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 *infection*	HBeAg positive	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis
HBsAg	High		Low	Intermediate
HBeAg	Positive		Negative	Negative
HBV DNA	>10E7 IU/mL		<2,000 IU/mL°°	>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

HBsAg Loss/Occult Hepatitis B

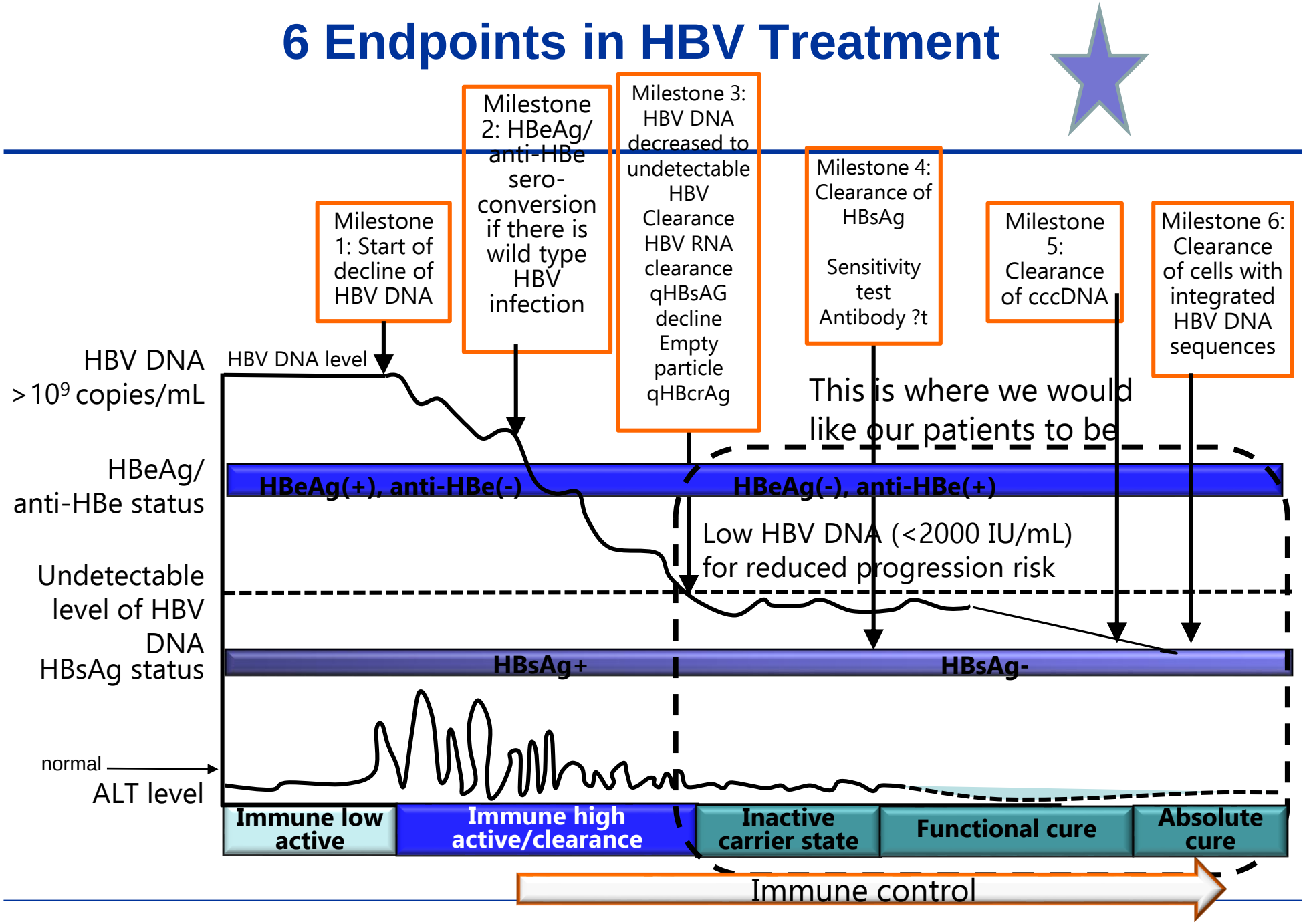
- Serum HBV DNA phases, alternating undetectable and very low but detectable
- Detectable HBV DNA in the liver
- Intrahepatic replication-competent HBV genomes such as HBV cccDNA
- Integrated HBV DNA

*Persistently or intermittently

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

EASL 2017 Clinical Practice Guidelines on HBV, J Hepatol 2017

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)

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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)

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When Antiviral Treatment Should Be Initiated?

APASL, AASLD & EASL recommend

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

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

Terrault et al, Hepatology 2016;63:261. Sarin et al, Hepatol Int 2016;10:1. EASL, J Hepatol 2017;67:370-398

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)
- **deoxyguanosineanalogues (**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)

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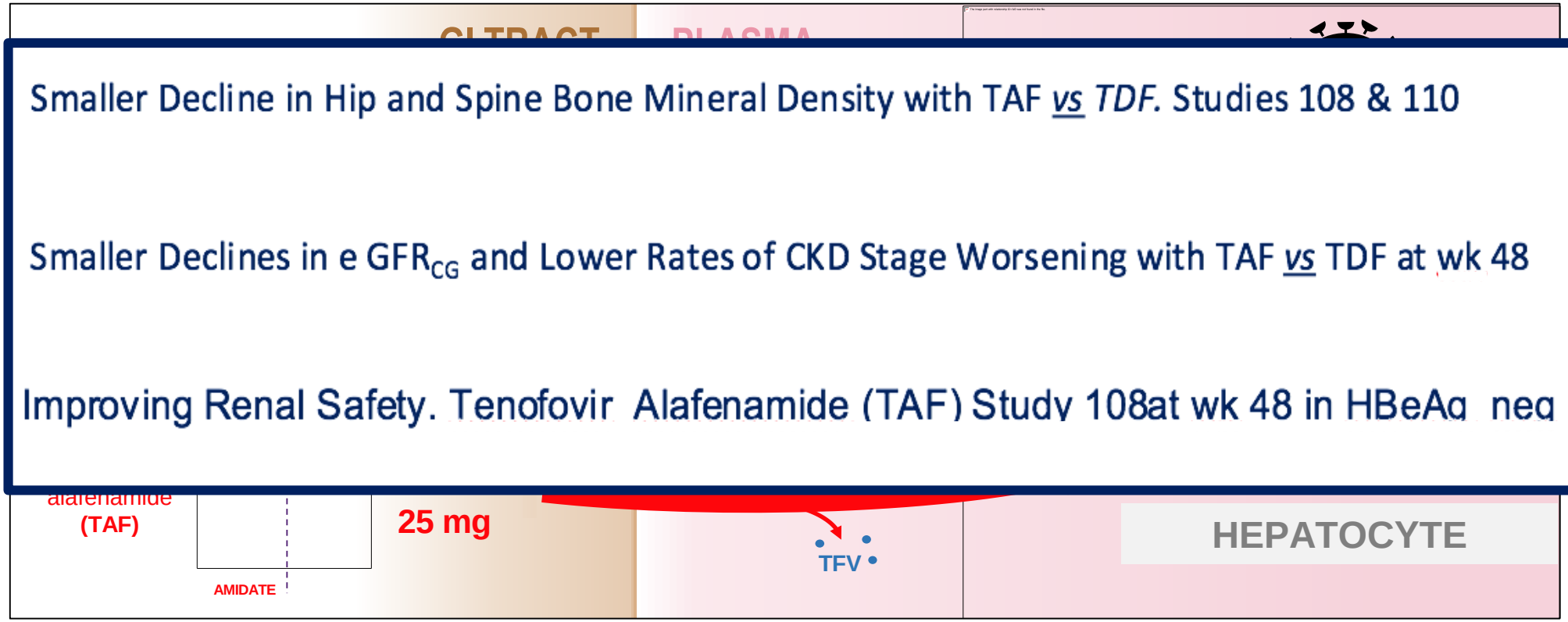
Tenofovir Alafenamide (TAF) Prodrug of TFV Reduces Circulating TFV



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

Agarwal K J Hepatology. 2015; Lee W Antimicr Agents Chemo 2005;. Agarwal K J Hepatology 2015;.Murakami E Antimicrob. Agents Chemother.13 Apr 2015 . Kearney BP Clin Pharmacokinet. 2004

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 min/ml/1.73 m^2
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.

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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%
HBV DNA <60–80 IU/ml	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%

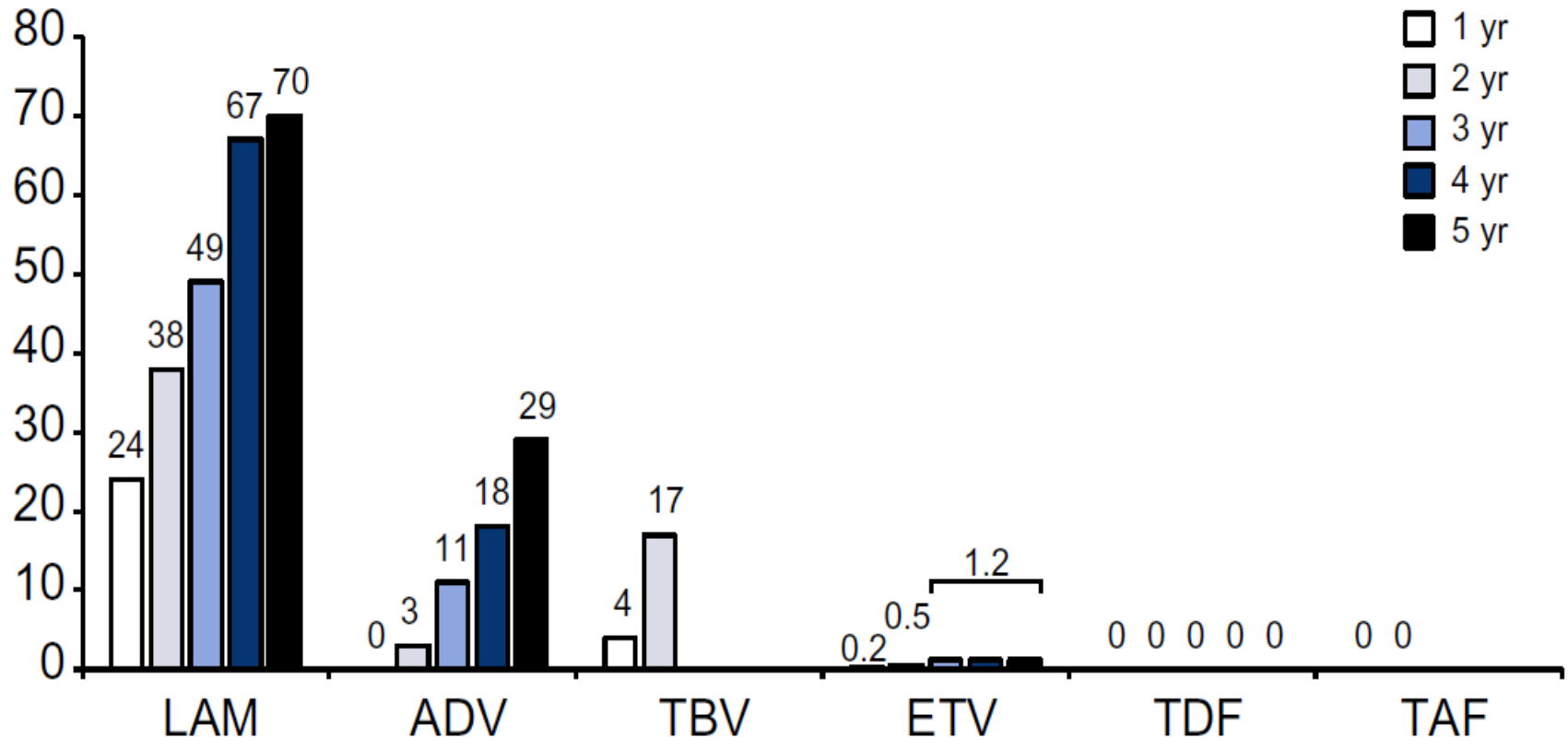
HBeAg neg.

	Nucleoside analogues			Nucleotide analogues		
	LAM	**TBV**	**ETV**	**ADV**	**TDF**	**TAF**
Dose	100 mg	600 mg	0.5 mg	10 mg	245 mg	25 mg
HBV DNA <60–80 IU/ml	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%

CPG on HBV Therapy J Hepatol 2017

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

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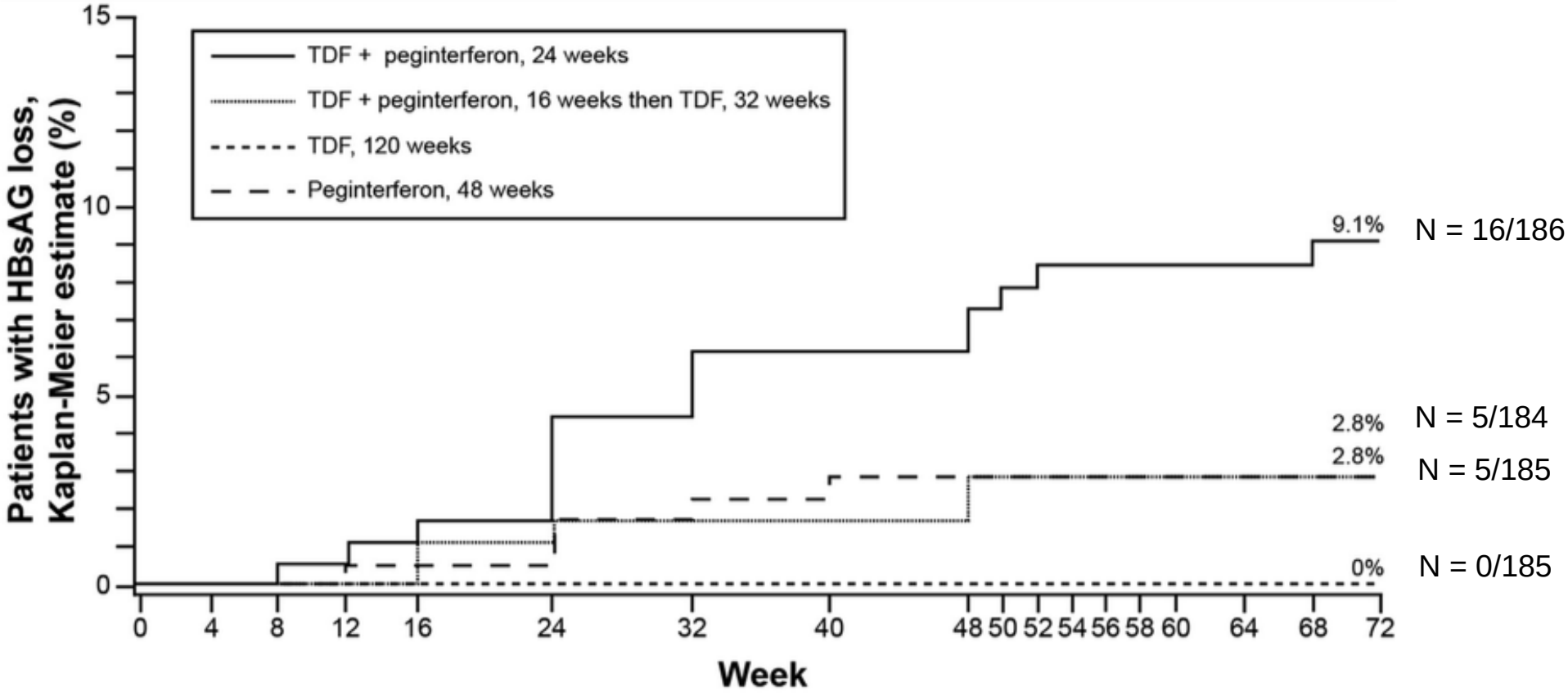
Extended NA in Naive. HBV Replication Is Successfully Controlled with Little/No Resistance

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

.CPG on HBV Therapy J Hepatol 2017

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

HBsAg loss in 6/17 HBV geno A



Marcellin P et al. Gastroenterol 2016; 150: 134

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

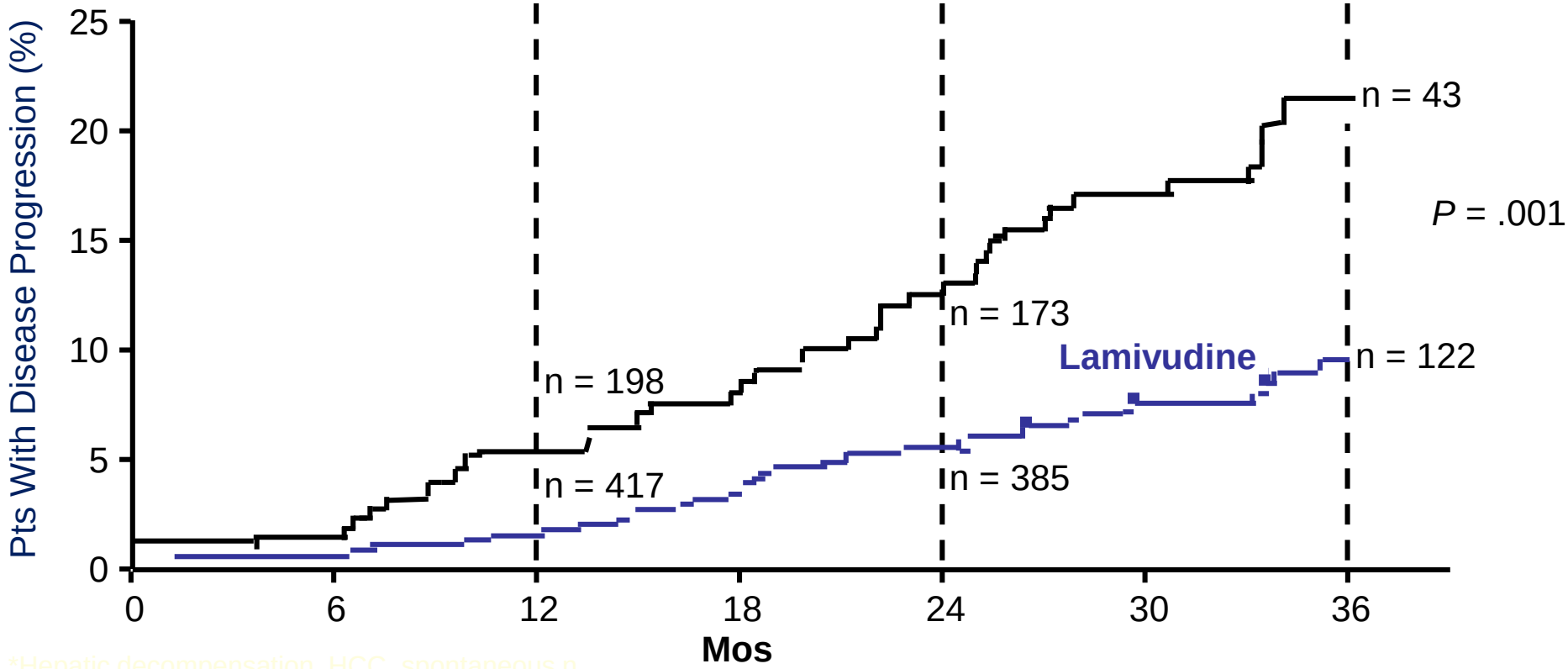
HBeAg seroconversion

Disease remission
HBsAg loss/seroconversion
Prevention of HCC
Increased Survival

Van Zonneveld Hepatology 2004, Hoofnagle Ann Intern Med 1981

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

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

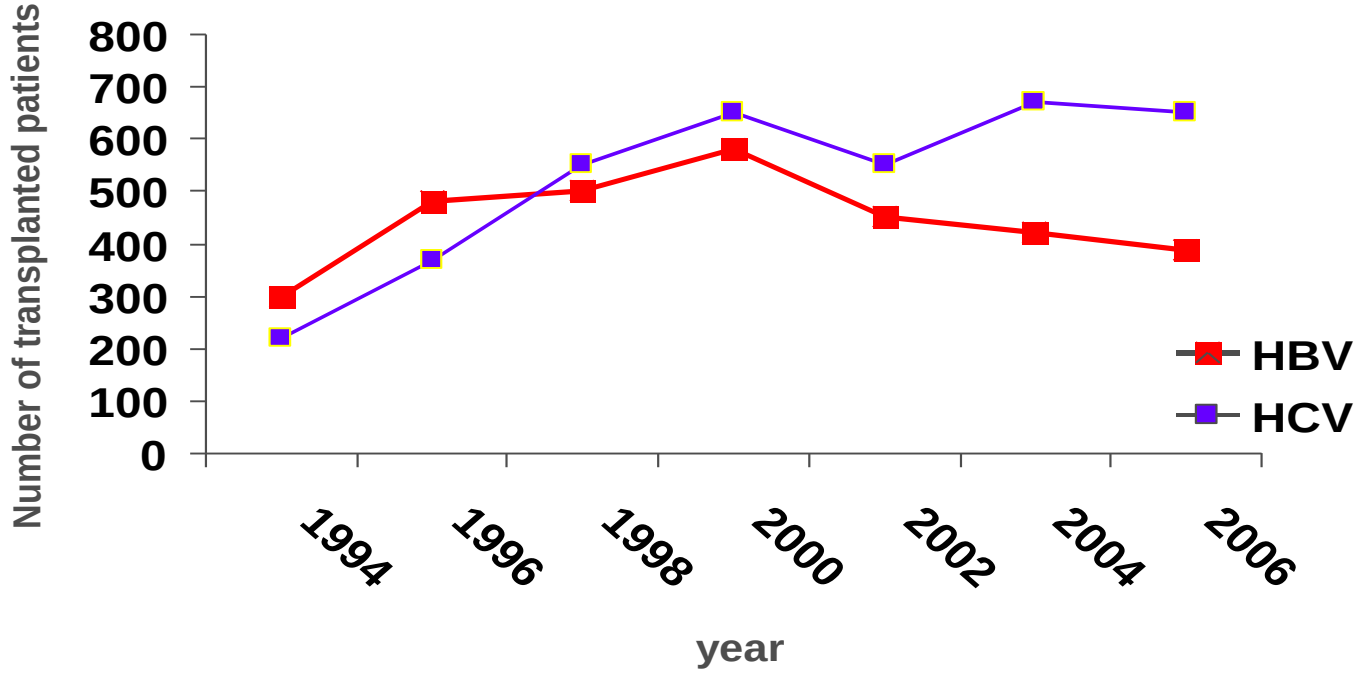


*Hepatic decompensation, HCC, spontaneous n
bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

Liaw YF, et al. N Engl J Med. 2004;351:1521-1531.

Decline of liver transplantation for HBV cirrhosis in US

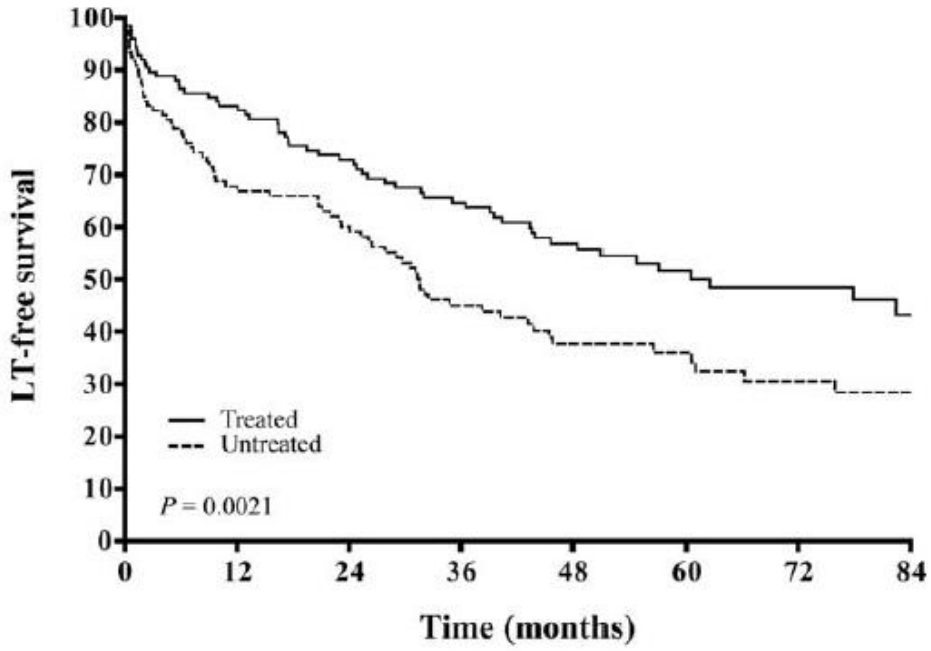
The pattern of liver transplantation waiting list registration among patients with hepatitis B suggests that the widespread application of oral antiviral therapy for HBV contributed to the decreased incidence of decompensated liver disease.



Kim WR, Gastroenterology 2009

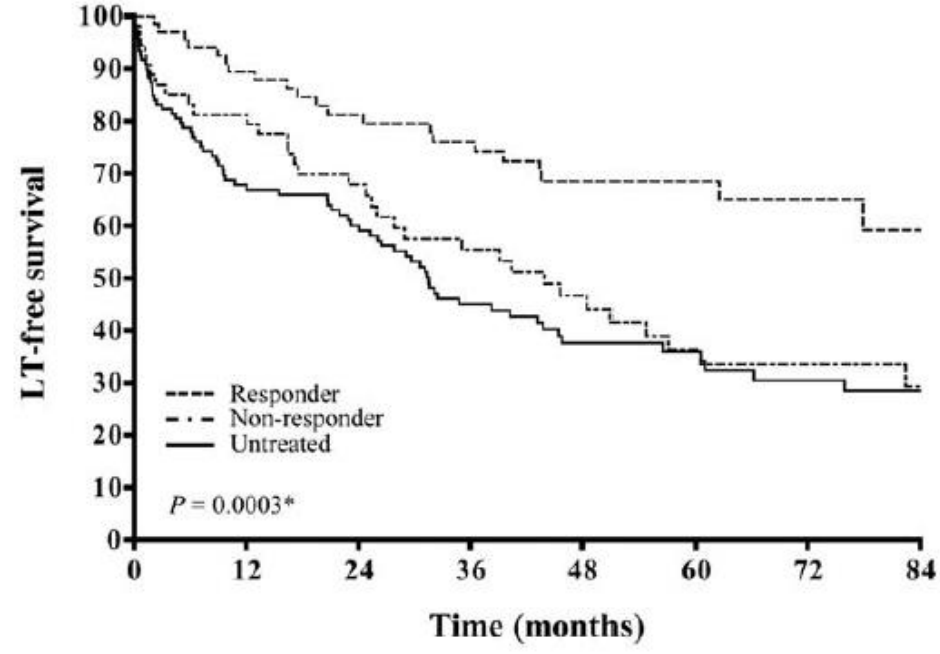
Survival Benefits of NUC Therapy in HBV Patients with Decompensated Cirrhosis

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

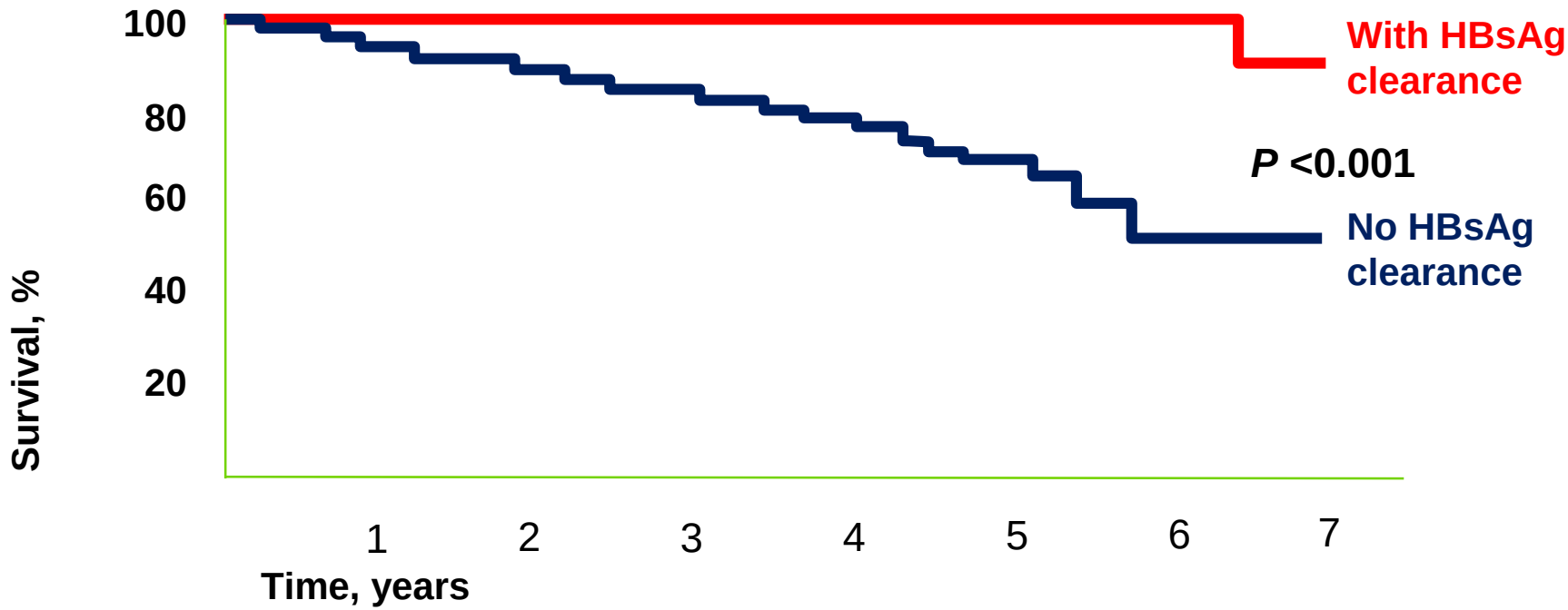
34% of treated patients delisted for LT

Jang et al, Hepatology 2015;61:1809-20

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



Fattovich G, et al. *Am J Gastroenterol*. 1998;93:896–900.

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%

Liu J, Gut 2014; 63: 1648-57

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.

Lok AS, et al. Hepatology. 2009.

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)

EASL 2017 Clinical Practice Guidelines on HBV, J Hepatol 2017

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

Kho-Herman SGR & Chan HLY,Liver Res. 2017

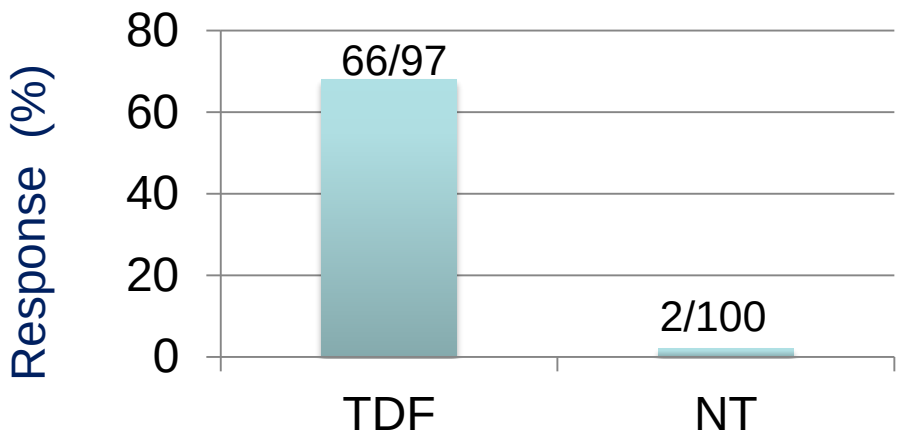
Clinical Questions Evaluated

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

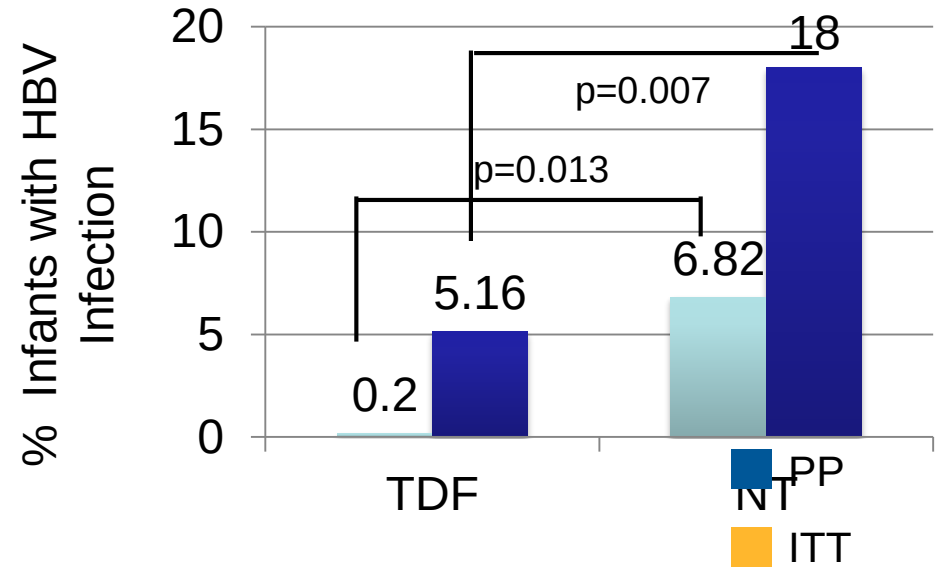
Terrault NA, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016

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

Pan CQ, et al. New Engl J Med 2016 374 2324-34

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 HBeAg-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