Hepatitis B: How to manage

Seyed Moayed Alavian M.D.
Professor of Gastroenterology and Hepatology
Editor-in-chief of Hepatitis Monthly
E mail: editor@hepmon.com

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 Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 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

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

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HBeAg	Positive		Negative	Negative
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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
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Initial management of hepatitis B infection

Complete history and physical examination to assess for **signs of cirrhosis**, **alcohol** and **metabolic** risk factors, and **family history of hepatocellular carcinoma**.

Routine laboratory tests should include assessment of liver disease activity and function (**complete blood count**, aspartate aminotransferase, **ALT,** total bili, alkaline phosphatase, **albumin**, international normalized ratio), markers of HBV replication (HBeAg/anti-HBe, **HBV DNA quantitation**), tests for coinfection with HCV, **HDV**, and HIV, and assessment of HAV immunity to determine need for vaccination.

Initial Evaluation of HBsAg-Positive Patient

	History/Physical Examination	Routine Laboratory Tests	Serology/Virology	Imaging/Staging Studies
All patients	Symptoms/signs of cirrhosis Alcohol and metabolic risk factors Family history of HCC Vaccination status	CBC including platelet count, AST, ALT, total bilirubin, alkaline phosphatase, albumin, INR	HBeAg/anti-HBe HBV DNA quantitation Anti-HAV to determine need for vaccination	Abdominal ultrasound Vibration-controlled transient elastography or serum fibrosis panel (APRI, FIB-4, or FibroTe
Select patients		Tests to rule out other causes of chronic liver diseases if elevated liver test(s) AFP, GGT	HBV genotype Anti-HDV Anti-HCV Anti-HIV in those who have not undergone one-time screening (ages 13-64)	Liver biopsy

Patients should be educated on measures to **prevent transmission** and **prevention** of further liver damage (e.g., limiting alcohol intake and medications or supplements that could be hepatotoxic) and the importance of long-term monitoring, particularly with regard to the risk for **hepatocellular carcinoma**.

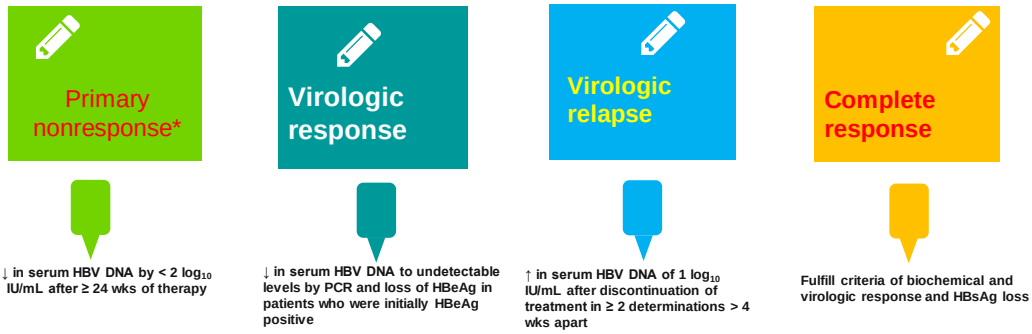
Terrault NA, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016

Parameters Used to Determine Candidates for Treatment of HBV

- **ALT**
  - "New" normal or "healthy" ALT: < 30 U/L for men and < 19 U/L for women[1]
  - Presence of 1 normal value does not exclude significant disease or subsequent complications
- **HBV DNA**
  - Predicts development of cirrhosis and HCC[2,3]
  - Interpret in conjunction with ALT and/or histology
- **Liver biopsy or Fibroscan**
  - Useful in situations where ALT or HBV DNA do not provide clear guidelines for treatment[1]

1. Lok AS et al. Hepatology. 2009. Iloeje UH et al. Gastroenterology. 2006, 3. Chen CJ et al. JAMA. 2006

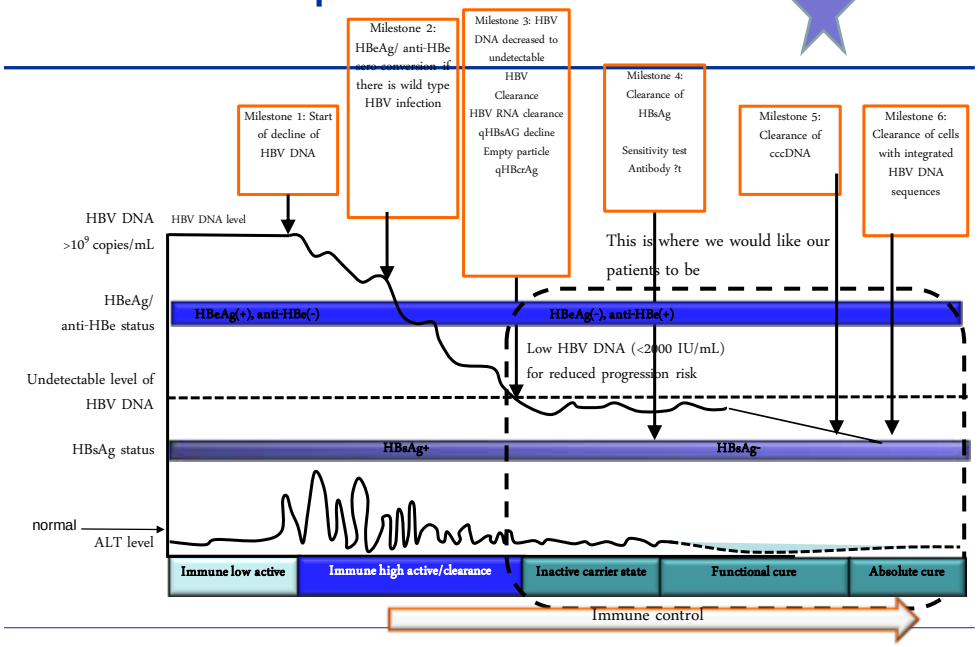
Definition of Response to Antiviral Therapy



*Not applicable to interferon therapy.

Asselah T, Marcellin P. An update in the management of chronic hepatitis B. Clinics in liver disease. 2013;

6 Endpoints in HBV Treatment



Who Should Be Treated?

- All HBV chronic patients are potential treatment candidates
- Not a question of whom to treat but when: treat now or monitor and treat later when indicated
- A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new and better treatments

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)

EASL 2017 CPG HBV, J Hepatol 2017

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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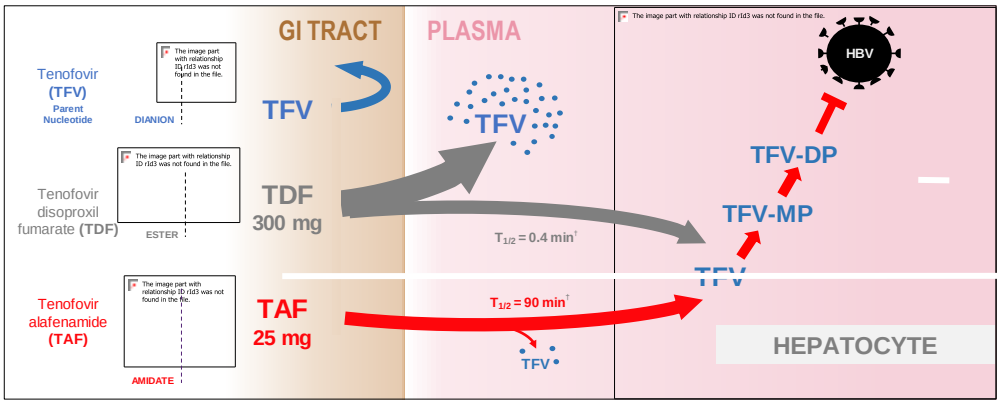
Tenofovir Alafenamide (TAF) Prodrug of TFV Reduces Circulating TFV



- 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

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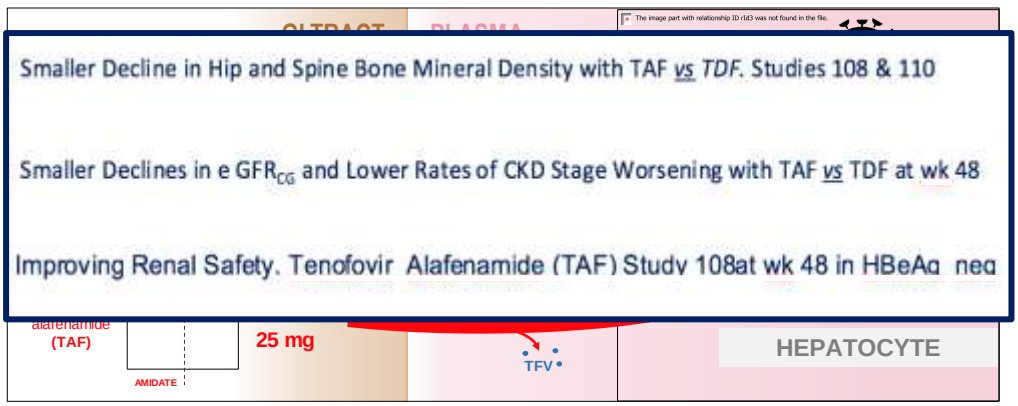

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Indications for Selecting Entecavir or Tenofovir Alafenamide (TAF) over Tenofovir Disoproxil Fumarate*

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%

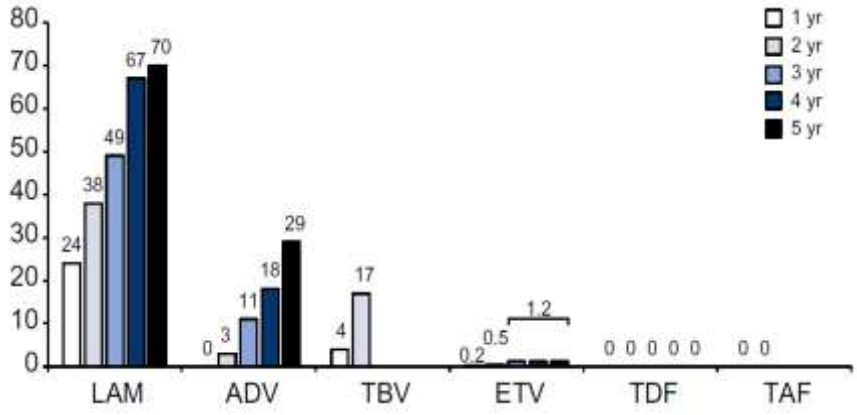
HBeAg neg.

	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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Outcome Following HBe Ag Seroconversion

HBe Ag Loss

↓

HBeAg seroconversion

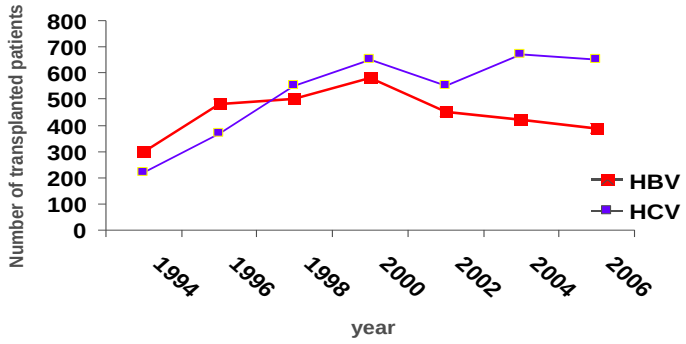
↓

Disease remission
HBsAg loss/seroconversion
Prevention of HCC
Increased Survival

Van Zonneveld Hepatology 2004, Hoofnagle Ann Intern Med 1981

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.

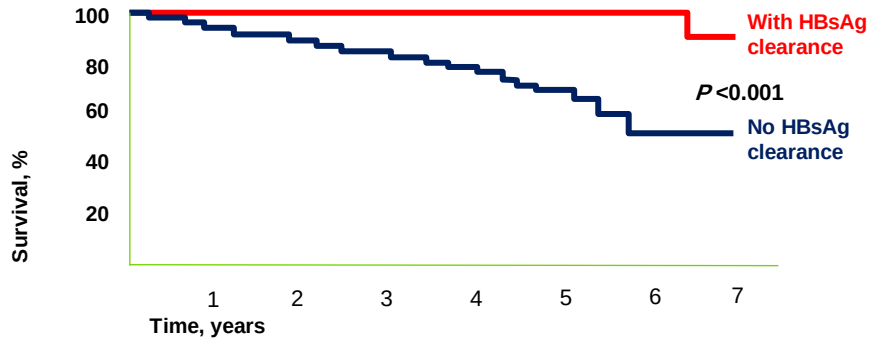


Kim WR, Gastroenterology 2009

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.

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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)

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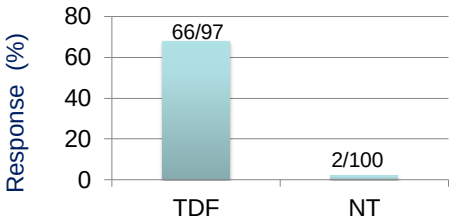
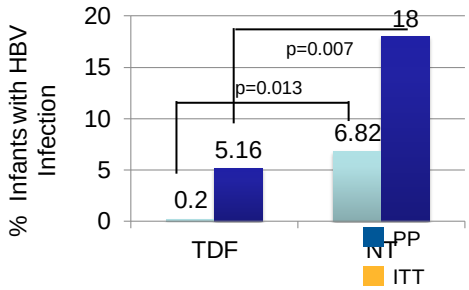
TDF Reduces Perinatal Transmission of Hepatitis B Virus in Highly Viremic Mothers: A Multi-Center, Prospective, RCT

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

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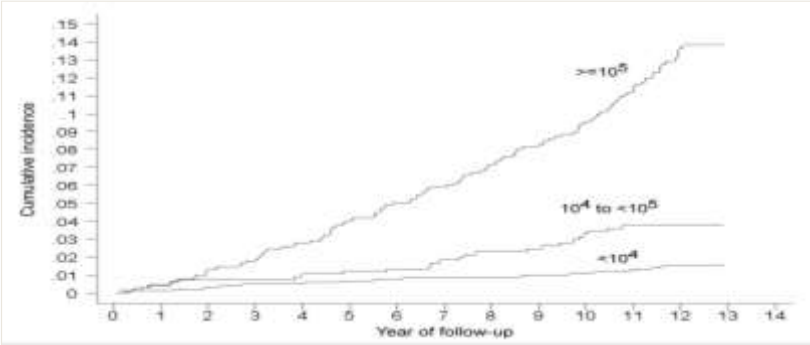
Viral Load Associated with Risk of HCC



Chen et al. 14th APASL. 2004. Poster

HCC screening

- The AASLD Practice Guideline for HCC recommended surveillance of carriers at high risk of HCC with US every 6-12 months and AFP.

- **Recommendations for HCC Screening:**
- HBV carriers at high risk for HCC such as Asian men over 40 years and Asian women over 50 years of age, persons with cirrhosis, persons with a family history of HCC, any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV DNA level >2,000 IU/ml should be screened with US examination every 6-12 months.

Elevated ALT in HBsAg Positive

- A 32 year-old asymptomatic man was referred to us after recognition of HBsAg positivity on blood donation. No finding on examination, and hyper echo on abdominal sonography. The laboratory tests showed : ALT: 55 to 65 and AST: 50 to 60 in repeated sessions. HBe Ag negative, Anti HDV Ab negative. HBV Viral Load by Amplicor test: 5,000 copies/ml.
- **What is your plan?**

- Think about metabolic syndrome and fatty liver in every case of HBs Ag positive and elevated ALT