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Clinical Practice Guidelines

ALEH position statement on the management of hepatitis B virus infection 2025

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ABSTRACT

Chronic hepatitis B virus (HBV) infection remains a major cause of cirrhosis and hepatocellular carcinoma worldwide, with substantial public health implications in Latin America. Despite the availability of an effective vaccine, HBV continues to be underdiagnosed and undertreated across the region, where healthcare access is often limited and heterogeneous. In alignment with the World Health Organization's 2024 strategy for HBV elimination, the Latin American Association for the Study of the Liver (ALEH) presents updated regional guidelines to simplify diagnosis, expand treatment eligibility, and improve vaccination coverage. The recommendations emphasize the use of rapid diagnostic tests and reflex HBV DNA testing to overcome barriers to laboratory access, while promoting non-invasive methods to assess liver disease severity. Expanded treatment criteria include patients with significant fibrosis, elevated HBV DNA levels, co-infections, and other risk factors, ensuring broader access to antiviral therapy with tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), or entecavir (ETV). Preventing mother-to-child transmission through

Abbreviations: 3TC, lamivudine; AASLD, American Association for the Study of Liver Diseases; ALEH, Latin American Association for the Study of the Liver; ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; anti-HBs, hepatitis B surface antibody; APASL, Asian Pacific Association for the Study of the Liver; APRI, aspartate aminotransferase-to-platelet ratio index; ARFI, acoustic radiation force impulse; AST, aspartate aminotransferase; cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; CI, confidence interval; COVID-19, coronavirus disease 2019; DNA, deoxyribonucleic acid; EASL, European Association for the Study of the Liver; ELISA, enzyme-linked immunosorbent assay; ETV, entecavir; FIB-4, fibrosis-4 index; FTC, emtricitabine; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBcrAg, hepatitis B core-related antigen; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IgM, immunoglobulin M; IU/L, international units per liter; IU/mL, international units per milliliter; kPa, kilopascal; LATAM, Latin America; LMICs, low- and middle-income countries; LoE, level of evidence; LT, liver transplantation; MSM, men who have sex with men; MTCT, mother-to-child transmission; NAT, nucleic acid testing; NITs, non-invasive tests; NUCs, nucleos(t)ide analogues; OCEBM, Oxford Centre for Evidence-Based Medicine; PCR, polymerase chain reaction; PEG-IFNa, pegylated interferon alpha; pgRNA, pregenomic RNA; POC, point-of-care; PWID, people who inject drugs; qHBs, quantitative hepatitis B surface antigen; RDTs, rapid diagnostic tests; RIPS, Registro Individual de Prestación de Servicios de Salud; SC, subcutaneous; SIVIGILA, Sistema de Vigilancia en Salud Pública; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TE, transient elastography; ULN, upper limit of normal; VCTE, vibration-controlled transient elastography; WHO, World Health Organization

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universal screening, maternal prophylaxis, and timely neonatal vaccination is prioritized. Additionally, universal HDV testing in HBV-infected patients is recommended. These guidelines highlight the urgent need for decentralization, simplification, and equity in HBV management to achieve elimination goals in Latin America by 2030.

1. Introduction

Hepatitis B remains a significant public health concern globally, with approximately 296 million people living with chronic hepatitis B virus (HBV) infection. The burden is particularly high in regions like Latin America, where healthcare systems face significant challenges in achieving universal access to HBV diagnosis and treatment. Despite the availability of an effective vaccine since 1982, the World Health Organization (WHO) estimates that viral hepatitis, including hepatitis B, accounts for 1.1 million deaths annually, making it one of the leading causes of death worldwide [1]. In response, WHO set ambitious global targets in its 2024 guidelines, aiming to eliminate hepatitis B as a public health threat by 2030, with the goal of reducing new infections by 90% and HBV-related deaths by 65% through expanded prevention, testing, and treatment [2].

ALEH recognizes the urgency of this challenge in Latin America, where HBV is underdiagnosed and undertreated, with substantial disparities in healthcare access across urban and rural settings. To achieve the elimination targets, ALEH emphasizes the need to simplify both the diagnosis and treatment of HBV, adapting WHO's global recommendations to the specific context of Latin America. Simplified approaches are crucial in the region, where healthcare infrastructure, financial constraints, and the availability of specialized personnel often impede timely diagnosis and access to care.

One of the most significant barriers to effective HBV management in Latin America is the complexity of current diagnostic algorithms, which rely on advanced laboratory tests such as HBV DNA quantification, liver biopsies, or transient elastography to assess disease progression. However, these tools are often unavailable in resource-limited settings. In the WHO 2024 guidelines, simplification is a core strategy for expanding access to HBV care, particularly in low- and middle-income countries (LMICs). WHO recommends the use of more accessible diagnostic tools, such as point-of-care tests for hepatitis B surface antigen (HBsAg), which can be implemented in primary care settings with minimal infrastructure requirements. This approach aligns with the broader WHO vision of decentralizing HBV services and integrating them into primary healthcare systems, a model that ALEH strongly supports for the Latin American region.

Simplification of treatment is equally vital to improving HBV care and achieving elimination in Latin America [3]. Current guidelines recommend treating individuals with chronic hepatitis B who are at risk of liver disease progression, including those with cirrhosis or elevated liver enzymes. However, many patients across Latin America face barriers to initiating treatment, including limited access to antiviral medications and a lack of trained healthcare providers. The WHO's 2024 guidelines advocate for the broader use of TDF and ETV as first-line treatments for HBV due to their safety, efficacy, and availability as generic medications. Simplifying treatment protocols to focus on these first-line therapies, which do not require frequent monitoring of HBV DNA levels, can facilitate more widespread access to antiviral therapy in LMICs, including Latin America.

Another challenge specific to Latin America is the high rate of undiagnosed infections, with many individuals unaware of their HBV status until they develop severe liver disease. The WHO emphasizes the importance of scaling up HBV screening efforts, particularly among high-risk groups such as healthcare workers, people who inject drugs, and individuals living with HIV. ALEH advocates for implementing mass screening programs that leverage simplified diagnostic tools and are integrated into existing public health initiatives, such as maternal and child health programs, to maximize reach and cost-effectiveness. In addition, addressing the stigma associated with viral hepatitis in many Latin American countries is essential to improving access to testing and treatment.

To overcome these barriers and reach the WHO's elimination targets, ALEH's HBV guidelines call for a concerted effort to decentralize HBV care, simplify diagnostic and treatment protocols, and strengthen the capacity of primary healthcare providers. Training healthcare workers to diagnose and treat HBV using simplified algorithms is critical to expanding access to care, particularly in rural and underserved areas where specialist care is often unavailable. Furthermore, ensuring the availability of affordable diagnostic tools and antiviral medications across the region is essential to improving outcomes for individuals living with HBV.

In conclusion, the elimination of hepatitis B in Latin America by 2030 will require a shift towards simplified, decentralized care models that align with the WHO's 2024 guidelines. By focusing on reducing the complexity of HBV diagnosis and treatment and integrating these services into primary healthcare systems, Latin American countries can make significant strides toward meeting the global elimination targets. ALEH is committed to supporting these efforts through the development of evidence-based guidelines that are tailored to the specific needs of the region and that emphasize equity, access, and simplification in the management of HBV.

1.1. Methodology and implementation

The development of this ALEH position statement on the management of HBV infection in 2025 followed a comprehensive, evidence-based process designed to ensure the validity, reliability, and applicability of the recommendations.

1.1.1. Expert panel formation

An expert panel of hepatology specialists was convened by the ALEH Governing Board. Members were selected based on their expertise, clinical experience, and significant contributions to HBV and HDV research and clinical management in Latin America.

1.1.2. Literature review and evidence synthesis

A thorough, non-systematic literature review was conducted by the panel to identify relevant studies, systematic reviews, meta-analyses, and clinical trials related to HBV and HDV infection. The evidence reviewed included publications available up to August 2025.

1.1.3. Evidence grading

The quality of evidence was assessed using the criteria of the Oxford Centre for Evidence-Based Medicine (OCEBM), adapted from the Oxford 2011 Levels of Evidence [4].

1.1.4. Recommendations

Recommendations were developed through a collaborative process that integrated the findings from the literature review—with the corresponding levels of evidence—with expert opinion.

Each recommendation was carefully formulated, considering several key factors, including the level of evidence, clinical experience, potential benefits, associated risks, and patient preferences.

Recommendations were categorized into two strength levels (strong or weak) [4].

2. Diagnosis: laboratory-based HBV DNA reflex testing for measurement of HBV DNA viral load

In Latin America, HBV prevalence varies widely, ranging from approximately 0.2% in some countries to as high as 37% in certain indigenous populations [5]. Despite the availability of effective diagnostic tools, substantial gaps remain, only 13% of individuals with CHB worldwide were diagnosed by 2022, and fewer than 3% were receiving antiviral treatment [2]. Closing these diagnostic and treatment gaps is essential for reducing HBV-related morbidity and mortality.

An efficient HBV diagnostic strategy is also critical for achieving high-quality service delivery for expanded HBV treatment uptake. In the WHO framework, several core approaches relate directly to diagnosis, including (i) strategies to increase testing uptake and strengthen linkage to care, (ii) integration of hepatitis services with other platforms (e.g., HIV services and primary care), and (iii) decentralization of testing and treatment at primary health facilities. While expanded access to HBV DNA testing remains a priority, consistent with WHO 2024 guidance, treatment initiation may be appropriate in selected clinical scenarios even when NAT is not available, supporting simplification and expansion of care.

2.1. Who should be tested for HBV?

Screening for HBV is essential to mitigate its burden, particularly in Latin America, where resource constraints and endemicity necessitate targeted approaches. Testing should prioritize individuals with elevated risk profiles or clinical indications (Table 1) [2,4,6].

2.2. Overview of HBV serological markers

Serological markers form the backbone of HBV diagnosis, staging, and monitoring, providing critical information about the infection's phase and activity [4]:

HBsAg (Hepatitis B surface antigen): This antigen is the primary marker for active HBV infection, whether acute or chronic. Chronic HBV infection is defined by the persistence of HBsAg for more than six months.

Anti-HBs (Hepatitis B surface antibody): The presence of anti-HBs signifies immunity, acquired either through vaccination or recovery from a prior HBV infection. Protective levels (≥10 IU/L) indicate effective immunity.

Anti-HBc (Hepatitis B core antibody): Anti-HBc indicates a previous or ongoing HBV infection. IgM anti-HBc is associated with acute or recent infections, while total anti-HBc remains detectable in chronic or resolved infections. IgM anti-HBc can also be detected during hepatitis B reactivation (flare) in chronic cases.

HBeAg (Hepatitis B e antigen): HBeAg correlates with high levels of viral replication and increased infectivity. It is commonly found during acute infections and active phases of chronic HBV.

Anti-HBe (Hepatitis B e antibody): Anti-HBe suggests reduced viral replication and infectivity, often aligning with the inactive carrier state of chronic infection.

HBV genotype: There are 10 HBV genotypes labeled A through J, with typical geographical distribution. Genotypes F [7] and H [8] are characteristic in our region. Although HBV genotypes are associated with disease progression and response to interferon, their determination is not widely available, and there is no strong evidence that genotypes predict response to nucleos(t)ide analogs (NUCs) treatment [9].

The interpretation of these markers in combination allows clinicians to classify HBV phases and tailor patient management accurately.

2.3. Initial testing

The European Guidelines recommend initial testing with HBsAg, anti-HBc and anti-HBs [4]. There is a strong correlation between anti-HBc and anti-HBs in populations with high hepatitis B endemicity, so a positive isolated anti-HBc may be sufficient to assume immunity (i.e., not requiring vaccination). In areas of low seroprevalence (<0.4%), a second HBsAg is recommended for HBV diagnosis, which improves the positive predictive value [10]. Anti-HBs is less available or more expensive than anti-HBc in some countries of our region. As HBV vaccination coverage increases in the region and HBV prevalence decreases, anti-HBs could be a more suitable initial test, along with HBsAg.

2.4. Rapid diagnostic tests (RDTs)

RDTs for HBsAg detection are single-use assays in simple formats that use only the kit reagents. They usually use a lateral flow immunoassay format. These tests can be read visually after 15 to 30 minutes of testing blood collected by a finger-stick procedure with a lancet, although they can also use whole blood, serum, or plasma, and even saliva. These are usually reserved for settings where fewer than 40 samples per day per operator are analyzed [10].

These tests exhibit high sensitivity and specificity, often exceeding 98%, and provide same-day results, enabling timely clinical decisions [11,12]. In general, they are comparable to standard laboratory tests, but they have a slightly lower analytical sensitivity, meaning they may miss cases with very low levels of HBsAg [10]. Their simplicity and portability make them particularly suitable for rural and underserved regions. RDTs significantly improve screening uptake and early diagnosis in remote settings and have high levels of acceptance among subjects [13].

2.5. HBV DNA: viral load measurement

Quantitative measurement of HBV DNA is the cornerstone of molecular diagnosis, offering direct evidence of viral replication. This test informs both clinical decision-making and therapeutic monitoring. HBV DNA levels guide the initiation of antiviral therapies and provide critical insights into treatment efficacy over time.

Table 1
Individuals with elevated risk profiles or clinical indications where testing should be prioritized.

Group	Rationale
High-risk populations	Diagnosis in individuals from intermediate/high endemicity regions (HBsAg prevalence ≥2%), household/sexual contacts of HBsAg-positive individuals, people who inject drugs, men who have sex with men, people deprived of liberty, sexual workers, HCV and HIV infected patients, indigenous people from high prevalence regions, hemodialysis patients, and healthcare workers at occupational risk.
Pregnant women	Routine screening is recommended to prevent perinatal transmission, which accounts for 90% of new infections in high-prevalence regions.
Immunosuppressed patients	Testing prior to immunosuppressive therapy or chemotherapy to prevent HBV reactivation.
Patients with abnormal liver function	To identify potential viral etiologies of liver disease.

Contemporary assays show high sensitivity, detecting viral loads as low as 10-20 IU/mL, thereby facilitating precise monitoring and detection of reactivation or viral breakthroughs [2]. HBV DNA should be expressed in IU/mL. Several manufacturers (Abbott, Qiagen, Bioneer, Roche, Hologic) offer very accurate and validated assays with costs as low as 10 USD per sample, but require expensive equipment, infrastructure, and specialized personnel [2]. Elevated HBV DNA levels are closely associated with adverse clinical events, such as cirrhosis and hepatocellular carcinoma, underscoring the prognostic value of this marker [14]. Even though HBV viral load determination is becoming more available, it still is an expensive and cumbersome technique that require specialized central laboratories.

2.6. Point of care (POC) DNA testing

Laboratory-based testing is considered the gold standard for HBV DNA quantitation [2,10]. Unfortunately, access to these assays is limited in low- and middle-income countries because of costs and the need for specialized personnel and laboratory infrastructure. Point-of-care (POC) DNA testing allows for the decentralized quantification of HBV DNA, offering comparable accuracy to centralized laboratory assays. These tests deliver rapid results, often within an hour, and have been successfully used for NAT testing in HIV [15] and tuberculosis [16].

Currently there are 2 platforms available for POC HBV DNA testing: Xpert HBV Viral Load and Truenat HBV. The cost per assay is in the range of 12 to 15 USD, but the cost of the equipment ranges from 17,000 to 70,000 USD per machine [17].

A systematic review and meta-analysis of the impact of POC HBV DNA testing showed short turnaround times (from 1 to 11 days) and high diagnostic accuracy, with a pooled sensitivity and specificity of 98 and 99%, respectively [18].

Integration of POC DNA testing can reduce diagnostic delays and may improve adherence to treatment protocols in resource-constrained regions. In practice, POC testing may serve as an appropriate confirmatory or follow-up test after a positive RDT in settings with limited access to centralized laboratories. POC platforms may be particularly useful to expand timely access to treatment for pregnant women in remote locations where specimen transport is challenging.

2.7. HBV DNA reflex testing

One of the key barriers to initiating HBV treatment after an HBsAg-positive result is limited access to NAT and the need for additional visits to obtain confirmatory samples and results. These extra steps increase loss to follow-up and delay treatment initiation. Reflex testing addresses this gap by automatically triggering follow-up HBV DNA testing when an initial HBsAg test is positive, thereby shortening time to diagnosis and improving linkage to care.

HBV DNA reflex testing with a laboratory can be performed either using the same blood sample or a duplicate sample. An example of a similar strategy successfully deployed in the region is the reflex HCV RNA testing for all anti-HCV positive samples in Chile, using the same blood sample where the antibody tested positive.

Clinic-based reflex testing involves a single encounter: the subject gets an RDT; if it is positive (after a 15-minute wait), a blood sample is collected to be sent to a laboratory or to a POC DNA testing.

A WHO systematic review and meta-analysis evaluated eight studies for the impact of reflex testing on linkage to care, treatment initiation rate and turnaround times. Reflex testing achieved HBV DNA testing in 100% of HBsAg-positive samples, compared with 50-55% in sites without reflex testing. In the included studies, results were available a median of 105 minutes after HBV DNA testing, and treatment was initiated a median of 40 minutes after the HBV DNA result was reported [2].

The current WHO Guideline conditionally recommends HBV DNA reflex testing as an additional strategy to expand access to NAT testing after a positive HBsAg test [2]. This strategy should be adapted for each country and region. A limitation of this strategy is that a viral load is not always clinically needed for a patient with a positive HBsAg, for example, in acute HBV infection or follow-up of chronic carriers.

2.8. Quantitative HBsAg (qHBs)

Quantitative HBsAg is a relevant diagnostic tool, offering nuanced insights into HBV activity and its clinical phase, by reflecting the intrahepatic burden of covalently closed circular DNA (cccDNA) and integrated viral DNA, qHBs complements HBV DNA measurements [18].

This marker aids in distinguishing active from inactive HBV states, enabling more precise stratification of patients. Declining qHBs levels are predictive of favorable responses to interferon-based therapies and correlate with progress toward functional cure, defined as HBsAg seroclearance. It may be an indispensable diagnostic tool when newer HBV treatments are available.

2.9. Newer and emerging HBV markers

Emerging diagnostic markers offer promising avenues for more refined HBV management. Among these, HBcrAg (Hepatitis B core-related antigen) has garnered attention as a surrogate for intrahepatic cccDNA. This non-invasive marker facilitates monitoring of viral activity and can predict relapse following treatment discontinuation [19]. HBV RNA, particularly pregenomic RNA (pgRNA) provides insight into transcriptionally active cccDNA, complementing other markers by elucidating replication dynamics and antiviral resistance [20].

Multi-marker algorithms, integrating conventional and emerging diagnostics, represent a paradigm shift that enhances diagnostic accuracy and patient stratification. These approaches align with the evolving goal of achieving a functional cure in HBV infection.

2.10. Integration with other services

The integration of HBV diagnostic services with other health programs can enhance resource utilization and efficiency. Combining HBV and HIV testing addresses the high prevalence of co-infection, which may be higher than 3-4% in some Latin American regions [21]. Similarly, embedding HBV screening within maternal health programs can reduce vertical transmission risks [22]. HBsAg, HIV and syphilis universal testing is recommended as early as possible during pregnancy [22,23]. Data from integrated programs in other regions have shown increased vaccine uptake and improved patient retention [2]. Multiplex RDTs include HIV, HBV and HCV, and they are inexpensive (1-2 USD) and accurate [12,23].

2.11. Recommendations

1. Test all high-risk populations (>2% prevalence), pregnant women, patients undergoing immunosuppression, and patients with elevated aminotransferases (strong recommendation).
2. Each country should have a policy for expanding HBV testing. RDTs are an inexpensive way to achieve this objective (strong recommendation).
3. Initial testing should include HBsAg (either serological or RDT) and anti-HBc or anti-HBs antibody (strong recommendation).
4. For subjects testing positive for HBsAg, further investigation should include HBV DNA quantitation, HBeAg and anti-HBe.

Reflex HBV DNA testing is a reasonable choice in some settings (strong recommendation).
5. If available, HBsAg quantification should be performed to characterize disease phase, define prognosis, and guide treatment (strong recommendation).
6. The absence of HBV DNA and HBeAg/anti-HBe testing availability does not impede starting treatment in certain circumstances (strong recommendation).
7. HBV DNA can be performed in a central laboratory, either quantitatively or qualitatively. POC HBV DNA assays are an alternative approach in specific settings (strong recommendation).
8. HBV DNA reflex testing is a strategy that may simplify diagnosis and increase treatment uptake (strong recommendation).
9. More advanced tests like HBV genotype and resistance testing may be desirable, but their absence should not preclude treatment initiation (strong recommendation).
10. Hepatitis B testing should be considered as part of an integrated testing strategy. HBsAg, HIV, and syphilis universal testing is recommended as early as possible during pregnancy (strong recommendation).

3. Non-invasive assessment of liver disease stage at baseline and during follow-up

Over the past decade, non-invasive tests have become the primary approach for staging liver disease, offering a viable alternative to liver biopsy. These tests can be repeated throughout the course of the disease, making it easier to assess liver disease progression and identify advanced cases that require prioritization for antiviral treatment.

Non-invasive tests (NITs) are now the preferred approach for staging liver disease in chronic HBV because they are broadly accessible, repeatable over time, and avoid the risks and limitations of liver biopsy. In routine practice, NITs include: 1). **Serum Markers of Fibrosis:** These blood tests measure specific biomarkers that help assess liver damage. The Aspartate Aminotransferase to Platelet Ratio Index [24–29]. 2). **Imaging Methods** like Transient Elastography (FibroScan®) are highly effective in detecting liver fibrosis. For significant fibrosis (>F2), the cutoff is >7.0 kPa, with a sensitivity of 75.1% (95% CI: 72.2-77.7%) and a specificity of 79.3% (95% CI: 76.2-82.2%). For cirrhosis (F4), the cutoff is >12.5 kPa, with a sensitivity of 82.6% and specificity of 89% [30,31]. Other non-invasive methods for diagnosing liver fibrosis include ARFI, Magnetic Resonance Elastography, and Shear Wave Elastography. However, these methods are more expensive, less available, and have unvalidated cutoffs for Hepatitis B.

We surveyed 168 Latin American physicians (60% were hepatologists, 33% were gastroenterologists, and 7% other specialties) to characterize real-world use of non-invasive methods for HBV staging. Overall, 95% reported using non-invasive tools in patients with chronic HBV; 68% reported using them specifically to guide fibrosis assessment and treatment initiation. Serum-based indices (liver enzymes, APRI, and FIB-4) were used by 95% of respondents, and 85% reported access to vibration-controlled transient elastography (VCTE). The main barriers identified were limited availability and the cost of imaging-based non-invasive methods.

3.1. Recommendations

1. Noninvasive methods are preferentially recommended to determine the presence of significant or advanced fibrosis. They can be serum-based, imaging-based, or combined. (LoE 1, strong recommendation).
2. APRI: AST-to-Platelet Ratio Index, with a cutoff value for ≥F2 >0.5 and F4 >1 [25] (LoE 2, strong recommendation).
3. FIB-4: Index derived from AST, ALT, platelet concentrations, and age. FIB-4 <1.45, little or no liver fibrosis, >3.25, high risk of advanced fibrosis [28] (LoE 2, strong recommendation).
4. Transient Elastography (FibroScan®): an imaging method to measure liver stiffness as a surrogate indicator of fibrosis. For ≥F2 >7.0 kPa and F4 >12.5 kPa. (LoE 1, strong recommendation).

4. Prevention of mother-to-child HBV transmission

MTCT of HBV is a primary global public health concern, predominantly affecting low- and middle-income countries. Implementing effective healthcare policies is of paramount importance, as this mode of transmission accounts for more than one-third of chronic HBV infections worldwide [32].

The necessity of universal vaccination programs targeting newborns is underscored by the fact that the progression to chronicity in children under one year of age exceeds 90%, compared to 30% in children under five years and 10% in adults [33].

It is important to note that the cumulative five-year risk of cirrhosis in patients with chronic HBV is between 8% and 20%, while the annual risk of hepatocellular carcinoma in HBV-associated cirrhosis is between 2% and 5% [4].

The WHO has set the goal of eliminating HBV infection as a global public health threat by 2030, with a key target of reducing HBsAg prevalence to 0.1% in children up to five years of age. Preventing MTCT of HBV is crucial in achieving this objective, as it represents the most significant risk factor for chronic HBV infection, particularly when compared to horizontal transmission [34].

The success of universal vaccination programs is exemplified by Taiwan's initiative, where, after 25 years of implementation, the prevalence of HBsAg among individuals born after the program's initiation decreased from 10% to 0.9% (1984 vs. 2009) [35]. Three decades later, the overall prevalence of HBsAg was reduced by 52%, and among children under five, by 97%, preventing 28 million chronic infections and five million HBV-related deaths [36].

In 1992, the WHO recommended incorporating vaccination programs, and by 2009, it advised newborn vaccination within the first 24 hours of life, followed by a second dose at 1 month and a third at 6 months [33,37].

As of the WHO's latest 2024 report, 115 countries had introduced newborn vaccination programs; however, only 45% of newborns received the vaccine in 2022. That year, among the 38 WHO target countries (including four in Latin America), 25 (65%) had established vaccination programs. In nearly all these countries, vaccines are available free of charge, with coverage exceeding 70%. Newborn vaccination rates in Latin America are heterogeneous, and not all countries provide data for analysis. Considering the countries monitored by the WHO, we observe the following percentage coverage for the hepatitis B birth dose: Colombia: 85%; Brazil: 82%; Peru: 79% and Mexico: 50% [37].

The combination of routine screening and antiviral prophylaxis in pregnant women with hepatitis B, along with newborn vaccination, is fundamental for eliminating HBV MTCT, particularly in regions such as sub-Saharan Africa, where newborn vaccination rates remain critically low (approximately 18%). In the Americas, including WHO target countries, newborn vaccination coverage in 2022 was 65%. Achieving the WHO's 2030 goals requires strict adherence to global health strategies [37].

A critical challenge has been the impact of the COVID-19 pandemic, which significantly delayed the WHO's proposed vaccination programs [38].

Universal vaccination effectively prevents both vertical and horizontal HBV transmission, reduces morbidity and mortality associated with chronic hepatitis B, and is cost-effective. Thus, its efficient

implementation remains a priority, as current coverage remains suboptimal [33].

Moreover, screening pregnant women for HBV infection, implementing post-exposure prophylaxis for infants, and administering maternal antiviral therapy are effective strategies to reduce further MTCT rates and the burden of new chronic HBV infections [39].

Another highly effective intervention in preventing vertical transmission is the administration of hepatitis B immunoglobulin (HBIG), typically in conjunction with the first vaccine dose. This approach is generally recommended for newborns of HBsAg-positive mothers [4,6]. The administration of HBIG and a vaccine dose within 24 hours of birth, followed by the recommended vaccination schedule, can prevent MTCT in up to 95% of cases [32].

Immunity confirmation through anti-HBs titers should be performed 1–2 months after completing the vaccine series and between 9 and 15 months of age in those who also received passive immunization. MTCT prevention failure may result from delays or omission of HBIG or vaccine administration, particularly in newborns of highly viremic mothers [40].

Antiviral therapy administered to HBsAg-positive pregnant women during the third trimester can further reduce the risk of MTCT. HBV DNA quantification is recommended for all HBsAg-positive mothers, and HBV treatment with TDF or TAF should be initiated at 24–32 weeks of gestation when viral loads exceed 200,000 IU/mL. Importantly, TDF/TAF is safe during pregnancy and lactation [4,6,41–47].

In areas where HBV DNA testing is unavailable, positive HBeAg, irrespective of HBV DNA level, could be treated to prevent mother-to-child transmission [4].

It is essential to highlight that patients who have used TDF/TAF and discontinued the medication should be monitored for flare-ups every 1 to 3 months for up to 6 months postpartum [40].

TDF was the preferred treatment option due to its efficacy and safety during pregnancy; however, increasing evidence supports the use of TAF as a first-line option [47].

In pregnant women on antiviral therapy, TDF/TAF should be continued; ETV or adefovir should be switched to tenofovir TDF/TAF [4].

Given the cost and difficulty of obtaining HBIG, it is worth noting a multicenter study suggesting a strategy that does not use HBIG for HBV MTCT prevention. In a study of 1,194 HBsAg-positive pregnant women, using a rapid diagnostic test for HBeAg and an alanine aminotransferase-based algorithm to assess eligibility for TDF, this strategy effectively prevented vertical HBV transmission when antiviral prophylaxis was initiated at least 4 weeks before birth [48]. Despite these findings, the ideal MTCT prevention approach includes both active and passive immunization, as well as TDF/TAF when indicated. A systematic review and meta-analysis evaluating 300 studies across different geographic regions using various prevention strategies confirms this assertion [49].

Cesarean section is not recommended to reduce the risk of HBV MTCT in HBsAg-positive women; however, it may be considered in Asian women who are HBeAg-positive and/or have high HBV viral loads if they have not received antiviral therapy during pregnancy [50].

The implementation of the measures presented here, while capable of eliminating HBV-related infant mortality, may pose challenges in countries where a substantial percentage of births occur at home, access to diagnostic tests (particularly HBV DNA testing) is limited, and HBIG is unavailable [40].

4.1. Recommendations

1. All pregnant women should be screened for HBsAg during prenatal care, ideally before the third trimester (LoE 1, strong recommendation).
2. HBsAg-positive pregnant women should undergo aminotransferase assessment, HBV DNA quantification, and/or HBeAg testing (LoE 1, strong recommendation).
3. Newborns of HBsAg-positive mothers should receive three vaccine doses (first within 24 hours) and, whenever possible, HBIG (LoE 1, strong recommendation).
4. TDF/TAF should be considered for untreated women with HBV DNA ≥200,000 IU/mL and/or HBeAg positivity, before the third trimester. When HBV DNA is not available, HBeAg-positive mothers should be treated (LoE 1, strong recommendation).
5. Breastfeeding should be encouraged unless the mother has detectable HBV DNA with nipple lesions, or the infant has oral ulcers (LoE 4, weak recommendation).
6. TDF should be considered in the third trimester, for untreated women with HBsAg positivity, in case HBV DNA quantitation is not available, especially in remote areas in our region (LoE 5, weak recommendation).

5. Who to treat – expanded treatment eligibility

Despite the existence of a safe and effective vaccine against the HBV for nearly four decades, CHB still affects around 300 million people worldwide and causes almost one million deaths directly related to HBV every year, primarily due to cirrhosis and HCC [4,6,51,52]. Antiviral therapy with high-barrier NUCs has changed the natural history of CHB, leading to a marked reduction in HBV-related liver complications and a dramatic decrease in the need for liver transplantation (LT) [4,6,51,52]. Unfortunately, HCC can still occur despite the use of NUCs, especially among patients with more advanced liver disease [4,6,51,52]. Current treatment recommendations for patients with CHB depend on the phase of the disease and vary across the most widely used guidelines, such as the ones published by the Asian Pacific Association for the Study of the Liver (APASL), the American Association for the Study of Liver Disease (AASLD), and the European Association for the Study of the Liver (EASL). Remarkably, evidence indicates that between 1/3 and 2/3 of CHB patients who develop HCC are outside the treatment recommendations of EASL, AASLD, and APASL [53]. Moreover, some authors showed that almost 40% of CHB patients do not fit clearly in any of the disease stages and are considered indeterminate, making it challenging to decide treatment initiation according to the disease phenotype [54]. A recent study showed that patients in the indeterminate phase have a risk of HCC that is 14-fold higher than those in the HBeAg-positive harmful infection (former inactive carrier phase) [55]. All these problems are amplified in Latin America (LATAM) due to the significant heterogeneity and disparities that characterize our region [56]. Many places lack liver specialists and accurate non-invasive methods to define liver fibrosis. In some areas, even HBV DNA viral load is not available regularly. In view of the current WHO global hepatitis strategy, which aims to reduce new hepatitis infections by 90% and deaths by 65% up to 2030, a more simplified and comprehensive algorithm to decide treatment initiation in CHB patients is urgently needed worldwide, especially in low-resource regions of the world such as LATAM [1]. In this regard, the recently published WHO guidelines proposed simplifying treatment criteria and expanding treatment eligibility, with a clear objective of removing barriers to treatment access [2]. This chapter of the Updated HBV Guideline of ALEH aims to suggest the necessary criteria for treatment of CHB patients in the LATAM Region, sharing the same WHO spirit of simplification and treatment expansion, while at the same time trying to consider the different levels of complexity that exist among the many health systems available throughout our region.

The objective of treatment is to prevent the adverse outcomes of CHB. The decision to treat is usually based on a combined assessment of the stage of liver disease together with levels of serum ALT and HBV DNA. Patients with advanced liver disease, such as cirrhosis or liver failure, require immediate treatment.

The newly recommended treatment eligibility criteria will markedly expand treatment access for most individuals testing positive for HBsAg [2].

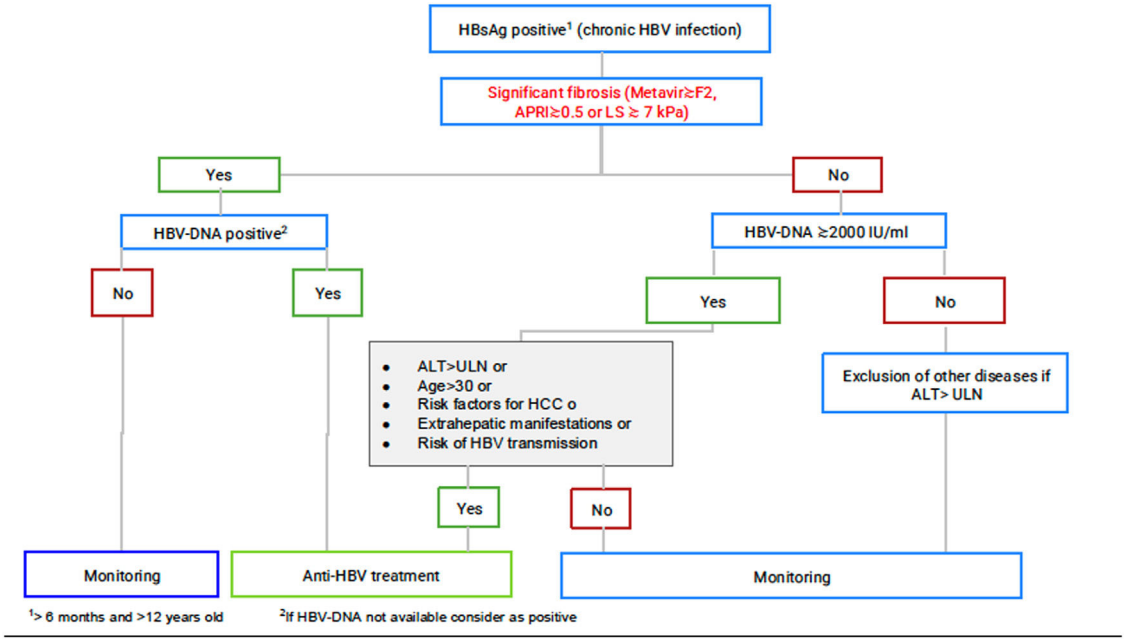

Fig. 1. Current algorithm for the treatment of chronic hepatitis B.

HBeAg or anti-HBe status will no longer be mandatory. The great advantage of these recommendations is that they are applicable in all the countries of our region.

Moreover, they will expand treatment for adolescent girls of reproductive age, which will complement the recommendations for expanded use of antiviral prophylaxis to reduce mother-to-child transmission. This represents a significant opportunity to reduce further new HBV infections among children, especially in endemic areas where coverage of birth-dose HBV vaccination remains low.

Treatment is recommended for all adults and adolescents (aged ≥12 years) with CHB and any of the following (see Fig. 1):

- Significant fibrosis (>7 KPa based on transient elastography or APRI > 0.5) or evidence of cirrhosis (based on clinical criteria or elastography > 12.5 or APRI > 1) regardless of HBV-DNA and/or ALT levels. This recommendation alone may capture an estimated 20-25% of all HBsAg-positive people. The rationale of this recommendation is that patients with advanced fibrosis have a much higher risk of developing life-threatening complications of liver disease due to reactivation and flares, and therefore, it is reasonable to avoid or reduce them with therapy.
- Persistently elevated HBV DNA (>2000 IU/mL) in patients aged ≥ 30 years regardless of ALT levels. This recommendation is estimated to capture 20-35% of all HBsAg-positive people, depending on the region
- Persistently elevated HBV DNA (>2000 IU/mL) and ALT >ULN in patients aged less than 30 years.
- Co-infection (HIV, HCV, HDV), family history of liver cancer or cirrhosis based on clinical criteria, immunosuppression or chemotherapy, high risk of transmission, prevention of vertical transmission in selected cases, severe acute viral hepatitis B, diabetes, any other associated liver disease, and/or extrahepatic manifestations.

Although only two of the four criteria for treatment eligibility require access to HBV DNA level, it is strongly encouraged to have at least one HBV DNA test if available to provide a complete assessment before treatment. HBV DNA level will also be required for monitoring the treatment response.

It should be emphasized that these recommendations are intended to simplify treatment decisions and expand eligibility, in line with WHO elimination targets and contemporary international guidance, including the recently published EASL and AASLD recommendations [3,4,6].

These recommendations do not preclude the use of additional tools (e.g., HBeAg and other virological or serological markers) where available, to better characterize disease phase and support individualized management.

Regardless of the criteria used for treatment initiation, everyone initiating treatment is recommended to be monitored 6 months after starting therapy and then annually with HBV DNA, ALT, and APRI score, with ongoing adherence support and retention in care. Those who do not yet meet the treatment criteria will also require continued monitoring, as previously recommended [4,6].

5.1. Recommendations

1. Current treatment of CHB should aim to simplify treatment criteria and expand treatment eligibility, with a clear objective of removing barriers to treatment access.
2. Patients with significant fibrosis or cirrhosis or liver failure testing positive for HBsAg require immediate treatment, regardless of HBV DNA and/or ALT levels (LoE 1, strong recommendation).
3. Treatment is recommended in patients with persistently elevated HBV DNA (>2000 IU/mL) aged ≥ 30 years regardless of ALT levels (LoE 5, weak recommendation).
4. Treatment is recommended in patients with persistently elevated HBV DNA (>2000 IU/mL) and ALT >ULN aged less than 30 years (LoE 3, weak recommendation).
5. Treatment is recommended in HBsAg-positive patients with detectable HBV DNA and co-infection (HIV, HCV, HDV), family history of liver cancer or cirrhosis based on clinical criteria, immunosuppression or chemotherapy, high risk of transmission, prevention of vertical transmission, and/or extrahepatic manifestations (LoE 1, strong recommendation).

In selected cases, such as severe acute viral hepatitis B, diabetes, and/or any other associated liver disease, therapeutic decisions might be considered on a case-by-case basis (LoE 5, weak recommendation).

6. Current HBV treatment

HBV infection and its complications (cirrhosis and HCC) can be prevented through vaccination. However, universal vaccination, especially in newborns, while a goal to achieve and a proposal by WHO, still requires a maturation period before it can be widely implemented in all Latin American countries [34]. This is further compounded by the fact that despite vaccination, a substantial number of people have already been infected with HBV and remain at risk of developing progressive liver disease. In these cases, disease progression can be prevented through antiviral therapy.

It is essential to highlight that of the 38 countries selected for follow-up by the WHO, four are from Latin America (Brazil, Colombia, Mexico, and Peru), and in these countries, only 21.2% of those infected with HBV are diagnosed, and only 20.9% of these are treated [34]. It is therefore clear that the care cascade, particularly for patients with HBV, needs to be significantly improved.

In the treatment of HBV, two classes of drugs can be considered. Pegylated interferon alpha, which has modest antiviral activity but can enhance the degradation of cccDNA and the immune response against HBV, and NUCs that inhibit the reverse transcription of the pregenomic RNA into HBV DNA. The latter have no direct effect on cccDNA, and viral relapse is almost universal when treatment is discontinued.

Current treatments with NUCs are effective in suppressing HBV replication, reducing inflammation and hepatic fibrosis, and therefore the consequent risk of progression to cirrhosis and HCC. Despite this, loss of HBsAg occurs very infrequently, and the risk of HCC remains, albeit at lower rates [40].

Pegylated Interferon Alpha: Pegylated interferon alpha is administered at a dose of 180 μg once a week (subcutaneous injections of pegylated interferon alpha 2a) for 48 weeks in both HBeAg-positive and HBeAg-negative patients with chronic HBV hepatitis [6]. Although only about 30% of patients eliminate HBeAg and 3.0% eliminate HBsAg in the months following treatment, rates of HBsAg loss increase in long-term follow-up [57]. An interesting prospective cohort study with an average follow-up of over 7 years showed that almost half of the patients achieved a sustained response (defined in the survey as not requiring further use of NUCs due to low viremia and normal liver enzymes), with functional cure in over 15%, and none of them progressed to cirrhosis or HCC [58].

Pegylated interferon alpha is associated with many side effects. Flu-like symptoms are almost universal and occur during the first few weeks of use. However, several other manifestations can occur, such as bone marrow suppression (with neutropenia and/or thrombocytopenia), depression, and, less commonly, exacerbation or precipitation of autoimmune diseases. It is important to remember that interferon can cause an ALT “flare” mediated by the immune system, which could lead to hepatic decompensation [6,57].

Due to its side effects, interferon is used much less frequently than NUCs. Its most common indication is in young, HBeAg-positive patients who do not want to undergo prolonged or indefinite treatment, especially those with elevated aminotransferase levels, low viral load, and HBV genotype A infection [57]. Since these patients are generally younger and have fewer comorbidities, side effects are better tolerated than in patients treated for HCV infection [6].

Interferon is contraindicated in pregnant patients, decompensated cirrhosis, autoimmune diseases, or severe depression, and should be used cautiously in patients with compensated cirrhosis showing evidence of portal hypertension [6].

Although it is a finite treatment and indicated in special situations, due to its side effects and the need for more complex follow-up, the WHO 2024 guidelines do not list it as a therapeutic tool. On the other hand, they emphasize the role of NUCs, as they are very effective in preventing disease progression to cirrhosis, reducing the incidence of HCC, and improving long-term survival [2].

NUCs: Six NUCs have been approved for oral use (lamivudine, adefovir, ETV, TDF, telbivudine, and, more recently, TAF). Among them, TDF and ETV are preferred due to their potent antiviral activity and low risk of viral resistance compared to others.

While data from all LATAM countries are not uniformly available, an evaluation of the four WHO focus countries on the region (Brazil, Colombia, Mexico, and Peru) reveals that all have incorporated TDF and ETV into their national hepatitis treatment guidelines and essential medicines lists, in alignment with WHO guidance. TAF is currently included in the national guidelines of two of these countries (Brazil and Mexico) [37].

In the absence of monotherapy with TDF or ETV, the WHO recommends, in developing countries, the combination of 3TC or FTC as an alternative for adults with HBV mono-infection, given their low cost and greater availability.

A systematic review and meta-analysis evaluating the efficacy of TDF + FTC therapy versus TDF did not show differences in outcomes, including undetectable HBV DNA, normalization of aminotransferases, loss of HBsAg, loss of HBeAg, and HBeAg seroconversion. The TDF + FTC and TDF groups also did not differ significantly in terms of safety outcomes [2].

NUCs act late in the viral replication cycle, so they do not impact cccDNA and, consequently, do not directly affect HBsAg expression, and thus usually do not induce a functional cure [59].

A functional cure is defined as undetectable HBV DNA below <10 IU/mL associated with the loss of HBsAg (using a test with a detection limit of 0.05 IU/mL) after 24 weeks of treatment suspension [60].

Only 27% to 38% of HBeAg-positive patients eliminate HBeAg, and only 3% to 5% of them eliminate HBsAg after 10 years of treatment. Therefore, NUCs are generally administered for many years, often for life, particularly in patients with cirrhosis, to prevent the ALT flare associated with viral relapse [40].

An international multicenter cohort study involving over 7,500 patients with chronic HBV treated with ETV or TDF reported cumulative HBsAg seroconversion at 8 years of 1.69% and 1.34%, respectively, with no difference between the drugs. Therefore, they have similar outcomes with respect to functional cure [61].

Some studies suggest there is no difference between ETV and TDF in treating HBV hepatitis in terms of reducing the incidence of HCC [62,63]. However, a recent individual patient data meta-analysis suggests that patients treated with TDF have a significantly lower risk of HCC compared to those treated with ETV, particularly those with HBeAg-positive [64]. It is understood that the position on this matter is not yet consensual and requires further studies to define it.

Interestingly, another multinational study did not demonstrate differences in all-cause mortality and liver disease-related mortality in HBV patients treated with ETV or TDF [65].

Given these findings, it appears that treatment should be primarily guided by patient tolerance and medication accessibility, as these appear equally effective.

Another factor to consider in choosing the type of NUCs to administer is viral resistance. Resistance is defined as an increase of more than 1 log in HBV DNA levels during treatment, which may be accompanied by the rise in aminotransferases or even liver dysfunction.

Resistance to ETV is observed in approximately 1% of naïve patients and up to 50% of patients previously treated with lamivudine after 5 years of administration. For phenotypic resistance to ETV to develop, at least three substitutions must occur: rtL180M (where rt refers to reverse transcriptase), T184L, and M204V.

Unlike what happens with ETV, no resistance has been observed with TDF in patients who have received it for up to 10 years. Although a quadruple mutation conferring resistance to TDF has been identified, computational analysis of complete HBV sequences suggests that this mutation is rare [65,66].

Both TDF and TAF are active against HBV resistant to lamivudine, telbivudine, ETV, and adefovir. Monotherapy with TDF is equally

effective at suppressing these resistance variants compared to the combination of TDF and ETV or emtricitabine [40].

NUCs have excellent long-term safety. TDF is associated with a small risk of renal failure and decreased bone mineral density. TAF, a prodrug of TDF, improved renal and bone safety [68]. Therefore, ETV or TAF are preferred in patients with risk factors for renal failure or osteoporosis. ETV and TDF are given less frequently if creatinine clearance is less than 50 mL/min. TAF does not require dose adjustment in patients with a creatinine clearance of at least 15 mL/min and should not be used in patients with a creatinine clearance of less than 15 mL/min who are not on hemodialysis. For patients on hemodialysis, it should be administered after each dialysis [40].

In HBeAg-positive patients without cirrhosis, NUCs can be discontinued once they have completed 12 months of treatment post-seroconversion. Approximately 50% of patients will remain in virological remission.

Although virological relapse is almost universal when NUCs are discontinued before HBsAg loss, not all patients experience clinical relapse. Furthermore, some studies have shown that treatment interruption in HBeAg-negative patients who have completed more than 2 to 3 years of treatment with undetectable HBV DNA has higher rates of HBsAg loss compared to those who did not interrupt treatment. This paradoxical finding occurs mainly in non-Asian individuals. In fact, Asian patients with HBsAg <100 UI/mL at the time of stopping NUCs are less likely to lose HBsAg than Caucasian patients with HBsAg <1000 UI/mL at the time of stopping NUCs. It is worth noting that relapse seems to occur earlier with TDF withdrawal than with ETV, as well as the need for strict surveillance to prevent more severe clinical manifestations [69,70].

Therefore, it seems that the best candidates for NUCs discontinuation are non-cirrhotic patients with viral suppression and low HBsAg levels (Caucasians <1000 UI/mL and Asians <100 UI/mL), who, after two years of treatment suspension, have a probability of HBsAg loss of around 30% [71]. It is always important to remember that since treatment interruption carries the risk of hepatic decompensation, the benefits and drawbacks should be carefully weighed, and the decision to discontinue NUCs should be made jointly between the patient and their physician. Treatment should be resumed before any increase in serum aminotransferase levels or if a rapid increase in HBV DNA levels (3 to 4 log10 IU per milliliter) is detected [67].

6.1. Recommendations

1. Due to its side effects and only in selected cases, interferon could be used in young, HBeAg-positive patients who do not intend to undergo prolonged or indefinite treatment, especially if they have elevated aminotransferase levels, low viral load, and HBV genotype A infection (LoE 2, strong recommendation).
2. NUCs with a low genetic barrier to resistance (lamivudine, adefovir, or telbivudine) may cause drug resistance and are not recommended (LoE 1, strong recommendation).
3. Preferred regimens are NUCs with a high genetic barrier to drug resistance (TDF, TAF, or ETV) (LoE 1, strong recommendation).
4. Exceptionally, when monotherapy with tenofovir is unavailable, tenofovir associated with lamivudine or FTC can be used as an alternative (LoE 2, strong recommendation).
5. ETV or TAF is recommended in patients with established osteoporosis and/or impaired renal function (LoE 5, strong recommendation).
6. NUCs treatment should be stopped after confirmed HBsAg loss with or without anti-HBs seroconversion in the absence of coexisting risk factors (LoE 2, weak recommendation).
7. NUCs treatment discontinuation may be considered in patients without evidence of cirrhosis who can be monitored long-term after treatment cessation in:
   a. HBeAg positive patients: when there is loss of HBeAg and seroconversion to anti-HBe after maintaining at least 12 additional months of treatment, provided the patient has normal aminotransferases and persistently undetectable HBV DNA levels (LoE 2, weak recommendation).
   b. In HBeAg-negative patients when there is a functional cure with loss of HBsAg, or in exceptional cases in patients with normal aminotransferases and persistent viral suppression, low HBsAg levels (Caucasians <1000 UI/mL and Asians <100 UI/mL), after providing adequate information (LoE 2, weak recommendation).

7. Hepatitis delta virus (HDV)

7.1. Who to test for hepatitis delta infection

Hepatitis D virus (HDV) is a defective circular single−stranded RNA virus of the Deltaviridae family. It requires the presence of HBV to complete its life cycle, replicate, and cause liver damage. This is because it uses HBsAg to assemble and propagate [72].

HDV is among the most aggressive types of viral hepatitis. Compared with HBV mono-infection, HDV co-infection is associated with faster progression to advanced fibrosis, cirrhosis, and HCC. HDV shares the same routes of transmission as HBV, HCV, and HIV including injection drug use, and percutaneous or mucosal exposure to infected blood or body fluids. Despite increasing recognition of HDV burden, anti-HDV testing is not routinely performed in many settings; therefore, HDV testing should be obtained in all patients with chronic HBV infection. When resources are limited, prioritization may be reasonable for higher-risk groups (e.g., people who inject drugs, individuals with high-risk sexual behavior including MSM, hemodialysis patients, immigrants from high-prevalence areas, and patients with advanced liver disease) [72−74].

In LATAM, the prevalence of HDV varies by region, with foci of high endemicity in the Amazon, parts of Venezuela, Colombia, Peru, and Brazil. It is essential to mention that the significant migration originating in recent years in Venezuela to several countries in the region, without adequate control and surveillance, and the possibility of vaccines and treatment in the host countries, the magnitude of which has not yet been quantified, may have an impact on health policies and recommendations in LATAM.

In Brazil, the prevalence of both HDV and HBV is highly dependent on the region from which an individual is. While many studies provide estimates for the Amazon, a region with a high burden, fewer studies exist in the major population centers, where prevalence is relatively low. The anti-HDV prevalence reported in the literature was 3.2%. However, this was neither weighted by population nor HBV infections [18]. A previous analysis using data from 2016 and 2017 found that 0.6% of 5 million rapid HBsAg tests conducted among 15-69-year-olds across Brazil were HBsAg-positive. After adjusting for regional populations and factoring in cases from various special populations (prisoners, drug users, sex workers, men who have sex with men, patients with HIV, patients on dialysis, army conscripts, and indigenous peoples), the HBsAg+ prevalence among 15-69-year-olds was estimated to be 0.8% [19−29] This was then combined with the regional estimates from the aforementioned published study to estimate an anti-HDV prevalence of 1.7% [18]. The details of these calculations can be found in the supplementary information. Based on Ministry of Health data, the HDV RNA prevalence was assumed to be 75% [75].

In Colombia, the literature review identified one study reporting an anti-HDV prevalence of 5.2% [36]. However, this study was not representative of the general population, as it was conducted in higher prevalence regions as well as among risk groups such as indigenous peoples. There is a high heterogeneity of HBV and HDV

infections in Colombia. We estimated HDV prevalence by dividing the number of delta patients under care in the public system (RIPS) by the number of individuals diagnosed with HBV (SIVIGILA) [37,38]. The anti-HDV prevalence was 1% (CI 0.6-1.2%). The expert panel estimated an anti-HDV prevalence of 1% based on their clinical experience. The HDV RNA prevalence was estimated at 70% in a published study from the Amazon [76].

HDV infection was reported among native communities in the Peruvian jungle and in some locations in the Peruvian highlands, such as Abancay and Huanta, where a prevalence of 14% of HDV infection has been reported in apparently healthy school-age children. In addition, studies also found that 17% of individuals with HBV infection and 56.5% of HBsAg carriers had co-infection with HDV [77]. Significant rates of HBV and HDV co-infection were previously reported in the Amazon and inter-Andean valleys of Peru (Huanta, Abancay).

Cabezas et al. found in 2020, a low prevalence of anti-HDV among HBsAg carriers. These results showed a decrease in the prevalence of HDV infection, in contrast to previous reports from Peru. This reduction in the prevalence of HDV infection is also the result of universal vaccination against HBV in Peru, since reducing the rate of HBsAg carriers will decrease the rates of HBV and HDV co-infection. Whereas the prevalence of HBV and HDV has changed from intermediate (2 % - 7 %) to low (< 2 %) because of the universal vaccination program against HBV [78].

According to international guidelines on HDV, the EASL recommends screening for HDV infection in all HBsAg-positive individuals [4,79]. However, AASLD suggests screening only in high-risk populations such as individuals with HIV, people who inject drugs, men who have sex with men, and individuals from endemic areas [6]. Another recommendation for HDV testing is that patients with high-risk sexual behavior and areas with high prevalence of HDV who develop acute decompensation of liver disease or elevations of liver enzymes should be retested for HDV infection [80].

Improving coverage of the prophylactic HBV vaccine is the most effective strategy to reduce HBV and HDV infections worldwide [81].

In many countries in our region, guidelines recommend testing for HDV in individuals with chronic HBV infection who are at high risk of acquiring HDV (Argentina and Brazil 2021, Uruguay 2022). In contrast, the Chilean Guideline 2021 recommends universal HDV testing for patients with chronic HBV infection, like the new WHO Guideline 2024. Our current ALEH recommendation aligns with the WHO 2024 recommendation for universal HDV testing in patients with chronic HBV infection (Table 2) [3,4,6,82].

7.2. How to test for HDV

Most countries in our region (PAHO 2015, Colombia 2016, Brazil 2022) screen with anti-HDV, followed by HDV-RNA testing for patients who test positive for antibodies against hepatitis delta antigen (anti-HDV). In this regard, our current recommendation in the ALEH guideline is to maintain this approach (Table 2) [6,82].

7.3. Available diagnostic methods

7.3.1. Serological tests

Anti-HDV (IgG/IgM):

Use: Initial detection of HDV exposure.

Limitations: Does not distinguish between active and resolved infection.

Recommendation: If anti-HDV is positive, confirm with HDV RNA viral load.

HBsAg + anti-HDV positive: Indicator of possible active infection.

Recently, the use of a rapid HDV test (not yet validated in Latin America) for detecting anti-HDV in serum and plasma has been reported. The test is based on a large recombinant hepatitis delta antigen that can detect anti-HDV in a concentration-dependent manner, with pangenotypic activity, with a sensitivity of 94.6% and a specificity of 100% compared to a reference ELISA test [83]. This rapid HDV test could become an essential tool for epidemiological studies and clinical diagnostics.

7.3.2. Molecular detection (gold standard)

HDV-RNA (qualitative/quantitative PCR):

Use: Confirmation of active infection and monitoring of treatment response. Tests validated by the WHO/EASL (e.g., Altona Diagnostics, Robogene) should be preferentially used.

Genotyping: Genotypes 1, 3 (Amazon), and 8 predominate in Latin America.

7.3.3. Liver fibrosis assessment

Elastography (FibroScan®), APRI, FIB-4, or liver biopsy to stage the disease.

7.4. Treatment options

Bulevirtide (Hepcludex®) – HDV entry inhibitor (approved in Europe, under study in Latin America).

Dose: 2 mg SC/day.

Efficacy: reduces HDV-RNA in ~50% at 48 weeks.

Peginterferon alfa (Off-label) – Only treatment available in many regions.

Dose: 180 μg/week for 48 weeks.

Sustained response: ~25-30%.

Nucleo(t)ide analogues (TDF/TAF) for suppressing HBV – Necessary but insufficient if used alone.

7.5. Role of the hepatitis B vaccine in preventing HDV

Universal vaccination against HBV is the primary strategy for preventing HDV. It is important to note that during the COVID-19 pandemic, vaccination rates declined alarmingly in several countries worldwide. Added to this are anti-vaccine campaigns by individuals and organizations in several countries in the region. Therefore, the challenge is to prioritize and recover pre-pandemic vaccination rates to ensure population protection and reduce new infections.

Table 2
Current ALEH recommendation for universal HDV testing in patients with chronic HBV infection.

Who to test for HDV Infection	How to test for HDV infection
Universal HDV testing among people with chronic HBV	Serological assay to detect total anti-HDV in case of HBsAg-positive. NAT to detect DNA-RNA
Prioritized in case of limited laboratory capacity where prevalence of infection is higher: • People born in HDV-endemic countries. • People at higher risk of acquiring HDV: PWID, MSM, sex workers, HBV co-infection: HCV or HIV, hemodialysis recipients; children and family members with HDV infection and patients with advanced liver disease.	Reflex testing for anti-HDV antibody testing.

7.6. Recommendations

1. Test all HBsAg-positive patients for HDV, especially in endemic areas (LoE 2, strong recommendation).
2. Confirm active HDV-RNA infection before treating (LoE 2, strong recommendation).
3. Prioritize therapy with bulevirtide (if available) or peginterferon in selected cases (LoE 2 for PEG-IFNa and LoE 3 for bulevirtide, strong recommendation).
4. Maintain optimal HBV suppression with TAF/TDF (LoE 5, strong recommendation).
5. Promote universal HBV vaccination to eradicate HDV in the long term (LoE 1, strong recommendation).

8. Recommendations for hepatitis B vaccination in Latin America

HBV transmission mechanisms vary between countries, from vertical (MTCT), sexual, parenteral, and through contact with body fluids. The prevalence varies across countries, from low (<2%) in Chile and Argentina to intermediate (2-7%) in Brazil, Peru, and Venezuela [3,84].

Vaccination, although not yet universally adopted for the entire population in the Americas, is the most effective strategy for preventing infection and its complications, such as cirrhosis and hepatocellular carcinoma. Countries with vaccination coverage >90% have successfully reduced the prevalence of hepatitis B from > 10% to <0.1% within < 5 years. This document provides updated recommendations based on recent evidence for HBV vaccination in the region.

8.1. Vaccination recommendations

8.1.1. General population

- **Newborns:**
  Universal vaccination within the first 24 hours of life [2]. This strategy, in addition to reducing the risk of vertical transmission, increases the likelihood of completing the vaccination schedule in populations with limited access to health services.
  Schedule: 3 doses (0, 1-2, and 6 months) or accelerated schedules based on availability [3].
- **Unvaccinated children and adolescents:**
  Implement catch-up strategies for children under 18 years of age [84] and administer or complete the 3-dose schedule.
- **Adults aged 19-59 years and for those aged 60 years and older:**
  Universal vaccination for adults aged 19-59 years and for those aged 60 years and older with risk factors: Vaccination in adults based on risk factors results in suboptimal coverage. In well-resourced health systems, universal vaccination of all adults aged 19–59, regardless of risk, increases vaccination coverage, is a cost-effective strategy, and reduces hepatitis B cases [85].

8.1.2. High-risk groups

In addition to universal vaccination of children under 5 years of age, starting the schedule within the first 24 hours of birth, in health systems without sufficient resources to provide universal vaccination for adults, hepatitis B vaccination should be provided to the following high-risk adult groups:

- **Healthcare personnel:**
  Mandatory vaccination and verification of anti-HBs titers (≥10 mIU/mL) [2]
- **Patients with chronic diseases:**
  Cirrhosis, hepatitis C, HIV, solid organ transplant recipients, chronic kidney disease, and diabetics [3,6].
- **Key populations:**
  Men who have sex with men (MSM), sex workers, people deprived of their liberty, and injection drug users [3], healthcare workers, and other people who may be exposed to blood and blood products through their work; patients on hemodialysis; people with multiple sexual partners; sexual partners (after HBV infection has been ruled out), or cohabitants of a patient with HBV hepatitis.
- **Pregnant Women and Prevention of Vertical Transmission**
  Universal screening: All pregnant women should be evaluated for HBsAg. The Engerix-B, Recombivax HB, or Twinrix vaccines have been approved for use during pregnancy and are highly recommended for pregnant women who have not previously been immunized [84].
- **Prophylaxis in newborns of HBsAg-positive mothers:**
  Vaccine + HBIG within 12 hours of delivery [84] (Table 3).

8.2. Monitoring and boosters

- **Post-vaccination serology:** Recommended in at-risk groups (anti-HBs ≥10 mIU/mL) [1].
- **Boosters:** Not routine, except in immunocompromised patients with titers <10 mIU/mL, and in high-risk populations who do not achieve protective titers (anti-HBs ≥10 mIU/mL) after a first 3-dose regimen, in whom repeat vaccination is indicated [6].

8.3. Barriers and challenges to HBV vaccination in Latin America

- Unequal coverage: Countries with fragmented health systems have lower access.
- Lack of awareness: Educational programs for professionals and the general population.

8.4. Recommendations

1. Universal vaccination of newborns and at-risk groups is key to eliminating HBV in Latin America (LATAM) **(LoE 1, strong recommendation).**
2. Public policies that strengthen access and serological monitoring are needed (**strong recommendation**).
3. Universal vaccination of adults aged 19-59, regardless of risk, is a cost-effective and desirable measure in health systems with sufficient resources for its implementation **(LoE 1, strong recommendation).**

9. Comparative summary of HBV guidelines: ALEH vs. EASL, WHO, and AASLD

Before preparing this Position Statement, EASL and WHO guidelines had been released, and in the meantime, the AASLD guideline was released [3,4,6]. All four documents converge on the same goal, reducing HBV-related cirrhosis, HCC, and mortality and contributing to the WHO 2030 elimination targets. Still, they differ in scope, complexity, and the extent to which they expand treatment eligibility.

Table 3
HBV vaccination schedules.

Schedule	Dosage	Interval
Standard:	0, 1, 6 months	Ideal for the general population
Accelerated:	0, 1, 2, 12 months	Travelers or emergencies
Ultra-rapid:	0, 7, 21 days + booster	Post-exposure

The WHO 2024 guideline adopts a global public health perspective, prioritizing decentralized and simplified HBV care in low- and middle-income countries. In contrast, the EASL 2025 guideline provides a comprehensive, specialist-oriented framework that includes detailed recommendations on diagnostics, treatment algorithms, surveillance strategies, and management of special populations. The AASLD 2025 update remains more focused, addressing discrete areas such as the immune-tolerant and indeterminate phases, mother-to-child and horizontal transmission, HCC surveillance, and NUCs withdrawal. Our 2025 statement, however, adapts explicitly WHO's simplification philosophy to the realities of Latin America—characterized by heterogeneous health systems, substantial under-diagnosis, and limited access to laboratory and imaging resources—while simultaneously expanding treatment eligibility beyond the thresholds used in EASL and AASLD.

Across all guidelines, treatment is consistently recommended for cirrhosis or decompensation regardless of ALT or HBV DNA, with high-barrier antivirals (TDF, TAF, ETV) endorsed as first-line agents. All four also acknowledge that rigid disease-phase classifications fail to identify many high-risk patients, particularly those in the "indeterminate" phase. The differences emerge most clearly in treatment thresholds: WHO proposes the most simplified and liberal approach, relying on a single HBV DNA cut-off (>2,000 IU/mL) combined with ALT and fibrosis assessment. AASLD retains a classical, phase-based model with distinct HBeAg-stratified DNA thresholds and higher ALT cut-offs. At the same time, EASL occupies an intermediate position, preserving detailed phase definitions yet encouraging broader treatment when fibrosis or other risk factors are present.

ALEH Statement diverges more substantially by embracing a markedly expanded treatment strategy tailored to regional epidemiology and healthcare limitations. We recommend treatment for all individuals with significant fibrosis (transient elastography >7 kPa or APRI >0.5) or cirrhosis (>12.5 kPa or APRI >1), regardless of ALT or HBV DNA levels. Furthermore, we incorporate age as a determinant of therapy, advising treatment for adults ≥30 years with HBV DNA >2,000 IU/mL, even when ALT is normal, and for younger patients when HBV DNA exceeds 2,000 IU/mL and ALT is elevated. It also endorses treatment for HBsAg-positive individuals with co-infections, immunosuppression, high risk of mother-to-child or household transmission, severe acute HBV, or extrahepatic manifestations. Importantly, there is evidence that one-third to two-thirds of HBV-related hepatocellular carcinoma occurs in patients who would not meet traditional treatment criteria, reinforcing its rationale for broader eligibility.

Regarding diagnostics and service delivery, WHO and ALEH both prioritize simplified staging using APRI, FIB-4, and elastography, enabling treatment decisions in settings where biopsy or full laboratory panels are unavailable and supporting decentralized models of care. EASL and AASLD also endorse non-invasive fibrosis assessment but assume a more robust specialist-level diagnostic infrastructure. In terms of prevention and surveillance, all guidelines converge on recommending TDF/TAF/ETV as first-line therapy, universal HBsAg screening during pregnancy, timely birth-dose vaccination, HBIG where available, maternal tenofovir prophylaxis, routine HDV testing, and semi-annual HCC surveillance with ultrasound (± AFP).

Our Statement is between specialist-driven Western guidelines and the WHO public-health framework. Philosophically, it aligns closely with the WHO by promoting simplified treatment eligibility criteria, decentralized models of care, and an explicit focus on HBV elimination. At the same time, we maintain pragmatic consistency with EASL and AASLD by preserving essential clinical details, such as fibrosis assessment, virological markers, and comorbid conditions, while intentionally expanding treatment thresholds to include high-risk individuals in the indeterminate phase who more conservative criteria may overlook. Significantly, our recommendations are regionally adapted to address the substantial diagnostic and therapeutic gaps that persist across LATAM, thereby offering a framework that is both clinically grounded and operationally feasible for the region's diverse healthcare systems.

In summary, ALEH's recommendations are more expansive than EASL/AASLD's in expanding who should receive treatment, and more operationally feasible than WHO's model because they are adapted to the realities of Latin American health systems.

The following tables provide a structured comparative analysis of the ALEH 2025 Position Statement in relation to the most recent international hepatitis B guidelines issued by WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6]. The comparison focuses on key domains that determine eligibility for antiviral treatment, including cirrhosis, fibrosis stage, ALT thresholds, HBV DNA cut-offs, age as a treatment determinant, and specific high-risk clinical scenarios. This side-by-side evaluation highlights both conceptual and operational differences among guidelines, as well as the distinctive regional adaptation and expanded treatment strategy proposed by ALEH (Tables 4-10).

Table 4
Treatment Indications for Adults with Cirrhosis Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Guideline	Treat?	ALT Requirement	HBV DNA Requirement	Comments
ALEH 2025	Always	Not required	Not required	Aligned with all major guidelines.
WHO 2024	Always	—	—	Fully simplified global recommendation.
EASL 2025	Always	—	—	Includes compensated and decompensated cirrhosis.
AASLD 2025	Always	—	—	No exceptions.

Table 5
Fibrosis-Based Treatment Criteria in Non-Cirrhotic Adults Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Guideline	Fibrosis Threshold	Criteria	Comments
ALEH 2025	TE >7 kPa or APRI >0.5	Treat regardless of ALT/DNA	Highly expansive; adapted to Latin America.
WHO 2024	APRI >0.5 or FIB-4 elevated	Treat if significant fibrosis	Simplified approach for LMIC settings.
EASL 2025	≥F2	Based on TE or biopsy	Traditional staging approach.
AASLD 2025	≥F2	Based on TE or biopsy	Phase-structured strategy.

Table 6
ALT Thresholds for Initiation of Antiviral Therapy Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Guideline	ALT Threshold	Comments
ALEH 2025	ULN: 35M/25F	Treatment allowed even with normal ALT if risk factors present.
WHO 2024	Not essential	ALT not mandatory when fibrosis or DNA criteria met.
EASL 2025	ALT > ULN	More ALT-dependent but flexible with fibrosis.
AASLD 2025	ALT ≥ 2 × ULN	Most conservative definition of immune-active disease.

Table 7
HBV DNA Cut-Offs for Treatment According to HBeAg Status Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Guideline	HBeAg +	HBeAg -	Comments
ALEH 2025	Not required	>2,000 IU/mL	Treatment expanded; age and ALT modifiers.
WHO 2024	Same threshold	>2,000 IU/mL	Uniform simplified rule.
EASL 2025	>20,000 IU/mL	>2,000 IU/mL	Retains phase distinctions.
AASLD 2025	>20,000 IU/mL	>2,000 IU/mL	Most structured phase-based approach.

Table 8
Use of Age as an Independent Criterion for Treatment Initiation Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Guideline	Age Criterion	Comments
ALEH 2025	≥30 years + DNA >2,000 IU/mL	Unique among all guidelines; major innovation.
WHO 2024	None	No age-based thresholds.
EASL 2025	None	Considers age but not as a formal cutoff.
AASLD 2025	None	Does not use age for treatment decisions.

Table 9
Antiviral Treatment Recommendations in Special Populations Across International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Condition	ALEH 2025	WHO 2024	EASL 2025	AASLD 2025
Co-infection (HIV/HCV/HDV)	Treat always	Treat	Treat	Treat
Immunosuppression	Prophylactic treatment	Same	Same	Same
Family history of HCC	Treat if DNA detectable	Not explicit	Risk factor	May influence decisions
Extrahepatic disease	Treat always	Considers	Considers	Considers

Table 10
Clinical Scenarios in Which ALEH Recommends Broader Antiviral Treatment: This table summarizes key clinical situations in which ALEH expands treatment eligibility beyond the criteria proposed by other international guidelines, particularly in indeterminate phases, patients with normal ALT but significant viral replication, and individuals with high transmission risk. International HBV Guidelines: WHO (2024) [3], EASL (2025) [4], and AASLD (2025) [6].

Situation	ALEH 2025 Recommendation	Other Guidelines
Indeterminate phase	Treat more expansively	EASL acknowledges; AASLD conservative
Normal ALT + DNA >2,000 + ≥30 years	Treat	Not recommended by others
Fibrosis + low DNA	Treat	WHO yes; EASL/AASLD not consistently
High intrafamilial transmission risk	Treat	Only WHO discusses as a factor

10. Expert opinion / conclusion

The updated ALEH hepatitis B guidelines are more than a technical document; they are a call to action for the region. Latin America cannot afford to lag in the global effort to eliminate HBV. Despite decades of vaccine availability and highly effective antivirals, diagnosis and treatment remain the Achilles' heel of HBV control in our countries. Too many patients are still not diagnosed or diagnosed at late stages of liver disease, often when cirrhosis or hepatocellular carcinoma has already developed.

By advocating for simplifying diagnostic algorithms, expanding treatment eligibility, and integrating HBV care into primary health care systems, these guidelines chart a pragmatic and equitable path forward. They are not limited to hepatologists and are intended to empower general practitioners, maternal-to-child health care providers, and community-based programs to take ownership of HBV elimination.

The message is clear: if we simplify, decentralize, and scale up vaccination and treatment, elimination by 2030 is within reach. The real challenge now lies in political will, resource allocation, and regional collaboration. These guidelines are the roadmap—but it is up to us, as clinicians, policymakers, and advocates, to turn them into action and ensure that HBV becomes a disease of the past in Latin America.

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