

Hepatitis B: How to manage in 2018

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HBV is a life long, dynamic disease

➤ Changes over time

➤ Risk of end stage liver disease and HCC increases with ongoing inflammation and viremia in adults

➤ Fibrosis can be reversible

➤ Drugs can decrease fibrosis progression

➤ HBV can be controlled but not cured

➤ Reactivation can occur even in those who have lost HBsAg

Barriers for Therapy in CHB

- Despite the approval of several anti-viral agents, **very few patients** are actually on treatment. There are many possible reasons for this, including the need for **lifelong treatment**, **lack of education and awareness** of the disease in the community, under screening for the condition in primary care settings,

Goals of treatment in chronic viral hepatitis B

- **Prevention of long-term negative clinical outcomes** (eg, cirrhosis, HCC, death) by durable suppression of HBV DNA
- **Remission of liver disease**
- **Primary treatment endpoint:** Sustained decrease in serum HBV DNA level to **low or undetectable**
- **Secondary treatment endpoints**
 - Decrease or normalize serum ALT
 - Induce HBeAg loss or seroconversion
 - Induce HBsAg loss or seroconversion
 - Improve liver histology

Natural History of HBV - Revised Nomenclature

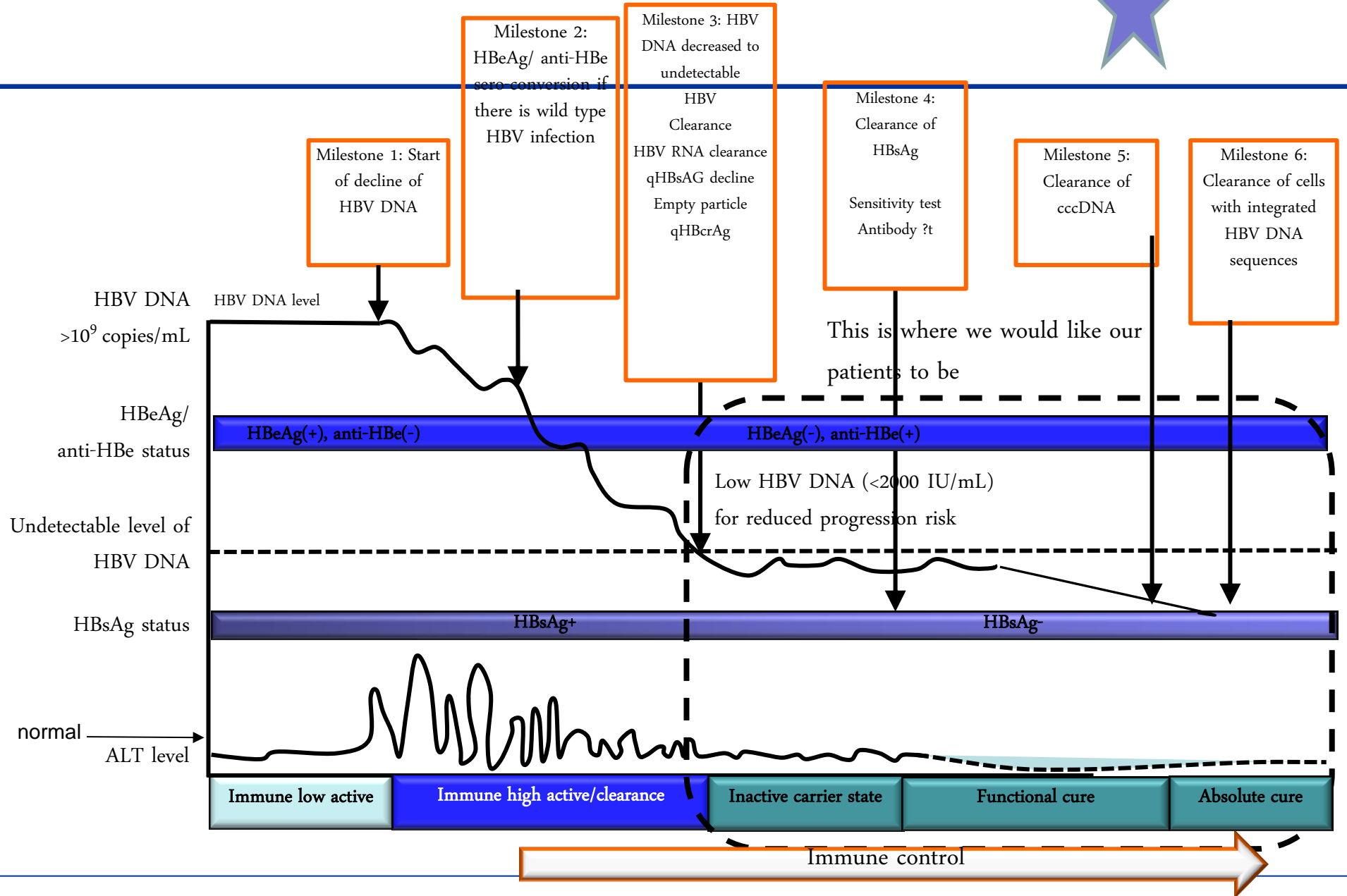
EASL CPG on HBV

	HBeAg positive Chronic <u>infection</u>	HBeAg positive HBsAg Loss/Occult Hepatitis B	HBeAg negative Chronic <u>infection</u>	HBeAg negative Chronic <u>hepatitis</u>
HBsAg	High	<ul style="list-style-type: none"> • Serum HBV DNA phases, alternating undetectable and very low but detectable • Detectable HBV DNA in the liver • Intrahepatic replication-competent HBV genomes such as HBV cccDNA • Integrated HBV DNA 	Low	Intermediate
HBeAg	Positive		Negative	Negative
HBV DNA	>10E7 IU/mL		<2,000 IU/mL ^{oo}	>2,000 IU/mL
ALT	Normal		Normal	Elevated*
Liver disease	None/minimal		None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative Chronic hepatitis

*Persistently or intermittently

^{oo} HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

6 Endpoints in HBV Treatment



Clinical Practice Guidelines Endpoints of Antiviral Therapy

1. The induction of **long-term suppression of HBV DNA** levels represents the **main endpoint** of all current treatment strategies.

(Evidence level I, grade of recommendation 1)

2. **HBeAg loss**, with or without anti-HBe seroconversion, in HBeAg-positive CHB patients is a **valuable endpoint**, as it often represents a partial immune control of the chronic HBV infection.

(Evidence level II-1, grade of recommendation 1)

3. A biochemical response defined as **ALT normalization** should be considered as an **additional endpoint**, which is achieved in most patients with long-term suppression of HBV replication.

(Evidence level II-1, grade of recommendation 1)

4. **HBsAg loss**, with or without anti-HBs seroconversion, is an **optimal endpoint**, as it indicates profound suppression of HBV replication and viral protein expression.

(Evidence level II-1, grade of recommendation 1)

Clinical Practice Guidelines General Indications for Treatment

1. **Patients with HBeAg-pos. or -neg. chronic hepatitis B**, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis.

(Evidence level I, grade of recommendation 1)

2. Patients with compensated or decompensated **cirrhosis**, with any detectable HBV DNA level and regardless of ALT levels.

(Evidence level I, grade of recommendation 1)

3. **HBV DNA >20,000 IU/ml and ALT >2xULN** regardless of the degree of fibrosis.

(Evidence level II-2, grade of recommendation 1)

4. **HBeAg-pos.chronic HBV infection** (persistently normal ALT and high HBV DNA levels) > 30 yr regardless of histology

(Evidence level III, grade of recommendation 2)

5. HBeAg-pos./ HBeAg-neg. **chronic HBV infection** + family history of HCC or cirrhosis and extrahepatic manifestations

(Evidence level III, grade of recommendation 2)

When Antiviral Treatment Should Be Initiated?

APASL, AASLD & EASL recommend

Start treatment ASAP in life-threatening disease
regardless of HBV-DNA and ALT levels

- Acute liver failure
- Decompensated cirrhosis
- Severe exacerbation of chronic hepatitis B

Drugs for HBV

- Seven drugs are now available for the treatment of chronic hepatitis B: they include
- Conventional interferon alpha, and Pegylated interferon alpha
- NUCs for HBV therapy belong to three classes:
- **L-nucleosides**(lamivudine, telbivudine, emtricitabine)
- **deoxyguanosine analogues** (entecavir)
- **acyclic nucleoside phosphonates** (adefovir and tenofovir).

- **Entecavir and tenofovir** are potent HBV inhibitors and they have a high barrier to resistance.
- Thus they can be confidently used as **first-line mono-therapies**.

Nucleos(t)ide Analogue (NAs) for Treatment-Naive Chronic HBV patients

1. The **long-term administration of a potent NA** with high barrier to resistance **is the treatment of choice** regardless of the severity of liver disease

(Evidence level I, grade of recommendation 1)

2. The **preferred regimens** are Entecavir, Tenofovir Disoproxil Fumarate (TDF) and TAF as monotherapies

(Evidence level I, grade of recommendation 1)

3. Lamivudine, Adefovir and Telbivudine **are no longer recommended** in the treatment of chronic hepatitis B

(Evidence level I, grade of recommendation 1)

Tenofovir Alafenamide (TAF) Prodrug of TFV Reduces Circulating TFV

Smaller Decline in Hip and Spine Bone Mineral Density with TAF vs TDF. Studies 108 & 110

Smaller Declines in e GFR_{CG} and Lower Rates of CKD Stage Worsening with TAF vs TDF at wk 48

Improving Renal Safety. Tenofovir Alafenamide (TAF) Study 108 at wk 48 in HBeAg neg



- TAF is more stable in plasma compared with TDF
- TAF 25 mg has 92% lower circulating plasma TFV levels compared to TDF 300mg

Indications for Selecting Entecavir or Tenofovir Alafenamide (TAF) over Tenofovir Disoproxil Fumarate*

1. Age >60 year

2. Bone disease

Chronic steroid use or use of other medications that worsen bone density

History of fragility fracture

Osteoporosis

3. Renal alteration**

eGFR <60 ml/min/1.73 m²

Albuminuria >30 mg or moderate dipstick proteinuria

Low phosphate (<2.5 mg/dl)

Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if eGFR <50 ml/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) 15 ml/min or in patients with CrCl <15 ml/min who are receiving haemodialysis.

Naive. Virological and Biochemical Response Rates Following 48/52 weeks of NA Therapy

HBeAg pos.

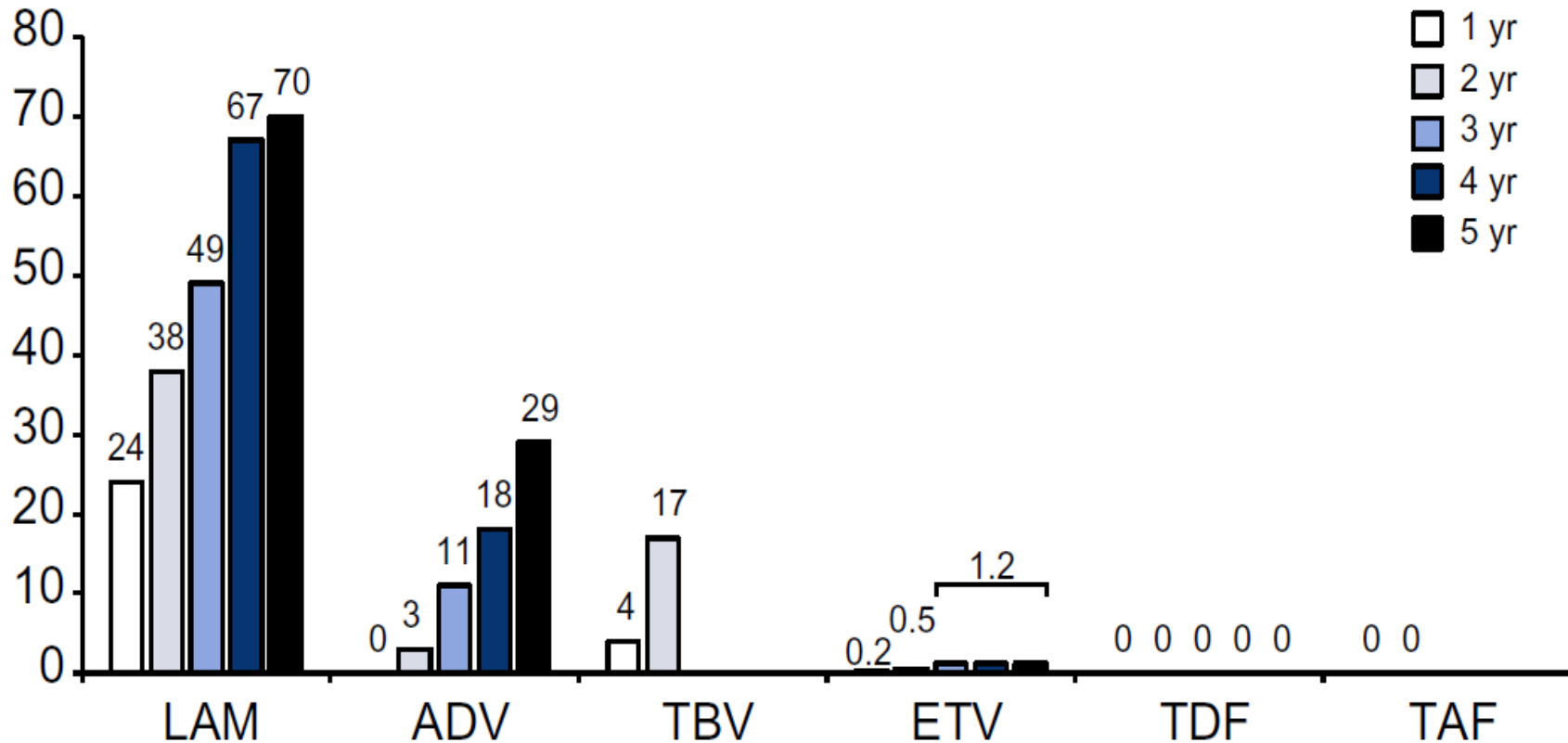
	Nucleoside analogues			Nucleotide analogues		
	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
Anti-HBe-seroconversion	16-18%	22%	21%	12-18%	21%	10%
<u>HBV DNA <60-80 IU/ml</u>	36-44%	60%	67%	13-21%	76%	64%
ALT normalisation#	41-72%	77%	68%	48-54%	68%	72%
HBsAg loss	0-1%	0.5%	2%	0%	3%	1%

HBeAg neg.

	Nucleoside analogues			Nucleotide analogues		
	LAM	TBV	ETV	ADV	TDF	TAF
Dose*	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
<u>HBV DNA <60-80 IU/ml</u>	72-73%	88%	90%	51-63%	93%	94%
ALT normalisation#	71-79%	74%	78%	72-77%	76%	83%
HBsAg loss	0%	0%	0%	0%	0%	0%

Cumulative Incidence of Selection of HBV Strains Resistant to Nucleos(t)ide analogues

Currently available data from pivotal trials (not head-to-head)
in nucleos(t)ide-naïve patients with chronic hepatitis B



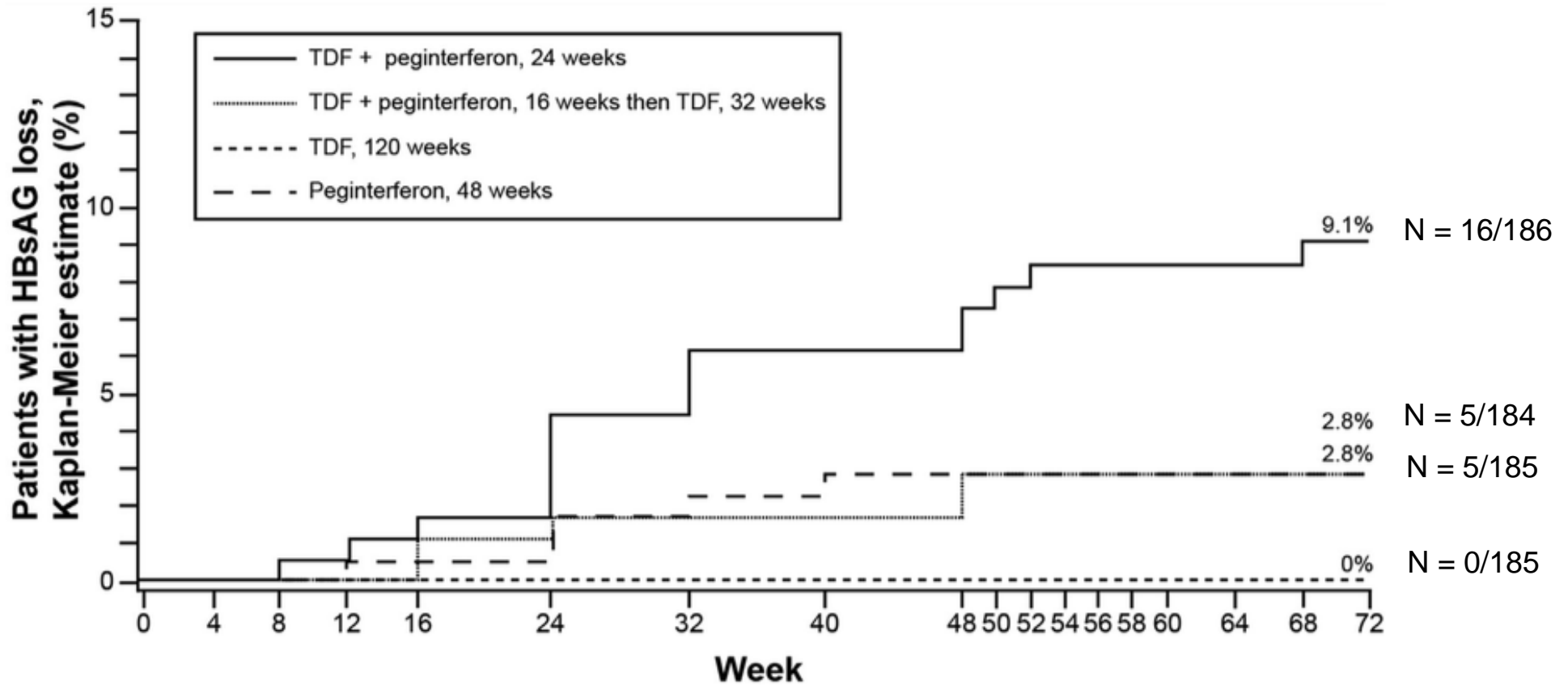
No evidence of resistance has been shown after 8 years of TDF treatment

Extended NA in Naive. HBV Replication Is Successfully Controlled with Little/No Resistance

Response	Entecavir		Tenofovir	
	HBeAg + (yr 5)	HBeAg - (yr 5)	HBeAg + (yr 5)	HBeAg - (yr 8)
HBV DNA suppression	99%	98%	97%	99%
<u>Resistance</u>	1%	1%	0%	0%
HBsAg loss (seroconversion)	NR	NR	10% (8%)	<1%

Tenofovir + PEG-IFN Increases HBsAg Loss Benefit Mainly in Geno A

HBsAg loss in 6/17 HBV geno A



Clinical Practice Guidelines 2017. Management of Patients Who Select Resistant Strains

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-resistance: 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-R: add ETV [*]
Multidrug resistance	Switch to ETV plus TDF or TAF combination

* The long-term safety of these combinations is unknown.

** Not seen clinically so far; do genotyping and phenotyping in an expert laboratory to determine the cross-resistance profile.

*** Especially in patients with ADV resistant mutations (rA181T/V and/or rN236T) and high viral load, the response to TDF (TAF) can be protracted.

Outcome Following HBe Ag Seroconversion

HBe Ag Loss



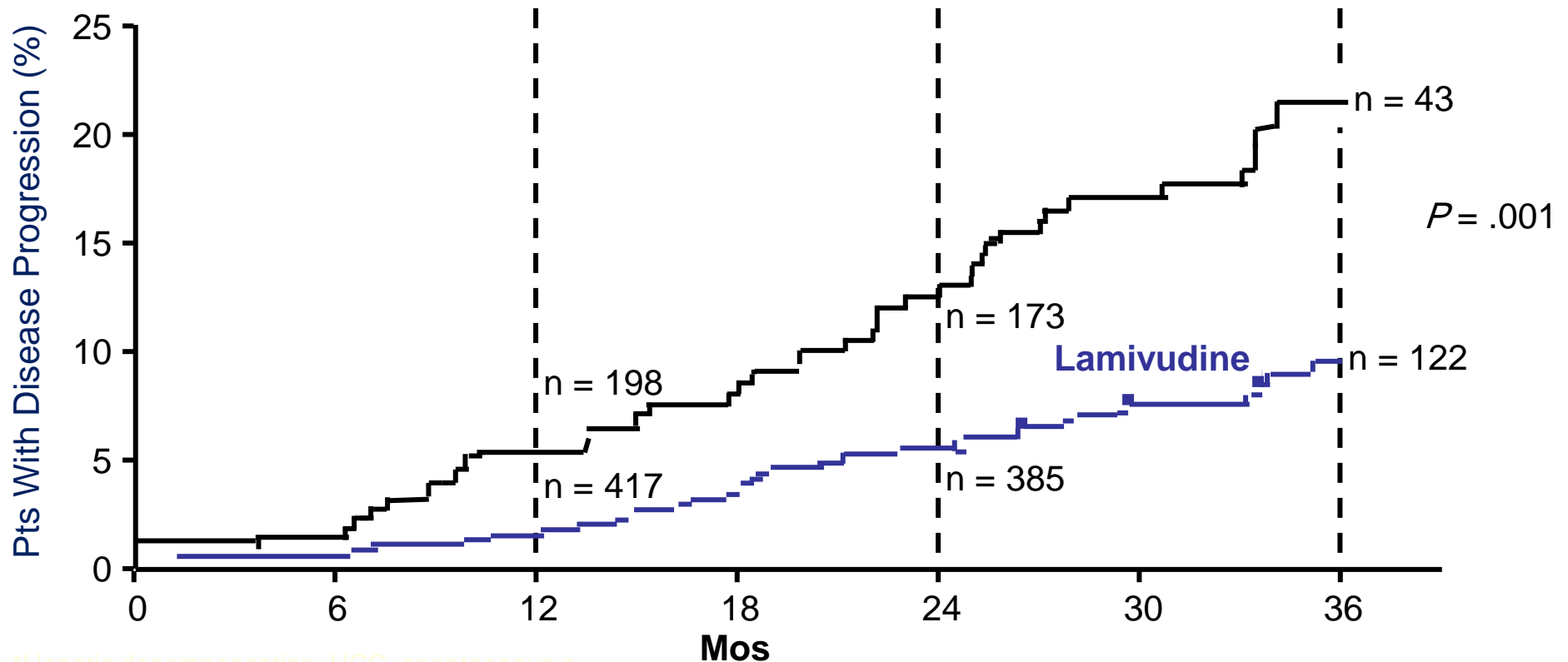
HBeAg seroconversion



Disease remission
HBsAg loss/seroconversion
Prevention of HCC
Increased Survival

Lamivudine Reduces Risk of HBV Progression Including Decompensation. A RCT in AP

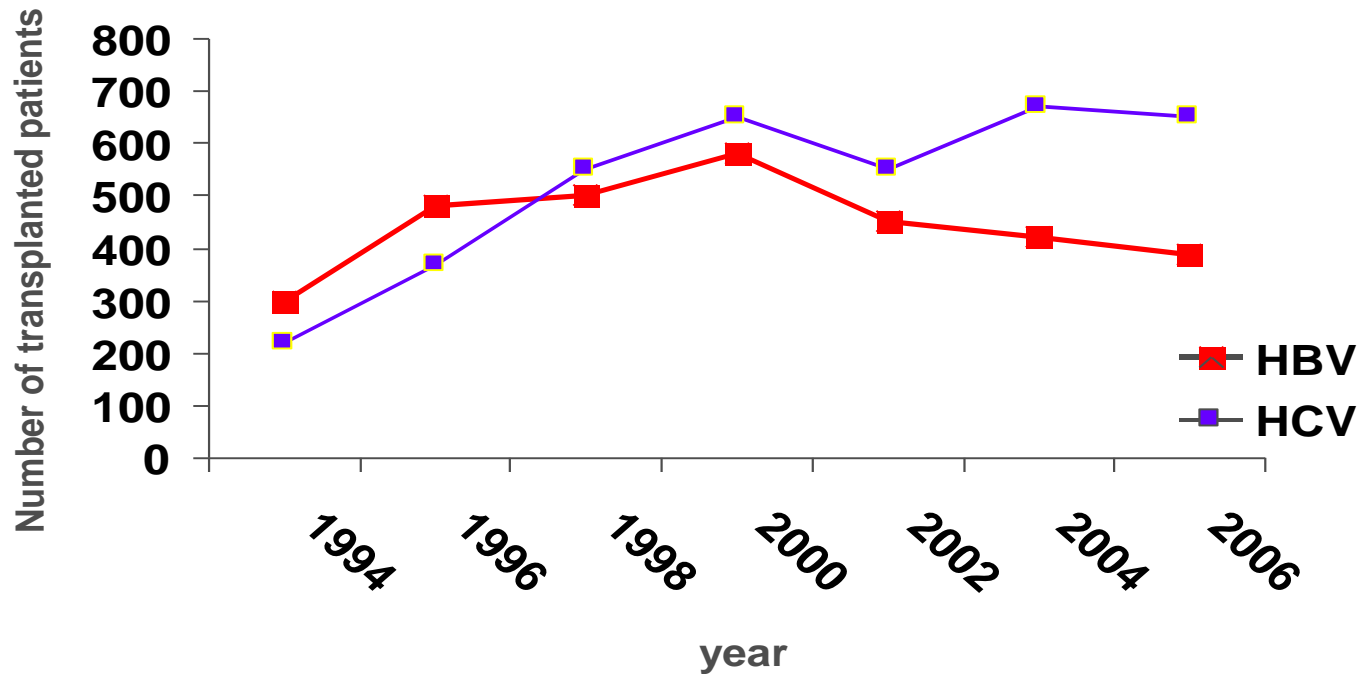
- 651 with HBV cirrhosis followed until HBeAg seroconversion or disease progression



*Hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

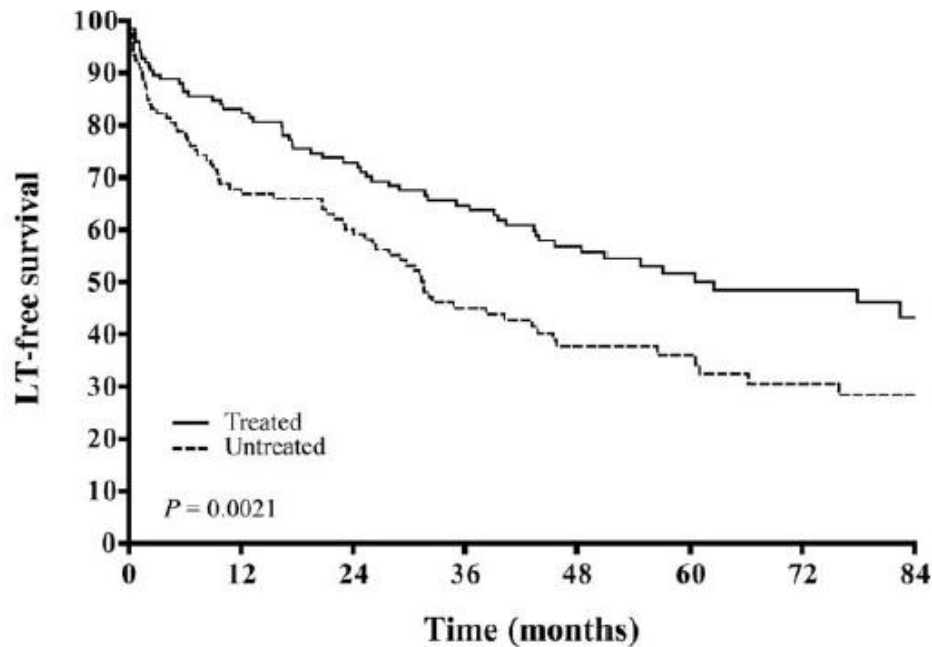
Decline of liver transplantation for HBV cirrhosis in US

The pattern of liver transplantation waiting list registration among patients with hepatitis B suggests that the widespread application of oral antiviral therapy for HBV contributed to the decreased incidence of decompensated liver disease.



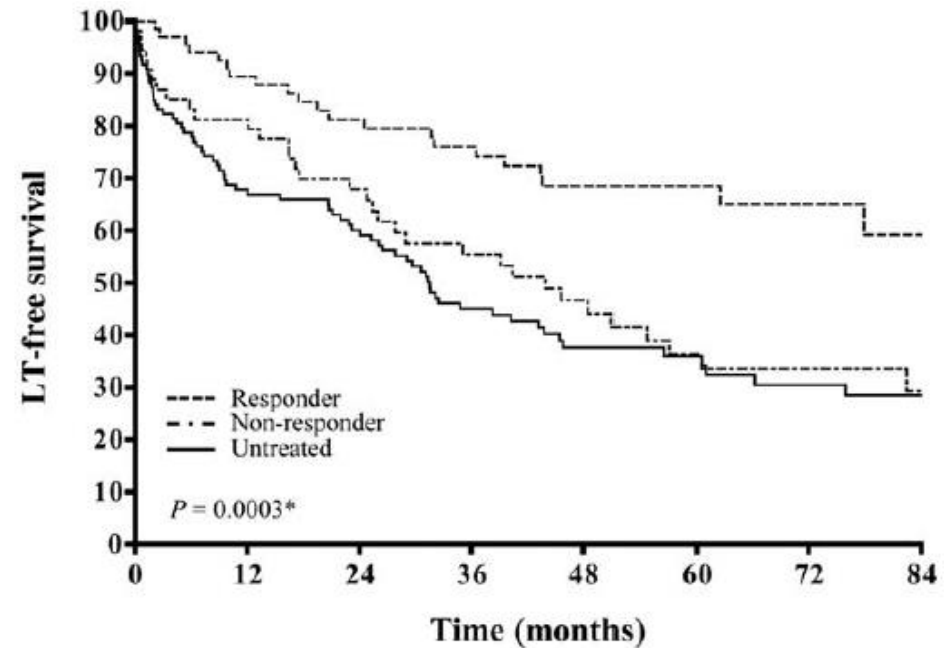
Survival Benefits of NUC Therapy in HBV Patients with Decompensated Cirrhosis

Survival of treated vs untreated



Treated	127	103	84	70	53	36	29	17
Untreated	127	73	62	41	28	21	16	14

Survival by treatment response



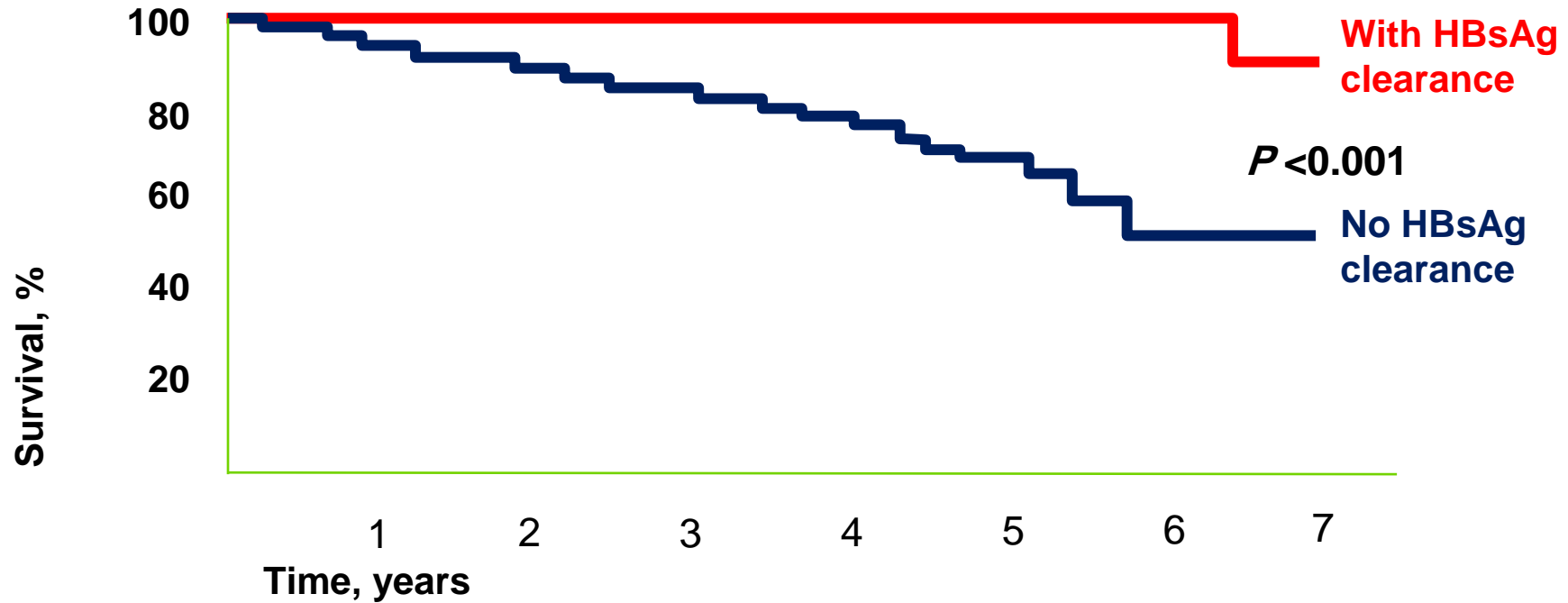
Responder	72	59	50	43	32	22	17	9
Non-responder	55	44	34	27	21	14	12	8
Untreated	127	73	62	41	28	21	16	14

34% of treated patients delisted for LT

HBsAg Clearance Improves Survival

Survival in patients with and without HBsAg seroconversion:

retrospective study of 309 patients over a mean follow-up of 5.7 years



HBsAg Loss Decreases Subsequent Risk of HCC

REVEAL 2964 HBsAg, no cirrhosis

➤ Hazard ratio for HCC after sero clearance

- HBeAg	0.63
- HBV DNA	0.24
- HBsAg	0.18

➤ Among HBeAg (-) lifetime cumulative incidence of HCC for those clearing

- Both HBV DNA and HBsAg	4.0%
- HBV DNA only	6.6%
- Neither	14.2%

Barriers to Curing Chronic Hepatitis B

Barriers

- Reservoir of cccDNA
- Dysfunctional T-cell response/exhaustion
- Insufficient or inadequate B-cell response

Strategic to overcome these barriers

- Deplete or silence cccDNA
 - Improve potency of Polymerase inhibitors
 - Broaden viral targets
 - Activate antiviral immunity
-

The Clinical Benefits of Current NA Monotherapy

Take Home Message

➤ Current NAs improve disease outcome

- Viral suppression and normalization of transaminases
- Prevention of progression/regression of liver disease
- Risk reduction of HCC
- Reduced liver related mortality
- Finite therapy possible following HBsAg loss/seroconversion

➤ No cure for HBV due to persistence of cccDNA

Duration of NUCs therapies

- Finite-duration treatment with NUCs is achievable for HBeAg-positive patients who develop HBe seroconversion on treatment.
- Long-term treatment with NUCs is necessary for patients who cannot achieve a sustained virological response off-treatment and require extended therapy, i.e. for HBeAg-positive patients who do not develop HBe seroconversion and in HBeAg-negative patients

AASLD Guideline Recommendations for Duration of NA Treatment

HBeAg-positive chronic hepatitis B:

Treatment should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV DNA and completed at least 6 months of additional treatment after appearance of anti-HBe.

- Close monitoring for relapse is needed after withdrawal of treatment.

HBeAg-negative chronic hepatitis B:

Treatment should be continued until the patient has achieved HBsAg clearance.

EASL Clinical Practice Guidelines 2017

Can NAs Be Discontinued?

NAs should be discontinued

1. **After confirmed HBsAg loss**, with or without anti-HBs seroconversion

(Evidence level II-2, grade of recommendation 1)

NAs can be discontinued

2. **In non-cirrhotic HBeAg pos.** patients **who achieve stable HBeAg seroconversion** and undetectable HBV DNA and after completing ≥ 12 months of consolidation therapy. Close post-treatment monitoring is warranted

(Evidence level II-2, grade of recommendation 2)

3. **In selected non-cirrhotic HBeAg-neg.** patients who have achieved long-term (3 years) virological suppression under NA(s) if close post-NA monitoring can be guaranteed

(Evidence level II-2, grade of recommendation 2)

Stopping Rules for NA Therapy in Chronic Hepatitis B

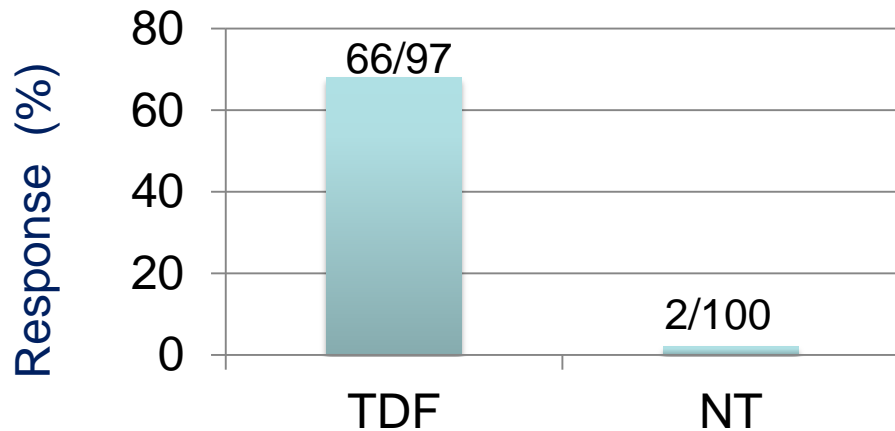
Patient hepatitis status	APASL 2016	EASL 2017	AASLD 2016
without liver cirrhosis	therapy, but preferably after 3 years of additional therapy after HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels	NA therapy after HBeAg seroconversion, or treat until HBsAg loss	of NA therapy after HBeAg seroconversion with undetectable HBV and persistently normal ALT levels, or treat until HBsAg loss
HBeAg (-) without liver cirrhosis	i) HBsAg loss, following either anti- HBs seroconversion, or at least 12 months of post-HBsAg clearance consolidation period, or ii) after treatment of at least 2 years with undetectable HBV DNA documented on 3 separate occasions, 6 months apart	i) HBsAg loss ii) selected patients who have achieved long-term (≥ 3 years) virological suppression under NA	Long term treatment with NA until HBsAg loss.
Liver cirrhosis	Indefinite treatment with NA regardless of HBV DNA levels and HBeAg status	Indefinite treatment with NA regardless of HBeAg status or HBeAg seroconversion	Indefinite treatment with NA regardless of HBeAg status or HBeAg seroconversion

Clinical Questions Evaluated

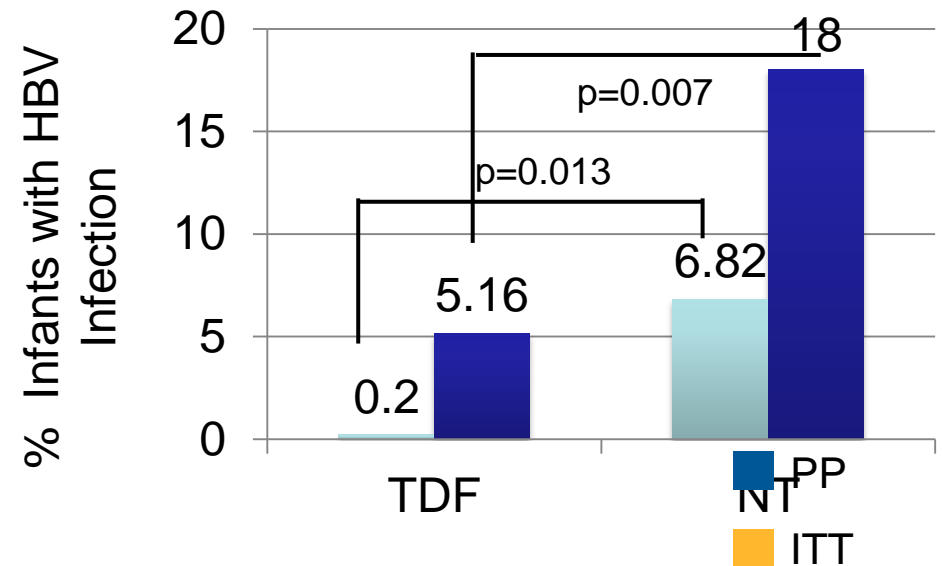
Question	Population	Intervention	Comparison	Outcome(s)
1	Immune-active CHB	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, loss of HBsAg
2	Immune-tolerant CHB, adults	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, loss of HBsAg
3	HBeAg-positive immune-active chronic hepatitis, with HBeAg seroconversion on therapy	Continued antiviral therapy	Stopping antiviral therapy	Cirrhosis, HCC, reactivation, seroreversion, decompensation, loss of HBsAg
4	HBeAg-negative immune-active chronic hepatitis, with viral suppression on antiviral therapy	Continued antiviral therapy	Stopping antiviral therapy	Reactivation, decompensation, loss of HBsAg
5	CHB on treatment with oral therapy	Tenofovir	Entecavir	Renal function, hypophosphatemia, bone health
6	CHB on treatment with oral therapy with persistent viremia	Continue therapy	Change or switch therapy	HBV resistance, clinical flare, decompensation, loss of HBeAg
7	CHB with cirrhosis, with HBV DNA <2,000 IU/mL	Antiviral therapy	No treatment	Decompensation, HCC, death
8	Pregnant women with CHB	Antiviral therapy in third trimester	No treatment	CHB in the infant, maternal safety, fetal/infant safety
9	HBeAg-positive CHB, children/adolescents	Antiviral therapy	No treatment	Cirrhosis, decompensation, HCC, death, HBeAg seroconversion, loss of HBsAg

TDF Reduces Perinatal Transmission of Hepatitis B Virus in Highly Viremic Mothers: A Multi-Center, Prospective, RCT

Virologic response in mothers, VL < 200,000 IU/mL



MTCT at W 28 PP



- Birth defect rates : 2.11% with TDF exposure vs. 1.14% without exposure(P = 1.00)
- The HBV serologic outcome did not differ between groups

Clinical Practice Guidelines

NA + NA and NA + Peg-IFNa Combinations

NOT RECOMMENDED :

1. **De novo combination** of NA and Peg-IFN a .

Evidence level I, grade of recommendation 1

2. In **treatment naïve HB|eAg-pos** patients, short-term NA treatment before Peg-IFN a.

Evidence level II, grade of recommendation 1

3. In **long-term NA suppressed** CHB patients, adding Peg-IFN a or switching to Peg-IFN a

Evidence level II, grade of recommendation 1

4. De novo **combination therapy with two NAs** with high barrier to resistance

Evidence level I, grade of recommendation 1