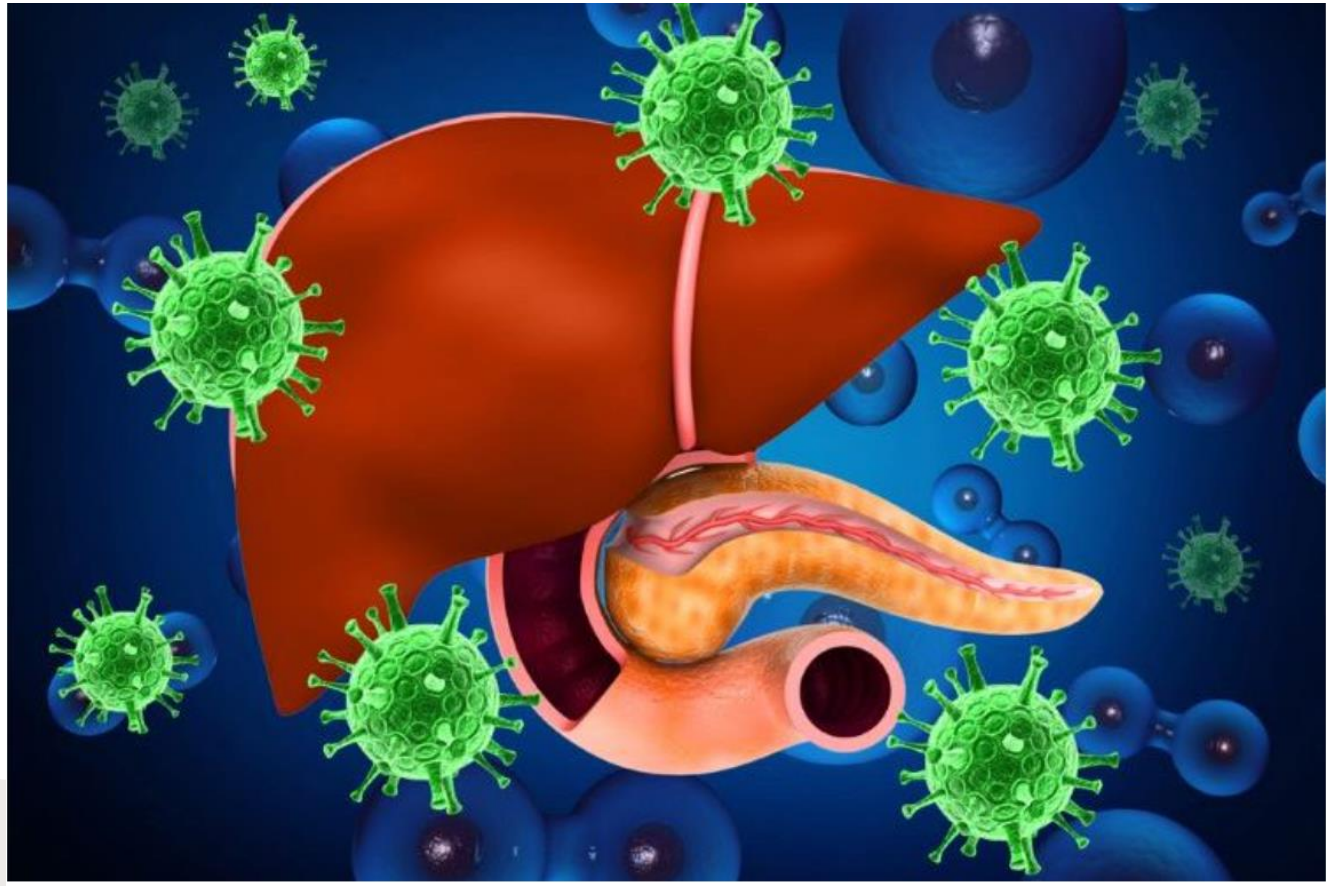
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection 2025



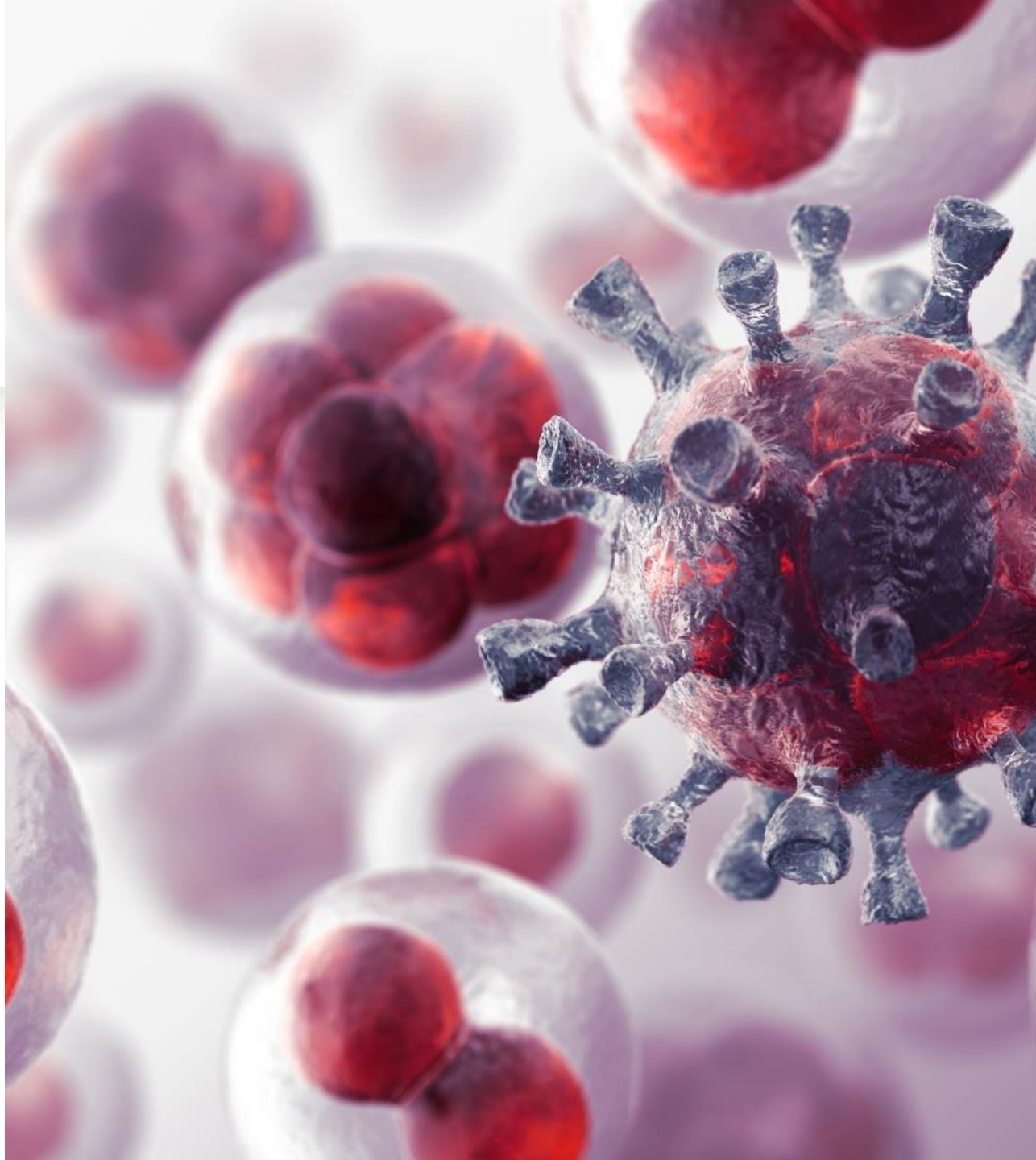
EASL

The European Association for the Study of the Liver (EASL) clinical practice guidelines (CPGs) on HBV have been developed to serve as a practical resource for physicians, encompassing both general practitioners and specialists, who play a pivotal role in the care of individuals with HBV infection

guideline covers a wide spectrum of topics, ranging from diagnostics, patient evaluation and treatment indications to antiviral therapy options, monitoring strategies, HCC surveillance, considerations for special populations, prophylaxis of HBV reactivation (HBVr), and finally the prevention of HBV

Worldwide Deaths from Chronic Viral

Hepatitis as Compared with Deaths from T.B, HIV Infection, and Malaria.



Numbers of deaths and DALYs due to Hepatitis

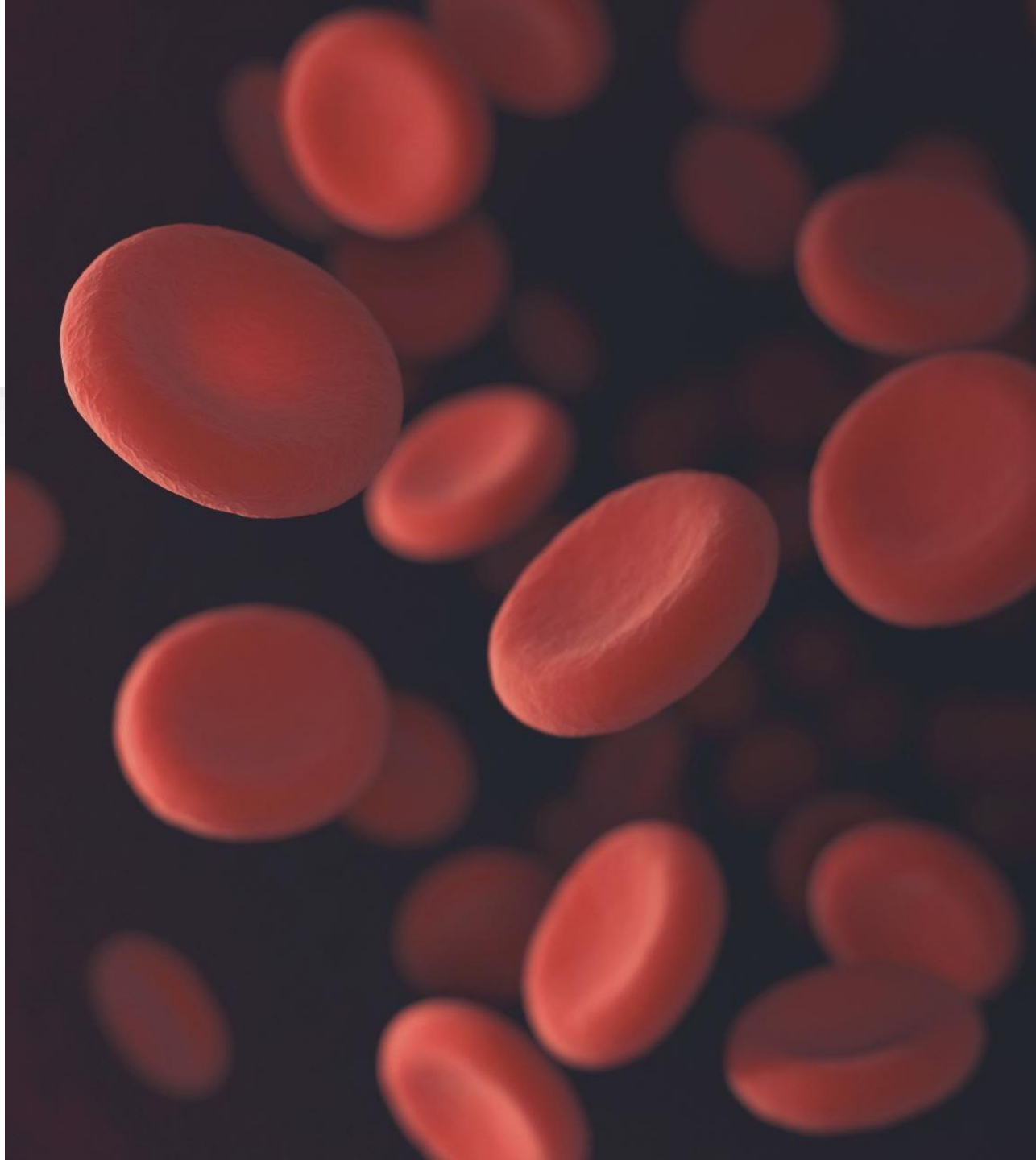
Increased between 1990 and 2020, the relative importance of mortality(62%) and DALYs(34%) due to viral hepatitis .

One million global and 6000/year Iran

premature death from viral hepatitis

Priorities in viral hepatitis

Elimination



How Can We Achieve the elimination goals of WHO

- ❑screening
- ❑Prevention
- ❑Treatment
- ❑ Vaccination
- ❑Measures Expand testing

Hepatitis B

A symptomatic until the later stages

Bleeding,HCC,Ascites,.....

New developments have encourage

HBV VACCINE CONVEYS 95 PERCENT IMMUNITY IN THREE DOSES.

HBV TREATMENT CAN CURE > 90%

Iran HBV vaccination program

was very protective in >95%

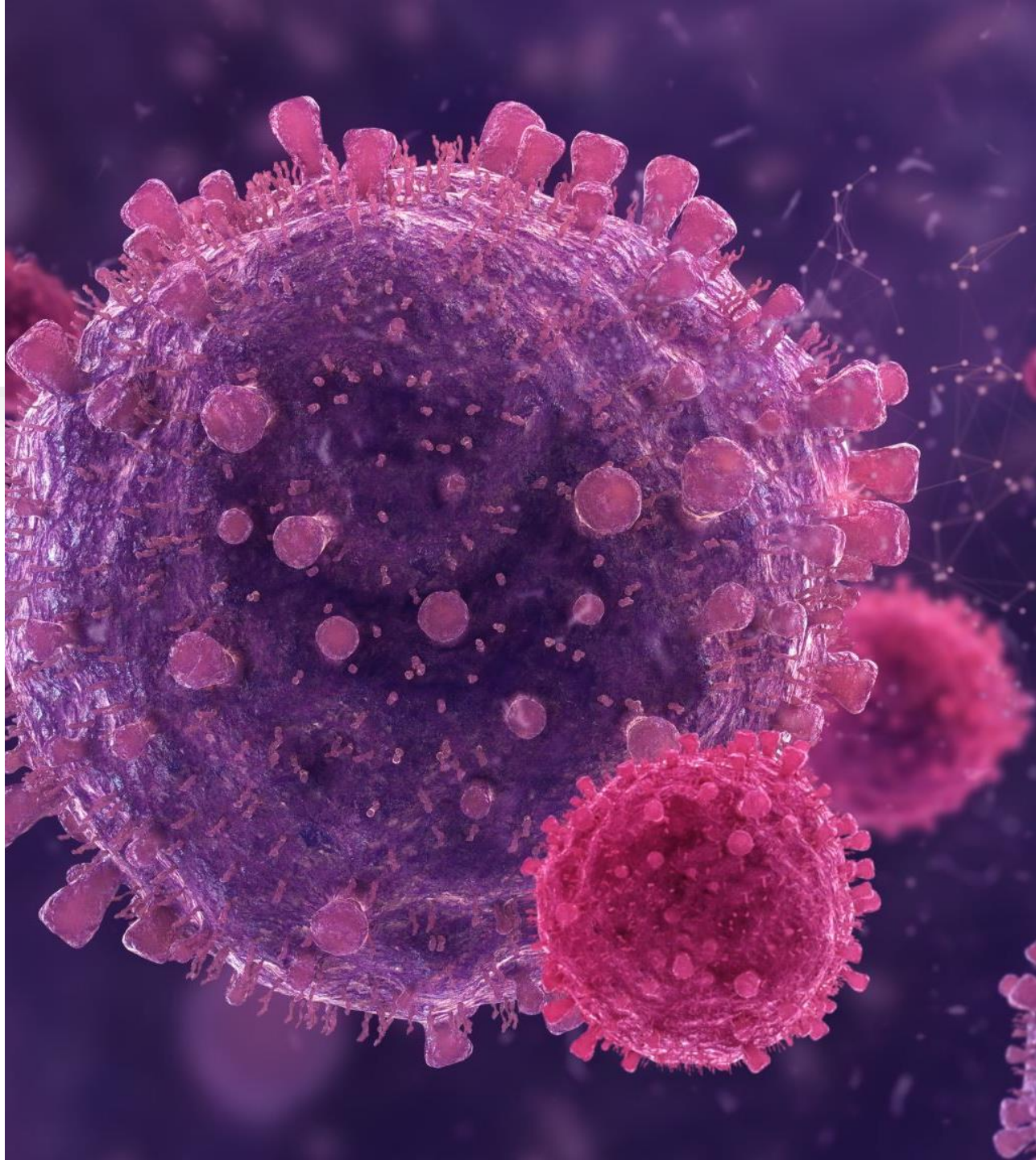
HBV In Iran

Hepatitis B virus (HBV) is the most common

cause of chronic hepatitis and HCC in the

world and Iran .

IRAN has estimated 1.4 to 1.5 million people have chronic hepatitis B; almost 1,000 new acute infections occur every year.



Acute HBV

Natural history Acute HBV infection is often asymptomatic but can lead to severe hepatitis and, in some adult cases, to fulminant hepatitis and liver failure. It may also progress to chronic infection, particularly if transmitted from mother to child or acquired during childhood or adolescence.

Should patients with acute HBV infection be treated with antiviral therapy

Statement Given the high spontaneous clearance rate of HBsAg during acute HBV infection in adults, antiviral treatment is not required in this clinical setting as long as synthetic liver function is not impaired (strong consensus). Recommendation Patients with acute hepatitis B and impaired synthetic liver function should be treated with NAs and should be managed in cooperation with a transplant centre.

Treatment

Treatment is mainly supportive. The likelihood of acute liver failure from acute HBV is less than 1 percent, and in immunocompetent adults, the likelihood of progression to chronic HBV infection is less than 5 percent .

Acute liver failure

- ❑ Altered mental status (hepatic encephalopathy)
- ❑ Prolonged prothrombin time (INR ≥1.5)

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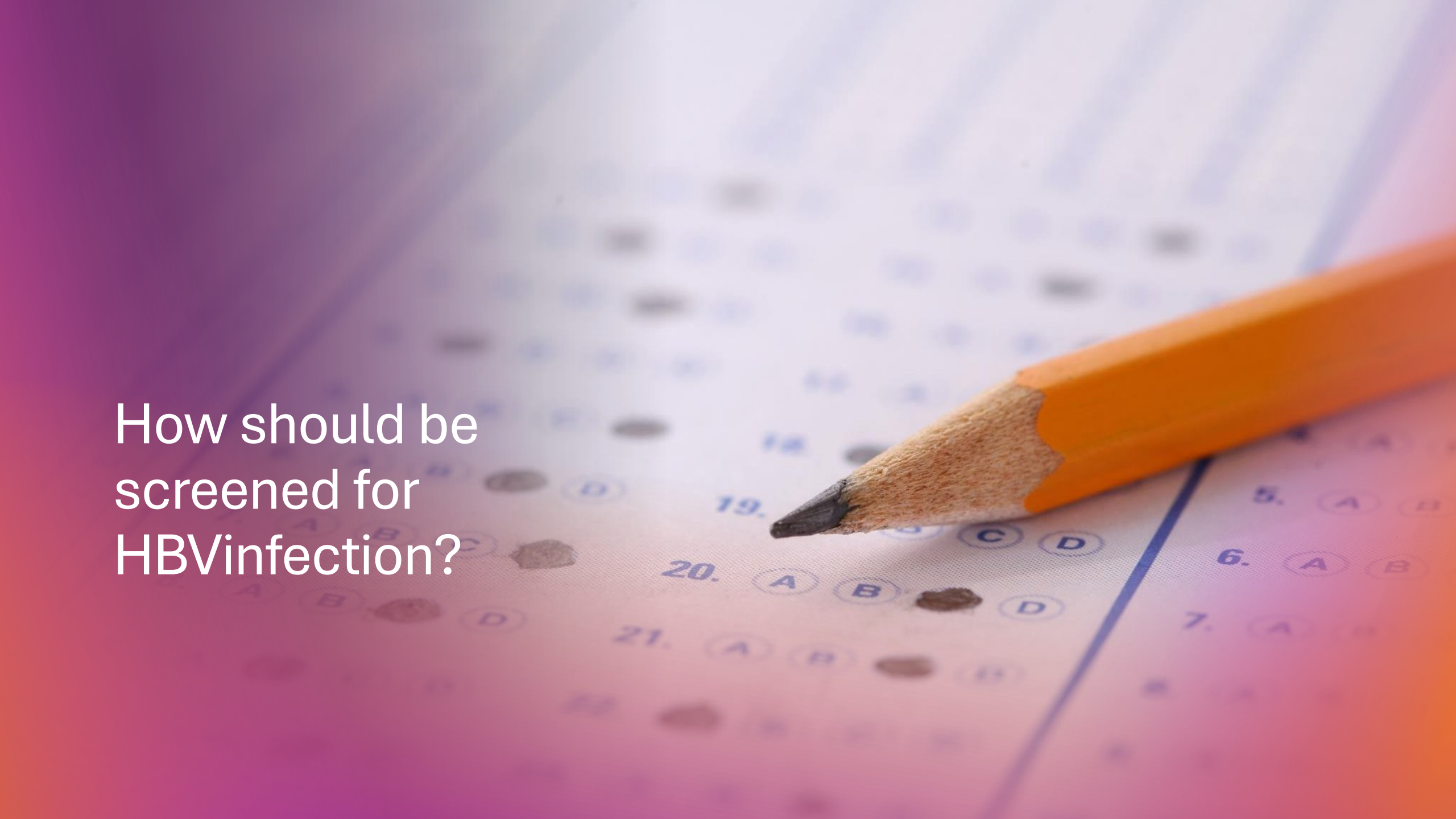
severe or a protracted course

Treat patients with a severe or a protracted course, such as those who develop a coagulopathy (international normalized ratio [INR] >1.5) or those with persistent symptoms or marked jaundice (bilirubin >3 mg/dL) for more than four weeks after presentation . We also treat patients with acute liver failure (coagulopathy and encephalopathy) due to HBV to reduce the likelihood of reinfection post-liver transplant, should a liver transplant become necessary.

NA therapy

ETV, TDF, or TAF should be used at acute hepatitis. When selecting between ETV, TDF and TAF, comorbidities (especially renal insufficiency and reduction in bone density).

How should be screened for HBVinfection?



For initial screening of HBV infection,HBsAg and anti HBc should be determined

Who should be screened for HBV infection?

patient with elevated liver enzymes and/or clinical signs of liver disease

- with cirrhosis/fibrosis of the liver
- with liver cancer (HCC or biliary tract cancer)
- with extrahepatic manifestations possibly related to HBV
- with end-stage kidney disease undergoing haemodialysis
- with HIV infection
- with HCV infection
- being considered for or undergoing immunosuppressive/ immunomodulatory therapy or chemotherapy
- with congenital immunodeficiency
- considered for stem cell/bone marrow or organ transplants and recipients of such transplants
- with an increased risk of exposure to HBV
  - individuals from regions with intermediate to high HBsAg prevalence
  - family or household members of HBV-infected individuals
  - sexual partners of HBV-infected individuals
  - individuals in care/correctional facilities
  - individuals with multiple sexual partners
  - individuals who seek examination or treatment for sexually transmitted diseases
  - individuals with nonmedical exposure to body fluids
  - active and former people who inject drugs

HBV screening (HBsAg [anti-HBc not required) should b
performed to prevent transmission in **(strong recommen
dation, strong consensus)**:

- Blood, tissue, semen, and organ donors
- Healthcare workers
- Pregnant women

HBsAg is typically measured using highly sensitive enzyme immunoassays with a limit of detection(LOD)of HBV.

False-negative and-positive HBsAg

False-negative HBsAg results may occur due to variations in HBsAg epitopes not recognised by all assays. Additionally, different HBsAg tests use various antibodies and have different capabilities to dissociate HBsAg from immune complexes, potentially leading to conflicting results. Anti-HBc and HBV DNA testing are reliable methods to resolve these discrepancies.

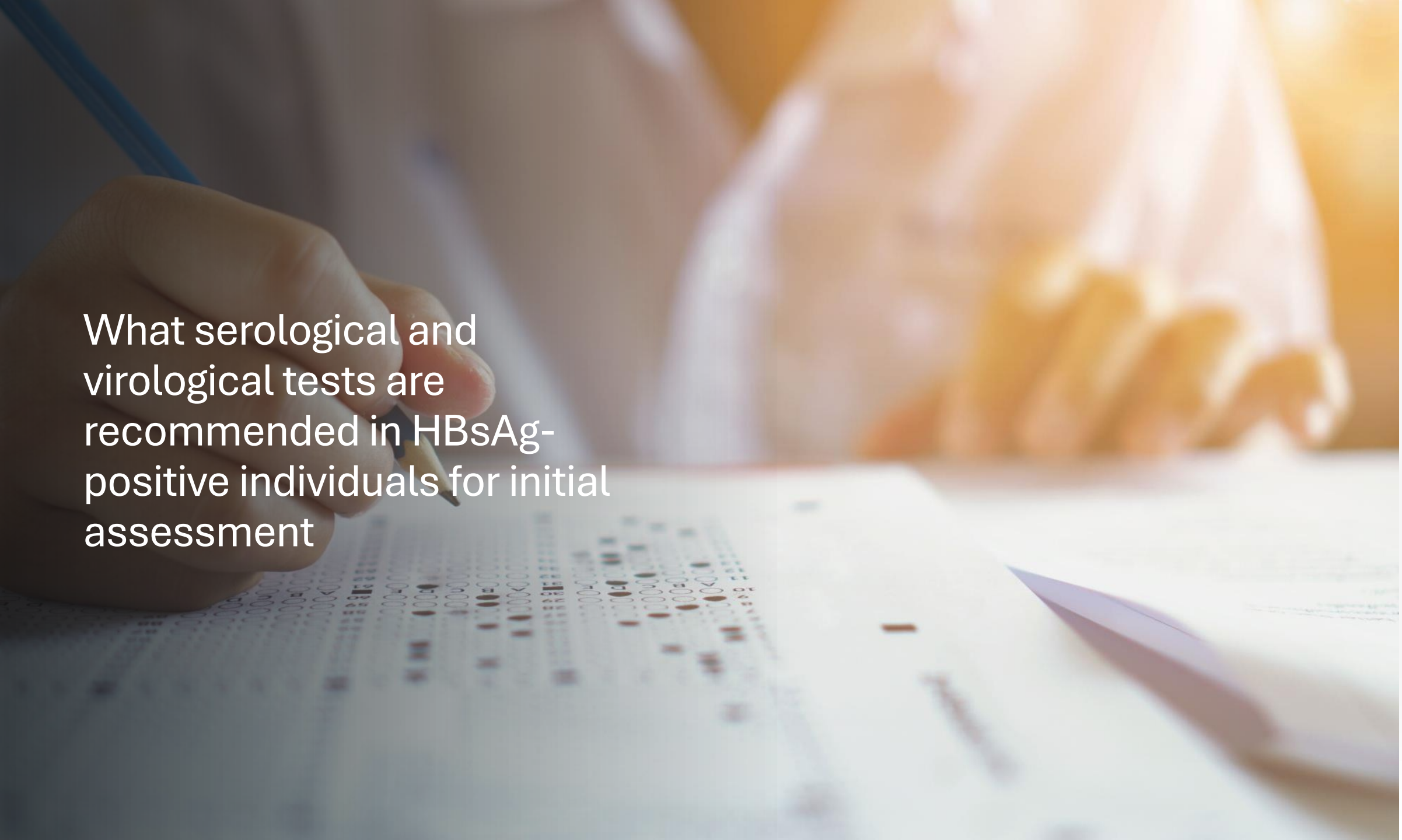
False-positive HBsAg

False-positive HBsAg results, which can occur in patients on haemodialysis, post-mortem organ donors, individuals with heterophilic antibodies, or those receiving G-CSF, can generally be ruled out by performing neutralisation with anti-HBs, the manufacturer-recommended confirmatory test. Sequential HBsAg measurements, combined with other virological markers, can further enhance diagnostic accuracy and provide a more comprehensive understanding of the infection status.

Anti-HBc antibodies may arise after any encounter with HBV and indicate a past or current infection.

ANTI HBC

Importantly, detection of anti-HBc IgG alone does not indicate whether the infection is ongoing or resolved. These in dividuals may be HBsAg-negative but anti-HBc-positive, necessitating monitoring and/or preventive measures. Thus, anti-HBc screening enhances the understanding of an individual’s HBV history and informs appropriate clinical actions to manage reactivation risks.


What serological and virological tests are recommended in HBsAg-positive individuals for initial assessment

What test

- HBV DNA quantitative
- HBsAg quantitative
- HBeAg
- HBV genotype HDV screening HCV screening HIV screening

Table 5. Recommended serological and virological diagnostics for HBsAg-positive/anti-HBc-positive individuals.

Diagnostic test	Recommendation	Grade
HBV DNA quantitative	HBV DNA should be tested, as it serves as the most important prognostic marker and is critical for treatment indication and treatment monitoring	Strong
HBsAg quantitative	HBsAg quantification should be tested to characterize disease phase, define prognosis and guide treatment	Strong
Anti-HBs	Anti-HBs is not necessary for diagnosis of HBV infection; anti-HBs is useful to determine immunisation status if HBsAg is negative and to evaluate seroconversion after HBsAg loss	Weak
HBeAg	HBeAg should be tested to define the disease phase	Strong
Anti-HBe	Anti-HBe can be tested to define the disease phase (especially if HBeAg is negative)	Weak
Anti-HBc IgM	If acute hepatitis B is suspected, anti-HBc IgM can be tested (ideally quantitative)	Weak
HBV genotype	Genotype can be tested to optimise stratification for interferon-based treatment and estimate risk of HCC	Weak
HDV screening	Anti-HDV should be tested	Strong
HCV screening	Anti-HCV should be tested	Strong
HIV screening	Anti-HIV1/2 should be tested	Strong

HDV

Assessment of relevant coinfections Hepatitis D, also known as Delta hepatitis, is a special form of viral hepatitis, as it is always a coinfection with HBV. Infection with the hepatitis D virus (HDV), a small RNA virus, occurs exclusively in patients with HBV infection, as HDV requires the HBV envelope (HBsAg) to infect hepatocytes and egress from hepatocytes

Assessment of relevant coinfections

- **Hepatitis D :The detection of anti-HDV antibodies is carried out by immunoassays,67 but testing for serum/plasma HDV RNA is needed to confirm an ongoing HDV infection.**
- **Hepatitis C (AB,RNA)**
- **HIV AB**

What additional investigations are recommended for dis ease assessment in HBsAg-positive individuals?

Baseline liver disease assessment

Abdominal ultrasound should be performed at diagnosis in all HBsAg-positive individuals.

Non-invasive methods should be used to assess liver f ibrosis and stage liver disease in all HBsAg-positive in dividuals.

Liver biopsy can be performed in case of diagnostic uncertainty, discordant non-invasive test results or the presence of liver-related comorbidities recommendation, strong consensus.

SONOGERAPHY

Ultrasound examination of the abdomen is recommended to detect potential liver tumours, identify coexisting conditions (e.g. hepatic steatosis), and look for signs of portal hyperten sion. For details on using ultrasound for HCC surveillance see section.

FIBROSCAN

Fibrosis stage Thresholds Significant fibrosis (F2 or F3 or F4)

APRI

World Health Organization (WHO) guidelines suggest the use of an APRI score of >0.5 to detect significant fibrosis, but acknowledge a high rate of false-positive results. Other tests such as FibroTest require specialised lab facilities.

This evaluation includes measuring liver inflammation markers (aspartate aminotrans ferase [AST], ALT), synthetic liver function parameters (total bilirubin, albumin), and coagulation status (e.g. prothrombin time expressed as international normalised ratio [INR]) and full blood count.

Table 4. Phase of chronic HBV infection, modified based on.[5]

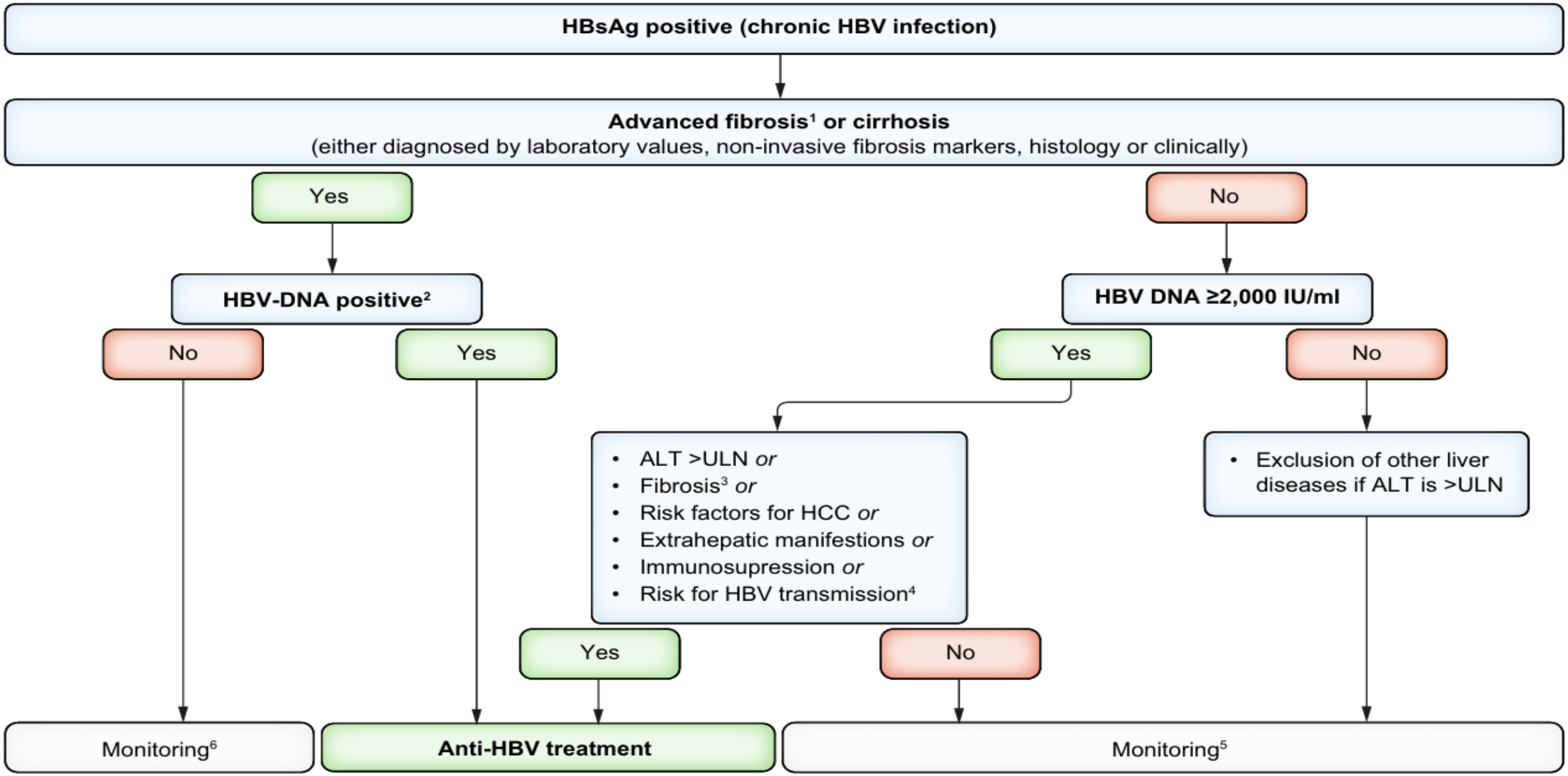
	Phase 1	Phase 2	Phase 3	Phase 4
	HBeAg-positive chronic infection	HBeAg-positive chronic hepatitis	HBeAg-negative chronic infection	HBeAg-negative chronic hepatitis
HBsAg	High	Intermediate to high	Low, usually <1,000 IU/ml	Intermediate, usually >1,000 IU/ml
HBV DNA	High, usually $\geq 10^7$ IU/ml	Moderate to high, usually 10^4-10^7 IU/ml	Usually <2,000 IU/ml	Usually, >2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease progression (if untreated)	None/minimal	Moderate to severe	None	Mild to severe

NOVEL biomarkers

New viral biomarkers Recently, emerging non-invasive biomarkers reflecting the intrahepatic pool of transcriptionally active HBV covalently closed circular DNA (cccDNA) have been proposed, comprising quantification of serum hepatitis B core-related antigen (HBcrAg) and HBV RNA.

Which patients with chronic HBV infection should be treated?

all HBsAg-positive individuals with detectable HBV DNA are candidates for antiviral therapy. The indica tion for treatment is primarily based on HBV DNA and ALT levels, fibrosis stage and risk of liver disease progression and HCC (strong consensus).


HBsAg positive (chronic HBV infection)
Advanced fibrosis[1] or cirrhosis
(either diagnosed by laboratory values, non-invasive fibrosis markers, histology or clinically)
Yes
No
HBV-DNA positive[2]
HBV DNA ≥2,000 IU/ml
No
Yes
Yes
No
• ALT >ULN or
• Fibrosis[3] or
• Risk factors for HCC or
• Extrahepatic manifestions or
• Immunosupression or
• Risk for HBV transmission[4]
• Exclusion of other liver diseases if ALT is >ULN
Yes
No
Monitoring[6]
Anti-HBV treatment
Monitoring[5]

Host factors	
Cirrhosis	Strongest risk factor for HCC[161,167,169] HCC risk remains after viral suppression[170,171]
Low platelets*	Indicator for cirrhosis[195]
Family history of HCC	Independent risk factor in all phases of chronic HBV infection[192,193,216]
Age*	HCC risk increases with age, with most studies focusing on individuals older than 30 years.[161,185] Evidence increases with age ≥35,[166] ≥40,[163] ≥50.[167] HCC risk varies in different age groups for men and women and for different ethnic groups[191]
Sex*	Higher risk among males[161,166,169,185]
ALT*	Elevated (or in the upper normal range)[163,166,167,185]
Type 2 diabetes mellitus (T2D)	T2D is independently associated with HCC.[183,217,218] Glycaemic burden is associated with HCC.[219] T2D is included in HCC risk scores[168,218] However, one analysis showed that T2D was not independently associated with HCC in chronic HBV infection[179]
Steatotic liver disease (SLD)	Conflicting data: - Increased risk of HCC and cirrhosis[188] - Lower risk of HCC, cirrhosis, and mortality[180,182,189]
Body mass index (BMI)	High BMI ≥30,[179] HR stronger in females[178]
Metabolic syndrome	Multiple (≥3) metabolic risk factors or increasing burden of metabolic dysfunction are associated with HCC[180–182,190]
Cigarette smoking	Present[181,184–187]
Alcohol consumption	Heavy alcohol intake ≥60 g/d[161]
Ethnicity	Evidence low or absent: - Birth in Africa/Oceania: linked to very early-onset HCC[194] - Sub-Saharan Africans with HBV in Europe: lower HCC incidence, similar risk factors to general population[195] - Western *vs.* Eastern studies: no significant age-adjusted differences in HCC incidence[161]
Environmental factors	
Aflatoxin B1 (AFB1)	In high-exposure areas, AFB1 and HBV synergistically increase HCC risk; reducing aflatoxin exposure could lower HCC cases by 23%[198]
Air pollution	Association between fine particulate matter and HCC[200,201]

Treatment goals

What are the goals of antiviral therapy for chronic HBV infection?

Statement

- The clinical goal of treating chronic HBV infection is to reduce morbidity (cirrhosis, hepatic decompensation, liver failure, HCC) and improve survival.

Since clinical endpoints such as cirrhosis, end-stage liver disease and HCC manifest over a longer period of time, surrogate markers are instrumental in defining treatment success **(strong consensus):**

- Persistent suppression of HBV DNA (preferably undetectable HBV DNA) is the primary goal of antiviral therapy.
- HBsAg loss is the ultimate goal of therapy.
- Normalisation of ALT is an additional endpoint.

Confirmed loss of HBeAg and seroconversion to anti HBe antibodies (for HBeAg-positive patients)

Table 7. Monitoring intervals for HBsAg-positive individuals who are not receiving antiviral treatment*.

Population	Monitoring
HBeAg-positive infection[1]	• ALT every 6 months[2] • HBV DNA every 6 months • HBsAg quantitative every 12 months • HBeAg//anti-HBe every 6-12 months • Non-invasive fibrosis assessment every 12-24 months based on clinical assessment
HBeAg-negative infection (HBV DNA <2,000 IU/ml) [1]	• ALT every 12 months[3] • HBV DNA every 12 months[4] • HBsAg quantitative every 12 months[4] • Fibrosis assessment every 2-3 years
HBeAg-negative infection (HBV DNA ≥2,000–20,000 IU/ml) [1]	• ALT every 6 months • HBV DNA every 6 months • HBsAg quantitative every 12 months • Fibrosis assessment every 12-24 months based on clinical assessment • If stable for ≥3 years, monitoring intervals can be extended
HBeAg-negative infection (patients with compensated cirrhosis, undetectable HBV DNA and normal ALT) [1]	• ALT every 6 months • HBV DNA every 6 months • HBsAg quantitative every 12 months • HCC surveillance every 6 months • Fibrosis assessment is not required but LSM and platelet count can be used to assess the risk of clinically significant portal hypertension and the need for EGD surveillance[85]

TREATMENT

Treatment Which treatment options are recommended for patients with chronic HBV infection? Statement Two different therapeutic options are recommended for the treatment of chronic HBV infection: NAs or PEG-IFNa

Table 9. Differences between PEG-IFNα and NA therapy.

Features	ETV, tenofovir (TDF, TAF)	PEG-IFNα
Strategy	Preventing disease progression through persistent HBV suppression	Induction of an off-treatment response finite treatment
Administration	Oral, once daily	Subcutaneous, once weekly
Treatment duration	Long-term	Finite (48 weeks)
Response guided treatment	Criteria for stopping long-term therapy before HBsAg loss (see "When can antiviral therapy for hepatitis B with NAs be stopped?")	Stopping rules after 12-24 weeks of thera "How should therapy with PEG-IFNα be a tered in patients with chronic HBV infectio
Side effects	Very low	Moderate to high
Contraindications	Very few (*e.g.* ETV in pregnancy)	Numerous
Level of viral suppression	High	Low to high, depending on patient profile
HBeAg/anti-HBe seroconversion rates	Initially low, moderate during long-term treatment	Low to high, depending on patient profile
HBsAg loss	Very low	Low, higher compared to NAs
Risk of viral resistance	Very low	Absent

NA therapy

NA therapy NAs integrate into viral DNA during HBV replication, causing premature termination of the DNA chain and effectively preventing further viral replication. This inhibition reduces HBV DNAlevels in the bloodstream. Approved NAs for the treatment of chronic HBV infection include lamivudine, adefovir dipivoxil, ETV, telbivudine, TDF, and TAF. These drugs are categorised by their resistance profiles into low-barrier NAs (lamivudine, adefovir dipivoxil, telbivudine) and high-barrier NAs (ETV, TDF, TAF). ETV, TDF, and TAF offer predictable, long-term antiviral efficacy, along with a favourable safety profile and the conve nience of oral dministration

- **ETV, TDF, or TAF should be used as first-line NA therapy. When selecting between ETV, TDF and TAF, comorbidities (especially renal insufficiency and reduction in bone density) and concomitant circumstances (e.g. women of child bearing age, pregnancy, age) as well as previous therapies should be taken into account**

How should NA therapy be administered and what should be considered during long-term therapy?

Determination of HBV DNA and ALT levels should be carried out every 3-6 months until a virological response is achieved. Thereafter, the monitoring interval can be extended to 6-12 months for therapy with ETV or teno fovir (TDF or TAF)

. Definition of treatment response in NA-treated adherent patients.

Box 1. Definition of treatment response in NA-treated adherent patients.

- **Complete virological response** is defined as undetectable HBV DNA measured with a sensitive assay (<20 IU/ml).
- **Partial virological response** is present if HBV DNA does not decline steadily and remains >2,000 IU/ml.
- **Virological non-response** is defined by a decline <1 $\log_{10}$ at 6 months of NA treatment.
- **Virological resistance** is assumed if HBV DNA increases to ≥1 $\log_{10}$ above nadir.

HBsAg status should be tested every 12 months. Ideally, a quantitative determination of HBsAg should be performed

What are the treatment recommendations for pregnant HBsAg-positive women

Pregnant women on antiviral therapy,tenofovir(TDF,TAF) shouldbe continued,ETV or adefovir should be switched to tenofovir (TDF, TAF). Treatment with PEG-IFNa should be discontinued and switched to tenofovir (TDF, TAF) .

. HBV DNA levels > −200,000 IU/ml, to prevent mother-to child transmission of HBV. Positive HBeAg irrespective of HBV DNA level, in areas where HBV DNA testing is unavailable, to prevent mother-to-child transmission. Treatment to prevent mother-to-child transmission should ideally be started before the last trimester of pregnancy. Tenofovir(TDF,TAF).

Maternal antiviral prophylaxis with tenofovir can be continued long-term post-delivery to maintain viral sup pression. During maternal antiviral prophylaxis with tenofovir, the newborn can be breastfed

Drug safty

Lamivudine, ETV, and adefovir are classified by the FDA as "Category C" drugs, indicating that side effects have been observed in animal studies. In contrast, tenofovir and telbivudine are classified as "Category B" drugs, meaning that while no evidence of adverse effects on the foetus has been observed in animal studies, controlled human studies are lacking. Despite this, sufficient clinical data from studies and large pregnancy registries support the safety of lamivudine, telbivudine, and tenofovir (both TDF and TAF). No increased risk of foetal malformations has been found with these medications, even when used in the first trimester. Therefore, tenofovir is the recommended antiviral drug during pregnancy and treatment should be continued (or started) if the treatment indications are met and to prevent MTCT

Most studies have started treatment between weeks 28 and 32.

Breastfeeding

Breastfeeding and antiviral therapy Concerns about potential drug transfer through breast milk often influence the decision to initiate breastfeeding post partum. However, lamivudine, TDF, and TAF concentrations in breast milk are very low, with infant exposure to TDF during breastfeeding being lower than in utero

A study showed no detectable TAF in breast milk, while TDF was present at low levels in both breast milk and cord blood. Data from women using TDF for HIV treatment or pre-exposure prophylaxis have raised no safety concerns.499,500 Based on current evidence, breastfeeding should not be discouraged if tenofovir (TDF, TAF) therapy is continued

A systematic review of 10 studies found no difference in HBsAg status between breastfed and non-breastfed infants of vaccinated HBsAg-positive mothers. However, breastfeeding should be avoided in cases of bloody skin lesions. One study suggested non-breastfeeding may slightly reduce MTCT risk in HBeAg-positive mothers with very high HBV DNA (>8 log10 IU/ml) who do not receive antiviral therapy, though the absolute risk reduction was modest, with 65 women needing to abstain to prevent one additional MTCT case. This reinforces the importance of early antiviral therapy in pregnancy to minimise HBV DNA levels and MTCT risk from the outset.

C/S AND RISK OF MTCT

Role of caesarean section in preventing MTCT The question of whether a caesarean section reduces the risk of MTCTremains debated.

A systematic review of 30 studies (9,906 cases) found that elective caesarean delivery may lower the relative risk of MTCT compared to vaginal birth, though data were highly heterogeneous. Another review (18 studies, 11,446 cases) did not confirm this finding but noted a possible benefit for mothers with high HBV DNA levels (> –200,000 IU/ ml). Another study of 1,409 cases supported that caesarean section has a benefit when HBV DNA is > –200,000 IU/ml. Most studies were conducted in China, with limited data on newborn vaccination timing. Timely active-passive immunisa tion, ideally within 12 (the eralier the better) hours of birth, re mains critical.

Given the lack of generalisable evidence, routine caesarean section for MTCT prevention is not recommended. However, if maternal HBV DNA is > –200,000 IU/ml at birth, caesarean section may be considered after a thorough risk benefit discussion with the patient.

HCC surveillance

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