Hepatitis B
From guidelines to real practice

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Disclosures

Abbvie, Gilead,Intercept

Patient case

- 33 years-old
- Born in Mali, In France for 10 years
- 4 children, last one born in France
- Hepatitis B diagnosed during the last pregnancy
- Another pregnancy planned

Patient case

Age / Gender	33-years / female
Ethnicity	Mali
Children	3, latest born in France
HBV diagnosis	2015 during pregnacy
Route of transmission	No clear risk factor
ALT	17 IU/mL (NV<40 IU/mL)
HBeAg	Positive
HBV DNA	7.5 Log IU/ml
Platelets (G/L)	320 000
US	Normal
Liver stiffness (kPa)	4.2 kPa
Comorbidity	No - BMI 25

How do you classify this hepatitis

How do you classify this hepatitis

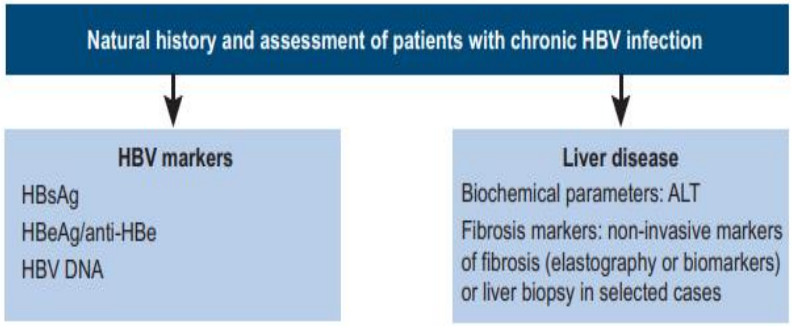
Immune tolerant patient

AASLD update 2018
Immune-Tolerant

- HBsAg present for 6 months
- HBeAg positive
- HBV-DNA levels typically >1 million IU/mL.
- Normal or minimally elevated ALT and/or AST
  - a ULN for ALT of 35 U/L for males and 25 U/L for females is recommended
- Liver biopsy or noninvasive test results showing no fibrosis and minimal inflammation

TERRAULT ET AL. HEPATOLOGY, April 2018 1572

EASL guidelines 2017



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	$>10^7$ IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml°°	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Fig. 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers. *Persistently or intermittently. °°HBV DNA levels can be between 2,000 and 20,000 IU/ml in some patients without sings of chronic hepatitis.

EASL, Journal of Hepatology 2017 vol. 67 j 370–398

How do you classify this hepatitis

Immune tolerant patient

↓

HBeAg-positive chronic infection

Do you treat this patient?

1)Yes, to prevent the risk of HCC

2)Yes, to prevent high risk of contamination

3)Yes, because she wants another child

4)Yes, because EASL recommendations say yes…

EASL Guidelines 2017

Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions

– Evidence level III, grade of recommendation 2.

EASL 2017 unresolved issues

When to start antiviral therapy in patients with HBeAg positive chronic infection…

AASLD update 2018

the lack resistance with long-term use. Patient-specific factors that need to be considered in choosing between peg-IFN, entecavir, and tenofovir include the following:

- Desire for finite therapy (see below).
- Anticipated tolerability of treatment side effects.
- Comorbidities: peg-IFN is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenia, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis.
- Previous history of lamivudine resistance (entecavir is not preferred in this setting).
- Family planning: finite therapy with peg-FN prepregnancy or use of an oral antiviral agent that is safe in pregnancy (preferably TDF) is best.
- HBV genotype: A and B genotypes are more likely to achieve HBeAg and HBsAg loss with peg-IFN than non-A or non-B genotypes.
- Medication costs.

7. Peg-IFN is preferred over nonpegylated forms for simplicity.
8. For patients treated with peg-IFN, 48 weeks' duration is used in most studies and is preferred. This treatment duration yields HBeAg seroconversion rates of 20%-31% and sustained off-treatment HBV-DNA suppression of <2,000 IU/mL in 65% of persons who achieve HBeAg to anti-HBe seroconversion. The combination of peg-IFN and NAs has

TREATMENT OF IMMUNE-TOLERANT ADULTS WITH CHRONIC HEPATITIS B

2A. The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB

Quality and Certainty of Evidence: Moderate
Strength of Recommendation: Strong

Technical Remarks

1. ***Guidance:*** *Immune-tolerant status should be defined by ALT levels, utilizing 35 U/L for men and 25 U/L for women as ULN rather than local laboratory ULN.*

2B. The AASLD suggests that ALT levels be tested at least every 6 months for adults with immune tolerant CHB to monitor for potential transition to immune-active or immune-inactive CHB

Quality and Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

2C. The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis

Quality and Certainty of Evidence: Very Low
Strength of Recommendation: Conditional

Technical Remark

1. Moderate-to-severe necroinflammation or fibrosis on a liver biopsy specimen is a reason to consider initiation of antiviral therapy if other causes of liver disease are excluded.

AASLD update 2018

- Patients HBeAg positive, after a 3- to 6-month **period of elevated ALT levels greater than 2 times the upper limit of normal (>50 U/L for women and >70 U/L for men)** should be considered for antiviral treatment.

- Treat patients over age 40 who have been infected with HBV from a young age with **moderate-to-severe inflammation** (A3 or higher) and/or fibrosis (F2 or higher)

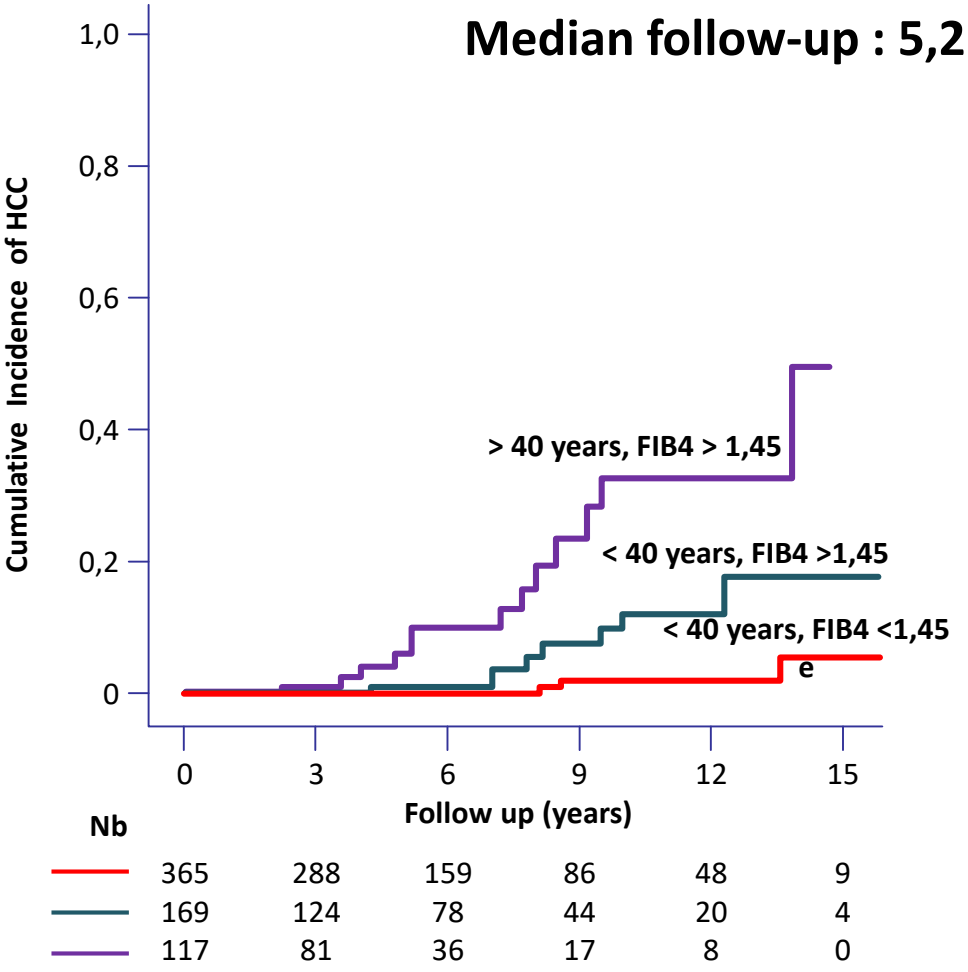
TERRAULT ET AL. HEPATOLOGY, April 2018 1572

What is the risk of HCC at 5 years in this patient ?

1) Low
2) Medium
3) High

Immune tolerant patients over 40 with high FIB-4

HCC cumulative incidence according to age and FIB-4
Median follow-up : 5,2 years (1 - 17,8 years)



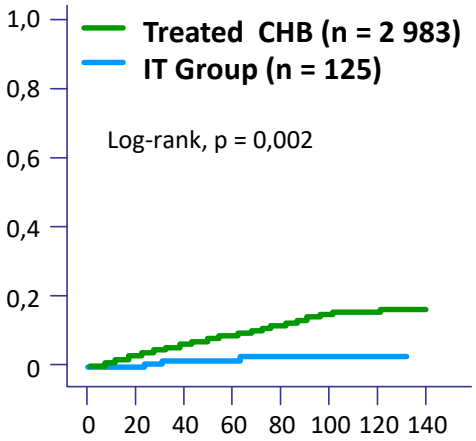
	5 years	10 years
Age < 40 and FIB-4 < 1,45 (n = 365)	0 %	2,0 %
Age < 40 and FIB-4 ≥ 1,45 (n = 20)	0 %	9,1 %
Age ≥ 40 and FIB-4 < 1,45 (n = 149)	1,1 %	12,7 %
Age ≥ 40 and FIB-4 ≥ 1,45 (n = 117)	5,9 %	32,7 %
p	< 0,001	

Seong G,, EASL 2019, Abs. THU-231

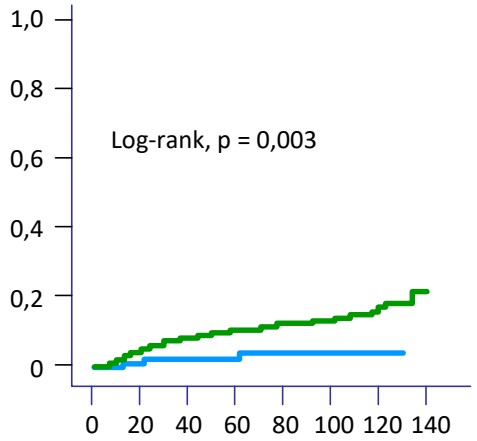
Immune tolerant : What are the risks?

Cumulative Incidence median follow up 64 months

HCC

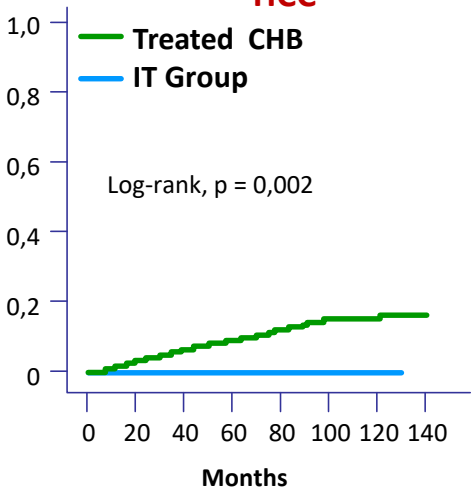


OLT or death

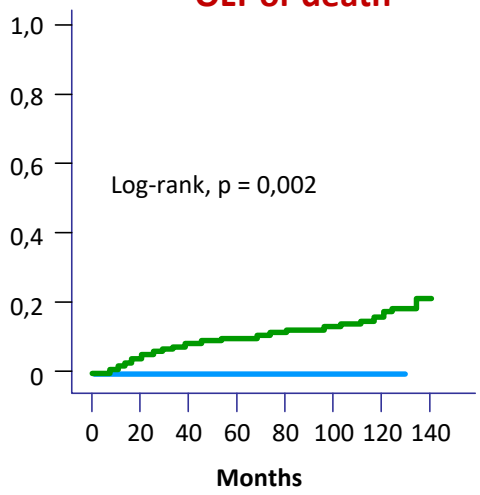


Cumulative Incidence (reactivation excluded)

HCC



OLT or death



Severe complications

	HCC n (%)	OLT or death n (%)
All IT (n = 126)	3 (2,4)	4 (3,2)
IT persistant (n = 46)	0	1 (2,2)
IT with switch for Inactive carriers (n = 1)	0	0
IIT with switch for minimal activity (n = 14)	0	0
IT IT with switch for Active phase and treated (n = 64)	3 (4,7)	3 (4,7)
Chronic hepatitis treated	282 (9,5)	320 (10,7)

Jeon MY, EASL 2019, Abs. FRI-179

Do you consider the patient for HCC screening?

Research Article

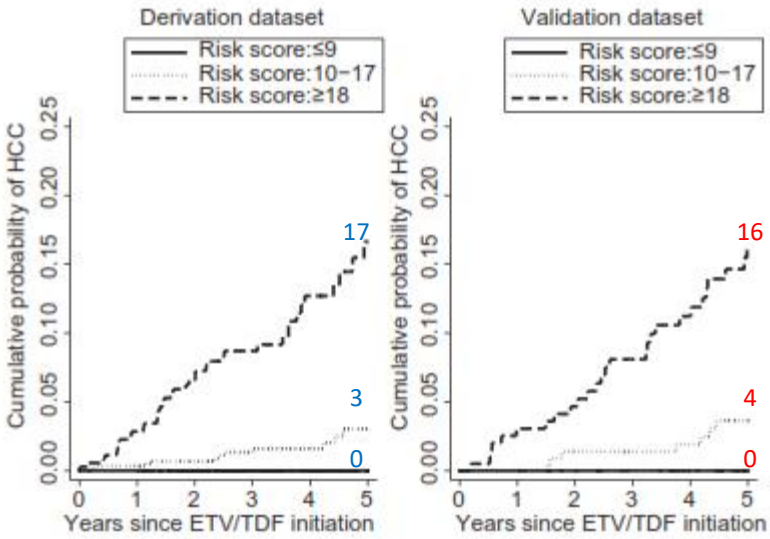
CrossMark

EASL JOURNAL OF HEPATOLOGY

PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

George Papatheodoridis[1,2,*], George Dalekos[3], Vana Sypsa[4], Cihan Yurdaydin[5], Maria Buti[6], John Goulis[7], Jose Luis Calleja[8], Heng Chi[9], Spilios Manolakopoulos[2], Giampaolo Mangia[10], Nikolaos Gatselis[3], Onur Keskin[5], Savvoula Savvidou[7], Juan de la Revilla[8], Bettina E. Hansen[9], Ioannis Vlachogiannakos[1], Kostantinos Galanis[3], Ramazan Idilman[5], Massimo Colombo[10], Rafael Esteban[6], Harry L.A. Janssen[9,11], Pietro Lampertico[10]

Age (yr)		Gender		Platelets (G/L)	
16-29	0	Female	0	≥200	0
30-39	2	Male	6	100-199	6
40-49	4			<100	9
50-59	6				
60-69	8				
≥70	10				



Patient case

- The patient doesn’t want to be treated

How do you follow her?

1) Every year
2) Every 6 months

EASL 2017

Patients with HBeAg-positive chronic HBV infection who remain untreated should ideally have ALT determinations at least every 3 months, HBV DNA determinations every 6–12 months and assessment of liver fibrosis every 12 months.

→ What is the place for non invasive tests?

Patient case

- She finally got pregnant

- HBV DNA at 6 months of pregnancy:

  8. 7 Log IU/mL

Do you treat the patient?

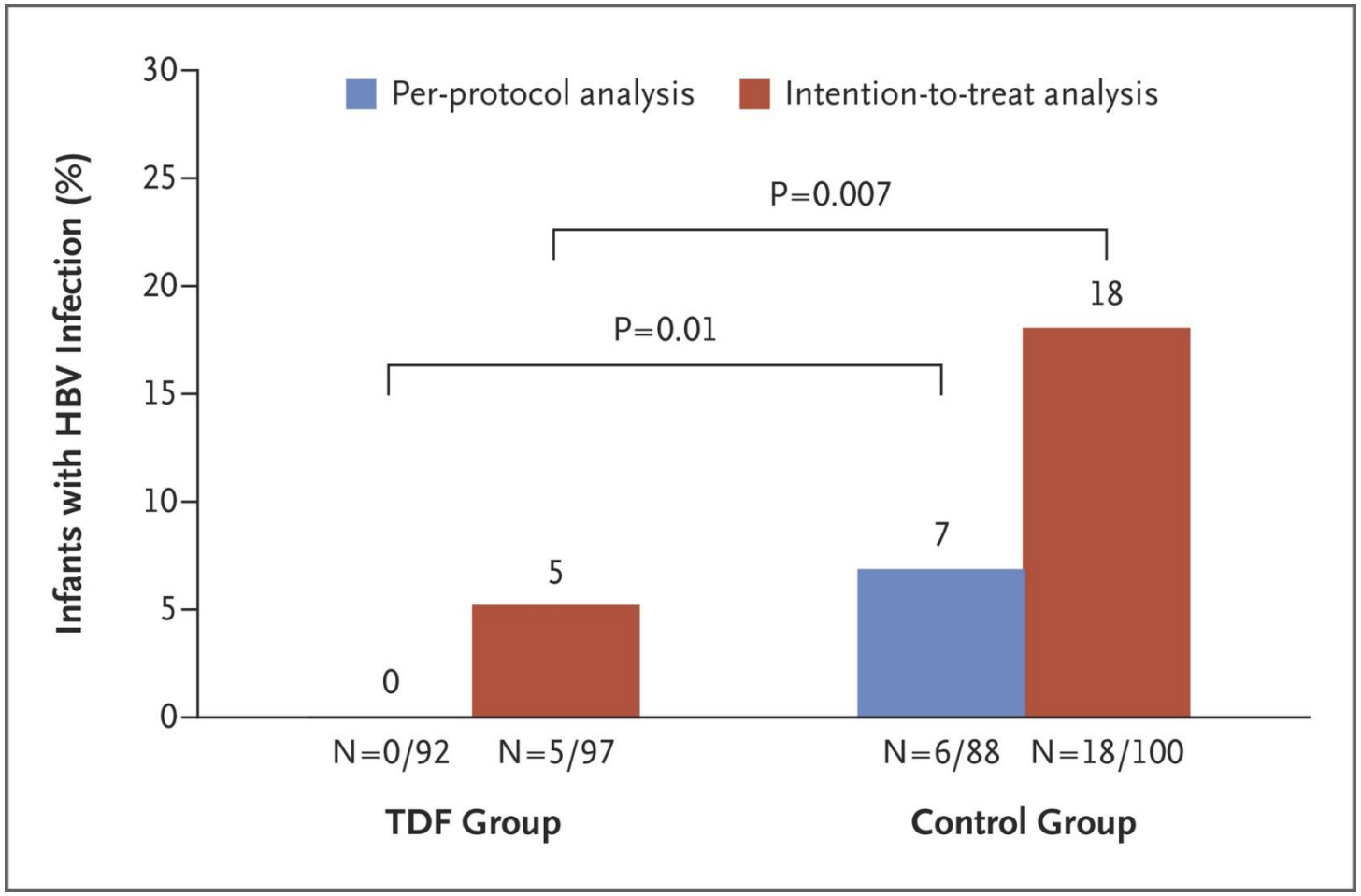
1) Yes
2) No

EASL 2017

In all pregnant women with high viral load >200 000 IU/ml or AgHBs Levels > 4 Log IU/ml, antiviral prophylaxis with TDF should start at week 24-28 of gestation

Evidence 1, Grade of recommendation 1

TDF to prevent HBV transmission during pregnancy



Pan CQ et al, N Engl J Med, 2016: 374:2324-34

Do you stop the treament after delivery?

1) Yes
2) No

EASL 2017

In all pregnant women with high viral load >200 000 IU/ml or AgHBs Levels > 4 Log IU/ml, antiviral prophylaxis with TDF should start at week 24-28 of gestation and continue for up to 12 weeks after delivery

Evidence 1, Grade of recommendation 1

Patient Case

	Baseline	W24	W48
HBV DNA Log IU/mL	8.7	3.8	4.1
ALT	17	18	15
Hbe Ag	Positive		Positive

→ **Partial Virologic Response**

EASL 2017

It is always important to check for compliance.

Partial virological response under ETV or TDF is associated with a very high pretreatment viral load and not the result of a lack of efficacy but rather of the potency limit of the antiviral drug.

In such patients with a partial virological response at week 48, the HBV DNA levels at week 48 and their kinetics must be taken into account.

Patients with declining serum HBV DNA levels may continue treatment with the same agent given the rise in rates of virological response over time and the very low risk of resistance with long-term monotherapy with both agents.

In those with plateauing levels of HBV DNA a switch to the other drug or a combination of ETV + TDF/TAF can be envisaged

Patient case

- Add on Entecavir if no pregnancy

- HBV DNA Week 72 <10 IU/mL