Republic of the Philippines
Department of Health
OFFICE OF THE SECRETARY

October 12, 2020

DEPARTMENT MEMORANDUM
No. 2020 - 0532

FOR : **UNDERSECRETARY AND ASSISTANT SECRETARIES OF FIELD IMPLEMENTATION & COORDINATION TEAM; DIRECTORS OF CENTERS FOR HEALTH DEVELOPMENT; CHIEFS OF DOH MEDICAL CENTERS, HOSPITALS, SANITARIA, AND DOH-DESIGNATED HIV TREATMENT HUBS AND PRIMARY HIV CARE FACILITIES; AND OTHERS CONCERNED**

SUBJECT : **Revised Interim Guidelines on the Management of Patients with Hepatitis B Infection**

I. BACKGROUND

An estimated 10% of all adult Filipino population are chronically infected with the Hepatitis B virus (HBV). In the Philippines, chronic Hepatitis B infection (CHB) is the leading cause of cirrhosis and hepatocellular carcinoma (HCC), which develop in up to 30% of patients with CHB. Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally, with HCC accounting for about 90% of all primary liver cancers.

The need to eliminate viral hepatitis, including Hepatitis B, as a public health threat was emphasized in the 2014 World Health Assembly and its inclusion in the Sustainable Development Goals (SDG) under SDG target 3.3.

As part of the country's commitment to the World Health Assembly (WHA) declaration, the DOH issued DM No. 2019-0062 on the Integration of Chronic Hepatitis B Management in Selected Health Facilities in the National Capital Region and Region III (A Demonstration Project). Also, annexed in this issuance is the interim guidelines for the management of patients diagnosed with Chronic Hepatitis B. These guidelines were developed in collaboration with the World Health Organization (WHO) and the Hepatology Society of the Philippines (HSP). Also, the Hepatitis B services was further expanded outside the demonstration sites through DM No. 2019-0465. This mandated all DOH medical centers, hospitals, sanitaria, treatment and rehabilitation centers, and HIV treatment hubs to include the management of Hepatitis B and provide free antiviral therapy to all treatment-eligible patients.

As such, the interim guidelines on the management of Hepatitis B patients is revised based from the implementation experience of the demonstration project.

II. OBJECTIVE

To provide all physicians with evidence-based recommendations in the management and treatment of patients with Hepatitis B infection in the Philippines. consult

III. GENERAL GUIDELINES

A. All clients and/or patients accessing services through the healthcare provider network, especially those who are 40 years old and above shall be offered free HBsAg testing service.
B. For clients and/or patients screened to be positive for Hepatitis B, contact tracing shall be initiated. HBsAg testing service shall likewise be offered for the identified contacts (i.e. sexual partners, children and other family members and close household contacts).
C. All Hepatitis B infected persons should be properly assessed for treatment eligibility.
D. Where resources are limited, less costly but reliable alternative diagnostic tests/indices may be utilized to guide the clinician in the decision to initiate treatment, and in monitoring response to treatment and disease progression.
E. Healthcare providers in primary care must be trained to manage Hepatitis B infected persons to ensure early assessment and timely initiation of treatment, especially in resource-limited settings. Opportunities for collaboration with specialists involved in the care of Chronic Hepatitis B patients should be made available.
F. Treatment-eligible chronic Hepatitis B patients should have access to effective and safe antiviral therapy.
G. Chronic Hepatitis B patients started on treatment shall be closely monitored for adherence, response to treatment, adverse effects, drug resistance, treatment failure, and liver disease progression.

IV. SPECIFIC GUIDELINES

A. Diagnosis and Initial Evaluation of Chronic Hepatitis B

1. In those above 1 year of age, Hepatitis B infection shall be diagnosed using a serologic assay for the Hepatitis B Surface Antigen (HBsAg) either through a Rapid Diagnostic Test, or in the form of a laboratory-based immunoassay.
2. In the absence of recent history of possible exposure in the past 6 months to Hepatitis B, a single positive serological assay for detection of HBsAg, warrants the consideration of Chronic Hepatitis B.
3. Comprehensive patient education and counselling should be provided to all patients who are diagnosed with Hepatitis B infection. See Table 1.
4. Following a positive HBsAg test result, the presence of cirrhosis must be assessed based on clinical parameters (i.e., physical exam and laboratory tests) or when available, based on liver biopsy findings or non-invasive testing for fibrosis (NIT).
5. In resource-limited settings, the aspartate aminotransferase/platelet ratio index (APRI) is the preferred NIT to assess for the presence of cirrhosis (APRI score >2 in adults). Other proprietary NITs may be used where they are available, and cost is not a major constraint. Table 2 shows the cut-off values of these non-invasive tests
6. Quantitative HBV DNA levels and HBeAg status, when available, should be taken at baseline to guide decisions on initiating treatment.

7. For those with risk factors, testing for Hepatitis C Virus (HCV) (Table 3 in Annex) and Human Immunodeficiency Virus (HIV) (See Table 4 in Annex) is encouraged at baseline. HCV and HIV screening are required for all patients who are to start Hepatitis B antiviral therapy.
8. For those with risk factors for hepatocellular carcinoma (HCC) (Table 5), screening and surveillance for HCC (e.g. AFP and ultrasound) should be done every 6 months.
9. For clients and/or patients who were previously screened as HBsAg positive more than 6 months ago, a repeat RDT is recommended. For those previously screened as HBsAg positive less than 6 months ago, assess presence of cirrhosis and proceed through the algorithm in Annex A.

B. Criteria for initiation of antiviral therapy in patients with CHB (Figure 1)

1. Only positive HBsAg tests from DOH-accredited laboratories or OFW clinics shall be considered for diagnosis. All patients referred to the treatment facility will be tested with an FDA-approved Rapid Diagnostic Test for HBsAg.
2. Patients diagnosed with Chronic Hepatitis B shall be evaluated for cirrhosis at baseline entry. Cirrhosis can be diagnosed through the presence of any the following:
    a. On history or physical exam: presence of jaundice, coagulopathy, ascites, variceal hemorrhage, hepatic encephalopathy, hepatomegaly, splenomegaly, pruritus, fatigue, spider angiomata, and palmar erythema, or;
    b. APRI score of > 2 or other proprietary non-invasive tests for fibrosis (see Table 2 and Glossary of Terms in Annex B), or;
    c. Imaging tests indicating cirrhosis (ultrasound, CT or MRI), when available, or
    d. Liver biopsy showing cirrhosis, when available.
3. Adults, adolescents and children with CHB and clinical evidence of compensated or decompensated cirrhosis shall be prioritized and given antiviral therapy, regardless of ALT levels, HBeAg status or HBV DNA levels.
4. Adults with CHB who are **not cirrhotic**, but have **persistently abnormal ALT levels**, together with evidence of significant HBV replication, should be treated with antiviral therapy. The following are the **recommended cut-offs for significant HBV replication based on HBeAg status:**

Cut-off Values for Significant HBV Replication Based on HBeAg Status

HBeAg Status	HBV DNA Value
Positive	≥ 20,000 IU/mL
Negative	≥ 2,000 IU/mL

5. **When HBeAg testing is not available:** treatment may be considered for those with persistently abnormal ALT levels and HBV DNA ≥ 20,000 IU/mL.
6. **When HBV DNA testing is not available:** Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status, but other common causes of consistently raised ALT such as nonalcoholic fatty liver disease (NAFLD), chronic alcohol abuse, Hepatitis C infection **must be excluded first. Specialist referral is recommended in patients starting antiviral therapy based on this indication.**
7. Continued monitoring is necessary in all persons with CHB. Special attention should be given to those **who do not currently meet the recommended criteria for treatment**

currently but may require antiviral therapy in the future to prevent progressive liver disease.

C. Initiating Treatment for Treatment eligible patients

1. For all patients who satisfy criteria for initiation of antiviral therapy, only nucleos(t)ide analogues (NAs) that have a high barrier to drug resistance are recommended for antiviral therapy for CHB. These include tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir (ETV).
   Recommended NAs for treatment-naïve patients in whom antiviral therapy is indicated:
   a. All adults including pregnant women – TDF, TAF, and ETV
   b. Adolescents and children aged 12 years or older – TDF and ETV
   c. Children aged 2-11 – ETV
   For patients who are treatment-experienced (treated with NAs in the past), the recommended NA is TDF or TAF.
2. The dose of antiviral therapy for both adults and children and the dose adjustment for adult patients with renal impairment, are outlined in Tables 6, 7 and 8. Children who require antiviral treatment should be comanaged with a pediatric gastroenterologist or hepatologist.
3. Avoidance of TDF and use of ETV or TAF instead, or dose reduction of TDF (guided by Table 8) is advised in those at risk of renal and bone disease (Table 9).
4. The use of TDF is not recommended in any child with renal impairment.
5. Nucleos(t)ide analogues with a low barrier to resistance (lamivudine, adefovir telbivudine or clevudine) are associated with high rates of drug resistance and should not be used.
6. Recommended duration of antiviral therapy and criteria for discontinuation of NAs.
   a. Persons with compensated or decompensated cirrhosis-should NOT discontinue treatment and need nucleos(t)ide analogues (NAs) lifelong.
   b. In all other patients, lifelong therapy is likewise recommended because of the high rates of virologic breakthrough after discontinuation
   c. Discontinuation of antiviral therapy may be considered ***exceptionally ONLY*** in those who satisfy ALL of the following criteria:
      i. **No** clinical or diagnostic evidence of cirrhosis **and,**
      ii. Persistently normal ALT level and persistently undetectable HBV DNA level (when testing is feasible). Persistently normal ALT level and persistently undetectable DNA level is defined as normal ALT levels and undetectable DNA levels respectively at 3 determinations taken at 6-month intervals over 2 years **and,**
      iii. Can be followed up carefully long term for reactivation **and,**
      iv. In persons initially HBeAg-positive, HBeAg loss and seroconversion to anti-HBe **and** after completion of at least one additional year of treatment after seroconversion.
   d. Discontinuation of antiviral therapy may also be considered in cases where the patient becomes HBsAg negative, following either antiHBs seroconversion or at least an additional 12 months of treatment following HBsAg loss.
   e. Monitoring in those who discontinue antiviral therapy
      i. Discontinuation of antiviral therapy will require close monitoring for reactivation and should be done under the supervision of a specialist (gastroenterologist/hepatologist for adults and pediatric gastroenterologist/hepatologist for children).

ii. ALT and HBV DNA (when HBV DNA testing is available) should be monitored monthly for the first 3 months then every 3 months for 1 year, then every 6 months thereafter.

f. Resumption of prior antiviral therapy should be considered if there are signs of reactivation which include any of the following:
   i. HBsAg or HBeAg becomes positive from negative
   ii. Increasing ALT levels
   iii. HBV DNA becomes detectable again (when HBV DNA testing is available)

D. Monitoring of patients diagnosed with Chronic Hepatitis B

1.Monitoring during antiviral therapy

a. Persons initiated on antiviral therapy should be seen every 3 months. Adherence and signs of treatment failure should be ***strictly*** monitored regularly and at each visit. More frequent monitoring, and specialist referral shall be done for patients with decompensated cirrhosis.

b. In persons on antiviral therapy the following should be monitored at least annually:
   i. AST, ALT, and platelet count
   ii. APRI score (calculated from AST and platelet count)
   iii. HBsAg
   iv. HBeAg, anti-HBe (for those who are HBeAg-positive and when available) and HBV DNA levels (when available)
   v. Signs of treatment failure (i.e., rising ALT or AST levels, rising HBV DNA levels (when available), or development of clinical signs and symptoms of decompensation (i.e., jaundice, ascites, encephalopathy, weight loss)

c. Renal function should be monitored annually. It should be monitored every 6 months in patients at high risk of renal toxicity, including those with CrCL < 50 ml/min. Monitoring of renal function may be through the following:
   i. Serum creatinine and estimated GFR trend (preferred)
   ii. Monitoring for proteinuria and glucosuria (urine dipstick)
   iii. Serum Phosphate

d. Growth monitoring, as well as specialist follow-up by a pediatric gastroenterologist or a pediatrician in children (above 12 years of age) on tenofovir disoproxil fumarate.

2.Monitoring of those not currently on antiviral therapy

a. In persons who do not yet meet the criteria for antiviral therapy, the following should be monitored at least annually:
   i. ALT, AST and platelet count
   ii. APRI score (calculated from AST and platelet count)
   iii. HBsAg
   iv. HBeAg, anti-HBe (for those who are HBeAg-positive and when available) and HBV DNA levels (when available)
   v. Noninvasive tests for fibrosis (eg Liver Elastography or proprietary blood tests for fibrosis) to assess for cirrhosis, in those without cirrhosis at baseline (when available).

b. More frequent monitoring shall be done every 6 months in:
   i. Persons who have intermittently abnormal ALT levels

ii. HBeAg positive persons who have fluctuating HBV DNA levels between 2000 IU/mL and 20,000 IU/mL (when HBV DNA testing is available)
iii. HIV and HCV co-infected persons

c. Screening for Hepatocellular Cancer in high risk HBsAg positive individuals.
   i. Liver ultrasound and AFP testing every 6 months is recommended for those who have risk factor(s) for HCC (Table 5).

E. Special populations

1.HBV-HCV Co-infection
   a. Persons with HBV-HCV co-infection have increased risk for hepatocellular carcinoma.
   b. Screening for HBV is recommended for all patients with CHC.
   c. Persons with HBV-HCV co-infection should be assessed for eligibility for HBV treatment based on Section IV-B.
   d. If they do not satisfy current criteria for initiating antiviral therapy for HBV, they should be given antiviral therapy for HBV for the duration of the antiviral therapy for CHC and for 6 months after the end of treatment. The antiviral medication of choice is Tenofovir Disoproxil Fumarate 300 mg a day. Co-administration of Tenofovir Disoproxil Fumarate with Velpatasvir requires close monitoring for adverse effects related to Tenofovir Disoproxil Fumarate.

2.HIV-HBV Coinfection
   a. All HIV-HBV coinfected individuals must be started on appropriate ART regimens regardless of CD4 count.
   b. HIV-HBV-coinfected persons should be simultaneously treated for both HIV and HBV infection, and receive antiretroviral therapy (ART) that is active against both viruses to reduce the risk of resistance. A tenofovir-based regimen is the recommended therapy, which should include tenofovir/lamivudine, or tenofovir/ emtricitabine (provided there is no contraindication to tenofovir), together with a third drug efavirenz, to prevent the selection of HIV-resistant mutants.

3.Pregnant women
   a. All pregnant women should be screened for Hepatitis B at the first prenatal visit.
   b. Indications to treat Chronic Hepatitis B in adults as already outlined above also apply to pregnant women.
   c. To prevent mother-to-child HBV transmission, the first dose of hepatitis B vaccine should be given to the infant within the first 12-24 hours of life followed by 2-3 doses of the vaccine as prescribed by the DOH EPI schedule.
   d. When it is available, for babies born to HBsAg+ mothers, Hepatitis B Immunoglobulin 0.5 ml should be administered IM as soon as possible after birth (within 12-24 hours) at the same time but at a different site as the birth dose of the Hepatitis B vaccine.
   e. Tenofovir disoproxil fumarate (TDF) is the preferred antiviral if treatment is deemed necessary during pregnancy.
   f. Pregnant women considered for antiviral treatment should be co-managed with specialists (hepatologist or gastroenterologist or OB-Infectious Disease specialists).
   g. For mothers who do not satisfy criteria for antiviral therapy as outlined in Section IV-B, antivirals may be indicated to decrease the risk of neonatal transmission of Hepatitis

B when maternal HBV DNA > 200,000 IU/mL. Short-term treatment with antivirals starting from 28 to 32 weeks of gestation is recommended using TDF for decreasing transmission.

h. For mothers who start TDF in the third trimester, nucleos(t)ide analogues can be stopped at birth, when breastfeeding starts, or 1-3 months after delivery, if there is no contraindication to stopping nucleos(t)ide analogues. Due to the uncertainty in long-term safety for the infants, the risk and benefits of breast-feeding and possible infant exposure to tenofovir must be discussed by the health provider with the mother.
i. Maternal liver disease status may be an indication to continue antivirals after delivery.
j. Pregnant women with Chronic Hepatitis B who remain untreated or discontinue antiviral treatment during pregnancy or early after delivery for any reason, need to be monitored closely for hepatitis flares especially after delivery.
k. Breastfeeding is not contraindicated in mothers who are Hepatitis B positive. TDF may be minimally excreted in breastmilk and are unlikely to cause significant toxicity. The unknown long-term risk of infant exposure to tenofovir must be made known to mothers. If the option of stopping antivirals after birth is taken, close monitoring for flares through ALT monitoring every 1-3 months must be done.
l. Post-vaccination testing with HBsAg and antiHBs of infants of HBsAg-positive mothers is recommended 1-2 months after the last dose of the Hepatitis B Vaccine.

4.Patients who are being enrolled in HIV Pre-Exposure Prophylaxis (PReP) Program

a. All persons starting PReP should be screened for Hepatitis B with HBsAg and anti-HBs.
b. If they are negative for HBsAg and anti-HBs, vaccination for HBV is recommended.
c. Indications to treat Chronic Hepatitis B in adults as already outlined in Section IV.B. also apply to CHB patients starting PReP.
d. If CHB patients starting PReP satisfy criteria for antiviral therapy as outlined in Section IV.B., they should be given antiviral therapy containing TDF and undergo monitoring as outlined in Section IV.D.1
e. For CHB patients who do not satisfy criteria for antiviral therapy as outlined in Section VI.B. and are started on PReP. A TDF-containing regimen must be used for PReP. These patients should be closely followed for adherence.
f. If a CHB patient on PReP decides to stop PReP, the following should be considered:
    i. If they had an indication for antiviral therapy for CHB as outlined in Section IV-B, they need to continue antiviral therapy for CHB with TDF and undergo monitoring as outlined in Section IV.D.1.
    ii. If they did not have an indication for antiviral therapy as outlined in Section IV-B, they need to be monitored closely for hepatitis flares especially after discontinuation of PReP. This is done through ALT monitoring every 1-3 months.

5.CHB Patient who are already on antiviral therapy.

a. These patients should be evaluated according to Section IV.A.
b. HBV DNA testing within 6 months of clinic visit is mandatory in these patients.
c. If HBV DNA is not detectable, the patient can be continued on TDF or switched to TAF if they were already of TDF or switched to TDF or TAF if they were on a NA other than TDF or TAF.
d. These patients should then undergo monitoring as outlined in Section IV.D.1.
e. If HBV DNA is detectable, referral to a specialist is recommended for co-management.

6.Patients with decompensated cirrhosis

a. Specialist (Hepatologist or Gastroenterologist) referral should be done.
b. For patients with signs of hepatic decompensation (encephalopathy, jaundice, coagulopathy), treatment should be initiated promptly with entecavir or TDF.

7.Patients at risk for or with renal impairment

a. For patients at risk for kidney disease, TAF or ETV are the preferred antivirals. (See Appendix Tables 8 and 9)
b. All NAs require dose adjustment and should be used with caution in persons with renal impairment or in renal transplant patients. They should be co-managed with a specialist in Hepatitis B and in kidney diseases
c. Unexpected deterioration of renal function during antiviral therapy may necessitate a change of treatment or further dose adjustment.
d. All HBsAg-positive persons undergoing renal transplantation should receive prophylactic NA therapy to prevent HBV reactivation.

8.Children

a. CHB is generally benign and asymptomatic in children (<19 years old) as they are generally in the immune tolerant phase of the infection.
b. For children with hepatitis B who are assessed to require treatment, refer for specialist consult
c. Antiviral therapy generally requires long-term treatment and there are concerns regarding long-term safety and drug resistance. Hence, a conservative approach is generally indicated unless the child presents with cirrhosis or evidence of severe ongoing liver inflammation on liver biopsy.
d. Criteria for the initiation of antiviral therapy for HBV in childhood follow the criteria used for adults (Refer to Section IV.B.)
    i. HBeAg positive children with ALT 1-2 times of the upper limit of the normal value (ULN) with HBV DNA> 20,000 IU/ml AND HBeAg negative children with ALT 1-2x of the ULN with HBV DNA > 2,000 IU/mL should have other liver diseases ruled out and preferably have liver biopsy to document moderate to severe necroinflammation prior to starting antivirals.
    ii. Non-invasive tests for fibrosis (i.e., APRI score, commercial biomarker tests, transient elastography) are not recommended for use in children. Currently, the utility of NIT's in the pediatric population, while promising, remain largely investigational.

F. Specialist care

1.Specialist care is warranted for CHB patients with the following conditions:

a. Decompensated cirrhosis
b. Uncertain progression of disease or with signs of treatment failure
c. Indications for treatment are uncertain
d. Family history of hepatocellular carcinoma
e. HIV or HCV co-infection
f. Renal impairment, on dialysis, or renal transplant patient
g. Current antiviral therapy for CHB with detectable HBV DNA
h. Pregnancy
i. Pediatric patients

j. Patients who will receive chemotherapy or immunosuppressive therapy including steroids
k. Hepatitis B-infected health care workers who need evaluation and clearance prior to performing Exposure Prone Procedures.

G. Programmatic Considerations

The Disease Prevention and Control Bureau shall augment resources of LGUs and DOH Hospitals on diagnosis and treatment commodities. Monitoring and evaluation shall be conducted by the National AIDS and STI Prevention and Control Program (NASPCP) in collaboration with the Epidemiology Bureau to ensure seamless implementation of this guideline. LGUs and hospitals should be encouraged to tap the Medical Assistance for Indigent Program should indigent patients need laboratory tests.

By Authority of the Secretary of Health

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Undersecretary of Health
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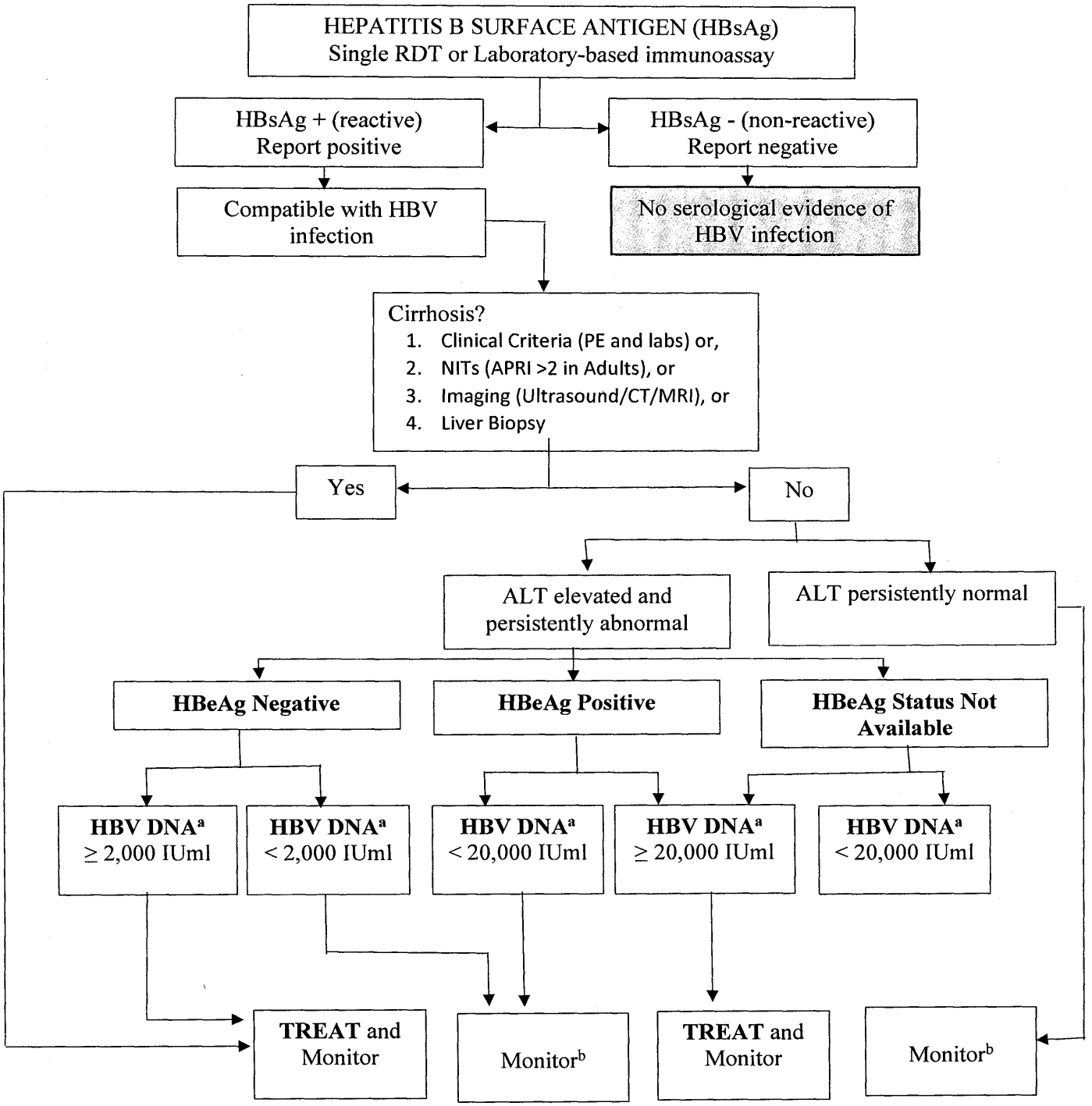
ANNEX A. Algorithm on the diagnosis, treatment, and monitoring of HBV infection



[a] When HBV DNA testing is not available: Treatment may be considered based on persistently abnormal ALT levels alone, regardless of HBeAg status, but other common causes of consistently raised ALT such as nonalcoholic fatty liver disease (NAFLD), chronic alcohol abuse, HCV infection must be excluded first.

[b] Monitor for: (1) HCC every 6 months (especially in those with cirrhosis and family history; (2) Monitor for liver disease progression and treatment response in all; (3) Toxicity monitoring in persons with treatment; (4) signs of treatment failure for those on antiviral treatment

ANNEX B. Glossary of Terms

A. Natural History of HBV Infection

1. Chronic Hepatitis B infection	Persistence of Hepatitis B surface antigen (HBsAg) for six months or more after acute infection with HBV. **For the purpose of this guideline, in the absence of a recent history of possible exposure in the past 6 months to Hepatitis B, a single positive serological assay for detection of HBsAg warrants the consideration of Chronic Hepatitis B infection.**
2. HBsAg loss	Two (2) consecutive HBsAg levels <0.05 IU/mL at least 1 year apart
3. HBeAg seroconversion	Loss of HBeAg and development of anti-HBe
4. HBsAg seroconversion	Loss of HBsAg and development of anti-HBs
5. Cirrhosis	An advanced stage of liver disease characterized by extensive hepatic fibrosis, nodularity of the liver, alteration of liver architecture and disrupted hepatic circulation
6. Decompensated cirrhosis	Clinical complications of cirrhosis become manifest, including jaundice, ascites, spontaneous bacterial peritonitis, esophageal varices and bleeding, hepatic encephalopathy, sepsis and renal failure
7. Hepatocellular carcinoma (HCC)	Primary cancer of the liver arising in hepatocytes

B. Serological Markers for HBV

1. Hepatitis B surface antigen (HBsAg)	HBV envelope protein and excess coat particles detectable in the blood in acute and chronic hepatitis B infection
2. Hepatitis B e-antigen (HBeAg)	Viral protein found in the high replicative phase of hepatitis B; marker of high levels of replication with wild-type virus. It appears early in the course of Hepatitis B infection.
3. Hepatitis B surface antibody (anti-HBs)	Antibody to HBsAg; develops in response to HBV vaccination and during recovery from acute Hepatitis B, denoting past infection and immunity.

4. Anti-HBe	Antibody to HBeAg. Detected in persons with lower levels of HBV replication but also in HBeAg-negative disease (i.e. HBV that does not express HBeAg).

C. Tests for the Assessment and Monitoring of Hepatitis B Infection

1. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)	Intracellular enzymes which, as they are released after cell injury or death, reflect liver cell injury
2. HBV deoxyribonucleic acid (DNA)	HBV viral genomes that can be detected and quantified in serum. HBV DNA correlates with levels of circulating viral particles. HBV DNA is measured as IU/mL or copies/mL (1 IU/mL ~ 5 copies/mL; values given as copies/mL can be converted to IU/mL by dividing by a factor of 5, i.e. 10000 copies/mL = 2000 IU/mL)
3. AFP (alpha-fetoprotein)	A host cellular protein. High levels can occur in persons with hepatocellular carcinoma (HCC).
4. Persistently abnormal ALT level	In adults: Two ALT determinations above the upper limit of normal at least 3 months apart. In children: Three ALT determinations greater than twice the upper limit of normal (to be monitored every 3 months for at least 6 months)

D. Assessment of Liver Fibrosis by Non-Invasive Tests (NIT)

1. Aspartate aminotransferase (AST)-to-platelet ratio index (APRI score)	Simple index for estimating hepatic fibrosis based on a formula derived from AST and platelet concentrations. $$APRI\ Score = \left(\frac{AST\ Level/ULN\ *}{\text{Platelet Count } (10^9/\text{L})}\right) \times 100$$ APRI Score can also be derived through the following electronic tools: 1) Online calculator: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri (see Figure 2 for the QR Code) 2) Mobile App: Calculate by QxMD, downloadable via iTunes App Store and Google Play Store (see Figure 3 for the QR Code) **ULN-Upper Limit of Normal*

2. Commercial biomarker test (LiverFast®)	Panel of tests that uses the results of six blood markers to estimate hepatic fibrosis
3. Transient elastography	A technique to measure liver stiffness (as a surrogate for fibrosis) and is based on the propagation of a shear wave through the liver