Update on HBV Treatment

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Intercept	Speaker
Merck	Grant/research support

Outline

- Indications for HBV Therapy
- Updates on Oral Antiviral Therapies
- Treatment Endpoints
- Special Populations with HBV Infection

Common Candidates for the Antiviral treatment

- AASLD (2015)
- EASL (2017)
- AAMR (Asian American Management Recommendations for Hepatitis B. In press, 2018)

HBV Treatment Guidelines from AASLD (2015) and EASL (2017)

Guideline	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Disease	HBV DNA, IU/mL	ALT	Liver Disease
AASLD[1]	> 20,000	≥ 2 x ULN	N/A	≥ 2000	≥ 2 x ULN	N/A
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis
EASL[2]	> 2000	> ULN*	Moderate inflammation or fibrosis*	> 2000	> ULN*	Moderate inflammation or fibrosis*
	N/A	N/A	Cirrhosis	N/A	N/A	Cirrhosis

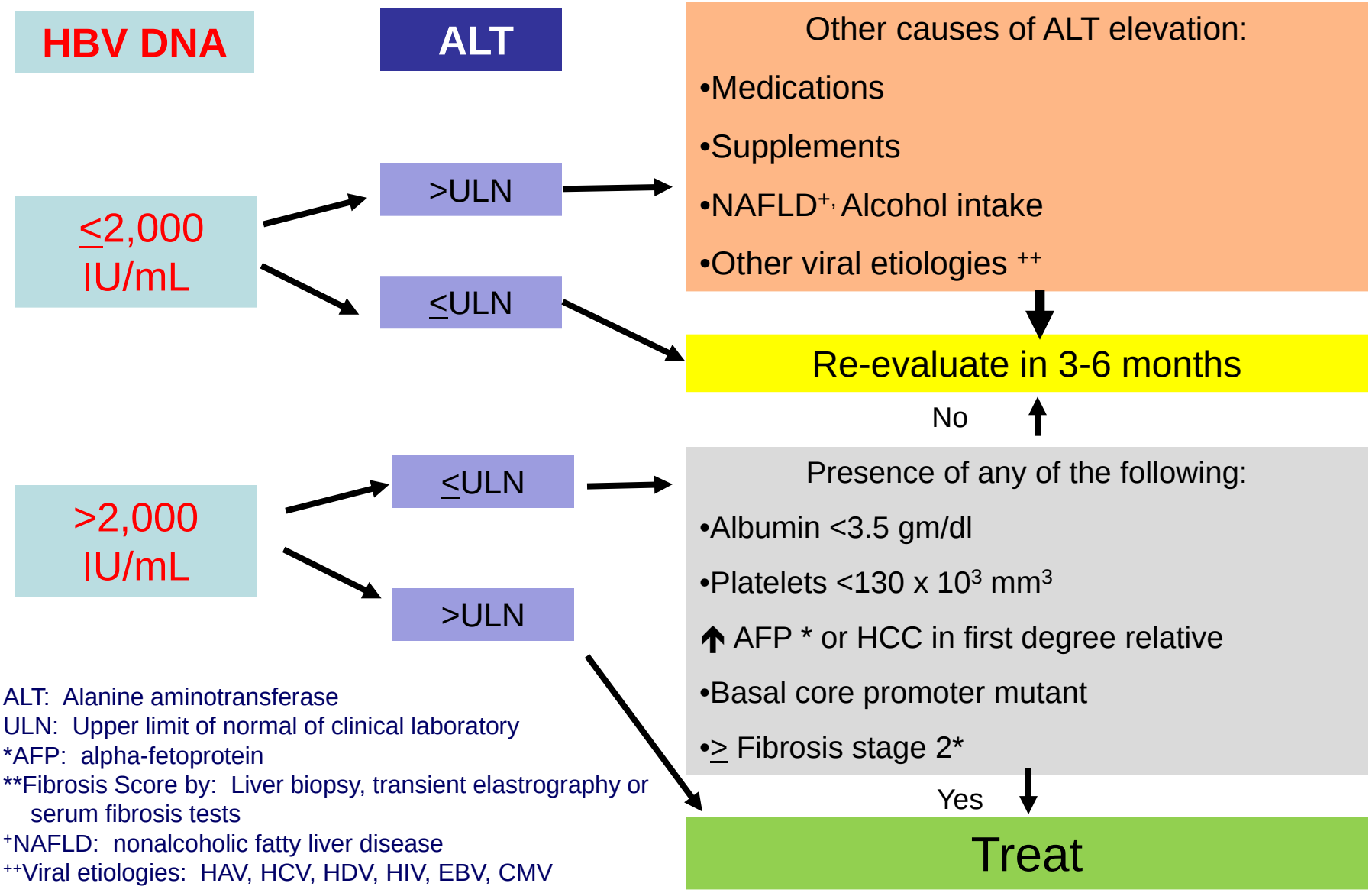
Agents Preferred:[1,2]

Peginterferon, entecavir, tenofovir disoproxil fumarate, tenofovir alafenamide,†

*In pts with HBV DNA > 2000 IU/mL, treatment indicated if ALT > ULN and/or at least moderate fibrosis.

†AASLD guidelines not yet updated since approval of tenofovir alafenamide.

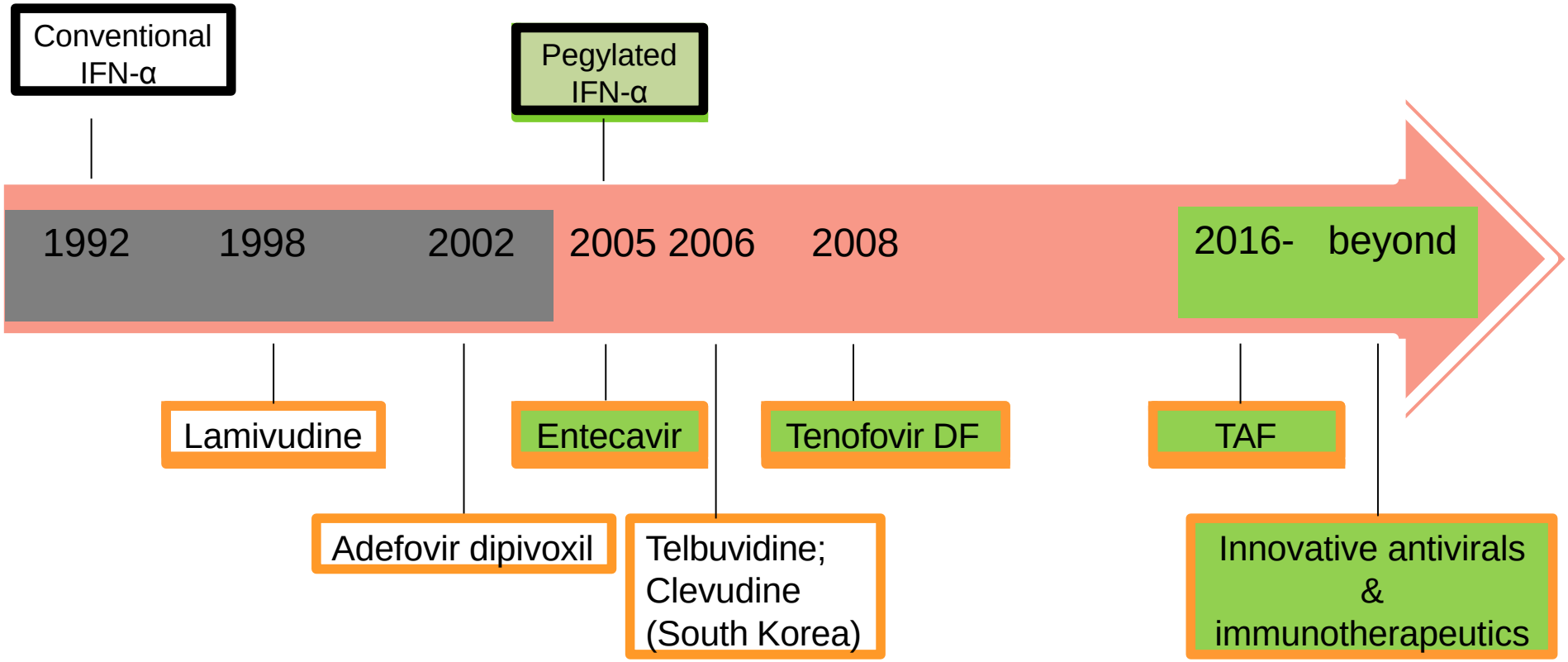
Asian American Hepatitis B Management Recommendations (2018)



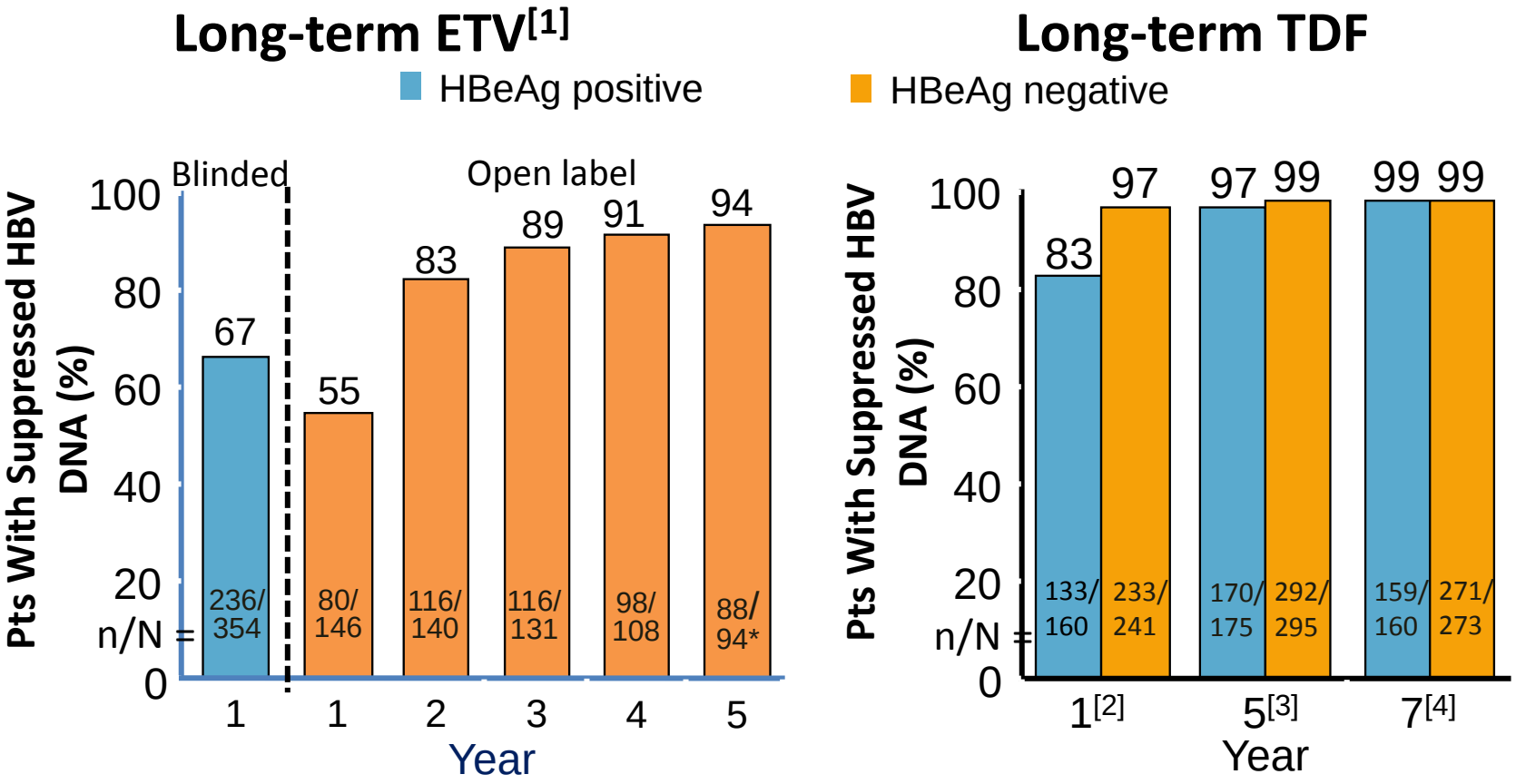
ALT: Alanine aminotransferase
ULN: Upper limit of normal of clinical laboratory
*AFP: alpha-fetoprotein
**Fibrosis Score by: Liver biopsy, transient elastrography or serum fibrosis tests
+NAFLD: nonalcoholic fatty liver disease
++Viral etiologies: HAV, HCV, HDV, HIV, EBV, CMV

Updates on Antiviral Therapies

Registered Treatments of CHB



Potent HBV DNA Suppression With Nucleos(t)ide Therapy



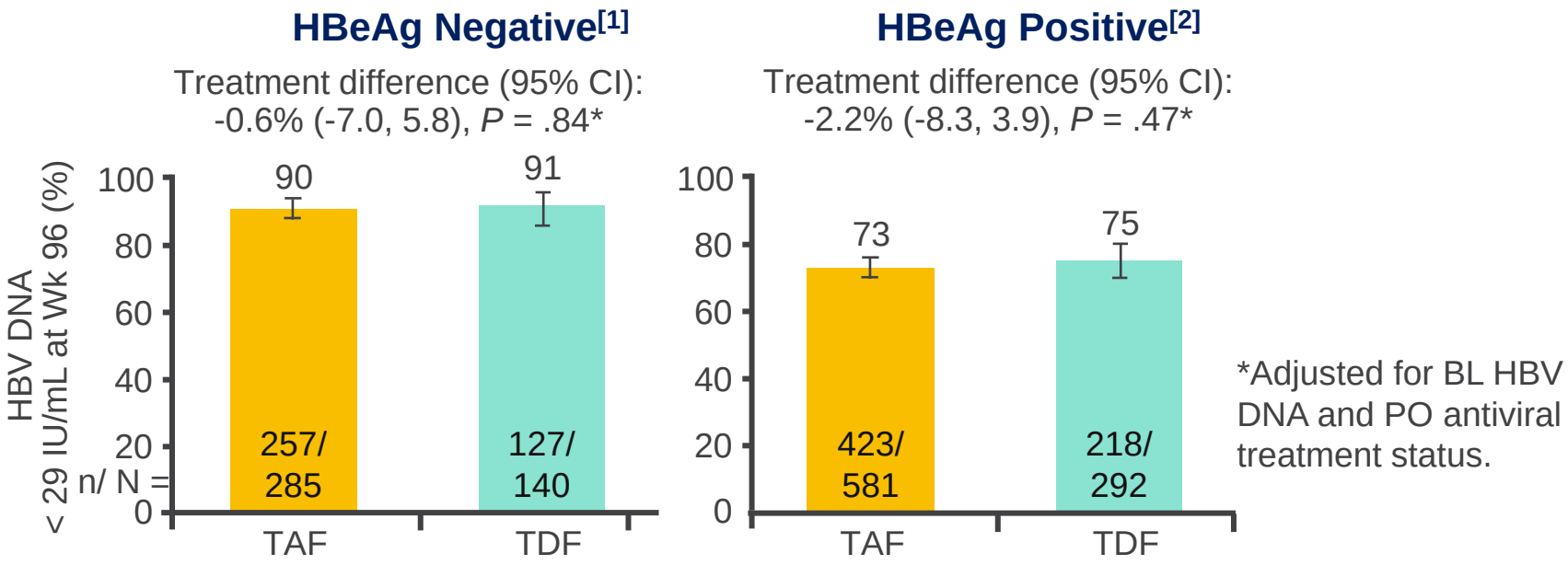
*5 additional pts who remained on treatment at the Yr. 5 visit had missing HBV DNA tests.

Long-term therapy with potent nucleos(t)ides leads to suppression in almost all pts

1. Chang TT, et al. Hepatology. 2010;51:422-430. 2. Marcellin P, et al. N Engl J Med 2008; 359:2442-2455. 3. Marcellin P, et al. Lancet. 2013;381:468-75. 4. Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.

TAF vs TDF in Chronic HBV Infection: Week 96 Efficacy

- **HBV DNA: TAF noninferior to TDF at Wks 48 and 96 in both studies; no resistance found in any arm**



- **ALT: significantly greater rate of ALT normalization at Wk 96 with TAF vs TDF**
- **HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 with TDF or TAF[2]**
- **HBeAg-negative pts: minimal decline in HBsAg with TDF or TAF for (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)[1]**

1. Brunetto M, et al. EASL 2017. Abstract PS-042. 2. Agarwal K, et al. EASL 2017. Abstract FRI-153.

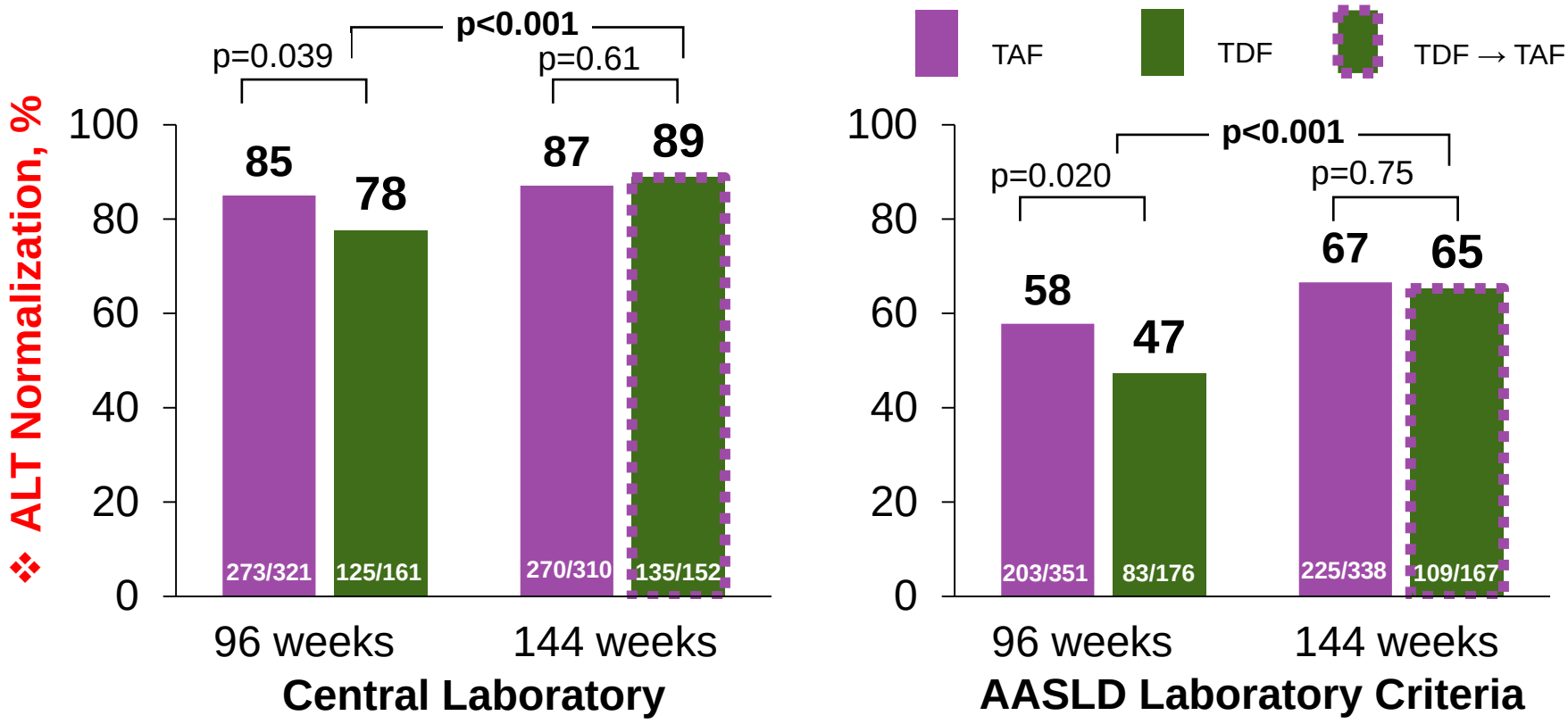
Safety of Tenofovir Alafenamide (TAF) vs TDF for treatment of CHB in Week 48

Parameters	Study 110 HBeAg Positive Patients			Study 108 HBeAg Negative Patients		
	TAF 25mg	TDF 300mg	P value	TAF 25mg	TDF 300mg	P value
	n=581	n=292		n=285	n=140	
Changes in Bone mineral density (Hip)	-0.1%	1.72%	<0.001	-0.29%	-2.16%	<0.001
Changes in Bone mineral density (Spine)	-0.42%	-2.29%	<0.001	-0.88%	-2.51%	<0.001
Changes in Serum creatinine	0.01 mg/dL	0.03 mg/dL	0.02	0.01 mg/dL	0.02 mg/dL	0.32
AEs leading to drug discontinuation, % (n)	1.0% (n=6)	1.0% (n=3)	ns	1.0% (n=3)	1.0% (n=2)	ns
The most commonly reported AEs	• Headache • URI • Nasopharyngitis • Cough		Occurred at similar rates among TAF vs TDF			

Buti M et al Lancet GH 2016, Chan HL et al Lancet GH 2016

Efficacy Endpoints in Studies 108 and 110: Switch to TAF vs TDF in CHB

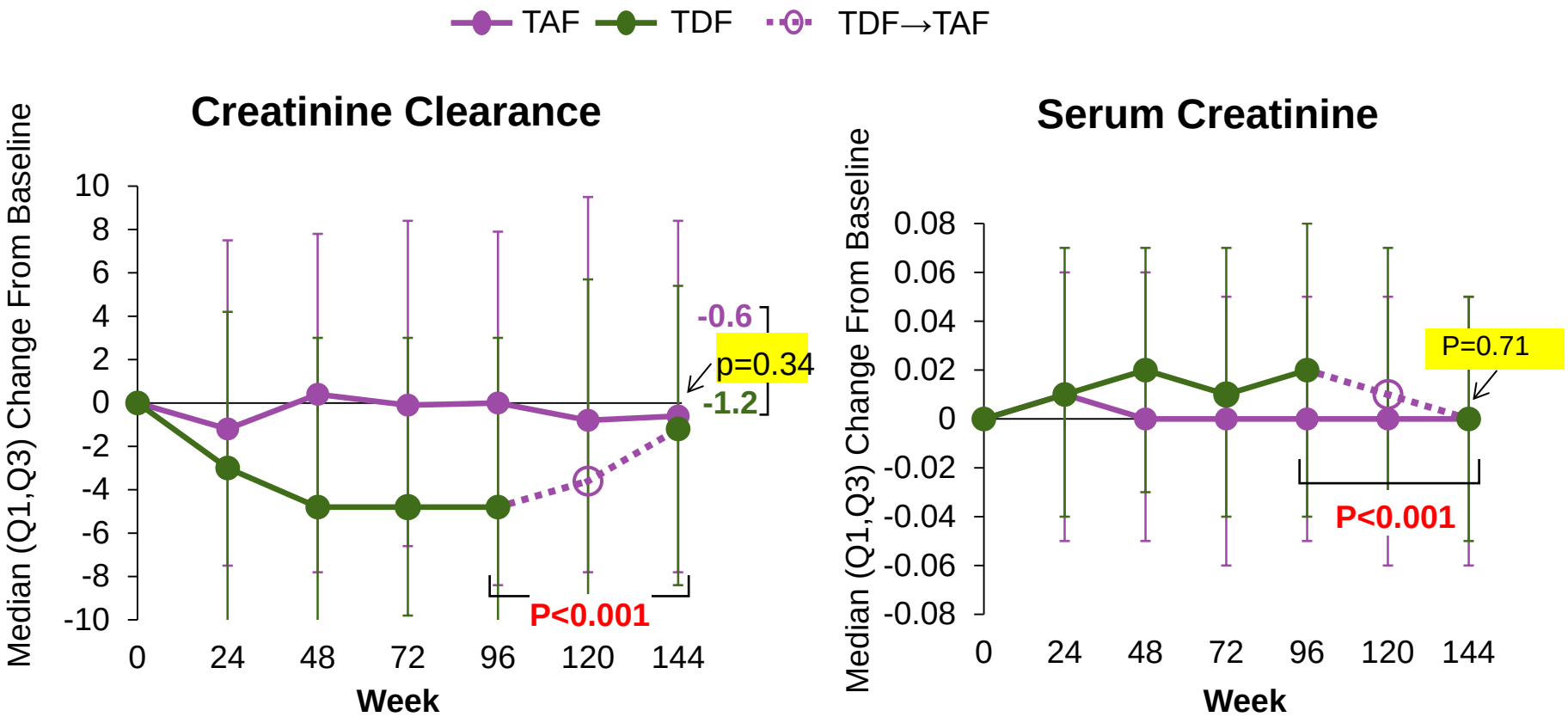
- **HBV DNA: 89% of pts achieved virologic suppression at Wk 96 (pre-switch) and Wk 144 (post switch)**



Central lab upper limit of normal (ULN): males ≤43 U/L, females ≤34 U/L (≥69 y, males ≤35 U/L, females ≤32 U/L); AASLD criteria ULN: males ≤30 U/L, females ≤19 U/L.

Pan CQ, et al. AASLD 2017-Abstract. Hepatology. 2017;(66):482A-482A .

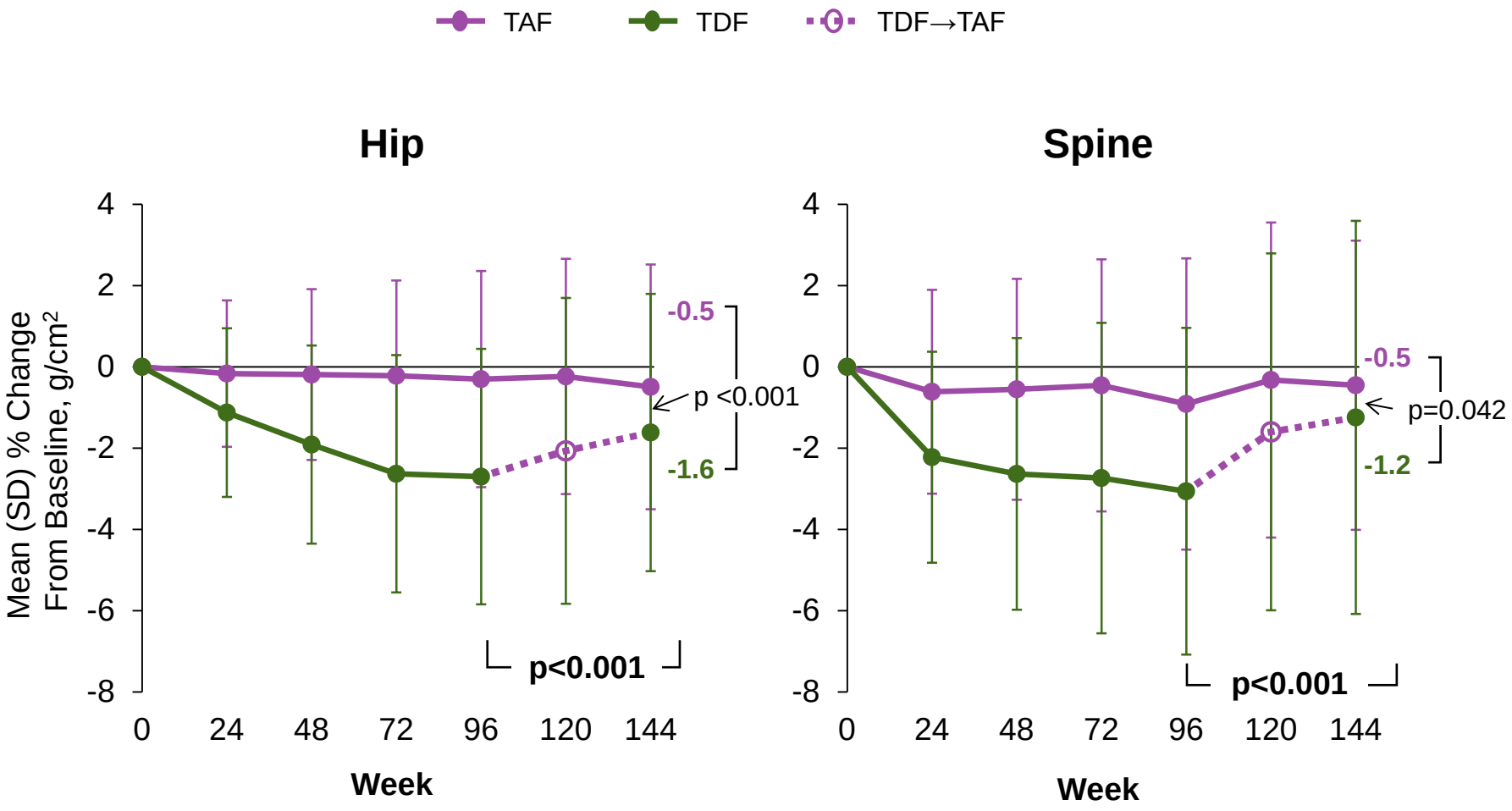
Changes from Baseline of Creatinine Clearance and Serum Creatinine After Switching from TDF to TAF



- The median change from baseline of creatinine clearance and serum creatinine significantly at 144 weeks in patients who switched from TDF to TAF at Week 96

Pan CQ, et al. AASLD 2017-Abstract. Hepatology. 2017;(66):482A-482A .

Changes in Bone Mineral Density After Switching TDF to TAF from Week 96



- A significant improvement in hip and spine BMD was observed at week 144 in patients who switched from TDF to TAF at 96 Weeks

Pan CQ, et al. AASLD 2017-Abstract. Hepatology. 2017;(66):482A-482A .

Choosing Antiviral Therapy and Managing Antiviral Resistance

- Monotherapy with ETV, TAF, TDF recommended based on high barrier to resistance
- PegIFN should only be considered as initial treatment for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)

ETV or TAF Preferred Over TDF When:

Older than 60 yrs of age

Bone disease
- Chronic steroids or other meds that affect bone
- History of fragility fracture
- Osteoporosis

Renal abnormalities
- eGFR < 60 min/mL/1.73 m^2
- Albuminuria > 30 mg or moderate proteinuria
- Low phosphate (< 2.5 mg/dL)
- Hemodialysis

TAF over ETV if previous NA exposure
No dose adjustment required for kidney disease on TAF; ETV needs dose adjustment for eGFR < 50 mL/min

Management of NA Resistance

LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	**LAM naive** ▪ Switch to ETV or TDF or TAF **LAM-R** ▪ Switch to TDF or TAF
TDF or TAF resistance???	**LAM naive** ▪ Switch to ETV **LAM-R** ▪ Add ETV
Multidrug resistance	Switch to ETV + TDF or TAF combination

EASL HBV Guideline 2017

Treatment Endpoints

Guidelines Regarding When to Stop NUCs

Status	Stopping rules	AASLD 2015	APASL 2016	EASL 2017	AAMR 2018
HBeAg+	HBeAg seroconversion	✔	✔	✔	✔
	Undetectable HBV DNA	✔	✔	✔	✔
	Persistently normal ALT	✔	✔	✔	✔
	≥12 mo consolidation	✔	✔	✔	Maybe
HBeAg-	HBsAg loss following either anti-HBs seroconversion or ≥12 mo of a post-HBsAg clearance consolidation period	✔	✔	✔	✔
	Undetectable HBV DNA ≥2 years on three separate occasions, 6 mo apart (APASL); Undetectable HBV DNA ≥3 years on non-cirrhotic patients (EASL).	✗	✔	Maybe	✗
Cirrhosis	INDEFINITELY	✔	✗	✔	✔
	May be considered with a careful off-therapy monitoring plan	✗	✔	✗	✗

AASLD: Terrault NA et al, APASL, AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.
APASL: Sarin SK et al, Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
EASL: EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2017.
AAMR: Asian American Hepatitis B Management Recommendations, accepted for publication in 2018 by Aliment Pharmacol Ther

Definitions of HBV Cure

Functional Cure- clinical resolution

Sustained off-treatment:

- No inflammation: ALT and liver biopsy
- Undetectable levels of serum HBV DNA
- HBsAg loss, or even HBsAb gain
- Possibly sustained off-treatment inactive disease without HBsAg loss (HBeAg negative, DNA undetectable, normal ALT, normal histology)

Complete cure- virological cure

- All of above plus
- Loss of cccDNA

HBsAg Loss to Approved Therapies in CHB Patients

Treatment Response	Approved therapies						
	LAM	ADV	ETV	LdT	TDF	PEG-IFN	PEG-IFN plus LAM
HBeAg-positive patients							
At week 48 or 52							
HBsAg loss, %	<1	0	2	0	3	3	3-7
During extended treatment							
HBsAg loss, % (years)	0-3 (2-3)	2 (5)	5 (2)	1.3 (2)	10 (5)	11 (3.5)	15 (3.0)
HBeAg-negative patients							
At week 48 or 52							
HBsAg loss, %	<1	0	<1	<1	0	4	3
During extended treatment							
HBsAg loss, % (years)	<1	5 (5)	NA	<1	0.3 (5)	8 (3)	8 (3)

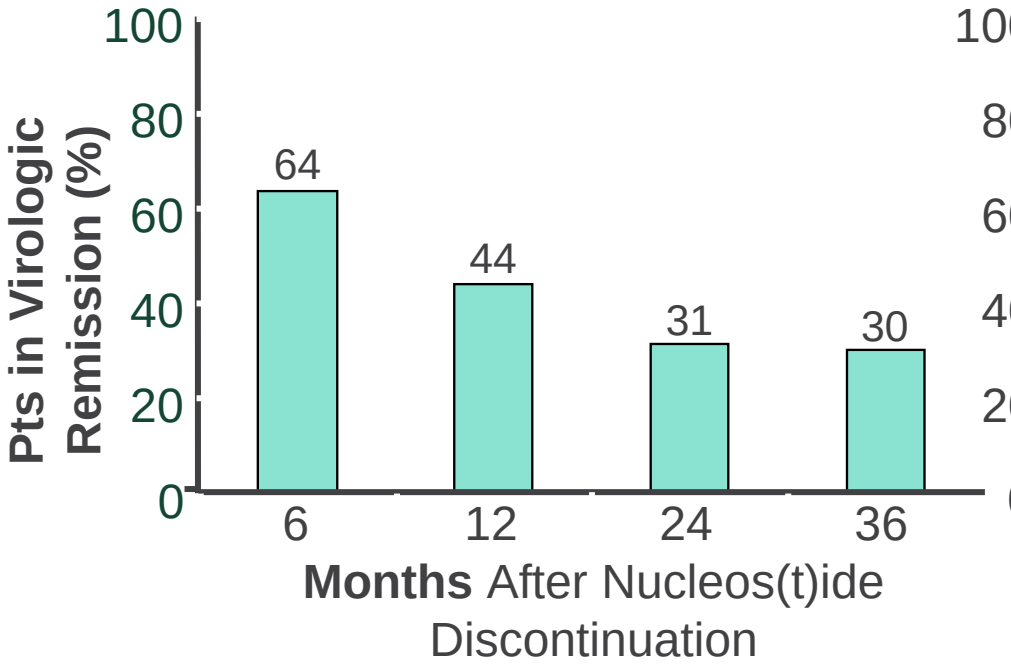
Yapali, S., et al. Clin Gastroenterol Hepatol 2014; Chang T, N Engl J. Med. 2006;354:1001-1010. Marcellin P. N Engl J Med 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129. Lai CL, et al. N Engl J Med. 2006;354:1011-1020. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Shouval D, et al. J Hepatol. 2009;50:289-295.

Is Long-term HBV Therapy Required?

- Systematic review of stopping nucleos(t)ide therapy in HBeAg-negative (n = 967) and HBeAg-positive (n = 733) pts

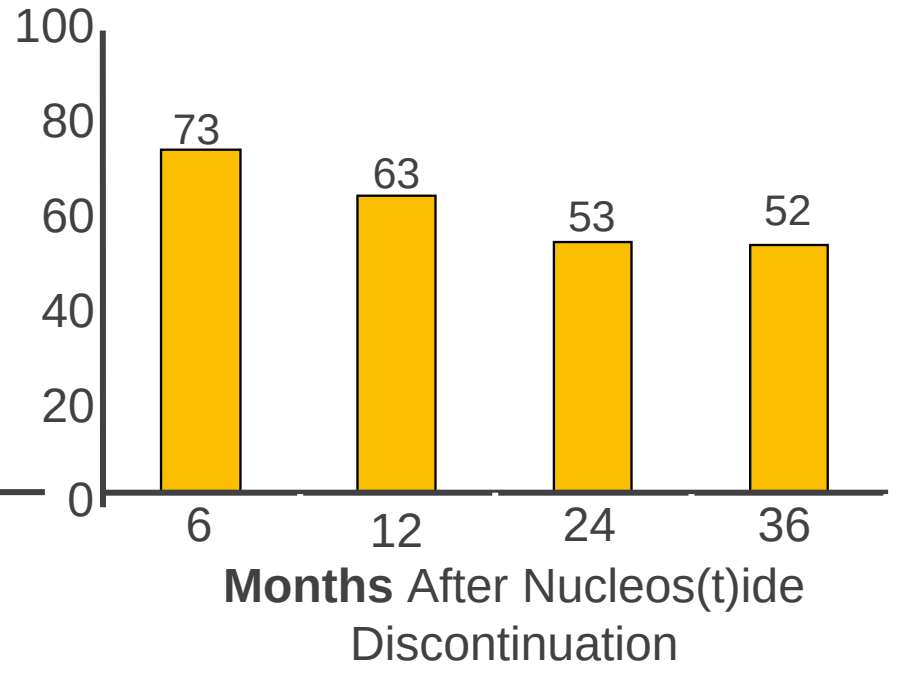
HBeAg-negative

Pooled HBsAg Loss: 1.7% (50/693)
Durable biochemical remission: 57% (394/687)



HBeAg-positive

Pooled HBsAg Loss: 1.0% (17/341)
Durable biochemical remission: 76% (268/403)



- High rate of relapse to active disease
- Low rate of HBsAg loss…long-term therapy required

Papatheodoridis GV, et al. Hepatol. 2016;63:1481-1492.

Factors Associated with Virological Remission After Discontinuation of NUCs

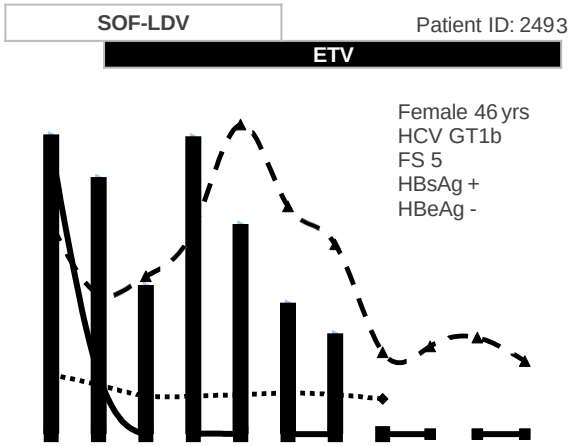
	Probability of Durable VR, % (95% CI)	Odds Ratio (95% CI)	*P*
All patients			
VR defined by HBV DNA			0.180
<200 IU/mL	34.1 (17.4-56.0)	1	
<2000 IU/mL	54.7 (41.9-66.8)	2.33 (0.83-6.57)	
<20,000 IU/mL	62.0 (38.3-80.9)	3.14 (0.84-11.71)	
Duration of on-NAs VR			0.616
<12 months	52.5 (28.1-75.8)	1	
12-24 months	48.1 (34.9-61.5)	0.84 (0.26-2.71)	
>24 months	61.1 (39.0-79.4)	1.42 (0.36-5.62)	
HBeAg-positive patients			
VR defined by HBV DNA			0.289
<200 IU/mL	42.0 (16.6-72.4)	1	
<2000 IU/mL	71.2 (52.2-84.8)	3.41 (0.74-15.71)	
<20,000 IU/mL	63.1 (32.8-85.7)	2.37 (0.39-14.33)	
Duration of on-NA VR			0.544
<12 months	53.2 (27.4-77.4)	1	
12-24 months	72.0 (49.2-87.2)	2.26 (0.52-9.84)	
>24 months	60.3 (27.1-86.1)	1.33 (0.22-7.98)	
Duration of consolidation therapy after HBeAg seroconversion			0.928
<12 months	62.6 (38.5-81.8)	1	
≥12 months	64.1 (42.2-81.3)	1.06 (0.28-4.02)	
HBeAg-negative patients			
VR defined by HBV DNA			0.513
<200 IU/mL	29.3 (10.8-58.7)	1	
<2000 IU/mL	48.0 (30.6-65.9)	2.24 (0.53-9.41)	
<20,000 IU/mL	51.4 (15.4-86.1)	2.56 (0.30-22.03)	
Duration of on-NA VR			0.017
<12 months	50.0 (14.9-85.1)	1	
12-24 months	34.1 (22.8-47.6)	0.52 (0.08-3.24)	
>24 months	75.0 (50.5-89.8)	3.00 (0.39-23.30)	

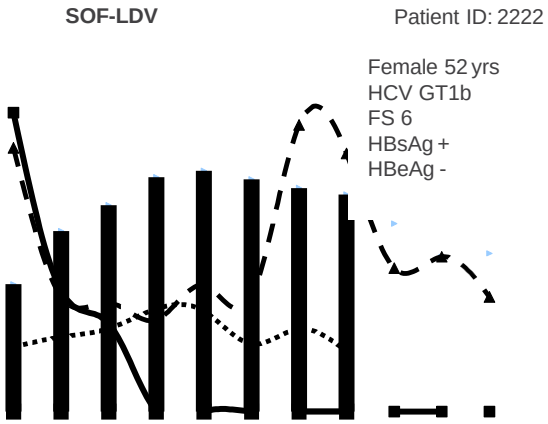
Papatheodoridis et al, HEPATOLOGY, VOL. 63, NO. 5, 2016

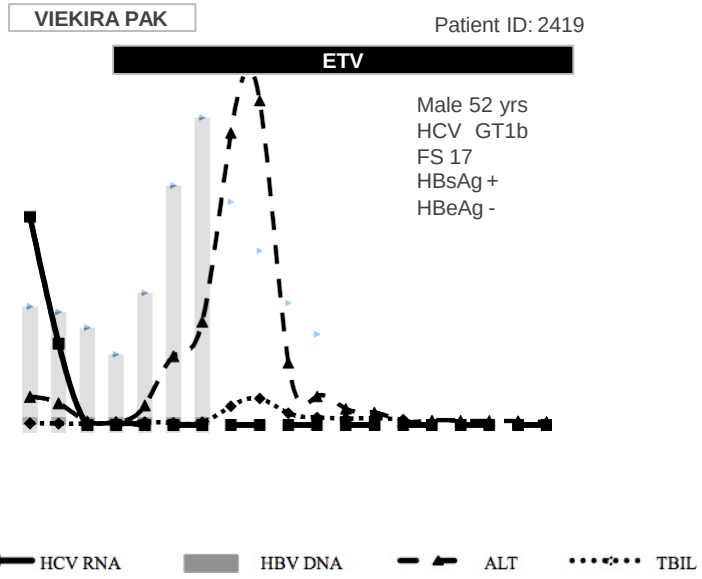
Special Populations with HBV

- HBV and HCV Co-infected Patients on DAAs
- Pregnant Mothers with Chronic Hepatitis B

HBV Reactivation in HBsAg+ Patients on DAA







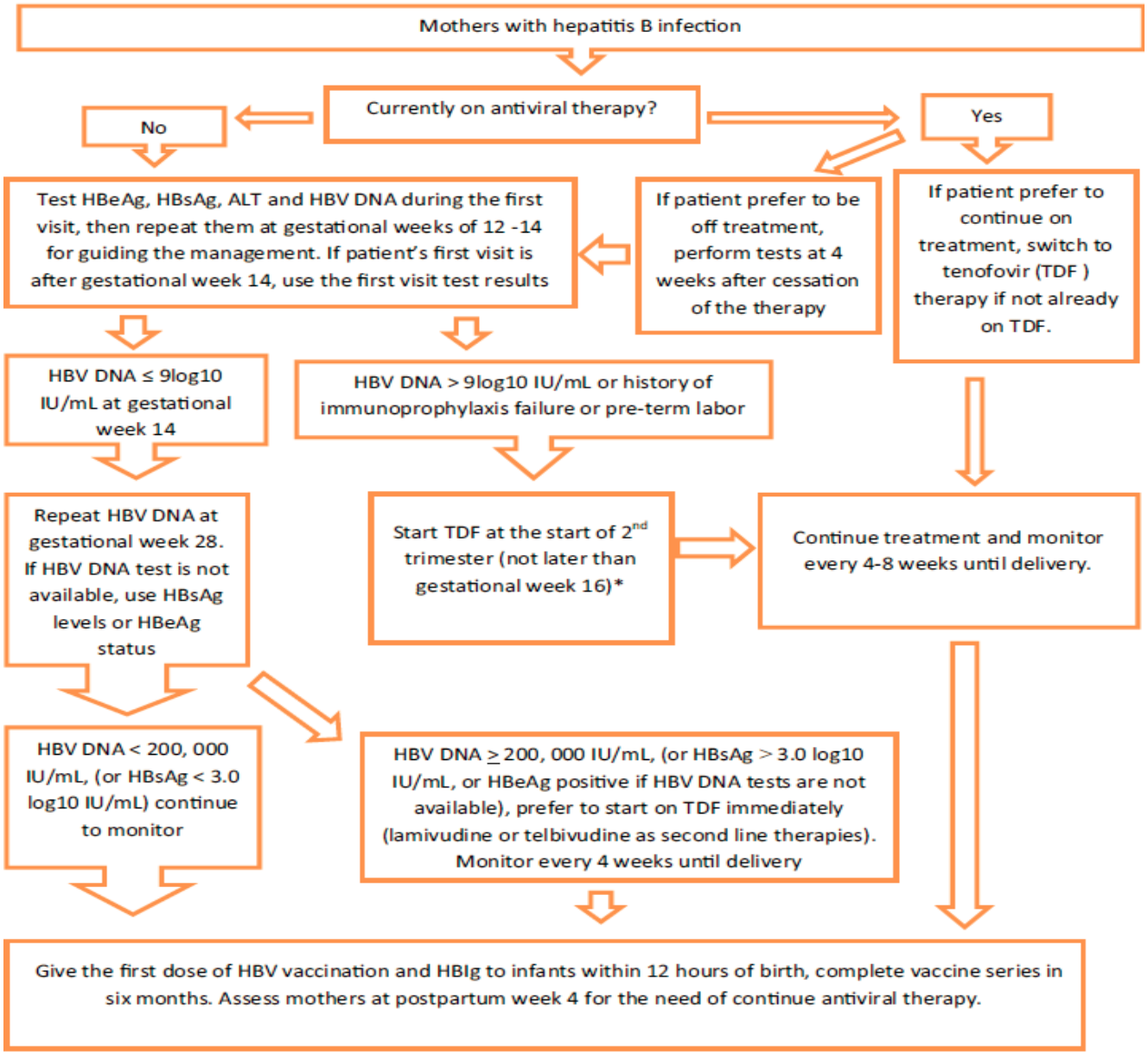
Wang C et al. Clin Gastroentrol Hepatol 2017;15: 132-136

Screening for HCV Patients Before DAA Therapy

	AASLD[1] (2017)	EASL[2] (2016)	US FDA[3]
Screening for HBV serology	✔	✔	✔
Preemptive NUCs	All HBsAg+ or Monitor Pt, treat if HBV DNA >10-fold of baseline or to >1000 IU/mL	All HBsAg+ or HBsAg- Occult CHB	Consult Hepatologist
Monitoring	✔	✔	✔

1. AASLD/ISDA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Updated September 2017
2. EASL recommendations on treatment of hepatitis C 2016. Journal of Hepatology.
3. The U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. 2016 [Nov, 2016]. http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm.

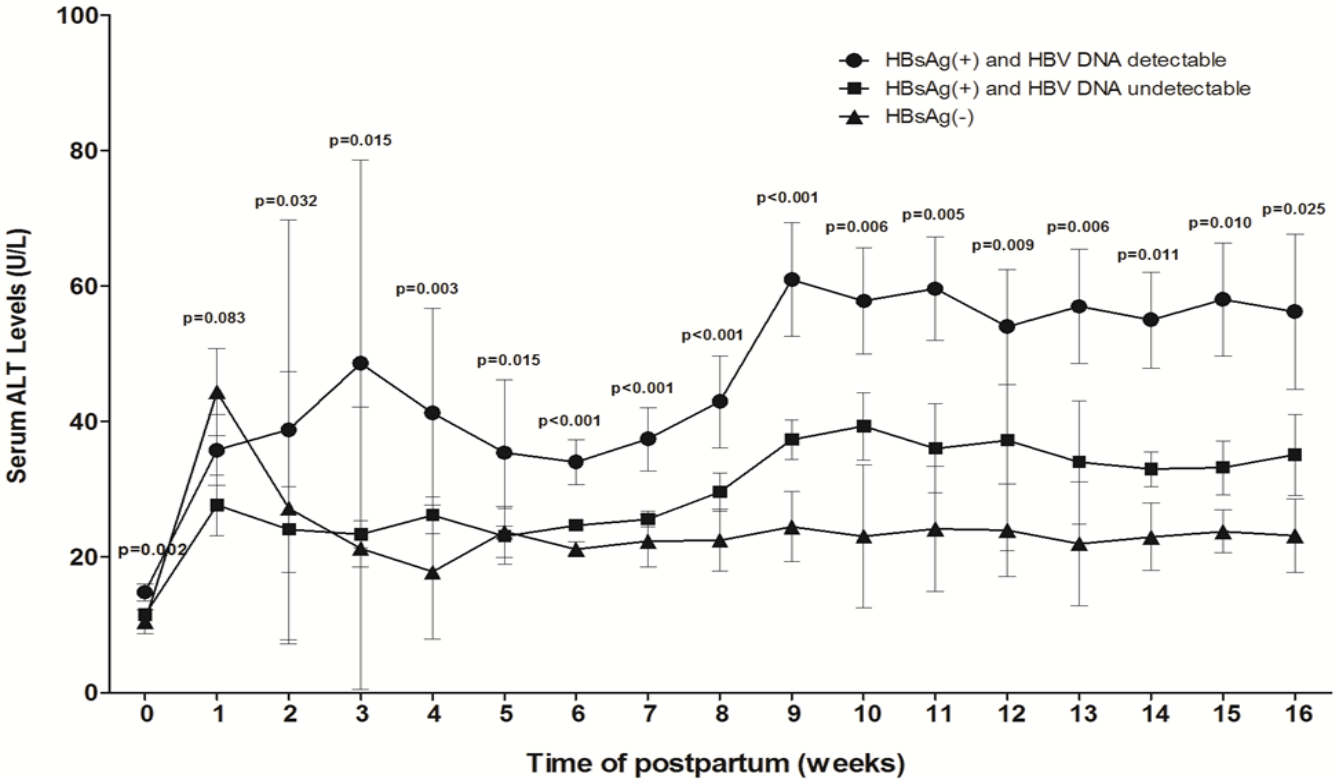
Management of Pregnant Women with CHB



Park, J and Pan, CQ. Hepatol Int 2017 (11):p476-480

Postpartum ALT Flares in Mothers Who Received No Antiviral Therapy During Pregnancy

4236 patients with 869 healthy and 3367 CHB mother. CHB mothers were further stratified into 2 subgroups by the presence (n = 1928) or absence (n = 1439) of detectable levels of HBV DNA



- ALT levels peaked at postpartum weeks 3–4 and 9–12.
- Elevated ALT and detectable HBV DNA levels at delivery were independent risk factors of flares .
- A cut-off level of 5 log10 IU/mL for HBV DNA at delivery predicted postpartum ALT events.
- The positive predictive value of this cut-off was 14.4%, with a negative predictive value of 98.2%.

Pan, CQ et al. AASLD oral presentation 2017; (66):100-101A. Manuscript in press, Am J Gastrol.

Summary

- **Who should be treated:**

Patients with HBV DNA levels >2,000 IU/mL and evidence of liver injury, either presented with abnormal ALT levels, or liver fibrosis stage ≥ F2. Cirrhotic patients should be treated regardless their HBV DNA or ALT levels.

- **What to use for CHB patients:**

First line therapies include entecavir, tenofovir-DF, and tenofovir-AF. Switching from TDF to TAF is supported by recent clinical trial data on certain sub-groups of patients.

- **When to stop the therapy:**

With available therapy, only a few patients could achieve clinical resolution (functional cure). High rate of relapse to active disease will be expected after the cessation of therapy in HBsAg+ patients.

- **HBV/HCV coinfection, or pregnant mothers:**

Screen HCV patients before DAA therapy, initiate prophylactic HBV therapy for those with detectable HBV DNA levels or HBsAg+, monitor HBV closely regardless the HBV treatment status. Mothers with CHB should be tested for HBV DNA at the second trimester. TDF therapy during the third trimester is indicated when maternal HBV DNA levels >200,000 IU/mL.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Thank You !


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