Update on Hepatitis B in 2021

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Disclosures

- Advisory Boards: Gilead, Salix, Intercept (HCV, HBV, NASH, HE)
- Speaking: Gilead, Salix, Intercept (HCV, HBV, NASH, HE)
- Research: Novo Nordisk (NASH), Allergan (NASH), Salix (HE)

Chronic HBV: Demographics

- Estimated up to 2 million persons in USA infected
- Vast majority are immigrants or first-generation Americans:
  - Southeast Asia, China
  - Sub-Saharan Africa
  - Eastern Europe
  - Likely acquired HBV via vertical transmission or from contaminated medical equipment in their homeland
- African Americans account for 20% of persons with chronic infection

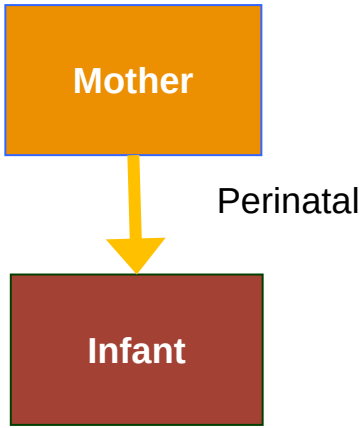
Transmission of HBV

Horizontal Transmission

- Child-to-Child
- Contaminated Needles
- Sexual
- Health Care Worker
- Transfusion
- Hemodialysis

No clear risk factors in 20%-30% of patients

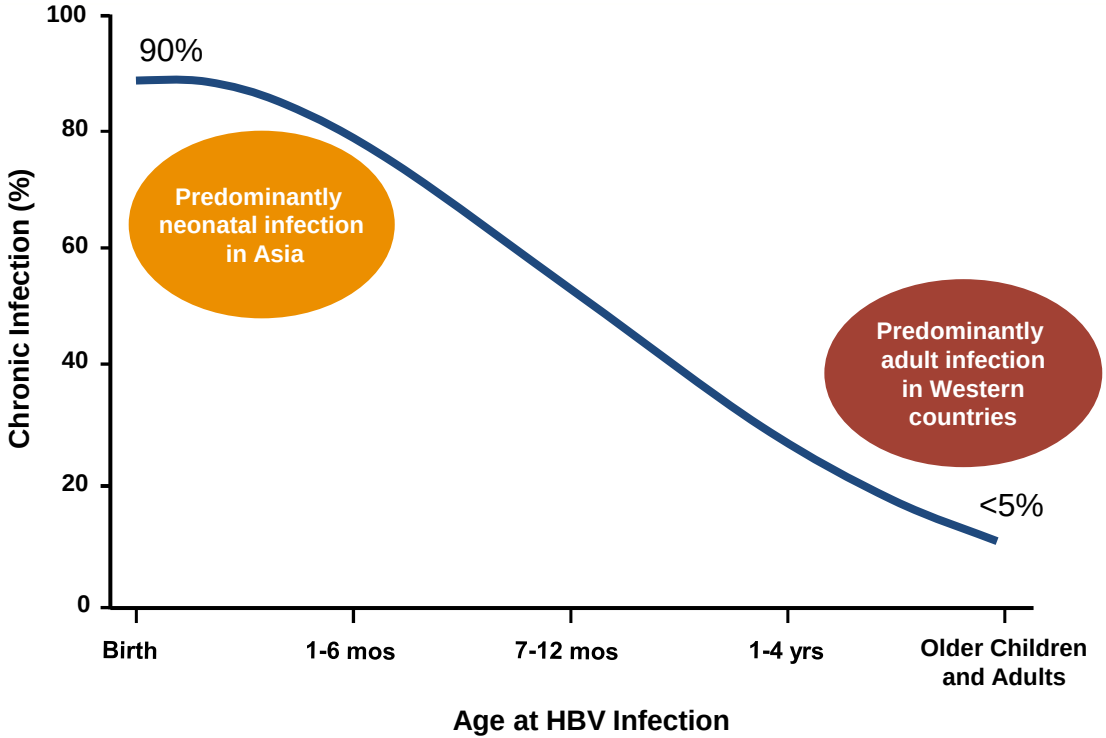
Vertical Transmission



Common in regions with HBsAg prevalence of >2%

CDC Fact Sheet. http://www.cdc.gov/hepatitis/B/PatientEduB.htm. Accessed August 13, 2009.
Lee WM. *N Engl J Med*. 1997;337:1733-1745.
Lavanchy D. *J Viral Hepat*. 2004;11:97-107.

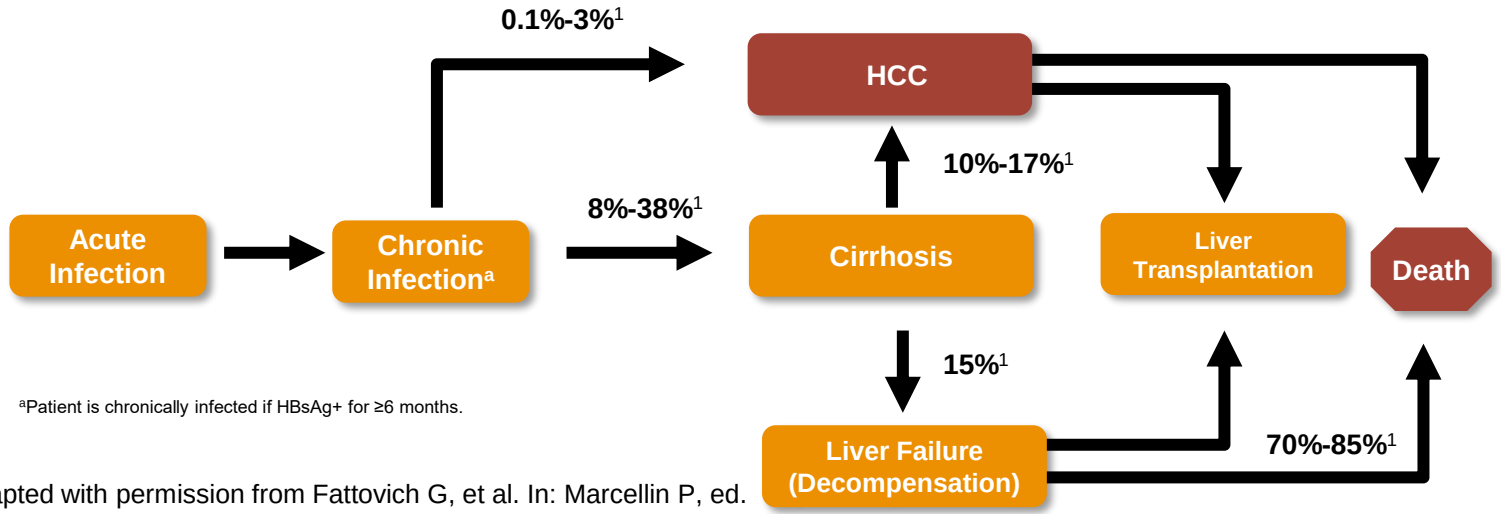
Progression to Chronic Infection is Dependent on the Age at Acute HBV Infection



Asian Liver Center. *2007 Physician's Guide to Hepatitis B: A Silent Killer*. http://liver.stanford.edu/files/2007Handbook.pdf. Accessed November 7, 2007.

CHB Is Associated With Severe Burden of Disease

Five Year Cumulative Incident Rates of Development of CHB Complications



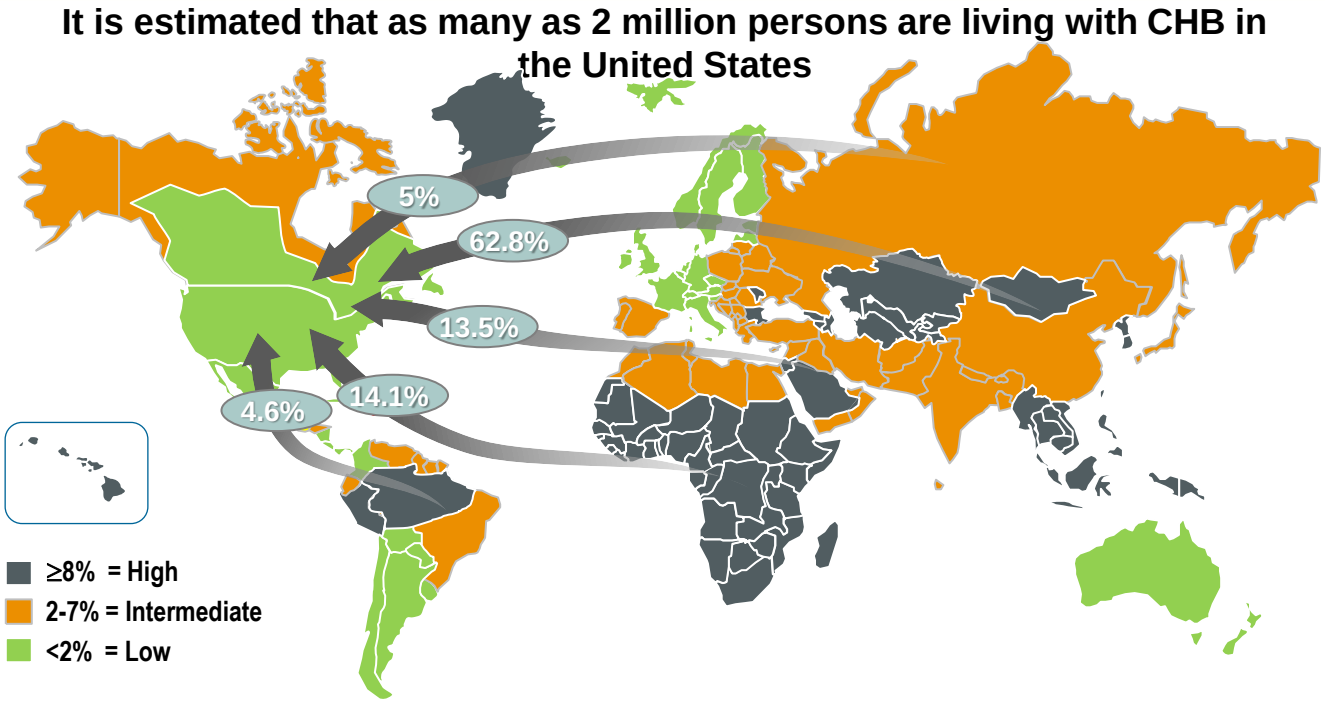
[a]Patient is chronically infected if HBsAg+ for ≥6 months.

Figure adapted with permission from Fattovich G, et al. In: Marcellin P, ed. *Management of Patients With Viral Hepatitis.* Paris: APMAHB; 2004

Fattovich G, et al. *J Hepatol.* 2008;48:335-352.

Lok ASF, McMahon BJ. *Hepatology.* 2009;50:1-36.

Worldwide Distribution of Chronic HBV Infection



Adapted from: *Centers for Disease Control and Prevention. Morb Mortal Wkly Rep. 2008;57:1-16;* Cohen C, et al. *J Viral Hepatitis.* 2011;18:377-383.; Liu SJ, et al. *J Immigr Minor Health.* 2015;17:7-12; Kowdley KV, et al. *Hepatology.* 2012;56:422-433.

US Prevention Services Task Force (USPSTF)

HBV Screening Recommendations

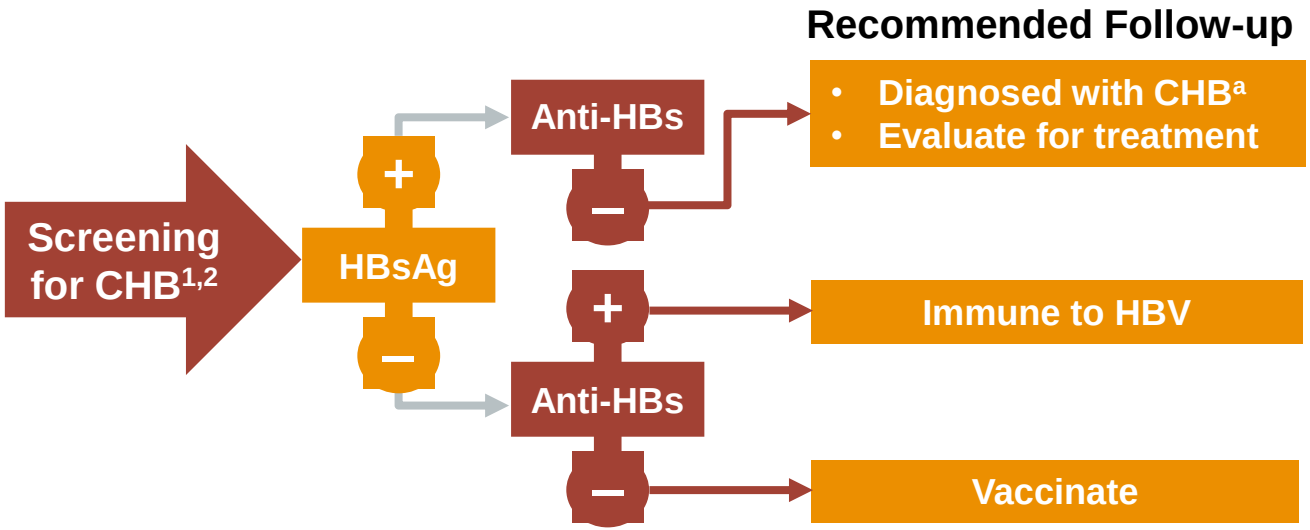
The USPSTF recommends screening for HBV infection in persons at high risk for infection[§]

- Persons born in countries and regions with a high prevalence of HBV infection (≥2%)
- U.S.-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection (≥8%), such as sub-Saharan Africa and central and Southeast Asia
- HIV-positive persons
- Injection drug users
- Men who have sex with men
- Household contacts or sexual partners of persons with HBV infection

§ Grade B recommendation

LeFevre ML, et al. *Ann Intern Med*. 2014; 27 May 2014

HBV Screening: Identifying Persons With CHB



[a]If HBsAg remains positive for 6 months.
CHB=chronic hepatitis B.

CDC. *Morb Mortal Wkly Rep*. 2008;57(No. RR-8):1-16. 2. Keeffe EB, et al. *Clin Gastroenterol Hepatol.* 2008;6:1315-1341.

Diagnostic Interpretation of HBV Serologic Markers

Serologic Marker				Interpretation
HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	
–	–	–	–	Never infected and no evidence of immunization
+	+	–	–	Chronic infection
+	+	+	–	Acute Infection
–	+	–	+	Recovered from past infection and immune
–	–	–	+	Immune after immunization
–	+	–	–	Past exposure with undetectable anti-HBs titers, previous chronic infection with loss of HBsAg or a false positive test

Adapted from Weinbaum CM et al. *MMWR.* 2008;57(RR08):1-20.

Historical Clinical Profiles of Chronic HBV Infection

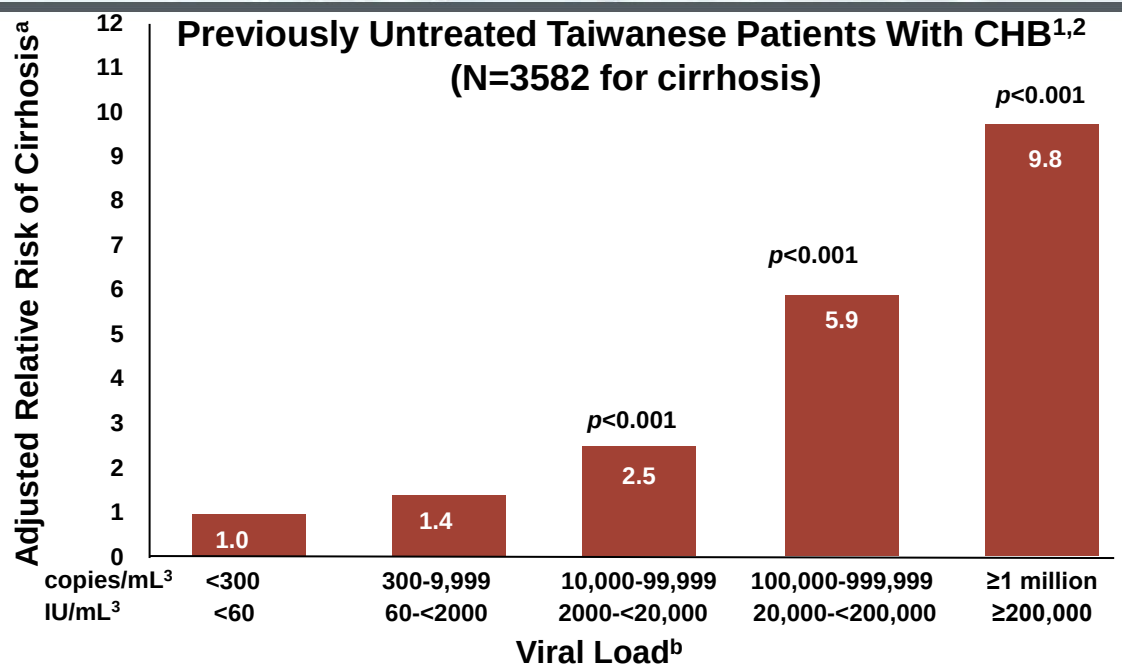
	Immune Tolerant	HBeAg (+) CHB	Inactive HBsAg Carrier	HBeAg (-) CHB (Precore Mutant)
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal	↑	Normal	↑
HBV DNA	>20,000 IU/mL (>10^5 copies/mL)	>20,000 IU/mL (>10^5 copies/mL)	<200 IU/mL (<10^3 copies/mL)	>2,000 IU/mL (>10^{4*} copies/mL)
Histology	Normal/Mild	Active	Normal	Active

HBeAg, hepatitis B e antigen.

*Expert opinions vary as to this value.

Adapted from Hoofnagle JH et al. *Hepatology.* 2007;45:1056-1075.

Higher HBV DNA Levels Associated With Increased Risk of Cirrhosis Over Time (REVEAL Study)



[a]Adjusted for age, sex, cigarette smoking, and alcohol consumption; risk of cirrhosis is independent of HBeAg status and ALT level.
[b]1 IU/mL is equivalent to ~5-6 copies/mL[3]

Iloeje UH, et al. *Gastroenterology*. 2006;130:678-686. 2. Chen CJ, et al. *JAMA*. 2006;295:65-73. 3. Keeffe EB, et al. *Clin Gastroenterol Hepatol*. 2008;6:1315-1341.

Goal of CHB Therapy

Aim of treatment of chronic hepatitis B:
Achieve sustained suppression of HBV replication
(associated with normalization of ALT, loss of HBeAg, and improvement in liver histology)

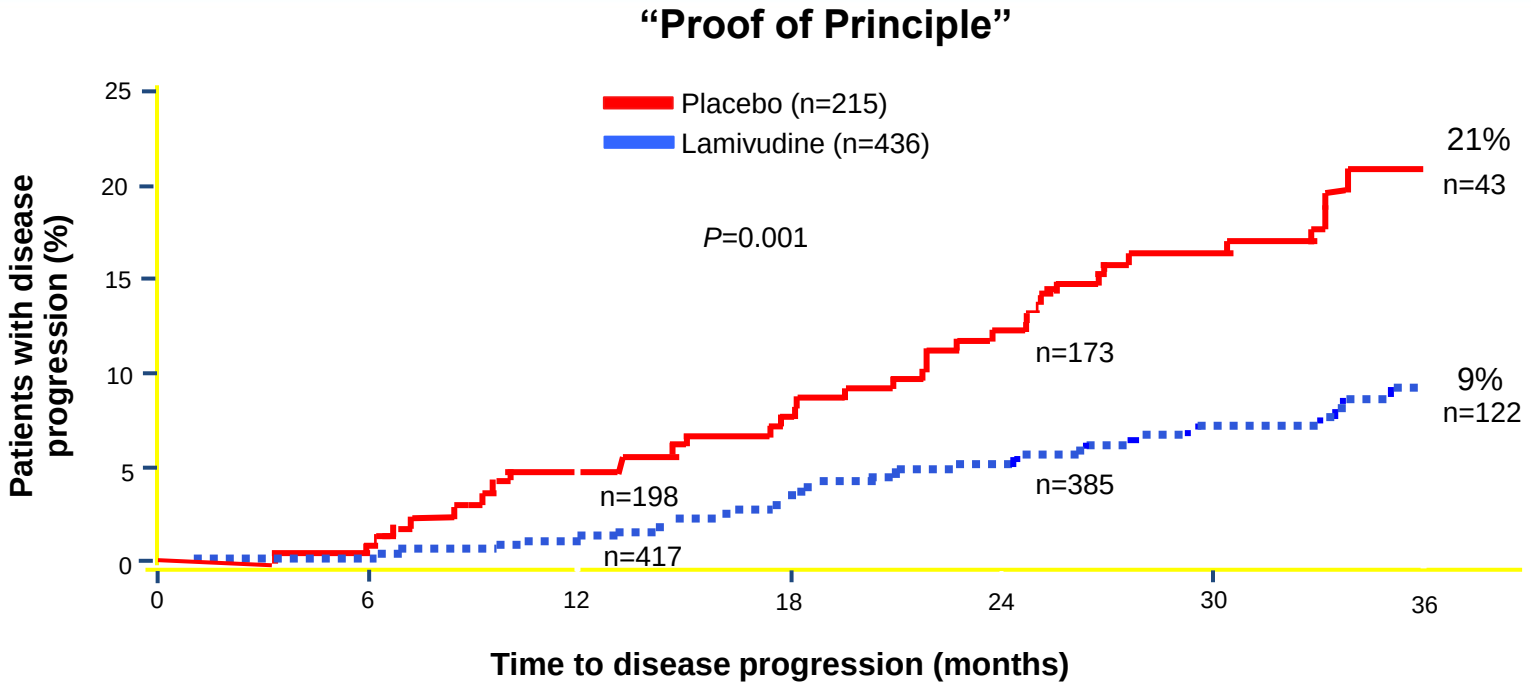
Goals of antiviral treatment:
Decrease CHB-related morbidity and mortality

Terrault NA, Bzowej NH, Chang KM, et al. Hepatology. 2016;63(1):261-83.

Chronic Hepatitis B: Goals of Treatment

- **Long-term outcomes:**
  - Sustained suppression of HBV replication
  - Prevention of end stage liver disease, HCC, transplant, and death
  - Similar goals for both HBeAg+ and HBeAg-
- **Therapeutic goals:**
  - Undetectable serum HBV DNA
    - Cannot eradicate HBV ccc DNA
  - Normalization of serum ALT level
  - Clearance of HBeAg
  - Loss of HBsAg
  - Improvement in liver histology

Antiviral Therapy Delays Overall Disease Progression in Chronic Hepatitis B



Liaw Y-F et al. *N Engl J Med.* 2004;351:1521-1531.

Who Should Be Treated?

Three Criteria Used: ALT, HBVDNA, Fibrosis

Key Test	Criterion	Comments
ALT	>2xULN (M>70, F>50 ULN males 35 ULN females 25	If ALT>ULN, increase monitoring and consider other factors
HBVDNA	>20,000 IU/mL if HBeAg pos >2000 IU/mL if HBeAg neg	Not absolutes Sufficient HBVDNA to cause elevated ALT (liver injury)
Other Factors	Presence of significant fibrosis Family history of HCC Age >40	All patients with cirrhosis should be treated Older age, Positive family history reasons to consider treatment even if ALT and HBVDNA thresholds not met

AASLD Guidance, Hepatology 2018

Diagnostic Criteria and Definitions for CHB

AASLD HBV 2018 Guidance

	ALT	HBV DNA	HBeAg	Liver Histology
Immune-tolerant CHB	Normal or minimally elevated ALT and/or AST	Elevated, typically > 1 million IU/mL	Positive	No fibrosis and minimal inflammation
Immune-Active CHB	Intermittently or persistently elevated ALT and/or AST	Elevated ≥ 20,000 IU/mL	Positive	Moderate-to-severe necroinflammation and with or without fibrosis
		Elevated ≥2,000 IU/mL	Negative	
Inactive CHB phase	Persistently normal ALT and/or AST levels	<2,000 IU/mL	Negative	Absence of significant necroinflammation and variable levels of fibrosis

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

AASLD HBV Guidance: ALT Upper Limits of Normal

- 2016 ULN for ALT: 30 U/L for males and 19 U/L for females[1]
- 2018 ULN for ALT: **35 U/L for males and 25 U/L for females**[2]
  - Therefore, ALT levels warranting HBV therapy consideration (≥ 2x ULN) are 70 U/L for males and 50 U/L for females
- Now ULN more consistent with ACG recommendations of 33 U/L for males and 25 U/L for females[3]

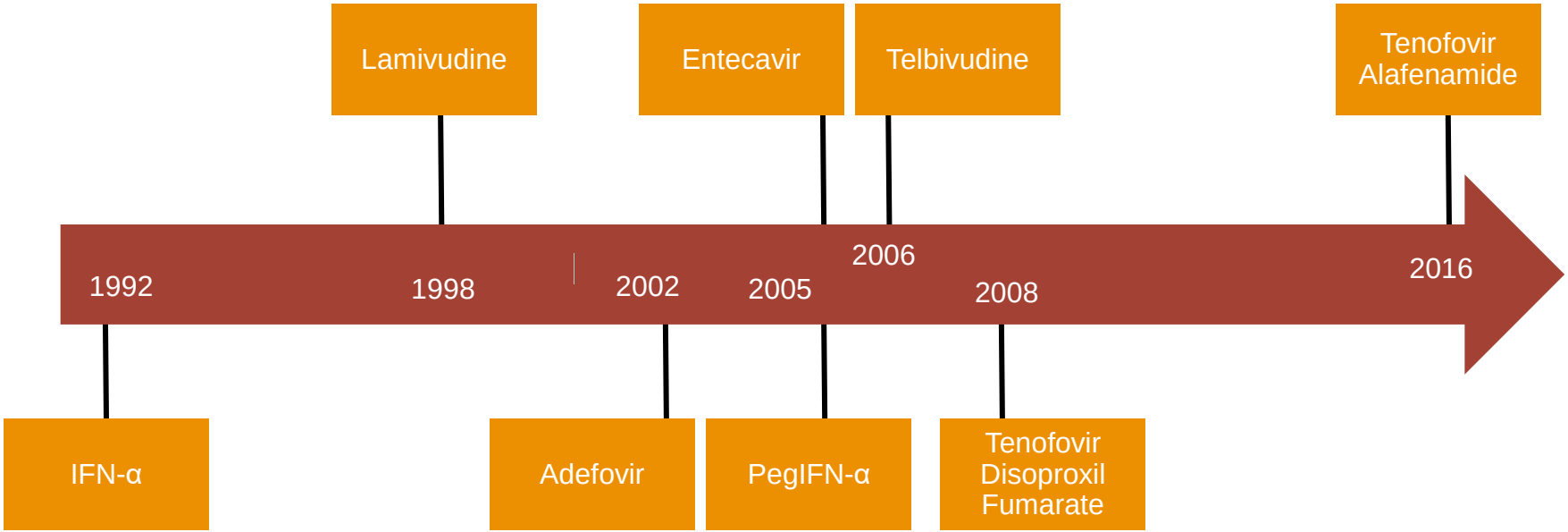
1. Terrault NA, et al. Hepatology. 2016;63:261-283. 2. Terrault NA, et al. Hepatology. 2018;67:1560-1599. 3. Kwo PY, et al. Am J Gastroenterol. 2017;112:18-35.

Patients With Normal ALT May Have Significant Liver Disease

- 37% of patients with chronic HBV and persistently normal alanine aminotransferase (ALT) had significant fibrosis (stage 2) or inflammation (grade 2)[1]
- In a large cohort (140,000 Koreans) an ALT >20 was associated with increased risk of death from chronic liver disease (CLD) over 8 years follow-up[2]
- Patients with ALT 0.5-1.0 upper limit of normal (ULN) had increased risk of adverse outcomes from CLD[3]

1. Lai M et al. *J Hepatol.* 2007;47:760-767.2. Kim HC et al. *BMJ.* 2004;328:983-987.3. Yuen M-F et al. *Gut.* 2005;54:1610-1614.

The Evolution of HBV Therapy



Treatment of Immune-Active CHB

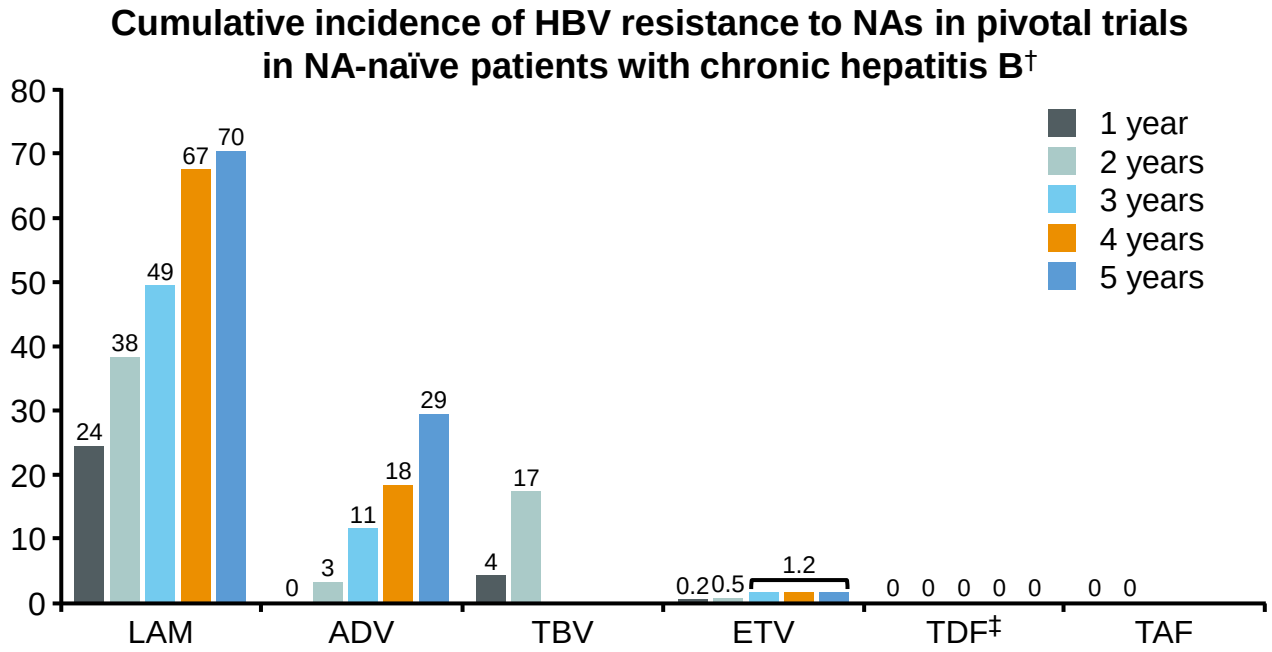
Definitions	• Defined by
	  • ALT > 2 x ULN* or significant histological disease
	  plus
	  • HBV DNA > 2,000 IU/mL (HBeAg negative) or
	  HBV DNA > 20,000 IU/mL (HBeAg positive)

Recommendation	• Antiviral therapy for adults with immune-active CHB • Therapy is also recommended for persons with immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level
Treatment	• TAF, TDF, ETV, or Peg-IFN are preferred • Consider TAF or ETV in patients with or at risk for renal dysfunction or bone disease • TAF is not recommended in patients with CrCl <15 mL/min or those on dialysis

*ALT ULN: Males 35 U/L, Females 25 U/L
CrCl, Creatinine clearance

Terrault NB et al. Hepatology 2018; Published online February 5, 2018: doi:10.1002/hep.29800.

Prevention of Resistance Should Rely on the Use of First-line NAs With a High Barrier to Resistance*



*Evidence level I, grade of recommendation 1; †Collation of currently available data – not from head-to-head studies;
‡No evidence of resistance has been shown after 8 years of TDF treatment.
EASL CPG HBV. J Hepatol 2017;67:370–98

Guidelines: What to Start as Initial HBV Therapy

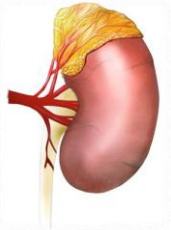
Treatment	Preferred[1,2]	Notes
Entecavir	Yes	High potency, high genetic barrier to resistance
TAF	Yes	High potency, high genetic barrier to resistance
TDF†	Yes	High potency, high genetic barrier to resistance
PegIFN	Should only be considered as initial therapy for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)	Less safe in pts with cirrhosis, contraindicated in pts with decompensated cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

†Pts receiving TDF: monitor renal function, consider monitoring BMD in pts at risk.[1]

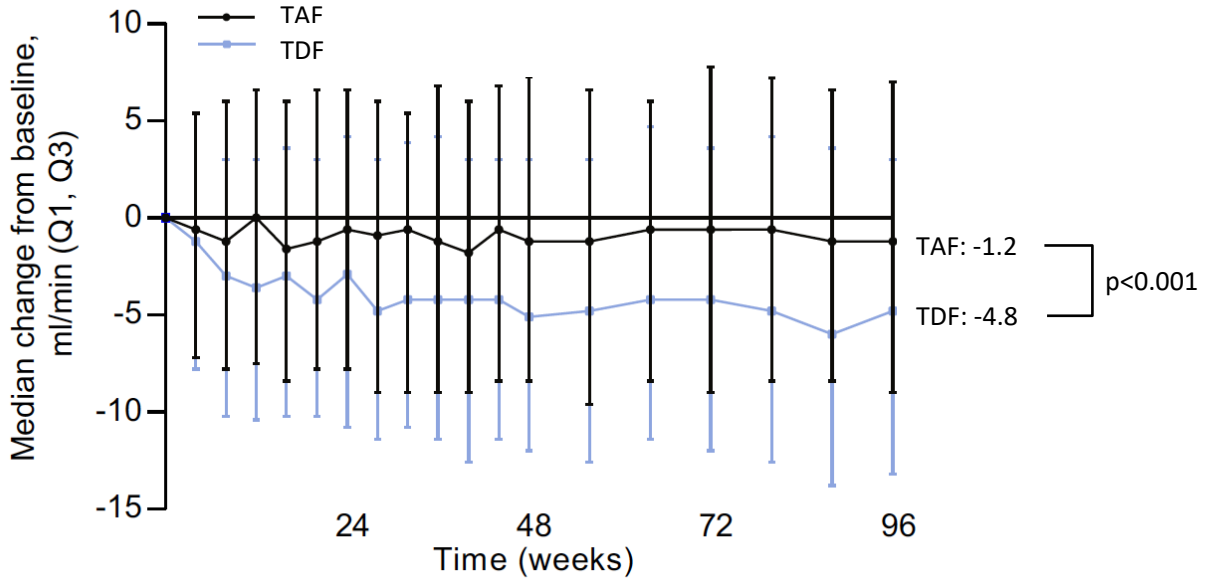
ETV, TDF, TAF have very favorable safety and resistance profiles[2]

1. Terrault NA, et al. Hepatology. 2016;63:261-283. 2. EASL. J Hepatol. 2017;67:370-398.

TAF vs. TDF for HBV: Change in eGFR

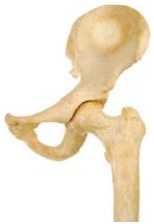


Median change from baseline in eGFR over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)



Agarwal K, et al. J Hepatol 2018;68:672–81

TAF vs. TDF for HBV: Change in BMD



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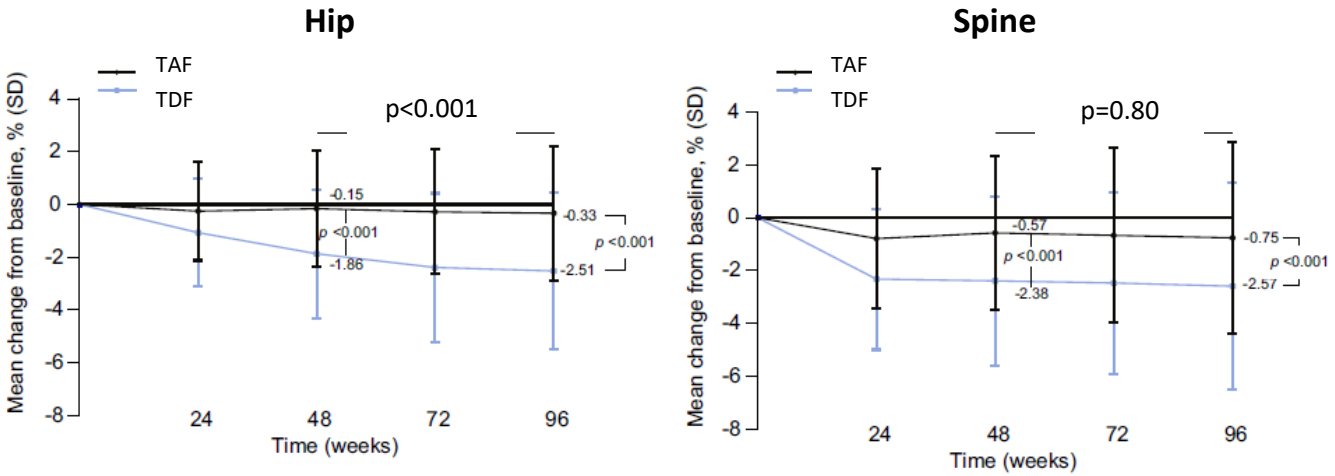
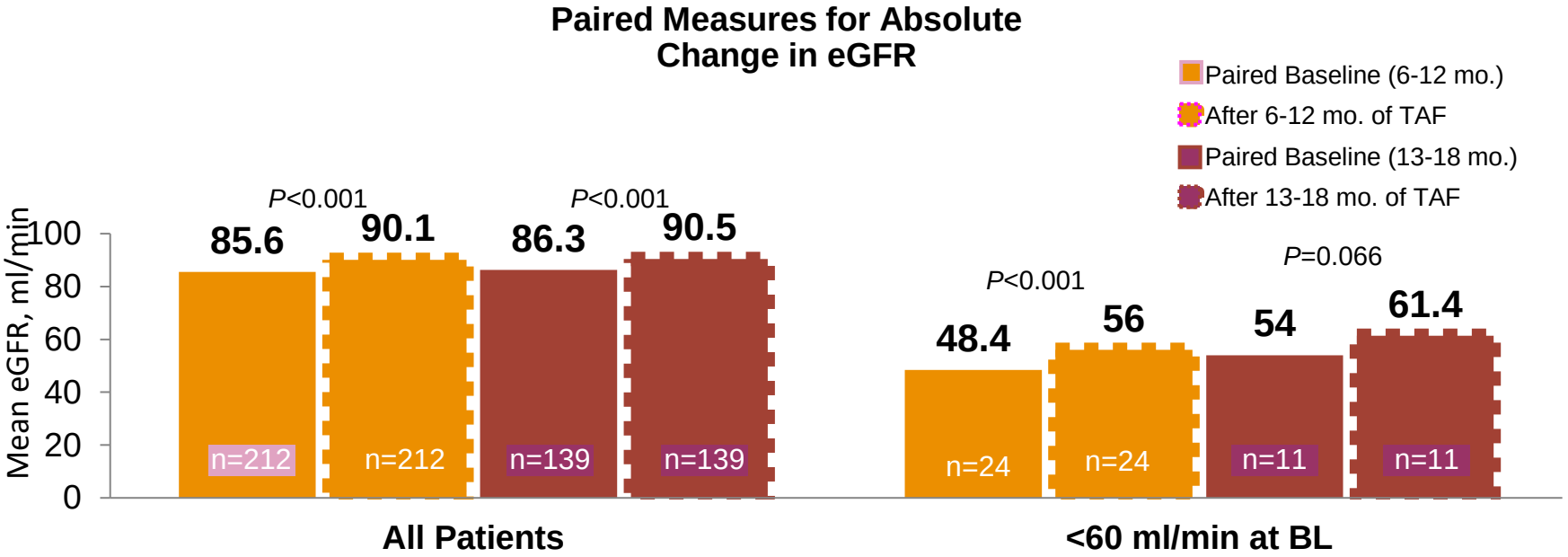


Agarwal K, et al. J Hepatol 2018;68:672–81

Real-World Experience of TAF for HBV in US Clinical Practice



TAF experience in the real world demonstrates improved renal function

eGFR calculated by CKD-EPI

Curry, EASL, 2019, FRI-167

Canadian Hepatitis B Network (CanHepB)

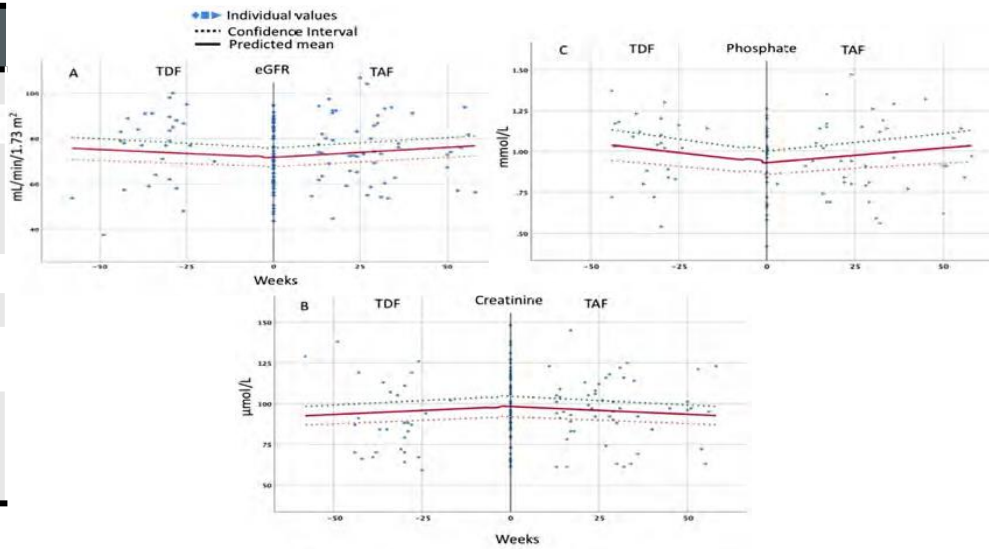
Real-World Experience of TAF pts with Mild Renal Impairment

Multicentre effectiveness and renal safety study of TAF in Canada

Baseline Demographics

	TAF n=170
Mean age, years	52 (12)
Male, n (%)	122 (74)
Race, %	
Asian	66
Caucasian	16
Black	10
HBV DNA <20 IU/mL, %	82
HBeAg positive, n (%)	51 (38)
Mean eGFR, mL/min/1.73 m² (SD)	82.7 (21.4)
Prior therapy, n (%)	
TDF	107 (63)
Another NUC	43 (25)
NUC naïve	20 (12)

Change in Renal Function



In CHB patients previously on TDF with mild renal impairment, switching to TAF led to a significantly improved kidney function

Farag, EASL, 2019, FRI-170

Who Do We Not Treat (Monitor)

Immune Tolerant

- Lack of effective therapies
- Low rate of HBeAg loss
- No HBsAg loss
- ? Early Rx alters HCC risk
- **Important to identify fibrosis if > 30 yo**

HBeAg Negative “Grey Zone”

- If high ALT and low HBVDNA consider other causes of ALT elevation
- Consider Rx if significant fibrosis/inflammation
- Natural history suggest majority evolve to inactive CHB over time
- **Serial ALT/HBVDNA to monitor and assess for fibrosis as indication for treatment**

HBV Treatment Paradigm is Changing

International Guidelines for Stopping NA Therapy

Patient Hepatitis Status	APASL 2016	EASL 2017	AASLD 2018
HBeAg+ without cirrhosis	12 mo NA therapy after HBeAg seroconversion (preferably 3 years) Or HBs Ag loss	HBsAg loss +/- seroconversion 12 mo NA therapy after HBeAg serconversion Plus ND HBVDNA	Minimum 12 mo NA therapy after HBeAg seroconversion Plus ND HBV Plus Normal ALT Or until HBsAg loss
HBeAg – without cirrhosis	HBsAg loss or serconversion ND HBVDNA for at least 2 years on 3 separate occasions each 6 mo apart	HBs Ag loss +/- serconversion Consider after > 3 years virological suppression after NA therapy	Long term treatment with NA until HBsAg loss
Liver Cirrhosis	Indefinite antiviral therapy	Indefinite antiviral therapy	Indefinite antiviral therapy

Hepatol Int 2016;10:1-98
J Hepatol 2017;67:370-98
Hepatology 2018;67(4):1560-99

Stopping NA Therapy in HBeAg Positive CHB

No Cirrhosis	Cirrhosis
• Until HBeAg seroconversion (plus undetectable HBVDNA and normal ALT) plus > 1 year consolidation • Alternative: until HBsAg loss	• Indefinitely or until HBsAg loss

AASLD HBV Treatment Guidelines 2018

Stopping NA Therapy in HBeAg Positive Patients

148 HBeAg+ patients treated for 142.6 +/- 59.7 weeks

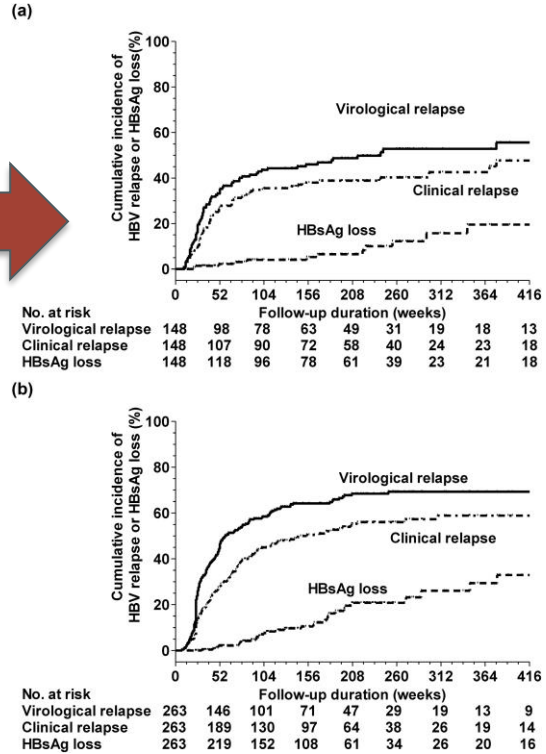
Met APASL criteria to stop

Cumulative rate at 8 years

Virologic relapse 56%

Clinical relapse 48%

HBsAg loss 20%



Clinical Microbiology and Infection 2018 24997-1003DOI: (10.1016/j.cmi.2017.12.013)

Predictors of Sustained Response to NA Withdrawal in HBeAg Positive Patients

- Age at HBeAg Seroconversion
  - Younger age (≤ 37-40)
- Duration of consolidation prior to withdrawal
  - Longer consolidation (≥11-15 months)
- HBVDNA during treatment (≥20IU/mL, <20 IU/mL, ND)
- ? Type of NA (Tenofovir vs Entecavir)
  - Need for retreatment (clinical relapse) may be higher in TDF treated patients upon withdrawal

Pan X, PLOS one 2013;8:e68568
Song MJ, WJ Gastro 2012;18:6277-83
Kuo MT, APT 2019;49:218-28
Fan R, CGH 2020;18:719-27

NA Withdrawal in HBeAg Positive Patients: Why Try?

- HBsAg loss occurs in 20% with up to 8 yr followup
- HBsAg ≤ 300 IU/mL at treatment end associated with much higher rates
- Primary benefit of NA withdrawal is finite therapy
  - HBeAg seroconversion plus consolidation for ≥ 1 year is associated with sustained response in 50%

Stopping NA Therapy in HBeAg Negative CHB

AASLD

- No Cirrhosis: Treat indefinitely (or until sAg loss)
- **Consider only if strong rationale to stop (patient preference, cost, toxicity)**
- Treat until HBsAg loss following sAb seroconversion or ≥12 mo of consolidation
- Cirrhosis: Indefinite

EASL

- Treat indefinitely (or until sAg loss)
- **Treatment for at least 4 years with undetectable HBVDNA for at least 18 months**
- Cirrhosis: indefinite

APASL

- Treat until HBsAg loss and either HBsAB seroconversion or ≥ 12 months consolidation
- **Treat for at least 2 years with undetectable HBVDNA for at least 18 months**
- Compensated cirrhosis: May consider with close monitoring

AASLD HBV Treatment Guidelines. Hepatology 2018; 67(4): 1560-99
EASL 2017 Clinical Practice Guidelines HBV. J Hep 2017;67(2): 370-98
APASL HBV Guidelines. Hepatol Int 2016;10:1-98

NA Withdrawal in HBeAg Negative Patients

Prospective, randomized

Endpoints

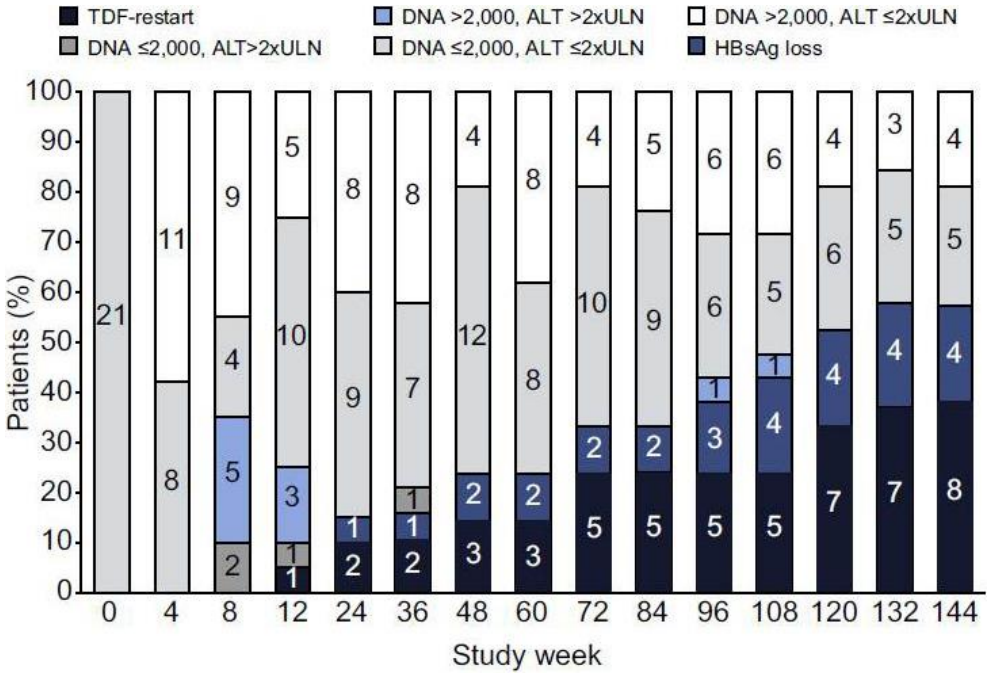
- Rate of HBsAg loss
- HBVDNA <2000 IU/mL

Tenofovir

≥3.5 years HBVDNA ND

Randomized 21 vs 21 patients

Only in those patients with NA withdrawal was sAg loss seen



Berg T et al. J Hepatol 2017;67:918-24

Predictors of Post-NA Treatment Response in HBeAg Negative Patients

- Younger age
- Low ALT at baseline
- Low HBVDNA at baseline
- Duration of consolidation treatment
- ? Level of HBsAg
- Novel markers (HBcrAg, HBVRNA)

Hadziyannis SJ, et al. Gastroenterology 2012;143:629-36
Honer Zu Siederdissen C, et al. J Infect Dis 2016;214:1492-97
Cai W, et al. J Clin Virol 2010;48:22-26
Liu F, et al. J Gastroenterol Hepatol 2011;26:456-60
Chan HL, et al. Antivir Ther 2011;16:1249-57
Ha M, et al. Adv Virol 2012;157:285-290
Seto WK, et al. Gut 2014;64:667-72
Matsumoto A, et al. Hepatol Res 2015;45:1195-1202
JSH Guidelines for Management of HBV Infection. Hepatol Res 2014;44:S1-S58

Heterogeneity in NA Withdrawal Results in HBeAg Negative Patients

- HBsAg loss ranges 0-55% at 3-5 years
- 50-75% patients may remain off treatment
- May be due to differences in
  - Genotype
  - Age, sex
  - Time/duration of NA therapy
  - Criteria for restarting NA (clinical vs virologic)
  - Followup period

Factors Relating to Clinical Relapse or Retreatment in HBeAg Negative Patients

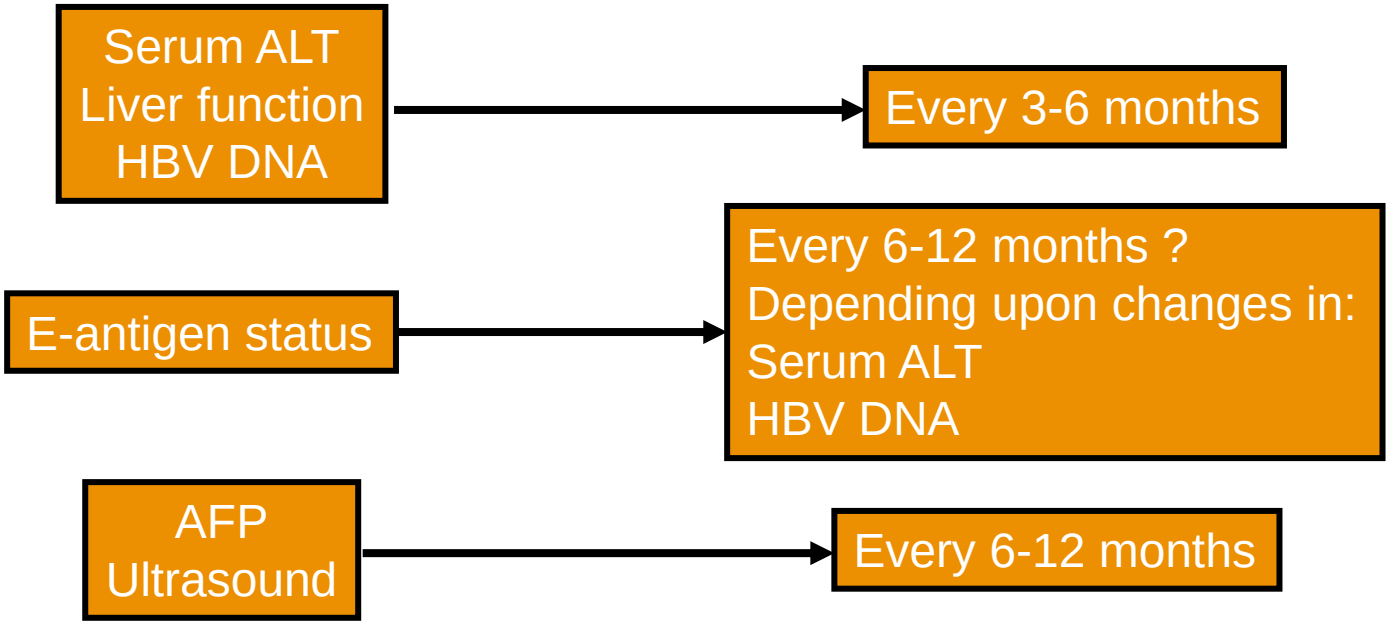
- Type of NA?
  - Earlier relapse with TDF but rates parallel later in followup
- HBsAg quantitation (11 studies Asian patients)
  - Relapse 15-29% if HBsAg $\leq$ 100 IU/mL at EOT
  - Relapse 48-64% if HBsAg > 100 IU/mL at EOT
- Duration of consolidation

Siederdissen HZ. J Infect Dis 2018;218(9): 1480-84
Liu J. Hepatology 2019;70(3): 1045-55
Jeng W. CGH 2016;14:1813-20

NA Withdrawal in HBeAg Negative Patients: Why Try?

- More strongly supported by APASL and EASL
- Functional Cure in up to 20% of patients at 3-5 years of followup
  - Flares important but unable to predict beneficial vs harmful flares with accuracy
- Inactive Carrier status achieved in 50-75% of patients
  - Allows for finite treatment duration
  - Low HBsAg levels, longer duration of treatment and longer consolidation predicts HBsAg loss

Hepatitis B Followup Recommendations



Lok AS, McMahon BJ.
Hepatology 2009;50:1-36.

Key Conclusions

- Treatment guidelines recommend initiation of HBV therapy in pts with elevated HBV DNA and ALT and in pts with cirrhosis
- Preferred initial therapies are ETV, TDF, and TAF due to favorable safety and resistance profiles
  - PegIFN may be considered in selected pts with mild/moderate chronic HBV infection
- NA choice should be informed by pt factors including age, comorbidities, pregnancy planning, LAM resistance history
- 2021 shifting focus to finite duration and achieving HBsAg loss
  - NA withdrawal strategy
  - Limited to non-cirrhotics
- Beyond 2021 additional strategies/drugs needed to achieve functional cure