Clinical Practice Guidelines

HBV

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About these slides

- These slides give a comprehensive overview of the EASL clinical practice guidelines on the management of hepatitis B infection
- The guidelines were published in full in the August 2017 issue of the Journal of Hepatology
  - The full publication can be downloaded from the Clinical Practice Guidelines section of the EASL website
  - Please cite the published article as: European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98
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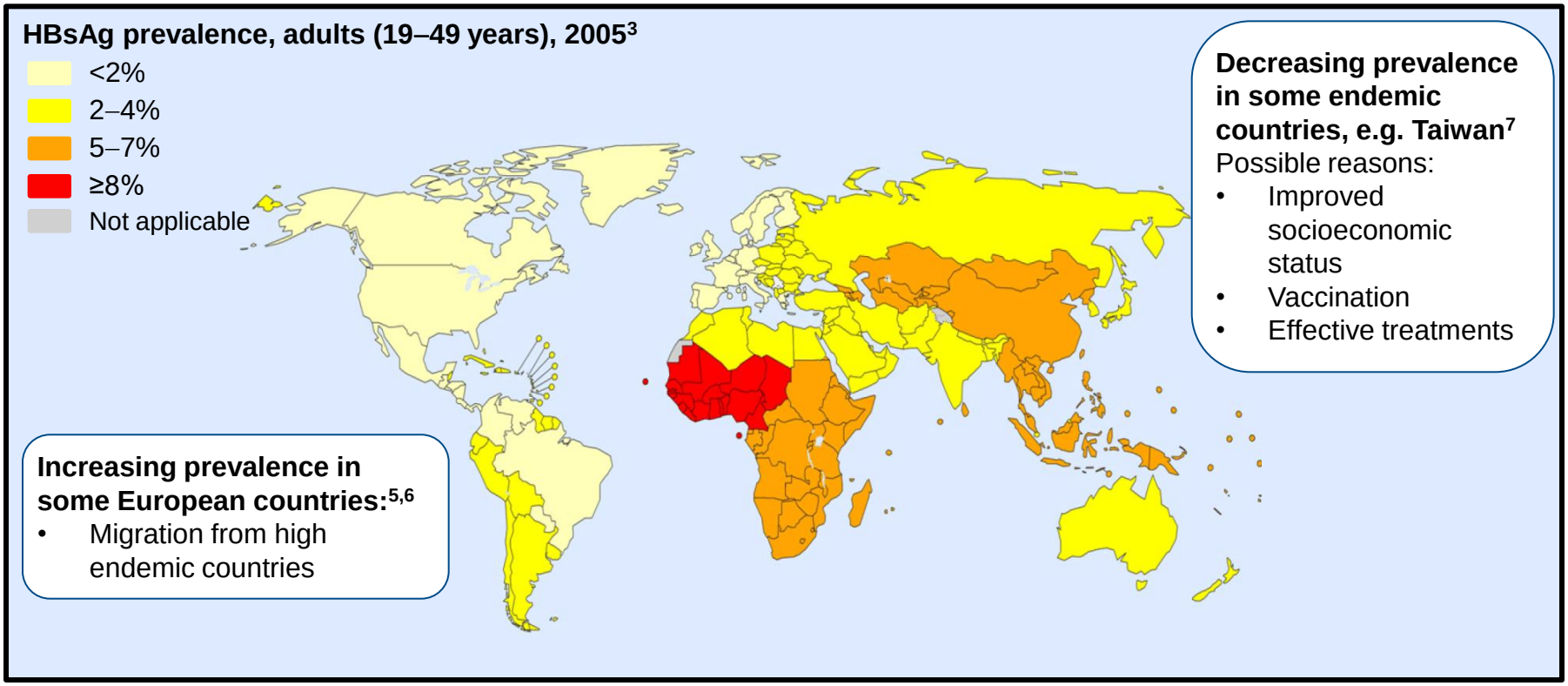
Epidemiology and public health burden[1]

- Worldwide ≈250 million chronic HBsAg carriers[2,3]
- 686,000 deaths from HBV-related liver disease and HCC in 2013[4]



1. EASL CPG HBV. J Hepatol 2017;67:370–98; 2. Schweitzer A, et al. Lancet 2015;386:1546–55;
3. Ott JJ, et al. Vaccine 2012;30:2212–9; 4. GBD 2013 Mortality and Causes of Death Collaborators. Lancet 2015;385:117–71;
5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2016;59:578–83; 7. Chen C-L, et al. J Hepatol 2015;63:354–63.

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New nomenclature for chronic phases

- The natural history of chronic HBV infection has been schematically divided into five phases

Chronic hepatitis B / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L). ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
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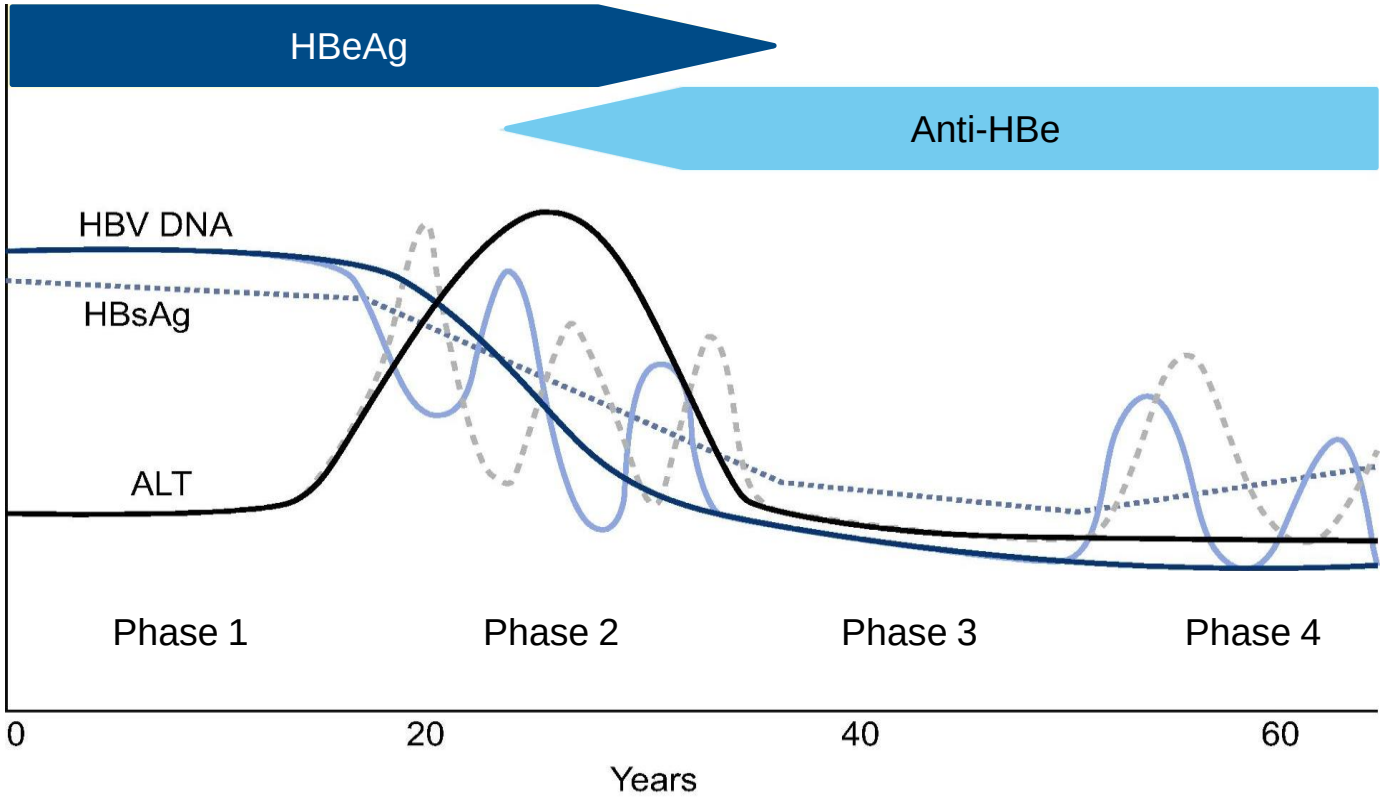
Phases of chronic HBV infection[1]



New nomenclature[2]	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B

1. Lok A, et al. J Hepatol 2017;67:847–61;
2. EASL CPG HBV. J Hepatol 2017;67:370–98

Indications for treatment

- Primarily based on the combination of 3 criteria
  - HBV DNA, serum ALT and severity of liver disease

Recommendations	Grade of evidence	Grade of recommendation
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
• Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	III	2
Can be treated		
• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	III	2

*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;
†Defined by persistently normal ALT and high HBV DNA levels;
‡ Even if typical treatment indications are not fulfilled
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Monitoring of patients currently not treated

- Patients with no current indication of antiviral therapy should be monitored
  - Periodical assessments of serum ALT, HBV DNA and non-invasive markers for liver fibrosis

Recommendations	Grade of evidence	Grade of recommendation
Follow-up at least every 3–6 months • HBeAg-positive chronic HBV infection, <30 years old	II-2	1
Follow-up at least every 6–12 months • HBeAg-negative chronic HBV infection and serum HBV DNA <2,000 IU/ml	II-2	1
Follow-up every 3 months for the first year and every 6 months thereafter • HBeAg-negative chronic HBV infection, serum HBV DNA ≥2,000 IU/ml	III	1

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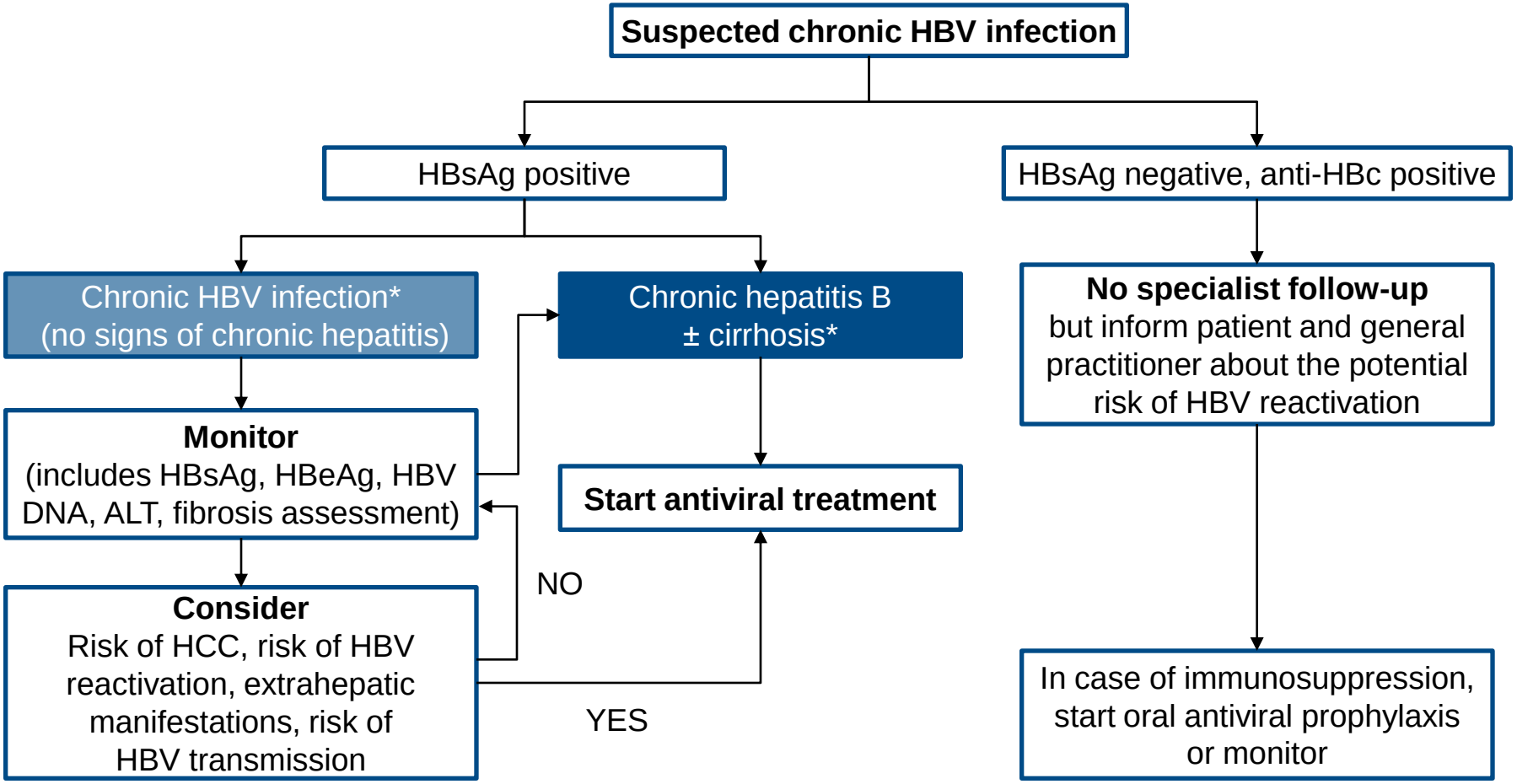
Algorithm for the management of chronic HBV infection



*See new nomenclature slide.

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Current treatment strategies for chronic hepatitis B: main concepts and features

Features	PegIFNα	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss*
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs†	Probably not‡
Contraindications	Many§	None‖
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate¶	Low in first year, moderate over long term
Effect on HBsAg levels	Variable¶	Low**
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none††

*Stopping NAs after some years might be considered in selected cases; †Psychiatric, neurological, endocrinological; ‡Uncertainties regarding kidney function, bone diseases for some NAs; §Decompensated disease, comorbidities etc.; ‖Dose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); ¶Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; ††So far no TDF or TAF resistance development has been detected

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Definitions of response to treatment

Responses	NA therapy	PegIFNα therapy
Virological (on-treatment)	**Response:** HBV DNA <10 IU/ml **Primary non-response:** <1 $\log_{10}$ decrease in HBV DNA after 3 months of therapy **Partial response:** HBV DNA decreased by >1 $\log_{10}$ but still detectable after ≥12 months of therapy in compliant patients **Breakthrough:** confirmed HBV DNA increase of >1 $\log_{10}$ above on-therapy nadir	**Response:** HBV DNA <2,000 IU/ml
Virological (off-treatment)	**Sustained response:** HBV DNA <2,000 IU/ml for ≥12 months after end of therapy	
Serological	HBeAg loss and development of anti-HBe* HBsAg loss and development of anti-HBs	
Biochemical	ALT normalization† (confirmed by ALT determination at least every 3 months for at least 1 year post-treatment)	
Histological	Decrease in necroinflammatory activity† without worsening in fibrosis compared with pre-treatment histological findings	

*Only for HBeAg-positive patients; †Based on traditional ULN (~40 IU/L);
†By ≥2 points in HAI or Ishak's system
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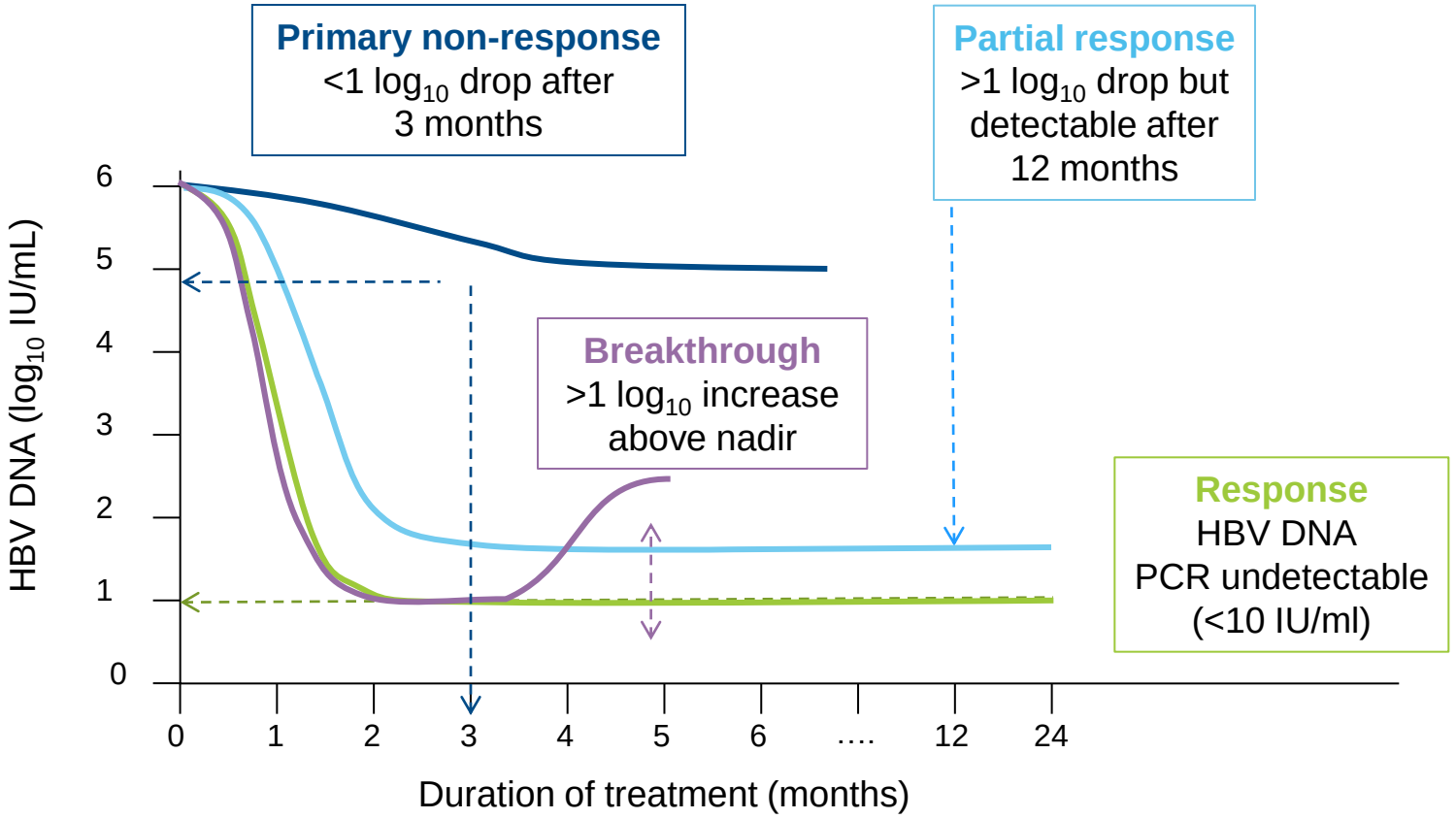
Virological responses on NA therapy



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NA monotherapy for treatment-naïve patients

- Long-term administration of a potent NA with a **high barrier to resistance** is the treatment of choice
  - Regardless of severity of liver disease

Recommendations	Grade of evidence	Grade of recommendation
Treatment of choice • Long-term administration of a potent NA with high barrier to resistance (regardless of severity of liver disease)	I	1
Preferred regimens • ETV, TDF and TAF as monotherapies	I	1
NOT recommended • LAM, ADV and TBV	I	1

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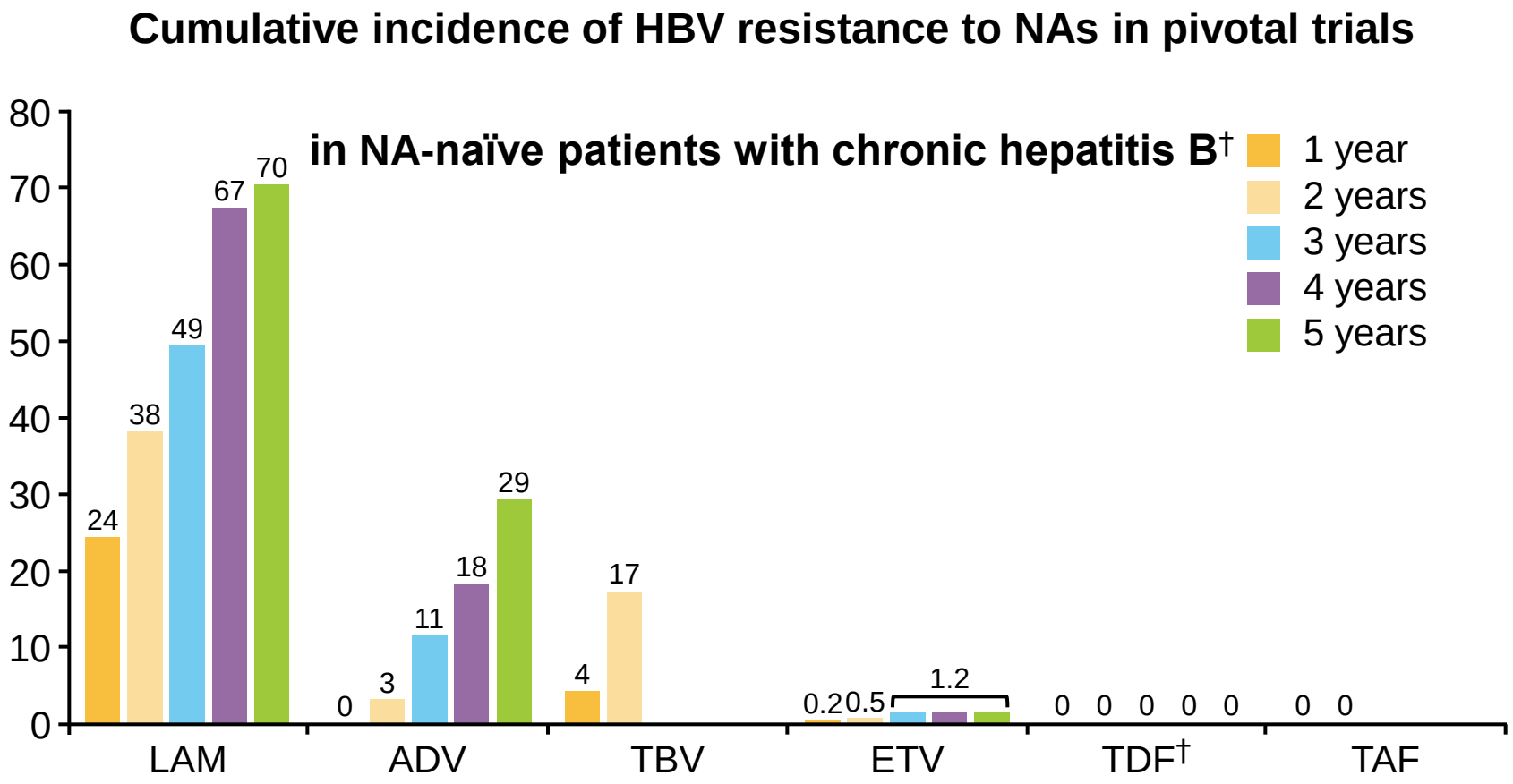
Prevention of resistance should rely on the use of first-line NAs with a high barrier to resistance*



*Evidence level I, grade of recommendation 1; †Collation of currently available data – not from head-to-head studies;
‡No evidence of resistance has been shown after 8 years of TDF treatment
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Monitoring patients treated with ETV, TDF or TAF

- Periodical monitoring and long-term surveillance is required in patients treated with an NA with a high barrier to resistance

Recommendations (monitoring)	Grade of evidence	Grade of recommendation
ALT and serum HBV DNA* • All patients treated with NAs	I	1
Renal monitoring† • Patients at risk of renal disease treated with any NA • All patients treated with TDF, regardless of renal risk	II-2	1
Switch to ETV or TAF‡ • Should be considered in patients on TDF at risk of development of and/or with underlying renal or bone disease	II-2/I	1
Recommendations (long-term surveillance)		
HCC surveillance recommended • All patients under effective long-term NA therapy	II-2	1
HCC surveillance mandatory • All patients with cirrhosis or with moderate or high HCC risk scores at the onset of NA therapy	II-2	1

*Liver function tests should be performed every 3–4 months during the first year and every 6 months thereafter. Serum HBV DNA should be determined every 3–4 months during the first year and every 6–12 months thereafter; †Including at least eGFR and serum phosphate levels. Frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration. Closer renal monitoring is required in patients who develop CrCl <60 ml/min or serum phosphate levels <2 mg/dl; ‡Depending on previous LAM exposure

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Discontinuation of NA treatment

- Long-term therapy with NAs is usually required
  - HBV eradication is not usually achieved

Recommendations	Grade of evidence	Grade of recommendation
NAs <u>should</u> be discontinued • After confirmed HBsAg loss (± anti-HBs seroconversion)	II-2	1
NAs <u>can</u> be discontinued • In HBeAg-positive patients, without cirrhosis, who achieve stable HBeAg seroconversion and undetectable HBV DNA and complete ≥12 months of consolidation therapy **Close post-NA monitoring is warranted**	II-2	2
NAs <u>may</u> be discontinued • In selected HBeAg-negative patients, without cirrhosis, who achieve long-term (≥3 years) virological suppression, **if close post-NA monitoring can be guaranteed**	II-2	2

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Management of patients with NA failure

- Treatment should be adapted as soon as virological failure under NAs is confirmed*

Resistance pattern	Recommended rescue strategies
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	If LAM-naïve: switch to ETV or TDF or TAF If LAM-resistant: switch to TDF or TAF If HBV DNA plateaus: add ETV† or switch to ETV
TDF or TAF resistance‡	If LAM-naïve: switch to ETV If LAM-resistant: add ETV§
Multidrug resistance	Switch to ETV + TDF or TAF combination

*Evidence level II-1, grade of recommendation 1; †Especially in patients with ADV-resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted; ‡Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile; §The long-term safety of these combinations is unknown

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PegIFNα monotherapy

- Only patients with milder disease should generally be considered for treatment with PegIFNα

Recommendations	Grade of evidence	Grade of recommendation
PegIFNα **can be considered as an initial treatment** option for patients with mild-to-moderate HBeAg-positive or -negative chronic hepatitis B	I	2
The standard duration of PegIFNα therapy is 48 weeks	I	1
Extension of PegIFNα therapy beyond Week 48 may be beneficial in selected HBeAg-negative patients with chronic hepatitis B	II-1	2

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Monitoring patients treated with PegIFNα

- Patients treated with PegIFNα require ongoing monitoring during treatment and after virological response

Recommendations	Grade of evidence	Grade of recommendation
Periodical assessments of at least full blood count, ALT, TSH, serum HBV DNA and HBsAg levels • All patients with chronic hepatitis B treated with PegIFNα	I/II-2	1
Periodical assessments of HBeAg and anti-HBe • HBeAg-positive patients with chronic hepatitis B treated with PegIFNα	I	1
Long-term follow-up • Patients with a virological response after PegIFNα therapy (risk of relapse)	II-2	1
Surveillance for HCC • Patients with **sustained responses** after PegIFNα therapy and high baseline HCC risk (even if they achieve HBsAg loss)	III	1

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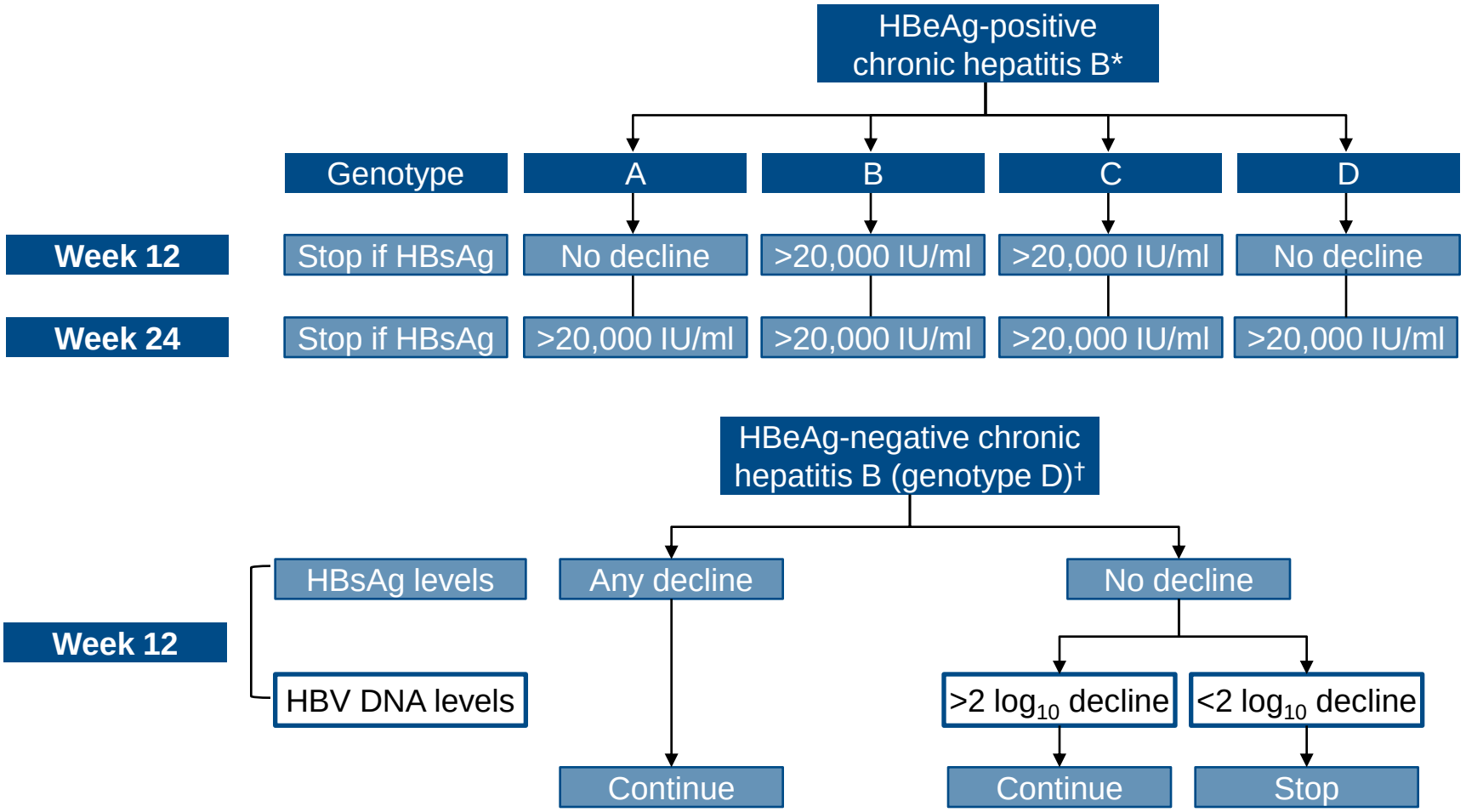
Predictors of PegIFNα response and stopping rules



*Evidence level II-2, grade of recommendation 2; †Evidence level II-2, grade of recommendation 1

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Combination therapy

- Combination therapy is generally not recommended

Recommendations (NA plus NA)	Grade of evidence	Grade of recommendation
NOT recommended • *De novo* combination therapy of two NAs with a high barrier to resistance (ETV, TDF, TAF)	I	1
Drug switch or combination may be considered • In treatment-adherent patients with incomplete HBV suppression reaching a plateau during ETV or TDF/TAF long-term therapy	III	2
Recommendations (NA plus PegIFNα)		
NOT recommended		
• *De novo* combination of NA and PegIFNα	I	1
• Short-term pretreatment with an NA before PegIFNα in treatment-naïve HBeAg-positive patients	II	1
• Adding PegIFNα or switching to PegIFNα in patients with long-term HBV DNA suppression on NA therapy	II	1

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Patients with decompensated cirrhosis

- Patients with decompensated cirrhosis should be referred for liver transplantation and treated with NAs as early as possible

Recommendations	Grade of evidence	Grade of recommendation
• **Immediate treatment** with an NA with a high barrier to resistance, irrespective of the level of HBV replication • Assessment for liver transplantation	II-1	1
PegIFNα is contraindicated	II-1	1
Patients should be **closely monitored for tolerability** of the drugs and the development of rare side effects like lactic acidosis or kidney dysfunction	II-2	1

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Preventing HBV recurrence after liver transplantation

- All patients who are candidates for liver transplantation should be treated with NAs to achieve undetectable HBV DNA
  - Reduce the risk of graft infection

Recommendations	Grade of evidence	Grade of recommendation
All **patients on the transplant waiting list** with HBV-related liver disease **should be treated with an NA**	II	1
After liver transplantation **combination** of hepatitis B immunoglobulin (HBIG) and a potent NA is **recommended** for the prevention of HBV recurrence	II-1	1
Patients with a low risk of recurrence **can discontinue HBIG** but need continued monoprophylaxis with a potent NA	II-1	2
HBsAg-negative patients receiving livers from donors with evidence of past HBV infection (anti-HBc positive) are at risk of HBV recurrence and should receive antiviral prophylaxis with an NA	II-2	1

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Special patient groups: HCV co-infection

- HCV co-infection accelerates liver disease progression and increases the risk of HCC in patients with chronic HBV infection
  - All patients with chronic HBV infection should be screened for HCV and other blood-borne viruses

Recommendations	Grade of evidence	Grade of recommendation
Treatment of HCV with DAAs may cause reactivation of HBV. Patients fulfilling the standard criteria for HBV treatment should receive NA treatment	II	1
HBsAg-positive patients undergoing DAA therapy should be considered for concomitant NA prophylaxis until 12 weeks after completion of DAA treatment, and monitored closely	II-2	2
HBsAg-negative, anti-HBc-positive patients undergoing DAA therapy should be monitored and tested for HBV reactivation in case of ALT elevation	II	1

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Special patient groups: HIV or HDV co-infection

- The risk of fibrosis progression, cirrhosis and HCC is greater in patients also infected with HDV or HIV

Recommendations (HIV)	Grade of evidence	Grade of recommendation
All HIV-positive patients with HBV co-infection should start antiretroviral therapy (ART) irrespective of CD4 cell count	II-2	1
HIV/HBV co-infected patients should be treated with a TDF- or TAF-based ART regimen	I (TDF) II-1 (TAF)	1
Recommendations (HDV)		
PegIFNα for at least 48 weeks is the current treatment of choice in HDV/HBV co-infected patients with compensated liver disease	I	1
In HDV/HBV co-infected patients with ongoing HBV DNA replication, NA therapy should be considered	II-2	1
PegIFNα treatment can be continued until Week 48 irrespective of on-treatment virological response if well tolerated	II-2	2

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Special patient groups: acute hepatitis B

- Preventing the risk of acute or subacute liver failure is the main treatment goal
  - Treating to improve quality of life and reducing risk of chronicity are also relevant treatment goals

Recommendations	Grade of evidence	Grade of recommendation
More than 95% of adults with acute HBV hepatitis do not require specific treatment	II-2	1
Only patients with severe acute hepatitis B, characterized by coagulopathy or protracted course, should be treated with NAs and considered for liver transplantation	II-2	1

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Special patient groups: pregnant women

- Management may depend on severity of liver disease and timing of a future pregnancy

Recommendations	Grade of evidence	Grade of recommendation
Screening for HBsAg in the first trimester is strongly recommended	I	1
In women of childbearing age without advanced fibrosis planning a pregnancy in the near future, it may be prudent to delay therapy until the child is born	II-2	2
In pregnant women with chronic hepatitis B and advanced fibrosis or cirrhosis, therapy with TDF is recommended	II-2	1
In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF	II-2	1
In all pregnant women with HBV DNA >200,000 IU/ml or HBsAg >4 $\log_{10}$ IU/ml, antiviral prophylaxis with TDF should start at Week 24–28 of gestation and continue for up to 12 weeks after delivery	I	1
Breast feeding is not contraindicated in HBsAg-positive untreated women or those on TDF-based treatment or prophylaxis	III	2

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Special patient groups: children

Recommendations	Grade of evidence	Grade of recommendation
In children, the course of the disease is generally mild, and most children do not meet standard treatment indications. Thus, **treatment should be considered with caution**	II-3	1
In children or adolescents who meet treatment criteria, ETV, TDF, TAF, and PegIFNα can be used	II-2	2

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Special patient groups: patients undergoing immunosuppressive therapy or chemotherapy

Recommendations	Grade of evidence	Grade of recommendation
All candidates for chemotherapy and immunosuppressive therapy **should be tested** for HBV markers prior to immunosuppression	I	1
All HBsAg-positive patients should receive ETV, TDF, or TAF as treatment or prophylaxis	II-2	1
HBsAg-negative, anti-HBc-positive subjects should receive anti-HBV prophylaxis if they are at high risk of HBV reactivation	II-2	1

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Special patient groups: patients undergoing dialysis and renal transplant

Recommendations	Grade of evidence	Grade of recommendation
All dialysis and renal transplant recipients **should be screened** for HBV markers	II-2	1
HBsAg-positive dialysis patients who require treatment **should receive** ETV or TAF	II-2	1
All HBsAg-positive renal transplant recipients **should receive** ETV or TAF as prophylaxis or treatment	II-2	1
HBsAg-negative, anti-HBc-positive subjects **should be monitored** for HBV infection after renal transplantation	III	1

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Special patient groups: patients with extrahepatic manifestations

- Some extrahepatic manifestations can be associated with HBV infection
  - Vasculitis, skin manifestations (purpura), polyarteritis nodosa, arthralgias, peripheral neuropathy and glomerulonephritis
- HBsAg-positive patients with extrahepatic manifestations and active HBV replication may respond to antiviral therapy
  - PegIFNα can worsen some immune-mediated extrahepatic manifestations

Recommendations	Grade of evidence	Grade of recommendation
Patients with replicative HBV infection and extrahepatic manifestations should receive antiviral treatment with NAs	II-2	1
PegIFNα should not be administered in patients with immune-related extrahepatic manifestations	III	1

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