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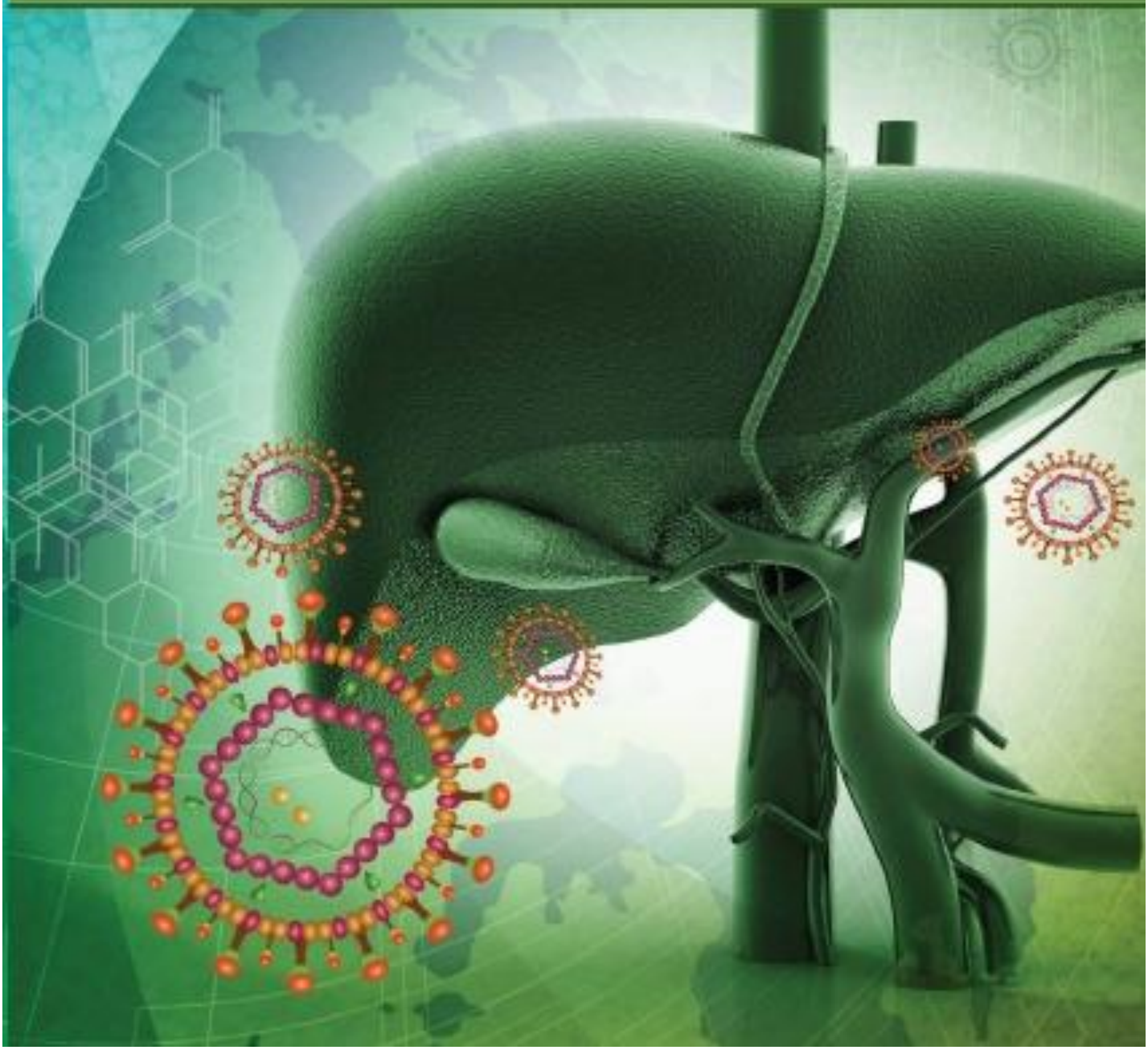
MANAGEMENT of PATIENTS with HEPATITIS B in SPECIAL POPULATIONS



2020 Update to the Consensus Statements on the Diagnosis and Treatment of Hepatitis B: Special Populations

Hepatology Society of the Philippines (HSP) Hepatitis B Virus (HBV) Consensus Core Group

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ABBREVIATIONS

ADV	adefovir
AASLD	American Association for the Study of Liver Diseases
ALF	acute liver failure
Anti-HBc	hepatitis B core antibody
Anti-HBe	hepatitis B e antibody
anti-HBs	hepatitis B surface antibody
APASL	Asian Pacific Association for the Study of the Liver
ART	antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CKD	chronic kidney disease
CLV	clevudine
CTP	Child-Turcotte-Pugh
DAA	direct-acting antiviral
DNA	deoxyribonucleic acid
eGFR	estimated glomerular filtration rate
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
ETV	entecavir
HAART	highly active antiretroviral therapy
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBIG	hepatitis B immune globulin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HIV	human immunodeficiency virus
IFN	interferon
IgG	immunoglobulin G
IgM	immunoglobulin M
LAM	lamivudine
Ldt	Telbivudine
MELD	Model for end-stage liver disease
MTCT	mother-to-child transmission
NA	nucleos(t)ide analogue
NK	natural killer
Peg-IFN	pegylated interferon
RCT	randomized controlled trial
SAE	serious adverse event
SVR	sustained viral response
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
ULN	upper limit of normal

FOREWORD

In 2014, the Hepatology Society of the Philippines published the 2014 Consensus Statements on the Diagnosis and Treatment of Hepatitis B. However, the Society recognizes that certain population subgroups of patients with hepatitis B should be given special care due to conditions that may affect viral kinetics, immune response to infection, the pharmacokinetics and pharmacodynamics of pharmacotherapy or increase the risk of complications of hepatitis B. Hence, this Update was developed to provide additional guidance to clinicians in the management of hepatitis B infection in these special populations.

METHODOLOGY

This update was developed through the initiative of the Hepatology Society of the Philippines, which created a consensus core group composed of local experts in hepatology. The members of the core group performed a literature search for all available literature on the treatment of hepatitis B, with focus on the appropriate treatment according to the various identified special populations, namely those with acute hepatitis B, those with decompensated cirrhosis, liver transplant recipients, non-liver solid organ transplant recipients, those receiving immunosuppressive therapy, those with chronic kidney disease, pregnant patients and children with hepatitis B. Efficacy and safety data of treatments were extracted and evaluated and recommendations were developed for treatments with net benefit that are currently available in the Philippines. Recommendations were discussed and revised until consensus within the core group was achieved. Recommendations were rated according to an adaptation of GRADE (Table 1).

Table 1. Grading evidence and recommendations (adapted from GRADE system)

QUALITY OF EVIDENCE	
HigH (I)	Randomized, controlled trials
Moderate (II)	II-1 Controlled trials without randomization
	II-2 Cohort or case-control analytical studies
	II-3 Multiple time series, dramatic uncontrolled experiments
Low (III)	Opinions of respected authorities, descriptive epidemiology
LEVEL OF RECOMMENDATION	
Strong recommendation	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted Recommendation is made with less certainty: higher cost or resource consumption

PATIENTS WITH ACUTE HEPATITIS B

Recommendations

- Patients with severe acute hepatitis B infection should be treated with NAs*(Moderate quality of evidence; strong recommendation)*
- Patients with fulminant hepatitis B must be evaluated for liver transplantation (*High quality of evidence; strong recommendation)*

The incidence of acute hepatitis B infection has declined dramatically in nearly all countries since 1992 when the World Health Organization recommended that the hepatitis B vaccine should be included in all infant immunization programs.[1] Moreover, in areas of the world with low prevalence, acute infection most commonly occurs in nonvaccinated teenagers or adults who have sexual interactions or share items of personal hygiene or objects to administer illicit drugs with a chronically infected person. In the vast majority of these cases, the patient is unaware their partner in these activities has chronic hepatitis B. Patients can also acquire HBV during medical procedures, either through breaks in universal precautions from health care workers with chronic hepatitis B or from contaminated medical equipment. Although serologic testing has been utilized to screen blood products for the presence of HBV for several decades, the risk of developing acute HBV following a blood transfusion is currently estimated to occur in 1:63,000 units transfused.[2]

HBV is transmitted by percutaneous or mucosal exposure through infectious blood or body fluids. Although HBV has been detected in many body fluids, only blood, saliva and semen appear to contain sufficient levels of virus to be infectious.[3]

The course of acute hepatitis B is divided into the incubation period andpreicteric, icteric and convalescence phases over a course of 75 days (range 40–140 days). The onset of hepatitis B is typically insidious, with nonspecific symptoms of malaise, poor appetite, nausea and pain in the right upper quadrant of the abdomen. With the onset of the icteric phase, symptoms of fatigue and anorexia typically worsen. Jaundice can last from a few days to several months (average of 2–3 weeks).[4] Itching and pale stools may occur.

The convalescent phase of hepatitis B begins with the resolution of jaundice. Fatigue may persist for many months into convalescence. The physical signs of typical acute hepatitis B are not prominent. Variable degrees of jaundice are present. The only other common physical finding in a patient with acute hepatitis B is mild and slightly tender hepatomegaly. Mild enlargement of the spleen or lymph nodes are uncommon.[4]

Detection of HBsAg along with anti-HBc IgM is the serologic hallmark of acute HBV infection.[5]HBsAg appears in serum during the incubation phase, approximately 2 to 6 weeks before the onset of symptoms.[6,7]Highly sensitive molecular virologic assays can detect HBV DNA in the serum during the incubation phase, approximately 10 to 20 days before the appearance of HBsAg.[8] Anti-HBcappears at the onset of symptoms or liver test abnormalities.[6,7] Anti-HBc IgM remains detectable for approximately 6 months following the acute exposure. Thereafter, IgM antibody is lost. IgG anti-HBc remains detectable lifelong.

Patients with acute hepatitis B infection should be considered infectious and capable of passing HBV to other persons at risk until they develop anti-HBs. Patients with complete resolution of HBV infection have both anti-HBc and anti-HBs. Over many decades following

acute HBV infection, the level of anti-HBs may decline to levels that are undetectable with current assays. These patients remain anti-HBc positive as their only marker of previous exposure to HBV. During the resolution phase,HBeAg is lost prior to HBsAg and anti-HBeappears before anti-HBs.[6,7]

About 1% of patients with acute hepatitis B may develop ALF. The risk of developing ALF with an acute hepatitis B is increased in older individuals and in patients with chronic hepatitis C and hepatitis D.[9-11] Survival without liver transplantation occurs in only about 25% of patients with ALF secondary to acute hepatitis B. It is therefore imperative that patients with severe acute hepatitis B be transferred to a liver transplant center for evaluation, management, and consideration for liver transplantation if indicated and appropriate.

More than 95% of adults with acute hepatitis B do not require specific treatment because they will fully recover spontaneously. Antiviral treatment is indicated for only those with acute hepatitis B who have ALF or who have a protracted or severe course, as indicated bytotal bilirubin >3 mg/dL (or direct bilirubin >1.5 mg/dL), international normalized ratio >1.5, encephalopathy or ascites. ETV and tenofovir are the preferred antiviral drugs. Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. Peg-IFN is contraindicated. For those diagnosed with chronic hepatitis B by failing to clear HBsAg after 6 to 12 months, ongoing management should follow the guidelines for chronic hepatitis B.[12-14]

In a study among patients with severe acute hepatitis B patients,LAM caused a greater decrease in HBV DNA levels but did not cause significantly greater biochemical and clinical improvement as compared to placebo.[14]However, in another RCTthat included severe acute hepatitis patients,LAMshowedstatistically significant improvements in mortality and incidence of ALF compared with placebo.[15]

Case reports and case series have reported clinical improvement with the following NAs: tenofovir monotherapy; include tenofovir withLAM; ETV; ADVwithLAM; and LdT.[16-20]

Establishing a diagnosis of acute hepatitis B is important, as the majority of adult patients presenting as acute hepatitis B have reactivation of chronic hepatitis B infection. A definite history of exposure, positive HBeAg and IgM anti-HBc with low HBV DNA levels and liver biopsy in doubtful cases can help to establish the diagnosis of acute hepatitis B and exclude the diagnosis of HBV reactivation. When the distinction between true severe acute hepatitis B and spontaneous reactivation of chronic HBV infection is difficult, NA treatment should be administered.[21]

PATIENTS WITH DECOMPENSATED HEPATITIS B-RELATED CIRRHOSIS

Recommendations

- HBsAg-positive adults with decompensated cirrhosis should be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status or ALT level to decrease the risk of worsening liver-related complications *(High quality of evidence; strong recommendation)*
- ETV and tenofovir are recommended as first-line agents *(High quality of evidence; strong recommendation)*
- Patients with decompensated Hepatitis-B related cirrhosis must be evaluated for liver transplantation *(High quality of evidence; strong recommendation)*
- Surveillance for HCC should continue despite the use of antiviral agents*(Moderate quality of evidence; strong recommendation)*

In general, a CTPscore≥7isconsideredashepatic decompensation.[22] Hepatic decompensation among chronic HBV carriers is associated with high mortality and has a reported 5-year survival rate of 14–35%, which is significantly lower than the rate of 80–85% among those with compensated cirrhosis.[23-26]However, anti-HBV therapy significantly modifies the natural history of decompensated cirrhosis, improves liver function and increases survival. Early intervention with potent antivirals improves virologic and serologic responses in these patients and maintained virologic response in patients under antiviral therapy leads to better long-term liver transplant-free survivalcompared to non-responders or untreated patients.[27]

ETV and tenofovir are the recommended drugs.[12,13,21] The licensed entecavir dose for patients with decompensated cirrhosis is increased to 1 mg once daily (instead of 0.5 mg for patients with compensated liver disease). However, antiviral therapy may not be sufficient to rescue all decompensated patients and they should be considered for liver transplantation at the same time.[21]The establishment of liver transplant programsface several challenges in developing countries[28], which should be considered when deciding on the best treatment approach for patients with decompensated liver disease.

The use ofLAM, ADV, and ETV was associated with a decrease in CTP scores of >2 points and normalization of serum ALT. Transplant-free survival varied between 78% and 87% at 1 year with the various agents. Other beneficial effects with the oral NAs include removal from the liver transplantation waiting list in 6% of patients receiving ADV, 21% receivingLAM and 11% treated with ETV. Development of HCC at 1 year was reported in 3%, 7% and 6% of patients receivingLAM, ADV, and ETV, respectively.[29] However, in another study using ETV, treatment did not entirely eliminate the risk of developing HCC in patients with cirrhosis. Thus, strict surveillance for HCC is warranted for patients with liver cirrhosis.[30]

TAF has not been studied in patients with decompensated cirrhosis, thus limiting recommendations to use this drug in these patients. However, TAF or ETV should be considered in patients with decompensated cirrhosis who have renal dysfunction and/or bone disease. The doses of all NAs need to be adjusted in patients with low creatinine clearance (≤50 ml/min). Patients should be monitored closely for the development of adverse effects of antiviral therapy, such as renal insufficiency and lactic acidosis.[12,13,21]

Renal insufficiency is defined as an increase of serum creatinine by ≥0.5 mg/dL over baseline. It occurred in 9% (5–17%) of patients treated with ADV and 10% (6–17%) of patients treated with ETV. In contrast, none of the studies usingLAM reported any instances of renal insufficiency. In a prospective RCT of LdT andLAM, there was a greater improvement in the calculated eGFR from baseline among patients treated with LdT as compared toLAM.[31] Renal insufficiency was also reported in 10% of patients treated with ETV in a systematic review.[29] Tenofovir was also associated with renal insufficiency in 9% in one study and the need for dose reductions in three additional patients.[32]In another study, the incidence of renal insufficiency at 1 year was similar between ETV and TDF.[32]In another study among HBV-related compensated or decompensated cirrhosis, there was no significant difference concerning impaired renal function between ETV and TDF for 2 years.[33]Because of treatment-related renal safety concerns, renal function should be monitored regularly, especially high-risk patients such as those with baseline low eGFR, diabetes mellitus, and those receiving concomitant nephrotoxic drugs.[33]

Lactic acidosis has been reported to develop with some NAs, particularly ETV, in treated patients with advanced decompensated cirrhosis (MELD score >20) – although in one analysis, lactic acidosis and mitochondrial toxicity were reported in only one of the 100 ETV-treated patients and it resolved despite continuing ETV.[22] Therefore, clinical and laboratory parameters should be closely monitored in this setting.

None of the studies ofLAM reported any SAEs associated with this agent. ADV was associated with an SAE in 4% of treated patients.[34]ETV was associated with an SAE in 6% of treated patients in a pooled analysis of two studies.[32] Comparison of ADV and ETV in one prospective study and of TDF and ETV in another prospective study showed similar rates of SAEs.[22,32]

In a systematic review, all the available oral agents can lead to improved virologic, biochemical and clinical parameters among patients with decompensated HBV cirrhosis at 1 year of follow-up. Furthermore, the use of these agents in decompensated HBV patients was found to be generally safe and well-tolerated at 1 year. However, the increased incidence of nephrotoxicity with prolonged ADV therapy and its slower onset of action made it a less attractive option for this patient population. The increased rates of drug-resistant HBV with prolonged use ofLAM, ADV, and LdT monotherapy also made these three agents less attractive for decompensated HBV patients.[29] Therefore, although the review found thatETV and TDF had similar 1-year efficacy toLAM and LdT, the lower rate of drug resistance associated with ETV and TDF during prolonged use would make them more attractive as initial agents for decompensated HBV patients who require lifelong treatment.[35]

Lastly, IFN is not recommended, being poorly tolerated in patients with decompensated HBV cirrhosis and is also associated with disease flares and worsening liver disease status.[36] Peg-IFN is also contraindicated in patients with decompensated cirrhosis because of similar safety concerns.

PATIENTS WITH EXTRAHEPATIC MANIFESTATIONS OF HEPATITIS B

Recommendations

- Acute and chronic hepatitis B may be associated with extrahepatic manifestations *(High quality of evidence; strong recommendation)*
- Viremic HBsAg positive patients with documented extrahepatic manifestations may benefit from antiviral therapy*(Moderate quality of evidence; strong recommendation)*
- Plasmapheresis, corticosteroids and or IV IG may be beneficial when used in tandem with NA treatment for patients with immune-mediated extrahepatic hepatitis B disease*(Moderate quality of evidence; strong recommendation)*
- Peg-IFN may worsen immune-related extrahepatic manifestations of hepatitis B*(Low quality of evidence; strong recommendation)*

Various extrahepatic syndromes are associated with hepatitis B infection.[37]These include the following:

- Polyarteritis nodosa (PAN)
- Glomerulonephritis (membranous, mesangial proliferative or membranoproliferative)
- Serum sickness-like prodrome
- Essential mixed cryoglobulinemia
- Dermatologic manifestations
- Arthritic manifestations
- Neurologic manifestations
- Thyroid dysfunction

The proposed mechanisms for these syndromes are typically immunological, including circulating immune complexes, reactions caused by viral-induced autoantibodies, and/or direct viral reactions to extrahepatic tissue sites such as the skin, muscle, joints, and kidneys.[37,38] Of these syndromes, the best-described ones are PAN, found more frequently in the first 6 months of infection, and glomerulonephritis.[21,39,40]PAN is less common in Asian countries where HBV infection typically occurs perinatally. Membranous glomerulonephritis (MGN) is the most common form of hepatitis B-relatedglomerulonephritis, seen in endemic areas and usually presents as nephrotic syndrome with proteinuria, edema, and hypertension. Both PAN and MGN are mediated by the presence of circulating immune complexes triggered by viremia.

Although immunosuppression with various agents and plasmapheresis may be used in the early phases of treatment, controlling viral replication with potent NAs seem to be essential in the long term for many of these manifestations.[40]

LIVER TRANSPLANT RECIPIENTS

Recommendations

- Oral antivirals with a high genetic barrier to resistance (i.e., ETV, TDF and TAF) should be given to patients waiting for a liver transplant to achieve undetectable HBV DNA levels and reduce the risk of HBV recurrence.*(High quality of evidence; strong recommendation)*
- Prophylactic antiviral therapy after liver transplant should be given indefinitely.*(Moderate quality of evidence;strong recommendation)*
- Among low-risk patients (i.e., with undetectable HBV DNA levels at the time of transplant), HBIG-free regimens can be used. High potency NAs (i.e., ETV, TDF, TAF) should be given indefinitely. *(Moderate quality of evidence;strong recommendation)*
- High-risk patientsshould receive HBIG (e.g., 10,000 IU intravenous HBIG given in the anhepatic phase followed by short-term (<1 year) intramuscular HBIG administration) given together with oral antivirals with a high genetic barrier to resistance. *(Moderate quality of evidence;strong recommendation)*
- Serial monitoring of HBsAg and HBV DNA is sufficient for HBsAg-negative/anti-HBc positive recipients who are receiving HBsAg negative/anti-HBc negative liver grafts. *(Moderate quality of evidence; weak recommendation)*
- Serial monitoring for HBV in the post-transplant setting includes HBsAg and HBV DNA every 3 months in the first year and every 6 months thereafter. *(Low quality; strong recommendation)*
- HBsAg-negative patients receiving HBsAg-negative/anti-HBcpositive liver grafts should receive antiviral prophylaxis with either ETV, TDF or TAF. *(Moderate quality of evidence;strong recommendation)*

In liver transplant recipients who have chronic hepatitis B, it is important to prevent HBV recurrence, which can lead to graft loss.[12,13,21,41] Treatment against HBV should be started as soon as diagnosed in decompensated cirrhosis (*see Chapter on Decompensated Hepatitis-B related Cirrhosis*), and ideally before transplantation in those who are liver transplant candidates so that HBV DNA levels can be suppressed at the time of liver transplantation.[12,13,21,41,42] HBV recurrence rates are lowest when HBV DNA levels are not detectable at the time of liver transplantation.[43] The recommended antiviral agents in these patients are ETV and TDF.[12,13,21,42] TAF has not been fully evaluated in patients with decompensated cirrhosis or liver transplant recipients but is the logical drug of choice in treatment-experienced patients and/or those at risk of bone and kidney disease.[13,41] Peg-IFN is not recommended in patients with decompensated cirrhosis.[12,13,41] Antiviral therapy should be continued indefinitely after liver transplantation because HBV DNA has been shown to persist beyond 10 years after liver transplantation.[44]

The AASLD and APASL classify HBV-infected liver transplant recipients into low- and high-risk groups for HBV recurrence after liver transplantation.[13,21] Those who have undetectable HBV DNA at the time of liver transplantation are considered to have a low risk of HBV recurrence and may be given an HBIG-free prophylactic regimen.[13,21] Fung et al showed that in 265 patients given ETV monotherapy after liver transplant, 92% were negative for HBsAg and 100% were negative for HBV DNA. HBV DNA level at the time of liver transplantation was

associated with HBsAg seroclearance. An undetectable HBV DNA level at the time of liver transplant was associated with an HBsAg seroclearance rate of 98% at 1 year after transplant compared to 92%, 81% and 60% for HBV DNA at transplant of <4 logs IU/mL, >4 to 6 logs IU/mL and over 6 logs IU/mL, respectively ($p<0.001$).[43]

Those who have a high risk of HBV recurrence (**Table 2**) should receive HBIG in addition to oral antiviral therapy to reduce the risk of HBV recurrence.[13,21,45] However, universal use of HBIG after liver transplantation is not practical because of the high cost and the inconvenience of parenteral HBIG administration.[21] The availability of potent antiviral agents with high genetic barrier to resistance (e.g., ETV, TDF and TAF) allows the use of HBIG to be modified after liver transplantation.[41] These modifications, such as low-dose intramuscular HBIG regimens and shortened-duration HBIG treatment regimens, may be used as alternatives to long-term intravenous HBIG regimens. The use of low-dose intramuscular HBIG (400 or 800 IU daily for one week then monthly thereafter) together withLAM 100 mg daily was associated with an HBV recurrence rate of 4% at 5 years.[46] Withdrawal of HBIG after ≤1 year with the continuation of oral antiviral therapy has been associated with low HBV recurrence rates although drugs with a high genetic barrier to resistance should be used.[45,47,48]Another study treated 176 patients with either ETV or TDF after liver transplantation. Thirty-five (20%) patients had HBV DNA >2,000 IU/mL.HBIG was given at a dose of 10,000 IU intravenously in the anhepatic phase followed by 600–1000 IU/day intramuscularly f for 7 days, weekly for 3 weeks and then monthly to keep anti-HBs levels >100 mIU/ml for 1 year. HBIG was then stopped at 1 year. HBV recurrence was observed in only two patients after a mean follow-up of 43 months.[49]

In the Philippines as well as in many parts of the world where HBV is endemic, many prospective donors are HBsAg-negative but anti-HBcpositive. HBsAg-negative patients who receive a liver graft from an HBsAg-negative/Anti-HBcpositive donor are at risk of developing de novo HBV infection. This risk depends on the anti-HBc and anti-HBs status of the recipient.[50] The risk is highest in patients who are anti-HBcnegative and anti-HBsnegative, with a de novo HBV infection rate of 47.8%. The risk is 13.1% in those who are anti-HBcpositive/anti-HBsnegative; and lowest (1.4%) in those who are anti-HBcpositive/anti-HBspositive.[51]Therefore, the recommendation is to give prophylactic therapy to HBsAg-negative patients receiving HBsAg-negative/anti-HBc-positive liver grafts using oral antiviral agents.[13,50,52] HBIG is not needed in these cases.Because recipients who are anti-HBcpositive/anti-HBspositive have low rates of de novo HBV infection after liver transplantation, consideration can be given to serial monitoring and initiation of antivirals once de novo HBV infection occurs.[51,52]

HBsAg-negative/anti-HBc-positive (with or without anti-HBs) liver transplant recipients who are receiving HBsAg-negative/anti-HBcnegative grafts are at low risk of developing HBV recurrence and are not deemed to be in need of antiviral prophylaxis.[41] Serial monitoring and initiation of antivirals once de novo HBV infection occurs are sufficient. Serial monitoring for HBV in the post-transplant setting includes HBsAg and HBV DNA every 3 months in the first year and every 6 months thereafter.[41]

TABLE 2. High risk for HBV recurrence after liver transplantation
• High HBV DNA (≥ 100 IU/mL) at the time of liver transplantation • HIV or hepatitis D coinfection • Lack of access to ETV, TDF or TAF • Poor compliance with antiviral therapy • Presence of HBV drug resistance • HCC at the time of liver transplantation

**Adapted from AASLD[13] and APASL[21]*

NON-LIVER SOLID ORGAN TRANSPLANT RECIPIENTS

Recommendations:

- Screening for HBsAg, anti-HBc, and anti-HBs should be part of the evaluation for patients referred for non-liver solid organ transplant *(Moderate quality of evidence; strong recommendation)*
- Patients who are HBsAg-positive and have decompensated liver disease or significant portal hypertension should be offered liver transplantation in addition to the non-liver solid organ transplant *(Moderate quality of evidence; strong recommendation)*
- All patients who are HBsAg-positive undergoing non-liver solid organ transplant should receive antiviral prophylaxis indefinitely to prevent HBV reactivation *(Moderate quality of evidence; strong recommendation)*
- For HBsAg-negative/anti-HBcpositive recipients and recipients of a graft from an HBsAg-negative/anti-HBcpositive donor, a short course of antiviral prophylaxis (up to 12 months) immediately after transplant can be considered to decrease the risk of either HBV reactivation or de novo HBV infection *(Weak quality of evidence; conditional recommendation).* Alternatively, careful serial monitoring for HBV reactivation or de novo HBV infection using serial ALT and HBV DNA every 3 months for at least 1 year post-transplant may be considered especially in patients who are anti-HBs positive *(Weak quality of evidence; conditional recommendation)*

Screening for hepatitis B should be part of the evaluation of patients being considered for a solid organ transplant other than the liver.[13,50,53]Screening should include HBsAg, anti-HBc, and anti-HBs. Those who test negative for HBsAg and anti-HBs should be offered HBV vaccination.[50,52] Those who test positive for HBsAg should undergo evaluation for the presence and severity of HBV-related liver disease as is done in any patient with chronic hepatitis B.[50]

Patients with decompensated cirrhosis or those with compensated cirrhosis with significant portal hypertension should undergo liver transplantation together with transplantation of the initial non-liver solid organ.[13,50] Those without cirrhosis or those with compensated cirrhosis without portal hypertension can proceed with non-liver solid organ transplantation with appropriate antiviral therapy to prevent HBV reactivation.[50,54]

Drugs with high potency and a high genetic barrier to resistance are recommended and should be given indefinitely.[13,50] These drugs include ETV, TDF and TAF.Non-liversolid organ transplant recipients who are HBsAg-negative but anti-HBcpositive have a low risk of HBV reactivation posttransplant.[50] Either careful serial monitoring or a short course of antiviral prophylaxis (6–12months) immediately after transplant and close monitoring (every 3 months thereafter) of ALT and HBV DNA levels are reasonable strategies.[13,50]

Non-liver solid organ transplant recipients who receive a graft from an HBsAg-negative/anti-HBcpositive donor have a low risk of developing de novo HBV infection unlike the situation in liver transplantation.[1] This has been best studied in patients for kidney transplantation, where the risk of developing de novo HBV infection can be as low as 1% or less.[16]Those recipients who are anti-HBs positive have the lowest risk for developing de novo

HBV infection. Giving a short course of antiviral prophylaxis (12 months) immediately after transplant may be considered to further decrease this risk.[13,50,52]Careful serial monitoring is also an alternative.

PATIENTS RECEIVING IMMUNOSUPPRESSIVE AND CYTOTOXIC TREATMENT

Recommendation

- HBsAg and anti-HBc (total or IgG) testing should be performed in all patients prior to initiation of any immunosuppressive, cytotoxic or immunomodulatory therapy *(High quality of evidence; strong recommendation)*
- HBsAg-positivepatients should initiate anti-HBV prophylaxis before immunosuppressive or cytotoxic therapy *(Moderate quality of evidence; strong recommendation)*
- HBsAg-negative, anti-HBc positive patients could be carefully monitored with ALT, HBV DNA and HBsAg with the intent of on-demand therapy. Exceptions include patients receiving B-cell depleting agents(e.g., rituximab) or undergoing stem cell transplantation, for whom anti-HBV prophylaxis is recommended. *(Moderate quality of evidence; strong recommendation)*
- Antiviral prophylaxis should be prescribed continuously until at least 6 months after the cessation of chemotherapy or immunosuppression, and for at least 12 months after completion of immunosuppressive therapy for those receiving B-cell depleting agents. *(Moderate quality of evidence; weak recommendation)*
- Anti-HBV drugs with a high resistance barrier (ETV, TDF or TAF) are preferred over low-barrier agents. *(Moderate quality of evidence, strong recommendation)*
- For patients being monitored without prophylaxis, HBV DNA levels should be obtained every 1 to 3 months. Patients should be monitored for up to 12 months after cessation of anti-HBV therapy. *(Moderate quality of evidence, weakrecommendation)*

Patients with HBV infection are at risk of virus reactivation when immunosuppressive therapy is initiated for various diseases.[55-57]Reactivation of HBV replication can lead to hepatocellular injury, elevated ALT levels, symptoms of acute hepatitis, liver failure and even death.[57]Multiple studies have shown that antiviral prophylaxis before initiation of immunosuppressive treatment can markedly decrease the risk of HBV reactivation.[58-63]

With increasing recognition of reactivation risk and the availability of effective prophylactic treatment, interest in appropriate HBV screening before chemotherapy initiation has grown.[56,64]The strategy to prevent HBV reactivation includes the identification of patients with HBV infection prior to immunosuppressive therapy, initiation of prophylactic antiviral therapy in those at moderate to high risk of reactivation, and close monitoring of patients not treated prophylactically so that antiviral therapy can be initiated at the first sign of HBV reactivation.[65]

DEFINITIONS

HBV REACTIVATION

- A detectable HBV DNA level when they previously had undetectable HBV DNA, or,
- A rise in HBV DNA of more than 2 $\log_{10}$ international units/mL in patients who had detectable HBV DNA at baseline, or,
- Reverse seroconversion (when a patient previously HBsAg- negative/anti-HBc-positive becomes HBsAg-positive).

HBV flare

- An abrupt elevation of serum ALT to >5 ULN or a greater than threefold increase in serum ALT.

HBV-associated liver failure

- Impaired synthetic function (total bilirubin >3 mg/dL or international normalized ratio >1.5), or,
- Ascites, or,
- Encephalopathy, or,
- Death following HBV-associated liver flare due to HBV reactivation.

SCREENING RECOMMENDATIONS IN THE SETTING OF IMMUNOSUPPRESSIVE OR CYTOTOXIC DRUGS

The rate of HBV reactivation in patients receiving chemotherapy for solid tumors and hematologic malignancies without HBV prophylaxis was 4-68% (median 25%); rates vary according to specific types of cancers.[66] Therefore, all candidates for chemotherapy and immunosuppressive therapy should be screened for HBsAg, anti-HBs and anti-HBc prior to immunosuppression treatment to institute appropriate prophylactic therapy and/or monitoring. Screening may also reveal previously unrecognized chronic HBV infection and its liver-related complications.

Certain approaches to screening for HBV in patients receiving chemotherapy or immunosuppression include:

- Screen all patients prior to chemotherapy/immunosuppression.[67,68]
    - This strategy would identify patients who would potentially benefit from: (1) antiviral prophylaxis; (2) HBV serology and HBV DNA monitoring (without antiviral prophylaxis); (3) immunization against HBV; (4) evaluation for complications of chronic hepatitis B; or (5) contact tracing of family members for chronic hepatitis B and their subsequent management.
- Screen only patients in the “high risk” groups according to the CDC.
- Screen only patients who, if serological testing would be positive, would be prescribed antiviral prophylaxis.

Consideration must also be given to which serological test(s) are to be used for screening. These include:

- **Test HBsAg, anti-HBc and anti-HBs.** Test HBV DNA if HBsAg or anti-HBcis positive (the latter in case of occult HBV infection)
- **Test HBsAg, anti-HBc only.** The role of anti-HBs in HBV reactivation is unclear. The role of anti-HBs in screening prior to immunosuppressive therapy has not yet been established. The presence of anti-HBs does not prevent HBV reactivation, but anti-HBs may be useful for detecting prior infection in HBsAg negative, anti-HBc positive patients and in surveillance as the loss of anti-HBs may be a predictor of HBV reactivation.

- **Test anti-HBc only.** If positive, proceed to test for HBsAg and HBV DNA.

The risk of HBV reactivation can be classified as high (>10%), moderate (1–10%) or low (<1%).The cost-effective approach to screening for HBV in patients at risk of HBV reactivation is unclear. The American Gastroenterological Association recommends HBV serological screening in patients with "moderate to high risk" according to their risk stratification paradigm (**Table 3**).[67,68]

ANTIVIRAL PROPHYLAXIS VS ON-DEMAND TREATMENT

HBsAg-positive patients

- These patients are at high risk of HBV reactivation, especially if their HBV DNA levels are elevated. They should receive anti-HBV prophylaxis prior to the initiation of immunosuppressive or cytotoxic therapy. This is supported by threeRCTsthat included HBsAg-positive, anti-HBcpositive patients receiving anticancer therapy.[69-72]

HBsAg-negative, anti-HBcpositive patients

- These patients are at a lower risk of HBV reactivation than HBsAg-positive patients. Depending on their clinical situation and feasibility of close monitoring, they could be given anti-HBV prophylaxis or monitored with the intent of on-demand anti-HBV therapy at the first sign of HBV reactivation.
- Patients with rheumatologic conditions receiving biologic therapies, those with inflammatory bowel disease treated with TNF inhibitors, andthose with psoriasis treated with biologics or conventional immunosuppressive therapies have been managed successfully with monitoring without anti-HBV prophylaxis.[73-77]
- Although lymphoma patients have been successfully managed with close monitoring and on-demand antiviral therapy while receiving rituximab or conventional anti-cancer therapy without adverse liver outcomes[78,79], prophylaxis is recommended for HBsAg-negative/anti-HBcpositive patients on B-cell depleting drugs such as rituximab.

PREFERRED ANTIVIRALS AND DURATION OF TREATMENT

Prophylactic antiviral therapy should be administered to patients with chronic hepatitis B before the onset of anticancer therapy or a finite course of immunosuppressive therapy regardless of baseline serum HBV DNA level.[80]In literature, antivirals were most often given 7 days prior to anti-cancer or immunosuppressive therapy. High potency, high resistance barrier first-line NAs (e.g., ETV or tenofovir) should be preferred over other NAs, as multiple meta-analyses have demonstrated reduced reactivation, hepatitis, mortality and anticancer therapy interruption with these agents.[80-82]

The most commonly studied and recommended duration of prophylactic antiviral therapy is 6 to 12 months after discontinuation of anticancer or immunosuppressive therapy.[80]Reactivation beyond 12 months has been documentedparticularly for patients who received anti-CD20 antibody therapy.[83-85]

Table 4shows a summary of the American Gastroenterology Association guidelines on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy.

Table 3. Risk estimates of HBV reactivation according to drug class[67,68]

Risk estimate of HBV reactivation	Drug class	Drug
High (>10%)	Bcell-depleting agents	Rituximab (anti-CD20) Ofatumumab (anti-CD20)
	Anthracycline derivatives	Doxorubicin Epirubicin
	Corticosteroids (high dose)	e.g., Prednisone ≥20 mg for ≥4 weeks
Moderate (1-10%)	TNFa inhibitors	Infliximab Etanercept Adalimumab
	Cytokine inhibitors Integrin inhibitors	Abatacept (anti-CD80, -86) Ustekinumab (anti-IL12, -23) Natalizumab (binds α4-integrin) Vedolizumab (binds integrin α4β7 [LPAM-1]
	Tyrosine kinase inhibitors	Imatinib Nilotinib
	Corticosteroids (moderate dose)	E. g., Prednisone <20 mg for ≥4 week
Low (<1%)	Corticosteroids (low dose)	E. g., Prednisone for <1 week
	Corticosteroids (intra-articular)	
	Traditional immunosuppression	Azathioprine 6-mercaptopurine Methotrexate

Adapted from the American Gastroenterology Association guidelines.[67,68]

Table 4. Summary on the prevention and treatment of hepatitis B reactivation during immunosuppressive drug therapy[67,68]

Population at risk of HBV reactivation	Screening test	Is antiviral prophylaxis recommended?		Antiviral drug recommended for prophylaxis	Monitoring in untreated HBsAg (-)/anti-HBc(+) patients
		HBsAg positive	HBsAg negative/ anti-HBc positive		
High risk of HBV reactivation(>10%) • B-cell depleting agents • Anthracycline derivatives • High-dose corticosteroids(≥20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology positive	Yes (high quality;strong recommendation) Continue at least6 months after completion of chemotherapy and at least 12 months for B-cell depleting agents.	Yes (high quality;strong recommendation) if taking:B-cell depleting agents or anthracycline derivatives. Continue until atleast 12 monthsafter completion of chemotherapy for B-cell depleting agents.	Drug with high barrier to resistance is favored overLAM (moderate quality;weak recommendation) .	No recommend-ation provided
Moderate risk of HBV reactivation(1-10%) • TNFa inhibitors • Cytokine or integrin inhibitors • Tyrosine kinase inhibitors • High-dose corticosteroids (<20 mg prednisone for ≥4 weeks)	HBsAg and anti-HBc; HBV DNA if serology positive	Yes (moderate quality;weak recommendation) Continue until at least 6 months after completion of chemotherapy.	Yes (moderate quality;weak recommendation) if takingTNFa inhibitors, cytokine or integrin inhibitors, or tyrosine kinase inhibitors. Continue until at least 6 months after completion of chemotherapy.	Drug with high barrier to resistance is favored overLAM (moderate quality;weak recommendation) .	No recommend-ation provided
Low risk of HBV reactivation (<1%) • Traditional immunosuppression • Intra-articular corticosteroids • Systemic corticosteroids for <1 week	Routine screening not recommended. Screen for HBV as per CDC guidelines; manage accordingly	Not recommend-ed(moderate quality;weak recommendation)	Not recommend-ed(moderate quality;weak recommendation)	Not applicable	No recommend-ation provided

Adapted from the American Gastroenterology Association guidelines.[67,68]

PATIENTS COINFECTED WITH HEPATITIS B AND HIV

Recommendations

- All HBsAg-positive patients contemplated for antiviral treatment should be screened for HIV before starting treatment.*(Moderate quality of evidence; strong recommendation)*
- All HIV-HBV coinfected persons must be started on appropriate ART regardless of CD4 cell count. Both infections should be simultaneously treated using ART that is active against both viruses to reduce the risk of resistance.*(Moderate quality of evidence; strong recommendation)*
- The recommended regimen is TDF/TAF (provided there is no contraindication to tenofovir) plus emtricitabine/ LAM, plus efavirenz to prevent the selection of HIV-resistant mutants. *(High quality of evidence; strong recommendation)*
- LAM, TDF, TAF and ETV should not be used as monotherapy in coinfected patients. *(High quality of evidence; strong recommendation)*
- ETV may be a reasonable alternative if needed against HBV in HIV-HBV coinfection, but only in addition to a fully suppressive HIV ART regimen.*(High quality of evidence; conditional recommendation)*
- When coinfected patients are already on ART, drugs that are active against HBV should not be abruptly discontinued without replacing it with another fully suppressive drug against HBV.*(High quality of evidence; strong recommendation)*
- Treatment regimens that include TDF and emtricitabine need renal dose adjustment if creatinine clearance <50 ml/min. Regimens with TAF and emtricitabine are not recommended when creatinine clearance <30 ml/min.*(High quality of evidence; strong recommendation)*

Studies have shown higher rates of liver-related morbidity and mortality in individuals with HIV-HBV infection compared with those infected with only one of either virus.[86] The possibility of fibrosis progression, cirrhosis and hepatocellular cancer make it important to give antiviral regimens that are able to suppress both viruses sufficiently, regardless of current HIV status and liver histology.

In a meta-analysis of over 12,283 HIV-HBV coinfected patients, there was increased rates of death in studies done both before and after HAART was commenced.[87]There is evidence that HIV infection leads to increased HBV DNA polymerase activity, increased HBV viral load, and decreased rated of HBeAg seroconversion. The rates of hepatitis B reactivation and the risk of cirrhosis also increase with coinfection.[88-91]While there are still conflicting data on the effect of HBV on the natural prognosis of HIV infection and AIDS-related mortality, several studies have shown that hepatitis B infection may impair the rise of CD4 while on ART and increases AIDS-related mortality.[92,93] These support the need to suppress both infections during treatment.

LAM, tenofovir and emtricitabine have activity against both HIV and HBV.LAM monotherapy should be avoided due to the emergence of resistance; hence a tenofovir-based treatment is preferred. If available, TAF may be preferable over TDF due to a better kidney and bone safety profile. Two randomized, controlled non-inferiority studies that included>1,600

patientsfound that equivalent virological success was achieved with TAF and TDF given with ART, with a significant decrease in creatinine and bone mineral density adverse effects in TAF vs TDF.[94]

ETV has been shown to have anti-HIV activity and should not be used without a fully suppressive anti-HIV regimen as it has been shown to induce the development of the M184T resistance mutation in both ART-naïve and ART-experienced patients.[95]

Flares from hepatitis B may occur in the first few weeks of ART treatment due to immune reconstitution but can also occur when drugs with anti-HBV activity are inadvertently discontinued when a patient with HIV-HBV coinfection has a change of ART regimen. Due to the many reasons for increase in ALT levels in patients with HIV (e.g.,drug-induced liver injury, opportunistic infections, etc.), it is prudent to monitor virologic suppression of HBV periodically, especially when the cause of ALT elevation is uncertain.[13]

PATIENTS COINFECTED WITH HEPATITIS B AND C VIRUSES

Recommendations

- All HBsAg-positive patients should be tested for coinfection with HCV.*(Low quality of evidence; strong recommendation)*
- HCV treatment should be initiated for all patients with HCV viremia.*(High quality of evidence; strong recommendation)*
- HBsAg-positive patients who fulfill the standard criteria for hepatitis B treatmentbased on ALT and DNA levels(as with mono-infected patients) should be started on NA treatment.*(High quality of evidence; strong recommendation)*
- DAA treatment may cause reactivation of hepatitis B and subsequent clinical flares in HBV-HCV coinfected individuals. Close monitoring with HBV DNA or at least ALTshould be considered.*(Moderate quality of evidence; strong recommendation)*
- HBsAg-negative, anti-HBc–positive patientswho are started on DAA should haveALT levelsmonitored. HBV reactivation should be considered as a cause when there is ALT elevation. (*Moderate quality of evidence; strong recommendation)*
- Cirrhotic patients with HBV-HCV coinfection should receive antiviral treatment for both hepatitis B and C. (*Low quality of evidence; strong recommendation)*

Due to the similar modes of transmission, coinfection with HBV and HCV is not rare. In HBV-HCV coinfected patients, the host's immune system determines the ability of either virus to replicate in the host, with one virus (usuallyHCV) typically predominating over the other. The dominant virus responsible for liver disease and liver-related morbidity can be determined by checking both HBV DNA and HCV RNA. Hepatitis C treatment is an evolving area of study; hence, standard updated professional guidelines should be followed.[96]

In 2016, the US Food and Drug Administration issued a warning for patients with HBV-HCV coinfection on DAAs due to reported cases of HBV reactivation while on DAA treatment.[97,98] Recent studies including systematic reviews have shown that there is a higher risk of HBV reactivation after DAA treatment compared to what was previously noted in IFN-based regimens. In a systematic review with a pooled sample of 1,621 patients, reactivation was noted in 24% (95% CI 19–30%) of HBsAg-positive patients vs only 1.4% in patients with past hepatitis B (HBsAg-negative, Anti-HBc positive). The risk of reactivation was found to be higher in patients with HBV DNA levels ≥ 20 IU/mL at baseline.[98] Reactivation has also been reported in cirrhotic individuals with HBV HCV coinfection.[99] Reactivation of hepatitis B can be catastrophic for these individuals and prophylactic HBV treatment may be warranted in this subset of patients.

More studies need to be done to guide protocols for monitoring and screening for HBV reactivation in the setting of DAA treatment for HBV-HCV coinfection. The AASLD suggests monitoring DNA and ALT every 4-8 weeks during and until 3 months after DAA treatment for HBsAg-positive patients. For patients with past hepatitis B, ALT monitoring at baseline, at end of treatment and at follow-up is suggested to screen for reactivation.[13,97] The EASL, on the other hand, suggests outright empiric HBV prophylactic treatment with NAs until 12 weeks after

ending DAA treatment.[12] In instances that DAAs and tenofovir need to be administered together, there may be a need to monitor TDF-related adverse events when the drug is used as drug levels may be increased when coadministered with some DAAs (e.g.,sofosbuvir/ledipasvir or sofosbuvir/velpatasvir).[100]

PATIENTS WITH CHRONIC KIDNEY DISEASE

Recommendations

- All candidates for dialysis should be tested for HBsAg, anti-HBs, and anti-HBc before starting therapy. If HBV seronegative, vaccination is recommended.*(Moderate quality of evidence; strong recommendation)*
- For known responders to vaccination, annual determination of anti-HBs titer is recommended. If the anti-HBs titer is <10 mIU/ml, a booster dose is recommended.*(Moderate quality of evidence; strong recommendation)*
- Hepatitis B surveillance using HBsAg and anti-HBs determinationis recommended for CKD patients on regular hemodialysis. *(Moderate quality of evidence; strong recommendation)*
- For patients who are immune to hepatitis with an anti-HBs titer of >100mIU/ml, hepatitis B surveillance should be done every 6 months.*(Moderate quality of evidence; strong recommendation)*
- For patients who are non-immune to hepatitis with an anti-HBs titer of <10mIU/ml, hepatitis B surveillance should be done every 3 months.*(Moderate quality of evidence; strong recommendation)*
- Enhanced surveillance is encouraged for high-risk patients.*(Moderate quality of evidence; strong recommendation)*
- CKD patients with chronic hepatitis B should be evaluated for treatment similar to non-CKD patients. Indications and treatment monitoring are similar to non-CKD patients, as indicated in sections 4 and 5 of the 2014 HSP Consensus Statement on the Management of Chronic Hepatitis B.*(Moderate quality of evidence; strong recommendation)*
- ETV and TAF are the preferred agents for patients with CKD because of better renal and bone safety profiles.*(High quality of evidence; strong recommendation)*
- Dosing of antiviral agents should be adjusted based on the eGFR (**Table 5**). *(High quality of evidence; strong recommendation)*

CKD patients on hemodialysis are at highrisk ofchronic hepatitis B because they are susceptible to nosocomial transmission and occult HBV infection.[101] The latter might account for the potential risk of transmission during hemodialysis and HBV reactivation after kidney transplantation.

Vaccination is a vital component of preventive healthcare measures among CKD patients and should not be underutilized because of poor response.[102] Special vaccination regimens are recommended, including double-dose vaccination (40 mg each) in four doses, preferably given before hemodialysis initiation. Anti-HBs titer determination should be performed every year and a booster dose of hepatitis B vaccine should be given if antibody titers are below 10 mIU/mL.

Hepatitis B surveillance is recommended for CKD patients on regular hemodialysis. Enhanced surveillance is encouraged for high-risk patients. These patients include those who have:[103]

- Recently injected illicit drugs
- Other blood-borne virus infections

- Unexplained abnormal aminotransferase levels
- Recently received a kidney transplant or blood from a donor known to be infected with blood-borne viruses
- Sexual partners who inject illicit drugs or have blood-borne virus infections
- Recently received healthcare overseas

Additional parameters complicating the diagnosis and clinical course of chronic hepatitis B in patients on hemodialysisinclude the minimal or no increase in liver function tests, the lower viral load levels because of viral clearance by hemodialysis,and the high bleeding risk related to clotting disorders and intra- dialysis anticoagulant therapies.[104,105]

Management of HBV patients with CKD requires special consideration, a multidisciplinary approach, and thorough and regular monitoring of renal function. The administration of NAs has improved the prognosis of patients with CKD immensely and has prevented HBV recurrence after kidney transplantation.[106] Among CKD patients who are not candidates for kidney transplantation, antiviral treatment should be reserved for those with active liver disease and those with significant fibrosis. The dose of NAs should be adjusted according to eGFR, as shown in **Table 5**.[107]

With the advent of NAs, IFN use has been limited to young patients with HBV-related glomerulopathy without cirrhosis, psychosis or autoimmune disease.[108] IFN is poorly tolerated by patients with CKD, has shown relatively low efficacy, and has set kidney transplant recipients under the risk of acute rejection. [104] Hence, IFN is contraindicated in patients with CKD.

NAs with high genetic barrier for resistance are the preferred agents for HBV-positive patients with CKD. In patients with treatment indications for HBV infection, ETV is considered the first choice, regardless of viremia.[107] TAF is likewise a good treatment option because of its better bone and safety profile compared to TDF. However, studies on the routine use of TAF in CKD patients are lacking and further research is needed.

Table 5. Dosage adjustment of NAs according to creatinine clearance.[107]

CrCL (mL/min)	LAM	LdT	ADV	ETV	TDF	TAF
≥50	100 mg/day	600 mg/day	10 mg/day	0.5 mg/day	245 mg/day	25 mg/day
30-49	50 mg/day	600 mg every 2nd day	10 mg every 2nd day	0.25 mg/day	245 mg every 2nd day	25 mg/day
10-29	25 mg/day	600 mg every 3rd day	10 mg every 3rd day	0.15 mg/day	245 mg every 3rd to 4th day	25 mg/day
<5-10 or hemodialysis	10 mg/day	600 mg every 3rd to 4th day	10 mg every week	0.5 mg/week	245 mg/week	25 mg/week

*In patients undergoing hemodialysis, all agents should be given once weekly after an HD session.
** For LAM, resistance, dosage of ETV is doubled.

RECOMMENDATIONS FOR DRUG RESISTANCE

Recommendations

- For resistance toLAM, LdT or CLV, add-on ADV, TDF or TAF therapy *(High quality of evidence;strong recommendation)* OR switching to TDF or TAF is indicated *(Moderate quality of evidence;strong recommendation)*
- For resistance to ADV, add-on ETVOR switching to ETV, TDF or TAF is indicated *(Moderate quality of evidence;strong recommendation)*
- For resistance to ETV, add-on ADV or TDF or TAF *(Moderate quality of evidence;strong recommendation)* OR switching to TDF or TAF is indicated *(Moderate quality of evidence;strong recommendation)*
- For resistance to both ADV AND eitherLAM, LdT or CLV, switching to ETV plus TDF, or to TDF or TAF alone, is indicated *(Moderate quality of evidence;strong recommendation).*
- For resistance to any NA, switching to IFN-based therapy may be considered *(Moderate quality of evidence;strong recommendation).*
- Management of drug resistance in the treatment of HBV is complex. Referral to a specialist is recommended.*(Low quality of evidence; strong recommendation).*\

Drug resistance is identified by an initial non-response to treatment or virological breakthrough in the presence of established treatment compliance.[23]Ideally, drug resistance testing is performed to tailor rescue therapy but may not be feasible in resource-limited settings. Alternatively, add-on treatment or switching to different antivirals is guided by available cross-resistance data.[109]

Among antiviral agents,LAM yields the highest year-on-year rates of HBV resistance in treatment-naive patients.[23]ETV and TDF have the lowest documented resistance rates although data for TDF is limited.[110]

In patients withLAM resistance, add-on ADV enhances viral suppression, prevents virologic breakthrough and is more effective than switching to ADV alone.[111,112]Moreover,LAM plus ADV was significantly better than ETV monotherapy (1 mg/day) inenhancing viral suppression and reducing virologic breakthrough rates.[113]However, ETV may still be offered to patients not amenable to other antivirals. Switching to TDF monotherapy has been shown to be effective forLAM or ADV resistance.[114]ETV plus TDF should be considered for patients resistant to combined nucleoside and nucleotide analogs.

IFN-based treatment has also been used for patients with NA resistance. A 48-week course of peg-IFN versus continuous ADV treatment in HBeAg-positive patients withLAM resistance showed that peg-IFN was superior to ADV in inducing HBeAg seroconversion after 72 weeks (or 6 months after peg-IFN treatment) (p=0.01). However, only 10.6% of peg-IFN treated patients had HBV DNA <80 IU/mL versus 22.5% in ADV-treated patients during the same time period.[115]

TAF, similar to TDF, is a phosphonate prodrug of tenofovir. It has enhanced antiviral potency with improved renal and bone safety profile compared to TDF. Moreover, TAF has

greater plasma stability than TDF, allowing more efficient delivery of the active metabolite intracellularly at much lower doses.[116,117]In vitro, TAF has shown potent activity againstLAM-resistant and ETV-resistant recombinants, with mean changes in half-maximal effective concentration (EC_{50}) values of less than two-fold compared with wild-type virus.[118] Pooled analysis of phase III studies on TAF showed that majority (89.2%) of patients had wild-type virus at baseline and that the number of patients with resistance mutations associated with other NSs was small.[119]

PREGNANT WOMEN WITH CHRONIC HEPATITIS B INFECTION

Recommendations

- All pregnant women should be screened for hepatitis B. *(Moderate quality of evidence; strong recommendation).*
- Infants born to chronic hepatitis B mothers should receive timely prophylaxis with HBIG and the first dose of HBV vaccine within 12 hours of birth. *(Moderate quality of evidence; strong recommendation).*
- Pregnant women with HBV DNA >200,000 IU/mL should receive antiviral therapy during the third trimester up to the first 6 weeks postpartum, if started solely for MTCT. Monitoring should still be done after discontinuation of antivirals. *(Moderate quality of evidence; strong recommendation).*
- Preferred agents for use in pregnant women with chronic hepatitis B are LAM, LdT and TDF are considered safe for pregnancy, with TDF being the preferred agent. *(Moderate quality of evidence; strong recommendation)*
- The mode of delivery should still be guided by obstetric indications rather than HBV infection status. *(Low quality of evidence; strong recommendation).*
- Breastfeeding should not be withheld. *(Low quality of evidence; strong recommendation).*

Vertical or MTCT is still the predominant mode of HBV spread in hyperendemic areas of the world (>8% prevalence of HBsAg seropositivity) such as Asia and the South Pacific.[120-122]The Philippines has an HBsAg seroprevalence of 16.7%, classifying it as one of these hyperendemic countries.[123]

Screening for HBVinfection during pregnancy identifies seropositive women, whose neonates are at highest risk of perinatal spread.[124]Preventing vertical transmission heavily depends on prenatal screening of pregnant women for HBsAg. Those identified to be positive will need to do further tests, such as HBeAg, ALT, HBV,and DNA, the latter being the most important predictor of perinatal transmission.[125,126]Infants born to chronic hepatitis B mothers need to receive timely prophylaxis with HBIG (0.5 mL intramuscularly) and the first dose of HBV vaccine within 12 hours of birth.[127]This combination of passive and active immunization decreases the rates of MTCT from 90% to 10%.[127,128]

Despite immunoprophylaxis, 10–30% of infants born to chronic hepatitis B mothers with HBV DNA levels >200,000 IU/ml still acquire HBV. Therefore, pregnant women with HBV DNA >200,000 IU/mL should receive antiviral therapy during the third trimester (week 28 onward) to further reduce the chances of perinatal transmission.[13,122,129] Threatened preterm labor, prolonged uterine contractions and a previous child in whom immunoprophylaxis had failed are also indications for initiating antiviral treatment. This antiviral treatment should be continued for the first 6 weeks postpartum, if started solely for MTCT.[122] Monitoring should still be done after discontinuation of antivirals.

LAM, LdT, andTDF are considered safe for pregnancy, with TDF being the preferred agent. As of late, there is still no published safety profile for TAF in pregnant women.[12,130]

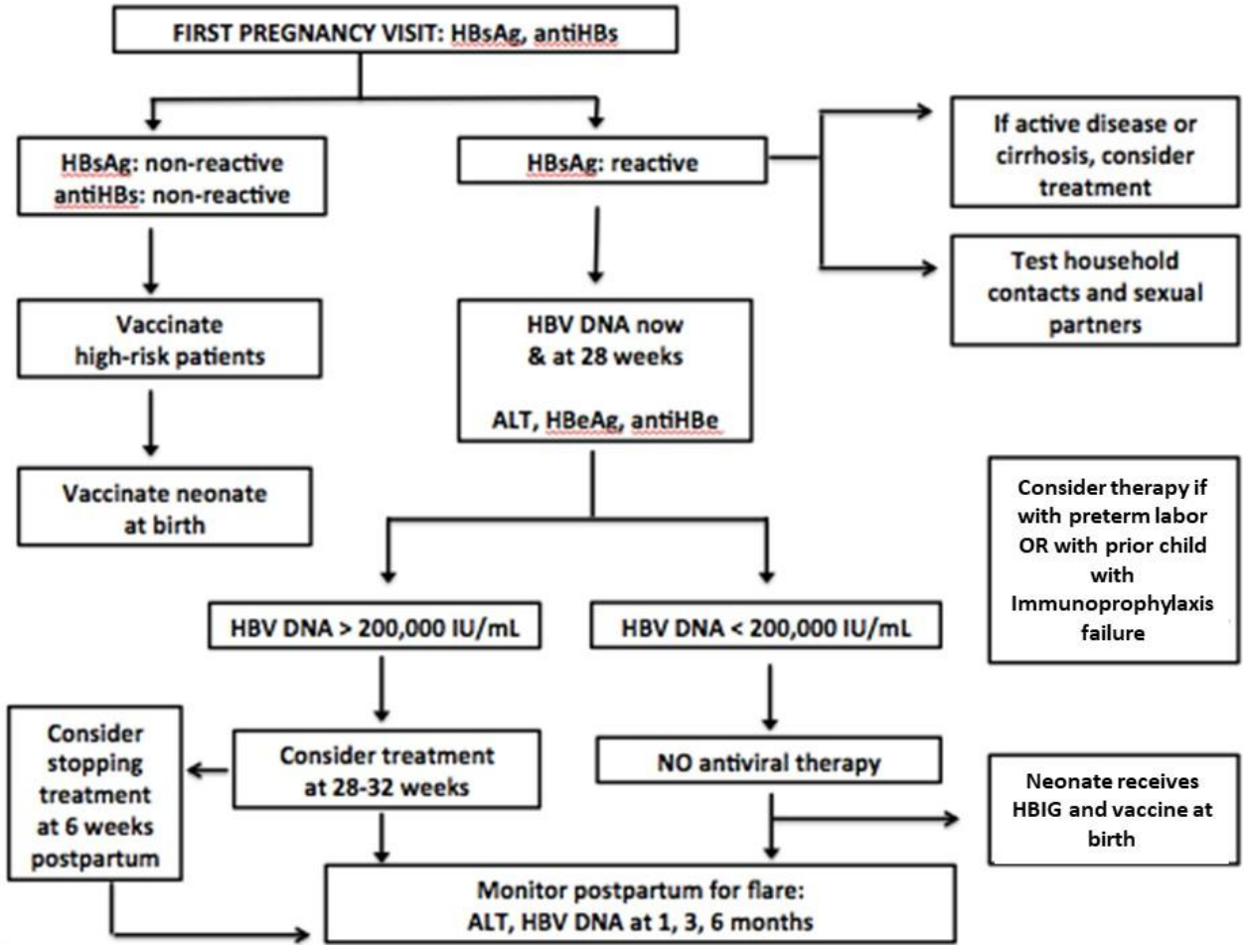
Pregnant patients without active or advanced chronic HBV infection can have their antiviral treatment deferred until after childbirth.

Data on the benefit of doing a Cesarean section for chronic hepatitis B mothers are conflicting and nonconclusive. To date, the recommendations for the mode of delivery should still be guided by obstetric indications rather than HBV infection status.[13]

Breastfeeding has significant maternal and infant benefits and does not seem to increase HBV transmission risk from mother to child. Hence, breastfeeding should not be withheld. Antivirals, if necessarily taken postpartum, are minimally excreted in breast milk and are not likely to cause significant toxicity.[12,13]

Figure 1 summarizes the management of chronic hepatitis B in pregnant women.[13,131]

Figure 1. Management of Chronic Hepatitis B in Pregnant Women[13,131]



Adapted from American Association for the Study of Liver Diseases[13] and Ayoub and Cohen (2016)[131]

CHILDREN WITH CHRONIC HEPATITIS B

Recommendations

- Treatment is indicated for children with HBeAg-positive chronic hepatitis B and persistently elevated ALT with moderate to severe inflammation and fibrosis *(High quality of evidence; strong recommendation)*
- Treatment is indicated for children with HBeAg-negative chronic hepatitis B infection and persistently elevated ALT with moderate to severe inflammation and fibrosis *(High quality of evidence; strong recommendation)*
- Treatment is indicated for children with chronic hepatitis B infection and compensated cirrhosis *(High quality of evidence; strong recommendation)*
- Treatment is indicated for children with chronic hepatitis B infection and decompensated cirrhosis*(High quality of evidence; strong recommendation)*
- Liver biopsy is recommended to establish liver histology prior to commencing anti-viral treatment for chronic hepatitis B infection in children *(High quality of evidence; strong recommendation)*
- In children with chronic hepatitis B, antiviral therapy may be started without a prior in the following conditions: decompensated cirrhosis; HBeAg-positive, > 20,000 IU/ml HBV DNA and ALT 2x ULN for >12 months; and HBeAg-negative, > 2,000 IU/ml HBV DNA and persistent ALT 2x ULN*(Moderate quality; strong recommendation)*
- Tenofovir and ETV are first-line antivirals for children with chronic hepatitis B infection requiring treatment *(Moderate quality; strong recommendation)*
- Lifelong post-treatment monitoring for SVR, clinical decompensation and adverse effects of treatment is recommended in children with chronic hepatitis B*(Moderate quality; strong recommendation)*

Management of chronic hepatitis B in children requiresspecial attention.Many aspects of care remain unproven, such as the long-term effectiveness of anti-viral treatment in preventing liver cirrhosis orHCC.Data on treatment in children are more recent compared to adults.Although IFN has been used for chronic HBV infection in children in the 1980s, it is only recently that NAs have been approved.As such, the optimal duration and adverse effects of treatment remain unclear.Guidelines for the management of chronic hepatitis B in children have been published by a consensus group from the United States as well as ESPGHAN, AASLD and APASL to guide practitioners in the management of hepatitis B in children, given the limitations in clinical evidence.[21,132-134]

Treatment in children impacts the prevalence of cirrhosis and HCC, both in adults and children.These complications are reported in children at a rate of 0.6-3.8% and 0.01-2.8%, respectively.[135-144]Identified risk factors for HCC specific to children include early HBeAg seroconversion, presence ofcirrhosis,male sexand pre-S2 deletion mutants.[136,138,142,145-147]In a nationwide multicenter survey of children with chronic HBV infection in Japan, HCC was diagnosed in children as young as 9 years old, with a reported median age of 15 years.[144]

The natural course of illness of chronic hepatitis B in the pediatric agegroup has peculiarities.Treatment is not indicated during the immune-tolerant phase, which may be prolonged in children, sometimes lasting >3 decades following vertical transmission.[132]Maternal

HBeAgtransferredtransplacentallyhas been postulated to induce tolerance to HBeAg of the helper T cells of the infected infant.[148]

In children, treatment is recommended for a prolonged immune-reactive phase and during the reactivation phase (HBeAg negative, Anti-HBc/anti-HBs positive chronic hepatitis B) since necroinflammation exists at these times with resulting progression of liver disease.[133] Children with chronic hepatitis B-related cirrhosis require treatment even with normal ALT levels and without the need for liver biopsy.[21,23]

In the pediatric age group, chronic hepatitis B infection may coexist with another primary liver condition.This situation should be considered in the following circumstances:(1) HBeAg-positive with intermediate or low viral load and persistent elevation of ALT for any duration; (2) HBeAg-negative with low viral load and persistently elevated ALT; and (3) HBeAg-negative with intermediate to high viral load and ALT elevated ≤2x ULN.Once other primary liver disease conditions are ruled out, treatment for chronic hepatitis B infection may commence as indicated by a liver biopsy showing moderate to severe inflammation and significant fibrosis.[21]

A liver biopsy remains a useful tool in the determination of treatment indication in children with chronic hepatitis B.Hence, a liver biopsy is recommended prior to antiviral treatment. However, no liver biopsy is required in HBeAg-positive chronic hepatitis B with high viremia and ALT>2x ULN persisting for 12 months andHBeAg-negativechronic hepatitis B with HBV DNA >2,000 IU/ml and persistent ALT >2x ULN.[21]Decompensated cirrhosis is an indication for treatment that requires no liver histologic analysis.[132,133]The use of non-invasive tests such as APRI,transient elastography (e.g.,FibroScan) or FibroTest is not yet recommended for children.[42]

Table 6 summarizes the indications for the treatment of children with hepatitis B, as recommended by guidelines.

Treatment should be considered for children with a family history of HCC or cirrhosis, even if mild histologic changes are mild, because of the increased risk of HCC.[21]

The goals of treatment in children include sustained HBeAg seroconversion, undetectable serum HBV DNA, ALT normalization, histologic improvement and regression of liver fibrosis. Conventional IFN-alpha, LAM, ADV, ETV, and TDF have all been evaluated for safety and efficacy in children. Antiviral drugs with a high genetic barrier to resistance (i.e., tenofovir or ETV) are recommended first-line treatments for both adults and children by the World Health Organization. LAM, ADV, and LdT are not recommended because of the low barrier to resistance.[42]IFN-alpha was superior to placebo in maintaining SVR and ALT normalization in a systematic review and meta-analysis that included children with HBeAg-positive chronic hepatitis B.[149] A phase IIIb open-label study of peg-IFN alfa-2a monotherapy started in 2012 will be completed in 2021.[150]

Although lifelong NAs treatment is recommended in adults with cirrhosis, the duration of treatment in children is unclear. In children, NAs are recommended until the therapeutic endpoint of HBeAg seroconversion is achieved. Thereafter, consolidation therapy for 12 months is given to prevent virological relapse. For HBeAg-negative chronic hepatitis B, prolonged NA treatment is given and HBsAg loss is the therapeutic target to address the high relapse rate.[21]The IFN-alpha treatment recommendation is finite at 24 weeks.

Following treatment, monitoring of children is recommended every 3 months for at least 1 year to detect recurrent viremia, ALT flares, and clinical decompensation.[134]

Table 6. Indications for the treatment of children with chronic hepatitis B

	Serum HBV DNA IU/mL	ALT	Duration	Liver histology	Ruled out primary liver disease?
HBeAg (+) Child					
APASL 2015[21]	2000-20,000	Persistently elevated	6 months*	Moderate or severe inflammation & fibrosis	Yes
	>20,000	1-2x ULN	>1 year	Moderate or severe inflammation & fibrosis	Not recommended
	>20,000	>2x ULN	>1 year	Not recommended	
US Consensus 2010[132] ESPGHAN 2013[133]	> 2000	1.5x ULN or 60IU/L	6 months	Moderate or severe inflammation & fibrosis	-
HBeAg (-) Child					
APASL 2015[21]	<2000	Persistently elevated	3-6 months*	Moderate or severe inflammation & fibrosis	Yes
	>2000	1-2x ULN	3-6 months*	Moderate or severe inflammation & fibrosis	Yes
	>2000	>2x ULN	3-6 months*	Not recommended	Not recommended
ESPGHAN 2013[133]	> 20,000	1.5x ULN	12 months	Moderate or severe inflammation & fibrosis	-
US Consensus 2010[132]	>2000	1.5x ULN or 60 IU/L	12 months	Moderate or severe inflammation & fibrosis	-

** Implied but not directly stated.*

Table 7 summarizes the dosing and monitoring of drugs used to treat chronic hepatitis B in children.

Table 7. Details of pharmacotherapy for chronic hepatitis B in children

Drug	Dose	Monitoring	Remarks
Tenofovir	300 mg once daily	Nephrotoxicity; decreased bone mineral density possible	≥12 years old; weight at least 35 kg; for NA treatment-naive & LAM-refractory
ETV	Dose (mL) of 10 mg/0.5 mL solution by bodyweight (kg): 10 to 11 kg: 3 mL >11 to 14 kg: 4 mL >14 to 17 kg: 5 mL >17 to 20 kg: 6 mL >20 to 23 kg: 7 mL >23 to 26 kg: 8 mL >26 to 30 kg: 9 mL >30 kg: 10 mL	High genetic barrier to drug resistance but resistant variants reported to be slightly higher in children than in adults	≥2 years old; weight at least 10kg; for NA treatment-naive
Interferon-alpha	5–10 million units per square meter, 3x weekly for 6 months	No resistance; serious potential adverse effects	Contraindications: decompensated cirrhosis, cytopenia, autoimmune disorders, cardiac or renal failure, transplanted patients

Adapted from Sokal EM, Paganelli M, Wirth S, et al. Management of chronic hepatitis B in childhood: ESPGHAN clinical practice guidelines: consensus of an expert panel on behalf of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Hepatol 2013;59:814-29 and World Health Organization (2015). Guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection.

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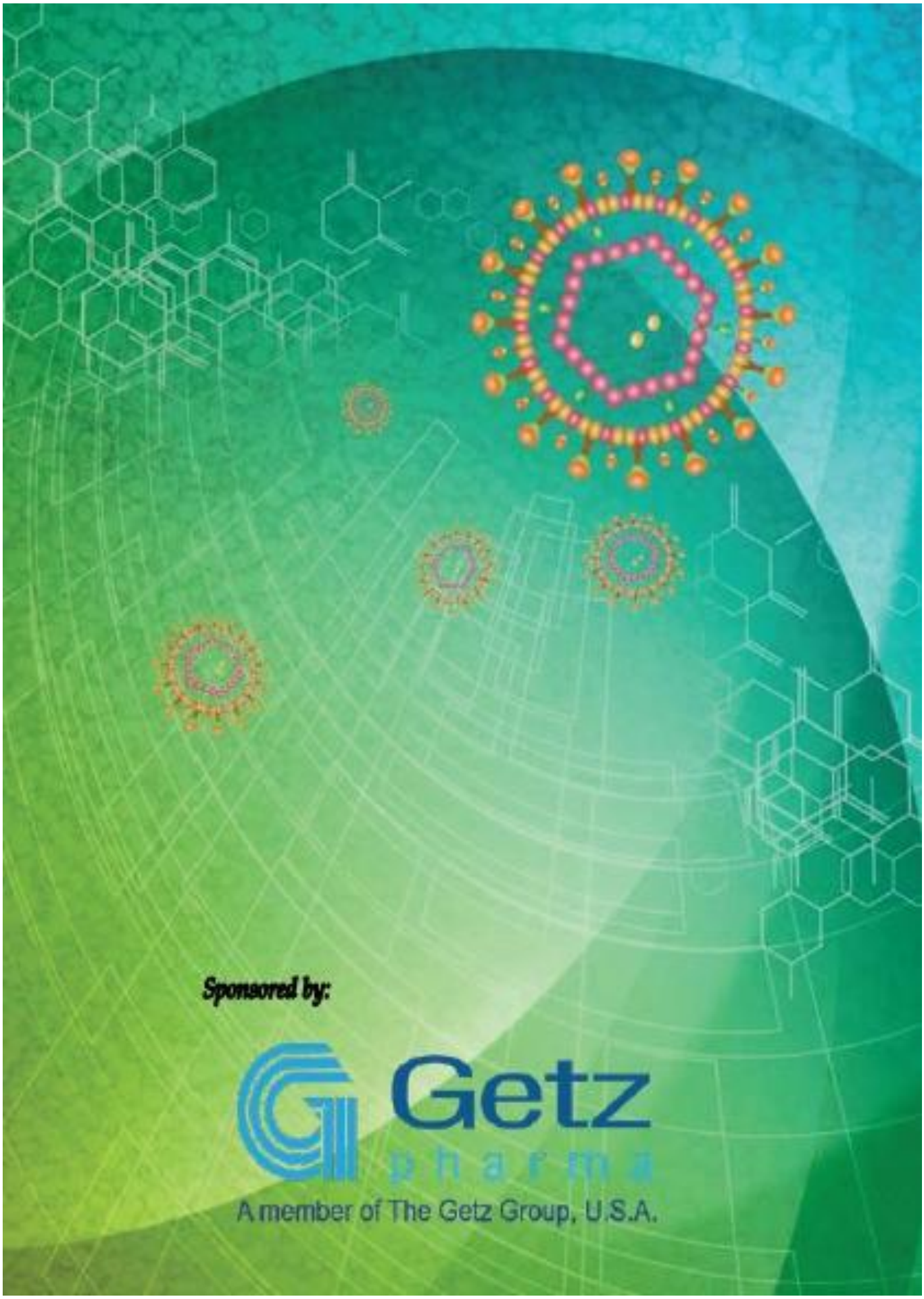
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