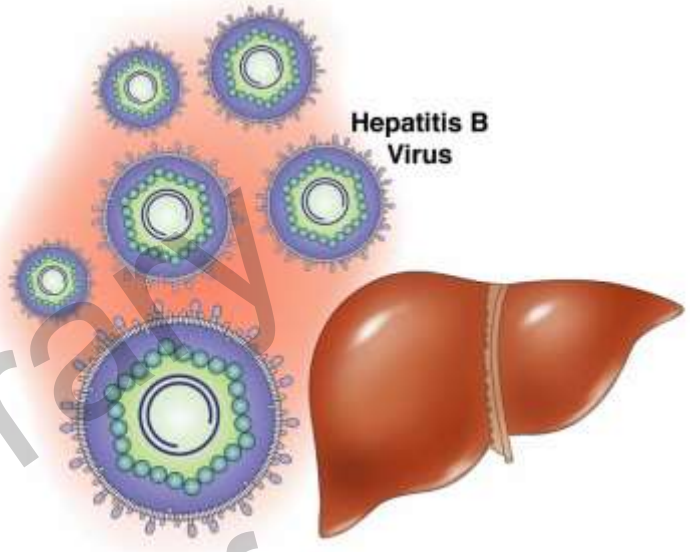

Who should be treated for hepatitis B in 2018?

Dominique Salmon
Paris Descartes University, Paris, France
ESCMID Study Group for Viral Hepatitis (ESGVH)

ECCMID, Madrid, April 24, 2018

Agenda

- How to differentiate HBV chronic infection and HBV chronic hepatitis?
- When to treat HBV chronic hepatitis?
- When to treat HBV infection ?
- Treatment indications for special groups
- Monitoring of patients not treated

EASL 2017 Guidelines on the management of hepatitis B virus infection

- **Chair**
  - Pietro Lampertico
- **Panel members**
  - Kosh Agarwal, Thomas Berg, Maria Buti, Harry LA Janssen, George Papatheodoridis, Fabien Zoulim, Frank Tacke (EASL Governing Board representative)
- **Reviewers**
  - Maurizia Brunetto, Henry Chan, Markus Cornberg


Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection

European Association for the Study of the Liver

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

Other recent guidelines

- **AASLD 2016 Guidelines for the treatment of chronic hepatitis B.** Terrault NA. Hepatology 2016.

- **Asian-Pacific 2015 Guidelines on the management of hepatitis B : a 2015 update**. Hepatol Int, 2016, 10: 1-98

Assessement of patients with chronic HBV infection

HBV markers

HBsAg

HBe Ag/anti HBe

HBV DNA

Liver disease markers

ALT

Fibrosis (elastometry/biomarkers/ biopsy in selected cases)

Comordidities

Alcohol, autoimmune, metabolic liver disease, steatosis

HDV, HIV, HCV Coinfections

HAV (vaccinate if negative)

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398

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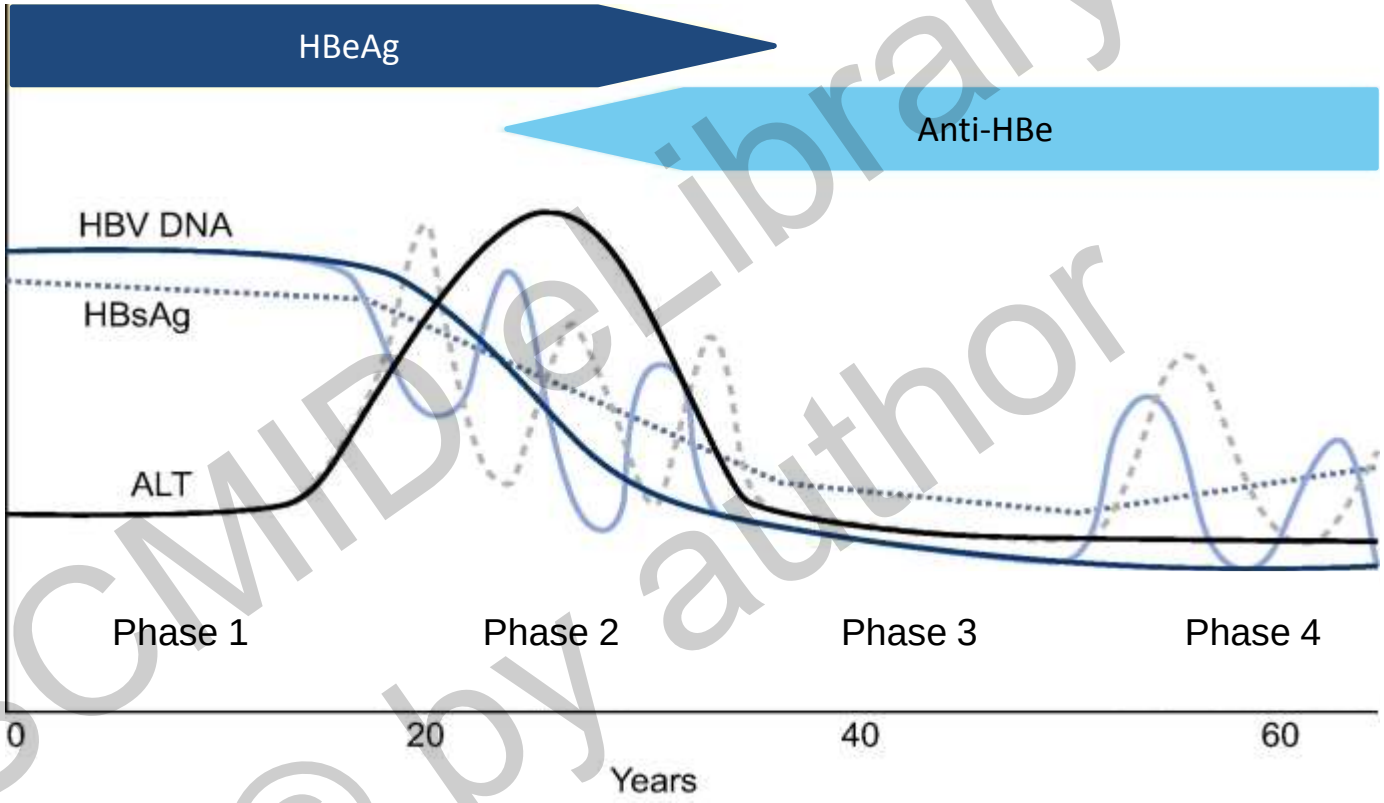
Phases of chronic HBV infection



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

New classification of chronic hepatitis B phases

- The natural history of chronic HBV infection is now schematically divided into five phases

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

New classification of chronic hepatitis B phases

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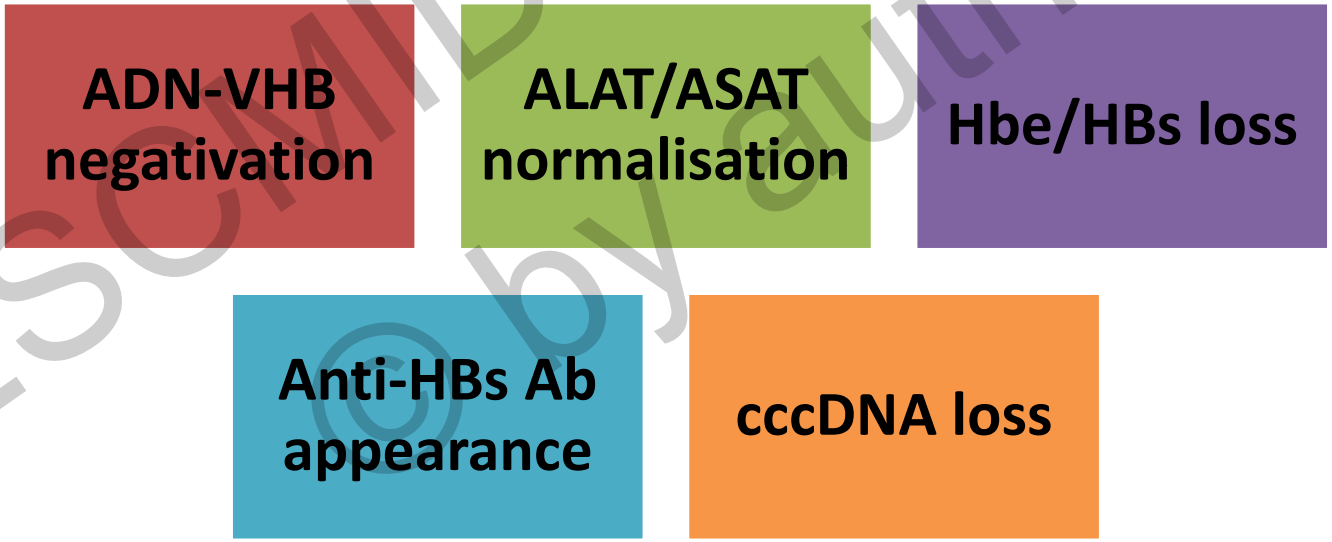
EASL CPG HBV. J Hepatol 2017;67:370–98

Objectives of therapy

Goals

- Improve survival
- Prevent disease progression and hepato cellular carcinoma
- Additionals: to prevent transmission and HBV reactivation

Endpoints



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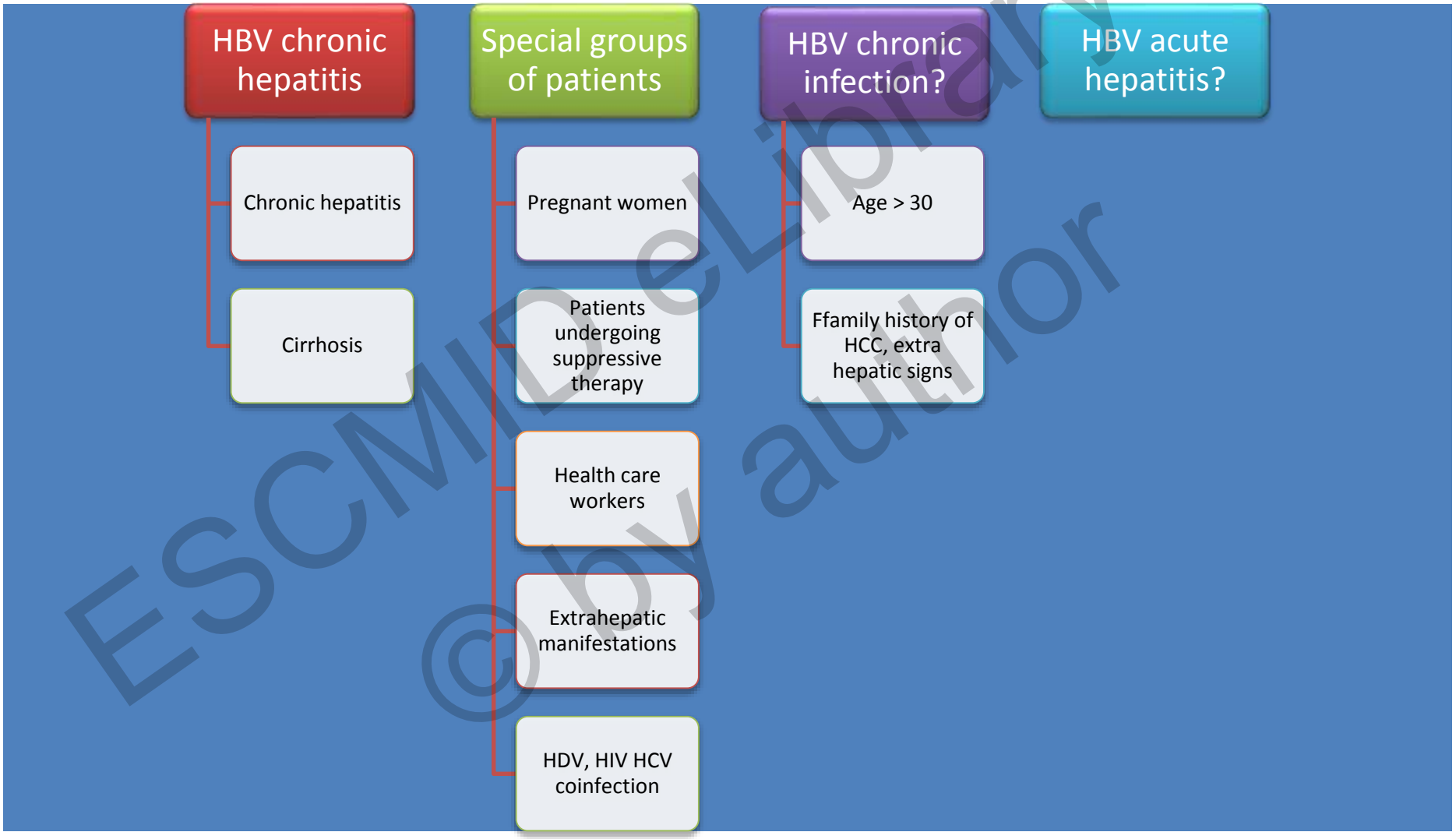
Target populations for HVB therapy for EASL 2017



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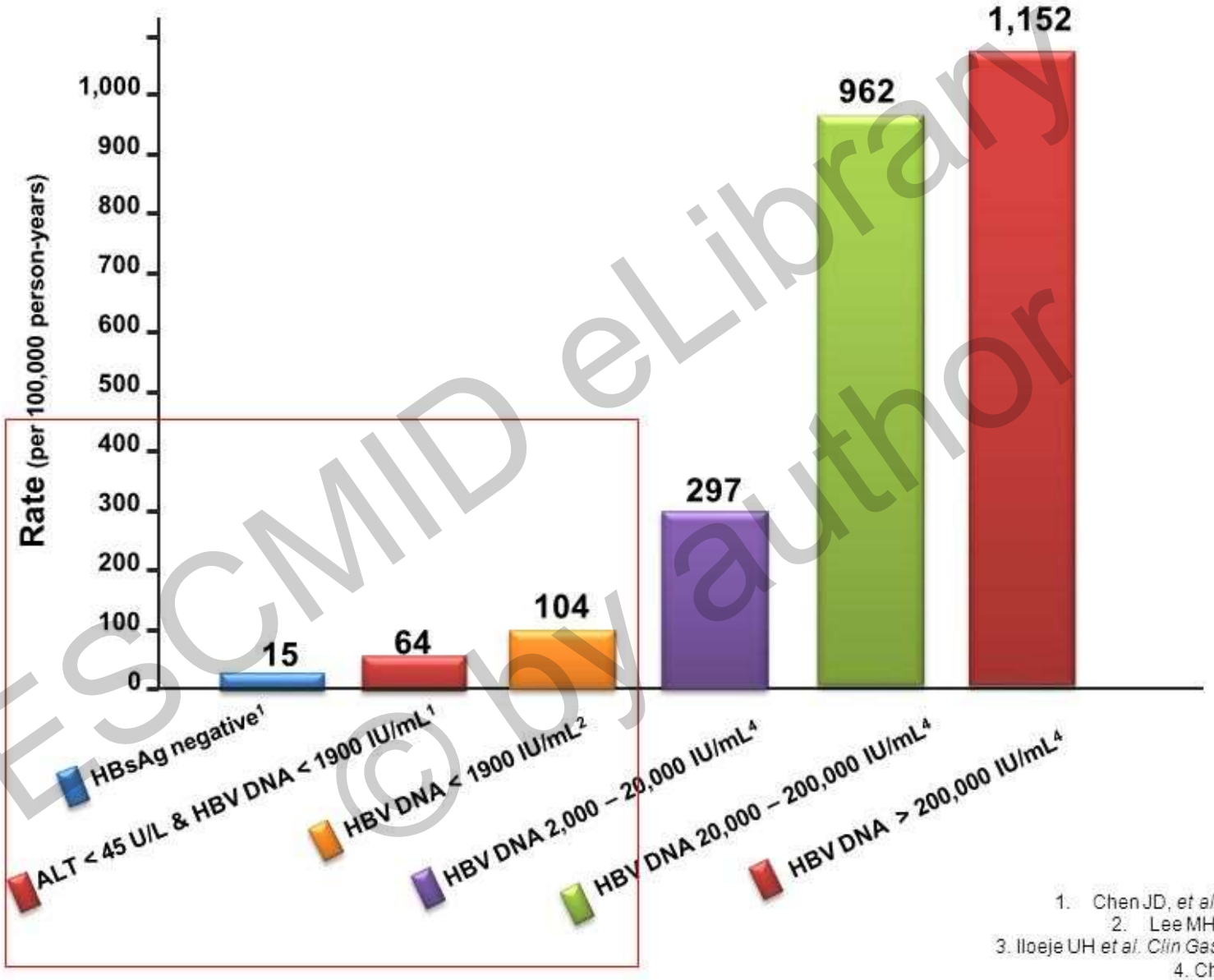
HBV: chronic hepatitis

Incidence of HCC in chronic HBV infection (REVEAL study)



1. Chen JD, *et al. Gastroenterology*. 2010
2. Lee MH, *et al. Hepatology*. 2013
3. Iloeje UH *et al. Clin Gastroenterol Hepatol*. 2007
4. Chen JC, *et al. JAMA* 2006

HBV Chronic hepatitis : treatment indications

HBV-DNA > 2.000 UI/ml

+ ALT> N

+ or > A1F1*

* Liver biopsy or non invasive test (Elastometry)

HBV-DNA > 20.000 IU/ml

+ ALAT > 2N**

** Even without fibrosis assessment

Cirrhosis+
HBV DNA detectable

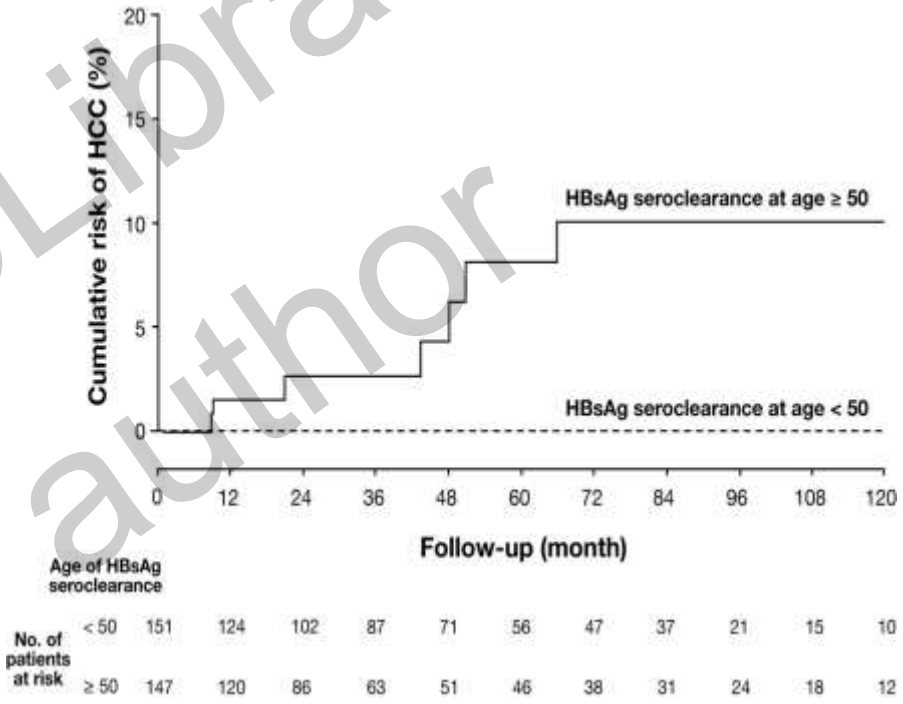
EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398

HBV: infection (targeted indications)

EASL, 2017

HBV: HBeAg + chronic infection "immunotolerant patients"

- **Do we treat "immuno tolerant" patients?**
  - **High HBV DNA**
  - **But persistently normal ALT**
  - **No fibrosis**
- Usually HBV infection acquired at birth
- After initial tolerance phase, immune clearance phase
- Delayed seroconversion is a risk factor for cirrhosis and HCC



EASL CGP on the management of HBV. J. Hepatol, 2017 67, 370-398

HBV: HBeAg + chronic infection "immunotolerant patients"

- **Monitor**
  - ALT, HBV DNA every 6 months
- **Can be treated if**
  - Age > 30 y-o (evidenced III, grade 2)
  - Familial history of HCC of cirrhosis
  - And certainly if occurrence of signs of chronic hepatitis (ALT, fibrosis>F1) or extra hepatic manifestations

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398

HBV: Hbe Ag-negative chronic infection ("inactive chronic carriers")

- **Defined by**
  - Normal ALT and HBV DNA < 2000 UI/ml (intermittently between 2000-20.000)
- **Monitor ALT, HBV DNA**

HBe negative + HBV DNA < 2000	HBe negative +HBV DNA > 2000
/ 6-12 months Quantitative HBsAg levels may be useful (< 1000)	/ 3 months then every 6 months
Fibrosis, HBV DNA every 2-3 years	

- **Can be treated in case of**
  - Age > 30 y-o (evidence III, grade 2)
  - Familial history of HCC or cirrhosis
  - Occurrence of signs of chronic hepatitis (ALT, fibrosis>F1) or extra hepatic manifestations

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398

HBV: Acute hepatitis

- More than 95% of adults with acute B hepatitis do not require specific treatment, because they will recover spontaneously.

- **Goal of therapy**
  - Prevent the risk of acute liver disease
  - Improve quality of life by shortening the risk of chronicity

- **Only patients with severe acute hepatitis B, should be treated with NA**
  - Signs of liver failure, coagulopathy (INR > 1.5)
  - Protacted course (persistent symptoms or marked jaundice > 4 weeks)
  - Indication for liver transplantation

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398

HBV: acute hepatitis

- Early treatment with nucleosid analogs (NA) in severe cases
  - can prevent acute liver failure and subsequent liver transplantation[1, 2]
  - does not increase the risk of chronicity but do not seem to prevent progression to chronic hepatitis [3]

- ETV or LAM can be used (and probably TFV)

[1,] Tillmann J Viral Hepatitis 2006; [2]Wiegand J Viral Hepaptitis 2014; [3] Ito, Hepatology , 2014

HBV: special groups

HBV: patients undergoing immunosuppressive therapy

- The spectrum of HBV reactivation may vary from

asymptomatic reactivation ⟶ liver failure ⟶ death

HBsAg+ pts and **HBs Ag- but anti HBc+ pts**

are concerned

All candidates for immunosuppression should be screened for HBsAg, Anti HBs, anti HBc

Vaccinated if HBV seronegative

Reddy, Gastroenterology, 2015

The risk of HBV reactivation can be classified as high (>10%), moderate(1-10%) or low depending on the drug

	Drugs	Disorders for receiving the drugs
High risk group (> 10%)	**B cell–depleting agents : anti CD20, CD56**	- Lymphoma/leukemia - Rheumatoid arthritis/ Idiopathic thrombocytopenic purpura, Cryoglobulinemia
	Anthracycline derivatives doxorubicin, epirubicin	Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization
	Corticosteroid therapy for 4 wk (moderate/high dose)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders
	IST for transplantation (stem cell, solid organ)	
Moderate risk (1-10%)	**TNF-α inhibitors**: etanercept, adalimumab, certolizumab, infliximab	Inflammatory bowel disease, rheumatoid arthritis, ankylosing spondylitis
	Other cytokine inhibitors and integrin inhibitors: abatacept, ustekinumab, natalizumab, vedolizumab	Plaque psoriasis, inflammatory bowel disease
	Tyrosine kinase inhibitors: imatinib, nilotinib	Breast, ovarian, uterine, and lung cancers; lymphoma and leukemias; transarterial chemoembolization; Chronic myelogenous leukemia, gastrointestinal stromal tumors
	Corticosteroid therapy for 4 wk (low dose > 10 mg QD)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders
	Other IST without steroids	
Low risk (< 1 %)	**Traditional immunosuppressive agents**: azathioprine, 6-mercaptopurine, methotrexate	Inflammatory bowel disease, psoriasis, sarcoidosis, autoimmune liver disease, arthritis
	Intra-articular corticosteroids	Arthritis
	Corticosteroid for 1 wk	Asthma, contact dermatitis
	Corticosteroid therapy for 4 wk if HBsAg-/Anti HBc+ (low dose ≤ 10 mg/d)	Inflammatory bowel disease, vasculitis, sarcoidosis, autoimmune disorders

Perillo, Review on treatment and prevention of HBV reactivation in patients receiving immunosuppressive agents, Gastroenterology 2015

The risk of HBV reactivation also depends of HBV profile (HbsAg + or anti HBc +)

	Drugs	HBV profile concerned
High risk group (> 10%)	B cell–depleting agents	HBsAg+/anti-HBc+: 30%–60% HBsAg -/anti-HBc +: >10%
	Anthracycline derivatives	HBsAg+/anti-HBc+: 15%–30%
	Corticosteroid therapy for 4 wk (moderate/high dose)	HBsAg+/anti-HBc+: >10%
Moderate risk (1-10%)	TNF-a inhibitors:	HBsAg +/anti-HBc+: 1%–10% HBsAg -/anti-HBc+: 1%
	Other cytokine inhibitors and integrin inhibitors	HBsAg+/anti-HBc+: 1%–10% HBsAg-/anti-HBc+: 1% HBsAg+/anti-HBc+: 1%–10%
	Tyrosine kinase inhibitors:	HBsAg-/anti-HBc +: 1%
	Corticosteroid therapy for 4 wk (low dose)	HBsAg +/anti-HBc+: 1–10%
Low risk (< 1%)	Traditional immunosuppressive agents	HBsAg +/anti-HBc+: <1% HBsAg -/anti-HBc +: <<1%
	Intra-articular corticosteroids,	HBsAg +/anti-HBc +: <<1% HBsAg -/anti-HBc +: <<1%
	Corticosteroid for 1 wk, Corticosteroid therapy for 4 wk B (low dose)	HBsAg +/anti-HBc+: <1% HBsAg -/anti-HBc +: <<1%

Perillo, Treatment and prevention of HBV reactivation in patients receiving immunosuppressive agents, Gastroenterology 2015

HBV: patients undergoing immunosuppressive therapy

- **Candidates for HBV therapy**
  - **All Hbs Ag+ patients : prophylactic treatment**
    - chronic hepatitis (treatment) or infection (prophylaxis)
    - TDF, ETV or TAF (no LAM: residual risk reactivation and resistance)
  - **Anti HBc + but HBs Ag- patients**
    - High risk group (rituximab, SCT) : prophylactic treatment (LAM)
    - Moderate/low risk : Test HBV DNA
      - If HBV DNA +: prophylactic treatment
      - If HBV DNA – and moderate/low risk : preemptive therapy upon monitoring HBs Ag and HBV DNA every 1-3 months during and after immunusuppression

Cholongitas, World J Gastroenterol 2015; Vigano, Expert Opin Biol Ther, 2016; *EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398*

HBV: patients undergoing immunosuppressive therapy

Duration of HBV treatment

- continue at least 12 months after the end of immunosuppression (18 months if hematological disease)
- and stop only if underlying disease is in remission and there is no liver disease

Cholongitas, World J Gastroenterol 2015; Vigano, Expert Opin Biol Ther, 2016; *EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398*

HBV: health care workers (HCW)

- HBV should not disqualify HCW from work
- Per cutaneous injuries during dental, obstetrical surgical procedures, may provide transmission to patients and providers.
- HBV transmission is rare. No case reported from HCW if HBV DNA < 200 UI/ml.
- HCW including surgeons, gynecologists and dentists, with HBs Ag+ and HBV DNA > 200 UI/ml, may be treated to reduce transmission if HBV DNA > 200 UI/ml, even if they do not fufill typical indications for therapy [1].

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017 67, 370-398;

HBV: health care workers (HCW)

- Threshold before resuming prone procedures varies between countries [1]
  - < 200 IU/ml (EASL)
  - < 1000 IU/ml (CDC)
  - < 2000 IU/ml (many countries)

- If not treated and around the treshold, HCW performing exposure prone procedures, should be more frequently retested (HBV DNA fluctuations) [2].

1- Lewis J, World Journal Hepatol, 2015; 2- Raven S, SHEA 2016.

HBV: Pregnancy

- Risk of HBV perinatal transmission greatest during intrapartum period.
- Prevention is based on :
  - **Screening for HBsAg during the 1st trimester of pregnancy +++**
  - **HBIG and vaccination** in the 12h of birth to children born from mothers with HBs Ag+.

  $\Rightarrow$ Reduces transmission from 90 to < 10%
- Perinatal transmission of HBV still occurs in approximately 9% of children, exclusively for mothers highly viremic
  - HVB DNA > 200,00 IU/mL or HbsAg > 4 log

Pan CQ, N Engl J Med, 2016

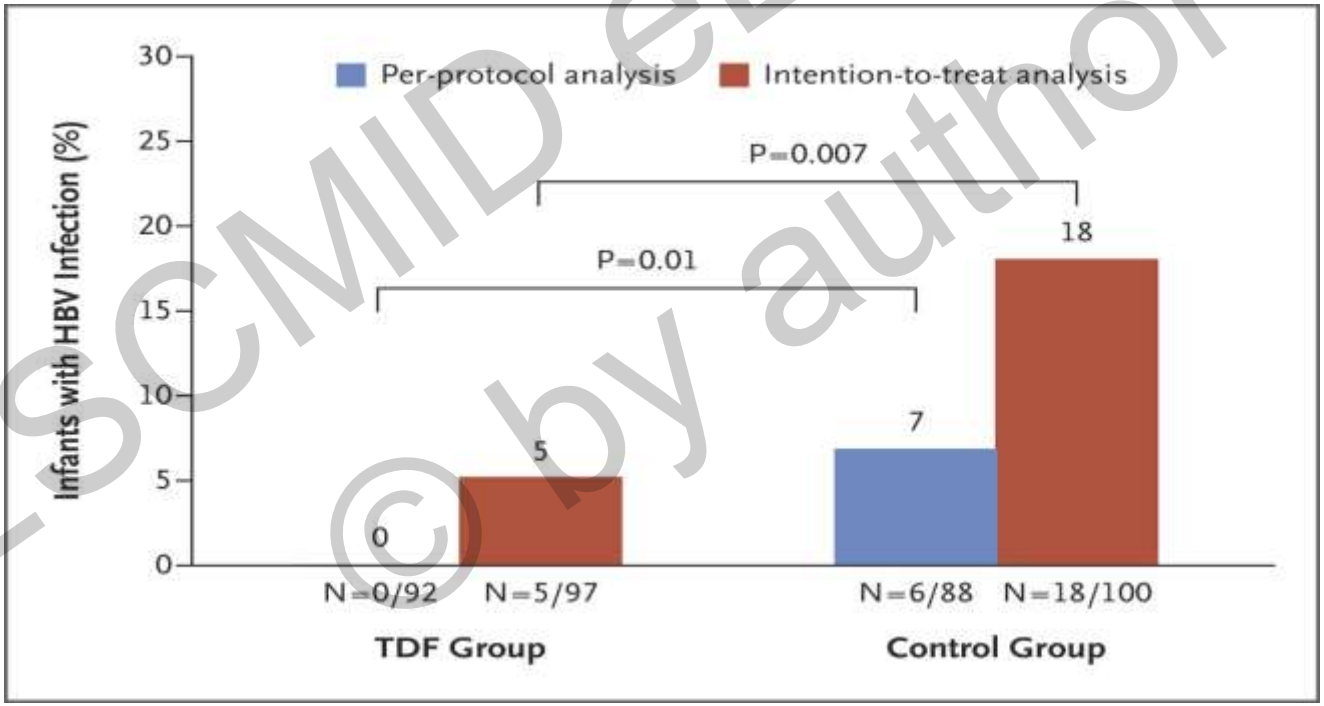
HBV: Pregnancy

- The following pregnant women should be treated during pregnancy:
  - CHB and advanced fibrosis or cirrhosis => TDF immediately
  - HBV DNA > 200,000 IU/ml or HBsAg > 4 log=> start treatment at week 24-28 of gestation [2]. TDF preferred agent. NUCs can be stopped 1-3 months after delivery.
  - Already on NA therapy before pregnancy => continue or switch for TDF

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load

- 200 mothers, HBV DNA > 200.000 UI/mL randomized for TDF or Pbo from 30-32 wk gestation until 4w post delivery.
- All infants received immunoprophylaxis



Pan CQ, N Engl J Med, 2016

HBV: extra hepatic manifestations

- Patients with HBV replication should receive NA therapy
- NA were shown to stop manifestations such as
  - Vasculitis, skin manifestations, polyarteritis nodosa, arthralgias, peripheral neuropathy, glomerulonephritis,
  - with or without biological markers: mixed, cryoglobulinemia, rheumatoid factor, low complement, ..
- PegIFN should not be administered in case of immune related manifestations.
- Plasmapheresis, cortosteroids and/or other immunosuppressive drugs could be useful during the initial phase in addition with NA.

Mazzaro C, Digestive Liver Disease, 2016

HBV: viral coinfections

- **Delta virus infection**
  - HDV is often the predominant virus
  - Considerable fluctuating activity of both viruses
  - **In case of HBV replication, NA therapy recommended**
  - For HDV, PegIFN at least 48 weeks is the treatment of choice
- **HIV**
  - **TDF- or TAF-based cART is recommended in all HIV/HBV patients** irrespective of their CD4

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017

HBV: viral coinfections

- **Hepatitis C infection (HCV)**
  - DAA for HCV can cause HBV reactivation
  - HBsAg + patients receiving DAA
    - should be considered for concomittant NA therapy until 12 post DAA
  - HBsAg -, anti HBc+ patients receiving DAA
    - should be tested for HBV reactivation in case of ALT elevation

EASL Clinical Practice Guidelines on the management of HBV. J. Hepatol, 2017

Conclusion

- HBV chronic infection is now classified into five phases : chronic hepatitis (HBeAg+ and HBeAg-), chronic infection (HBeAg+ and HBeAg-), occult hepatitis

- Indication to anti HBV therapy have been enlarged
  - Classical indications : cirrhosis, chronic hepatitis (decreased HBV DNA threshold)
  - Additional indications :
    - PMTCT in mothers with high viremia
    - Prevention of reactivation in immunosuppressed patients
    - Coinfection with HIV, HDV, HCV patients (under DAA)
    - Extrahepatic manifestations
    - Health care workers
    - Health care workers
    - HBV chronic infection (age > 30, familial history of HCC), severe acute hepatits

- Areas of uncertaincy still exist: treatment of immuno tolerant? when to stop HBV therapy?..

- Field that could rapidly evolve with the arrival of new drugs

When to stop treatment?

- HBsAg loss or anti-HBs seroconversion with undetectable HBV DNA are clear indications to discontinue the treatment
- Sustained undetectable HBV DNA in patients who are anti Hbe+ without significant fibrosis might be another indication