2020 Consensus document of the Spanish Association for Study of the Liver on the treatment of hepatitis B virus infection

M Buti, MD
Hospital Universitario Valle Hebrón and CIBER EHD del Instituto Carlos III
Barcelona Spain

Disclousures

- Speaker and Advisor

  Abbvie and Gilead Sciences

- Advisor

  Assembly, GSK and Altoinmune

Asociación Española
para el Estudio del Hígado

Gastroenterología y Hepatología 2020;43(9):559–587

Gastroenterología y Hepatología

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CLINICAL PRACTICE GUIDELINES

Consensus document of the Spanish Association for Study of the Liver on the treatment of hepatitis B virus infection (2020)☆

Manuel Rodríguez[a,*], María Buti[b], Rafael Esteban[b], Sabela Lens[c], Martín Prieto[d], Emilio Suárez[e], Javier García-Samaniego[f,*]

Why to update AEEH Hepatitis B Guidelines?

- 2012 AEEH consensus document on the treatment of hepatitis B virus Hígado
- Changes in the epidemiology and the understanding of the natural history of hepatitis B,
- Changes in the diagnostic methods and treatment indications
- No major advances in the treatment of chronic hepatitis B

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Methodology

- An expert panel to review and update the document.
- The final version was approved by the Governing Board.
- The recommendations were based on the available scientific evidence. If information was insufficient or non-existent, recommendations were based on the opinions and personal experience of the experts themselves.
- The recommendations were classified according the quality of the scientific evidence into three levels: high (A), moderate (B) or low (C).
- Two levels of recommendation: strong (1) or weak (2).

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Hepatitis B Epidemiology in Spain

- HBsAg in the general population from 2% to 7% (Intermediate prevalence)
- In 1990 Hepatitis B vaccine was added to s National Health Programm
- Vaccine coverage above 95%
- Current prevalence of HBsAg around 0.5%-0.8% (low endemicity)
- Incidence from 2008 until now stable, 1.27 to 1.65 cases per 100,000 population

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Epidemiology of Hepatitis B in Spain

Hepatitis B was made a notifiable disease in Spain in 1995
Cases are declared individually on a weekly basis, with an epidemiological survey
Case definition included probable and confirmed cases

Figura 1. Número de casos y tasas por 100.000 habitantes de Hepatitis B. España, 2008-2019

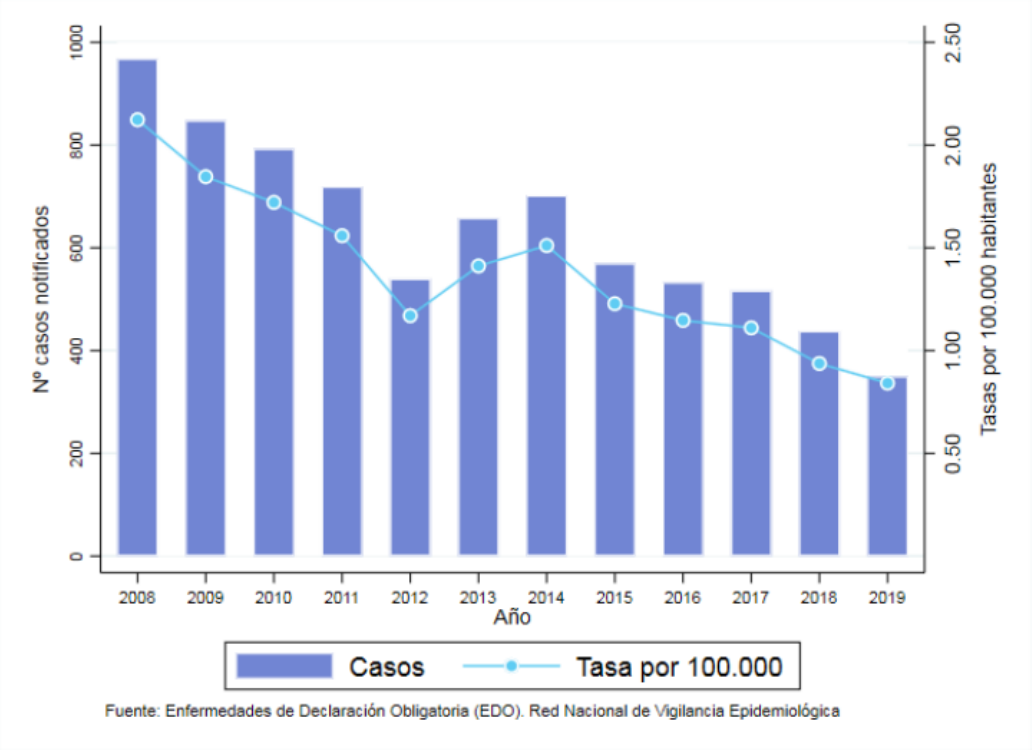
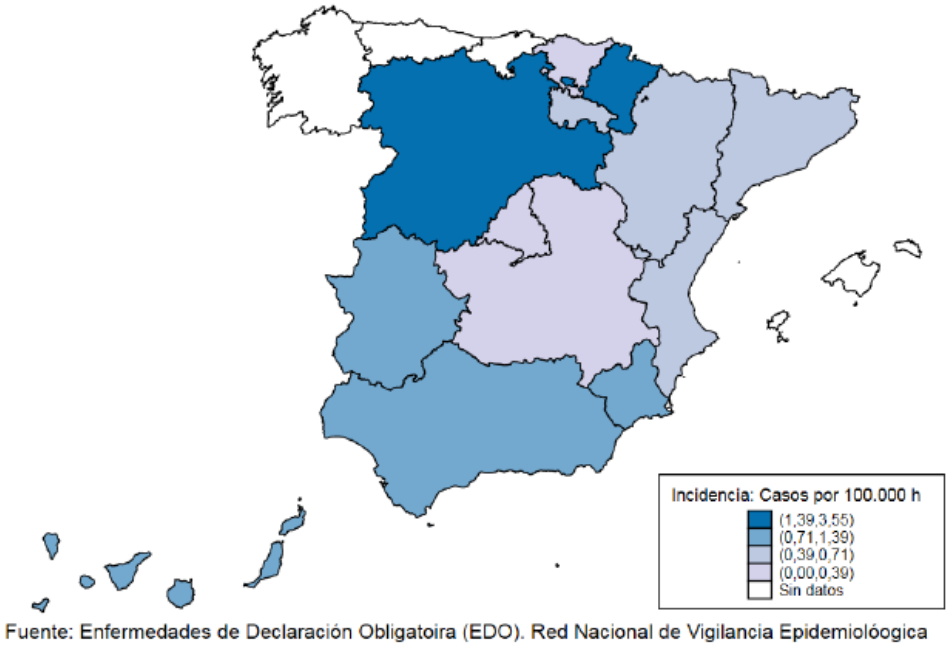


Figura 2. Incidencia de Hepatitis B por Comunidad Autónoma, 2019
Tasas por 100.000 habitantes



Fuente: Centro Nacional de Epidemiología, Instituto de Salud Carlos III. Vigilancia epidemiológica de la Hepatitis B en España, 2019. Madrid; octubre 2020.
https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Paginas/HepatitisB.aspx

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Factors associated with HBsAg decline

- Hepatitis B Vaccination
- Systematic control of blood donations
- Screening of pregnant women
- Programs to avoid high risk behaviors: Harm reduction programs, condoms, tattoos and body piercing under unhygienic conditions

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Recommendations:

- *As it is a notifiable disease, cases of hepatitis B (probable or confirmed) should be sent to the Centro Nacional de Epidemiologia (A1).*
- *Most people infected with HBV will not develop symptoms during the course of the infection, so serological screening is recommended in at-risk populations (A1).*

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Characteristics of the phases of chronic hepatitis B virus infection

	HBeAg-positive		HBeAg-negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
Prior terminology	Immune tolerant	HBeAg + immune-active phase	Inactive carrier	HBeAg-negative chronic hepatitis
qHBsAg (IU/ml)	Very high	High	Low[a]	Intermediate
HBV DNA (IU/ml)	>10 million	20,000-10 million	<2,000 (or <20,000)[b]	>2,000 (or >20,000)
ALT (IU/l)	Normal	High	Normal	High
Histology	Normal/minimal changes	Inflammation ± fibrosis	Normal	Inflammation ± fibrosis

[a] Generally <1,000 IU/ml.
[b] Some HBeAg-negative patients with chronic infection have persistently normal ALT levels with HBV DNA levels in the range 2,000-20,000 IU/ml and a good long-term prognosis.

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Recommendations:

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- *An accurate diagnosis is necessary to determine the current stage of the natural history of liver disease, based on the determination of HBeAg, anti-HBe, HBV DNA and ALT (A1).*
- *The determination of qHBsAg is useful for the diagnosis of HBeAg-negative chronic infection (B1).*
- *Liver elastography is the non-invasive method of choice for assessing liver injury due to its greater diagnostic precision, especially for ruling out advanced fibrosis (A1).*
- *Biomarkers seem to have lower diagnostic precision, so further studies are needed to expand their use (B1).*
- *Ultrasound is useful for diagnosing liver cirrhosis and HCC (A1).*
- *Liver biopsy is indicated in patients with associated liver disease and in whom the elastography value is in the grey area (B1).*

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Recommendations

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1 *In individuals with chronic hepatitis B, treatment is indicated if ALT levels are elevated, HBV DNA levels are higher than 2,000 IU/ml and/or there is at least moderate necroinflammatory activity and/or fibrosis (A1).*
2 *Patients with compensated liver cirrhosis should be treated if HBV DNA is detectable, even if ALT levels are normal (A1).*
3 *Patients with decompensated cirrhosis should be treated without delay with potent nucleos(t)ide analogues, regardless of HBV DNA and ALT levels (A1).*
4 *Patients with a family history of HCC or extrahepatic manifestations may be treated even if they do not meet all the criteria (B2).*
5 *Patients with chronic hepatitis B not receiving treatment should be followed up every six months (A1).*

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Treatment recommendations: Advantages and Disadvantages

	Nucleos(t)ide analogues	Pegylated interferon
Treatment duration	Indefinite	Limited (12 months)
Route of administration	Oral	Subcutaneous
Antiviral activity	Potent	Modest
Development of resistance	Extremely uncommon	Never
Loss of HBeAg and HBsAg	Uncommon	Modest, genotype-dependent
Adverse effects	Rare	Common
Safety in pregnancy	TDF: class B	Class C
Contraindications	None	Common

Recommendations

1 *Initial treatment of chronic hepatitis B, whether HBeAg-positive or HBeAg-negative, is based on single-drug therapy with a nucleos(t)ide analogue or PEG-IFN (A1).*
2 *The choice of one or the other strategy will depend on the stage of liver fibrosis, virological factors, the patient's comorbidity profile and the patient's own preferences (B1).*

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Choice of analogue in special situations.

Situation	Preference
CKD stage >2 (eGFR <60 ml/min)	ETV (with dose adjustment) or TAF
Predisposing factors of CKD	ETV or TAF
Poorly controlled diabetes or hypertension	
Use of potentially nephrotoxic drugs	
Proteinuria	
Active glomerulonephritis	
Age >60 years	
Osteoporosis or corticosteroid therapy	ETV or TAF
Pregnancy	TDF
Previous treatment with nucleos(t)ide analogues	TDF or TAF
Decompensated cirrhosis	ETV or TAF
HIV co-infection	TDF or TAF

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

TDF, TAF, Entecavir and PegINF are approved and fully reimboused except TAF, only reimboursed in patients with renal disease

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Recommendation of therapy duration with PEG-IFN

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- Duration of PEG-IFN therapy is 48 weeks (B1)

- In HBeAg+ve patients with genotype A or D who, after 12 wks of PegIFN, have qHBsAg >20,000 IU/ml and the absence of a decrease compared to baseline, treatment can be stopped due to lack of efficacy (B1)

- In HBeAg-ve patients with genotype D infection who, after 12 wks of treatment, show the absence of a decrease in qHBsAg levels combined with no decrease in HBV DNA by< 2log both compared to baseline, treatment can be stopped due to lack of efficacy (B1).

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Recommendation therapy duration with Nucleos(t)ide Analogues

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- *Initially, the duration of treatment with a nucleos(t)ide analogue is indefinite. The safest strategy for stopping treatment is based on doing so once negative results for HBsAg have been achieved; therefore, treatment should be stopped once that goal has been reached and confirmed to have been reached (B1).*
- *In patients with HBeAg-positive chronic hepatitis, treatment can be stopped before negative results for HBsAg have been achieved in case of virological response and HBeAg seroconversion confirmed by two determinations three to six months apart after at least 12 months of consolidation therapy (B2).*
- *In patients with HBeAg-negative chronic hepatitis, stopping treatment before achieving negative results for HBsAg can be considered in patients without advanced fibrosis or cirrhosis at the start of treatment, with a sustained virological response for at least three years, once HBsAg levels <100 IU/ml have been achieved, provided they are willing to be closely monitored after discontinuation (C2).*
- *In any event, treatment should not be stopped before the infection is resolved in patients with liver cirrhosis diagnosed at the start of or during treatment, patients with systemic manifestations of the disease, patients on immunosuppressant treatment and patients not willing to undergo close monitoring (B1).*

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Recommendations for Nucleoside analogues

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- In any situation involving the absence of virological response to analogue therapy, the degree of adherence to treatment should be investigated (B1).

- In patients with partial virological response at week 48, If HBV DNA levels continue to decline, the same analogue should be continued; if they do not, switching to another analogue or combination therapy with ETV + TDF or TAF should be considered (B2)

- In patients who develop resistance to ETV, switching to TDF or TAF is recommended (A1)

- In the hypothetical case of resistance to TDF or TAF switching to ETV or add ETV to TDF or TAF in case of a history of resistance to LAM

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Monitoring during therapy

- Periodic testing should be done to check ALT, HBV DNA and qHBsAg levels

- In patients treated with nucleos(t)ide analogues, kidney function and serum phosphate levels should be periodically monitored, while in those treated with PEG-IFN, tests should include a complete blood count and TSH (A1)

Table 3 Dose adjustment of ETV, TDF and TAF based on estimated glomerular filtration rate (eGFR).

	ETV[a]	TDF	TAF
eGFR ≥50 ml/min	0.5 mg/d	245 mg/d	25 mg/d
eGFR 30-49 ml/min	0.25 mg/d or 0.5 mg/48 h	245 mg/48 h	25 mg/d
eGFR 10-29 ml/min	0.15 mg/d or 0.5 mg/72 h	245 mg/72-96 h	25 mg/d[b]
eGFR <10 ml/min	0.05 mg/d or 0.5 mg/5-7 d	No recommendations	No recommendations
Haemodialysis or peritoneal dialysis	0.05 mg/d or 0.5 mg/5-7 d[c]	245 mg/7 d[c]	25 mg/d[c]

eGFR: estimated glomerular filtration rate.

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Recommendations for Patients with Decompensated Cirrhosis

- **Patients with decompensated cirrhosis** should be treated without delay with an analogue with a high genetic barrier to resistance, regardless of their HBV DNA levels (A1)

- These patients on analogue therapy should be closely monitored for treatment-related adverse effects such as kidney failure and lactic acidosis (A1)

- Patients with decompensated cirrhosis should be referred for assessment for liver transplantation if they are potential candidates, without waiting for HBV DNA levels to become undetectable (A1)

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Algorithm for prophylaxis for hepatitis B recurrence in de novo patients.

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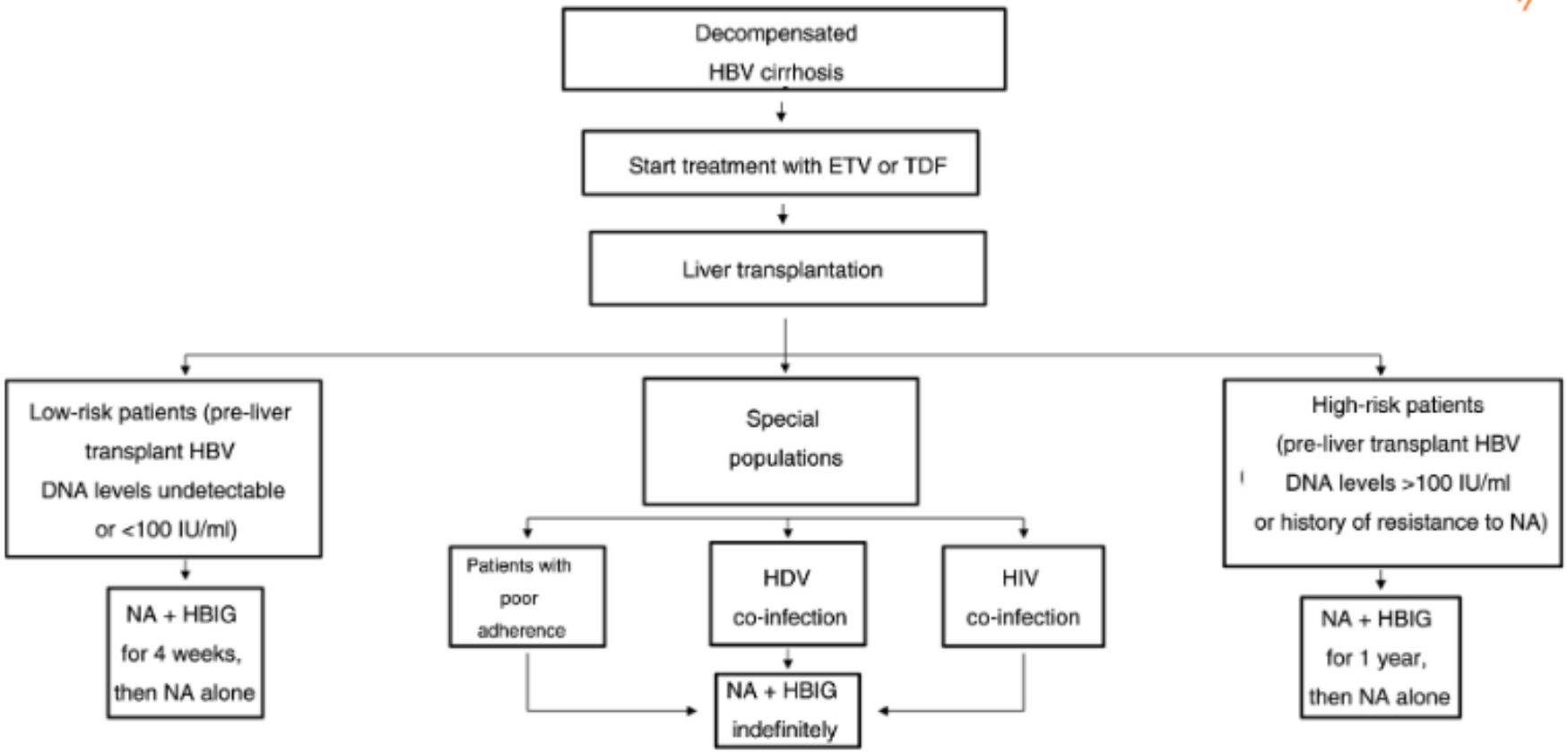

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Recommendations for HBV Liver Transplant

- All patients on the liver transplant waiting list due to HBV-related liver disease should be treated with an analogue with a high genetic barrier to resistance (A1)

- Prophylaxis for post-liver transplant hepatitis B recurrence should be based on indefinite administration of ETV or TDF/TAF (A1)

- A personalised approach to HBIg use is recommended based on risk of post-liver transplant HBV infection recurrence (A1)

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Recommendations for HBV Coinfected Patients

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- **HIV and HBV**

The indications for treatment of hepatitis B in HIV+ve patients are the same as in non-HIV-positive.

All co-infected patients should treated with combinations based on TDF/TAF with LAM/emtricitabine, regardless of their CD4+ lymphocyte count(A1)

- **HDV and HBV**

PEG-IFN for 48 wks is the recommended for compensated chronic hepatitis D and achieves virological response in 25% of patients

Oral antivirals for HBV are not effective for HDV, but should be used if there is active HBV replication (HBV DNA >2,000 IU/ml in patients without cirrhosis or any HBV DNA levels in patients with cirrhosis) (A1).

- **HCV and HBV**

In patients co-infected with hepatitis B and C, there is a risk of reactivation of HBV during or after treatment with direct antivirals. HBV DNA levels should be closely monitored in HBsAg+ve patients being treated for hepatitis C, treatment should be started with nucleos(t)ide analogues (ETV or TDF/TAF) if it is indicated and in the remaining patients prophylaxis should be considered

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Recommendations related HCC

- Patients with cirrhosis due to HBV should have ultrasound screening for HCC every six months (A1)

- In patients without cirrhosis but have a family history of HCC or are from an African or Asian country and> 40 yrs (if male) or >50 yrs (if female), especially in case of vertical transmission or genotype C infection, ultrasound screening for HCC every 6 months is recommended (B1)

- In patients treated with ETV or TDF, it is recommended that the PAGE-B score be calculated at the start of treatment. High-risk patients (score ≥18 points) should be included in a programme of screening for HCC every six months; screening may be considered for moderate-risk patients (10-17 points) (B2)

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Hepatitis B pregnancy and children

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• In pregnant women, treatment decision-making must weigh the severity of the disease and the risk of perinatal transmission. Besides, active and passive immunoprophylaxis(vaccine+HBIG) in all newborns, in women with high viraemia (>200,000 IU/ml) TDF is recommended at wks 24-28 of pregnancy.

In women already being treated with analogues, the medication should not be discontinued, but they should be switched to TDF if they were receiving another antiviral (A1).

• The incidence of HBV infection in children has decreased significantly in recent years (A1). In the few cases in which treatment is indicated, ETV and TDF are the drugs of choice, as in the adult population (B1).

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Recommendations: Hepatitis B and Immunosuppression

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- All candidates for chemotherapy and immunosuppressant or biologic therapy should undergo screening for HBV (A1)
- Antiviral prophylaxis is recommended in HBsAg+ve patients at moderate/high risk of reactivation and in HBsAg-ve, anti-HBc+ve patients at high risk of reactivation. For HBsAg-ve, antiHBc+ve patients at moderate/low risk, monitoring during and for 6 months after immunosuppression is recommended (B1)
- The recommended drugs in antiviral prophylaxis are ETV, TDF and TAF (A2)
- Antiviral prophylaxis should preferably be started 2 wks prior immunosuppression, especially in cases with detectable HBV DNA, and should be continued for 12 mo (18 mo for rituximab or other anti-CD20 antibodies) after therapy discontinuation (B1)

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Type of immunosuppressant treatment	HBsAg positive	HBsAg negative and anti-HBc positive
B-cell–depleting therapies (e.g. rituximab, natalizumab or alemtuzumab)	High	High
Immunosuppression associated with bone marrow transplantation	High	High
Potent TNF⟨ inhibitors (e.g. infliximab, adalimumab, certolizumab or golimumab)	Moderate/high	Low/moderate
Anthracycline derivatives (e.g. doxorubicin)	High	Low/moderate
Local treatment of HCC (TACE)	High	Low/moderate
Systemic chemotherapy or cytokine or integrin inhibitors (e.g. abatacept, ustekinumab, natalizumab or vedolizumab)	Moderate	Low/moderate
Cyclophilin inhibitors (e.g. ciclosporin)	Moderate	Low/moderate
Tyrosine kinase inhibitors (e.g. imatinib)	Moderate	Low/moderate
Proteasome inhibitors (e.g. bortezomib)	Moderate	Low/moderate
Histone deacetylase inhibitors (e.g. romidepsin)	Moderate	Low/moderate
Less potent TNF-⟨ inhibitors (e.g. etanercept)	Moderate	Low
Prednisone (or equivalent) ≥10 mg/d ≥4 weeks	High	Moderate
Prednisone (or equivalent) <10 mg/d ≥4 weeks	Moderate	Low
Prednisone (or equivalent) <1 week	Low	Low
Antimetabolites (e.g. AZA/6-MP or methotrexate)	Low	Low
Intra-articular corticosteroid injections	Low	Low

AZA: azathioprine; HCC: hepatocellular carcinoma; MP: mercaptopurine; TACE: transarterial chemoembolisation; TNF: tumour necrosis factor.

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