The Institute of Medicine recommendations [37], they found that US and many other countries infrastructure for management of chronic viral hepatitis was poor, and broadly recommended three important initiatives: increased disease surveillance, improved provider and community education, and integration and enhancement of viral hepatitis services. In particular, the viral hepatitis services should encompass five core elements in a coordinated and comprehensive manner - outreach and awareness**;** prevention of new infections**;** identification of infected people**;** social and peer support**;** and medical management of infected people, as otherwise newly diagnosed patients will be lost and will not receive the benefit of potential therapy that may be lifesaving.

Consequently, the logistic chain of screening begins with information and education, followed by agreement to undergo testing, testing itself, and then evaluation; it ends with treatment in those who need it. Moreover, many stakeholders need to come together and coordinate efforts and resources in order for this strategy to be effective. However, screening itself is a major exercise. National programs are required to plan screening and treatment strategies. Building on country-specific information on policies and structures will be necessary to increase the availability of treatment for those infected.

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Table 1. Groups at high risk for HBV infection who should be screened [38-40]

No.	Groups at high risk for HBV infection
1	All persons born in Myanmar as routine checkup testing (because of Myanmar is being in region of high prevalence of HBV infection)
2	Persons with chronic liver disease
3	Individuals with elevated ALT or AST of unknown etiology
4	HCV- or HIV-infected individuals
5	Family members, household contacts, sex partners of a person infected with chronic hepatitis B
6	Infants born to HBsAg-positive mothers
7	Persons needing immunosuppressive or cancer chemotherapy
8	Injection drug users with needle-sharing
9	Persons who receive unsafe injections (used syringes or needles) or persons who are the source of blood or body fluid exposures that might require post-exposure prophylaxis
10	Health care and public safety workers at risk for occupational exposure to blood or blood-contaminated body fluids
11	Men who have sex with men (MSM), persons with multiple sexual partners, history of sexually transmitted diseases (STDs)
12	Routine screening to all pregnant women
13	Dialysis patients
14	Donors of blood, plasma, organs tissues, or semen
15	Inmates of correctional facilities
16	Travelers to and families adopting from countries where hepatitis B is common (e.g. Asia, Africa, South America, Pacific Islands, Eastern Europe, and the Middle East)

Recommendations (Screening)

1. **Screening is recommended in all persons especially in high risk groups by using HBsAg testing.**
2. **Screening for anti-HBc to determine prior exposure is not routinely recommended but is an important test in patients who are about to undergo chemotherapies or other immunosuppressive therapies and in donated organ for liver transplantation.**
3. **Screening should be linked to appropriate counseling and referral for further care including clinical evaluation, need for treatment and vaccination if found to be negative for HBV infection.**

2.2 Counseling of Persons who are HBsAg Positive

Patients with chronic HBV infection should be counseled regarding lifestyle modifications and prevention of transmission as well as the importance of lifelong monitoring. No specific dietary measures have been shown to have any effect on the progression of CHB per se, but metabolic syndrome and fatty liver contribute to liver-related morbidity. [41,42] Ingestion of > 7 drinks of alcohol per week for women and > 14 drinks per week for men are associated with increased risk of cirrhosis and HCC. [43,44] Studies evaluating the risk of lesser amounts of alcohol intake are sparse [45] but the conservative approach is to recommend abstinence or minimal alcohol ingestion. [46,47] Individuals with CHB should be immunized against hepatitis A if not already immune. [48]

HBsAg-positive persons should be counseled regarding transmission to others (Table 2). Because of increased risk of acquiring HBV infection, household members and sexual partners should be vaccinated if they test negative for HBV serological markers. For casual sex partners or steady partners who have not been tested or have not completed the full immunization series, barrier protection methods should be utilized. Transmission of HBV from infected health care workers (HCWs) to patients has been shown to occur in rare instances. [49] For persons with CHB who are HCWs, the Centers for Disease Control and Prevention recommends that those who perform exposure prone procedures should seek counseling and advice from an expert review panel. [50] If serum HBV DNA exceeds 1,000 IU/mL, antiviral therapy is recommended, and performance of exposure-prone procedures is permitted if serum HBV DNA is suppressed to <1,000 IU/mL and maintained below that cutoff. [50]

Unless prone to biting, no special arrangements need to be made for HBV-infected children in the community other than practicing universal precautions in daycare centers, schools, sports clubs, and camps. [38]

Table 2. Recommendations for Infected Persons Regarding Prevention of Transmission of HBV to Others

No.	Persons Who Are HBsAg Positive Should:
1	Have household and sexual contacts vaccinated
2	Use barrier protection during sexual intercourse if partner is not vaccinated or is not naturally immune
3	Not share toothbrushes or razors
4	Not share injection equipment, glucose testing equipment
5	Cover open cuts and scratches
6	Clean blood spills with bleach solution
7	Not donate blood, organs, or sperm
8	Can participate in all activities, including contact sports
9	Children should not be excluded from daycare or school participation and should not be isolated from other children
10	Can share food and utensils and kiss others

Recommendations (Counseling of Persons who are HBsAg Positive)

4. **HBsAg-positive persons should be counseled regarding prevention of transmission of HBV to others according to Table 2.**
5. **Abstinence of alcohol is recommended in chronic HBV-infected persons.**
6. **Optimization of body weight and treatment of metabolic complications, including control of diabetes and dyslipidemia, are recommended to prevent concurrent development of metabolic syndrome and fatty liver.**
7. **Health care workers and students who are HBsAg positive should not be excluded from training or practice but they should not perform exposure-prone procedures if their serum HBV-DNA level exceeds 1,000 IU/ml. They can perform exposure-prone procedures if their HBV DNA level is reduced or maintained below 1,000 IU/ml and on NA therapy.**
8. **Chronic HBV-infected subjects should not be discriminated and stigmatized in the society or in their work place.**
9. **HBV-infected children should not be isolated in the educational and social environment.**
10. **Sexual and household contacts of chronic HBV-infected persons who are negative for HBV seromarkers should receive hepatitis B vaccination.**

2.2.1 Counseling of HBsAg- positive women in pregnancy

All pregnant women should be screened for HBsAg. Pregnant women with HBsAg positive should be encouraged to discuss with Hepatologist and obstetrician and/or pediatrician for the prevention of mother-to-child transmission. Chronic HBV infection does not usually affect the outcome of pregnancy unless the mother has cirrhosis or advanced liver disease. However, extra care is necessary to evaluate the mother and to ensure that the infant receives hepatitis B immune globulin (HBIG) and hepatitis B vaccine (HBV vaccine) within 12 hours of birth. [38,51] HBIG and concurrent hepatitis B vaccine have been shown to be 95 % efficacious in the prevention of perinatal transmission of HBV; the efficacy is lower for mothers with very high serum HBV DNA levels (>7–8 log10 IU/ml). [52,53] However, in very resource-limited settings, universal vaccination alone is optimal. [54] Infants of HBsAg-positive mothers should undergo post vaccination testing at 9-15 months of age.

Antiviral therapy in the third trimester is recommended for pregnant women with serum HBV DNA >200,000 IU/mL. [55,56] AASLD recommended that Tenofovir Disoproxil Fumarate (TDF) is the preferred choice owing to its antiviral potency and concerns for resistance with the other antiviral agents.

The risk of mother-to-child transmission must be considered when assessing the potential benefit of amniocentesis in highly viremic women. Although antiviral drug labels do not recommend breastfeeding when taking these drugs, clinical studies support the safety of TDF drugs during breastfeeding. [57,58] Sexual partners of women identified as HBV infected during pregnancy should be assessed for HBV infection or immunity and receive HBV vaccine if appropriate.

Recommendations (Counseling of HBsAg- positive women in pregnancy)

11. **Women identified as HBsAg positive during pregnancy should be linked to care for additional testing (ALT, HBeAg, HBV DNA, USG) and determination of need for antiviral therapy.**
12. **Women who meet standard indications for HBV therapy should be treated. Women who meet prophylaxis indications to prevent mother-to-child transmission should be treated in the second trimester.**
13. **HBV-infected pregnant women with cirrhosis should be managed in high-risk obstetrical practices and treated with Tenofovir Disoproxil Fumarate (TDF) to prevent decompensation.**
14. **Tenofovir Disoproxil Fumarate (TDF) is safe in pregnancy.**
15. **Breastfeeding is not prohibited while the mother is on anti-viral therapy or infants who receive active/passive immunization.**
16. **Newborns of HBV-infected mothers should receive HBIG and HBV vaccine within 12 hours of delivery and complete the recommended vaccination series according to EPI (Expanded Program on Immunization) Program. Infants of HBsAg-positive mothers should undergo post vaccination testing at 9-15 months of age.**
17. **Sexual partners of women identified as HBV infected during pregnancy should be assessed for HBV infection or immunity and receive HBV vaccine if appropriate.**

2.3 Prevention for Chronic Hepatitis B

2.3.1 Prevention through avoiding to risk of HBV transmission

Hepatitis B virus (HBV) can cause acute, fulminant, or chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC). Despite the progress of antiviral therapy against HBV to suppress viral replication and to reduce complications in those with chronic hepatitis B, a cure for infection is still not possible. So, prevention is more effective than therapy for HBV infection. To prevent HBV infection effectively, it is crucial to understand its route of transmission. HBV infection is transmitted through either a horizontal route or through a mother-to-infant route, and the latter is the major route in endemic areas.

The hepatitis B virus is transmitted through blood and sexual fluids. This can most commonly occur in the following ways (Table 3):

Table 3. Routes of transmission for HBV infection

No.	Routes of transmission for HBV infection
1	Direct contact with infected blood and blood products
2	From an infected pregnant person to their newborn during pregnancy and childbirth
3	Needles and other medical/dental equipments or procedures that are contaminated or not sterile
4	Unprotected sex
5	Use of illegal or "street" drugs
6	Body piercing, tattooing, acupuncture and even nail salons
7	Sharing sharp instruments such as razors, toothbrushes, nail clippers, earrings and body jewelry

WHO and most other international guidelines recommend that high-risk groups should be screened for HBsAg and that those at risk and not immune should be offered hepatitis B vaccination. Other prevention strategies, such as screening the blood products, proper sterilization of injection needles and syringes, and avoidance of risky behaviors, such as parenteral drug abuse, tattoo, or skin piercing, may preclude HBV horizontal transmission. Education to avoid high-risk behaviors should be advocated in addition to vaccination.

Myanmar is one of the countries for the high prevalence and transmission of HBV infection. So, people who live in Myanmar should be tested for HBV infection and people who do not have HBV infection should be vaccinated against for HBV infection. The most important thing also is people who live in Myanmar must be known the risk of transmission for HBV infection and should be avoided HBV transmission routes (Table 3).

2.3.2 Prevention through HBV vaccination

The global public health response to viral hepatitis recognizes that surveillance and control are vital to ensuring that testing, care, and treatment are available to all people who need these services in every country around the world. As there is an effective vaccine for hepatitis B, immunization has been a central strategy for most countries to reduce the burden of hepatitis B. [59] HBV immunization can be classified into passive and active immunization. Passive immunization using hepatitis B immunoglobulin (HBIG) provides temporary immunity, whereas active immunization by the vaccine yields long-term immunity.

Prevention of HBV infection by immunization is the best way to eliminate HBV-related diseases. The HBV vaccine is the first human vaccine using a viral antigen from infected persons, which is safe and either passive immunization by hepatitis B immunoglobulin (HBIG) or active immunization by HBV vaccine is effective, and a combination of both yields the best efficacy in preventing HBV infection.

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. The impact of universal HBV immunization is huge, with 90% - 95% effectiveness in preventing chronic HBV infection. It is the first cancer preventive vaccine with a protective efficacy against HCC of ~ 70%. Nevertheless, further effort is still needed to avoid vaccine failure and to increase the global coverage rate.

The global hepatitis B vaccine coverage rate was estimated at 75%, and was as high as 91% in the Western Pacific and 89% in the Americas. Coverage in Southeast Asia reached 52% in 2010. In 2011, 180 countries had introduced infant HBV vaccination, and the global HBV vaccination coverage rate for the third dose was estimated to be ~ 78%.

2.3.2.1 Vaccination for Infants

Universal HBV vaccination in infancy is more effective than selective immunization for high-risk groups. Considerable progress has been made towards eliminating the perinatal transmission of HBV through universal infant HBV immunization, including the timely hepatitis B birth dose, which has been highly effective in reducing new infections among children. Since 2009, WHO has recommended that all infants receive 3–4 doses of HBV vaccine, with the first dose administered as soon as possible after birth, preferably within 24 hours, and followed by subsequent doses of HBV vaccine according to Expanded Program of Immunization policies. That means, the birth dose should be followed by two or three doses to complete the primary series to induce protective antibody concentrations in more than 95% of infants. The last vaccine dose should not be given before 24 weeks of age. [60] Only monovalent HBV vaccine should be used for preterm or term infants younger than 6 weeks.

In Myanmar, Expanded Program of Immunization (EPI) schedule is recommended that the single dose monovalent vaccination should be within 12 hours of birth for first dose of HBV vaccination followed by second dose in 4 weeks, third dose in 8 weeks, fourth dose in 24 weeks and booster dose in one and half year of age. The dosage for newborn is 10 μg regardless of the birth weight.

Universal HBV immunization programs still have not been established all over the world, mainly because of limited resources. However, in 2022 hepatitis B birth-dose coverage was only 45% globally, with the lowest coverage (18%) in the WHO African Region. Although hepatitis B vaccine administered at birth or early childhood has been effective in reducing the incidence and prevalence of hepatitis B in most endemic regions [61], it will not affect the rates of end-stage liver disease or HCC for 20–40 years after the introduction of universal infant immunization. [62] Further increase of the global coverage rates of infant HBV vaccination is an important issue toward a better control of hepatitis B and HCC.

In Myanmar, the Ministry of Health introduced the hepatitis B vaccine combined with routine Expanded Program of Immunization (EPI) for all infants in 2003 with assistance from Global Alliance for Vaccines Introduction (GAVI). The coverage of hepatitis B vaccination in the EPI was gradually increased 62% to 90% from 2005 to 2010 in all states and divisions in Myanmar. Recombinant hepatitis B vaccine plant at Department of Medical Research (DMR) has the capacity to produce 5 million doses annually for infants and approval from Myanmar FDA was obtained in 2007. [63] Extended program of hepatitis B vaccination at birth and other successful hepatitis B vaccination strategies will provide to dramatic reduction of hepatitis B transmission and maintain the control of chronic liver diseases related to hepatitis B viral infection in Myanmar. [64]

2.3.2.2 Prevention of mother to child transmission of HBV infection through vaccination

Most of the global burden of chronic hepatitis B (CHB) can be attributed to mother-to-child transmission at the time of or shortly after birth, and such perinatal infections lead to a high rate of chronicity. Because in endemic areas, the major infection route comes from maternal transmission, and the outcome of perinatal transmission results in a very high rate (90%) of chronic infection.

All pregnant women should be tested for HBsAg during a prenatal visit in the first trimester of their pregnancy and all HBsAg negative pregnant women should be vaccinated. Vaccination against HBV is both safe and efficacious during pregnancy. [65] In addition, titers of the passively transferred maternal antibody to newborns wane over time, as would be expected without the addition of active vaccination. [66] An accelerated vaccination schedule has been shown to be feasible and efficacious in high-risk pregnant women. [67]

WHO position papers on immunization recommend that all infants born to women whose HBsAg status is positive should receive their first dose of hepatitis B vaccine as soon as

possible after birth, preferably within 12 hours and that HBIG, which contains high levels of purified HBsAg-specific antibodies from plasma donors, is given simultaneously at different sites intramuscularly. The birth vaccine dose should be followed by 3 or 4 doses of hepatitis B vaccine to complete the primary series in order to achieve maximum efficacy (according to EPI policies). The dose of HBIG is 0.5mL (100 IU) and the dosage of HBV vaccine for newborn is 10 µg regardless of the birth weight.

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 [68], 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. [69] Preventing MTCT from highly viraemic mothers (HBV DNA >200,000 IU/ml) requires not only birth-dose vaccination but also pre-emptive antiviral therapy for the mother.

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 and should be received routine birth dose HBV vaccine within 12 hours of birth followed by Expanded Program of Immunization policies in Myanmar.

2.3.2.3 Catch-up and Adult Vaccinations

In addition to infants, every person may be at some risk for a hepatitis B infection during their lifetime. So, other populations with a high risk of transmission (Table 1) should be targeted for catch-up vaccination as well as other preventive strategies.

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 6, (Table 4). 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.

The World Health Organization (WHO) recommends the hepatitis B vaccine for all newborns, children up to 18 years of age, and all adults at higher risk for infection. The U.S. Centers for Disease Control and Prevention (CDC) recommends the hepatitis B vaccine for all newborns, children up to age 18, adults 19-59 years of age, and adults 60 and older who are at high-risk for infection. [50,70] HBV monovalent vaccines should be given as a 3-dose series at 0, 1, and 6 months. An alternate 4-dose schedule given at 0, 1, and 2 followed by a dose at 12 months can be used. [71] All doses of the vaccine are required in order to be fully protected against hepatitis B.

Table 4. 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 (monovalent)	Week 8 (Pentavalent)	Week 16 (Pentavalent)	Week 24 (Pentavalent)
	Child/Adult	Month 0	Month 1	Month 2	Month 12
	People who inject drugs	Day 1	Day 7	Day 21	
	People living with HIV	Month 0	Month 1	Month 2	Month 12
	Hemodialysis Patients	Month 0	Month 1	Month 2	

The causes of breakthrough HBV infection in the vaccinated subjects include high maternal viral load, intrauterine infection, surface-gene mutants, genetic hypor-esponsiveness to the vaccine, and immune compromised hosts. In the era of post-HBV vaccination, even after complete immunization, vaccine failure still occurs. The leading cause of vaccine failure is the mother-to-infant transmission of HBV from highly infectious mothers. In children born to HBeAg-seropositive HBsAg carrier mothers, despite HBIG and three doses of the HBV vaccine, 9.26% still became HBsAg positive.

2.3.3 Post Exposure Prophylaxis for HBV infection

Health care personnel (HCP) are at risk of acquiring hepatitis B virus through exposure to infected blood and body fluids. Hepatitis B is a highly infectious blood-borne pathogen and

it can remain viable on environmental surfaces for at least 7 days and can be transmitted even in the absence of visible blood. [72]

The risk of occupational HBV transmission varies significantly based on the type of body fluid involved in the exposure. Higher HBV titers are found in blood than other body fluids and thus blood exposure carries the highest risk for HBV transmission. In addition to blood, cerebrospinal fluid, synovial fluid, pleural fluid, peritoneal fluid, pericardial fluid, and amniotic fluid are considered potentially infectious. [73]

If no post-exposure prophylaxis is administered for needle-stick occupational exposure to a nonimmune person is substantially higher than the risk of seroconversion to HCV or HIV (Table. 5). [73]

Table 5. Estimated risk of seroconversion with percutaneous injury with blood borne viruses

Virus	Risk of seroconversion
HIV	0.3%
Hepatitis C	2%
HBeAg negative HBsAg positive	23%–37%
HBeAg positive HBs Ag positive	37%–62%

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

- Wounds and skin sites should be washed with soap and water and mucous membranes (e.g., mouth, eyes) should be flushed or rinsed with water. If the exposure involves one or more eyes, the eye should be irrigated with clean water, saline, or sterile irrigating solution.
- For percutaneous injuries, do not squeeze the injury site and do not scrape or scrub the wound. Do not apply antiseptic solutions or caustic agents, such as bleach, to percutaneous or mucous membranes involved in the exposure
- 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

Post exposure management of health care personal after percutaneous or mucosal exposure to blood or body fluids depend on their vaccination status and HBsAg status of the

source of the person (Table 5). Source should be screened for HBsAg, HIV, and HCV antibodies. If source is not infected, baseline evaluation and testing is not required. If HBV positive source, exposed person should be tested for baseline HBsAg status and their vaccination status (HBsAb level).

If source is positive and the exposed person of HBV vaccination status is unknown or unimmunized, the first dose of the HBV vaccine with complete vaccination must be given and HBIG (derived from human serum containing high levels of anti-HBs with the protective effect lasting approximately 3 to 6 months) with the dose of 0.06 ml/kg or 500 IU should be administered simultaneously at separate injection site (e.g., HBIG given in buttock muscle and vaccine given in deltoid muscle) as a combination approach for HBV post-exposure prophylaxis. [75]

Immunoprophylaxis should be administered within 24 hours of exposure. Studies are limited on the maximum interval after exposure during which post-exposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures and 14 days for sexual exposures. Typically, HBIG is well tolerated and considered safe, even when used for pregnant or breastfeeding women. [73,75] Serious adverse reactions to HBIG are rare, and there is no evidence that HBIG has ever transmitted HBV or other blood-borne pathogens such as HIV and HCV.

Table 6. Post exposure management of health care personnel after occupational percutaneous or mucosal exposure to blood or body fluids [74]

Health Care Personal status	HCP testing (Anti-HBsAb)	HBIG	Vaccination
Documented responder after vaccine series		No action needed	
Documented non responder after 2 complete series		HBIG x 2, separated by 1 month	
Response unknown after complete series	<10 mIU/mL	HBIG x 1	Initiate revaccination
	≥10 mIU/mL	No action needed	
Unvaccinated/incompletely vaccinated		HBIG x 1	Initiate revaccination

2.3.4 Follow up HBsAb testing and Booster doses

Anti-HBs titers gradually decline with age in children immunized in infancy with hepatitis B vaccine, which is also seen in those who received a booster dose during childhood. Follow-up testing is recommended for those who remain at risk of infection, such as health care workers (HCWs), infants of HBsAg-positive mothers, sexual partners of persons with CHB, chronic hemodialysis patients, and immunocompromised persons, including those with HIV. They should be tested for their response to the vaccination 1-2 months after the last dose of vaccine. Furthermore, annual testing of hemodialysis patients is recommended given that immunity wanes rapidly in these individuals who are at a high risk of continued exposure to HBV.

For those who had received vaccinations in infancy, routine booster vaccination may not be required to protect against chronic HBV infection at least before 25 year of age. Booster doses are not also indicated in immunocompetent individuals if the primary vaccination series is completed, as long-term follow-up studies indicated that immune memory persists despite declining anti-HBs levels. [76] For individuals undergoing post vaccination serological testing, especially immunocompromised patients (such as persons on dialysis or with chronic inflammatory conditions, including HIV), a booster injection is advised when the anti-HBs titer falls below 10 mIU/mL.

The WHO also suggested that routine universal boosters are not recommended for children or adolescents. Nevertheless, it should be considered for those at high risk of HBV infection with anti-HBs < 10 mIU/mL after primary HBV vaccination. For those who are non-responders to the initial vaccination series, a second series of 0, 1, and 6-month vaccination is recommended. [77] For those who are immunocompromised, including those with HIV, on dialysis, or with cirrhosis, use of a double dose of vaccine has been shown to increase the percentage of patients achieving protective antibody titers, the level of anti-HBs achieved, and/or the duration of protection. [78-80]

Recommendations (Prevention)

18. **Prevention of HBV infection by immunization is the best way to eliminate HBV-related diseases.**
19. **All unvaccinated persons especially in high risk of transmission (Table 1) should be targeted for catch-up vaccination as well as other preventive strategies.**
20. **All HBsAg–negative screened persons including adults 60 and older who are at high-risk for infection should be vaccinated.**
21. **All pregnant women should be tested for HBsAg during a prenatal visit in the first trimester of their pregnancy and all HBsAg negative pregnant women should be vaccinated.**
22. **Vaccination against HBV is both safe and efficacious during pregnancy.**
23. **HBV monovalent vaccines should be given as a 3-dose series at 0, 1, and 6 months or an alternate 4-dose schedule at 0, 1, 2 and 12 months and as require as Table (4). All doses of the vaccine are required in order to be fully protected against hepatitis B.**
24. **Birth dose HBV monovalent vaccine within 24 hours is recommended for all infants followed by subsequent 3–4 doses of HBV pentavalent vaccine according to Expanded Program of Immunization policies in Myanmar.**
25. **The 10 ug dose (0.5 ml) is recommended for use in infants (regardless of the birth weight) and children up to 18 years of age.**
26. **The 20 ug dose (1 ml) is recommended for use in more than 18 years of age and should be increased to 40 mcg for people living with HIV or hemodialysis or immunocompromised patients including those with cirrhosis of liver.**
27. **All infants of HBsAg positive mothers is recommended to receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 12 hours and Hepatitis B immune globulin (HBIG) should be given simultaneously at different sites intramuscularly if available. The dose of HBIG is 0.5mL (100 IU) and the dosage of HBV vaccine for newborn is 10 µg regardless of the birth weight.**

Recommendations (Prevention)

28. **The birth dose vaccine must be followed by 3 or 4 doses of hepatitis B vaccine to complete the primary series in order to achieve maximum efficacy (according to Expanded Program of Immunization policies) for prevention of mother to child transmission (MTCT).**
29. **HBsAb (quantitative) is not routinely recommended to test after HBV vaccination. But health care workers, sexual partners of persons with chronic HBV infection, chronic hemodialysis patients, and immunocompromised persons (including those with HIV) should be tested for their response to the vaccination 1-2 months after the last dose of vaccine.**
30. **Furthermore, annual testing of chronic hemodialysis patients in vaccine responders is recommended given that immunity wanes rapidly in these individuals who are at a high risk of continued exposure to HBV.**
31. **For non-responders to the initial vaccine series, a repeat 3-dose vaccination series at 0, 1, and 6 months is recommended.**
32. **Booster doses or revaccination are not recommended in immunocompetent individuals if the primary vaccination series is completed except if anti-HBs remains <10 mIU/mL after initial vaccination of infants born to HBsAg-positive mothers, in health care workers, hemodialysis patients and other individuals who are immunocompromised.**
33. **HBV vaccination with or without HBIG (0.06 ml/kg or 500 IU) within 24 hours of exposure is recommended for post-exposure immunoprophylaxis of unimmunized individuals who have percutaneous, mucosal, or sexual exposure to HBsAg-positive sources.**

3. Definitions and Phases of Chronic Hepatitis B Infection

The diagnostic criteria for Chronic Hepatitis B Infection (CHB) and clinical terms relating to HBV infection are summarized in (Table 7). [81] The presence of HBsAg for at least 6 months establishes the chronicity of 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. Occult HBV chronic infection is characterized by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). Patients in this phase have normal ALT values and usually, but not always, undetectable serum HBV DNA. HBV DNA (cccDNA) can be detected frequently in the liver. [81]

The phases of chronic HBV infection are not necessarily sequential and includes the following phases.

Table 7. Phases of Chronic Hepatitis B 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

3.1. HBeAg-positive Chronic HBV Infection

Immune tolerant phase is characterized by the presence of serum HBeAg, very high levels of HBV DNA and ALT persistently within the normal range according to traditional cut-off values [upper limit of normal (ULN) approximately 40 IU/L]. [81] In the liver, there is minimal or no liver necro-inflammation or fibrosis but a high level of HBV DNA integration and clonal hepatocyte expansion suggesting that hepatocarcinogenesis could be already

underway in this early phase of the infection. [81,82] This phase is more frequent and prolonged in subjects infected perinatally and associated with preserved HBV specific T cell function at least until young adulthood. [83] The rate of spontaneous HBeAg loss is very low in this phase. These patients are highly contagious due to the high levels of HBV DNA.

3.2. HBeAg-positive Chronic Hepatitis B

It is characterized by the presence of serum HBeAg, high levels of HBV DNA and elevated ALT. In the liver, there is moderate or severe liver necro-inflammation and accelerated progression of fibrosis. [81] It may occur after several years of the first phase and is more frequently and/or rapidly reached in subjects infected during adulthood. The outcome of this phase is variable. Most patients can achieve HBeAg seroconversion and HBV DNA suppression and enter the HBeAg-negative infection phase. Other patients may fail to control HBV and progress to the HBeAg-negative CHB phase for many years.

3.3. HBeAg-negative Chronic HBV infection

Inactive carrier phase is characterized by the presence of serum antibodies to HBeAg (anti-HBe), undetectable or low (<2,000 IU/ml) HBV DNA levels and normal ALT. Some patients in this phase, however, may have HBV DNA levels >2,000 IU/ml (usually <20,000 IU/ml) accompanied by persistently normal ALT and only minimal hepatic necro-inflammatory activity and low fibrosis. These patients have low risk of progression to cirrhosis or HCC if they remain in this phase, but progression to CHB, usually in HBeAg-negative patients, may occur. [81] HBsAg loss and/or seroconversion may occur spontaneously in 1–3% of cases per year. [81] Typically, such patients may have low levels of serum HBsAg (<1,000 IU/ml). [84]

3.4. HBeAg-negative Chronic Hepatitis B

It is characterized by the lack of serum HBeAg usually with detectable anti-HBe, and persistent or fluctuating moderate to high levels of serum HBV DNA (often lower than in HBeAg-positive patients), as well as fluctuating or persistently elevated ALT values. The liver histology shows necro-inflammation and fibrosis. Most of these subjects harbor HBV variants in the precore and/or the basal core promoter regions that impair or abolish HBeAg expression. This phase is associated with low rates of spontaneous disease remission. [81]

3.5. HBsAg-negative phase

Occult HBV infection is characterized by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). This phase is also known as ‘‘occult HBV infection”. In rare cases, the absence of HBsAg could be related to the sensitivity of the assay used for detection. [85] Patients in this phase have normal ALT values and usually, but not always, undetectable serum HBV DNA. HBV DNA (cccDNA) can be detected frequently in the liver. [81] HBsAg loss before the onset of cirrhosis is associated with a minimal risk of cirrhosis, decompensation and HCC, and an improvement on survival. However, if cirrhosis has developed before HBsAg loss, patients remain at risk of HCC therefore HCC surveillance should continue. Immunosuppression may lead to HBV reactivation in these patients. [81]

4. Selected Diagnostic Tests Used in Management of Chronic Hepatitis B

The initial evaluation of a subject with chronic HBV infection should include a complete history, a physical examination, assessment of liver disease activity and severity and markers of HBV infection. The assessment of the severity of liver disease is important to identify patients for treatment and HCC surveillance. It is based on a physical examination and biochemical parameters (aspartate aminotransferase [AST] and ALT, gamma-glutamyl transpeptidase [GGT], alkaline phosphatase, bilirubin, and serum albumin and gamma globulins, full blood count and prothrombin time, Alphafetoprotein (AFP). An abdominal hepatic ultrasound is recommended in all patients. A liver biopsy or a non-invasive test should be performed to determine disease activity in cases where biochemical and HBV markers reveal inconclusive results. [86]

Non-invasive methods, which include liver stiffness measurements and serum bio-markers of liver fibrosis, the use of transient elastography has been mostly studied and seems to offer a higher diagnostic accuracy for the detection of cirrhosis. The diagnostic accuracy of all non-invasive methods is better at excluding than confirming advanced fibrosis or cirrhosis. [86,87]

4.1 HBV serological markers

HBV serological markers include HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc, and anti-HBc immunoglobulin M (IgM). Serological markers of hepatitis B infection and their interpretation are illustrated in (Table 8).

Table 8. 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
-	+	+	+ /-	+ / -	Acute resolving infection
-	+	-	+	-	Recovered from past infection and immune
+	+	-	-	+	Chronic infection
-	+	-	-	+ / -	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 ≥10mlU/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.

4.2 HBV-DNA quantitation

Quantification of serum HBV DNA is a crucial component in the evaluation of patients with CHB and in the assessment of the efficacy of antiviral treatment. Most HBV-DNA assays used in clinical practice utilize real-time polymerase chain reaction technology with a sensitivity of 5-10 IU/mL and a dynamic range up to 7 log10 IU/mL. [88]

4.3 HBV genotypes

Ten genotypes of HBV have been identified labeled A through J. [89,90] The HBV genotypes have distinct geographic distribution: genotype A has a universal distribution, being the predominant genotype in Europe, North and Central America, sub-Saharan Africa, and India. Genotypes B and C are predominant in Southeast Asia, China, Japan, and Australia. Genotype D is mainly found in the Middle East and the Mediterranean countries. Genotype E seems to be predominant in West Africa, whereas genotype G is distributed throughout the

USA, Mexico, and France. Genotype F is mainly found in Central and South America and Alaska. Finally, genotype H is unique to Central America and the USA. [91-93] In Myanmar, genotype C is most prevalent, with one study estimating 77% of HBV-infected patients in Yangon to have genotype C infection.

HBV genotypes may play an important role in the progression of HBV-related liver disease as well as response to interferon (IFN) therapy. [89,94] Genotype A (vs. B-D) is associated with significantly higher rates of HBeAg and HBsAg loss with IFN therapy. [84,85] Studies from Asia found that HBV genotype B is associated with HBeAg seroconversion at an earlier age, more sustained remission after HBeAg seroconversion, less active hepatic necro-inflammation, a slower rate of progression to cirrhosis, and a lower rate of HCC development compared with genotype C. [95] a significantly higher incidence of HCC has been reported in persons infected with genotypes C or F in Alaska compared with the others. [96]

4.3.1 Detection of drug-resistant mutations

The emergence of antiviral resistance has a close association with NA amino acid substitutions in the reverse transcriptase (RT region of the HBV genome), which are classified as primary and secondary self-compensatory resistance mutations. [97,98] The NA therapy can induce certain resistance mutations, and it is noticed that natural HBV RT mutations exist even in treatment-naïve patients. [99,100] HBV mutations may occur naturally in chronically infected subjects and may also be induced by antiviral therapy. Both lead to decreased sensitivity to antiviral drugs.

Resistance mutations are common in patients receiving Lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (LdT) but entecavir (ETV), tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) have high genetic barrier to resistance. Primary mutations are directly responsible for drug resistance, whereas compensatory (or secondary) mutations improve viral replication fitness. [101,102] The more primary mutations required for antiviral drug resistance, the higher the genetic barrier an NA antiviral has. A single primary mutation is necessary for HBV resistance to LAM, LdT and ADV, [103] whereas three mutations, including rtL180M, rtM204V/I, and any mutation at rtI169, rtT184, rtS202 or rtM250, are required for HBV resistance to ETV. [104,105] The rate of ETV resistance is 1.2% in NA-naïve patients and it increases up to 51% after 5 years of ETV treatment in patients with LAM-resistant HBV. [106,107] TDF resistance was not found in patients with long-term TDF treatment for up to 10 years. [108]

4.4. Quantitative HBsAg (q HBsAg Assay)

The desire to assess covalently closed circular DNA (cccDNA) inside hepatocytes led to development of reproducible, automated, and standardized (IU/mL) assays (Architect QT assay [Abbott], Elecsys HBsAg III Quant [Roche], Liaison XL [DiaSorin]) to quantify HBsAg. [109] Although quantitative HBsAg (qHBsAg) reflects cccDNA and intrahepatic DNA levels, it also measures HBsAg that arises from integrated DNA, thereby reducing its specificity as a biomarker for viral replication. qHBsAg levels vary by genotype (higher in A) and by presence of preS/S mutants or host immune control (inverse correlation with both). [109]

The levels of HBsAg are generally higher in HBeAg-positive patients than HBeAg-negative patients. [109,110] HBsAg level can assist the differentiation of immune tolerance and immune clearance in hepatitis B e antigen (HBeAg)-positive patients, and it can predict inactive disease and spontaneous HBsAg seroclearance in HBeAg-negative patients. In HBeAg-negative patients, low qHBsAg (<1,000 IU/mL) and low HBV DNA (<2,000 IU/mL) suggest inactive CHB. [111] qHBsAg<1,000 IU/mL predicts spontaneous HBsAg clearance in HBeAg-negative patients with a low viral load. Therefore, it can be used for selection of candidates to withdraw from therapy in combination with HBVDNA. It can also be useful in managing patients receiving Peg-IFN therapy.

Moreover, higher qHBsAg levels have been associated with progression to cirrhosis and HCC. [112] The REVEAL study, based on prospective observation of a predominantly untreated HBeAg-negative Asian cohort, demonstrated that lower HBsAg levels were associated with reduced HCC risk suggesting there may be a benefit to lowering HBsAg levels. [113] Those with an HBsAg level >100 - <1000 IU/mL and ≥1000 IU/ mL at entry into the study had 3.2- and 5.44-fold greater risks, respectively, of developing HCC, and 1.96- and 3.5-fold greater risks of developing cirrhosis compared with patients with an HBsAg level <100 IU/mL Also, among HBeAg negative patients with low HBV DNA (<2000 IU/mL), high HBsAg levels >1000 IU/mL were shown to be associated with a 13.7-fold increased risk of developing HCC compared to those with HBsAg levels <1000 IU/mL [114] A sustained reduction in HBsAg to low levels is, thus, a potentially clinically meaningful therapeutic endpoint.

Pre-operative HBsAg level is an important predictor of long-term recurrence and survival in patients with HBV-related HCC undergoing surgical resection. A preoperative HBsAg level of 1000 IU/mL or greater is an independent risk factor for HCC recurrence in patients with low HBV DNA levels. HBsAg level >200 IU/mL is also an independent predictor

for late recurrence (2 - 5 years post- resection), HBsAg levels >50 IU/mL could predict recurrence and mortality beyond 5 years. This suggests that different cut- off values of HBsAg may be useful to predict outcomes at different intervals after surgical resection. [116]

Long term HBsAg titre kinetics in patients receiving high-potency NAs (entecavir or tenofovir) can predict functional cure and low HBsAg levels. HBsAg levels markedly reduced in the first treatment year, followed by a second stepwise decrease between the 6th and 7th years. These patterns were more distinctly observed in HBeAg-positive patients with chronic hepatitis compared to liver cirrhosis and HBeAg-negative patients. Tenofovir showed a swifter decrease in HBs Ag level in the first year of treatment than entecavir. The baseline HBsAg of ≤3 log IU/mL and first-year reduction in HBsAg emerged as critical predictors for both functional cure and low HBsAg levels. [117]

4.5 Non-invasive diagnosis of liver fibrosis

4.5.1 Serological markers

Serological markers of liver fibrosis (e.g., AST to platelet ratio index [APRI] and the Fibrosis 4 score [FIB-4]) have been developed to assess significant/advanced fibrosis and cirrhosis. They have the advantages of simplicity and practicality; however, their dynamic changes cannot accurately reflect the reversal of liver fibrosis and clinical outcomes in patients with CHB receiving antiviral therapy. [118,119]

APRI and FIB-4 calculations

APRI = * ((AST/ULN) Í 100)/platelet count (109/L)

FIB-4 = (age (years) Í AST (IU/L)) / (platelet count (109/L Í [ALT (IU/L)1/2])

ULN signifies the upper limit of normal for AST in the laboratory where these investigations were undertaken.

For APRI, an online calculator can be accessed at https://www.hepatitisc.uw.edu/page/clinical-calculators/apri.

For FIB4, an online calculator can be accessed at http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4.

AST - Aspartate aminotransferase, IU- International Unit

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

4.5.2 Liver stiffness measurements (LSMs)

LSMs include transient elastography (TE), ultrasound-based point shear wave elastography (p-SWE), 2D shear wave elastography (2D-SWE), and magnetic resonance elastography (MRE). Transient elastography (FibroScan®) may be a preferable non-invasive test in settings where it is available. TE is widely used to accurately diagnose advanced liver fibrosis and early liver cirrhosis. [120] However, more clinical studies are warranted to determine whether the dynamic changes in TE reflect fibrosis reversal and clinical outcomes. [121-123]

Evidence of significant fibrosis (≥F2) should be based on an APRI score of >0.5 or transient elastography value of >7.0 kPa, and cirrhosis (F4) should be based on clinical criteria (or) an APRI score of >1.0 or transient elastography (FibroScan) value of >12.5 kPa). [124]

Table.9 Cut-off values for detecting significant fibrosis (≥F2) and cirrhosis (F4)

	APRI (low cut-off)	APRI (high cut-off)	Transient elastography (FibroScan)
Significant fibrosis (METAVIR ≥F2)	0.5	1.5	>7 kPa
Cirrhosis	1.0	2.0	>12.5 kPa

4.6 Imaging diagnosis

Imaging examinations include abdominal ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). The main purposes of imaging examinations are to monitor the clinical progression of chronic HBV infection, to determine whether liver cirrhosis and portal hypertension exist, [125,126] to locate space-occupying lesions and identify their characteristics, and to monitor and diagnose HCC in a timely manner. [127,128]

4.7 Liver biopsy

Liver biopsy is typically used to assess the degree of liver necro-inflammation and fibrosis in patients with chronic HBV infection and to rule out other liver diseases, providing evidence for diagnosis, predicting prognosis, initiating antiviral therapy, and monitoring antiviral therapy efficacy. The refined METAVIR and Ishak scoring systems, which are based on the Knodell and Scheuer scoring systems, are internationally recommended for grading hepatic necro-inflammation and the staging of liver fibrosis in patients with CHB. [129-131] METAVIR ≥F2 indicates significant liver fibrosis, and ≥F3 indicates advanced liver fibrosis. Currently in Myanmar, Liver biopsy is not recommended.

Recommendations (Definitions and Phases of Chronic Hepatitis B Infection)

34. **Quantitative HBV-DNA testing is useful for treatment decisions, including initiation of treatment and evaluation of a patient's response to antiviral treatment.**
35. **HBsAg quantitation is not recommended for the routine testing or follow-up of patients with CHB. But it can be useful in predicting outcome of patients receiving NA (functional cure) and for selection of candidates to withdraw from therapy in combination with HBV DNA. It should be checked every 6-12 months.**
36. **HBV genotyping can be useful in patients being considered for peg-IFN therapy, given that genotypes A and B are associated with higher rates of HBeAg and/or HBsAg loss than genotype C and D, but it is not recommended for routine testing or follow-up of patients with CHB because of genotype C is most prevalent genotype in Myanmar.**
37. **Testing for viral resistance is not usually done as we are using antiviral with high genetic barrier to resistant. It can be useful in patients with persistent viremia on NA therapy, or those who experience virological breakthrough during treatment.**

5. Screening for HCC

HCC surveillance should be performed at semiannual (approximately every 6 months) intervals using ultrasound and AFP. This recommendation was initially based on HCC tumor doubling time. [132]

HCC surveillance is considered cost-effective if the annual risk of HCC is >0.2% per year. [133] In CHB patients without cirrhosis, the incidence of HCC is increased compared to the general population and varies with geographical region: ranging from less than 0.2% per year in Europeans to 0.4-0.6% per year in Asians. [134] Presence of cirrhosis further increases HCC risk by over 10-fold. One-third of CHB patients with cirrhosis develop HCC in their lifetime. Among people with cirrhosis, the annual incidence of HCC is 2–3% in western countries and 6–11% in Asian populations. [135,136] At each stage of chronic hepatitis, a positive family history (in first-degree relatives) increases HCC risk. [137] Coexisting obesity, diabetes and non-alcoholic fatty liver disease (NAFLD) [138], together with alcohol and cigarette smoking [139], are additive risk factors for HCC development.

Recommendations (Screening for HCC)

38. **HCC surveillance should be performed using ultrasound and AFP at semiannual (approximately every 6 months) intervals in patients with compensated cirrhosis of liver, and in patients with CHB who have additional risk factors.**
39. **In patients with decompensated cirrhosis of liver, surveillance should be carried out every 3-4 months.**

6. Treatment of Chronic Hepatitis B

6.1 Goal of therapy

A major goal of CHB antiviral treatment is to prevent disease progression, HCC, and liver related mortality. Without a cure for CHB infection, an essential intermediate endpoint toward these goals is the long-term suppression of HBV replication, alleviate liver necro-inflammation and fibrosis, delay and reduce the progression of liver diseases, hepatic decompensation, HCC, and transmission to others, particularly mother-to-child transmission in pregnancy which is achievable by current antiviral treatment. [140-142]

6.2 Whom to treat

Currently, the decision to treat criteria established by international liver societies including AASLD, EASL & APASL are complex and complicated and usually based on a combined assessment of the liver fibrosis stage by liver biopsy or transient elastography, serum HBV DNA and ALT levels. [140-142] Moreover, there is no global consensus definition of normal ALT levels as well as HBV DNA cut-off among the international treatment recommendations. Based on these clinical practice guidelines, treatment initiation is typically recommended for patients with cirrhosis, for who have elevated detectable HBV DNA level, or those with active chronic hepatitis B exhibiting elevated levels of ALT. [140-142]

Unfortunately, these guidelines assume that elevated ALT levels indicate liver necro-inflammation and consistently undetectable HBV DNA levels signifies viral inactivity. Additionally, replacing liver biopsy with liver stiffness measurement is inaccurate in estimating

gray zone fibrosis. As a result, numerous individuals with chronic hepatitis B infection remain untreated according to guideline recommendation, leaving them vulnerable to the progression of liver disease, HCC and potential transmission of infection to others.

Emerging data highlights the need for early diagnosis and treatment of HBV. Patients with untreated compensated cirrhosis who have undetectable HBV DNA levels and do not meet the current criteria for treatment had higher rates of HCC compared to patients with compensated cirrhosis and suppressed HBV DNA by antiviral therapy. [143] A multinational study conducted across 14 sites in the USA, Europe, and Asia demonstrated that antiviral therapy reduced the risk of hepatocellular carcinoma (HCC) by 70% among treatment naïve patients with chronic hepatitis B who do not have advanced fibrosis and do not meet the current criteria for antiviral therapy. [144] An analysis of Korean cohort with treatment naïve chronic hepatitis B showed that proportion of patients who developed HCC outside treatment guideline recommendation according to APASL, AASLD and EASL ware 64%, 46% and 33.5% respectively. [145] Many patients who do not currently meet the criteria for antiviral treatment according to current guidelines remain at risk of adverse clinical events, particularly HCC.

The World Health Organization (WHO) endorsed the strategy to eliminate viral hepatitis as a public threat by 2023, targeted to 90% reduction in incidence and a 65% reduction in mortality of viral hepatitis B and C. [146] Currently, no country is on track to achieve the WHO's HBV mortality target for 2023. [147] To reach these target, the global health sector strategies concentrating on key areas such as disease burden, prevention coverage, harm reduction, blood safety, testing and treatment for hepatitis. Enhancing access to care, simplifying guidelines, and achieving a cure of HBV infection are all equally crucial step to find the missing millions living with hepatitis B. Broadening efforts for testing, vaccination, and treatment to meet hepatitis elimination goals greatly depends on decentralized care and primary healthcare providers. The global movement towards decentralization has initiated shifts, particularly evident in hepatitis C care, resulting in enhanced screening rates and improved access to care and treatment. [148] Expanding the allocation of task to primary care providers and frontline healthcare workers is equally vital for the successful elimination of HBV as a public health threat and ensuring equitable access to life saving care for patient with chronic hepatitis B.

However, current guidelines are often confusing and ambiguous, results in only a minority of the chronic hepatitis B patients being offered treatment. Nonetheless, across all the regions, only 13% of people living with chronic hepatitis B infection had been diagnosed and

approximately 3% (7 million) treated with antiviral therapy at the end of 2022 [146] due to the complexity and restrictiveness of clinical practice guidelines.

In 2016, the World Health Organization (WHO) recommended that all individuals living with HIV, regardless of clinical status or CD4 cell count, should provide with lifelong antiretroviral therapy. [149] Since then, a newer approach called the "Treat All" strategy, proposes treating all individuals diagnosed with chronic HBV infection without requiring assessment of HBV DNA level, ALT level, or fibrosis stage. [150-154] Similar to a "Treat all" approach for HIV or hepatitis C infection, the "Treat all" strategy for HBV infection could enable the initiation of antiviral treatment on the same days as a positive HBsAg screening test, eliminating the need for costly and complex clinical staging process. [152] Furthermore, implementing the "Treat all" approach or providing universal HBV treatment to all HBsAg-positive individuals can ensure sustained viral suppression, thereby preventing both the horizontal transmission and the progression of liver disease, even in the absence of a cure.

Recently, the Chinese Hepatology and Infectious Disease Societies have adopted an expanded treatment strategy. [155] In their guidelines, HBV treatment is recommended in all HBsAg-positive patients with detectable HBV DNA level (i.e., HBV DNA > 10-20 IU/mL) over the age of 30 years, regardless of ALT level. Under this strategy, 92% (75 million) of HBV infected patients in China are now considered eligible for treatment. Antiviral treatment is also recommended for HBV DNA detected individual younger than 30 years of age with persistently elevated ALT (i.e., > upper limit of normal), those with compensated cirrhosis, and those with risk of disease progression (≥ grade 2 inflammation or ≥ stage 2 fibrosis, family history of HBV-related cirrhosis or HCC, or HBV-related extrahepatic manifestation).

There are several other expanded treatment strategies proposed throughout the world including an East Asia expert opinion [156], a U.S treatment algorithm [157], a test-and-treat all HBsAg-positive patients' strategy, and expert recommendation for the simplification of current guidelines [158]. Both the recommendations from East Asia expert opinion and the U.S. treatment algorithm suggest initiating antiviral treatment for more CHB patients at risk of HCC and adverse liver outcomes than in current AASLD, APASL and EASL treatment guidelines.

In 2024, the World Health Organization (WHO) updated the guidelines expand eligibility for the treatment of hepatitis B, with four options for meeting treatment eligibility that apply to all adults with chronic hepatitis B. [159] Only one of the four options requires access to HBV DNA testing, which has been considered a major barrier to accessing treatment.

Overall, these four options mean that a much higher proportion (at least 50%) of all HBsAg positive people, depending on the region, will now be eligible for treatment compared with about 8–20% previously. The first option is to treat all individuals with significant fibrosis (≥F2) based on revised thresholds of non-invasive tests for staging of liver disease (APRI score >0·5 or transient elastography [if available] >7 kPa), or cirrhosis based on clinical criteria (or an APRI score >1·0 or transient elastography >12·5 kPa), regardless of HBV DNA or alanine aminotransferase (ALT) levels. The second option is to treat if HBV DNA is over 2,000 IU/mL (previously >20,000 IU/mL) and ALT is above the upper limit of normal. The third option is to treat if there is the presence of any of the following: co-infections (e.g., HIV, HDV, or hepatitis C); a family history of liver cancer or cirrhosis; immune suppression (e.g., long-term steroid use, solid organ or stem-cell transplant); co-morbidities (e.g., diabetes or metabolic dysfunction-associated steatotic liver disease); or extrahepatic manifestations (e.g., glomerulonephritis or vasculitis), regardless of HBV DNA or ALT levels. The fourth option is a conditional recommendation, in settings where there is no access to HBV DNA testing, to treat on the basis of persistently abnormal ALT levels alone. [159,160]

However, these guidelines continue to insist on evaluating HBV DNA and ALT level, as well as fibrosis assessment prior to treatment decision-making. Moreover, periodic assessment for treatment eligibility based on HBeAg, HBV DNA level, and ALT remains challenging in low-income and middle-income countries (LMICs). In contrast, the "test-and-treat-all" strategy, where all HBsAg-positive would be eligible for antiviral treatment, does not require HBV DNA testing and could reduce the diagnosis costs. However, implementing "Treat all" approach would necessitate mass screening to identify all HBsAg-positive patients, which carries significant implication for national public health policies. Furthermore, the acceptability of the "Treat all" approach is also debatable, as it mandates lifelong antiviral therapy even for individual who may not develop chronic liver disease. Despite the generally good tolerance of antiviral therapy like Tenofovir, adherence might be suboptimal. [161] Additionally, treatment interruptions carry a 1–2% risk of severe hepatic flare with liver decompensation. [162] Furthermore, the burden of treatment, including daily medication intake that might interfere with daily activities or lifestyle, cannot be overlooked. [163] Moreover, feasibility and acceptability of the "Treat all" approach have not been tested in a real-world setting.

However, a recent large-scale study conducted in Uzbekistan demonstrated the feasibility of a decentralized testing and simplified diagnostic algorithm and treatment of

uncomplicated cases by general practitioners in low-and middle-income countries (LMICs). [164] A test-and-treat-all protocol for HBV elimination has been successfully implemented in a national program in Uzbekistan; the first country to adopt a test and treat all guideline for HBV. [164]

Recent prospective studies favor early antiviral therapy that potential impact on hepatocarcinogenesis and clinical HBV parameters. These data support the early initiation of antiviral treatment to delay or even reverse chronic hepatitis B related disease progression and as a preventive strategy to reduce HBV related mortality.

During early phase of HBV infection, the immune system becomes activated as a natural defense mechanism, and this response is beneficial in in acute infection. However, persistent immune activation from chronic HBV infection initiates a series of molecular events [165] including carcinogenesis driven via HBV DNA integration, which occurs prior to observable histological liver damage, chromosomal instability, insertional mutagenesis, and the expression of mutant HBV genes or host oncogenes. [165-169] Higher level of integration have been observed among hepatitis B e antigen (HBeAg)- positive compared with HBeAg – negative patients [170], and among the HBeAg-negative patients, the highest number of integration has been reported among those with HBV DNA >20,000 IU/mL. [171] Antiviral treatment has been shown to reduce the number of transcriptional active integration in patients with HBV infection. [169,172,173]

Early initiation HBV therapy also has potential impact on various clinical parameter of HBV patients. A meta-analysis that includes two studies of immune tolerant patients found moderate-quality evidence for improved intermediate outcome (viral suppression, HBeAg seroconversion/loss) with antiviral therapy. [174] Analysis of 181 treatment naïve immune-tolerant patients, revealed that 33% of patients had evident histological liver injury (EHLI) at baseline. After 72 weeks of entecavir treatment, histological improvement and fibrosis reversal were observed in 82% and 78% of patients with evident histological liver injury (EHLI), respectively. Additionally, 73% of patients no longer having EHLI at the treatment period. [175]

A unique group of HBV patients, often co-infected with human immunodeficiency virus (HIV), typically receive early antiviral treatment irrespective of HBV DNA or ALT levels. Many antiretroviral regimens include a nucleoside/tide analogs (NAs) like Tenofovir Disoproxil Fumarate (TDF) or Tenofovir Alafenamide (TAF). [140-142] Among 3625 patients co-infected with HBV and HIV, the occurrence of hepatocellular carcinoma (HCC) remained

stable in those receiving nucleoside/tide analog (NA) treatment. However, there was a notable increase in HCC incidence among patients not undergoing NA-based treatment regimens. [176] Findings from a study involving antiviral-treated HBV mono-infected (n = 53,974) and HBV/HIV co-infected (n = 822) patients revealed a reduced incidence of hepatocellular carcinoma (HCC) among HBV/HIV co-infected individuals compared to HBV mono-infected patients. [177] Similarly, data from a US administrative claim analysis showed a decrease in the occurrence of hepatocellular carcinoma among HBV/HIV co-infected patients (n = 7764) compared to HBV mono-infected patients (n = 13,964). [178] The presence of HIV co-infection, which typically correlates with early HBV antiviral therapy, suggests that implementing universal antiviral treatment for chronic hepatitis B (CHB) patients might reduce the likelihood of developing hepatocellular carcinoma (HCC).

Indeed, there is valid concern regarding the potential safety implication of expanding the initiation of long-term antiviral treatment. Based on accumulating clinical experience, there is a minimal risk of side effect associated with current antiviral treatment option. Rare but potentially severe adverse events include lactic acidosis, osteoporosis and renal failure. [141] However, recent studies have demonstrated that the bone and renal effects of tenofovir are less common with Tenofovir Alafenamide (TAF) than with Tenofovir Disoproxil Fumarate (TDF). [140] This consideration must be balanced against the risk of disease progression and hepatocellular carcinoma (HCC) in untreated chronic hepatitis B patients. Another potential concern related to long-term antiviral treatment is the development of resistance and poor adherence. However, drug like ETV, TDF and TAF have a high barrier to resistance; no resistance to TDF or TAF has been detected, and resistance to ETV is rare among treatment naïve patients. [140,141] Moreover, adherence rates to nucleoside/tide (NA) therapies are generally very high, reaching up to 75%. [179]

The main reason for not recommending the “Treat all” policy for hepatitis B is likely the financial strain on any national health system. However, several studies have estimated that early initiation of antiviral treatment has been shown to be cost effective. The costs associated with expanded chronic hepatitis B therapy could be balanced by the decreased expenditure required for managing the future consequences of disease progression resulting from untreated chronic hepatitis B. [180-187]

After careful assessment of risk and benefit, as well as the availability of equally effective and safe generic, low cost tenofovir or entecavir, GI and Liver Foundation (GLF) Myanmar has recommended the early initiation of antiviral therapy with the “Treat all”

strategies in all adults (> 18 years old) individual with chronic hepatitis B infection. This approach is implemented regardless of the stage and phase of liver disease, and it is tailored to meet local needs and resources.

Recommendations (Treatment of Chronic HBV infection for adult > 18 years old)

Treatment is recommended for all adult (>18 years old) with chronic hepatitis B (CHB) with one of the following criteria

40. **HBsAg positive regardless of HBV DNA, ALT level or fibrosis stage following education on the importance of adherence to antiviral therapy.**
41. **Significant fibrosis (≥ F2) or cirrhosis (F4) regardless of HBV DNA or ALT level**
    - **Clinical criteria for cirrhosis**
    - **Non-invasive tests: APRI > 0.5 or transient elastography > 7 kPa**
42. **Detectable HBV DNA level**
43. **Persistently abnormal ALT level (Upper Limit Normal 30 U/L for men and 19 U/L for women),**
44. **Presence of any of following (regardless of fibrosis stage, HBV DNA, ALT level)**
    - **Coinfection (e.g. HIV, HCV)**
    - **Family history of liver cancer or cirrhosis**
    - **Immune suppression**
    - **Comorbidities (e.g. Diabetes, MASLD)**
    - **Extrahepatic manifestations (e.g. Glomerulonephritis or vasculitis)**

Recommendations (first-line antiviral therapies for all adults > 18 years old)

45. **Nucleoside analogues with a low genetic barrier to drug resistance such as lamivudine, adefovir or telbivudine can lead to drug resistance and are thus not recommended.**
46. **Nucleos(t)ide analogues that have a high genetic barrier to drug resistance such as tenofovir alafenamide (TAF), tenofovir disoproxil fumerate (TDF) or entecavir (ETV) are recommended as preferred regimens.**
47. **Tenofovir alafenamide (TAF), Entecavir is recommended as first-line therapy for people with age > 60 years, chronic steroid use or use of other medication that worsen bone density, history of fragility fracture, osteoporosis, eGFR < 60ml/min/1.73m^2, albuminuria > 30 gm/24 hr or moderate dipstick proteinuria, low phosphate (<2.5 mg/dl), hemodialysis.**

7. Monitoring and follow-up management of patients during antiviral therapy

Regular monitoring during antiviral therapy is intended to assess the effectiveness of the treatment, ensure patient compliance, detect drug resistance, identify adverse events, and monitor for the development of hepatocellular carcinoma (HCC).

Baseline tests should include the following:

(a) **Biochemical Tests**: ALT, AST, bilirubin, albumin, and other relevant markers.

(b) **Virological and Serological Markers**: HBV DNA level, HBsAg, HBeAg, and anti-HBe.

(c) **Blood Routine Tests**: Serum creatinine and other necessary markers.

(d) **Non-Invasive Fibrosis Detection**: Liver stiffness measurement (LSM) or other methods.

(e) **Renal Function Considerations**:

- For patients with creatinine clearance <50 mL/min who are being treated with ETV or TDF, dose adjustments are required.
- TAF is not recommended for patients with creatinine clearance <15 mL/min who are not on dialysis, and no dose adjustment is necessary in other cases.

7.1 Patient treatment compliance

Adherence to medication is essential to ensure that patients are aware of the potential risks associated with self-discontinuation of the drug. Promoting awareness and understanding of the importance of consistent treatment is key to improving patient compliance.

7.2 On Nucleos(t)ide Analogues

Routine blood tests, liver biochemical tests, monitoring of HBV DNA levels (optional), and HBV serum virological markers, along with liver stiffness measurements (LSMs), should be conducted every 6 months for patients without cirrhosis and every 3 months for those with cirrhosis. If needed, enhanced CT or enhanced MRI should be utilized for early detection of hepatocellular carcinoma (HCC). Additionally, for patients on medications that may impact renal function or bone metabolism, serum phosphorus and renal function markers should be tested every 6 to 12 months.

7.3 On Peg-IFN

Routine blood tests should be performed every 1 to 2 weeks in the first month of treatment. Additionally, routine blood tests and liver biochemical markers should be detected once every month after stabilization. Furthermore, thyroid function markers, blood glucose, and HBV serum virological markers should be detected every 3 months. Finally, LSM should be performed once every 6 months.

7.4 Prevention and treatment of rare adverse events

While nucleos(t)ide analogs (NAs) are generally safe and well-tolerated, rare but serious adverse events can still occur, such as renal insufficiency (particularly with TDF and ADV), hypophosphatemic bone disease (especially with TDF and ADV), myositis/rhabdomyolysis, and lactic acidosis (notably with ETV). To minimize potential risks, it is essential to thoroughly review the patient's relevant medical history before starting treatment. Additionally, patients who experience significantly elevated serum creatinine, creatinine kinase, or lactate dehydrogenase levels during treatment, along with corresponding clinical symptoms, should be closely monitored. If any of these adverse events occur, the medication should be discontinued immediately.

8. Management of Chronic Hepatitis B in Special Populations

8.1 Acute Hepatitis B infection

In cases of acute hepatitis B, the primary objective of treatment is to avert the risk of acute or subacute liver failure. Another important goal is to enhance the patient's quality of life by alleviating the symptoms associated with the disease and reducing the likelihood of it becoming chronic. According to the typical progression of the illness, more than 95% of adults will experience clinical and virological recovery, including seroconversion to anti-HBs, without the need for antiviral therapy. However, a severe or fulminant form of acute hepatitis B can be potentially life-threatening. This severe manifestation is characterized by coagulopathy (with an INR greater than 1.5), a prolonged course of illness with persistent symptoms, marked jaundice for four weeks, or signs of acute liver failure. [188]

Although randomized controlled trials are lacking, several cohort studies indicate that the early antiviral therapy with highly potent NAs can prevent progression to acute liver failure and subsequently liver transplantation or mortality. [189]

Despite the lack of observed benefit, treating all patients with acute liver failure attributed to HBV using an NA may be reasonable given its safety and the ultimate need for liver transplantation in many of these patients, for whom lower HBV-DNA levels are desirable to reduce the risk of recurrent hepatitis B after transplant. [190]

Early NA treatment does not increase the risk of chronicity (4) and observational data from a multicenter cohort even indicated reduced rates of chronicity, if NA treatment was initiated within 8 weeks of acute hepatitis B presentation. [191]

Recommendations (Acute Hepatitis B infection)

48. Antiviral treatment with TDF or TAF or Entecavir is recommended for a severe or fulminant form of acute viral hepatitis B.

49. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation.

8.2 Management of persons with persistent low-level viremia on NA therapy

Low-level viremia (LLV) is defined as persistent or intermittent episodes of detectable HBV DNA <2000 IU/ mL after 48 weeks of antiviral treatment. [193] Low-level viremia (LLV) has been suggested to be a possible cause of HCC in patients receiving NA treatment. [194] In general, real-world studies have suggested that 20% to 40% of patients will still develop LLV, even with first-line antiviral drugs for HBV. [195] The risk factors include HBeAg seropositivity, presence of cirrhosis, higher HBsAg levels and HBV DNA levels before antiviral therapy. [196]

At present, the mechanism of LLV remains unclear. The possible one is that NA cannot completely block the synthesis of the DNA strand and there is stable existence of covalently closed circular DNA (cccDNA) in the infected liver nuclei. As a result, the HBV DNA level in the serum of some patients with antiviral therapy is continuously or intermittently higher than the detection limit, as manifested as LLV. [197]

Regarding with the management, the AASLD recommendation for patients with LLV suggests that patients treated with ETV or TDF/TAF monotherapy should continue monotherapy, although the quality and certainty of evidence are low. [198]

EASL does not recommend changing the initial treatment strategy in patients with low HBV DNA levels (HBV DNA < 69 IU/mL) and/or declining HBV DNA concentrations on potent NA monotherapy; if the HBV DNA has plateaued (69 < DNA < 2000 IU/ mL), the possibility of switching to another drug or a combination of ETV+TDF/TAF should be considered. [198]

Virological breakthrough is defined by an increase in HBV DNA by >1 log compared to nadir or an HBV-DNA level of 100 IU/mL or higher in persons on NA therapy with a previously undetectable level (<10 IU/mL). [198] The virological breakthrough is identified in 3.6, 3.6 and 0.6 % of patients treating with tenofovir disoproxil fumarate at 12, 24 and 36 months [199] and 0.6 % of patients treating with entecavir for 3 years. [200]

The AASLD recommends two strategies for individuals experiencing virological breakthrough on entecavir or tenofovir monotherapy: either transition to another antiviral monotherapy with a high resistance barrier or augment with a second antiviral lacking cross resistance. Insufficient long-term comparative data hinders favoring one approach over another. Virological principles indicate lower viral resistance risk with combination antiviral therapy versus monotherapy. Up to a 5-year follow-up shows monotherapy, especially with antivirals like tenofovir, attains HBV DNA suppression rates akin to combination therapy. [201]

Recommendations (Persistent low-level viremia on NA therapy)

50. **Persons with persistent low level viraemia, who has been treated with ETV or TDF or TAF mono therapy, should continue mono therapy, regardless of serum ALT.**

51. **For persons on entecavir, TDF or TAF with virological breakthrough despite good compliance, hepatology referral is recommended.**

8.3 Renal and bone disease in persons on NA therapy

Entecavir and tenofovir are both approved as first-line therapeutic options for CHB. NUC-associated nephrotoxicity primarily results in proximal tubular toxicity rather than glomerular toxicity. The tubular damage leads to defective proximal tubular secretion (e.g. of creatinine) and reabsorption of several substances including phosphate, resulting in reduced serum phosphate levels (hypophosphatemia), elevated phosphate levels in the urine (phosphaturia) and elevated serum levels of creatinine. This effect, however, is not pronounced (approximately 6%) when renal function is normal but becomes more relevant when renal function is low. [202]

Regarding the impact of TDF on renal function, the degree of association between TDF treatment and changes in markers of renal function varies between studies. Possible reasons for the observed discrepancies include the use of different definitions and cut-offs for reporting renal toxicities, and differences in patient populations. [202]

A multicenter, matched case-control, retrospective cohort study in 103 patients treated for chronic HBV infection with TDF and 103 controls treated with ETV [matched by age (mean 44 years), gender, and baseline GFR (86.4% un-impaired), all Asian]. Over up to 40 months of treatment, there was no significant difference between TDF and ETV. [203]

The existing studies do not show significant differences in renal dysfunction, hypophosphatemia, or bone mineral density between HBV-infected persons treated with tenofovir (TDF) or entecavir. However, renal events, such as acute renal failure or hypophosphatemia, have been reported in TDF-treated persons. [204] Therefore, TDF can be used with negligible side effects in patients not at risk of renal dysfunction and bone disease.

Changes in renal function over time were observed, several factors were also found to show a significant association, particularly older age and preexisting renal insufficiency. [202]

In persons on TDF, renal safety monitoring with serum creatinine, phosphorus, urine glucose, and urine protein should be assessed before treatment initiation and periodically thereafter (e.g., at least annually and more frequently if the patient is at high risk for renal dysfunction or has a preexisting renal dysfunction). [204] TAF is a novel prodrug of tenofovir (TFV) which has shown potent inhibition of HBV replication at a low dose, with high intracellular concentration and more than 90% lower systemic TFV concentration than TDF.

Week 48 results of the phase 3 studies in patients with CHB confirmed comparable anti-viral efficacy of TAF compared with TDF. In contrast, significant differences were observed regarding the safety profile of the drugs. In the HBeAg-negative study, eGFR declined significantly in TDF- but not in TAF-treated patients. [202]

Likewise, the mean change from baseline of the T-score (DEXA scan of spine) was significantly higher in the TDF than in the TAF group (- 2.51% vs. - 0.88%, $P < 0.001$). Similar findings could be demonstrated also for the hip. [202]

In CHB patients with deteriorating renal function or low eGFR and/or osteopenia/osteoporosis, particularly in older age, the minimization of progression of the physiological decline into pathological abnormality should also be considered when choosing NA therapy. [205]

Table. 10 Recommended dosage for adults with renal impairment and decompensated cirrhosis and recommended dose reduction or dosing interval. [206]

Drug	CrCl (mL/min)[a]			
	>50	30–49	10–29	<10 Haemodialysis or continuous ambulatory peritoneal dialysis
TDF[b,c]	One 300-mg tablet every 24 hours (7.5 scoops of	One 300-mg tablet every 48 hours (or 160 mg [3 scoops] of powder every 24 hours)	One 300-mg tablet every 72–96 hours (or 60 mg [1.5 scoops] of powder every 24 hours)	Every seven days or one 300-mg tablet following completion of approximately every 12 hours of dialysis (or 20 mg [0.5 scoops] of powder following completion of approximately every 12 hours of dialysis)
ETV[d]	0.5 mg once daily	0.25 mg once daily **OR** 0.5 mg every 48 hours	0.15 mg once daily **OR** 0.5 mg every 72 hours	0.05 mg once daily **OR** 0.5 mg every 7 days
ETV (decom-pensated liver disease)	1 mg once daily	0.5 mg once daily **OR** 1 mg every 48 hours	0.3 mg once daily **OR** 1 mg every 72 hours	0.1 mg once daily **OR** 1 mg every 7 days
TAF	25 mg orally once a day	25 mg orally once a day	25 mg orally once a day CrCl at least 15 mL/min: no adjustment recommended. 25 mg once daily	CrCl less than 15 mL/ min) not receiving chronic haemodialysis: not recommended.

a Calculated using lean body weight.
b Tenofovir disoproxil fumarate (TDF) 300 mg is equivalent to tenofovir disoproxil 245 mg or tenofovir 136 mg.
c TDF is also available in a granule formulation (33 mg/g in a 60-g pack) for ease of swallowing. Dosing is the same for oral granules and tablets.
d For ETV doses less than 0.5 mg, oral solution is recommended. ETV is not recommended for those with 3TC resistance.

Recommendations (renal and bone disease in persons on NA therapy)

52. Consider TAF or entecavir in patients with or at risk for renal dysfunction or bone disease. TDF can be used with negligible side effects in patients not at risk of renal dysfunction and bone disease.

53. In cases of suspected TDF-associated renal dysfunction and/or bone disease, TDF should be discontinued and substituted with TAF or entecavir, with consideration for any previously known drug resistance.

54. In patients with impaired renal function, the dosage of NAs should be adjusted based on creatinine clearance, as recommended by manufacturers.

55. TAF is not recommended in patients with creatinine clearance <15 mL/min.

8.4. Management of Chronic Hepatitis B in Pregnancy

Mother-to-child transmission (MTCT) is responsible for a majority of chronic HBV infection in the Asia–Pacific region. As HBV infection in infancy or early childhood often leads to chronic infection, it is important to take appropriate measures to prevent MTCT. The HBsAg national prevalence in Myanmar was 6.5% according to the national prevalence survey done in 2015. [207] Hepatitis B surface antigen (HBsAg) prevalence among children under 5 years was 1.11% in 2020 and coverage of 3 doses of hepatitis B vaccine was 71% in 2022 in Myanmar according to WHO data. [208,209]

HBV MTCT can potentially occur prenatal or intra-uterine, natal or at the time of birth, and postpartum. Most HBV infections occur perinatally (at birth or soon after) in un-vaccinated infants. Approximately 3% to 8% of infections are thought to occur through the intra-uterine route. [210] Maternal HBeAg seropositivity and intra-uterine transmission of HBV is the most significant contributor to MTCT and immunoprophylaxis failure. [211]

Family planning should always be discussed with women of childbearing age before initiating HBV therapy. The woman should be informed about the safety data of TDF on a possible pregnancy.

8.4.1 Vaccination of infants born to HBsAg positive mothers

Without any intervention, MTCT of HBV is 70–90% if mother is HBsAg-positive and HBeAg-positive; and 10–30% if mother is HBsAg-positive only. [212] Timely hepatitis B vaccination birth dose alone is 70–95% effective in preventing MTCT. Timely Hepatitis B birth dose plus the completion of hepatitis B vaccine series is > 95% effective in preventing MTCT. [213]

WHO position papers on immunization recommend that all infants receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours and that HBIG, which contains high levels of purified HBsAg-specific antibodies from plasma donors, is given simultaneously at different sites intramuscularly. The birth vaccine dose should be followed by two or three doses of hepatitis B vaccine to complete the primary series. [213]

The estimated transmission rates without vaccination, with vaccination, and with vaccination plus HBIG, were 75%, 21%, and 6% in HBeAg-positive women and 10%, 3%, and 1% in HBeAg- negative ones, respectively. [214] Although the combination is superior to active vaccine alone, the HBIG coverage may not be sufficient in Myanmar because of the high costs, limited supply and need for cold chain.

Recommendations (Vaccination of infants born to HBsAg positive mothers)

56. All infants of HBsAg positive mothers should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours and Hepatitis B immune globulin (HBIG) should be given simultaneously at different sites intramuscularly if available. The dose of HBIG is 0.5mL (100 IU) and the dosage of HBV vaccine for newborn is 10 µg regardless of the birth weight.

57. The birth dose vaccine must be followed by 3 or 4 doses of hepatitis B vaccine to complete the primary series in order to achieve maximum efficacy (according to Expanded Program of Immunization policies) for prevention of mother to child transmission (MTCT).

Table. 11 Immunization program in Myanmar

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
Timing	Within first 24 hrs after birth (single dose monovalent vaccine)	Week 8 (Pentavalent vaccine)	Week 16 (Pentavalent vaccine)	Week 24 (Pentavalent vaccine)	One and half year (Pentavalent vaccine)

8.4.2 Treatment of patients who are already on long-term NA therapy before conception

In the patients who are already on long-term NA therapy before conception, there are two major considerations:

(1) whether NA would increase the risk of fetus anomalies if it is continued throughout the pregnancy and

(2) whether discontinuation of NA therapy would jeopardize the liver condition of the mothers and if in case becoming severe, adversely affects the fetus. [215]

Regarding the safety data of antivirals, there is absence of evidence on the hypothetical chance of teratogenic effects of the HBV treatment continuation from the experience from HIV pregnancy registry. According to the Antiretroviral Pregnancy Registry, of the 11 867 females on anti-retroviral therapies for HIV and/ or HBV infection, the rate of birth defects was 2.7% which is very similar to the rate (2.72%) in the general population. [216]

Concerning the risk of reactivation after treatment cessation, around 40–50% of non-pregnant chronic HBV-infected individuals would have ALT flares after NA cessation. According to one study, ALT flares occurred in 31% of pregnant women with high HBV DNA level who stopped NA during the first trimester. [217]

Therefore, it is recommended that in pregnant women already on NA therapy, TDF should be continued to reduce the risk of perinatal transmission of HBV. If the pregnant mother is concerned about the fetal anomalies risk of NA during first trimester, counselling should be done regarding the risk of HBV reactivation with NA discontinuation. If NA treatment is stopped during first trimester, close monitoring of liver function should be done to detect HBV flare. NA treatment should be restarted at second trimester of pregnancy. NA should be continued in patients with advanced fibrosis/cirrhosis.

8.4.3 Antiviral therapy for treatment naïve pregnant women

Infants born to mothers with HBV DNA levels above 200,000 IU/ml are at risk of failure of immunoprophylaxis and result in chronic HBV infection. Maternal HBV DNA level is found to be the most important predictor and independent risk factor for MTCT due to intrauterine transmission. [218] Therefore, pregnant women with an HBV DNA ≥ 5.3 log10 IU/mL (≥ 200,000 IU/mL) should receive antiviral prophylaxis for prevention of mother-to-child transmission of HBV in addition to appropriate immunoprophylaxis. If antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for antiviral prophylaxis. [215]

All pregnant women should also be assessed for eligibility for long-term treatment according to the indications for treatment of chronic HBV infection. [219] Among the available nucleotide analogues, TDF and Telbivudine are category B drugs. In a recent large meta-analysis that evaluated the effect of TDF 300 mg, lamivudine 100–150 mg, and telbivudine 600 mg, on reducing the risk of HBV MTCT, all antiviral drugs showed similar efficacy. This analysis confirmed that peripartum antiviral prophylaxis is highly effective at reducing the risk of HBV MTCT. [221]

TDF is recommended because of its favorable resistance profile and proven long-term safety for the fetus. [219] Although tenofovir alafenamide (TAF) has been recommended for CHB treatment in many parts of the world owing to its better renal and bone safety profile compared to TDF, there are limited data on the use of TAF in pregnancy. It is not recommended during breastfeeding. [220]

8.4.4 Timing of antiviral therapy

A meta-analysis and system review showed that the risk of MTCT decreased significantly in pregnant females accepting intervention before 28 weeks of gestation, as compared to those initiating after 28 weeks. [221] Some studies suggest that earlier start of NAs, i.e., in the second trimester, might be more efficacious than in the third trimester as this might lead to greater viral load reduction in females treated earlier. [222]

Pregnant females taking antivirals for preventing MTCT only can discontinue antiviral treatment immediately after delivery or continue up to 12 weeks postpartum and should be monitored closely for hepatitis flare and rebound of HBV DNA till at least 24 weeks. This suggests that discontinuation of TDF prophylaxis might not increase the risk of flare. Pregnant females with ALT flares during pregnancy or evidence of advanced liver fibrosis or cirrhosis should continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for chronic hepatitis B patients should be followed. [215]

Recommendations (Antiviral therapy in pregnant women)

58. **Screening for HBsAg in the first trimester of pregnancy is strongly recommended. HBV vaccination is safe in pregnancy, and pregnant women who are not immune to or infected with HBV should receive HBV vaccine series. Pregnant women with CHB and advanced fibrosis or cirrhosis, treatment with TDF is recommended.**
59. **In pregnant women already on NA therapy, TDF should be continued to reduce the risk of perinatal transmission of HBV.**
60. **Other NA should be switched to TDF during pregnancy.**
61. **If NA has already been stopped during first trimester, reassessment should be done to restart antiviral therapy.**
62. **For treatment-naïve HBsAg positive pregnant women, baseline HBV viral load testing should be done whenever available. If viral load testing is not available, the foundation assures that all HBsAg positive pregnant women should receive TDF from second trimester of pregnancy to prevent MTCT of HBV if there is no contraindication.**
63. **The recommendation to continue NA after pregnancy is the same as the recommendation for general population.**
64. **Caesarean section is not recommended to reduce the risk of HBV mother-to-child transmission in HBsAg-positive women.**
65. **Caesarean section may be recommended only in Asian HBeAg-positive women with high HBV DNA titer (>7 log10 copies/ml; 6.14 log10 IU/ml) who have not received antiviral therapy during pregnancy.**

8.4.5 Breast feeding

Concentration of HBV DNA in colostrum and mature breastmilk are significantly lower than that in serum and associated with serum HBV DNA level. If both active and passive immunization were received, HBV infection rate of breast-fed infants was not significantly different compared to formula-fed infants (11.1% and 2.2%, respectively, $p > 0.05$). Besides, the economic, immunological and developmental benefits of breastfeeding far outweigh the limited risk of MTCT. [224]

Therefore, breast feeding should not be discouraged for infants who receive active/passive immunization, although some caution should be applied to mothers with high serum HBV DNA load if the nipples are cracked and the infants have oral ulcers. However, HBsAg-positive mothers should not participate in donating breast milk.

In breastfeeding mothers on Tenofovir treatment, the safety of breastfeeding is still debated. Breast milk levels of tenofovir are lower than levels in the blood of mothers taking TDF and tenofovir is unlikely to have biological effects in the nursing infant. [225] The concentrations of tenofovir in the breast milk were significantly higher in mothers receiving TAF than in the TDF group, despite the lower dosage of TAF. However, tenofovir levels will gradually decline in the following postpartum period. [226] In terms of maternal and infant bone mineralization, TDF prophylaxis in HBV-mono-infected women in Asia appeared safe and maternal and infant bone mineral density 1 year after delivery/birth was not affected by maternal TDF use. So, TDF toxicity is unlikely to occur and breast-feeding is considered to be safe for infants born to mothers treated with TDF. [219]

Recommendations (Breast feeding)
66. Breastfeeding is not prohibited while the mother is on anti-viral therapy or infants who receive active/passive immunization.

8.5 Treatment of Chronic Hepatitis B in children and adolescents

Most children acquire HBV infection perinatally or during early childhood and develop a chronic hepatitis characterized by high viral replication and a low-inflammation phase of infection, with normal or only slightly raised aminotransferases. [227] 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. The main goal of antiviral therapy in children and adolescents is effective and sustained suppression of HBV replication and consequently to decrease the risk of disease progression to cirrhosis and hepatocellular carcinoma. [227]

Chronic HBV infection runs an asymptomatic course in most children, but the lifetime risk of significant clinical complications is not negligible. In children, the course of the disease is generally mild, and most of the children do not meet standard treatment indications. Thus, treatment should be considered with caution. [228]

Table. 12 Antiviral drugs approved for children and adolescents with hepatitis B virus infection

Antiviral drugs approved for children and adolescents with hepatitis B virus infection		
Drug	**Licensed age for use in children and adolescents**	**Dose**
Peg Interferon α 2a [229]	≥ 3 years	SC 180 ug/1.73 m^2 body surface area once a week
Entecavir [230]	≥ 2 years	Weight < 30kg - 0.015 mg/kg once daily (max 0.5mg) Weight ≥ 30kg – 0.5mg
Tenofovir disoproxil fumarate (TDF) [230]	≥ 2 years > 12 years or > 35kg	8 mg/kg once daily (maximum 300 mg daily) 300mg once daily
Tenofovir alafenamide (TAF) [230]	≥ 12 years	25 mg once daily

Recommendations (Treatment of HBV in adolescents)

67. **Treatment is recommended for all adolescents (aged 12–17 years) with CHB (including pregnant and non-pregnant adolescent girls of reproductive age) with**

    (a) Evidence of significant fibrosis (≥F2) based on clinical criteria or

    (b) APRI score of >0.5 or

    (c) transient elastography value of >7 kPa or

    (d) evidence of cirrhosis (F4) based on clinical criteria (or an APRI score >1 or transient elastography >12.5 kPa), regardless of HBV DNA or ALT levels.

68. **HBV DNA >2000 IU/mL and an ALT level above the ULN (30 U/L for boys and men and 19 U/L for girls and women). For adolescents, ALT>ULN at least twice in a 6- to 12-month period.**

69. **Presence of coinfections (such as HIV, HDV and HCV), family history of liver cancer or cirrhosis, immune suppression (such as long-term steroids, solid organ or stem cell transplant), comorbidities (such as diabetes, metabolic dysfunction–associated steatotic liver disease and iron overload secondary to treatment for disorders of the blood) or extrahepatic manifestations (such as glomerulonephritis or vasculitis), regardless of APRI score or HBV DNA or ALT level.**

70. **Persistently abnormal ALT levels (in the absence of access to an HBV DNA assay), regardless of APRI score.**

71. **Stopping rule is not considered due to emerging novel drug therapy in the near future.**

Recommendations (Treatment of HBV in children 2-12 years)

72. **Current evidence is insufficient to support extending the same treatment eligibility criteria used for adults and adolescents to include children with HBV 2–11 years old.**
73. **Treatment should be offered on a case-by-case basis to selected children in this age range who are identified to have the following: cirrhosis or advancing liver fibrosis stage ≥F2, persistent hepatitis flare with HBV DNA >2000 IU/mL, comorbidities that increase the risk of progressive liver disease, or a need for immunosuppressive therapy.**
74. **When oral antivirals are used, HBeAg seroconversion should be used as a therapeutic endpoint and treatment should be continued for an additional 12 months of consolidation.**
75. **Children who stop antiviral therapy should be monitored every 3 months for at least 1 year for recurrent viremia, ALT flares, and clinical decompensation.**

Recommendations (on choice of antiviral for adolescents and children)

76. **The nucleos(t)ide analogues that have a high genetic barrier to drug resistance – tenofovir disoproxil fumarate (TDF) or entecavir (ETV) are recommended as preferred regimens.**
77. **Entecavir (ETV) (for children aged two years or older) or tenofovir alafenamide fumarate (TAF) (for those aged 12 years or older) are recommended for children and adolescents with established osteoporosis and/or impaired kidney function.**

8.6. Treatment of hepatitis B in co-infected patients

8.6.1 HBV/HDV co-infected patients

Testing for HDV is recommended in hepatitis B patients at risk of HDV co-infection including those with HIV infection, persons who inject drugs, men who have sex with men, and immigrants from areas of high HDV endemicity (Mongolia, the Republic of Moldova and countries in western and central Africa, central Asia, eastern Europe). HBsAg-positive patients with low or undetectable HBV DNA but high ALT levels should be considered for HDV testing. The recommended screening test is anti- HDV, and if this test result is positive, it should be followed by HDV-RNA testing to diagnose active HDV infection. [231]

Until recently, the only approved treatment of chronic hepatitis D is interferon alfa (IFN-α). Peg-IFN is the drug of choice. Treatment success, defined as undetectable HDV RNA 24 weeks after completing treatment, ranges from 23% to 57%. Late relapses can occur with longer follow-up, leading to very low rates of sustained HDV-RNA un-detectability. [231]

Bulevirtide (BLV, formerly myrcludex B) is a synthetic myristoylated lipopeptide. BLV interferes with the cellular entry of both HDV and HBV. On-treatment data from a phase III trial of BLV monotherapy and real-life studies suggest consideration of BLV as a treatment option for CHD whenever available. [232] According to personal experience by Prof Khin Maung Win, the prevalence of HDV in Myanmar is absent. Currently we will not recommend hepatitis D treatment in this guidance.

8.6.2 HBV/HCV co-infected patients

In patients with HCV-HBV coinfection, the HBV DNA level is often low or undetectable. HCV is usually the main driver of chronic inflammatory activity. Patients should be carefully characterized for the replicative status of both HBV and HCV, Patients with HBV/HCV co-infection are at greater risk of progression to cirrhosis and HCC. In this population, treatment indications for HBV are the same as in mono-infected patients. [233]

HBV/HCV co-infected patients should be first assessed whether they meet HBV treatment criteria and if they do, they should be started on HBV treatment prior to initiating HCV treatment. There is a potential risk of HBV reactivation during DAAs therapy or after clearance of HCV. 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 transplantation, 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 and monitored monthly after stopping NA treatment. [234]

HBsAg-negative and anti-HBc-positive patients are also at risk of HBV reactivation during DAA treatment. Therefore, monitoring of serum HBV DNA and HBsAg levels is recommended in these patients with ALT elevation during the treatment. Antiviral therapy is recommended when HBsAg becomes positive in these patients. [233]

Recommendations (HBV/HCV co-infected patients)

70. **Treatment of HCV with direct-acting antivirals (DAAs) may cause reactivation of HBV.**
71. **Concomitant HBV treatment (NA) should be started in HBsAg-positive patients prior to receiving DAA therapy.**
72. **HBsAg-negative, anti-HBc positive patients undergoing DAA therapy should be monitored and tested for HBV reactivation in case of ALT elevation. NA treatment is recommended when HBsAg becomes positive.**

8.6.3 HBV/HIV co-infected Patients

Persons who are HBV/HIV co-infected are more adversely affected by their HBV infection as compared to the HBV mono-infected population. HBV/HIV co-infected patients face higher rates of conversion 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 should be initiated regardless of stage of liver disease as well as the level of CD4+T lymphocytes. [235]

For a highly active anti-retroviral therapy (HAART) regimen, TDF/TAF + lamivudine, or emtricitabine (FTC) (mixture formulations of TDF + FTC and TAF + FTC are available) are recommended. In addition, HBV related markers, such as HBV DNA, liver biochemical markers, and liver imaging markers, should be monitored during treatment. For HIV and HBV co-infected patients, it is not recommended to select a regimen that contains only one NAs that is effective against HBV (TDF/TAF, lamivudine, ETV, telbivudine, or ADV) to avoid the development of drug resistance to NAs. [236]

It should be noted that for patients with renal insufficiency:

a. If the creatinine clearance rate is <60 mL/min,

- TDF cannot be selected, and the dosage of TDF should be adjusted.

b. If the creatinine clearance rate falls between 30 mL/min and 50 mL/min,

- a regimen containing TAF+ (FTC or lamivudine) can be applied.

However, it is important to note that TAF has not been approved for use in patients with creatinine clearance rates <30 mL/min.

c. When TDF/TAF cannot be used, ETV should be added to the HAART regimen. [2]

For pregnant women co-infected with HIV and HBV, a regimen containing lamivudine (or FTC) + TDF is recommended.

Recommendations (HBV/HIV co-infected patients)

73. **All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count. The ART regimen should include 2 drugs with activity against HBV.**
74. **HIV-HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen.**
75. **When TDF/TAF cannot be used, ETV should be added to the fully suppressive ART regimen.**
76. **TAF may be an option for specific clinical situations in which renal or bone problems are a concern and for adolescents.**
77. **DTG in combination with an NRTI backbone is the preferred first-line drug regimen for adults, adolescents and children living with HIV and initiating ART, including those with HIV and HBV coinfection.**
78. **EFV at low dose (400 mg) is an alternative to DTG for adults and adolescents.**

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