Revista de Gastroenterología de México 86 (2021) 403–432

REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

www.elsevier.es/rgmx

GUIDELINES AND CONSENSUS STATEMENTS

Asociación Mexicana de Hepatología A.C. Clinical guideline on hepatitis B☆

F. Higuera-de-la-Tijera[a], G.E. Castro-Narro[b,*], J.A. Velarde-Ruiz Velasco[c], E. Cerda-Reyes[d], R. Moreno-Alcántar[e], I. Aiza-Haddad[f], M. Castillo-Barradas[g], L.E. Cisneros-Garza[h], M. Dehesa-Violante[i], J. Flores-Calderón[j], M.S. González-Huezo[k], E. Márquez-Guillén[b], L.E. Muñóz-Espinosa[l], J.L. Pérez-Hernández[a], M.V. Ramos-Gómez[m], J. Sierra-Madero[b], J.F. Sánchez-Ávila[n], A. Torre-Delgadillo[b], R. Torres[o], E.R. Marín-López[p], D. Kershenobich[b], E. Wolpert-Barraza[q]

[a] *Departamento de Gastroenterología, Hospital General de México ''Dr. Eduardo Liceaga'', Mexico City, Mexico*
[b] *Departamento de Gastroenterología, Instituto Nacional de Ciencias Médicas y Nutrición ''Salvador Zubirán'', Mexico City, Mexico*
[c] *Departamento de Gastroenterología, Hospital Civil de Guadalajara ''Fray Antonio Alcalde'', Guadalajara, Jalisco, Mexico*
[d] *Departamento de Gastroenterología, Hospital Central Militar, Mexico City, Mexico*
[e] *Departamento de Gastroenterología, Hospital de Especialidades del Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Mexico*
[f] *Clínica de Enfermedades Hepáticas, Hospital Ángeles Lomas, Mexico City, Mexico*
[g] *Departamento de Gastroenterología, Hospital de Especialidades del Centro Médico Nacional ''La Raza'', IMSS, Mexico City, Mexico*
[h] *Centro de Enfermedades Hepáticas, Hospital San José, Nuevo León, Monterrey, Mexico*
[i] *Fundación Mexicana para la Salud Hepática A.C. (FUNDHEPA), Mexico City, Mexico*
[j] *Departamento de Gastroenterología, Hospital de Pediatría del Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Mexico*
[k] *Servicio de Gastroenterología y Endoscopia Gastrointestinal, ISSSEMYM, Metepec, Estado de México, Mexico*
[l] *Clínica de Hígado, Departamento de Medicina Interna, Hospital Universitario ''Dr. José E. González'', Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, Mexico*
[m] *Departamento de Gastroenterología, Centro Médico Nacional ''20 de Noviembre'', ISSSTE, Mexico City, Mexico*
[n] *Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Mexico City, Mexico*
[o] *Hospital de Infectología del Centro Médico Nacional ''La Raza'', IMSS, Mexico City, Mexico*
[p] *Hospital Ángeles Puebla, Puebla, Mexico*
[q] *Clínica Lomas Altas, Mexico City, Mexico*

Received 12 January 2021; accepted 14 April 2021

☆ Please cite this article as: Higuera-de-la-Tijera F, Castro-Narro GE, Velarde-Ruiz Velasco JA, Cerda-Reyes E, Moreno-Alcántar R, Aiza-Haddad I, et al. Asociación Mexicana de Hepatología A.C. Guía Clínica de Hepatitis B. Rev Gastroenterol México. 2021;86:403–432.

* Corresponding author.
E-mail address: gracastron@yahoo.com (G.E. Castro-Narro).

KEYWORDS
Hepatitis B virus;
Acute hepatitis;
Chronic hepatitis;
Hepatitis B surface antigen;
Entecavir;
Tenofovir disoproxil fumarate;
Tenofovir alafenamide;
Transition elastography;
Noninvasive methods for evaluating fibrosis

Abstract Hepatitis B virus (HBV) infection continues to be a worldwide public health problem. In Mexico, at least three million adults are estimated to have acquired hepatitis B (total hepatitis B core antibody [anti-HBc]-positive), and of those, 300,000 active carriers (hepatitis B surface antigen [HBsAg]-positive) could require treatment. Because HBV is preventable through vaccination, its universal application should be emphasized. HBV infection is a major risk factor for developing hepatocellular carcinoma. Semi-annual liver ultrasound and serum alpha-fetoprotein testing favor early detection of that cancer and should be carried out in all patients with chronic HBV infection, regardless of the presence of advanced fibrosis or cirrhosis. Currently, nucleoside/nucleotide analogues that have a high barrier to resistance are the first-line therapies.

PALABRAS CLAVE
Virus de la hepatitis B;
Hepatitis aguda;
Hepatitis crónica;
Antígeno de superficie de hepatitis B;
Entecavir;
Tenofovir disoproxil fumarato;
Tenofovir alafenamida;
Elastografía de transición;
Métodos no invasivos para evaluar la fibrosis

Asociación Mexicana de Hepatología A.C. Guía Clínica de Hepatitis B

Resumen La infección por el virus de hepatitis B (VHB) continúa siendo un problema de salud pública mundial, en México se estima que podría haber por lo menos tres millones de personas adultas que han adquirido hepatitis B (anticuerpo anti-antígeno central del VHB [anti-HBc] positivo), de ellos cerca de 300,000 portadores activos (antígeno de superficie del VHB [HBsAg] positivo) podrían requerir tratamiento. Al ser prevenible por vacunación, debe enfatizarse la vacunación universal. Esta infección es un factor de riesgo mayor para el desarrollo de carcinoma hepatocelular, el estudio semestral con ultrasonido hepático y alfafetoproteína sérica favorece la detección temprana de esta neoplasia y debe realizarse en todo paciente con infección crónica por VHB, independientemente de la presencia de fibrosis avanzada o cirrosis. En la actualidad, la terapia de primera línea, son análogos nucleós(t)idos con alta barrera a la resistencia.

Introduction

Despite the fact that chronic hepatitis B virus (HBV) is preventable through a highly efficacious strategy, such as universal vaccination, today, according to the World Health Organization (WHO), it continues to be a worldwide health problem, now affecting an estimated 257 million people for the year 2015.[1] Even though Mexico is considered a geographic region with a low prevalence (infected population is <2%), there have been numerous advances with respect to the pathophysiology of the disease, diagnostic tools, and significant achievements regarding safer and more efficacious treatments since the First National Consensus on Chronic Hepatitis B in Mexico was formulated in 2005.[2] Therefore, the *Asociación Mexicana de Hepatología A.C.* (*AMH*) has taken the initiative to develop an updated clinical guideline on hepatitis B, integrating the new concepts on epidemiology, diagnosis, treatment, and follow-up of the patients that suffer the disease. Table 1 summarizes the recommendations issued in the present clinical guideline.

Methodology

In November 2019, Dr. Graciela Elia Castro Narro, president of the *AMH*, and Dr. José Antonio Velarde Ruíz Velasco, General Coordinator of Consensuses and Clinical Guidelines of the *AMH*, designated two expert professionals (Dr. Fátima Higuera-de-la-Tijera [FHT] and Dr. Juan Francisco Sánchez Ávila [JFSA]) to act as coordinators of the Clinical Guidelines on Hepatitis B. Their functions were: 1) to carry out a thorough search of the literature in the following databases: PubMed, Embase, Medline, Trip Database, Clinical Evidence, and the Cochrane Library to collect all the latest relevant information and 2) to put together a panel of experts, divided into 4 different work groups, according to their areas of greater expertise, to formulate the different statements and recommendations and grade the available evidence, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) classification (Table 2).[3]

Table 1 Recommendation summary.

Recommendation	Grade of recommendation	Level of evidence
Risk groups and forms of transmission		
Recommendation 1: All persons that have greater risk factors for acquiring HBV infection, or that acquired it in the past, should undergo serologic screening.	1	II-B
Recommendation 2: The most effective strategy for achieving the elimination of HBV transmission is universal vaccination.	1	II-B
Screening for and surveillance of the development of HCC		
Recommendation 3: Semiannual liver ultrasound and serum AFP determination favors early HCC detection and should be carried out in all patients with chronic HBV infection, regardless of the presence of advanced fibrosis or cirrhosis.	1	II-B
Suggestions concerning alcohol consumption, comorbidities related to metabolic syndrome, and the need for specific vaccine application		
Recommendation 4: In all patients that are carriers of HBV infection, and at all phases of the disease, abstinence from alcohol consumption is recommended.	1	II-B
Recommendation 5: In patients with chronic HBV infection, comorbidities related to metabolic syndrome should be treated and controlled.	1	II-B
Recommendation 6: All patients with chronic HBV infection, with no prior immunity to hepatitis A, should be vaccinated against hepatitis A.	1	II-B
Studies for carrying out the initial evaluation of the patient with chronic HBV infection		
Recommendation 7: HBeAg and anti-HBe status, as well as HBV DNA (viral load) level, must be determined in all patients with chronic HBV infection, to establish prognosis and guide treatment.	1	I-A
Recommendation 8: In addition to physical examination, the evaluation of liver disease severity requires biochemical tests, particularly ALT, and liver ultrasound.	1	II-A
Recommendation 9: The presence and grade of liver fibrosis can be determined through noninvasive radiologic methods.	1	II-B
Recommendation 10: The presence and grade of liver fibrosis can be determined through noninvasive serologic methods.	2	II-B
Recommendation 11: Liver biopsy is necessary for establishing the presence and grade of liver fibrosis, when the results of noninvasive methods are inconclusive.	1	II-B
Chronic hepatitis B treatment goals		
Recommendation 12: The primary treatment goal in patients with CHB is to prevent the development of cirrhosis, hepatic decompensation, HCC, and liver-related death.	1	II-B
Recommendation 13: Undetectable HBsAg in serum and eradication of HBV DNA (intrahepatic cccDNA and integrated HBV DNA) are necessary for complete cure.	1	III
Recommendation 14: Functional cure of HBV should be defined as the lasting loss of hepatitis B surface antigen (HBsAg), with or without HBsAg seroconversion and undetectable HBV DNA in blood, after completing a course of treatment.	1	II-B
Selection criteria for starting specific antiviral therapy in patients with chronic hepatitis B		
Recommendation 15: Antiviral therapy is recommended in adults with chronic HBV infection, in the immune-active phase (currently called phases 2 and 4).	1	I-A
Recommendation 16: Patients with CHB and cirrhosis, whether compensated or decompensated, should always receive specific antiviral treatment, in the presence of any positive HBV DNA concentration, regardless of ALT levels.	1	I-A

Table 1 (*Continued*)

Recommendation	Grade of recommendation	Level of evidence
Follow-up in patients with CHB that do not merit starting specific treatment		
Recommendation 17: The determination of serum HBV DNA and HBeAg levels, as well as age, are parameters to consider for carrying out follow-up in patients with chronic HBV infection. In patients in the immune-tolerant phase (phase 1), follow-up is recommended every 3–6 months. In patients in the inactive carrier phase (phase 3), follow-up should be every 3 months during the first year, and then every 6–12 months.	1	II-B
Recommendation 18: In HBsAg + patients, the risk for HCC, transmission, reactivation, and extrahepatic manifestations should be considered, thus strict surveillance is recommended.	1	II-B
Current therapeutic strategies, follow-up, and surveillance of patients during treatment		
Recommendation 19: Antiviral treatment for acute hepatitis due to HBV is indicated only in severe cases that present with signs of hepatocellular dysfunction (hyperbilirubinemia, coagulopathy) or criteria for acute liver failure.	1	II-B
Recommendation 20: In patients with CHB that meet the criteria for starting treatment, first-choice drugs include nucleoside analogues (ETV) and nucleotide analogues (TDF and TAF).	1	I-A
Recommendation 21: Treatment with pegIFN alfa-2a can be an option in a subgroup of patients with chronic hepatitis due to HBV that meet the criteria for starting treatment.	2	I-A
HIV-HBV coinfection		
Recommendation 22: Currently all patients coinfected with HIV and HBV should receive standard antiretroviral treatment that preferably includes the addition of FTC or 3TC to the TDF or TAF regimen.	1	I-A
Recommendation 23: In patients with HIV-HBV coinfection that cannot use TDF or TAF (glomerular filtration rate <50 mL/min or <30 mL/min, respectively), ETV, in addition to the antiretroviral regimen, is recommended, as long as there has been no previous exposure to 3TC or FTC in regimens without TDF or TAF.	1	I-A
HCV-HBV coinfection		
Recommendation 24: Patients with HCV that are coinfected with HBV are at risk of HBV reactivation upon receiving treatment with DAA agents.	1	II-B
Recommendation 25: In patients with HCV-HBV coinfection that are HBsAg-positive and will start specific treatment with a DAA against HCV, starting prophylaxis with nucleoside/nucleotide analogues should also be considered, to prevent HBV reactivation.	2	II-B
Recommendation 26: Patients that are HBsAg-negative and anti-HBc-positive have a low reactivation risk. Therefore, monitoring ALT figures during DAA therapy and 12 weeks posttreatment, is considered sufficient in those patients.	1	II-B
HBV-HDV coinfection		
Recommendation 27: Anti-HDV determination is recommended in HBsAg-positive patients that present with risk factors for acquiring and concomitantly presenting with HDV infection.	1	III
Recommendation 28: Treatment with pegIFN alfa is the only treatment approved for treating patients with HBV-HDV coinfection, without cirrhosis and with compensated cirrhosis, for 48 weeks.	1	I-A
Decompensated cirrhosis		
Recommendation 29: Patients with decompensated cirrhosis and CHB should receive treatment with nucleoside/nucleotide analogues that have a high barrier to resistance, as a priority and indefinitely, regardless of ALT figures, HBeAg status, or HBV DNA viral load. In addition, they should be considered for inclusion in a liver transplantation program.	1	II-B

Table 1 (*Continued*)

Recommendation	Grade of recommendation	Level of evidence
Recommendation 30: TAF can be used as a therapeutic alternative against HBV in patients with decompensated cirrhosis at high risk for kidney function decline or at high risk for bone deterioration.	1	III
Post-transplantation management following liver, kidney, or other solid organ transplant		
Recommendation 31: Post-liver transplantation patients should continue treatment with nucleoside/nucleotide analogues (TDF, TAF, o ETV) + HBIG, to prevent CHB relapse.	1	II-A
Recommendation 32: In post-kidney or other non-liver solid organ transplantation patients, prophylaxis or treatment for HBV should be individualized, according to HBsAg and anti-HBc status.	1	II-B
Reactivation risk in the patient undergoing immunosuppressive or cytotoxic treatment		
Recommendation 33: There is a risk for HBV reactivation in patients that are immunocompromised or that receive cytotoxic or immunosuppressive therapy.	1	II-B
Recommendation 34: In patients at moderate-to-high risk for HVB reactivation, prophylaxis with nucleoside/nucleotide analogues that have a high barrier to resistance should be indicated.	1	II-B
Pregnancy and breastfeeding		
Recommendation 35: TDF is the only drug that is approved for treating hepatitis B in pregnant women.	1	I-A
Recommendation 36: All newborns, whose mothers are active HBV infection carriers (HBsAg-positive), should receive HBIG and the anti-HBV vaccine, within 12 h after birth.	1	I-A
Recommendation 37: Antiviral prophylaxis with TDF should be started in highly viremic HBsAg-positive pregnant women at the beginning of the third trimester, to prevent vertical HBV transmission.	1	I-A
Recommendation 38: Breastfeeding is not contraindicated for women with hepatitis B.	2	III
Kidney disease and bone disease		
Recommendation 39: ETV is preferred in patients with established kidney or bone disease or in patients with high-risk factors for the deterioration of kidney function or bone.	1	II-B
Recommendation 40: TAF is preferred in patients with established kidney or bone disease or in patients with high-risk factors for the deterioration of kidney function or bone.	1	I-A

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; anti-HBc: total hepatitis B core antibody; anti-HBe: hepatitis B e antibody; AST: aspartate aminotransferase; cccDNA: covalently closed circular deoxyribonucleic acid; CHB: chronic hepatitis B; DAA: direct-acting antiviral; ETV: entecavir; FTC: emtricitabine; HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HBV DNA: deoxyribonucleic acid of the hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; HDV: hepatitis D virus; HIV: human immunodeficiency virus; pegIFN: pegylated interferon; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate; 3TC: lamivudine.

Epidemiologic overview in Mexico

Seroprevalence in Mexico varies from 0.47 to 0.15%, according to a report from the National Blood Transfusion Center, that, between 2000 and 2012, evaluated a total of 19,096,294 reports of subjects that arrived from different parts of the country to donate blood. The states with greater reported prevalence were Aguascalientes, Campeche, Chiapas, Durango, Estado de México, Hidalgo, Mexico City, Nayarit, Puebla, San Luis Potosí, Sinaloa, Sonora, Tabasco, and Veracruz.[4] Areas of high endemicity in indigenous communities have been described in Mexico. In epidemiologic studies, at least three million adults are estimated to have acquired hepatitis B (total hepatitis B core antibody [anti-HBc]-positive), of whom the nearly 300,000 active carriers (hepatitis B surface antigen [HBsAg]-positive) could require treatment. However, if we consider the indigenous population as a zone of high endemicity, the number of patients that have been infected could increase to 7 or 8 million Mexicans, and approximately one million chronic active HBV carriers. If that situation were confirmed, HBV infection is postulated to affect an even higher number of persons than hepatitis C virus (HCV) in Mexico.[5]

According to its genomic divergence, HBV is classified into 8 genotypes, designated with the letters A–H. Recent information suggests the existence of genotypes I and J. A characteristic of HBV infection is the heterogeneous geographic distribution of its genotypes worldwide. The B and

Table 2 Grade of recommendation and level of evidence (modified GRADE).

Grade of recommendation	
1	Strong, in favor of the intervention: the quality of evidence, from which important positive results are derived for the patient or for costs, influences the strength of the recommendation.
2	Weak, in favor of the intervention: variability in preferences and values, or uncertainty. Little, or low-quality, evidence showing benefit to the patients, or requires high cost or resource use.
Level of evidence	
I-A	Randomized controlled trials
II-A	Nonrandomized clinical trials
II-B	Observational studies: cohort studies or case-control studies
II-C	Observational studies: case series Non-controlled experiments
III	Expert opinion

Source: Manterola et al.[3]

C genotypes are mainly confined to the Asian continent and the A and D genotypes to Europe and the United States. The H genotype is predominant in Mexico, whereas the F genotype is predominant in Central America and South America. The native Mexican or mestizo population shows a predominance for the H genotype, followed by the A, D, and G genotypes.[6–9]

Genotype A is likely to be detected in acute infections associated with high viral loads, whereas genotype D manifests at very low or undetectable levels. The progression of chronic infection occurs primarily between mestizo adults through horizontal transmission, and to a lesser degree, in children through vertical transmission.[10]

In a recent analysis of native Mexican groups, differences in serum cytokine levels have been reported that can distinguish patients infected with the H genotype from patients in whom the infection was resolved. The role of the HBV genotypes in the progression of the infection is not fully understood. Nevertheless, HBV genotypes A and D are accepted as being associated with a low risk for developing complications due to the infection, whereas the B, C, and F genotypes are closely associated with a high risk for developing hepatocellular carcinoma (HCC). In general, cirrhosis of the liver and HCC associated with HBV infection do not frequently occur in indigenous populations in Mexico, even when compared with the rest of Latin America, suggesting that genetic and environmental factors can also modulate the degree of adaptation to HBV infection. Finally, an important aspect to consider is the usefulness of the detection of the viral genotypes in evaluating the progress and severity of the infection, as well as treatment response.[10–12]

I. Risk groups and forms of transmission

HBV is primarily transmitted via the skin, sexual contact, or perinatally. The manner in which HBV infection is acquired is a determinant of endemicity of that chronic disease in a given population. When the infection is community-acquired in early childhood, there is a greater risk for a high pattern of prevalence[13] (Table 3).

Recommendation 1: All persons that have greater risk factors for acquiring HBV infection, or that acquired it in the past, should undergo serologic screening

- *Grade of recommendation: 1; Level of evidence: II-B*

Risk groups are considered to be migrating persons from countries with intermediate-to-high endemicity; active drug users or persons with a history of inhaled or intravenous drug use; men that have sex with men; persons living with human immunodeficiency virus (HIV); patients with HCV; persons that for any reason are going to receive immunosuppressive or cytotoxic therapy, biologic therapy, or are in a solid organ or hematopoietic transplantation protocol; patients with chronic kidney disease; patients on hemodialysis or peritoneal dialysis; hemophiliacs; blood, semen, or any organ or tissue donors; pregnant women; neonates whose mothers are HBV carriers; patients with elevated alanine aminotransferase (ALT) levels or aspartate aminotransferase (AST) levels, with no other apparent cause; persons with chronic liver disease; sexual partners of persons that are HBV carriers; persons with multiple sexual partners; healthcare personnel, laboratory personnel, or persons with occupational risk for exposure to blood and body fluids; incarcerated persons; persons with a history of sharing needles; persons that have gotten tattoos or perforations or undergone cosmetic procedures without knowing if sterile needles were used; and persons that are not vaccinated or do not know if they have been vaccinated.[14] In those high-risk groups, screening for HBV infection should be carried out through HBsAg determination, which is the marker for active infection, and hepatitis B surface antibody (anti-HBs) and total hepatitis B core antibody (anti-HBc), which together enable a person exposed to HBV to be distinguished from a person that is immune due to vaccination. Table 4 shows the interpretation of HBV serology. HBsAg positivity for fewer than 6 months is considered acute HBV infection and positivity persisting for more than 6 months is considered chronic infection. In addition, the presence of immunoglobulin M (IgM) anti-HBc supports the diagnosis of acute infection.[15]

Recommendation 2: The most effective strategy for achieving the elimination of HBV transmission is universal vaccination

- *Grade of recommendation: 1; Level of evidence: II-B*

Table 3 Geographic variation in the prevalence of hepatitis B and the main transmission routes.

Geographic area	Prevalence	Percentage of the population HBsAg+	Predominant age at infection	Main transmission route
Alaska and Inuit communities, the Pacific Islands, Australian Aboriginal communities, the Arabian Peninsula, Sub-Saharan Africa, Central Asia, Southeast Asia	High (≥8%)	8–20%	Perinatal and infancy	Maternal (gestation, birth, breastfeeding).
				Percutaneous (e.g., unsterilized medical equipment, traditional medical practices).
Northern Europe, Eastern Europe, Japan, India, the Mediterranean, the Middle East, Central America, South America	Intermediate (2–7%)	2–7%	Childhood and adolescence	Percutaneous (e.g., horizontal transmission between children, through open wounds).
				Sexual.
North America (including the United States, Canada, and Mexico), Western Europe, Australia (excluding the aboriginal communities), New Zealand	Low (<2%)	0.2–0.5%	Adulthood	Sexual.
				Percutaneous (e.g., intravenous/inhaled drugs, tattoos and perforations done at unregulated sites).

Source: Croagh and Lubel.[13]
HBsAg+: positive hepatitis B virus surface antigen.

Table 4 Interpretation of hepatitis B virus serology.

Antigen or antibody	Result	Interpretation
HBsAg Anti-HBc Anti-HBs	Negative Negative Negative	Susceptible
HBsAg IgG anti-HBc Anti-HBs	Negative Positive Positive	Immune due to natural infection
HBsAg Anti-HBc Anti-HBs	Negative Negative Positive	Immune due to vaccination
HBsAg IgG anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Positive Negative	Acute infection
HBsAg IgG anti-HBc IgM anti-HBc Anti-HBs	Positive Positive Negative Negative	Chronic infection

Anti-HBc: total hepatitis B core antibody; Anti-HBs: hepatitis B surface antibody; HBsAg: hepatitis B virus surface antigen; IgG: immunoglobulin G; IgM, immunoglobulin M. Source: Croagh and Lubel.[13] and Schillie et al.[14]

Since 1991, the WHO has recommended the incorporation of anti-HBV vaccines in health programs. In Mexico, the anti-HBV vaccine became part of the immunization regimen in 1999.[16] The current recommendation is universal vaccination, a strategy that has dramatically reduced HBV transmission in the different populations in which it has been implemented. All persons born before 1999 that have not been vaccinated and all those that for whatever reason were not vaccinated at birth should also receive the vaccination regimen.[4,17]

II. Phases of chronic infection

- *Chronic HBV infection is a dynamic process with replicative and non-replicative phases - activity that depends on an interaction between the virus and the host*

The interaction between virus and host depends on many factors, such as the age of the patient upon acquiring the infection, viral factors (genotype, viral mutations, and replication level), host factors (sex, age, and immunologic status), exogenous factors (alcohol consumption), and coinfection with other hepatotropic or non-hepatotropic viruses, e.g., HCV or HIV.[18,19]

In the process of resolution of acute infection, viral clearance takes place through cytokine expression and neutralizing-antibody-producing B lymphocyte induction that eradicate the virus in serum. However, reactivation is possible in patients with resolved hepatitis B. Said reactivation can occur spontaneously, but it is more frequent in severely immunosuppressed patients, such as those receiving immunosuppressive therapy, patients with acquired immunodeficiencies, and posttransplantation patients.[19,20]

- *The natural history of chronic HBV infection has been divided into 5 phases, taking into account the serologic characteristics of hepatitis B, the viral load (HBV deoxyribonucleic acid [HBV DNA]), hepatitis B e antigen (HBeAg) positivity or negativity, ALT levels, and histologic findings in liver biopsy*

Phase 1: HBeAg-positive chronic HBV infection (previously known as the ''immune tolerant'' phase). It is characterized by the presence of HBeAg, elevated HBV DNA levels, normal ALT levels, with minimal or no inflammation or fibrosis in the liver biopsy.[21,22]

Phase 2: HBeAg-positive chronic hepatitis B (CHB) (previously known as the HBeAg-positive ''immune active'' phase). Patients in this phase are HBeAg-positive, with elevated levels of HBV DNA, elevated ALT levels, and signs of inflammation and necrosis in liver biopsy, with accelerated progression of fibrosis.[21,22]

Phase 3: HBeAg-negative chronic HBV infection (previously known as the ''inactive carrier'' phase). This phase is characterized by the presence of serum antibodies to HBeAg (anti-HBe), the HBV DNA viral load is generally undetectable or low (<2000 IU/mL), and ALT levels are close to normal (approximately 40 IU/l). The typical histologic characteristics are mild necroinflammatory activity, with a minimum of fibrosis, and a low risk for disease progression. Low levels of HBsAg (<1000 IU/mL) have been reported and spontaneous loss or seroconversion of HBsAg can occur in 1–3% of cases annually.[21,22]

Phase 4: HBeAg-negative CHB (previously HBeAg-negative ''immune active'' phase). These patients are characterized by the absence of serum HBeAg and are generally anti-HBe-positive, but with elevated and fluctuating levels of HBV DNA and ALT. Biopsy shows important necroinflammation and fibrosis. Patients in this phase have mutations in the precore region or in the basal core promoter region that impede HBeAg expression.[21,22]

Phase 5: ''Occult infection''. Patients in this phase are HBsAg-negative and anti-HBc-positive, with or without the

presence of anti-HBs. ALT levels are normal, and HBV DNA is undetectable in the majority of cases. HBsAg loss before the development of cirrhosis is a good outcome factor.[22]

III. Screening for and surveillance of the development of hepatocellular carcinoma

HCC is the most frequent tumor of the liver and is the fourth cause of cancer-related death worldwide. It is the fifth most frequent cancer in men and the ninth most frequent cancer in women. According to the report of the World Cancer Research Fund of the American Institute for Cancer Research, in 2018 there were more than 840,000 new cases.[23] Among the risk factors for the development of HCC, CHB accounts for 44% of all cases worldwide, the majority of which are in Asia, which has a high prevalence of CHB.[24] Other risk factors include HCV, aflatoxins, tobacco, alcohol, metabolic diseases (such as alpha-1 antitrypsin), hemochromatosis, and cirrhosis. Evidence also points to obesity as a possible risk factor.[25] Diabetes can increase the risk for HCC, regardless of the risk conferred by obesity alone.[26,27]

Recommendation 3: Semiannual liver ultrasound and serum alpha-fetoprotein (AFP) determination favors early hepatocellular carcinoma detection and should be carried out in all patients with chronic HBV infection, regardless of the presence of advanced fibrosis or cirrhosis

- *Grade of recommendation:1; Level of evidence: II-B*

Molecular studies have shown that the integration of HBV DNA into the genome of the host causes genomic instability that can lead to hepatocarcinogenesis.[28–30] HBeAg positivity is strongly associated with an increased risk for HCC.[31] The viral load level is another factor strongly associated with the risk for developing HCC. In a study by Chen et al., a serum HBV DNA level $\geq$ 10,000 copies/mL (equivalent to $\geq$2000 IU/mL) was associated with the risk of HCC, regardless of HBeAg, ALT, or the presence of cirrhosis.[32] In addition, Tseng et al. found that, similar to the HBV DNA viral load, HBsAg levels were also associated with the development of HCC. The risk increased significantly when HBsAg levels were >1000 IU/mL in HBeAg-negative patients with low viremia.[33]

In the REVEAL-HBV study, subjects that had an initial viral load below 2000 IU/mL had a low risk for HCC, and those in whom it was >20,000 IU/mL had a greater risk.[32]

Among the 10 HBV genotypes, genotypes C, D, and F are associated with a greater risk for developing HCC. In longitudinal studies, the Ce subtype has been shown to be an independent risk factor for developing HCC.[31,33,34]

Persistent inflammation caused by HBV before treatment, clinically characterized by high levels of aminotransferases and histologically reflected by necroinflammatory activity, is a main trigger in the development of HCC.[35]

AFP determination with a cutoff point >20 ng/mL for HCC diagnosis has 41–65% sensitivity and 80–95% specificity. However, up to 50% of patients with HCC have AFP values <20 ng/mL and false positive results related to other hepatic alterations can be found. AFP values >400 ng/mL are much more specific, but less sensitive, for diagnosing HCC.[36] AFP values >1000 ng/mL signify poor prognosis for liver resection, as well as for liver transplantation, and are related to a high risk of recurrence.[37,38]

Regarding liver ultrasound for HCC detection, Coli et al. reported 60.5% (44–76%) sensitivity, 96.9% (95–98%) specificity, a positive probability coefficient of 17.7 (8.5–36.9), and a negative probability coefficient of 0.5 (0.4—0.6). The combination of AFP determination and liver ultrasound can increase the detection rates, but it can also increase costs and false positives.[39]

Lesions smaller than 1 cm should be monitored with ultrasound at 3 months. If the lesion persists at the same size, ultrasound should be repeated in 3 more months. If the lesion has grown, other studies should be carried out, similar to when the detected lesion is larger than 1 cm, and dynamic tomography of the liver or magnetic resonance imaging are indicated.[40]

IV. Suggestions concerning alcohol consumption, comorbidities related to metabolic syndrome, and the need for specific vaccine application

Recommendation 4: In all patients that are carriers of HBV infection, and at all phases of the disease, abstinence from alcohol consumption is recommended

- *Grade of recommendation: 1; Level of evidence: II-B*

Alcohol consumption in quantities >60 g/day, in patients with CHB, accelerates the progression of liver disease to cirrhosis and the development of HCC.[41] A study showed that the relative risk (RR) for progression of liver disease in patients with CHB and concomitant alcohol consumption was 6.3 (95% confidence interval [95% CI]: 3.1–12.8). In a follow-up at 20 years of patients with CHB, alcohol consumption was also associated with a 6-fold increase in the risk of death due to cirrhosis and HCC.[42] Whether alcohol intake in low-to-moderate quantities in patients with CHB increases that risk as well, is a subject of debate.[41] Nevertheless, a systematic review and meta-analysis showed that no quantity of alcohol consumption can be considered safe, given that even amounts traditionally considered not to be a risk, were related to the development of liver disease in men and women. Those results suggest there is individual variability regarding susceptibility to damage, added to multiple factors that can be interrelated to favor liver damage associated with alcohol consumption.[43] Therefore, strict abstinence from alcohol is recommended in patients with HBV infection, at all phases of the disease.

Recommendation 5: In patients with chronic HBV infection, comorbidities related to metabolic syndrome should be treated and controlled

- *Grade of recommendation: 1; Level of evidence: II-B*

Even though CHB does not appear to increase the risk for metabolic syndrome, atherosclerosis, or type 2 diabetes mellitus[44]–some studies even suggest that the presence of HBV infection is associated with a decrease in the risk for metabolic syndrome–,[45] CHB *per se* is known to increase the risk for developing cirrhosis and HCC. Likewise, metabolic

syndrome, which is an increasingly prevalent condition, also increases the risk for HCC, regardless of the presence of cirrhosis.[46] Therefore, establishing the treatment and control of comorbidities characteristic of metabolic syndrome is recommendable in all patients with chronic HBV infection.

Recommendation 6: All patients with chronic HBV infection, with no prior immunity to hepatitis A, should be vaccinated against hepatitis A

- *Grade of recommendation: 1; Level of evidence: II-B*

Patients with CHB that acquire acute hepatitis A have a more severe clinical course and higher mortality rate, compared with healthy individuals that acquire hepatitis A infection. In addition, those differences are more pronounced in older adult patients and patients with histologic evidence of chronic hepatitis or cirrhosis, compared with HBV carriers that do not have those conditions. The available vaccines against hepatitis A are highly efficacious and safe. Thus, verification of the serologic status of hepatitis A is recommended in patients with chronic HBV infection, and if there are no antibodies to hepatitis A, the specific vaccination should be indicated.[47]

V. Studies for carrying out the initial evaluation of the patient with chronic HBV infection

Recommendation 7: HBeAg and anti-HBe status, as well as HBV DNA (viral load) level, must be determined in all patients with chronic HBV infection, to establish prognosis and guide treatment

- *Grade of recommendation: 1; Level of evidence: I-A*

Serum or plasma HBV DNA should be quantified through polymerase chain reaction (PCR) technology. For example, the Abbott RealTime HBV assay utilizes PCR technology, combined with homogeneous real time fluorescent detection to quantify HBV DNA. The selection of a highly conserved region of the gene that encodes HBsAg enables the detection of the A–H genotypes. The location of the target region in the N-terminal third of the surface gene guarantees that the assay is not affected by YMDD mutants, immune-escaped HBsAg mutants, or drug-resistant mutants, given that said region is essential for the binding and secretion of subviral particles and only tolerates major structural changes. The results can be reported in IU/mL or log IU/mL, or in copies/mL or log copies/mL. The conversion factor is 1 IU: 3.41 copies. The linear interval of the analysis is from 10 to 1 billion IU/mL.[48]

HBeAg positivity generally indicates active viral replication. The combination of HBeAg and high serum HBV DNA levels are related to an increased risk for developing cirrhosis, decompensation, and HCC.[31,32,49] Thus, seroconversion to an anti-HBe status is one of the treatment goals, which is usually achieved in 20–30% of the HBeAg-positive patients.[50]

The mutations in the precore and in the specific basal core promoter are among the most common mutations in HBV. They are associated with the reduction and abolition of HBeAg production, respectively. Said mutations emerge late in the course of the natural history of the disease, in the immunoreactive phase of HBeAg seroconversion.[51] Because they are late changes in the course of CHB, those mutations are related to the established presence of advanced fibrosis or cirrhosis at the time of diagnosis, as well as to the risk of necroinflammation flares, decompensation, and a greater risk for HCC.[52–55]

Serum HBsAg levels reflect active covalently closed circular DNA (cccDNA) and serve as an efficacy marker during treatment.[56] Low baseline serum levels of HBsAg (<1000 IU/mL), as well as a greater decrease of serum HBsAg levels during treatment, are useful for predicting HBsAg seroclearance,[57] particularly in patients treated with pegylated interferon (pegIFN), given that the value of quantifying HBsAg levels in patients treated with nucleoside/nucleotide analogues (NAs) is uncertain. Therefore, in clinical practice serum HBsAg quantification does not substitute HBV DNA quantification.[58]

HBV is characterized by high genetic heterogeneity, given that it replicates through an inverse transcriptase that lacks correction capacity. At present, ten genotypes (A–J) have been described. In general, genotype A is associated with a better response to treatment with pegIFN. Genotype C, and to a lesser degree genotype B, generally are risk factors for perinatal infection and are associated with advanced liver disease, cirrhosis, and HCC. Genotype D is related to deficient response to treatment with pegIFN. Therefore, genotype determination can play a prognostic role in patients that are going to be treated with pegIFN, but outside of that scenario, genotype determination is not indispensable, within the pre-treatment protocol of patients with CHB.[58]

Recommendation 8: In addition to physical examination, the evaluation of liver disease severity requires biochemical tests, particularly ALT, and liver ultrasound

- *Grade of recommendation: 1; Level of evidence: I-A*

High serum ALT is the most widely used indirect marker for necroinflammation in patients with CHB. It is one of the most important parameters to take into account for defining when treatment should begin and for monitoring the disease during treatment. Due to variability in the values considered normal, the cutoff point for the upper limit of normal (ULN) of ALT is recommended at 30 U/l in men and 19 U/l in women.[59]

Baseline liver ultrasound is obligatory, regardless of the presence and grade of fibrosis or cirrhosis, because it enables the evaluation of the hepatic morphology and is part of the screening of early HCC lesions, given the high risk inherent in CHB for the development of that neoplasm.[40]

Recommendation 9: The presence and grade of liver fibrosis can be determined through noninvasive radiologic methods

- *Grade of recommendation: 1; Level of evidence: II-B*

Radiologic methods have shown greater precision than serologic methods for classifying the grade of fibrosis in patients with CHB, given that they do not appear to change as markedly as the serologic tests, with respect to transaminase values.[60]

Transition elastography (TE) is the most validated, and thus preferred, radiologic method.[61] A meta-analysis showed that TE had good precision for classifying the grade of fibrosis in patients with CHB. Compared with biopsy, the overall sensitivity of TE for staging significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4) was 0.806 (95% CI: 0.756–0.847), 0.819 (95% CI: 0.748–0.874), and 0.863 (95% CI: 0.818–0.898), respectively. Overall specificity was 0.824 (95% CI: 0.761–0.873), 0.866 (95% CI: 0.824–0.899), and 0.875 (95% CI: 0.840–0.903), respectively. The corresponding areas under the curve were 0.88 (95% CI: 0.85–0.91), 0.91 (95% CI: 0.88–0.93), and 0.93 (95% CI: 0.91–0.95), respectively.[62]

Two-dimensional shear wave elastography (2D-SWE) has similar precision to that of TE. The most precise method of all appears to be magnetic resonance elastography (MRE), and it is superior to 2D-SWE.[23] In addition to staging the grade of fibrosis with excellent precision (areas under the curve for characterizing mild fibrosis [≥F1], ≥F2, ≥F3, and F4 of 0.961, 0.986, 1.000, and 0.998, respectively), MRE has been shown to be useful for estimating the grade of necroinflammation: mild (≥A1), moderate (≥A2), and severe (A3), with areas under the curve of 0.806, 0.834, and 0.906, respectively. A better characterization of liver damage is achieved, given that the presence and grade of necroinflammation is a relevant factor that overestimates the grade of fibrosis.[63,64] Those findings need to be validated because there are few studies with MRE in the context of patients with CHB.

Recommendation 10: The presence and grade of liver fibrosis can be determined through noninvasive serologic methods

- *Grade of recommendation: 2; Level of evidence: II-B*

Serologic markers have lacked precision in the context of the patient with CHB due to the fact that the increase in transaminases is a factor that can considerably overestimate the grade of fibrosis when those biomarkers are used. The most widely studied serologic markers in patients with CHB are the AST to Platelet Ratio Index (APRI) and Fibrosis-4 (FIB4). The majority of studies conducted agree that they lack precision in CHB patients. In a study that compared the performance of APRI and FIB4 versus the Ishak fibrosis stage by biopsy, the majority (81–89%) of the patients with advanced fibrosis or cirrhosis were not correctly detected by either of those indexes. Likewise, 71% of the patients with no fibrosis were incorrectly classified as patients with significant fibrosis or higher. In addition, both the APRI and the FIB4 applied at week 240 after treatment, underestimated the fibrosis stage, demonstrating that the reduction of necroinflammation associated with treatment modifies those indexes, and there was no correlation between them and the biopsy report.[65]

The GGT to platelet ratio (GPR), Lok index, Forns index, and e-antigen-positive CHB liver fibrosis (EPLF) score have been compared with the APRI and FIB4, in different studies, but none have conclusively been shown to be more precise for identifying the presence and grade of fibrosis in CHB.[66–69]

Wang et al. developed a new model based on the platelet (PLT) count, standard deviation of red blood cell distribution width (RDW-SD), alkaline phosphatase (ALP), and serum globulin, called the APRG index. The areas under the curve of the APRG index for predicting ≥F2, ≥F3, and F4 were 0.757 (95% CI: 0.699–0.816), 0.763 (95% CI: 0.711–0.816), and 0.781 (95% CI: 0.728–0.835), respectively. In that study, the APRG index was superior to others, such as the APRI, FIB4, GPR, RDW to PLT ratio, and AST to ALT ratio, for predicting significant and advanced fibrosis and cirrhosis. Nevertheless, it does not appear to be better than the noninvasive radiologic methods, according to the areas under the curve those authors reported, and so cannot yet be recommended.[70]

With respect to the commercial serologic methods, the performance of the FibroTest, compared with liver biopsy, for determining the grade of fibrosis in patients with CHB, was evaluated in a meta-analysis. The results showed that the FibroTest had greater diagnostic value for excluding the presence of cirrhosis in patients with CHB, but suboptimum precision for detecting significant fibrosis and cirrhosis, in which the area under the curve was 0.84 (95% CI: 0.78–0.88).[71]

The noninvasive serologic methods are recommended for evaluating the grade of fibrosis in patients with CHB, only as an alternative if radiologic methods are not available. Likewise, the serologic methods can add diagnostic value when combined with a noninvasive radiologic method, as said strategy increases diagnostic precision in determining the presence and grade of fibrosis.[72]

Recommendation 11: Liver biopsy is necessary for establishing the presence and grade of liver fibrosis, when the results of noninvasive methods are inconclusive

- *Grade of recommendation: 1; Level of evidence: II-B*

All the noninvasive methods are more precise for ruling out the presence of advanced fibrosis or cirrhosis than for confirming them. When there are confounding factors, such as in patients with CHB with high levels of ALT and important inflammation, the grade of fibrosis can be overestimated. When the noninvasive methods are not conclusive, liver biopsy should be the method resorted to, for evaluating the presence and grade of fibrosis.[73]

Liver biopsy continues to be considered the gold standard for evaluating the grade of damage in patients with HBV infection. The pathology of hepatitis B is diverse and reflects the natural history of the infection. Sampling error is the most important problem, leading to underestimating the grade of fibrosis. Adequate liver biopsy should consist of 11 portal tracts and a length of at least 1.5–2.0 cm, with no fragmentation. Cutting-type needles appear to be superior to suction-type needles for performing the procedure.[74]

VI. Chronic hepatitis B treatment goals

Recommendation 12: The primary treatment goal in patients with chronic hepatitis B is to prevent the development of cirrhosis, hepatic decompensation, hepatocellular carcinoma, and liver-related death

- *Grade of recommendation: 1; Level of evidence: II-B*

CHB is the main cause of liver-related morbidity and mortality worldwide.[75] Not treating the disease leads to an increased risk for progression to cirrhosis (>40%) and decompensation (ascites, variceal bleeding, encephalopathy), as well as to the risk for developing HCC. A study showed that up to 30% of the patients with cirrhosis due to CHB developed HCC during a 10-year follow-up period. In addition, patients with CHB can also develop HCC in the absence of cirrhosis (10% of the cases in a cohort that included 8539 patients).[76] Elevated serum HBV DNA is significantly associated with the development of liver failure, cirrhosis and HCC, making antiviral therapy crucial for modifying the natural history of CHB.[75]

Recommendation 13: Undetectable HBsAg in serum and eradication of HBV DNA (intrahepatic cccDNA and integrated HBV DNA) are necessary for complete cure

- *Grade of recommendation: 1; Level of evidence: III*

The primary goal of treatment of any chronic infection is the eradication of the infectious agent, ideally before it causes irreversible damage. Regarding CHB, even though, at present, we cannot achieve viral eradication, we can eventually achieve complete suppression of the virus with the treatments available today.[77]

The aim of new therapies is to cure HBV, i.e., to eliminate the virus, allowing treatment to be stopped with no risk of virologic relapse or progression of the liver disease. However, a true cure may not be feasible because the HBV DNA is integrated into the genome of the host. Even in persons that have recovered from acute HBV, viral cccDNA can be detected in the liver, which explains the reactivation of HBV replication when those ''recovered'' persons are profoundly immunosuppressed.[78,79]

Recommendation 14: Functional cure of HBV should be defined as the lasting loss of hepatitis B surface antigen (HBsAg), with or without HBsAg seroconversion and undetectable HBV DNA in blood, after completing a course of treatment

- *Grade of recommendation: 1; Level of evidence: II-B*

Three definitions of cure, in the context of HBV infection, have currently been proposed:

1 *Complete cure:* Undetectable HBsAg in blood and eradication of HBV DNA, including intrahepatic cccDNA and integrated HBV DNA.
2 *Functional cure:* Persistently undetectable HBV DNA and HBsAg in serum, with or without seroconversion to anti-HBs, after completing a finite course of treatment; resolution of residual liver damage; and a reduced risk for HCC over time.
3 *Partial cure:* Detectable HBsAg but persistently undetectable HBV DNA in serum, after completing a finite course of treatment.[78]

A document on treatment evaluation criteria to guide clinical trials whose aim is to ''cure'' HBV has recently been published. The expert panel suggested that the primary goal of phase 3 trials should be functional cure, described as HBsAg loss in $\geq$30% of the patients involved in the trials. An intermediate goal was sustained virologic suppression (undetectable serum HBV DNA) with no HBsAg loss, 6 months after treatment interruption. Finally, the majority of the participants agreed that the ''functional cure of HBV'' should be defined as the lasting loss of HBsAg (based on trials with lower limit of detection [LLOD] 0.05 IU/mL), with or without HBsAg seroconversion and undetectable serum HBV DNA, after completing a course of treatment.[79]

The goal of short-term viral eradication is to prevent complications of the disease. Hence, the usefulness of certain biomarkers has been suggested for evaluating the status of the disease. Unfortunately, none of the biomarkers available today ideally measure the efficacy of the treatment itself. Perhaps that is why the approval of new therapies for CHB by the licensing authorities has usually depended on the demonstration of significant improvements in two or more surrogate markers of disease progression with the treatment. Typically, the surrogates are: (1) biochemical (aminotransferase levels, in particular ALT), (2) virologic (HBV DNA, HBeAg, HBsAg levels), and (3) histologic (based on histologic scoring systems).[77]

It is not yet possible to achieve complete cure in patients with CHB, therefore functional or partial cures are more realistic goals to reach with the therapies available. In addition, another important goal should be the normalization of ALT.[78–80]

Several studies on HBeAg-positive patients with CHB have shown that treatment-induced HBeAg loss and seroconversion to anti-HBe, lead to a phase in which viral replication tends to be low, resulting in better long-term survival. Therefore, inducing HBeAg loss and seroconversion to anti-HBe, in addition to achieving an undetectable HBV DNA viral burden, is a valuable objective.[80]

VII. Selection criteria for starting specific antiviral therapy in patients with chronic hepatitis B

Recommendation 15: Antiviral therapy is recommended in adults with chronic hepatitis B virus infection, in the immune-active phase (currently called phases 2 and 4)

- *Grade of recommendation: 1; Level of evidence: I-A*

The indication for starting treatment is based on 3 criteria: serum HBV DNA levels, serum ALT levels, and the grade of liver disease determined through noninvasive methods or liver biopsy.[80]

The treatment goal is to reduce the risk of progression to cirrhosis and prevent the risk of developing HCC. Therefore, treatment is indicated in the immune-active phase of chronic HBV infection (also currently known as phases 2 and 4), which is when there is risk for liver damage and progression to liver fibrosis. Antiviral treatment should be started in all patients, regardless of fibrosis grade, that have signs of hepatic inflammation (ALT values $\geq$2-fold above the ULN defined in the present guideline), combined with significant HBV replication, which is defined as follows[77,80]:

If HBeAg is negative, consider a HBV DNA load >2000 IU/mL.[77,80]

If HBeAg is positive, consider a HBV DNA load >20,000 IU/mL.[77,80]

The persistent inhibition of HBV replication and normalization of ALT values correlate with the elimination of necroinflammatory activity and the risk for fibrosis progression in patients with CHB, which in turn, is associated with overall survival improvement, a reduced risk for developing HCC, and better patient quality of life. In addition, persistent inhibition of HBV replication prevents transmission.[80]

Recommendation 16: Patients with chronic hepatitis B and cirrhosis, whether compensated or decompensated, should always receive specific antiviral treatment, in the presence of any positive HBV DNA concentration, regardless of ALT levels

- *Grade of recommendation: 1; Level of evidence: I-A*

In patients with compensated cirrhosis, antiviral therapy with NAs that have a high barrier to resistance (tenofovir disoproxil fumarate [TDF], tenofovir alafenamide [TAF], and entecavir [ETV]) and viral load suppression (undetectable HBV DNA) that is achieved through said therapy have been shown to significantly reduce the risk for disease progression. Likewise, in patients with decompensated cirrhosis, antiviral therapy with NAs should be started as soon as possible, given that it has been shown to significantly modify the natural history of the disease due to the fact that it improves liver function and increases survival.[81–83] Those patients should also be evaluated for liver transplantation, but therapy with NAs can improve their condition. Up to 35% of patients treated with NAs were delisted for liver transplant because liver function improved.[84]

VIII. Follow-up in patients with chronic hepatitis B that do not merit starting specific treatment

Recommendation 17: The determination of serum HBV DNA and HBeAg levels, as well as age, are parameters to consider for carrying out follow-up in patients with chronic HBV infection

In patients in the immune-tolerant phase (phase 1), follow-up is recommended every 3–6 months.

In patients in the inactive carrier phase (phase 3), follow-up should be every 3 months during the first year, and then every 6–12 months.

- *Grade of recommendation: 1; Level of evidence: II-B*

Patients in the immune-tolerant phase (phase 1) of CHB, i.e., HBeAg-positive, with normal or slightly elevated ALT or AST, with no fibrosis or necroinflammatory activity, or mild or minimal inflammation, present with a low risk for disease progression, despite the fact that they tend to have a high viral load. In those patients, monitoring of ALT levels every 3–6 months is recommended. HBeAg status should be verified every 6–12 months. In patients whose viral load is persistently elevated (HBV DNA > 20,000 IU/mL) and that present with elevated ALT 2-fold <the ULN, the need to evaluate the grade of fibrosis through TE (FIB4 or FibroTest as alternatives) should be considered, or liver biopsy, if fibrosis ≥F2. In the presence of moderate-to-severe necroinflammatory activity (A2, A3), starting specific antiviral treatment is recommended.[80]

Patients in the inactive CHB phase (phase 3) (HBeAg-negative, anti-HBe-positive, normal ALT, HBV DNA <2000 IU/mL) are also characterized by presenting with minimal necroinflammatory activity and fibrosis. Therefore, they can be monitored with ALT level determination every 3 months for the first year, and then every 6–12 months. In addition, they should be evaluated yearly to verify HBsAg loss.[85] In HBeAg-negative CHB patients, if HBV DNA is >2000 IU/mL and ALT elevation is 2-fold < the ULN, the need to evaluate the grade of fibrosis through TE (FIB4 or FibroTest as alternatives) should be considered, or liver biopsy, if fibrosis is ≥F2. In the presence of moderate-to-severe necroinflammatory activity (A2, A3), the recommendation is to start specific antiviral treatment. If HBV DNA is maintained <2000 IU/mL, but there is an increase in ALT, evaluating possible additional causes that explain said increase is always recommendable, such as alcohol consumption, nonalcoholic steatohepatitis, hepatitis C, hepatitis D, autoimmune liver disease, or liver damage induced by drugs or herbal medicine.[86]

In patients that achieve HBsAg clearance spontaneously or through treatment, surveillance through ALT and HBV DNA levels is no longer necessary, given that those patients are in the ''functional cure'' stage (HBsAg-negative, anti-HBs-positive).[87]

Recommendation 18: In HBsAg+ patients, the risk for HCC, transmission, reactivation, and extrahepatic manifestations should be considered, thus strict surveillance is recommended

- *Grade of recommendation: 1; Level of evidence: II-B*

In all patients with CHB and advanced fibrosis or cirrhosis, maintaining HCC screening through liver ultrasound and serum AFP determination every 6 months is recommended. In patients with CHB and a family history of HCC, subjects that come from endemic geographic regions (e.g., Asian regions), patients whose CHB is diagnosed in early ages of life (childhood or adolescence), and in men above 40 years of age and women above 50 years of age, semiannual HCC screening should be carried out, regardless of the presence and grade of fibrosis.[88–90]

Another clinical scenario sometimes observed in patients coinfected with HIV or HCV, in immunocompromised patients, pregnant women, patients on dialysis, or in patients that are intravenous drug users, is the presence of isolated (negative HBsAg) positive IgG anti-HBc. Those cases do not require surveillance, except in cases of immunosuppression, in which, albeit infrequently, the risk of reactivation and start of prophylaxis should be considered.[91–93]

Starting treatment at any phase of the disease should be considered in patients at high risk for HBV transmission, such as patients that are inhaled or intravenous drug users, men that have sex with men, patients coinfected with HIV, patients with extrahepatic manifestations, and immunosuppressed patients due to any cause.[90]

IX. Current therapeutic strategies, follow-up, and surveillance of patients during treatment

Recommendation 19: Antiviral treatment for acute hepatitis due to HBV is indicated only in severe cases that present with signs of hepatocellular dysfunction (hyperbilirubinemia, coagulopathy) or criteria for acute liver failure

- *Grade of recommendation: 1; Level of evidence: II-B*

The diagnosis of acute HBV infection is confirmed by the presence of IgM anti-HBc in a HBsAg-positive subject. The majority of immunocompetent patients that acquire acute hepatitis B are self-limited and do not require treatment.[94] Even though it is an infrequent condition, acute liver failure (ALF) associated with HBV is a potentially lethal condition (as high as 40–50%),[95,96] characterized by massive necrosis of hepatocytes that clinically translates into jaundice (total bilirubin [TB] > 3.0 mg/dL or direct bilirubin [BD] > 1.5 mg/dL), coagulopathy (INR $\geq$ 1.5), encephalopathy, or ascites, in the absence of pre-existing liver disease.[96,97] The development of ascites (hazard ratio [HR] 10.5, 95% CI: 1.6–68.6; p = 0.01) and a MELD score >25 (HR 28.9, 95% CI: 4.7–177.3, p = 0.0001) have been described as the most relevant predictive factors associated with mortality or the need for transplantation.[98]

Even though the majority of evidence is sustained in studies that have explored the efficacy of lamivudine (3TC) in acute hepatitis B,[99–106] the therapeutic regimens with ETV, TDF, or TAF are currently preferred due to their lower risk for developing resistances. Case-control studies and cohort studies have shown comparable efficacy between 3TC, ETV, and TDF, in which the early start of treatment has been reported to reduce the risk of progression to ALF, the need for transplantation, and has also improved survival. [98,107,108] In all patients with the criteria for severe acute hepatitis, with a risk for progressing to ALF, specific antiviral treatment based on ETV, TDF, or TAF, should be indicated. In general, treatment should be continued until there is HBsAg clearance. If liver transplantation has been performed, the recommendation is for treatment to be carried out indefinitely.[109]

Recommendation 20: In patients with chronic hepatitis due to HBV that meet the criteria for starting treatment, first-choice drugs include nucleoside analogues (ETV) and nucleotide analogues (TDF and TAF)

- *Grade of recommendation: 1; Level of evidence: I-A*

ETV (0.5 mg/day), TDF (300 mg/day), and TAF (25 mg/day) are HBV polymerase inhibitors with high barriers to resistance. They are extremely potent for achieving profound suppression of viral replication and have an excellent safety profile. Given those characteristics, they are currently recommended as first-line therapy in patients with HBV infection. The 3 are comparable in efficacy in treatment-naïve patients.[110,111] However, ETV is not recommended in patients with previous exposure to 3TC, owing to the fact that patients that have developed resistance to 3TC tend to have 2 or 3 mutations required for developing resistance to ETV. Therefore, up to 51% of those patients will present with resistance to ETV within 5 years of treatment. TDF and TAF are better options in patients with prior exposure to 3TC.[112]

At 10 years of follow-up, TDF and ETV have shown effective suppression of the HBV DNA viral load of 94–99%, in HBeAg-positive patients, as well as in HBeAg-negative patients. HBeAg seroconversion in HBeAg-positive patients, with TDF or ETV, has been reported in 49–53% of the cases. ALT normalization has been achieved in 77–83% of the patients with CHB, treated with any of those regimens. Nevertheless, yearly frequency of HBsAg seroconversion is rare (<1% annually).[113]

Tenofovir is a dianion at physiologic pH, with poor membranal permeability and low availability, after its oral administration. To improve its bioavailability after oral administration, it should be administered as a prodrug (TDF or TAF).[113–115]

After its oral administration, TDF is hydrolyzed by gut and plasma esterases, to be converted into tenofovir diphosphate, its active metabolite. In contrast, TAF is stable in plasma and is metabolized mainly in the intracellular environment by means of cathepsin A, to be converted into its active form, tenofovir diphosphate.[114] TAF is indicated at a dose of 25 mg/day, and because it is a prodrug with greater stability in plasma than TDF, there is less exposure of the active metabolite, tenofovir diphosphate, in plasma. Therefore, the risk of renal and bone toxicity derived from its long-term administration is lower, compared with TDF.[115] The results of clinical trials show that TAF is as efficacious as TDF for achieving viral load suppression in treatment-naïve patients, treatment-experienced patients, HBeAg-positive patients, and HBeAg-negative patients at 48, 96, and 144 weeks of treatment.[116] Lampertico et al. demonstrated that switching TDF to TAF did not compromise therapeutic efficacy and they also confirmed lower renal and bone toxicity with TAF.[117] The most frequent adverse effects are similar to those with TDF (headache, abdominal pain, fatigue, cough, nausea).[116]

Follow-up and monitoring of patients undergoing treatment with NAs is carried out with: biochemical parameters (complete blood count [CBC], liver function tests [LFTs], blood chemistry tests, creatinine depuration), serologic parameters (HBsAg, anti-HBs, HBeAg, anti-HBe), and HBV DNA viral load, all of which are performed at baseline, every three months the first year, and then twice a year.[113,118–120]

Treatment response with NAs is defined as[118]:

a) **Virologic:** undetectable HBV DNA viral load
b) **Biochemical:** serum ALT normalization
c) **Histologic:** improvement in the grade of hepatic necroinflammation
d) **Serologic:** HBeAg seroconversion, and ideally, HBsAg seroconversion, although it does not frequently occur (3–11%).[119,120] Thus, treatment should be long-term, generally for life. However, in patients that have achieved HBsAg seroconversion, suspension can be considered, without stopping their surveillance and continuing biannual HCC screening, particularly in patients that achieve seroconversion at >50 years of age or in patients with cirrhosis.[118–120]

Starting treatment with NAs that have a low barrier to resistance, such as 3TC, adefovir (ADV), or telbivudine (TBV), is no longer recommended. In patients with a history of treatment with 3TC, ADV, or TBV, that have developed resistance, switching the drug to TDF or TAF is recommended. In the case of patients with resistance to ADV, the drug can be switched to ETV, as long as there has been no previous exposure to 3TC (prior exposure to 3TC confers cross-resistance to ETV, when the following mutations are present: rtM204V/I, rtT184, rtS202, tM250).[121–125] In patients with an elevated viral load and resistance to ADV associated with the rA181T/V or rN236T mutations, response to TDF or TAF can be prolonged. In such cases, adding ETV is recommended.[126] Patients with multiresistance are a true challenge and the current recommendation is the combined treatment of ETV plus TDF or TAF.[127] Park et al. described two cases of multiresistance, with partial response to TDF, that were successfully treated with a novel capsid assembly modulator (NVR 3-778), but those types of drugs are not yet available in clinical practice.[128]

In patients undergoing treatment with NAs with high barriers to resistance, treatment failure is defined as follows:

a) Partial virologic response to a decrease in the HBV DNA viral load >1 $\log_{10}$ IU/mL but still detectable after at least one year of treatment.[113]
b) Virologic breakthrough is defined as an increase in the HBV DNA viral load >1 $\log_{10}$ (or >100 IU/mL in patients with a previously undetectable viral load) during treatment.[113]

The majority of cases of those 2 scenarios are due to lack of treatment adherence. Nevertheless, in cases of partial response or virologic breakthrough, when lack of adherence has been ruled out, the emergence of variants associated with resistance should be suspected.[113]

In clinical practice, primary resistance to TDF or to TAF has not been documented in the long-term follow-up of patients with CHB, but if it were to be reported, the addition of ETV to the TDF or TAF regimen is suggested. Future alternatives could be the capsid assembly modulators (not yet available).[128] Primary resistance to ETV in treatment-naïve patients is estimated at around 1.2%, and the switch to TDF or TAF is effective in those cases.[113,129] The majority of cases first defined as partial responders are related to excessively elevated viral loads that resolve over time, continuing in treatment with NAs selected as the first treatment choice, with no changes.[126,127,130]

Recommendation 21: Treatment with pegIFN alfa-2a can be an option in a subgroup of patients with chronic hepatitis due to HBV that meet the criteria for starting treatment

- *Grade of recommendation: 2; Level of evidence: I-A*

Treatment with pegIFN alfa-2a is definitely contraindicated in patients with decompensated cirrhosis. Said treatment can be considered in patients with CHB that ideally do not have cirrhosis and have favorable criteria for achieving treatment response, such as HBeAg-positive patients, patients with genotype A or B (the genotypes that have shown better response, compared with others), young patients, patients with no comorbidities, patients with a low viral load, and those with ALT 2-fold above the ULN.[131] In HBeAg-negative patients, the favorable predictors of pegIFN response are youth, female sex, a low viral load, and high ALT levels.[132]

PegIFN is administered subcutaneously every week for 48 weeks. The extension to 72, or even 96 weeks, has been shown to increase the success rate for reaching sustained virologic response (SVR). However, its numerous adverse effects limit treatment adherence and tolerability by patients.[133,134] The SVR to treatment is evaluated 24 weeks after treatment completion. The response criteria are the same as those described for NAs, with the exception of the virologic criterion. In that case, reaching a HBV DNA viral load <2000 IU/mL is considered response (sustained response is achieved in approximately 30% of cases). HBsAg seroconversion (functional cure) is reached in barely 10% of cases.[118] Furthermore, pegIFN has not been on the Mexican market, ever since the appearance of new direct-acting agents for treating hepatitis C.

The criteria of treatment failure with pegIFN, for which the drug should be suspended, are:

HBeAg-positive patients: treatment should be suspended at week 12, if HBsAg levels in patients with genotypes A and D have not decreased, whereas treatment should be suspended in patients with genotypes B and C, if HBsAg levels are >20,000 IU/mL. At week 24 of treatment, all patients with serum HBsAg levels >20,000 IU/mL are very unlikely to respond to treatment with pegIFN, thus, it is a suspension criterion, no matter the genotype. In the case of failure, patients should be treated with first-line NAs.[135]

HBeAg-negative patients: regardless of genotype, not achieving a decrease in serum HBsAg levels and a decrease <2 log in the HBV DNA viral load at week 12 are considered treatment failure criteria.[136]

X. Chronic hepatitis B management in special populations

Human immunodeficiency virus-hepatitis B virus coinfection

Recommendation 22: Currently all patients coinfected with HIV and HBV should receive standard antiretroviral treatment that preferably includes the addition of emtricitabine (FTC) or lamivudine (3TC) to the TDF or TAF regimen

- *Grade of recommendation: 1; Level of evidence: I-A*

Progression to cirrhosis, advanced liver disease, decompensation, or the development of HCC are faster in coinfected HIV-HBV patients.[137] Therefore, all patients with said coinfection should receive antiretroviral treatment that always includes 2 different drugs that are active against HBV. Either TDF or TAF combined with FTC or 3TC, are all drugs that are approved for the treatment of HIV. They are also active against HBV and have a low resistance profile. Therefore, they are currently considered first-line drugs to be included in the antiretroviral regimen for patients with HIV-HBV coinfection.[138–140]

Antiretroviral regimens than contain only one drug that is active against HBV should not be used. Neither 3TC nor FTC should be used alone. For example, after 2–4 years of 3TC monotherapy, resistance of HBV to the drug was reported in 40–90% of patients.[141] Regimens based on TBV or ADV alone, or in combination with 3TC or FTC are not recommended either, given that they have a greater risk for treatment failure, for selecting HIV-resistant variants, and a higher frequency of toxicity and adverse effects, such as kidney function deterioration, myopathy, or neuropathy, compared with TDF + FTC or TAF + FTC.[142–144]

Recommendation 23: In patients with HIV-HBV coinfection that cannot use TDF or TAF (glomerular filtration rate <50 mL/min or <30 mL/min, respectively), ETV, in addition to the antiretroviral regimen, is recommended, as long as there has been no previous exposure to 3TC or FTC in regimens without TDF or TAF

- *Grade of recommendation: 1; level of evidence: I-A*

TDF + FTC and TAF + FTC regimens in patients with HIV-HBV coinfection are not approved in patients with a glomerular filtration rate <50 mL/min and <30 mL/min, respectively. An alternative for treating CHB in patients with kidney function decline and HIV-HBV coinfection is ETV. Nevertheless, in prescribing ETV in patients with HIV-HBV coinfection, one must always be certain the patient is receiving fully suppressive highly active antiretroviral therapy (HAART) because ETV use in HIV-HBV coinfected patients that do not receive that antiretroviral therapy has been shown to favor the selection of the M184V mutation that confers resistance of HIV to 3TC and FTC.[145] As long as ETV is administered together with HAART, it has been shown to be an efficacious and safe option in patients with HIV-HBV coinfection. A study in that context demonstrated that the treatment of HBV with ETV, in patients coinfected with HIV that were receiving the HAART regimen that included 3TC, produced a decrease of -4.20 $\log_{10}$ copies/mL, with respect to HBV DNA, at 48 weeks of treatment with HAART and ETV. There were no significant adverse events or relevant changes, with respect to HIV viremia or the CD4 cell count.[146]

Hepatitis C virus-hepatitis B virus coinfection

Recommendation 24: Patients with HCV that are coinfected with HBV are at risk of HBV reactivation upon receiving treatment with direct-acting antiviral (DAA) agents

- *Grade of recommendation: 1; Level of evidence: II-B*

HBV reactivation is defined as the loss of immune control that causes an abrupt increase in viral replication and can occur in 2 scenarios: 1) patients with chronic HBV infection (HBsAg-positive and anti-HBc-positive) and 2) patients previously exposed to HBV, but that had recovered (HBsAg-negative, anti-HBc-positive, generally anti-HBs-positive).[147] Clinically significant HBV reactivation is characterized by an increase in HBV DNA and ALT,[148] in both scenarios. Seroconversion is reversed specifically in the second scenario, i.e., there is a return to HBsAg positivity[149] (see the technical descriptions of reactivation and hepatitis flare further ahead in the ''*Reactivation risk in the patient undergoing immunosuppressive or cytotoxic treatment* section'').

The prevalence of HBsAg positivity in patients with HCV has been reported at 1.4–5.8%.[149,150] Patients with HCV-HBV coinfection that receive specific treatment with a DAA against HCV are considered at risk for HBV reactivation. From November 2013 to October 2016, the Food and Drug Administration (FDA) documented 29 cases of HBV reactivation in HBsAg-positive patients that received DAA therapy due to concomitant chronic HCV infection. Two of those patients died and one underwent liver transplantation.[151] Two later studies demonstrated a high risk of HBV reactivation (>10%) in HBsAg-positive patients during and after treatment with a DAA against HCV. In contrast, the risk for reactivation was considered low (<1%) in HBsAg-negative and anti-HBc-positive patients.[148,152–154]

Recommendation 25: In patients with HCV-HBV coinfection that are HBsAg-positive and will start specific treatment with a DAA against HCV, starting prophylaxis with nucleoside/nucleotide analogues should also be considered, to prevent HBV reactivation

- *Grade of recommendation: 2; Level of evidence: II-B*

To reduce the risk for reactivation, HBV status in all patients with HCV should be determined through a serology profile that includes HBsAg, anti-HBs, and anti-HBc determination, before starting treatment with a DAA.[151] HBsAg-positive patients have a higher risk for reactivation and for presenting with flares (ALT increase $\geq$3-fold above the patient's baseline value and >100 U/l) during treatment with a DAA. Therefore, the baseline status of the HBV DNA viral load and ALT values should also be determined in those patients. Administering prophylaxis with NAs during DAA therapy and up to 12 weeks after its completion should particularly be considered in patients with a detectable baseline HBV DNA viral load (Table 5). In patients with an undetectable baseline HBV DNA viral load, strict surveillance can be an option, i.e., monitoring ALT and HBV DNA values every 4 weeks. If the HBV DNA viral load becomes detectable and there is an increase in ALT, starting prophylaxis should be considered.[148,152–155]

Recommendation 26: Patients that are HBsAg-negative and anti-HBc-positive have a low reactivation risk. Therefore, monitoring ALT figures during DAA therapy and 12 weeks posttreatment, is considered sufficient in those patients

- *Grade of recommendation: 1; Level of evidence: II-B*

Patients that are HBsAg-negative and anti-HBc-positive have a low risk for reactivation, and so monitoring ALT values every 4 weeks and up to 12 weeks after DAA therapy is considered sufficient. If during that surveillance there is a persistent increase in ALT, HBsAg and HBV DNA viral load values should also be newly determined.[155]

The need for starting specific treatment for CHB in patients with HCV-HBV coinfection is determined utilizing exactly the same criteria previously described herein for patients with HBV monoinfection.[80]

Table 5 Prophylaxis to prevent HBV infection reactivation in patients that are receiving a DAA to treat hepatitis C or in patients that receive immunosuppressants or cytotoxic agents.

Drug and dose	Commentary	Duration
TAF 25 mg/day, taken orally	If creatinine depuration is $\geq$ 15 mL/min	a) Coinfection with HCV: up to week 12 after completing treatment with a DAA
	Preferable if there has been prior lamivudine use	b) Immunosuppressive therapy or cytotoxic agents with moderate-to-high risk for HBV reactivation: continue for >6 months after discontinuing immunosuppressive therapy or cytotoxic agents c) Immunosuppressive therapy or cytotoxic agents with very high risk for HBV reactivation: (B cell depleting agents, e.g., rituximab): continue for >12 months after discontinuing immunosuppressive therapy or cytotoxic agents
TDF 300 mg/day, taken orally	If creatinine depuration is $\geq$50 mL/min	
	Preferable if there has been prior lamivudine use	
Entecavir 0.5 mg/day, taken orally	In patients with no prior lamivudine use	
Entecavir 1 mg/day, taken orally	In patients with prior lamivudine use	

Source: Gane et al.,[153] Yi et al.,[219] and Tanaka et al.[220]
DAA: direct-acting antiviral; HBV: hepatitis B virus; HCV: hepatitis C virus; TAF: tenofovir alafenamide; TDF: tenofovir disoproxil fumarate.

Hepatitis B virus-hepatitis D virus coinfection

Recommendation 27: Anti-HDV determination is recommended in HBsAg-positive patients that present with risk factors for acquiring and concomitantly presenting with HDV infection

- *Grade of recommendation: 1; Level of evidence: III*

Few studies have evaluated the prevalence of HDV infection in Mexico. The frequency in patients with HDV due to HBV infection has been reported at 2.3–4.0%.[156] HDV can be acquired acutely or simultaneously with HBV (coinfection). That scenario is usually clinically characterized by severe acute hepatitis and is associated with increased mortality. It rarely progresses to chronicity. HDV infection can also present as a superinfection. In that context, acute HDV infection in a patient that previously presented with CHB, manifests as a clinical exacerbation in a previously stable CHB patient. It frequently progresses to chronicity and leads to a higher risk of HCC and decompensated liver disease.[157]

According to the WHO, at least 5% of the persons with chronic infection due to HBV are also infected with HDV. The number of persons infected worldwide has decreased since the 1980s, which is a trend that is primarily the result of the global vaccination program against HBV. HBV-HDV coinfection is considered the most severe form of chronic viral hepatitis, given its faster progression to HCC and its higher mortality rate associated with decompensated liver disease.[158]

The main HDV transmission routes are sexual and parenteral. Vertical transmission is possible but infrequent. The risk groups for acquiring hepatitis D are patients diagnosed with HIV; intravenous drug users; men that have sex with men; persons with numerous sexual partners that practice unsafe sex; persons with a history of sexually transmitted diseases; immigrants from regions with a reported high prevalence of the disease, such as Africa (Central and Western), Asia (Central and Northern, Vietnam, Mongolia, Pakistan, Japan, China, and Chinese Taipei), the Pacific Islands (Kiribati, Nauru), the Middle East (all countries), Eastern Europe (the Eastern Mediterranean zones and Turkey), South America (the Amazon basin), and Greenland; and patients with CHB that have low or undetectable HBV DNA, but high ALT or AST values. In all those patients, baseline hepatitis D screening is recommended, and in patients with persistent risk factors, periodic repeat screening (every 6 months) should be carried out. HDV infection is diagnosed by the presence of antibodies to HDV (anti-HDV) and is confirmed by the detection of serum HDV ribonucleic acid (HDV RNA), which is also useful for evaluating response to antiviral treatment. The WHO recommends HBsAg quantification for determining treatment response, if no tests for quantifying the HDV RNA are available. Reduced HBsAg titers tend to predict HBsAg loss and correlate with HDV clearance, albeit HBsAg loss is rare with treatmnt.[158–163]

Recommendation 28: Treatment with pegIFN alfa is the only treatment approved for treating patients with HBV-HDV coinfection, without cirrhosis and with compensated cirrhosis, for 48 weeks

- *Grade of recommendation: 1; Level of evidence: 1A*

Oral NAs employed for treating CHB are not active against HDV. In patients with HBV-HDV coinfection, specific HBV treatment should be started under the same rules and criteria previously described for patients with monoinfection.[163,164]

In treating patients with hepatitis D, the main goal is to inhibit HDV replication, i.e., to negativize the HDV RNA viral load. That is generally accompanied by the normalization of ALT values and a decrease in the necroinflammatory activity in the liver parenchyma. An additional goal should be HBsAg negativization. When HDV is actively replicating, meaning that the HDV RNA viral load is detectable and quantifiable, the only approved treatment is with pegIFN alfa (2a or 2b) for a minimum of 48 weeks, regardless of the response observed during treatment.[158] The overall SVR is low, around 25–30%,[164] and the long-term relapse rate (around 4.3 years) is high (barely 12% remain in SVR).[165] SVR (undetectable viral load 6 months after having completed treatment) following said treatment is an independent factor associated with a lower probability of liver disease progression.[158] Early viral response (undetectable viral load at 24 weeks during treatment) is considered a factor associated with SVR. The habitual pegIFN alfa 2b dose employed in different clinical trials evaluating its efficacy in patients with HDV was 1.5 μg/kg/week, subcutaneously,[166–168] and in the case of pegIFN alfa 2a was 180 μg/week, subcutaneously, both with similar efficacy.[169,170] The addition of 3TC,[171] ADV,[169] or ribavirin[168] to the pegIFN alfa regimen has not resulted in greater efficacy, and so the use of any additional drugs cannot be recommended. When treating patients with HBV-HDV in Mexico, it must be kept in mind that pegIFN alfa 2a and 2b are no longer available in the country, after having been discontinued as first-line therapy against HCV.

Decompensated cirrhosis

Recommendation 29: Patients with decompensated cirrhosis and CHB should receive treatment with nucleoside/nucleotide analogues that have a high barrier to resistance, as a priority and indefinitely, regardless of ALT figures, HBeAg status, or HBV DNA viral load. In addition, they should be considered for inclusion in a liver transplantation program

- *Grade of recommendation: 1; Level of evidence: II-B*

All patients with cirrhosis and HBV should receive treatment to (a) limit liver disease progression, (b) improve liver function, (c) reduce the risk for developing HCC, (d) and pretransplantation, to specifically reduce the risk of reinfection and to prevent the development of fibrosing cholestatic hepatitis, post-transplantation, and (e) reduce mortality. Treatment should be for an indefinite period of time due to the high risk of relapse upon its suspension. Ideally, the goal of maintaining undetectable HBV DNA viral load should be achieved, given that it is associated with a much lower risk for graft infection after liver transplant, in the case of said procedure. However, antiviral treatment *per se* has shown that 35% of patients on the liver transplant waiting list can

be delisted, due to improved liver function. [84,172] TDF and ETV (1 mg oral per day in decompensated cirrhosis) is currently considered the first choice in those patients, given that they are efficacious options, with high barriers to resistance, and they are safe, as well. ETV, in particular, is safer in patients at risk for osteopenia or osteoporosis, or at risk for kidney function deterioration.[173–179]

PegIFN alfa is contraindicated in patients with decompensated cirrhosis,[156] and currently, other therapies with low barriers to resistance that were used in the past, are no longer recommendable, because if resistance to them develops, it favors progression to decompensation.[180]

Despite receiving specific treatment for CHB, those patients remain at high risk for the development of HCC. Therefore, biannual screening with liver ultrasound and AFP determination should be continued.[181]

Recommendation 30: Tenofovir alafenamide can be used as a therapeutic alternative against HBV in patients with decompensated cirrhosis at high risk for kidney function decline or at high risk for bone deterioration

- *Grade of recommendation: 1; Level of evidence: III*

Kidney failure, as well as bone disease, are frequent conditions in patients with decompensated cirrhosis. Up to 24% of ambulatory cirrhotic patients are estimated to develop some type of kidney dysfunction, within the first year from the first ascites episode.[182] The prevalence of bone disease in patients with cirrhosis is estimated at 12–55%.[183] Even though there are no studies at present that have specifically explored the use of TAF in patients with HBV and decompensated cirrhosis, TAF is known to possess the advantage of having less kidney and bone toxicity, even requiring no adjustment in the habitual dose of 25 mg per day in patients with glomerular filtration rates >15 mL/min in patients with HBV monoinfection.[22] In addition, studies on other populations, such as patients with HIV[184–186] and patients with CHB, with and without compensated cirrhosis, have shown no inferiority, with respect to TDF, as well as a better kidney and bone safety profile.[187–189] Thus, the present panel is of the opinion that TAF can be used as a safe and efficacious alternative in decompensated cirrhotic patients at the same dose of 25 mg/day, orally, as in compensated patients or in patients without cirrhosis.

Post-transplantation management following liver, kidney, or other solid organ transplant

Recommendation 31: Post-liver transplantation patients should continue treatment with nucleoside/nucleotide analogues (TDF, TAF, or ETV) + hepatitis B immune globulin (HBIG), to prevent CHB relapse

- *Grade of recommendation: 1; Level of evidence: II-A*

The combination of a NA + HBIG in the post-transplanted patient, to achieve HBV DNA viral load suppression and titers of antibodies to HB above 100 IU/l, has been shown to prevent graft infection in 90–100% of patients and improve 5-year survival in 80%.[22,190,191]

Samuel et al.[192] were the first to demonstrate the usefulness of HBIG in reducing the risk for graft infection. They utilized high doses of HBIG (10,000 IU per day, intravenously) in the intraoperative anhepatic phase, followed by the same daily dose for the next 7 days, and then in the long term, i.e., the same dose but in monthly intervals (for more than 6 months). That strategy reduced graft infection from 90% to only 20–40% and significantly reduced the mortality rate in those patients.[192–196] The main limitation of HBIG use at high doses is its elevated cost and its side effects, such as headache, flushes, and chest pain, and very rarely, allergic reactions.[197] Later studies showed that the administration of HBIG together with specific antiviral therapy (TDF, TAF, or ETV, drugs with a high barrier to resistance that are today considered first-line therapies) enables the use of lower doses of HBIG (intravenous, intramuscular, or subcutaneous),[198–207] and in some cases even dispensing with the long-term administration of HBIG,[208] for example, in patients with no poor prognosis factors that impact the risk of graft infection, such as a history of HCC or active HCC as the main cause for transplantation, the presence of resistance to previous drugs, elevated HBV DNA viral load at the time of transplantation, coinfection with HIV or with HDV, and a history of poor treatment adherence.[209–220]

Combined with specific antiviral treatment, which should be administered indefinitely, the administration of HBIG (dose, administration route, duration) varies greatly at the different transplantation centers across the globe. In general, the different clinical trials that have shown efficacy have evaluated doses from 800 to 10,000 IU. Higher doses are generally opted for in the intraoperative anhepatic phase, continuing with the daily administration of similar doses for 5–7 days after transplantation, followed by the weekly administration of doses from 200 to 10,000 IU for the first month. When stopping maintenance HBIG is chosen, doses from 800 to 10,000 IU are administered once a month for an indefinite period of time.[192–207,209–220] In general terms, if regimens are used that include HBIG in post-transplantation prophylaxis in patients with HBV, to efficaciously prevent graft infection, anti-HBs titers are recommended to be kept >500 IU/l for the first 3 months and >250 IU/l from the third month for up to 6–12 post-transplant months. After that, maintaining the levels from 50 to 100 IU/l is sufficient.[197]

In selected low-risk cases, in which HBV DNA is undetectable at the time of transplantation and there is no prior history of resistance to NAs, a short course of HBIG administration, lasting one to 3 months, accompanied by NA therapy, and then followed by monotherapy with ETV, TDF, or TAF for an indefinite period of time, has been shown to efficiently prevent the recurrence of HBV infection.[191]

Recommendation 32: In post-kidney or other non-liver solid organ transplantation patients, prophylaxis or treatment for HBV should be individualized, according to HBsAg and anti-HBc status

- *Grade of recommendation: 1; Level of evidence: II-B*

In such cases, if HBsAg is positive, prophylaxis or treatment should be started, preferably with TAF or ETV because of their better safety profiles regarding kidney function. If HBsAg is negative but there is positive anti-HBc, monitor-

Table 6 Reactivation risk according to serologic status and viral load of HBV.

Reactivation risk	Parameters
High (>10%)	HBsAg-positive
	HBeAg-positive or negative
	HBV DNA > 2000 IU/mL
Moderate (1−10%)	HBsAg-negative
	Anti-HBs-negative
	IgG anti-HBc-positive
Low (<1%)	HBsAg-negative
	Anti-HBs-positive
	IgG anti-HBc-positive

Source: Jang et al.[84]
HBV DNA: deoxyribonucleic acid of the hepatitis B virus (viral load); IgG anti-HBc: immunoglobulin G antibody to hepatitis B core antigen; anti-HBs: hepatitis B surface antibody; HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus.

ing of HBsAg status during the follow-up is recommended in those patients. If there is seroconversion to positive HBsAg, therapy with ETV or TAF should be started immediately, regardless of ALT values.[22]

Reactivation risk in the patient undergoing immunosuppressive or cytotoxic treatment

Recommendation 33: There is a risk for HBV reactivation in patients that are immunocompromised or that receive cytotoxic or immunosuppressive therapy

- *Grade of recommendation: 1; Level of evidence: II-B*

Definition of reactivation:

a) Patients that are HBsAg-positive/anti-HBc-positive:
   1 Increase ≥2 log (100-fold) in the HBV DNA viral load, compared with baseline levels.
   2 HBV DNA ≥3 log (1000) IU/mL in patients with a previously undetectable viral load (given that HBV DNA levels can fluctuate).
   3 HBV DNA ≥4 log (10,000) IU/mL if the baseline viral load level is unknown.
b) Patients that are HBsAg-negative/anti-HBc-positive:
   1 Detectable HBV DNA.
   2 Reappearance of HBsAg.

A hepatitis flare in both scenarios is defined as an increase in ALT ≥3-fold above the baseline values of the patient and >100 U/l.[86]

The risk for reactivation is related to 3 main factors: (1) the patient's HBV status (Table 6), (2) the patient's concomitant disease that was the reason for starting immunosuppressive or cytotoxic therapy (the most commonly related diseases are cancer, chronic inflammatory pathologies, and autoimmune diseases), and (3) the immunosuppressive or cytotoxic agent utilized (Table 7).[221–223]

Table 7 Immunosuppressants with HBV reactivation potential and grade of risk.

Low risk (< 1%)	Methotrexate
	Azathioprine
	6-Mercaptopurine
	Corticosteroids for <1 week
	Intra-articular therapy with corticosteroids
Moderate risk (1−10%)	Calcineurin inhibitors (tacrolimus, cyclosporine).
	Tyrosine-kinase inhibitors (imatinib, nilotinib). Moderate risk if HBsAg + or HBsAg−/anti-HBc+.
	TNF-alpha inhibitors (infliximab, adalimumab, etanercept, certolizumab, golimumab). Moderate risk if HBsAg + or HBsAg−/anti-HBc+.
	Other cytokine inhibitors (abatacept, ustekinumab, natalizumab, vedolizumab). Moderate risk if HBsAg+ or HBsAg−/anti-HBc+.
	Anthracycline derivatives (doxorubicin, epirubicin). Moderate risk if HBsAg−/anti-HBc+.
	Prednisone: ≥10 mg/day for ≥4 weeks (or equivalent corticosteroid). Moderate risk if HBsAg−/anti-HBc+.
	Prednisone: <10 mg/day for >4 weeks (or equivalent corticosteroid). Moderate risk if HBsAg+.
High risk (>10%)	Systemic chemotherapy.
	B cell depleting agents (rituximab, ofatumumab, obinutuzumab, ocrelizumab). High risk if HBsAg + or HBsAg−/anti-HBc+.
	Anthracycline derivatives (doxorubicin, epirubicin). High risk if HBsAg+.
	Prednisone: ≥10 mg/day for ≥4 weeks (or equivalent corticosteroid). High risk if HBsAg+.

Source: Gane et al.,[153] Yi et al.,[219] and Tanaka et al.[220]
HBsAg+: hepatitis B surface antigen-positive; HBsAg-: hepatitis B surface antigen-negative; anti-HBc+: total hepatitis B core antibody-positive; TNF-alpha: tumor necrosis factor-alpha; HBV: hepatitis B virus.

Recommendation 34: In patients at moderate-to-high risk for HBV reactivation, prophylaxis with nucleoside/nucleotide analogues that have a high barrier to resistance should be indicated

- *Grade of recommendation: 1; Level of evidence: II-B*

In 5 controlled clinical trials that evaluated antiviral prophylaxis in 139 HBsAg-positive or anti-HBc-positive patients, versus 137 controls to whom on-demand rescue therapy was offered in the case of HBV reactivation, the pooled estimates showed that antiviral prophylaxis was associated with an 87% RR reduction for reactivation (95% CI: 70–94%), as well as an 84% RR reduction (95% CI: 58–94%) for hepatitis flares associated with HBV. In a subgroup analysis, the greatest benefit from having received antiviral prophylaxis was shown in the groups classified with moderate and high reactivation risks, whereas the benefit was not as significant in the group classified with low risk for reactivation.[223]

Despite the fact that the majority of studies on prophylaxis have been conducted using 3TC, that drug is no longer recommended. ETV, TDF, or TAF are preferred instead, given their high barriers to resistance. Of the 3, ETV is the most widely validated.[223,224]

In patients with a low risk for reactivation, starting prophylaxis is not recommended. In patients with moderate-to-high reactivation risk criteria, prophylaxis with NAs should be carried out during the entire time the patient requires immunosuppressive treatment and continued for at least 6 months after suspension of the immunosuppressant. If agents that induce B-cell depletion are being used, the recommendation is to extend the prophylaxis for a minimum of 12 months after suspending the immunosuppressant (Tables 6 and 7).[155]

Pregnancy and breastfeeding

Recommendation 35: Tenofovir disoproxil is the only drug that is approved for treating hepatitis B in pregnant women

- *Grade of recommendation: 1; Level of evidence: I-A*

Pregnant women that meet the aforementioned standard criteria for starting treatment against HBV should receive it, keeping in mind certain precautions. ETV and pegIFN alfa are classified as category C drugs in pregnancy, and thus should be avoided. Not enough studies have been conducted that evaluate the safety of TAF in pregnancy.[86] Antiviral treatment with TDF is safe and effective in pregnant women. In pregnant patients already receiving treatment with NAs, TDF should be continued, whereas ETV or any other NA should be switched to TDF.[22]

Recommendation 36: All newborns, whose mothers are active HBV infection carriers (HBsAg-positive), should receive hepatitis B immune globulin (HBIG) and the anti-HBV vaccine, within 12 h after birth

- *Grade of recommendation: 1; Level of evidence: I-A*

Perinatal HBV transmission mainly occurs during birth, whether through vaginal delivery or cesarean section. Standard immunoprophylaxis results in the prevention of transmission in close to 95% of cases and consists of the intramuscular administration of HBIG (200 IU/mL) and the anti-HBV vaccine immediately after birth (< 12 h), followed by 2 boosters of the vaccine applied within the following 6–12 months.[225,226] Due to the lower immunogenicity of the anti-HBV vaccine in low-weight newborns (< 2000 g), they should receive an additional booster, i.e., a total of 4 doses of the anti-HBV vaccine, starting the application of the first booster at one month of age.[14]

Prophylaxis efficacy should be confirmed through serologic testing after anti-HBs vaccination and through HBsAg determination, after completing the series of vaccines. However, the tests should not be performed before 9 months of age, to avoid the detection of passive anti-HB from the HBIG administered at birth and to maximize the probability of detecting late HBV infection. Performing anti-HBc tests in breastfeeding infants is not recommended because maternal anti-HBc passively acquired in infants born to HBsAg-positive mothers can be detected in infants up to 24 months of age. HBsAg-negative infants with anti-HB levels $\geq$10 mIU/mL are protected and do not require follow-up. HBsAg-negative breastfeeding infants with anti-HBs levels <10 mIU/mL should be revaccinated with a single dose of the anti-HBV vaccine and undergo serologic testing 1–2 months post-vaccination. Only breastfeeding infants that persist with levels <10 mIU/mL after single dose revaccination should receive 2 additional doses of the anti-HBV vaccine, to complete the second series, followed by serologic testing one to 2 months after the final vaccination dose. HBsAg-positive breastfeeding infants should be referred for adequate follow-up.[14,227,228]

Recommendation 37: Antiviral prophylaxis with TDF should be started in highly viremic HBsAg-positive pregnant women at the beginning of the third trimester, to prevent vertical HBV transmission

- *Grade of recommendation: 1; Level of evidence: I-A*

Standard immunoprophylaxis can fail to prevent HBV transmission in 8–30% of infants born to highly viremic mothers.[229] Therefore, TDF should be administered to mothers with a high viral load. In a multicenter, open, randomized, parallel group clinical trial, antiviral therapy with TDF begun at 30–32 weeks of gestation was shown to be effective and safe for preventing vertical transmission in pregnant women. There was no standard indication for starting treatment but it was begun if the pregnant patients were HBsAg-positive and had a HBV DNA viral load >200,000 IU/mL or HBsAg levels >4 $\log_{10}$ IU/mL.[230] In the same clinical context, other authors recommend starting TDF between 24 and 28 weeks of gestation.[22] Antiviral therapy to prevent vertical transmission can be discontinued 4–12 weeks after having given birth, inasmuch as prolonging it for a longer period of time has not shown any additional benefits.[86,230,231]

Recommendation 38: Breastfeeding is not contraindicated for women with hepatitis B

- *Grade of recommendation: 2; Level of evidence: III*

Despite the fact that HBsAg has been detected in breastmilk, breastfeeding is not contraindicated, even in HBsAg-positive women that have not received antiviral treatment. Small concentrations of tenofovir can be found in women treated with TDF, but its oral bioavailability is limited, and so breastfeeding is not contraindicated. However, the safety of other NAs during breastfeeding is uncertain.[12] Because HBV is transmitted through contact with blood, some experts recommend the temporary suspension of breastfeeding, in cases of cracks, abrasions, or lesions in the nipples.[14]

Kidney disease and bone disease

Recommendation 39: Entecavir is preferred in patients with established kidney or bone disease or in patients with high-risk factors for the deterioration of kidney function or bone

- *Grade of recommendation: 1; Level of evidence: II-B*

Numerous factors are related to the deterioration of kidney function in patients with CHB. Chronic HBV infection *per se* is associated with membranous glomerulonephritis.[232] The following are considered high-risk factors for kidney function decline: the presence of decompensated cirrhosis, glomerular filtration rate $\leq$60 mL/min, uncontrolled high blood pressure or diabetes, proteinuria, glomerulonephritis, concomitant use of potentially nephrotoxic drugs, and being a solid-organ transplant recipient.[22]

In a systematic review and meta-analysis that compared TDF versus ETV, TDF was associated with a higher risk for glomerular filtration rate deterioration (RR: 1.601, 95% CI: 1.035–2.478, p = 0.0034) and a higher incidence of hypophosphatemia (RR: 4.008, 95% CI: 1.485–10.820, p = 0.006).[233]

Likewise, switching TDF to ETV or TAF is suggested (taking into account previous exposure to 3TC, in which case ETV is not recommended). A retrospective study that included 103 patients treated with TDF, in whom the decision was made to switch the regimen to ETV, due to presenting a glomerular filtration rate <60 mL/min, hypophosphatemia (phosphate <2.5 mg/dL), or both conditions, showed that, after 46 weeks of treatment with ETV, all kidney function parameters improved significantly: creatinine of 1.3 to 1.1 mg/dL (p < 0.0001), glomerular filtration rate of 54–65 mL/min (p = 0.002), phosphate of 2.2–2.6 mg/dL (p < 0.0001), and tubular maximum reabsorption of phosphate (TmPO4/eGFR) of 0.47–0.62 mmol/L (p < 0.0001). HBV viral load suppression was maintained in the majority of cases, with the exception of 5% of patients, all of whom presented with resistance to 3TC. The accumulated probability of 5-year resistance to ETV was 0% in 3TC-naïve patients versus 11% in those with previous exposure and resistance to 3TC (p = 0.018).[234]

Recommendation 40: Tenofovir alafenamide is preferred in patients with established kidney or bone disease or in patients with high-risk factors for the deterioration of kidney function or bone

- *Grade of recommendation: 1; Level of evidence: I-A*

TAF has been shown to have a better safety profile than TDF, in relation to kidney function. At 96 weeks of follow-up in 2 phase 3 studies that included a total of 1298 patients, those that received TAF had less deterioration in the glomerular filtration rate (−2.4 mL/min), compared with those that received TDF (−6.7 mL/min; p = 0.008). A lower percentage of patients that received TAF presented with a reduction in the glomerular filtration rate >25%, compared with TDF (10 versus 18%; p = 0.002) or had a glomerular filtration rate <50 mL/min (0 versus 2%; p = 0.004).[232]

Lampertico et al. recently conducted a non-inferiority, multicenter, randomized double-blind, phase 3 clinical trial that included 488 patients with CHB. A total of 245 of those patients were randomized to continue treatment with TDF and 243 were randomized to switch the TDF regimen to TAF, with a follow-up at 48 weeks. Those authors demonstrated that TAF had a better kidney safety profile than TDF. In addition, the group that switched to TAF had a significant increase in bone mineral density at hip (0.66 $\pm$ 2.08% versus −0.51 $\pm$ 1.91%, difference in least square means 1.17% [95% CI: 0.80–1.54; p < 0.0001]); and at spine (1.74 $\pm$ 3.46% versus −0.11 $\pm$ 3.23%, difference in least square means 1.85% [1.24–2.46; p < 0.0001]).[117] Another study by Buti et al., at 48 weeks, showed that the group treated with TAF had a smaller reduction in the glomerular filtration rate (median −1.8 mL/min [IQR −7.8 to 6.0] versus −4.8 mL/min [−12.0–3.0]; p = 0.004), less bone mineral density decline (hip: −0.29% [95% CI −0.55 to −0.03] versus −2.16% [−2.53 to −1.79], adjusted percentage difference 1.87% [95% CI 1.42–2.32; p < 0.0001]; spine: −0.88% [−1.22 to −0.54] versus −2.51% [−3.09 to −1.94], adjusted percentage difference 1.64% [95% CI 1.01–2.27]; p < 0.0001).[116] Chan et al. also found less decline in kidney function and bone mineral density in the group treated with TAF than in the group that received TDF.[187]

Financial disclosure

These clinical guidelines were funded by the *Asociación Mexicana de Hepatología A.C.*

Conflict of interest

Fátima Higuera-de la Tijera is a speaker for Gilead, Medix, Abbott, Schwabe-Pharma, Scienty Med, and Takeda. Graciela E. Castro-Narro is a speaker for Gilead, Glaxo-Smith-Kline, Abbvie, Abbott, Eisai, Medix, and CellPharma. José A. Velarde-Ruíz Velasco is a speaker for Gilead, Abbott, and Takeda. Eira Cerda-Reyes is a speaker for Gilead, Abbvie, Takeda, Medix, Bayer, MSD, and Sanfer. Rosalba Moreno-Alcántar is a speaker for Gilead and Abbvie. Mauricio Castillo-Barradas is a speaker for Gilead, Abbvie, and Italmex. Laura E. Cisneros-Garza is a speaker for Abbvie, Gilead, and Bristol. Margarita Dehesa-Violante is a speaker for Abbvie. Linda E. Muñóz-Espinosa is a speaker for CellPharma. José L. Pérez-Hernández is a speaker for Schwabe-Pharma and Scienty Med. Aldo Torre-Delgadillo is a speaker for Gilead, Merz, Medix, and CellPharma. Rocío Torres is a speaker for Gilead and Abbvie. Enrique Wolpert-Barraza is a speaker for Gilead and Abbvie. Ignacio Aiza-Haddad, Judith Flores-Calderón, Saraí

González-Huezo, Ernesto Márquez-Guillén, Juan F. Sánchez-Ávila, Mayra V. Ramos-Gómez, Juan Sierra-Madero, Eduardo R. Marín-López, and David Kershenobich declare that they have no conflict of interest.

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