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The Impact of HBV Therapy on Fibrosis and Cirrhosis

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This program is supported by an educational grant from Gilead Sciences

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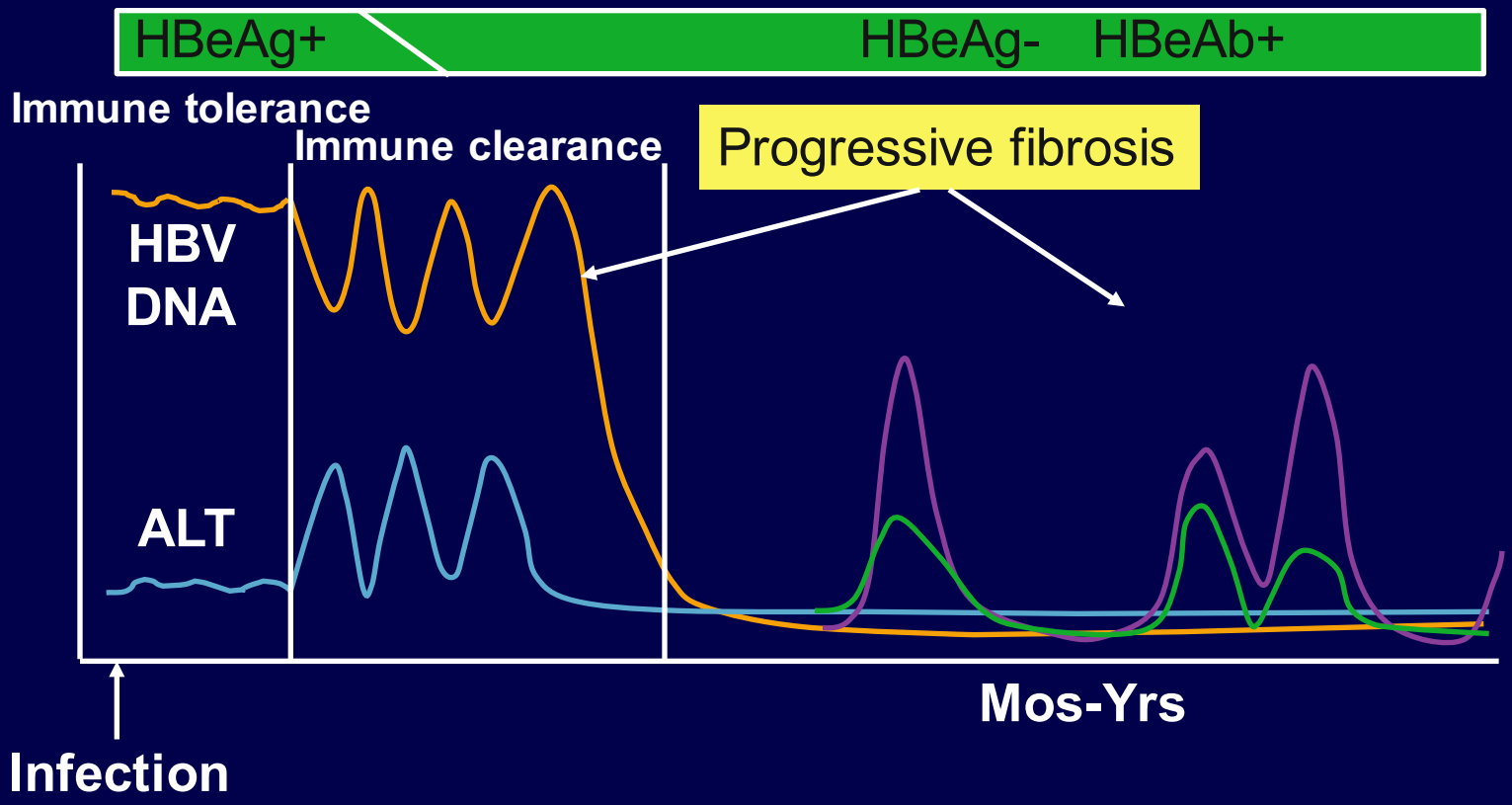
Disclosures

Jordan J. Feld, MD, MPH, has disclosed that he has received funds for research support from Abbott, AbbVie, Gilead Sciences, Janssen, Merck, and Regulus and consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck.

What Happens After HBeAg Loss?



Progressive fibrosis may occur more rapidly in HBV than in HCV infection

Slide courtesy of Jordan J. Feld, MD, MPH.

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Risk Factors for Progressive Fibrosis

- Host:
  - Male sex
  - Increasing age
  - Metabolic syndrome
  - Alcohol consumption
  - Coinfections
    - HCV, HDV, HIV
- Virus:
  - HBV DNA levels (except for immune tolerant)
  - HBeAg positive
  - HBV genotype (?)
    - C > B > A/D

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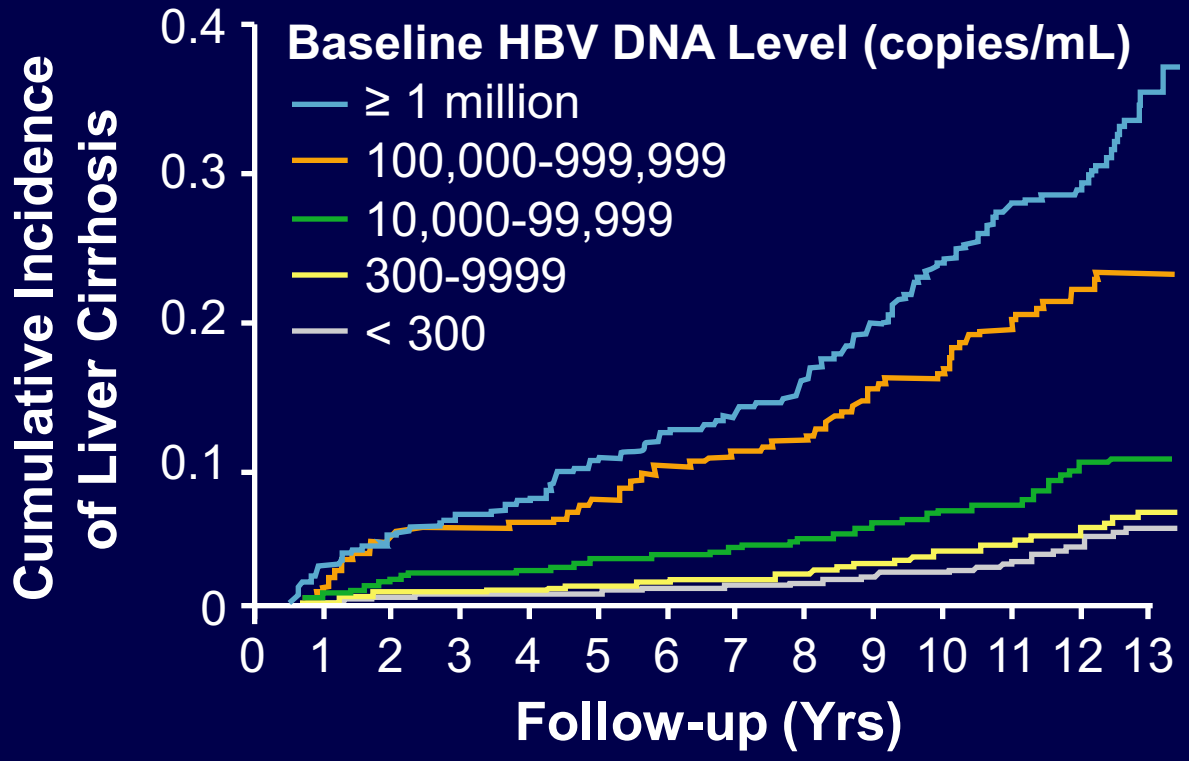
REVEAL: HBV DNA Level and Risk of Cirrhosis

- Long-term (mean follow-up: 11.4 yrs) cohort study to determine risk of cirrhosis and HCC in untreated, HBsAg-positive individuals in Taiwan (N = 3582)



Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

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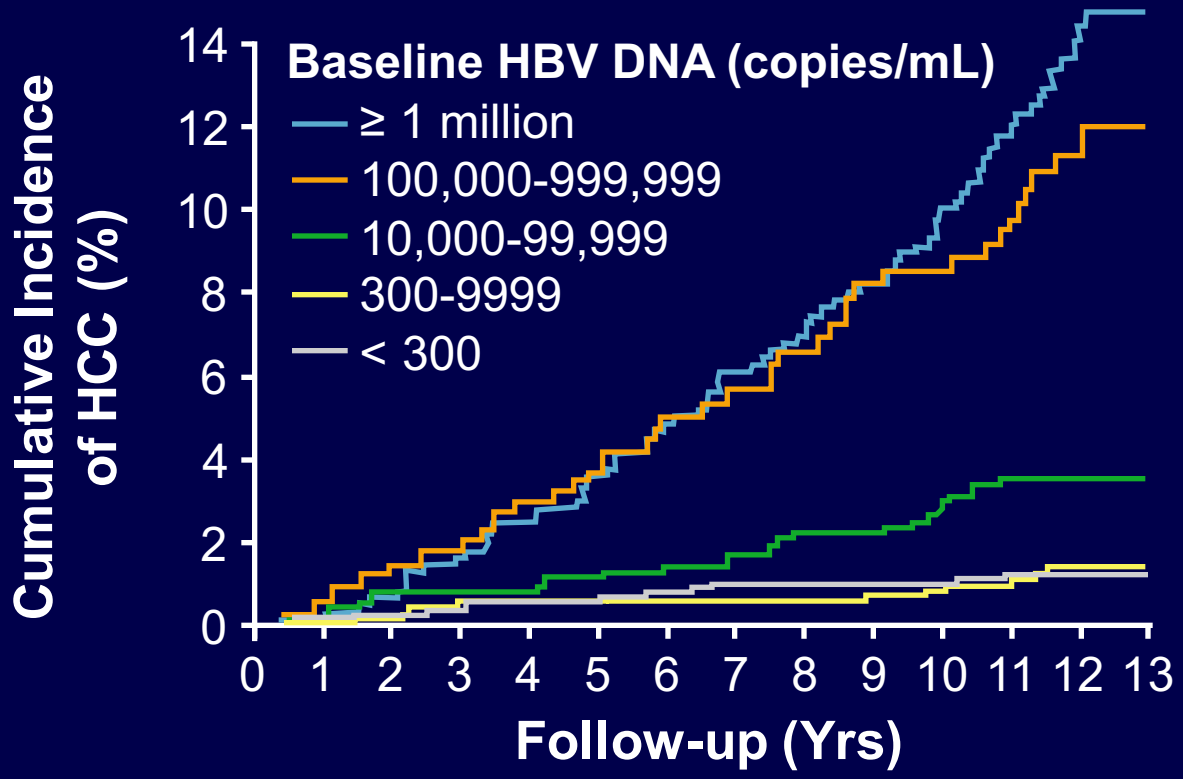
REVEAL: HBV DNA Level and Risk of HCC

- Prospective study in same REVEAL cohort (N = 3653)



- Increased HCC incidence with increasing DNA levels ($P < .001$)
- HCC can occur in the absence of cirrhosis

Chen CJ, et al. JAMA. 2006;295:65-73.

Slide credit: clinicaloptions.com

REVEAL: Risk Factors for HCC

Factor	Adjusted HR	95% CI	*P* Value
Male sex	2.1	1.3-3.3	.03
Age (per yr)	1.09	1.07-1.11	< .001
HBeAg positive	2.6	1.6-4.2	< .001
Cirrhosis	9.1	5.9-13.9	< .001
HBV DNA (copies/mL)			
▪ < 300	1.0	Ref	< .001*
▪ 300-9999	1.1	0.5-2.3	.86
▪ 10,000-99,999	2.3	1.1-4.9	.02
▪ 100,000-999,999	6.6	3.3-13.1	< .001
▪ ≥ 1,000,000	6.1	2.9-12.7	< .001

**P* value for trend.

Chen CJ, et al. JAMA. 2006;295:65-73.

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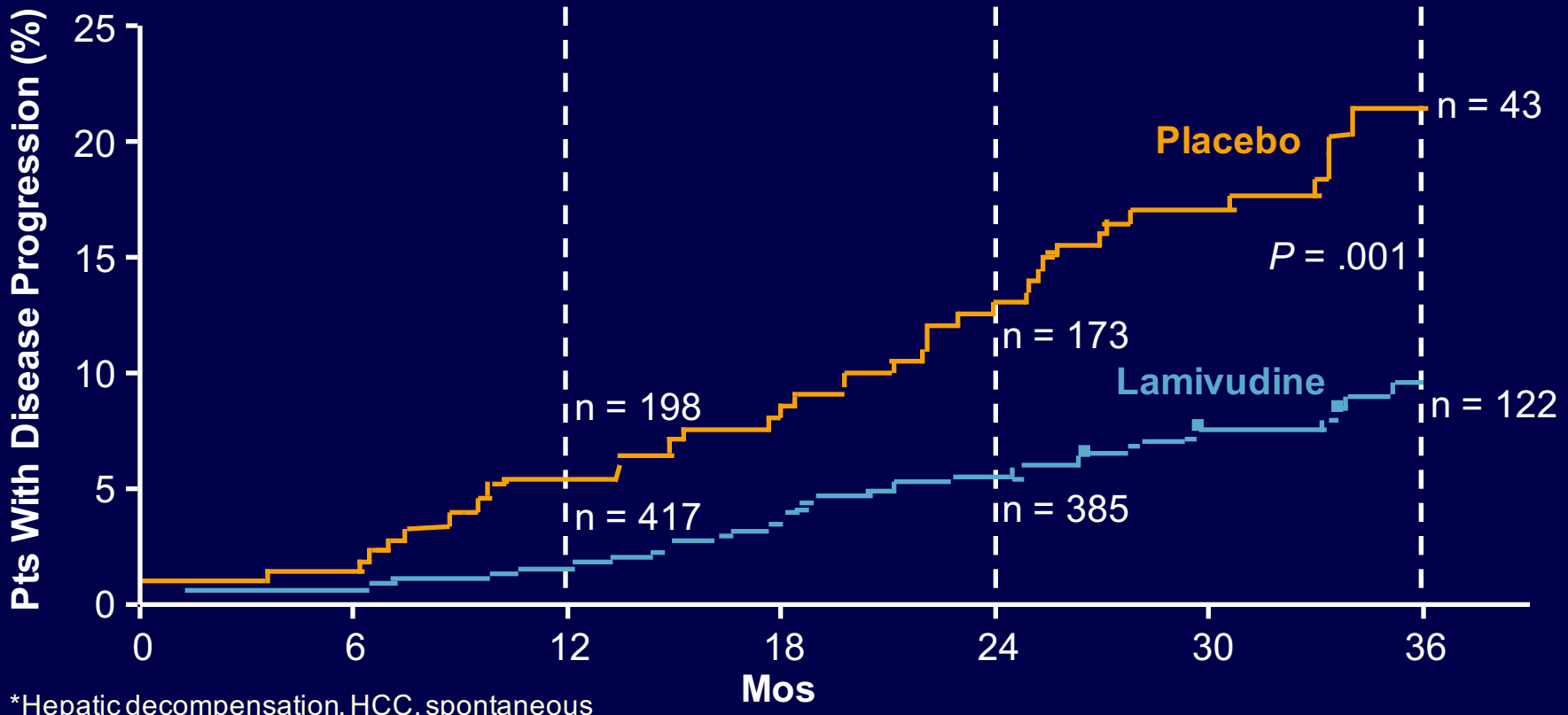
Does Therapy Change the Outcome?

HBV Treatment Reduces Risk of Disease Progression Including Decompensation

- Placebo-controlled, double-blind, parallel group study of pts with chronic HBV infection and cirrhosis (F4) (N = 651) followed until HBeAg seroconversion or disease progression*



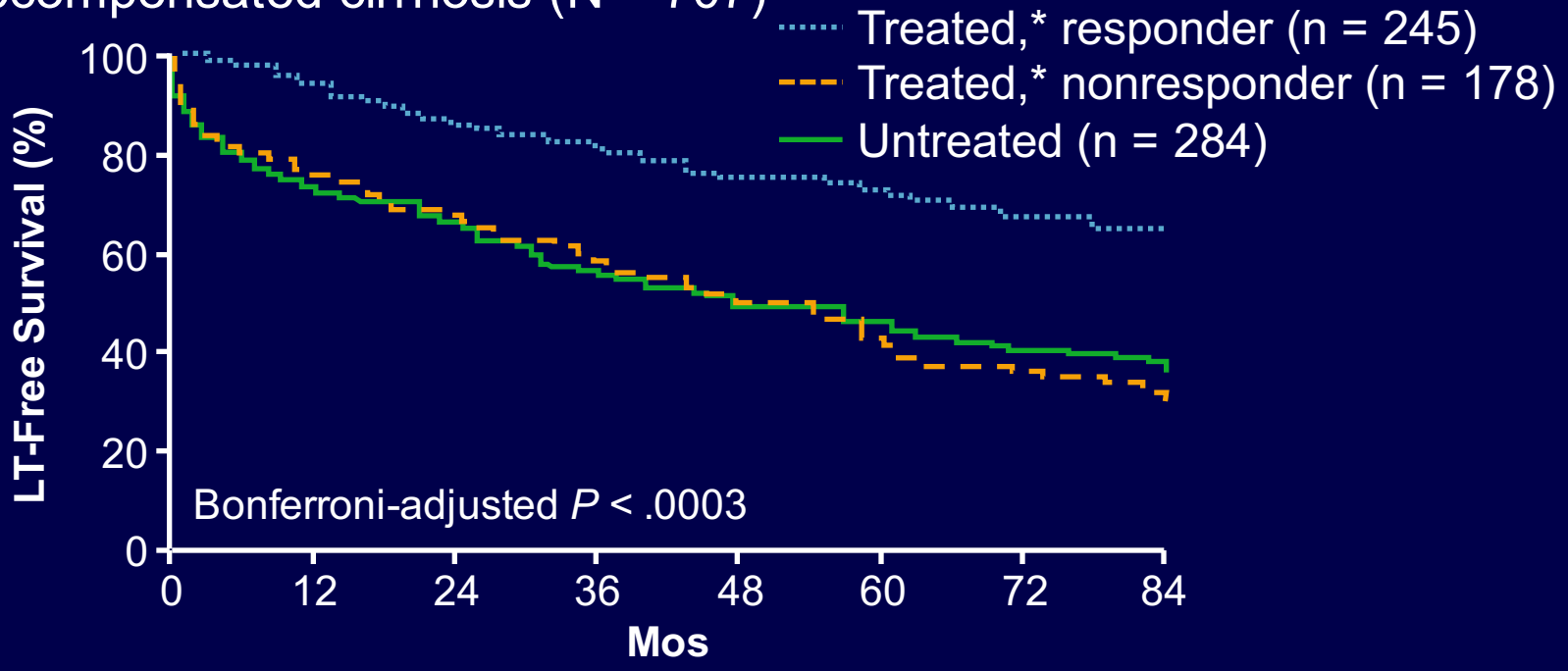
*Hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

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

Slide credit: clinicaloptions.com

HBV Treatment Reduces Risk of Liver Transplant

- 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).

- Antiviral therapy improved transplant-free survival over 5 yrs (*P* = .0098 vs untreated)

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

Many HBV Treatment Endpoints Indicate None Is Ideal; Need to Use Surrogates

- Complications take yrs to decades to develop—difficult to use as treatment endpoints
- Instead we use surrogate endpoints:
  - Biochemical
    - Normalization of ALT
  - Serologic
    - HBeAg loss and/or seroconversion for HBeAg positive HBV
    - Ideally HBsAg loss and/or seroconversion
  - Virologic
  - Histologic

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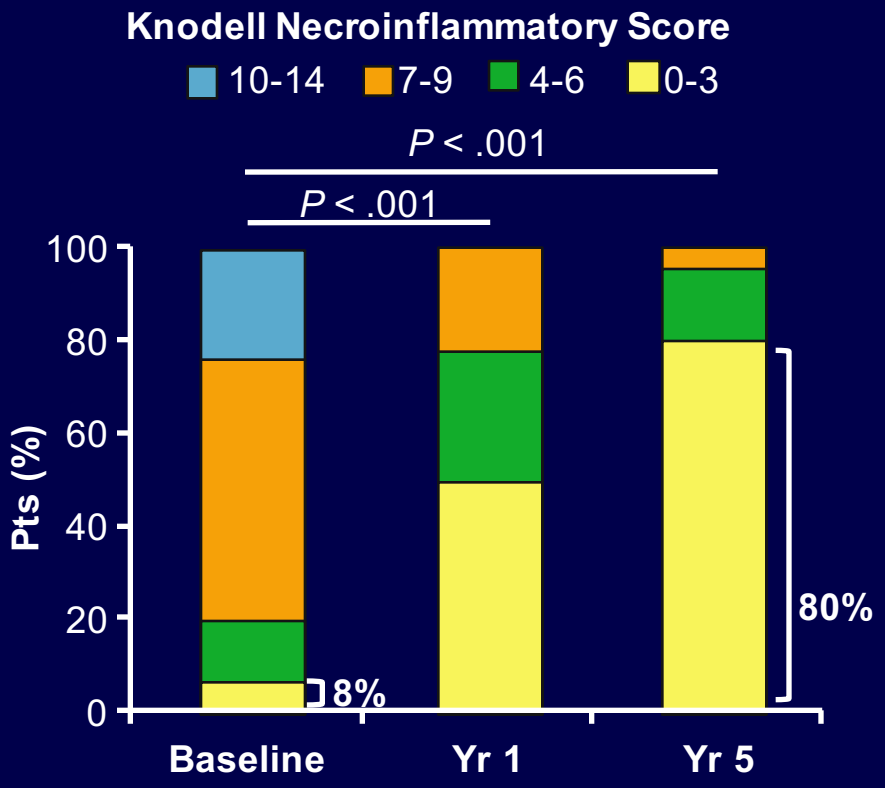
Long-term TDF in Pts With HBV: Reversal of Inflammation

- Open-label study of TDF in pts with chronic HBV infection (N = 585)

Parameter	Outcome at 7 Yrs[1]
Normalized ALT, % (n/N) ▪ ITT* ▪ On treatment	 57.1 (323/566) 80.0 (328/410)
HBV DNA < 29 IU/mL, % (n/N) ▪ ITT ▪ On treatment	 70.1 (418/596) 99.3 (430/433)
HBeAg loss,† % (n/N)	54.5 (84/154)
HBe seroconversion,† % (n/N)	39.6 (61/154)
HBsAg loss,† K-M % (95% CI)	11.8 (8.1, 16.9)
HBs seroconversion,† K-M % (95% CI)	9.7 (6.4, 14.6)

*Pts with data missing or FTC added counted as failures.
†HBeAg-positive population.

- Necroinflammation improved over 5 yrs (n = 348 matched biopsies)[2]

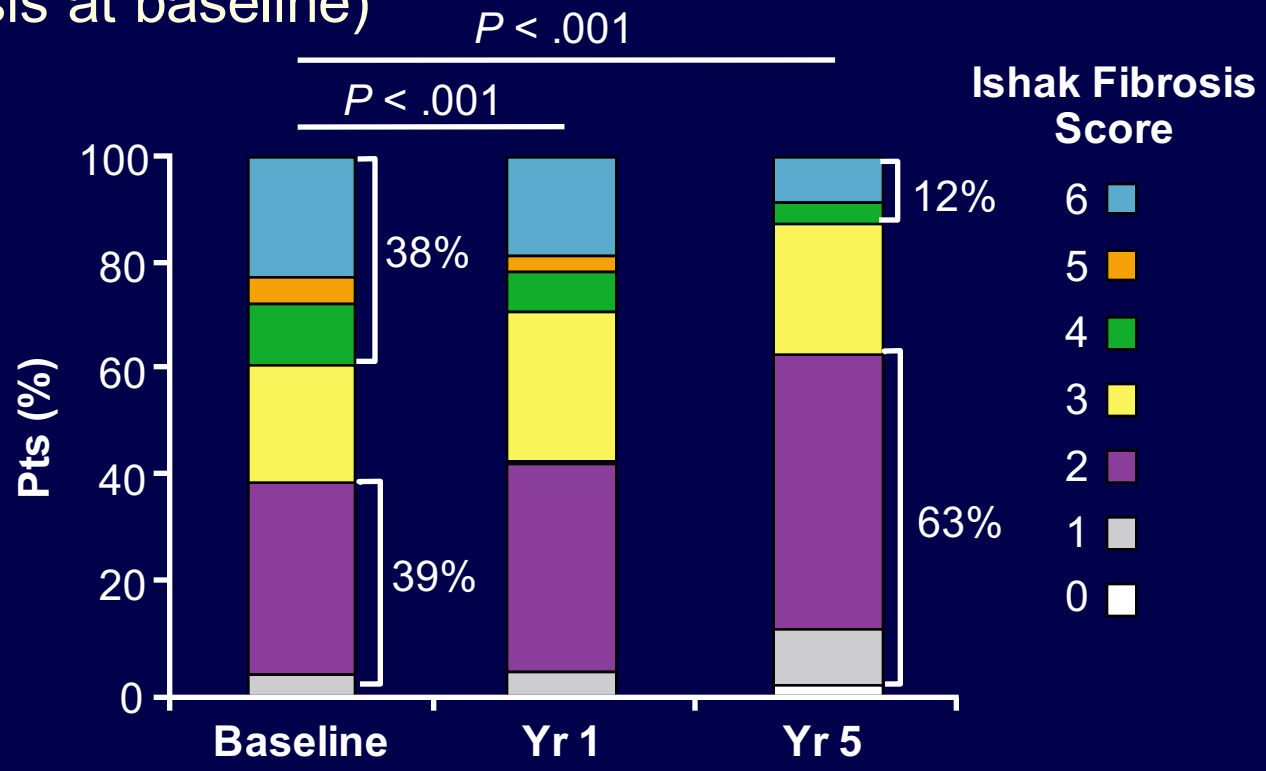


1. Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.
2. Marcellin P, et al. Lancet. 2013;381:468-475.

Slide credit: clinicaloptions.com

Long-term TDF in Pts With HBV: Regression of Fibrosis, Cirrhosis

- Overall regression of fibrosis in 51% of pts through 5 yrs (176/348 pts with matched biopsies)
- Reversal of cirrhosis in 74% of pts through 5 yrs (71/96 pts with cirrhosis at baseline)



Marcellin P, et al. Lancet. 2013;381:468-475.

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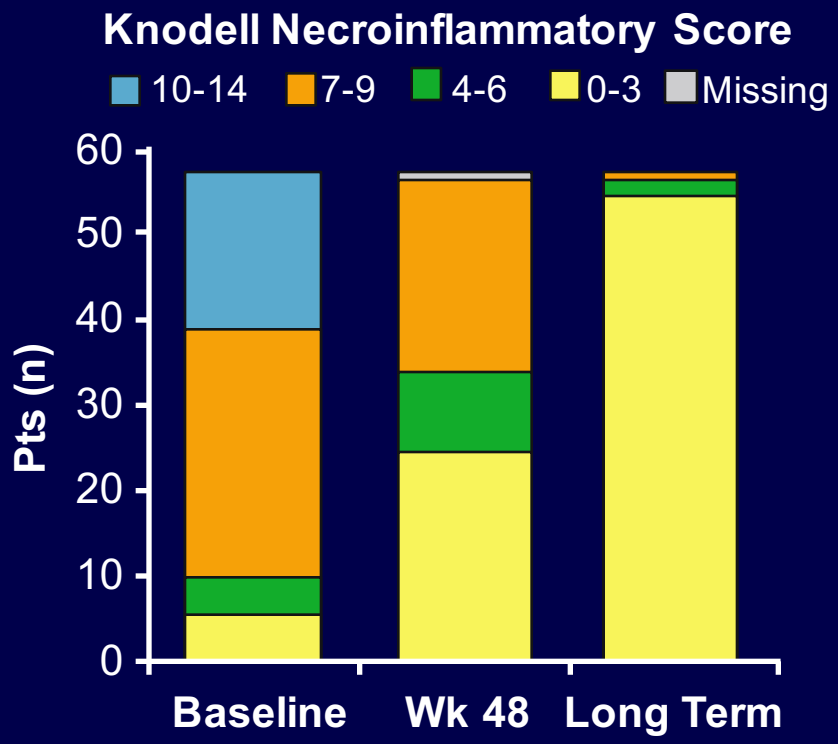
Long-term Entecavir in Pts With HBV: Reversal of Inflammation

- Histologic and virologic improvements evaluated by liver biopsy in HBV pts (N = 69) with ≥ 3-yr cumulative entecavir treatment
- Median time on entecavir: 6 yrs (range: 3-7)

Parameter, % (n/N)	Outcome
ALT ≤ 1 x upper limit of normal	86 (49/57)
HBV DNA < 300 copies/mL	100 (57/57)
HBeAg loss	55 (22/40)
HBe seroconversion	33 (13/40)
HBsAg loss	0 (0/56)



Chang TT, et al. Hepatology. 2010;52:886-893.

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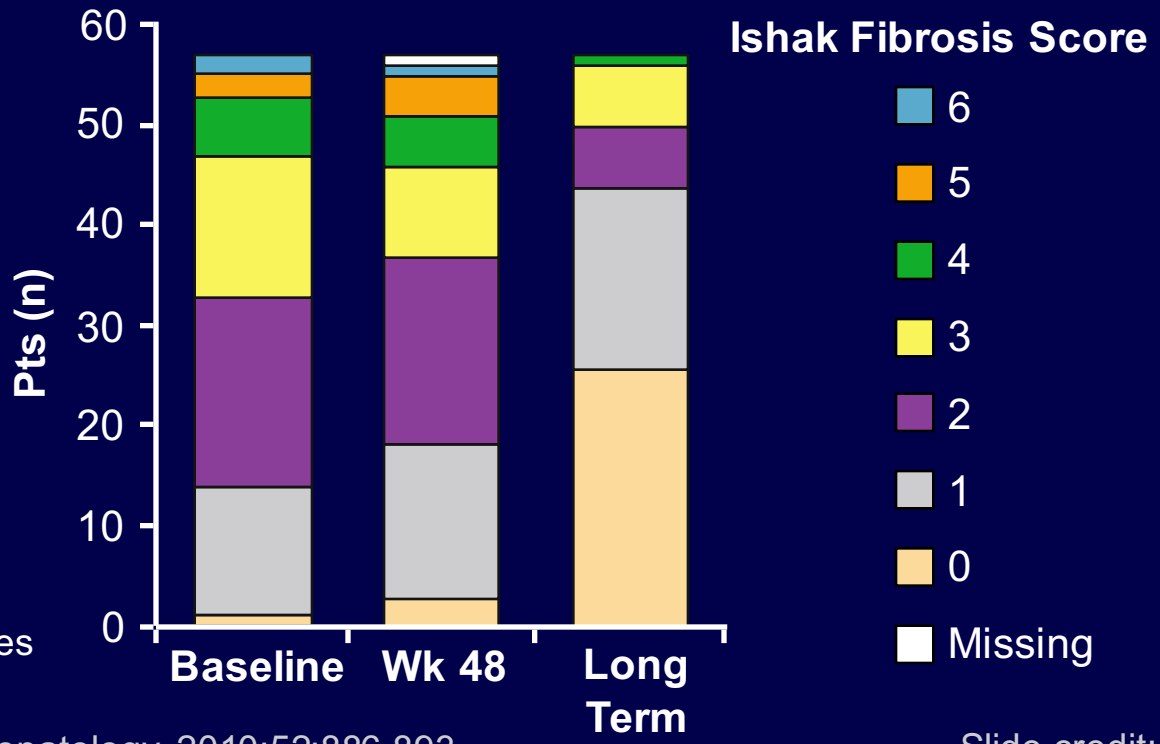
Long-term Entecavir in Pts With HBV: Regression of Fibrosis, Cirrhosis

- Regression of fibrosis (≥ 1-point decrease in Ishak score) in 88% of pts (50/57 pts with matched biopsies and baseline Knodell scores ≥ 2)
- Reversal of cirrhosis in 4/10 pts with cirrhosis at baseline (median decrease in Ishak score: 3 points)



n = 57
matched biopsies

Chang TT, et al. Hepatology. 2010;52:886-893.

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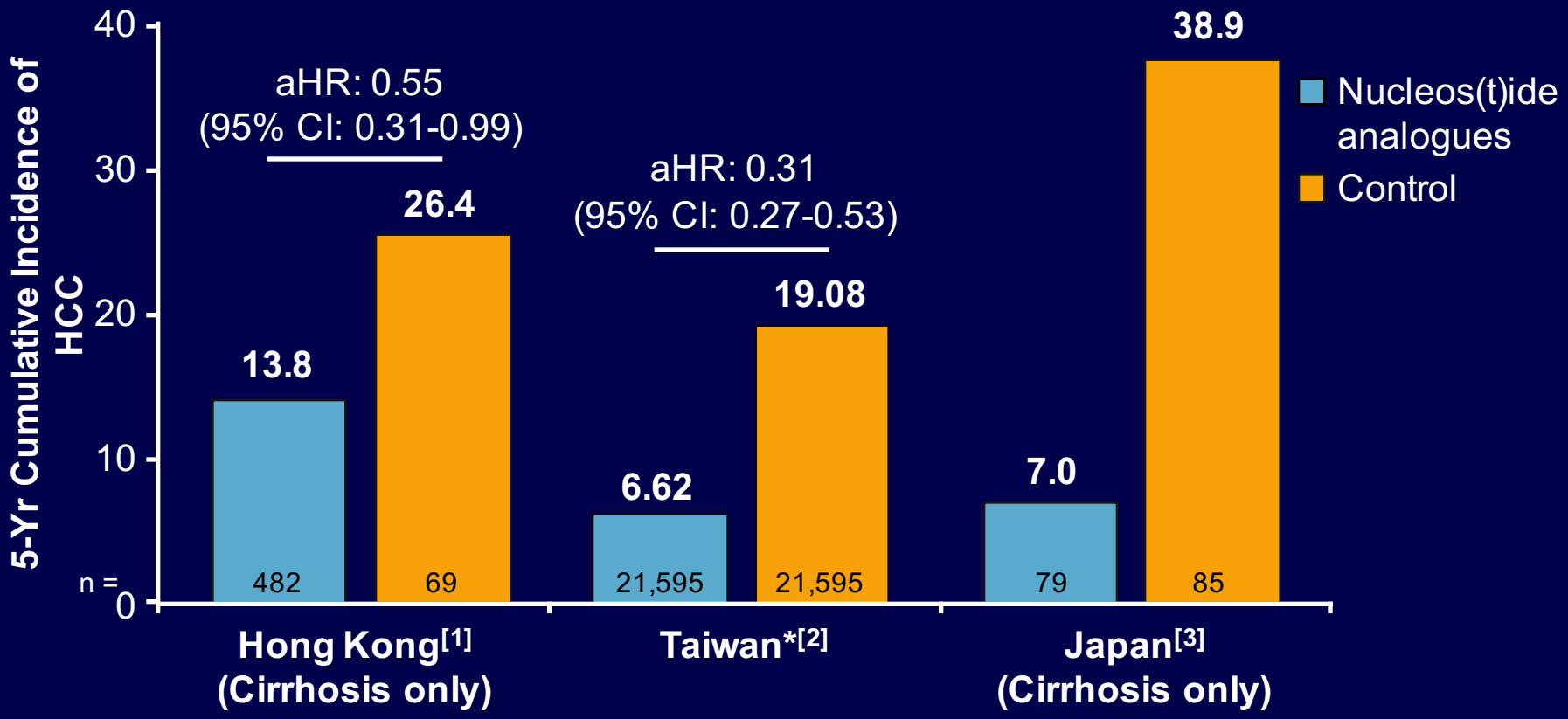
HCC Incidence in Pts With Chronic HBV Infection

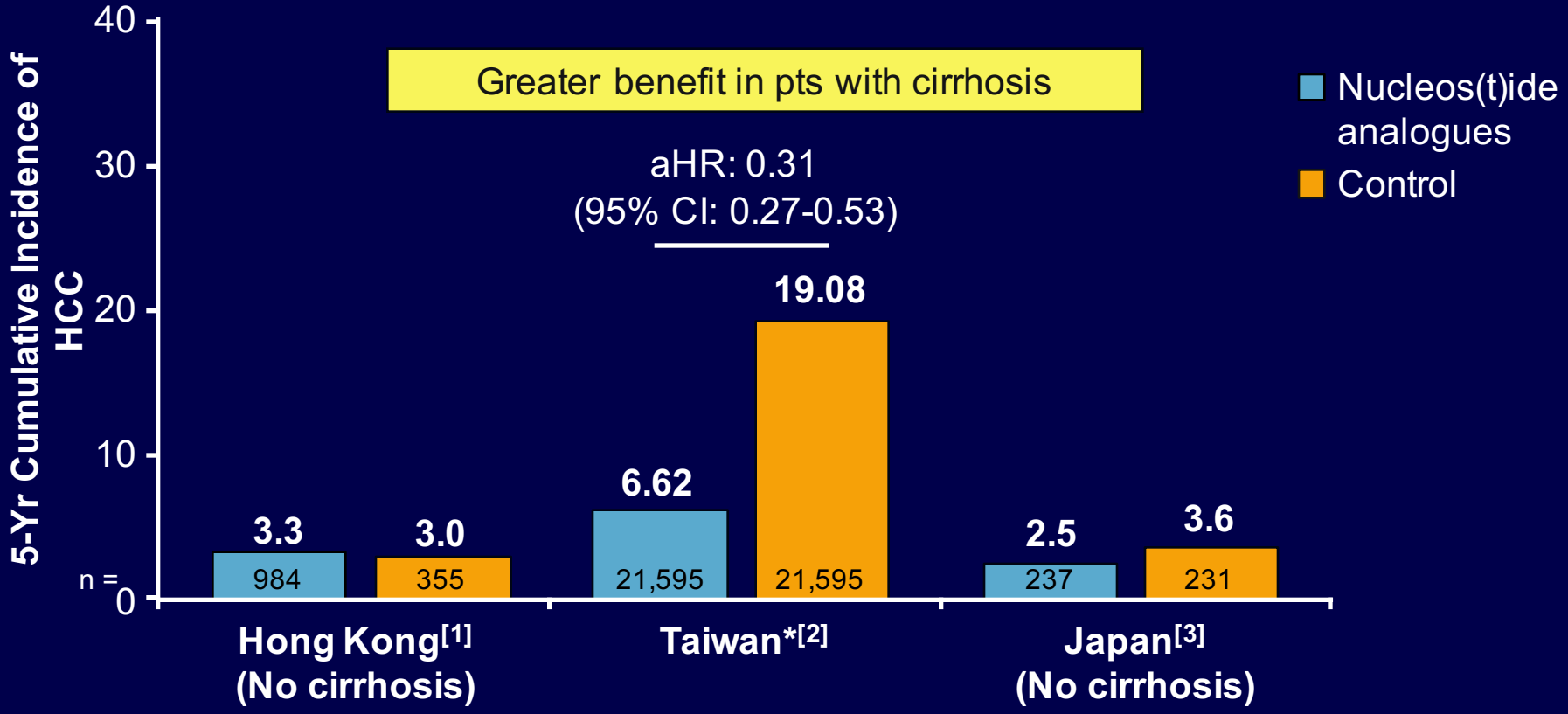


*Incidence rates include cirrhotic pts (13.6% of pts had cirrhosis at baseline) and noncirrhotic pts.

1. Wong GL, et al. Hepatology. 2013;5:1537-1547.
2. Wu CY, et al. Gastroenterology. 2014;147:143-151.
3. Hosaka T, et al. Hepatology. 2013;58:98-107.

Slide credit: clinicaloptions.com

HCC Incidence in Pts With Chronic HBV Infection but Without Cirrhosis



*Incidence rates include cirrhotic pts (13.6% of pts had cirrhosis at baseline) and noncirrhotic pts.

1. Wong GL, et al. Hepatology. 2013;5:1537-1547.
2. Wu CY, et al. Gastroenterology. 2014;147:143-151.
3. Hosaka T, et al. Hepatology. 2013;58:98-107.

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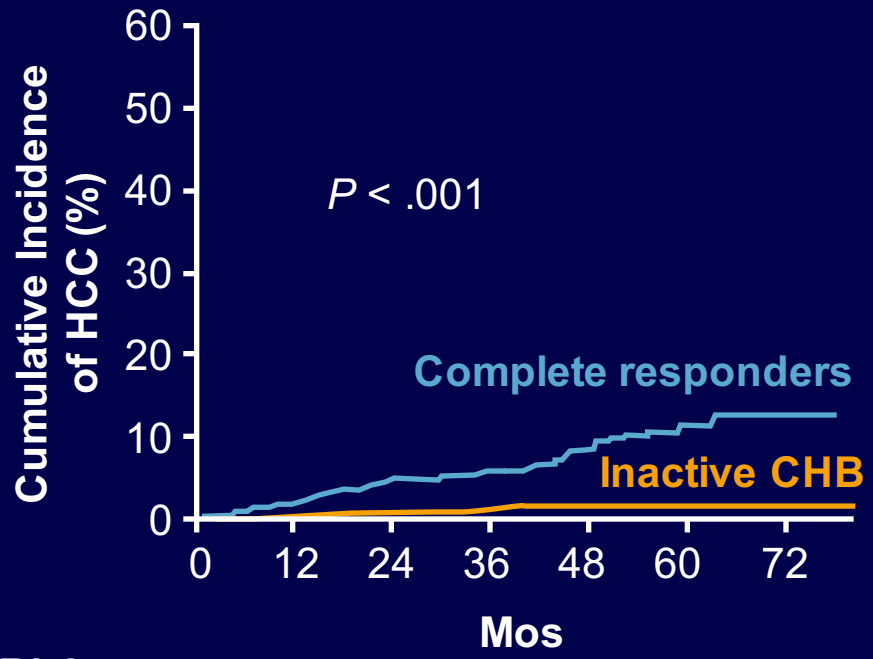
Is HBV Suppression the Same as Inactive Disease?

- Retrospective cohort study of treatment-naive pts with HBV starting oral nucleos(t)ide analogues (n = 1378) vs HBeAg-negative pts with inactive CHB (n = 1014)
  - Group receiving nucleos(t)ide analogues divided by continuous viral suppression (complete vs incomplete responder)
- Spontaneous control better than treatment



Pts at Risk, n

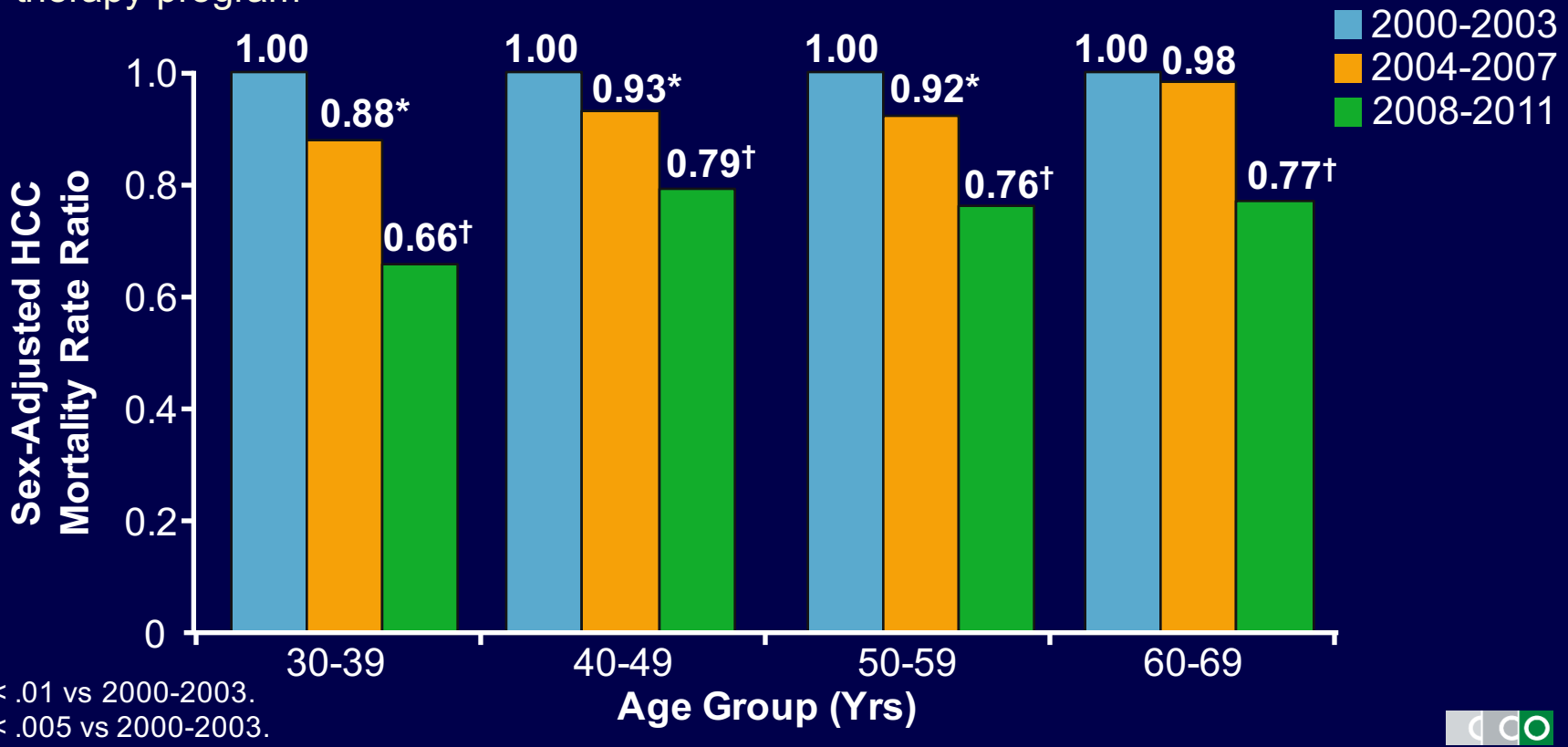
NUC CR	1132	848	564	497	380	128	19
Inactive CHB	1014	918	724	594	469	304	80

Cho JY, et al. Gut. 2014;63:1943-1950.

Slide credit: clinicaloptions.com

Reduction in HCC Mortality Through National Viral Hepatitis Therapy Program

- Pts receiving treatment for chronic hepatitis after start of program in 2003 in Taiwan: 157,570 (HBV) and 61,823 (HCV)
- Reduced rate of HCC mortality in all age cohorts by 5-8 yrs after introduction of national therapy program



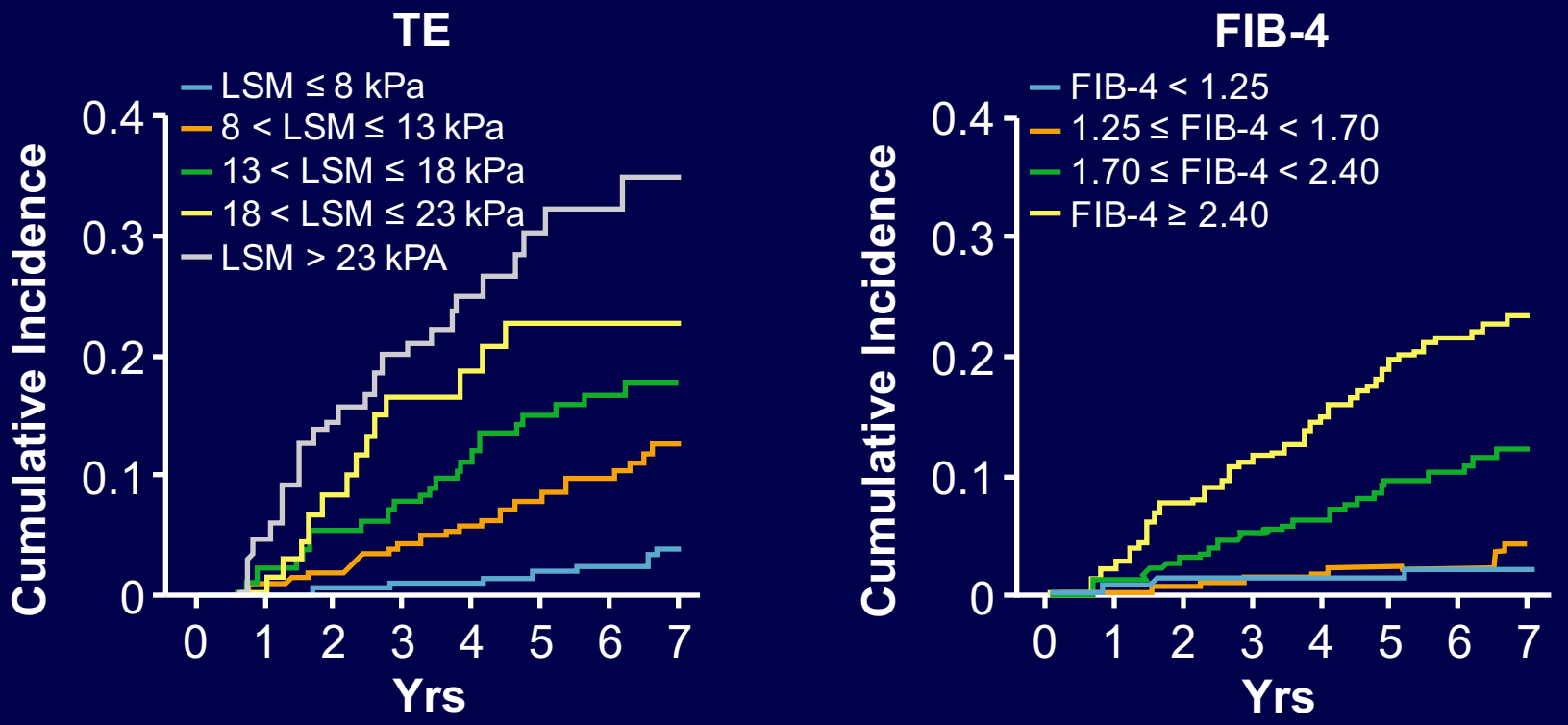
*P < .01 vs 2000-2003.
†P < .005 vs 2000-2003.

Chiang CJ, et al. Hepatology. 2015;61:1154-1162.

Slide credit: clinicaloptions.com

Identifying Risk of HCC: Transient Elastography vs Biomarkers

- Retrospective study comparing prognostic performance of TE vs FIB-4 serological biomarker score to identify risk of HCC in pts with CHB (N = 1308)



- TE was more accurate than FIB-4 at identifying low HCC risk

Kim SU, et al. Medicine (Baltimore). 2016;95:e3434.

Slide credit: clinicaloptions.com

Based on This . . .
Whom and How Should We Treat?

Updated AASLD Guidelines: When to Treat

HBeAg Positive			HBeAg Negative		
HBV DNA, IU/mL	ALT	Histologic Disease	HBV DNA, IU/mL	ALT	Histologic Disease
Any	> 2 x ULN	N/A	Any	> 2 x ULN	N/A
> 20,000	Any	Any	> 2000	Any	Any
Any	Any	Cirrhosis	Any	Any	Cirrhosis

Do not stop treatment in HBeAg-negative pts with cirrhosis

Changes to guidance:

- Lower threshold for treating HBeAg-negative pts
- Treat all pts with cirrhosis regardless of HBV DNA

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

AASLD Guidelines: Initial Treatment

Treatment	Preferred	Notes
Entecavir	Yes (unless previous history of lamivudine resistance)	High potency, high genetic barrier to resistance
Tenofovir	Yes	High potency, high genetic barrier to resistance
PegIFN	Yes	Less safe in pts with cirrhosis
Adefovir	No	Low genetic barrier to resistance
Lamivudine	No	Low genetic barrier to resistance
Telbivudine	No	Low genetic barrier to resistance

- Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk

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

TAF vs TDF in Pts With HBV Infection: Efficacy

- Multicenter phase III studies in pts with chronic HBV infection (N = 1298), including pts with compensated cirrhosis

	HBeAg-Positive Pts[2] (N = 873)			HBeAg-Negative Pts[3] (N = 425)		
Outcome, %	**TAF**	**TDF**	***P* Value**	**TAF**	**TDF**	***P* Value**
HBV DNA < 29 IU/mL at Wk 72[1]	71.6	71.9	.78	92.6	92.1	.84
ALT normalization at Wk 48						
▪ Central laboratory criteria*	72	67	.18	83	75	.076
▪ AASLD laboratory criteria†	45	36	.014	50	32	<.001
HBeAg						
▪ Loss at Wk 48	14	12	.47			
▪ Seroconversion at Wk 48	10	8	.32			
HBsAg						
▪ Loss at Wk 48	<1	<1	.52			
▪ Seroconversion at Wk 48	<1	0	.22			

*ULN for men, ≤ 43 U/L (≤ 35 U/L if age ≥ 69 yrs); for women, ≤ 34 U/L (≤ 32 U/L if age ≥ 69 yrs).
†ULN for men, ≤ 30 U/L; for women, ≤ 19 U/L.

1. Seto WK, et al. AASLD 2016. Abstract 67. 2. Chan HL, et al. EASL 2016. Abstract GS12. 3. Buti M, et al. EASL 2016. Abstract GS06.

TAF vs TDF in Pts With HBV Infection: Safety

- Multicenter phase III studies in pts with chronic HBV infection (N = 1298), including pts with compensated cirrhosis

Outcome	TAF	TDF	*P* Value
Mean change in BMD at Wk 72, %[1]			
▪ Hip	-0.16	-1.86	< .001
▪ Spine	-0.57	-2.37	< .001
Median change in serum creatinine at Wk 48, mg/dL[2]	0.01	0.02	.012
Median change in eGFR at Wk 48, mL/min[2]	-1.2	-5.4	< .001
Mean change in *FibroTest* score at Wk 48[3]			
▪ HBeAg-positive pts	-0.07	-0.04	.007
▪ HBeAg-negative pts	-0.05	-0.03	.028

1. Seto WK, et al. AASLD 2016. Abstract 67. 2. Agarwal K, et al. AASLD 2016. Abstract 1844. 3. Izumi N, et al. AASLD 2016. Abstract 1904.

Slide credit: clinicaloptions.com

Summary

- HBV is a very dynamic disease
- Fibrosis may progress quickly both in HBeAg-positive and HBeAg-negative disease
- Antiviral therapy can:
  - Suppress HBV DNA
  - Reduce inflammation—ALT and HAI
  - Reverse fibrosis
  - Reduce the risk of HCC and liver-related events
- New agents have similar efficacy on surrogate endpoints and a better safety profile

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