CLINICAL CARE OPTIONS®
HEPATITIS

Evolving Options for HBV Therapy: Navigating the New Treatment Landscape

This program is supported by an educational grant from
Gilead Sciences

About These Slides

- Please feel free to use, update, and share some or all of these slides in your noncommercial presentations to colleagues or patients
- When using our slides, please retain the source attribution:

Slide credit: clinicaloptions.com

- These slides may not be published, posted online, or used in commercial presentations without permission. Please contact permissions@clinicaloptions.com for details

Faculty

Robert S. Brown, Jr., MD, MPH
Gladys and Roland Harriman Professor of Medicine
Vice Chair, Transitions of Care
Clinical Chief, Division of Gastroenterology and Hepatology
Weill Cornell Medicine
New York, New York

Robert S. Brown, Jr., MD, MPH, has disclosed that he has received consulting fees from Bristol-Myers Squibb and Gilead Sciences and funds for research support from Gilead Sciences.

Faculty

Natalie H. Bzowej, MD, PhD
Director Transplant Research
Ochsner Health System
New Orleans, Louisiana

Natalie H. Bzowej, MD, PhD, has disclosed that she has received consulting fees from Gilead Sciences and funds for research support from Allergan, Cirius Therapeutics, and Gilead Sciences.

Faculty

Jordan J. Feld, MD, MPH
Associate Professor of Medicine
University of Toronto
Hepatologist
Toronto Centre for Liver Disease
Sandra Rotman Centre for Global Health
Toronto, Canada

Jordan J. Feld, MD, MPH, has disclosed that he has received consulting fees from AbbVie, ContraVir, Gilead Sciences, and Merck and funds for research support from AbbVie, Gilead Sciences, Janssen, Merck, and Wako Life Sciences.

Faculty

Norah Terrault, MD, MPH
Professor of Medicine and Surgery
Director, Viral Hepatitis Center
Division of Gastroenterology
University of California, San Francisco
San Francisco, California

Norah Terrault, MD, MPH, has disclosed that she has received consulting fees from Dynavax Technologies, Gilead Sciences, and Novartis and funds for research support from Gilead Sciences.

Faculty

Tram T. Tran, MD
Medical Director of Liver Transplant
Comprehensive Transplant Center
Cedars Sinai Medical Center
Professor of Medicine
Division of Gastroenterology
Geffen UCLA School of Medicine
Los Angeles, California

Tram T. Tran, MD, has disclosed that that she has received consulting fees from AbbVie, Gilead Sciences, and Merck and funds for research support from AbbVie and Gilead Sciences.

Outline

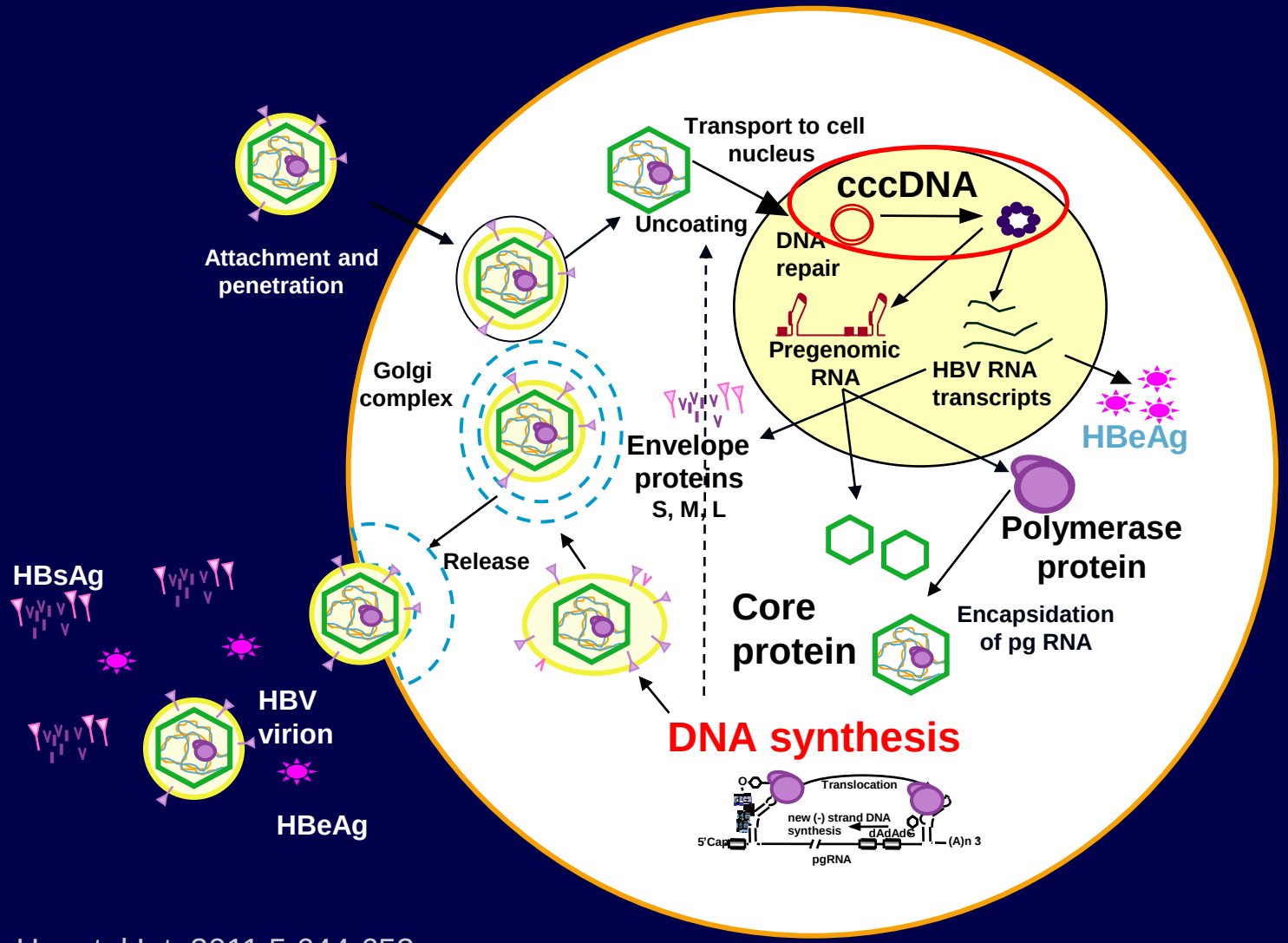
- Goals of Therapy
- When and What to Start: The Guidelines
- New Treatment Options
- Choosing Among Good Options

Cure as a Goal of Therapy

- **Actual cure**
  - True cure = all traces of HBV gone from the liver (like HCV)
  - VERY difficult (if not impossible) → cccDNA
- **Functional cure**
  - Use the markers of pts who do well:
    1. HBsAg loss (ideally with anti-HBs)
    2. Possibly sustained off-treatment inactive disease without HBsAg loss (HBeAg negative, DNA undetectable, normal ALT, normal histology)

Cure not so simple . . . reasons lie in the virology

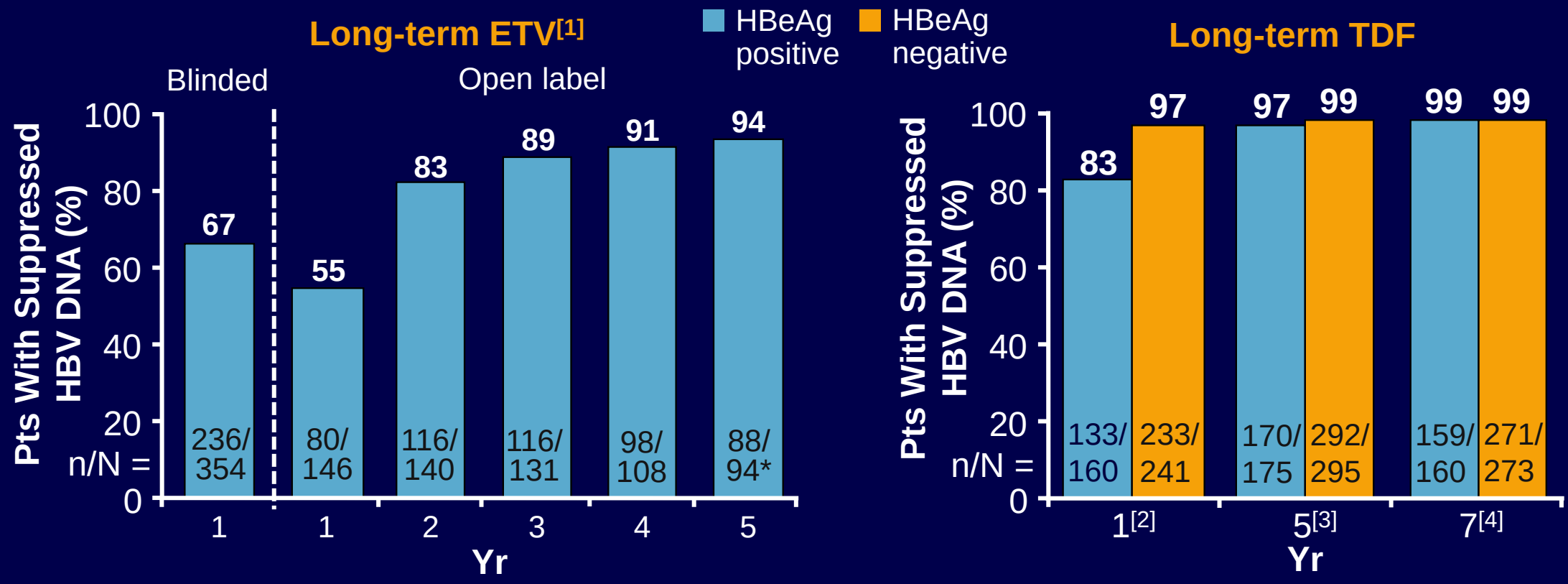
Why Is Cure Rare With Nucleos(t)ide Therapy?



Grimm D, et al. Hepatol Int. 2011;5:644-653.

Slide credit: clinicaloptions.com

Potent HBV DNA Suppression With Nucleos(t)ide Therapy



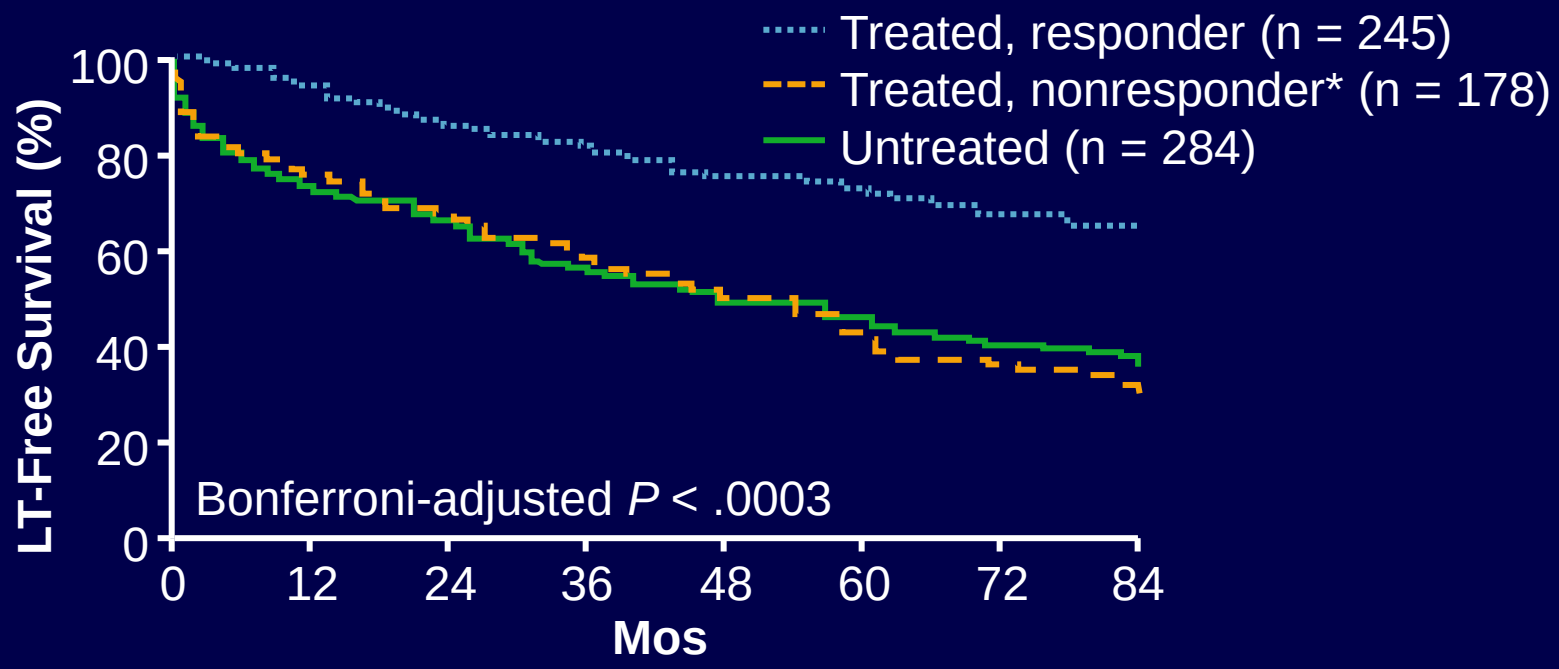
*5 additional pts who remained on treatment at the Yr 5 visit had missing HBV DNA measurements.

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.

HBV Therapy Reduces Risk of Disease Progression

- Prospective cohort study in pts with HBV and first-onset complications of decompensated cirrhosis (N = 707) treated predominantly with lamivudine (n = 203) or entecavir (n = 198)



*Nonresponders included pts with HBV rebound or genotypic resistance, primary nonresponse, NE due to early event (death, LT, LTFU).

- Antiviral therapy improved transplant-free survival over mean follow-up of 49 mos (*P* = .0098 vs untreated)

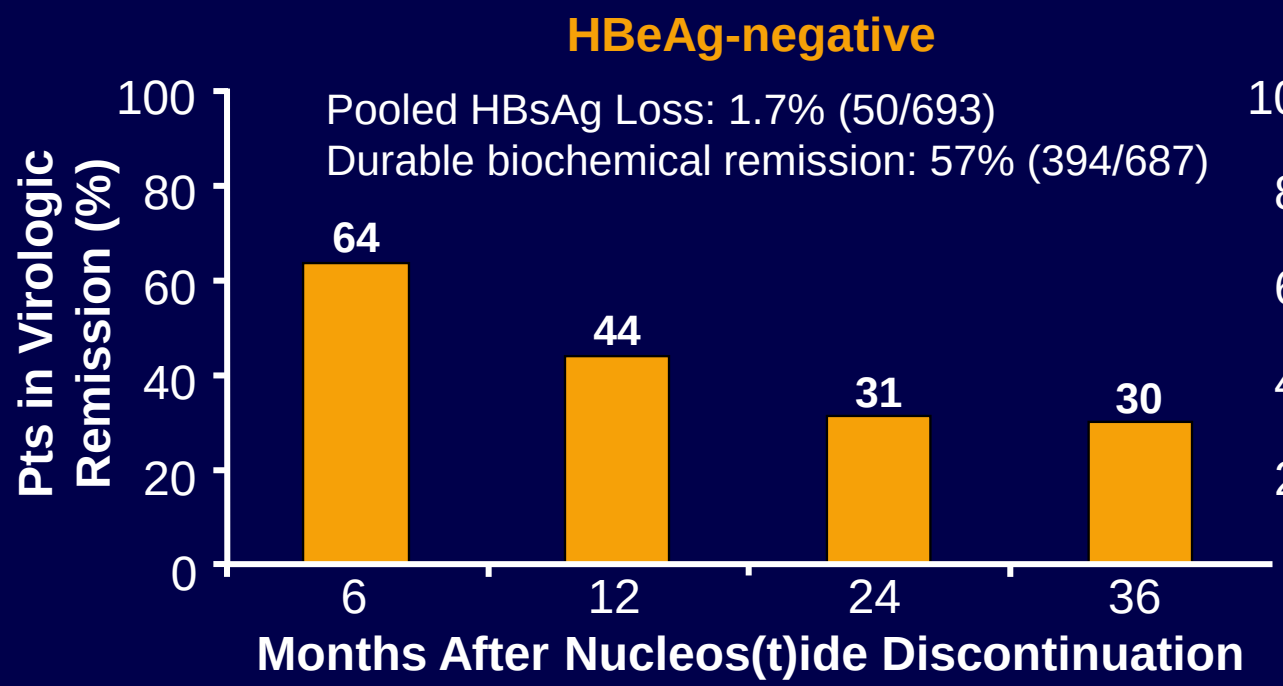
Jang JW, et al. Hepatology. 2015;61:1809-1820.

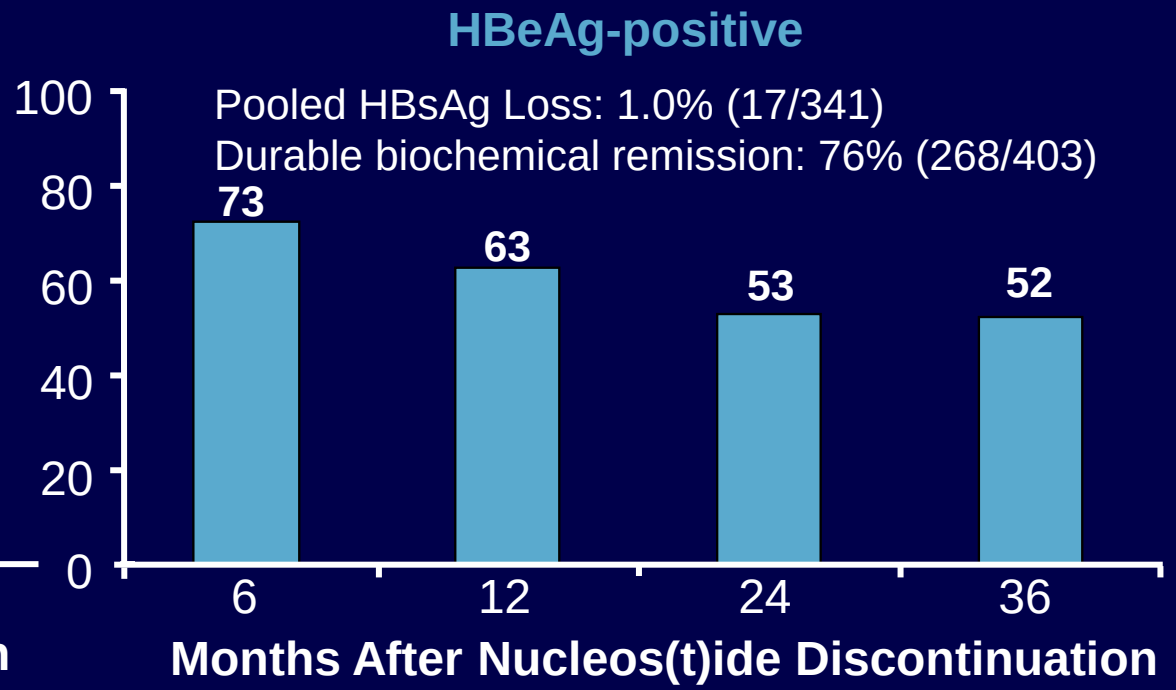
Slide credit: clinicaloptions.com

Need for Long-term Therapy

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





- 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.

Slide credit: clinicaloptions.com

Long-term Oral HBV Therapy is Highly Effective

- Suppresses HBV DNA[1,2]
- Normalizes ALT[2,3]
- Prevents fibrosis progression[3,4]
- Promotes fibrosis regression, even in cirrhosis[4]
- Prevents and even reverses hepatic decompensation[1]
- ***Reduces, but does not eliminate, the risk of HCC[1,5]***
- ***Long-term therapy is effective . . . but low rates of HBsAg loss[6]***

1. Lim YS, et al. Gastroenterology. 2014;147:152-161.2. Chang TT, et al. Hepatology. 2010;51:422-430.
3. Zoutendijk R, et al. Gut. 2013;62:760-765. 4. Marcellin P, et al. Lancet. 2013;381:468-475.
5. Papatheodoridis GV, et al. J Hepatol. 2015;62:363-370. 6. Papatheodoridis GV, et al. Hepatol. 2016;63:1481-1492.

Long-term Oral HBV Therapy: Downsides

- Toxicity
  - Potential for renal, bone complications with TDF
- Resistance
  - High with lamivudine (not preferred by guidelines)[1]
  - Very low with entecavir—unless already LAM resistant[2]
  - None with TDF in clinical trials (similar expected with TAF)[3]
- Cost
- Adherence

1. Hadziyannis SJ, et al. Hepatology. 2000 ;32:847-51. 2. Gish SR, et al. Gastroenterology. 2007;133:1437-44. 3. Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.

When and What to Start

Guidelines: When to Start HBV Therapy

Guidelines	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

Continue indefinitely in HBeAg-negative pts with cirrhosis

1. Terrault NA, et al. Hepatology. 2016;63:261-283.

Slide credit: clinicaloptions.com

Guidelines: When to Start HBV Therapy

Guidelines	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*
	> 20,000	> 2 x ULN	N/A	> 20,000	> 2 x ULN	N/A

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

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

Guidelines: What to Start as Initial HBV Therapy

Treatment	Preferred[1,2]	Notes
Entecavir	Yes	High potency, high genetic barrier to resistance
Tenofovir alafenamide*	Yes (EASL only)	High potency, high genetic barrier to resistance
Tenofovir disoproxil fumarate†	Yes	High potency, high genetic barrier to resistance
Peginterferon	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

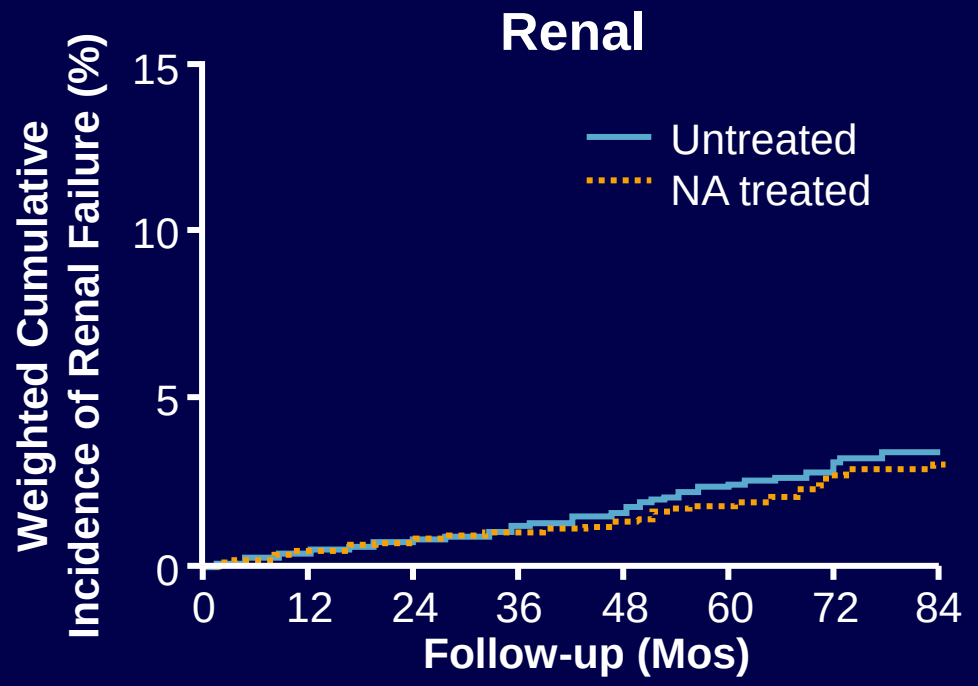
*AASLD guidelines not yet updated since approval of TAF.
†Pts receiving TDF: monitor renal function, consider monitoring BMD in pts at risk.[1]

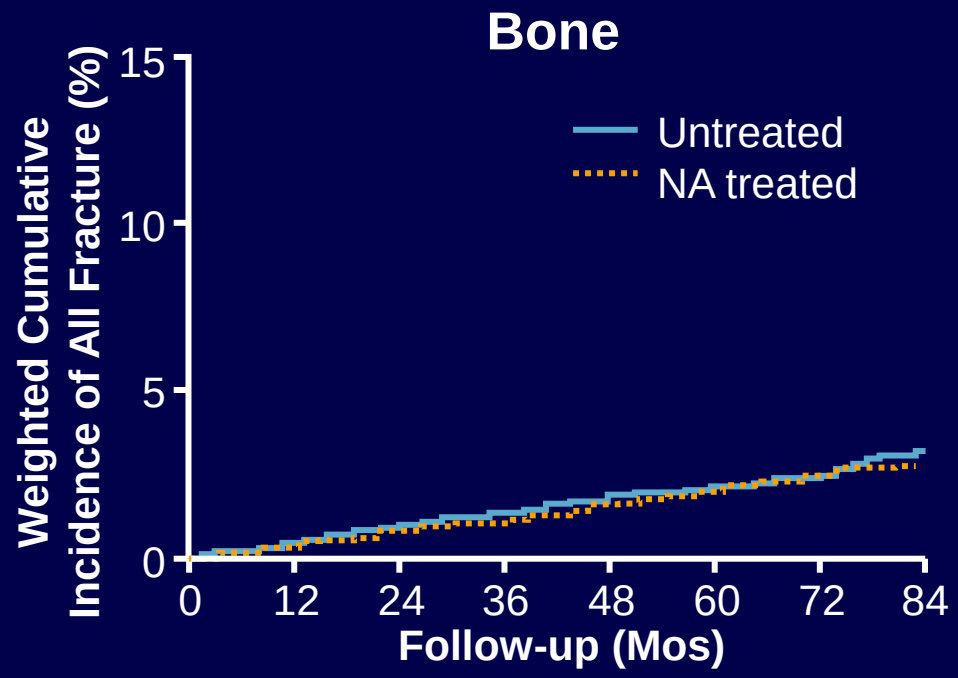
ETV, TDF, TAF have very favorable safety profiles[2]

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

Safety of Nucleos(t)ide Analogues in HBV

- Observational study of n = 46,454 untreated vs n = 7046 pts treated with NAs, median follow-up of 4.9 yrs
- Generally very good long-term safety . . . but individual pts may have toxicity





Wong G L-H, et al. Hepatology. 2015;62:684-693.

Slide credit: clinicaloptions.com

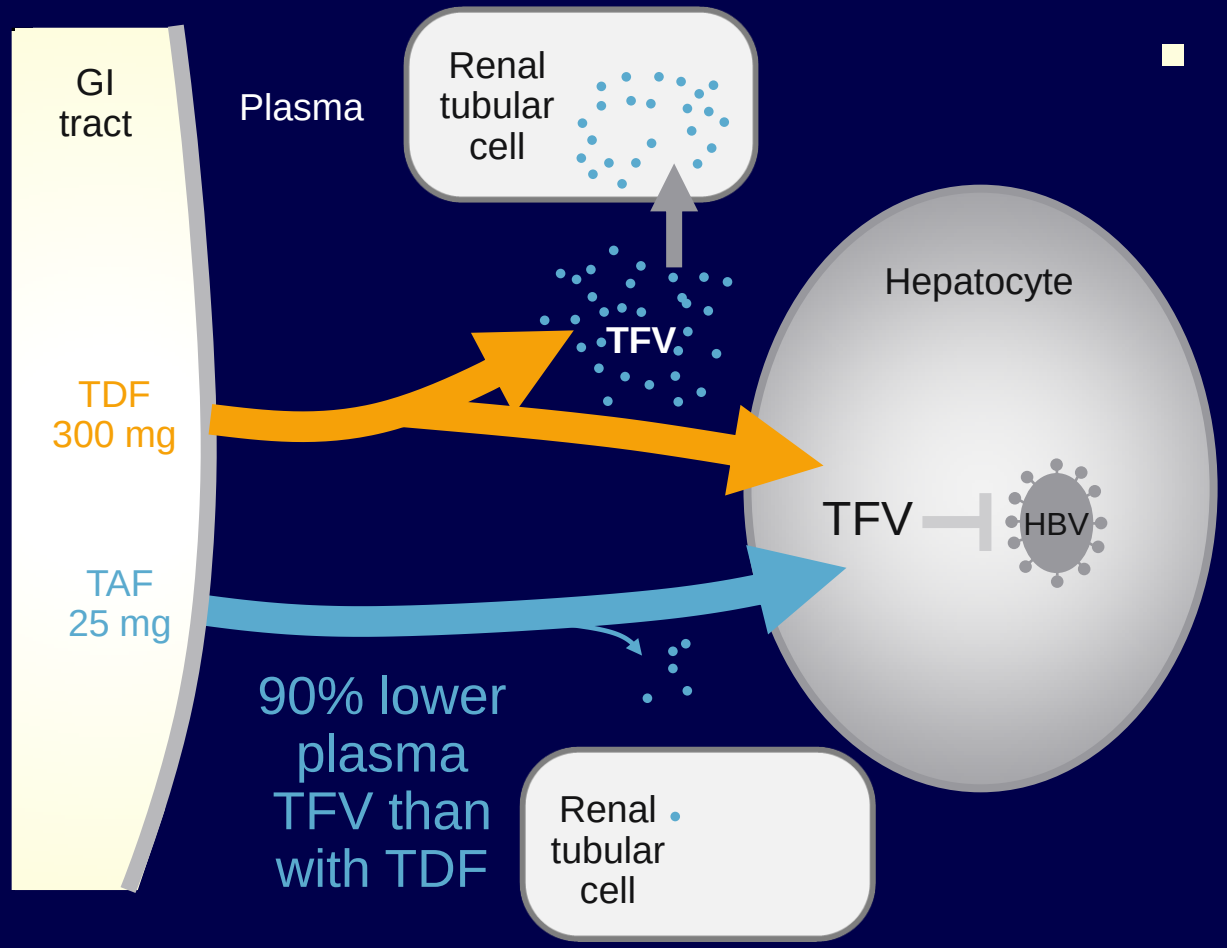
Current Options in 2017

Recommended Nucleos(t)ide Analogues for HBV

Nucleos(t)ide Analogue	Approval in HIV	Approval in CHB	QD Dose	Lowest CrCl Without Dose Adjustment (mL/min)
Entecavir	N/A	2005	0.5 mg	50
Tenofovir disoproxil fumarate	2001	2008	300 mg	50 (no dose recommendation at < 10 without dialysis)
Tenofovir alafenamide	2015 (as part of fixed-dose combination with antiretrovirals)	2016	25 mg	15 (not recommended at < 15 in HBV monoinfection)

Entecavir [package insert]. 2017. Tenofovir disoproxil fumarate [package insert]. 2017. Tenofovir alafenamide [package insert]. 2017.

TAF vs TDF: Mechanism of Action



- Tenofovir alafenamide: novel prodrug of tenofovir

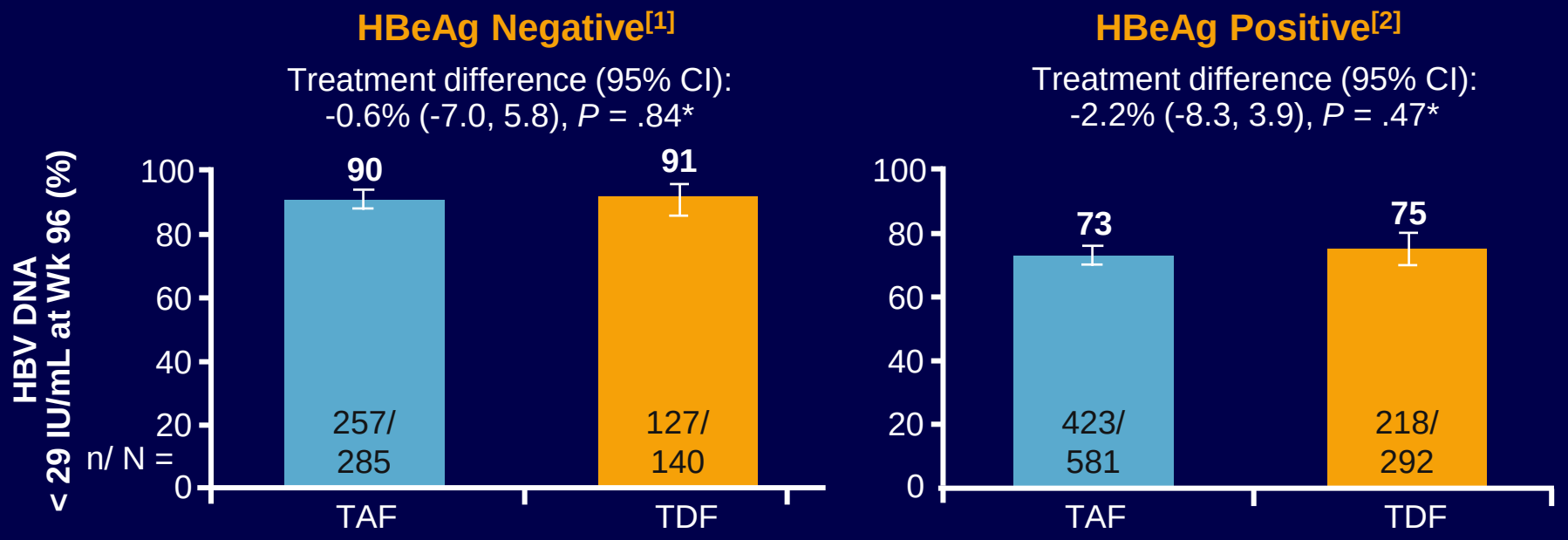
TAF: no dose adjustment needed in pts with CrCl > 15 mL/min

Arribas JR, et al. CROI 2017. Abstract 453. Duarte-Rojo A. Therap Adv Gastroenterol. 2010;3:107-119. Murakami E, et al. Antimicrob Agents Chemother. 2015;59:3563-3569. Tenofovir disoproxil fumarate [package insert]. 2017. Tenofovir alafenamide [package insert]. 2017.

Slide credit: clinicaloptions.com

TAF vs TDF in Chronic HBV Infection: Wk 96 Efficacy

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



*Adjusted for BL HBV DNA and PO antiviral treatment status.

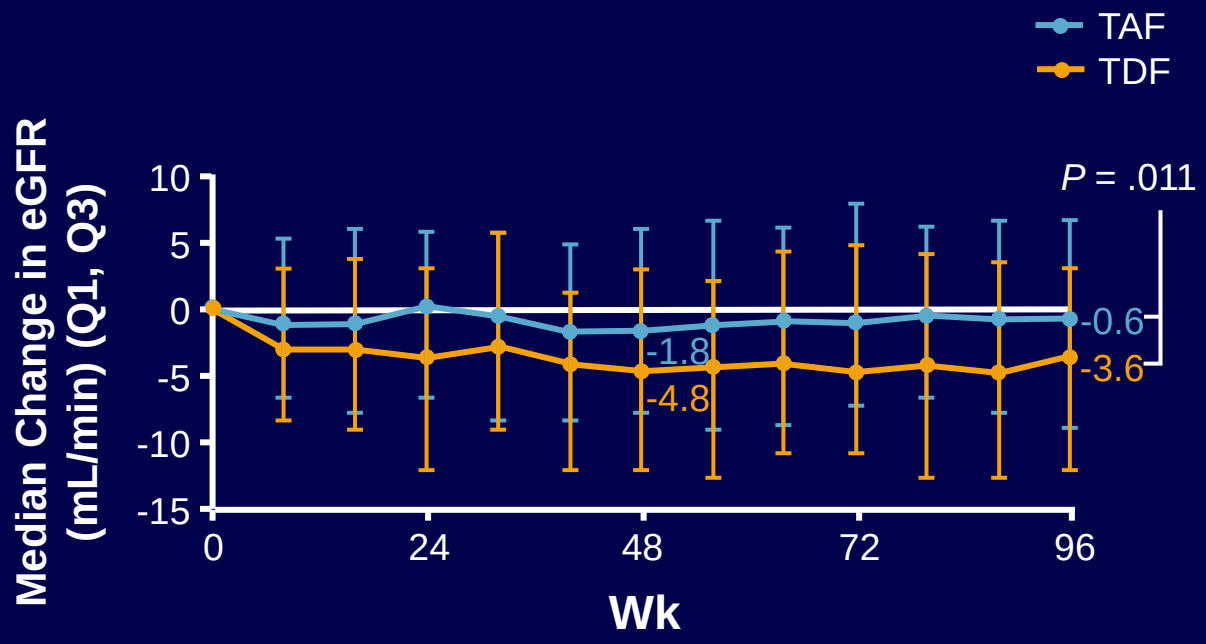
- ALT: significantly greater rate of ALT normalization at Wk 96 with TAF vs TDF
- HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 with TDF or TAF[2]
- HBeAg-negative pts: minimal decline in HBsAg with TDF or TAF for (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)[1]

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

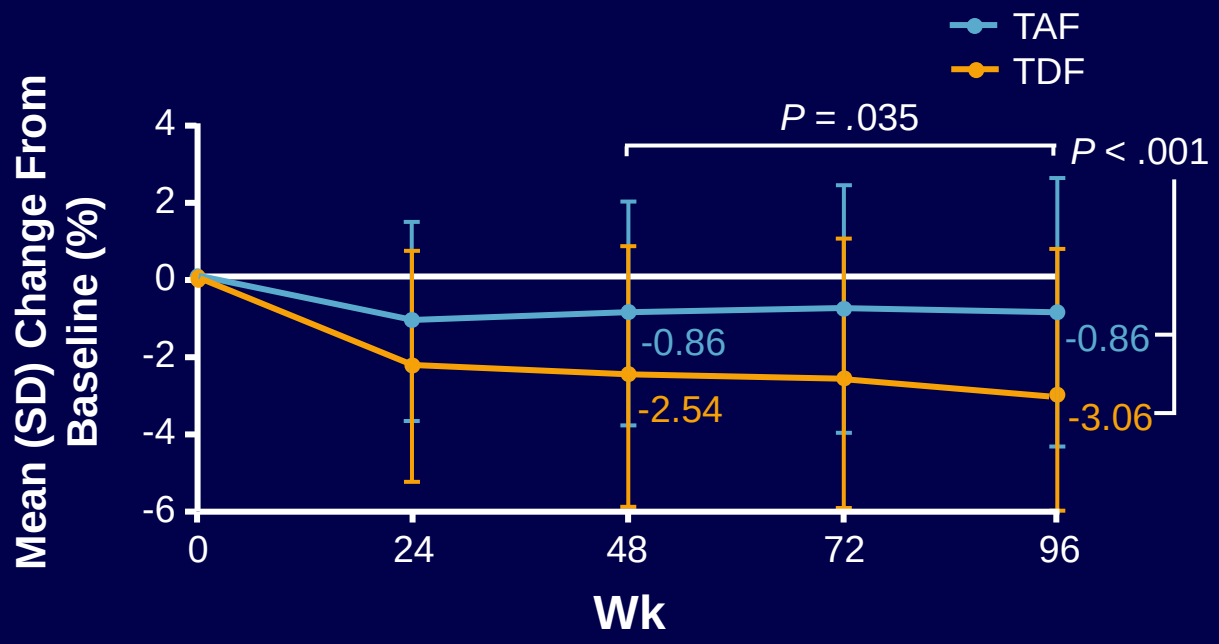
Slide credit: clinicaloptions.com

TAF vs TDF in Chronic HBV Infection: Renal and Bone Outcomes

- Significantly smaller effect on renal function with TAF at Wk 48 and Wk 96 in HBeAg-negative pts[1]



- Significantly smaller effect on spine BMD with TAF at Wk 48 and Wk 96 HBeAg-negative pts[1]



Similar results seen with HBeAg-positive pts[2]

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

Slide credit: clinicaloptions.com

Choosing Among Nucleos(t)ide Analogues

If no comorbidities (for most pts) → Monotherapy with ETV, TDF, or TAF[1,2]

If risk of or preexisting bone or renal disease, prioritize ETV or TAF[2]

- Age > 60 yrs
- Bone disease
  - Chronic steroids or other meds that affect bone
  - History of fragility fracture
  - Osteoporosis
- Renal abnormalities
  - eGFR < 60 mL/min/1.73 m^2
  - Albuminuria > 30 mg or moderate proteinuria
  - Low phosphate (< 2.5 mg/dL)
  - Hemodialysis

When to prioritize TAF over ETV

- Previous nucleoside exposure[2]
  - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥ 15 mL/min

When to prioritize ETV over TAF

- If less expensive (generic available)
- Dosing guidelines for CrCl < 15 mL/min

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

Chronic HBV Infection: Management of Pts With NA Resistance

Resistance	Switch Strategy	Add Strategy
Adefovir	Entecavir[1]	Entecavir[1]
Entecavir	Tenofovir*[1,2]	Tenofovir (or emtricitabine/tenofovir*)[1]
Lamivudine	Tenofovir*[1,2]	Tenofovir (or emtricitabine/tenofovir*)[1]
Telbivudine	Tenofovir*[1,2]	Tenofovir[1]
Multidrug	Tenofovir*[1]	Tenofovir* + entecavir[1,2]

*Includes either TDF or TAF in EASL guidelines; AASLD guidelines not yet updated since approval of TAF.

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

Chronic HBV Infection: Management of Pts With Renal Impairment

- All pts receiving TDF should undergo periodic monitoring of renal function, including phosphate levels[1]

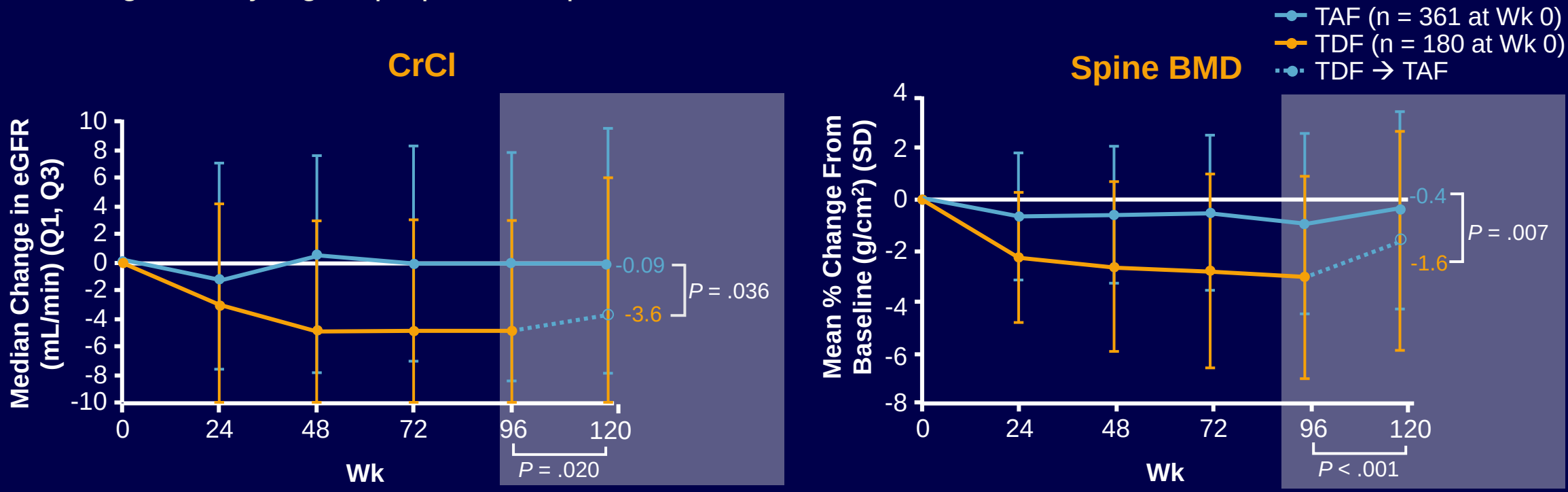
Entecavir[2]	Tenofovir Disoproxil Fumarate[3]	Tenofovir Alafenamide[4]
Reduce dose if CrCl < 50 mL/min	Reduce dose if CrCl < 50 mL/min	No dose reduction if CrCl ≥ 15 mL/min
	No dose recommendation at CrCl < 10 mL/min without dialysis	Not recommended at CrCl < 15 mL/min

1. EASL. J Hepatol. 2017;67:370-398. 2. Entecavir [package insert]. 2017. 3. Tenofovir disoproxil fumarate [package insert]. 2017. 4. Tenofovir alafenamide [package insert]. 2017.

Should Patients Receiving TDF Switch to TAF?

Switch to TAF vs Continuing TDF in Chronic HBV Infection: Renal and Bone Outcomes

- Analysis of open-label extension data from 2 phase III trials in HBV-infected pts switching from TDF to TAF at Wk 96
- 88% of pts achieved virologic suppression at Wk 96 (preswitch) and maintained to Wk 120 (post switch)
- Significantly higher proportion of pts achieved ALT normalization after switch to TAF



Chan HLY, et al. EASL 2017. Abstract PS-041.

Slide credit: clinicaloptions.com

Conclusions: Current Treatment Landscape

- In pts without comorbidities, 3 highly effective preferred options with high barrier to resistance: ETV, TAF, TDF
- ETV and TAF useful for pts at risk of or with current renal impairment or bone toxicity
  - In such pts, consider ETV if CrCl < 15 mL/min, TAF if previous nucleoside exposure
- Guidelines suggest useful to switch to TAF for pts with current toxicity
- Equally effective viral suppression with TAF as TDF with faster ALT improvement
  - Ongoing studies to better understand mechanism

Slide credit: clinicaloptions.com

Summary

- NA therapy is highly effective but not curative
  - HBV DNA suppressed but low HBsAg loss
- Long-term therapy required
- For most pts: ETV, TAF or TDF similar
- TAF has similar efficacy with improved renal and bone safety compared with TDF

Go Online for More CCO Coverage of HBV Infection!

Online Interactive Treatment Decision Tool on first-line treatment options

CME-certified Interactive Virtual Presentation reviewing key data and insights

ClinicalThought Commentaries from expert faculty

www.clinicaloptions.com/HBVlandscape

CLINICAL CARE OPTIONS®
HEPATITIS