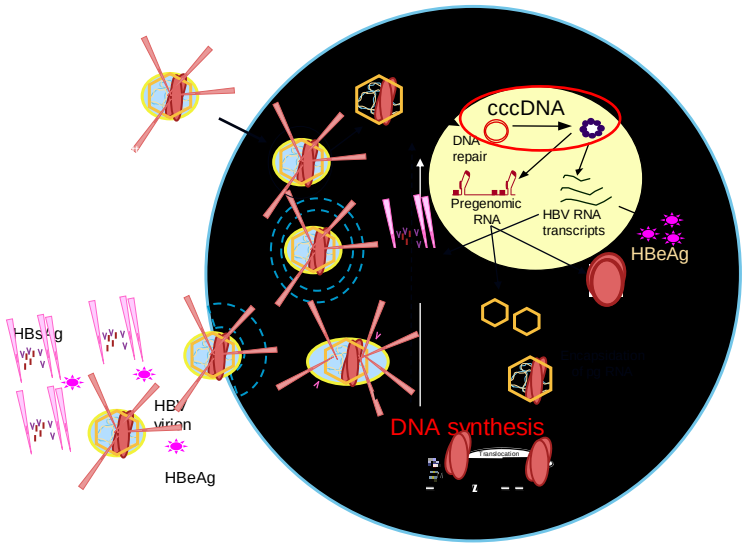
HBV Clinical Practice Guidelines

2017 Update

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL The Home of Hepatology

Why Is Cure Rare With Nucleos(t)ide Therapy?



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Goals and endpoints in HBV management

Goals

1. Prevent HBV infection transmission (HBV immunisation for HBs Ag-negative people)

Endpoint
• HBs Ab titer > 10 IU/ml

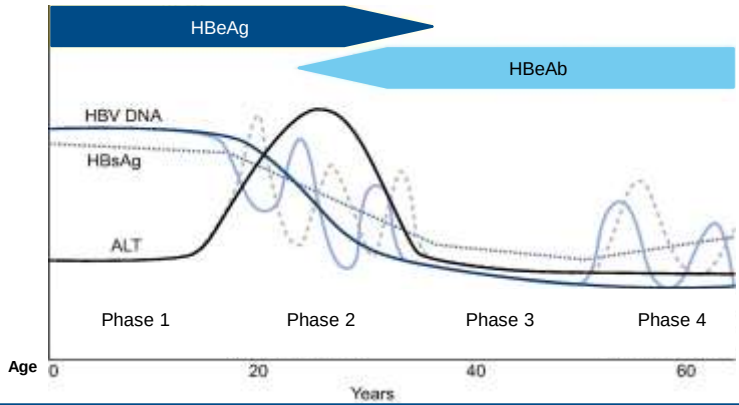
2. Preventing HBV infection reactivation (Suppression of HBV DNA for HBs Ag-positive people)
3. Preventing HBV disease progression and fibrosis (Suppression of HBV DNA for HBs Ag-positive people)
4. Preventing HBV related HCC mortality (Suppression of HBV DNA for HBs Ag-positive people)

Endpoints
Valuable endpoints • **ALT** normalization (biochemical response)† • **Undetectable** HBV-DNA **PCR**, • **HBeAg loss** (± anti-HBe seroconversion) in HBeAg-positive patients with CHB*
Optimal endpoint • **HBsAg loss** (± anti-HBs seroconversion)‡

† Achieved in most patients with long-term suppression of HBV replication;
* Often represents a partial immune control of the chronic HBV infection;
‡ Indicates profound suppression of HBV replication and viral protein expression

EASL CPG HBV. J Hepatol 2017;67:370–98

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
Old nomenclature	Immunotolerance	Immunoclearnace	Immune control (Non-replicative)	Immune scape (Immunomutant)

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

How to diagnose and stage HBV infection and liver disease in the HBsAg, HBeAg positive carrier?

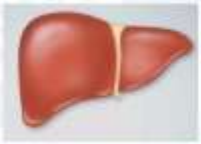
Key parameters for defining the phase of chronic HBV infection

Hepatitis B

✓HBeAg
✓HBV DNA levels
✓HBsAg levels

Recommendation 4 :
- Do [**Liver damage**] tests

Liver Disease



✓**Non-Invasive Markers** (**Ultrasound, PLT, INR, Alb**)
✓**Liver Biopsy** (**grade≥6/18, Stage≥2/6**)
✓ **Elastography (>9 Kpa)**

ALT levels

Recommendation 3 :
- Do [**AST, ALT**] tests

Terrault N, et al. AASLD 2018 Hepatitis B Guidance. Hepatology 2018
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017
Sarin SK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B. Hepatol Int. 2016

Normal ALT in chronic HBV infection

Traditional ALT ULN (40 IU/L): optimal

EASL HBV CPGs 2017, J Hepatol 2017;67:370-98. SK Sarin et al (APASL), Hepatol Int 2016;10:1-98.

Disadvantages of using a lower ALT ULN

- Unnecessary testing (more frequently HBV DNA, biopsy) and consultation
- Perhaps unnecessary therapy
- Anxiety

ALT ULN proposed by AASLD: 35/25 U/L for males/females

NA Terrault et al. Hepatology 2018;67:1560-99

Non-invasive markers as liver damage tests

- **Fibrosis-4 (FIB-4) Index for Liver Fibrosis** (Age, AST, ALT, PLT)
- **AST to Platelet Ratio Index (APRI)** (AST.PLT)
- **Fibrotest** (7 blood markers PLT, Alpha-2-macroglobulin, ALT, AST, Urea, INR, GGT)

Liver stiffness measurements in the management of HBeAg-neg. patients

- Liver stiffness >9 kPa if ALT ≤ULN
  or >12 kPa if ALT >ULN (<5xULN):

severe fibrosis or cirrhosis in chronic HBV

EASL-ALEH CPGs. J Hepatol 2015; 63: 237–64

- **If the above liver stiffness criteria fulfilled**

& HBV DNA >2000 IU/mL:

indication for HBV treatment regardless of ALT

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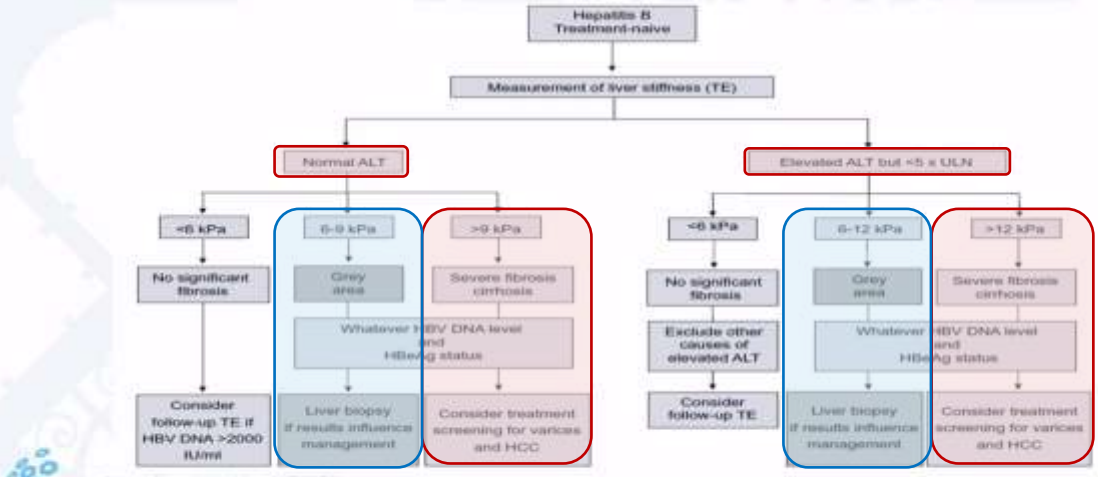
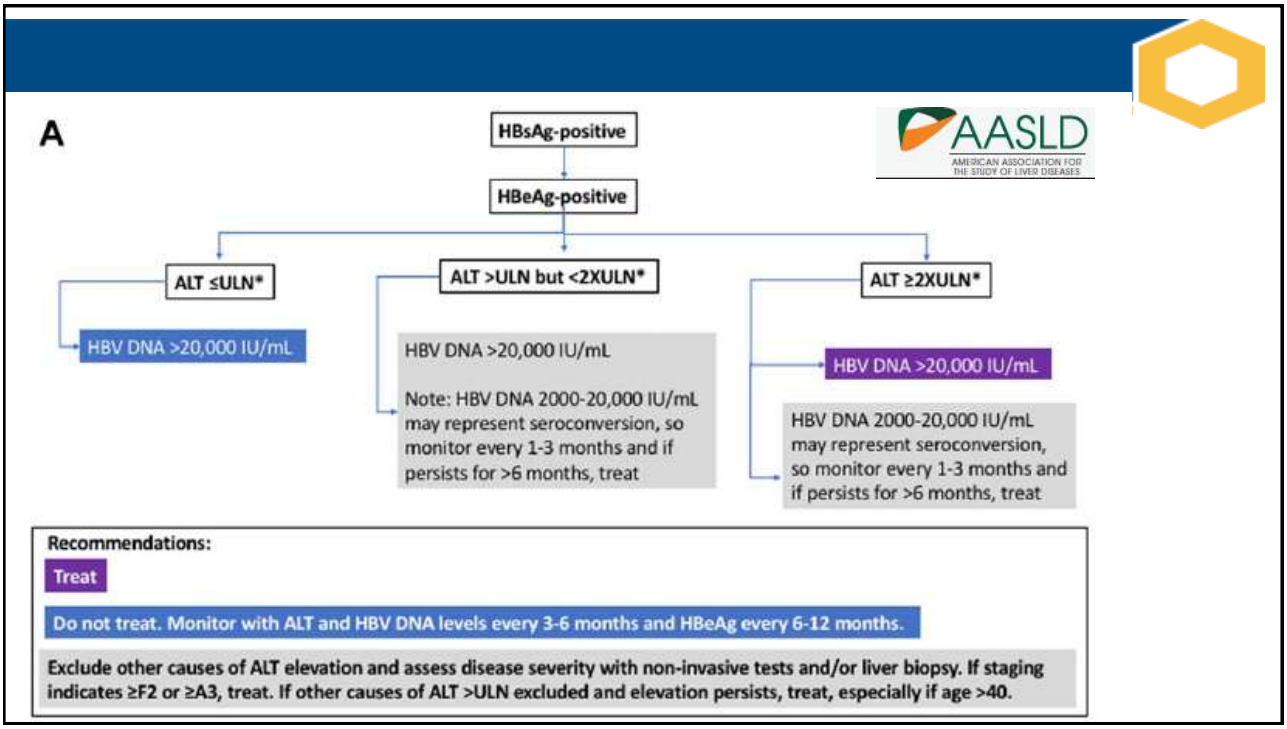
EASL HBV CPGs 2017. J Hepatol 2017;67:370-398.

EASL-ALEH Clinical Practice Guidelines: Non-Invasive tests for evaluation of liver disease severity and Prognosis



EASL-ALEH Clinical Practice Guidelines. J Hepatol. 2015 ;63(1):237-64



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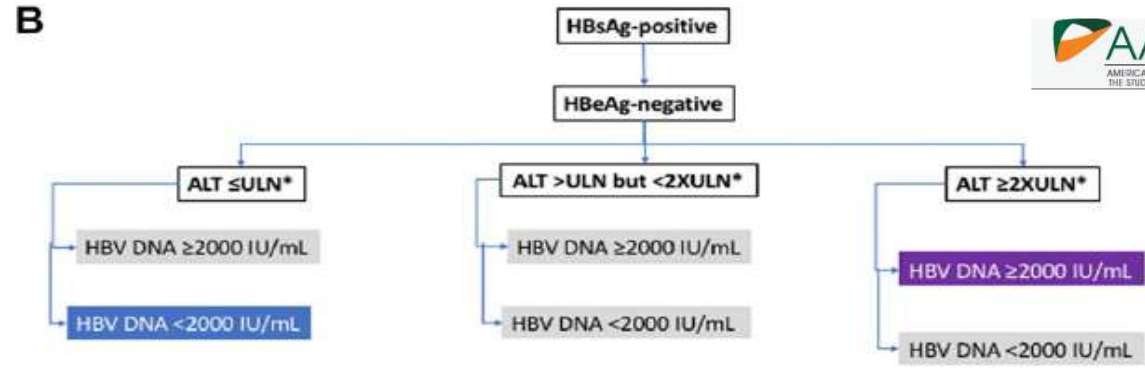

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Recommendations:

Treat

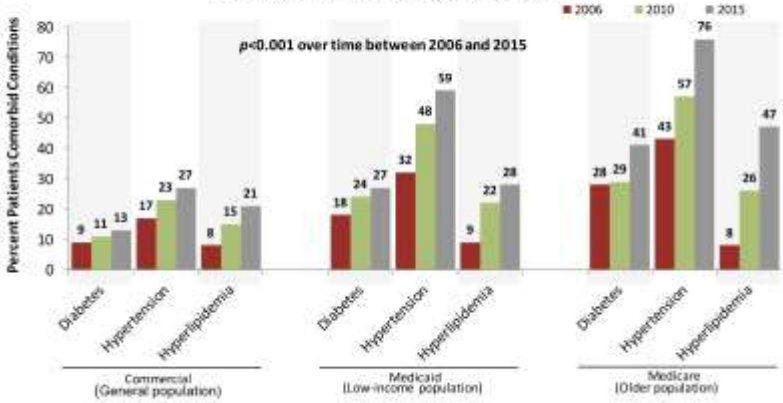
Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually.

If ALT ≤ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT >ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40.

Co-factors in chronic HBV patients

The proportion of CHB patients with metabolic comorbidities

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2004–2015



The proportion of CHB patients with metabolic comorbidities significantly increased between 2006 and 2015

The role of co-factors in HBeAg-negative chronic HBV

- Alcohol abuse
- Obesity – NAFLD
- HDV, HIV, HCV
- Other causes of liver injury (AIH)

- **Accelerate the progression of HBeAg-negative CHB**
- **Explain ALT elevations in some cases with low HBV DNA**
- **Not very helpful in patients with normal ALT**

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When to perform a liver biopsy?

- **In cases of potential cofactors**: Alcohol, obesity
- Clarifying discordance between clinical symptoms and the extent of fibrosis assessed by noninvasive approaches particularly in patients with **ALT values >0.5xULN but >1.0 of ULN and HBV DNA levels between 2.000 and 20.000 IU/mL**
- **Age > 40 years**
- **Addressing specific research questions**

Clinical case

Liver biopsy offers the only means of assessing both **fibrosis, inflammation and steatosis** If the biopsy specimen shows **moderate or severe inflammation** (A2 or A3) or **significant fibrosis** (≥F2), **treatment is recommended**

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Tapper EB, Lok ASF.N Engl J Med. 2017;377(23):2296-2297

How appropriately use non invasive markers of fibrosis?

EASL	AASLD	APASL
Fibrosis can be assessed by non-invasive methods. **Liver biopsy** reserved for cases where there is uncertainty or potential additional aetiologies	**Liver biopsy** should be considered in patients with persistent borderline normal or slightly elevated ALT levels, particularly in patients over age 40 who have been infected with HBV from a young age	**Biopsy** if ALT persistently elevated, or with family history of HCC or cirrhosis and/or to rule out other causes of elevated ALT
	Liver stiffness measurements are more accurate than serum fibrosis panels (*APRI, FIB-4*)	

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Terrault N, et al. AASLD 2018 Hepatitis B Guidance. Hepatology 2018
EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017
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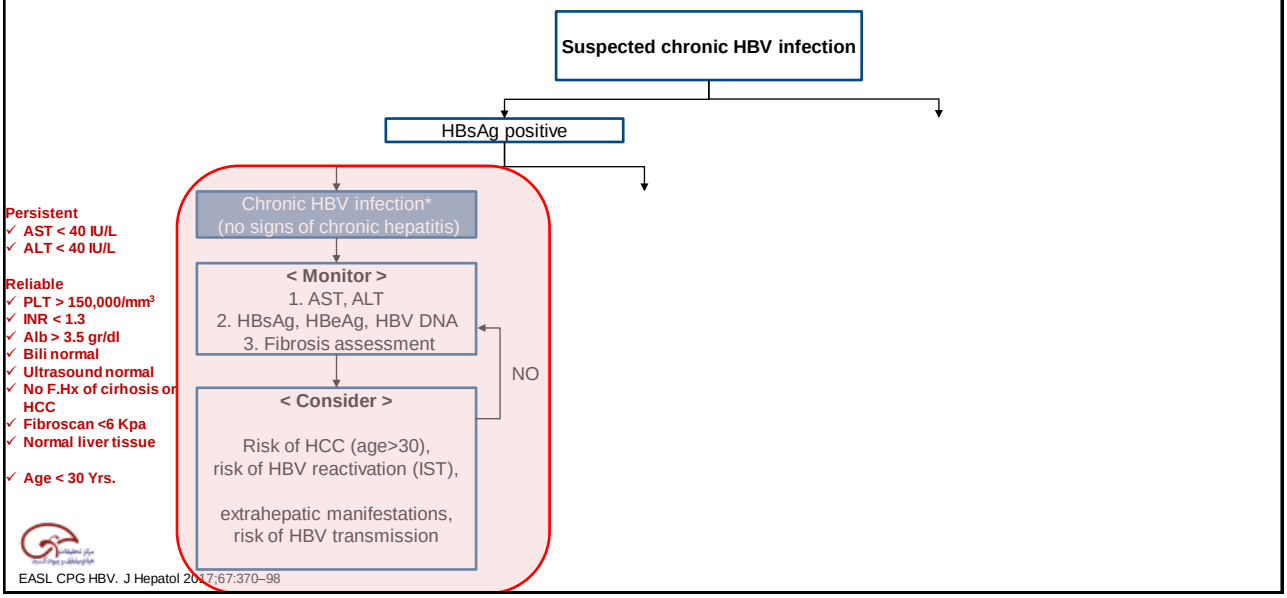
Algorithm for the management of chronic HBV infection



EASL CPG HBV. J Hepatol 2017;67:370–98

New nomenclature for chronic phases

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

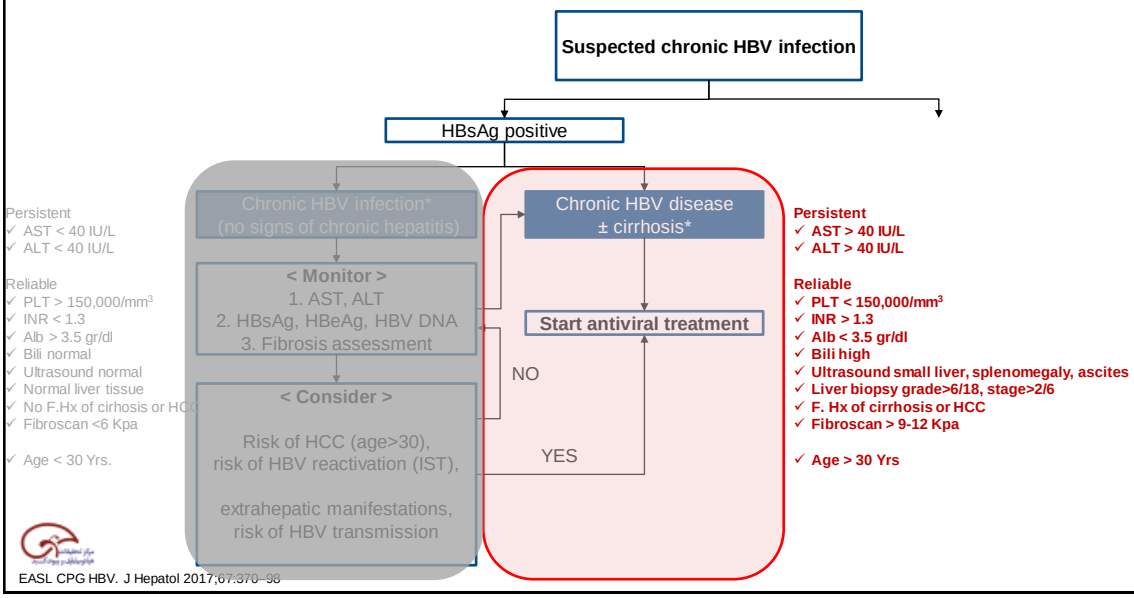
Chronic HBV disease / Chronic HBV infection	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic HBV disease	Chronic HBV infection	Chronic HBV disease	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	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

check ALT,AST Upto age 30, every 6 mo.

check ALT,AST < 2000, every 6 mo. > 2000, every 3 mo.

*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.
EASL CPG HBV. J Hepatol 2017;67:370–98

Algorithm for the management of chronic HBV infection



EASL CPG HBV. J Hepatol 2017;67:370–98

Indications for treatment

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

Recommendations

Should be treated

- HBeAg-positive or -negative chronic hepatitis B with **HBV DNA > 2,000, ALT > ULN and/or moderate liver necroinflammation or fibrosis**
- **Cirrhosis**, any detectable HBV DNA (regardless of ALT level)
- **HBV DNA > 20,000 IU/mL and ALT > 2 x ULN** (regardless of severity of histological lesions)

May be treated

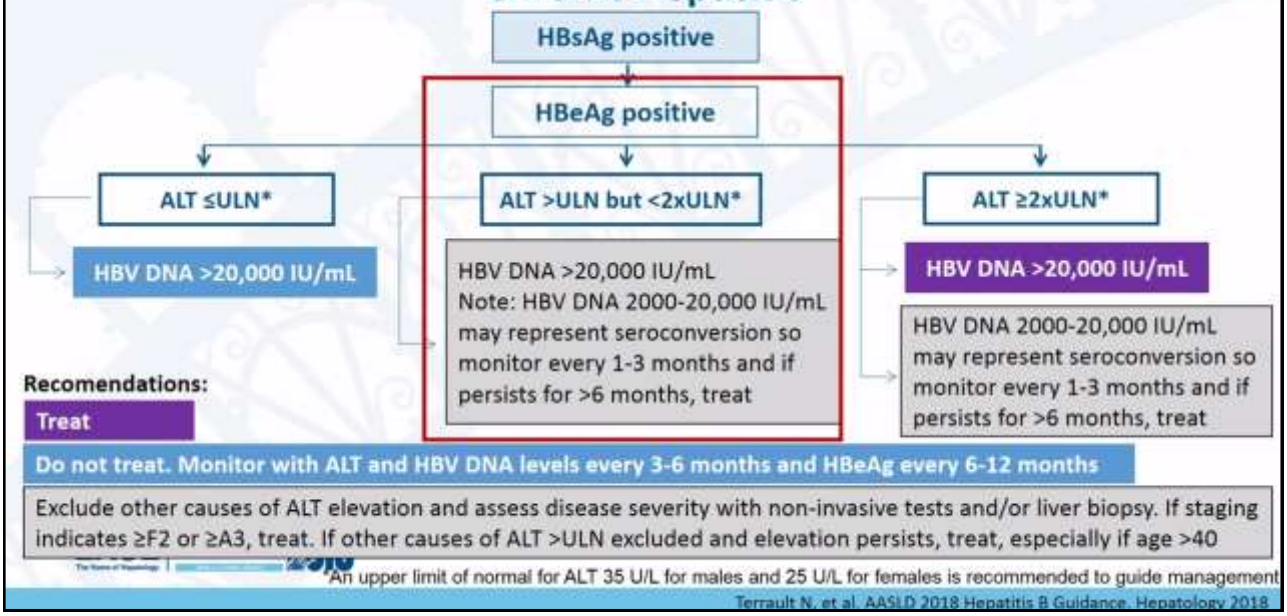
- **HBeAg-positive chronic HBV infection >30 years old**, regardless of severity of liver histology (HBV infection defined by persistently normal ALT and **high HBV DNA levels**)

Can be treated

- HBeAg-positive or -negative chronic HBV infection and **family history of HCC or cirrhosis and extrahepatic manifestations**, even if typical treatment indications are not fulfilled.

EASL CPG HBV. J Hepatol 2017;67:370–98

AASLD Algorithm for the Management of HBeAg positive Chronic Hepatitis



Terrault N, et al. AASLD 2018 Hepatitis B Guidance. Hepatology 2018

Does phase of chronic HBV infection influence treatment decision?

	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
Old terminology	Immune tolerant	Immune reactive	Inactive carrier	HBeAg- CHB
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/mL	10^4–10^7 IU/mL	<2000 IU/mL†	>2000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Treatment indication	**No**	**Yes**	**No**	**Yes**

*Persistently or intermittently; †HBV DNA levels can be between 2000 and 20,000 IU/mL in some patients without signs of chronic hepatitis; ULN 40 IU/mL
ALT: alanine aminotransferase; CHB: chronic hepatitis B;HBeAg: hepatitis B e antigen; HBsAg: hepatitis B surface antigen

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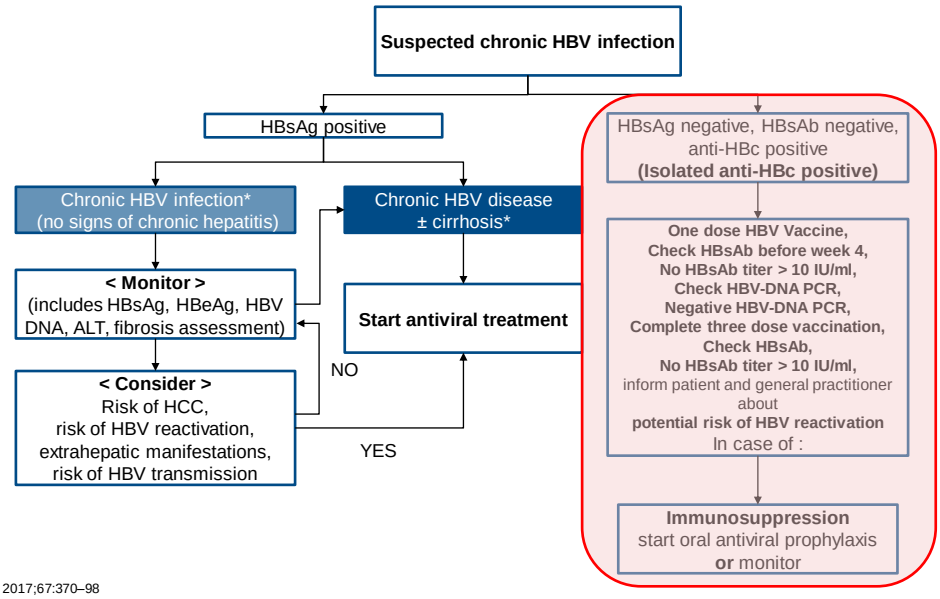
Algorithm for the management of chronic HBV infection



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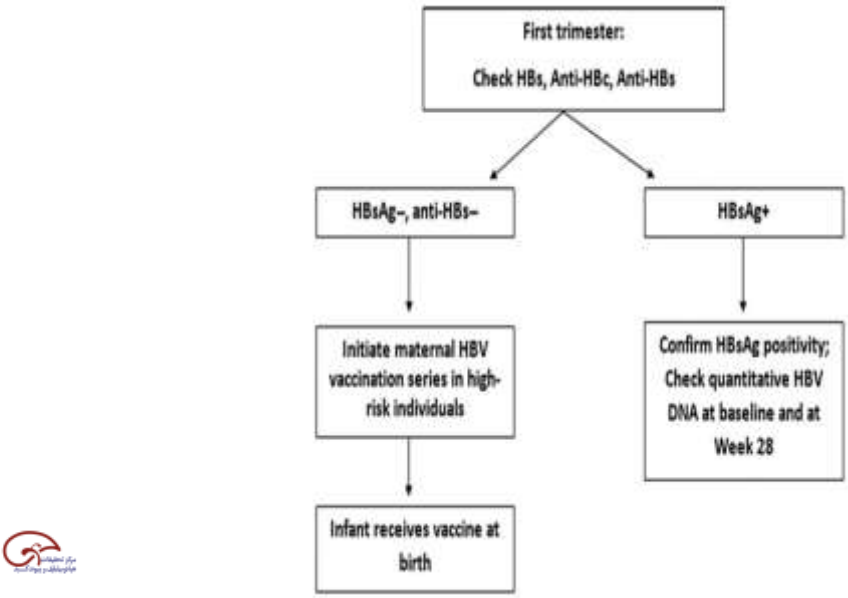
Suggested strategy for all pregnant women

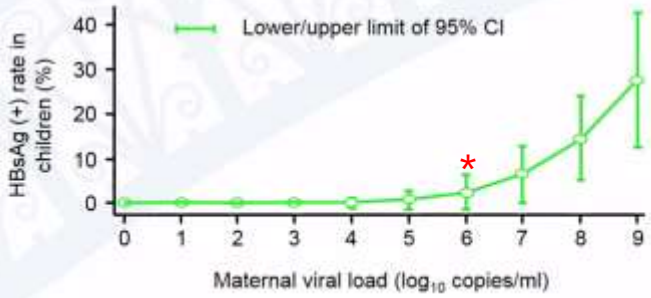


Recommendation 2 :

- Do [**HBV DNA qPCR**] test

HBV vaccine cannot protect all babies from high viral load carrier mothers

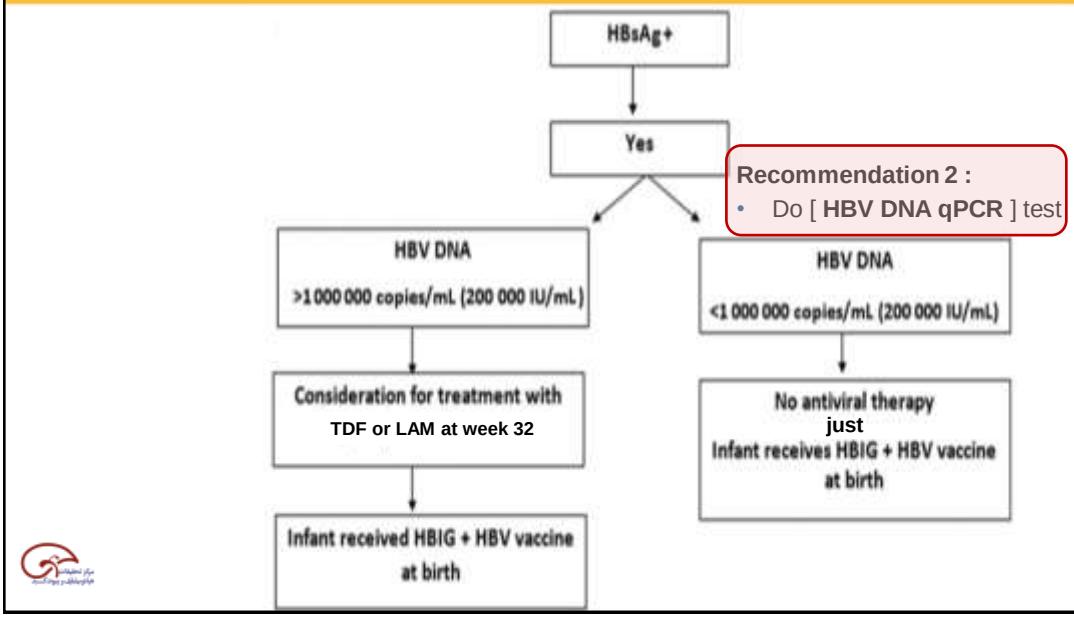
HBV DNA (log cp/ml)	Adjusted odds ratio	P value
5	0.9%	0.334
6 *	2.6%	0.165
7	6.6%	0.033
8	14.6%	0.001
9	27.7%	<0.001



- 10 of 303 babies born to HBV carrier mothers had HBV infection despite HBV vaccination
- All mothers of infected babies had positive HBeAg
- All infected babies had 3 doses of vaccine with HBIG at birth

Wen WH, et al. J Hepatol 2013;59:24–30

Suggested strategy for HBsAg–positive pregnant women



Recommendation 2 :

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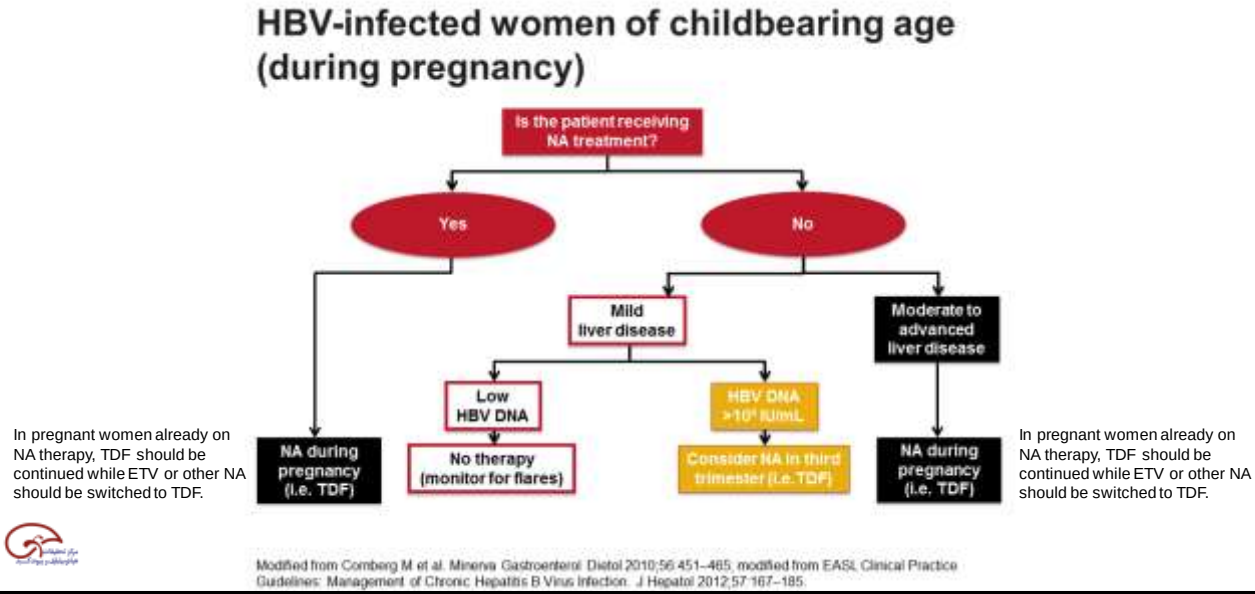
Suggested strategy for all pregnant women



In pregnant women already on NA therapy, TDF should be continued while ETV or other NA should be switched to TDF.

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Modified from Comberg M et al. Minerva Gastroenterol Dietol 2010;56:451–465, modified from EASL Clinical Practice Guidelines: Management of Chronic Hepatitis B Virus Infection. J Hepatol 2012;57:167–185.

Guidelines for stopping antiviral treatment in pregnant women on antiviral treatment

EASL 2017	AASLD 2016	APASL 2016
May be continued up to 12 weeks after delivery (Level 1, Grade 1)	Antiviral therapy was discontinued at birth to 3 months postpartum in most of the studies. With discontinuation of treatment, women should be monitored for ALT flares every 3 months for 6 months. (C1)	The NAs could be stopped at birth and when breastfeeding starts, if there is no contraindication to stopping NAs (B2)

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Terrault N, et al. Hepatology 2016;63:261–83;
EASL. J Hepatol 2017;67:370–98;
Sarin S, et al. Hepatol Int 2016;10:1–98.

Active HBV status surveillance candidate groups for Goal No. 2 or 4

Hepatitis B Virus markers			Hepatitis B Virus (HBV) status			Goals
HBsAg	HBsAb	HBcAb	HBV infection	HBV ccc-DNA	Immunity for HBV	Goals title
negative	positive	positive	no	yes	Natural immunity	**2.** Preventing HBV infection reactivation **4.** Preventing HBV related HCC mortality
positive	negative	positive	yes	yes	Would not have immunity	**2.** Preventing HBV infection reactivation **3.** Preventing HBV disease progression and fibrosis **4.** Preventing HBV related HCC mortality

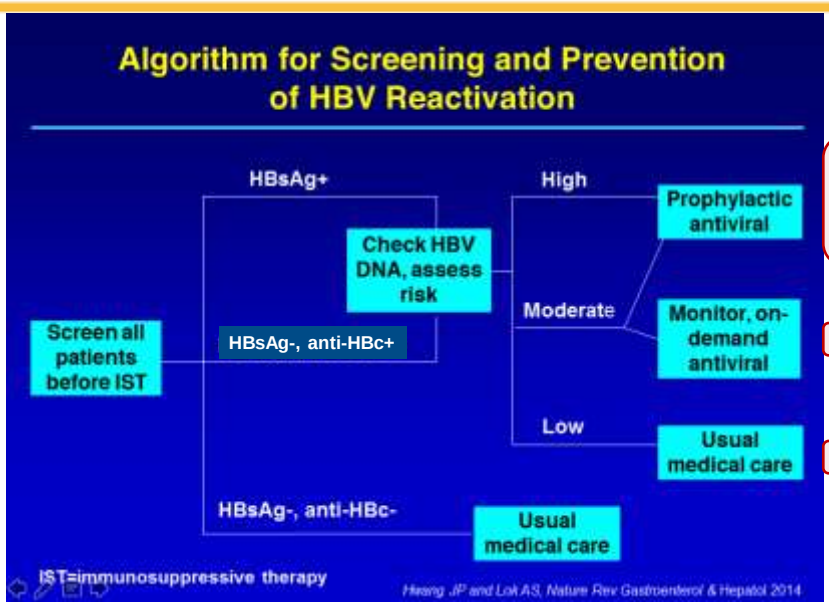
1. Immunosuppressive therapy candidate

   (corticosteroid, MTX, Anti-TNF, Rituximab, Transplantation, Cellcept, Prograf, Neoral, Immuran, mTORs)

2. Oncology patients

   (cancer systemic chemotherapy, TACE)

Strategy for Prevention of HBV Reactivation in IST Patients



- ✓ Start TDF or TAF
- ✓ Continue for 6 months after stopping IST
- ✓ Monitor all patients

- ✓ Monitor all patients

- ✓ Monitor all patients

Strategy for Prevention of HBV Reactivation in IST Patients

Risk-Based Prevention of HBV Reactivation

Risk	HBsAg+	HBsAg-, anti-HBc+	Antiviral therapy
High	Chemotherapy, anti-CD20 or anti-CD56, IST for transplantation, steroids in combination with other IST	Chemotherapy for hematologic malignancies, anti-CD20 or anti-CD56	Prophylaxis
Moderate	Anti-TNF, maintenance low dose steroid, other IST without steroid	Chemotherapy for solid tumors, IST for transplantation, steroids in combination with other IST	Prophylaxis or on-demand (monitor)
Low	Steroids alone for a few days	Anti-TNF, maintenance low dose steroid, other IST without steroid	No prophylaxis

IST = immunosuppressive therapy

Hwang JP and Lok ASF, Nature Rev Gastroenterol & Hepatol 2014

- ✓ Start TDF or TAF
- ✓ Continue for 6 months after stopping IST
- ✓ Monitor all patients

- ✓ Monitor all patients

- ✓ Monitor all patients

HCC risk assessment in patients with chronic HBV

Table 3. Construction of the PAGE-B risk score for prediction of hepatocellular carcinoma in Caucasian chronic hepatitis B patients under entecavir or tenofovir. The score ranges from 0 to 25.

Age (years)	Gender	Platelets (/mm³)
16-29: 0	Female: 0	≥200,000: 0
30-39: 2	Male: 6	100,000-199,999: 6
40-49: 4		<100,000: 9
50-59: 6		
60-69: 8		
≥70: 10		

PAGE-B score : (based on **age**, **gender** and **PLT**)

- low ≤ 9
- intermediate 10–17
- high ≥18

Other HCC risk scores: GAG-HCC, CU-HCC, REACH-B