Haga clic para modificar el estilo de

Long term efficacy and safety of NUCs

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CONFLICT OF INTEREST

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Consultant and Speaker Bureau
Abbvie, Arbutus, BMS, Gilead, Merck/MSD, Roche

Advantages and Disadvantages of the Current Nucleoside Analogues recommended for Hepatitis B treatment:

Features	ETV, TDF, TAF
Route of administration	Oral
Treatment duration	Long-term until HBsAg loss*
Tolerability	High
Long-term safety concerns	Probably not‡
Contraindications	Nonell
Strategy	Inhibition of viral replication
Level of viral suppression	Universally high
Effect on HBeAg loss	Low in first year, moderate over long term
Effect on HBsAg levels	Low**
Risk of viral resistance	Minimal to none††

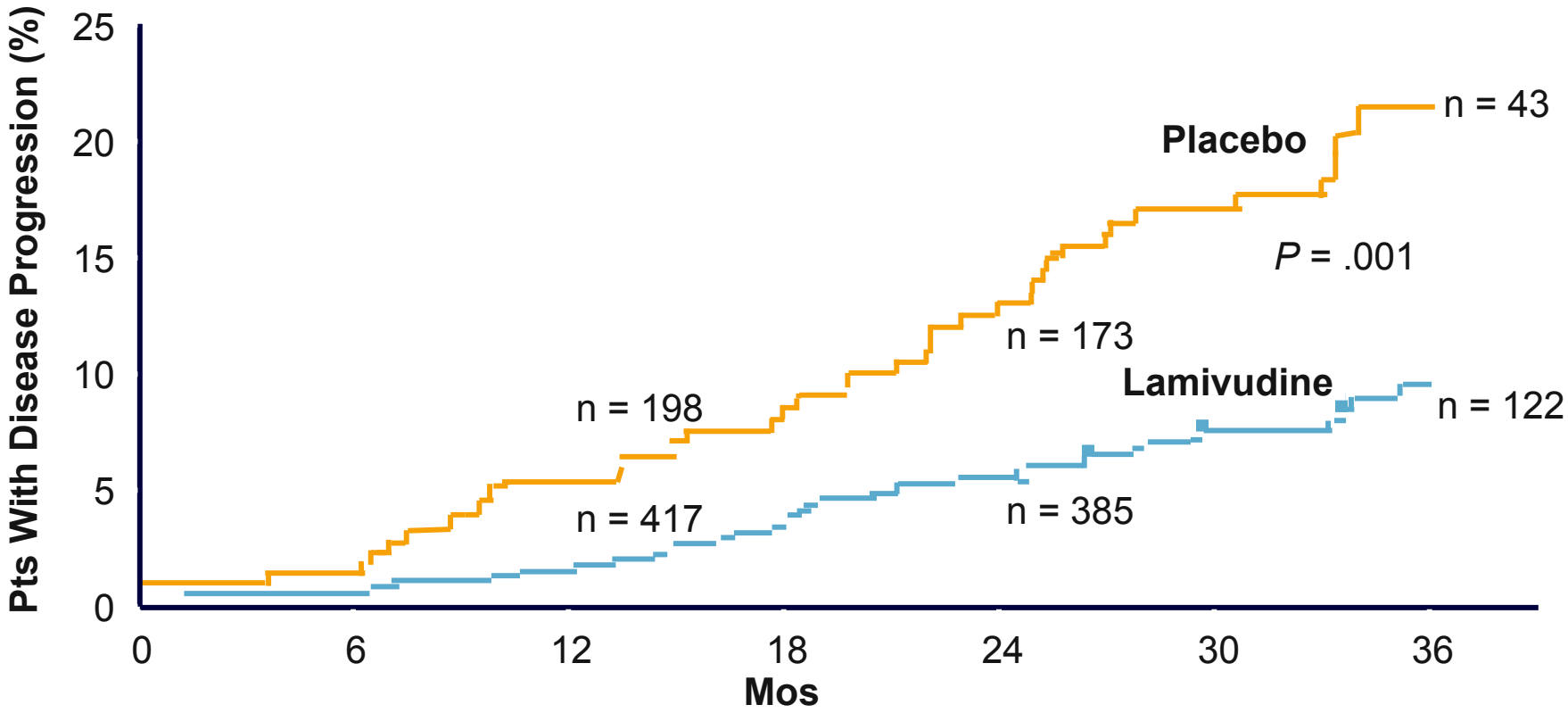
*Stopping NAs after some years might be considered in selected cases; †Psychiatric, neurological, endocrinological; ‡Uncertainties regarding kidney function, bone diseases for some NAs; §Decompensated disease, comorbidities etc.; ǁDose adjustments in patients with eGFR <50 ml/min are required for all NAs except for TAF (no dose recommendation for TAF in patients with CrCl <15 ml/min who are not receiving haemodialysis); ¶Depending on baseline characteristics; **Slowly increases with treatment time in HBeAg-positive patients (a plateau in serological responses has been observed beyond treatment Year 4), usually very low in HBeAg-negative patients; ††So far no TDF or TAF resistance development has been detected

EASL CPG HBV. J Hepatol 2017;67:370–98

Benefits of Achievement of Viral suppression have been proved in patients with HBV Cirrhosis and Decompensated Liver disease

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*



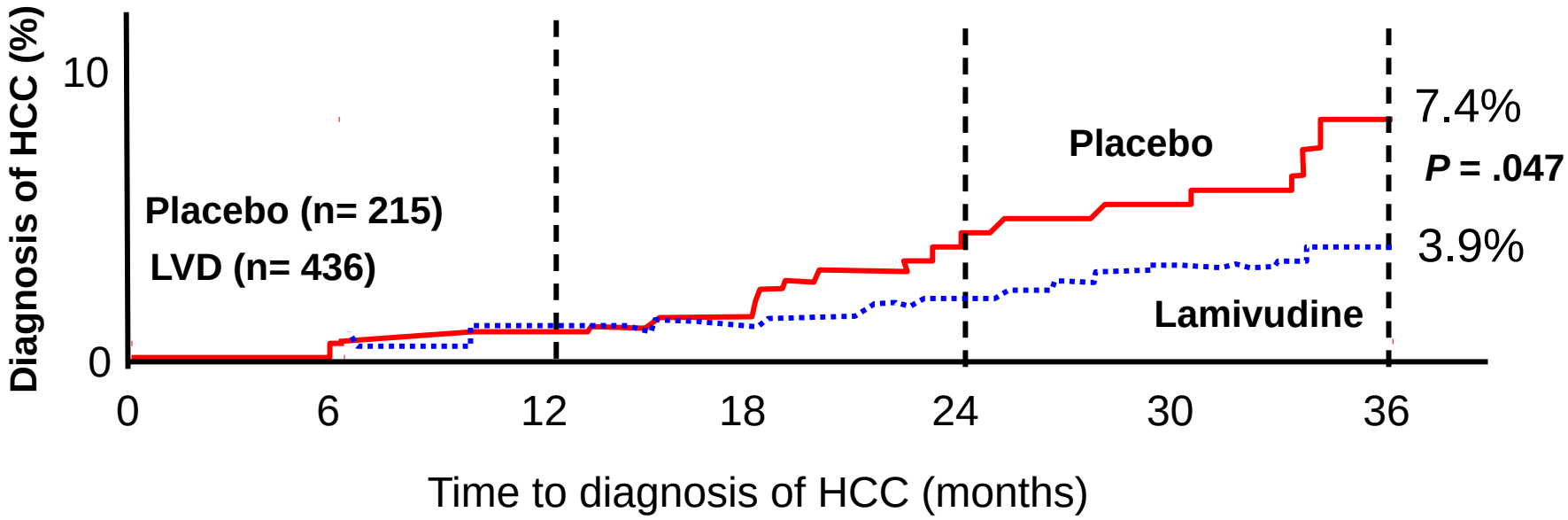
*Hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

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

Effects of Lamivudine on HCC Incidence

- Randomized controlled trial comparing lamivudine versus placebo In patients with advanced fibrosis or cirrhosis
  - Study terminated prematurely by DSMB (median Tx=32 mo)

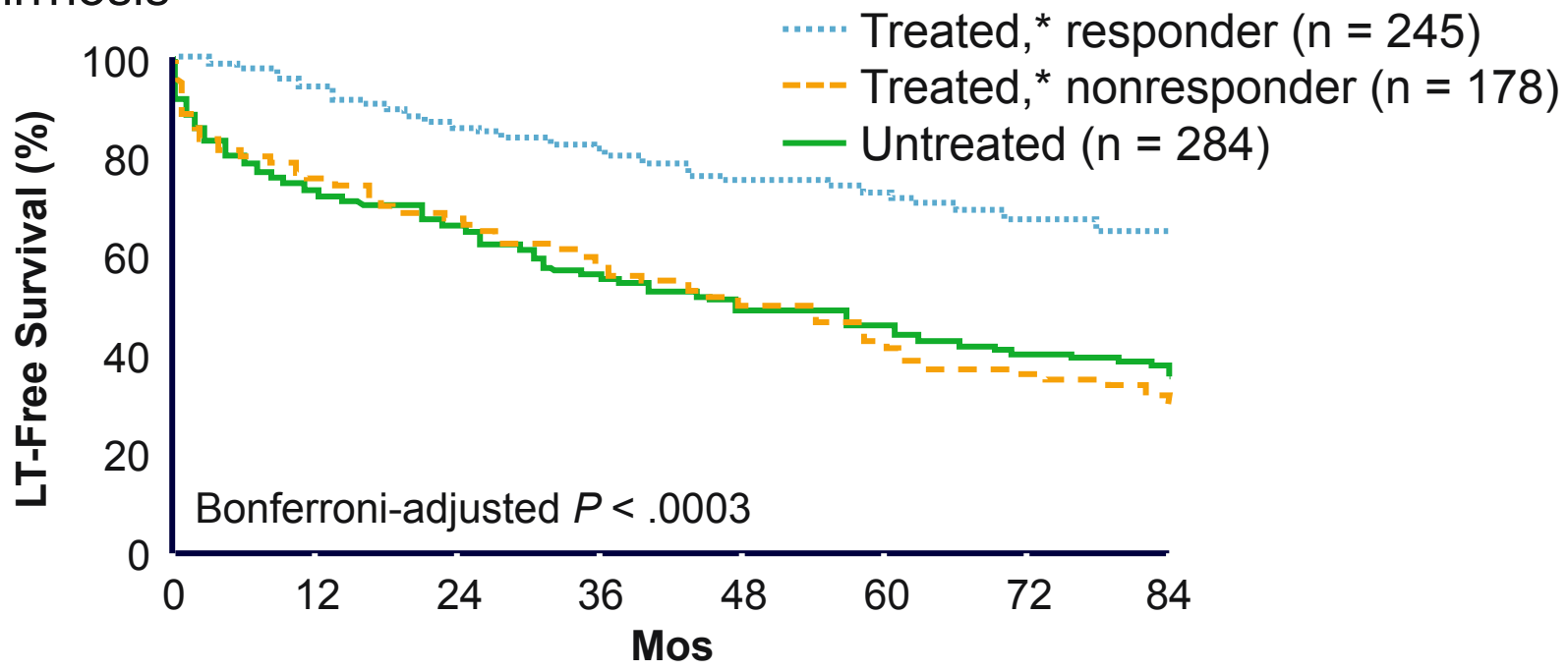
Risk of HCC reduced by 51% (p=0.047)



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

HBV Treatment Reduces Risk of Liver Transplant

- Prospective Multicenter cohort study in 707 pts with HBV and first-onset complications of decompensated cirrhosis



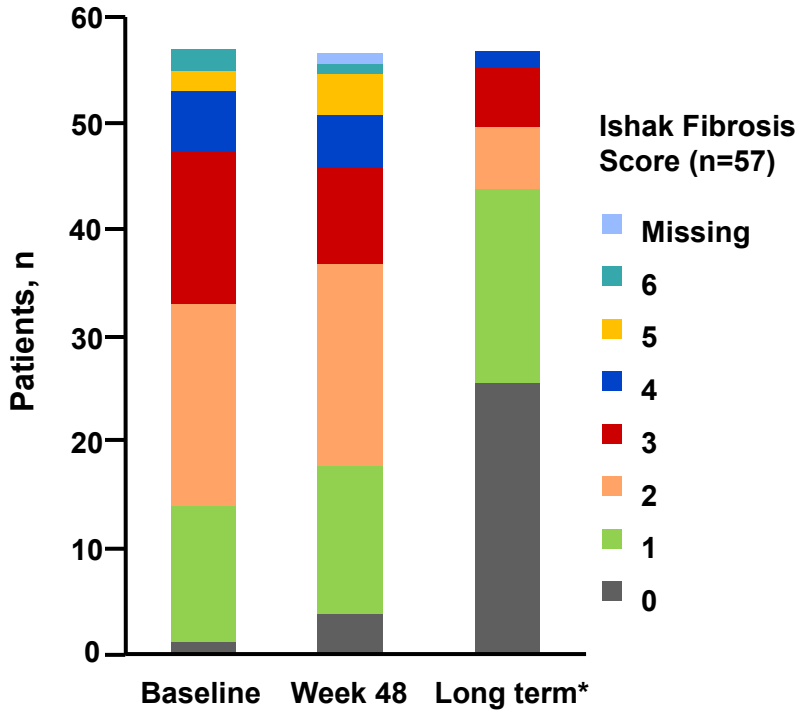
*Treated predominantly with lamivudine (n = 203) or entecavir (n = 198).

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

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

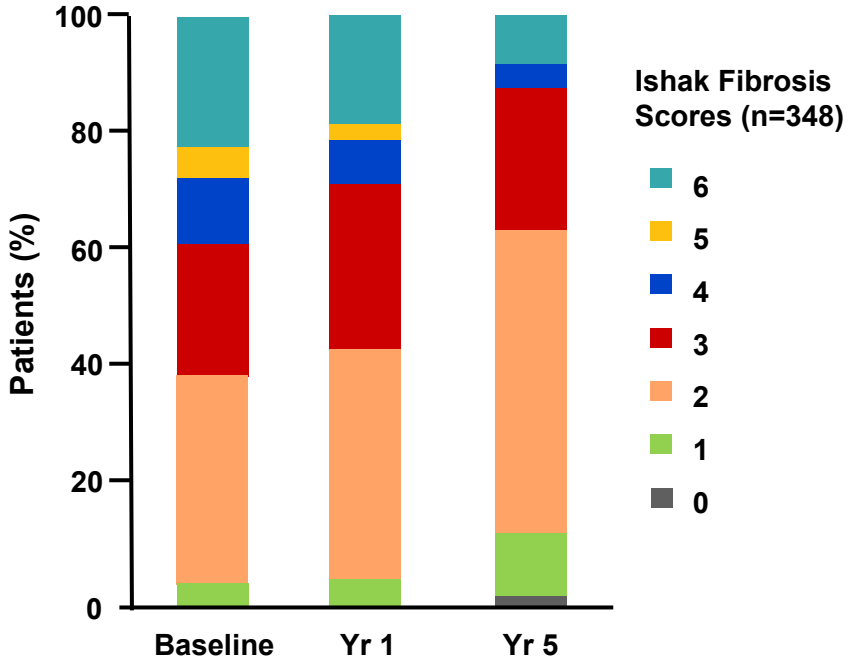
Benefits of Achievement of Viral suppression has been proved in patients with Chronic Hepatitis B

Long-term ETV and TDF Is Associated with Reversal of Liver Fibrosis in patients with CHB



Regression of fibrosis in 88% of pts

Reversal of cirrhosis in 4/10 pts with cirrhosis at baseline



Regression of fibrosis in 51% of pts through 5 yrs

Reversal of cirrhosis in 74% (71/96) of pts with cirrhosis at baseline

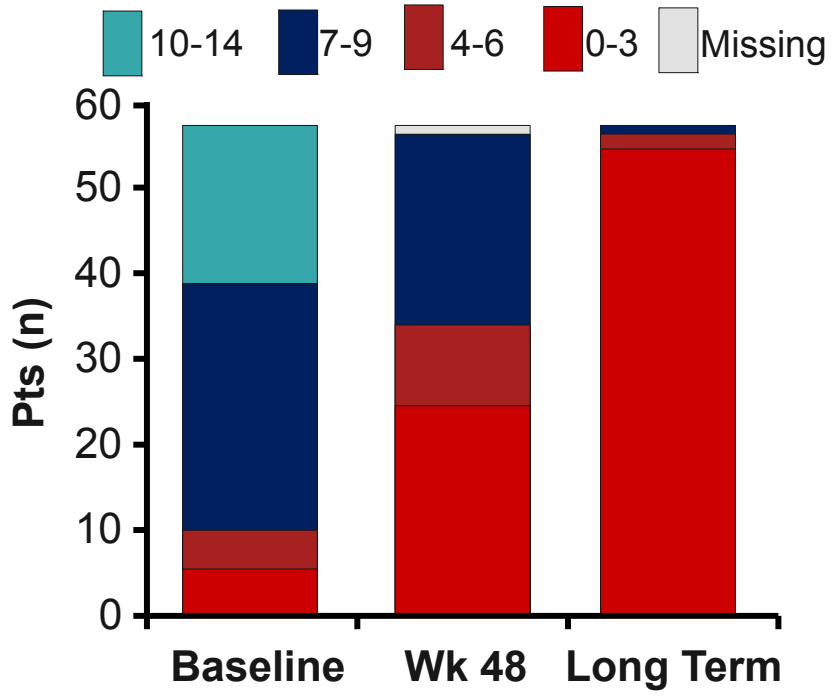
TDF: tenofovir disoproxil fumarate; ETV: entecavi* Long-term 7 years

Chang TT, et al. Hepatology 2010;52:886-893. Schiff ER, et al. Clin Gastroenterol Hepatol. 2011; 9:274-276. Marcellin P, et al. Lancet. 2013;381:468-475.

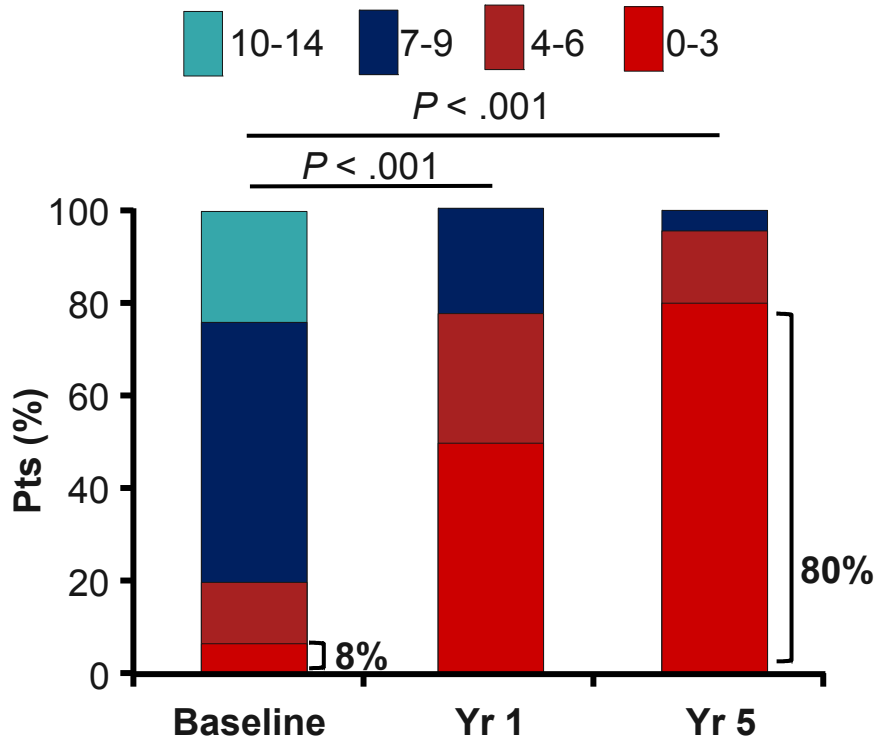
Long-term ETV and TDF Is Associated with Reversal of Liver Inflammation in patients with CHB

Knodell Necroinflammatory Score

ETV in pts with chronic HBV hepatitis (N = 69)

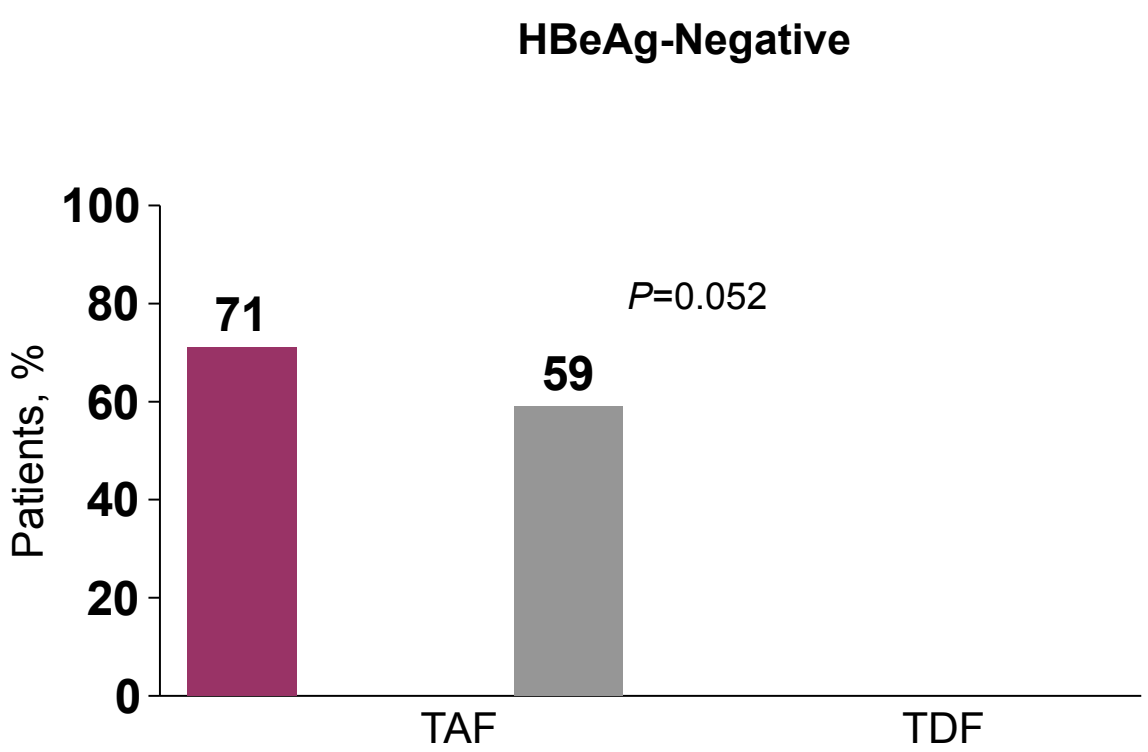


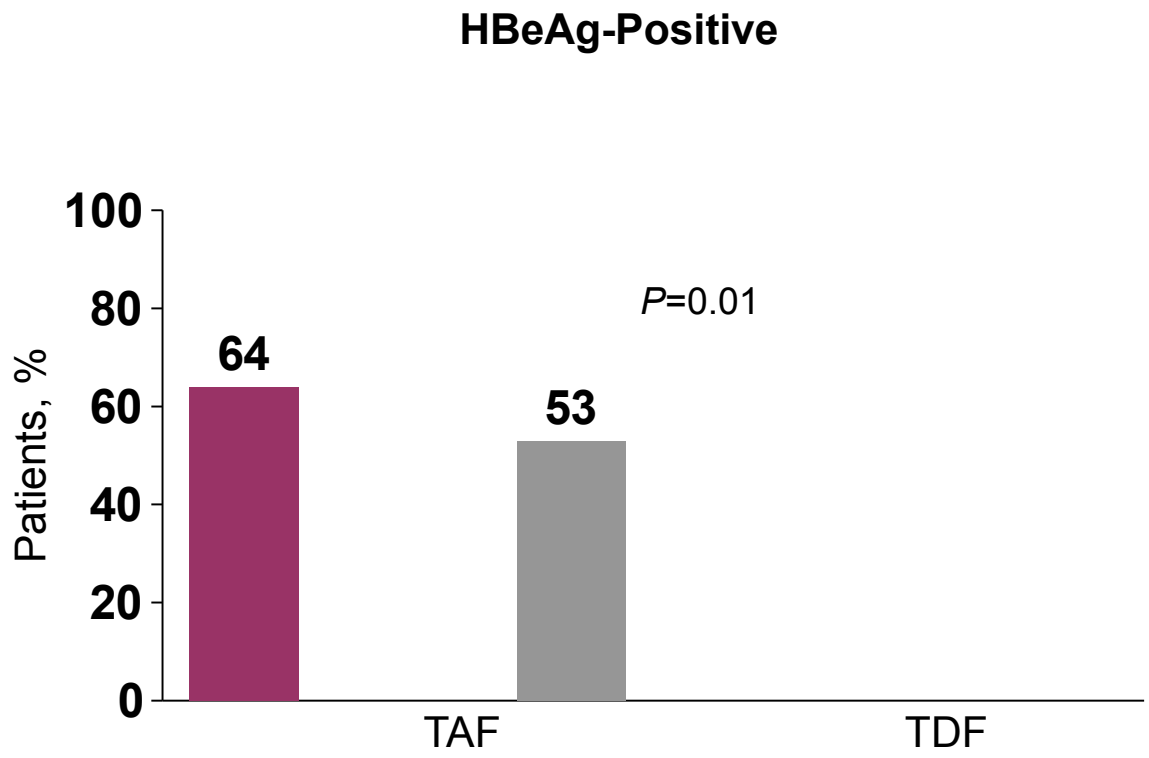
TDF in pts with chronic HBV infection (N = 585)



Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.Marcellin P, et al. Lancet. 2013;381:468-475. Chang TT et al Hepatoloy 2010;52:886-893

ALT Normalisation (AASLD 2018 Criteria) at Week 144





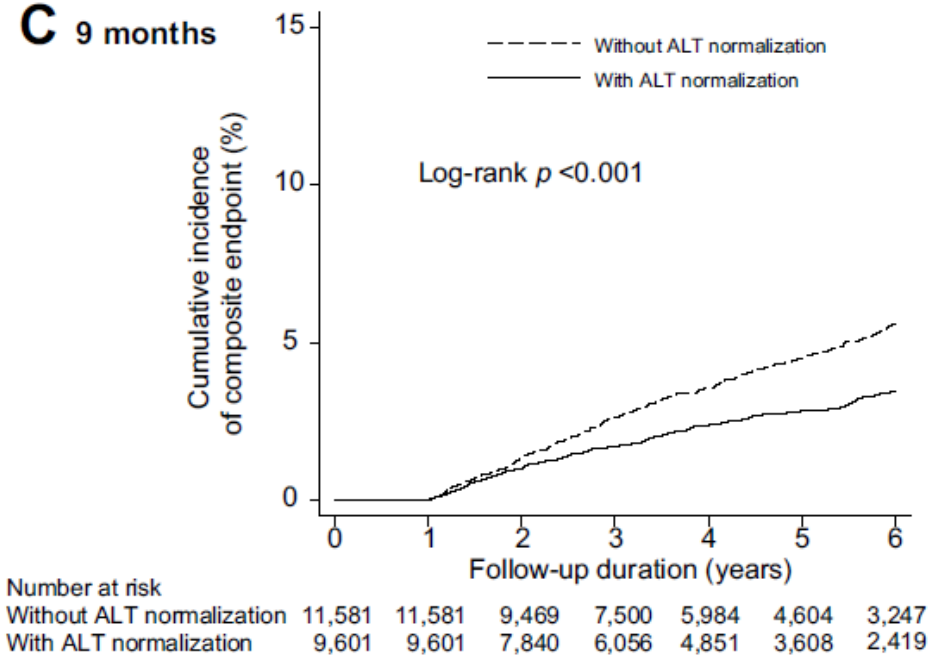
There were higher rates of ALT normalisation by AASLD 2018 criteria in patients on TAF compared to TDF

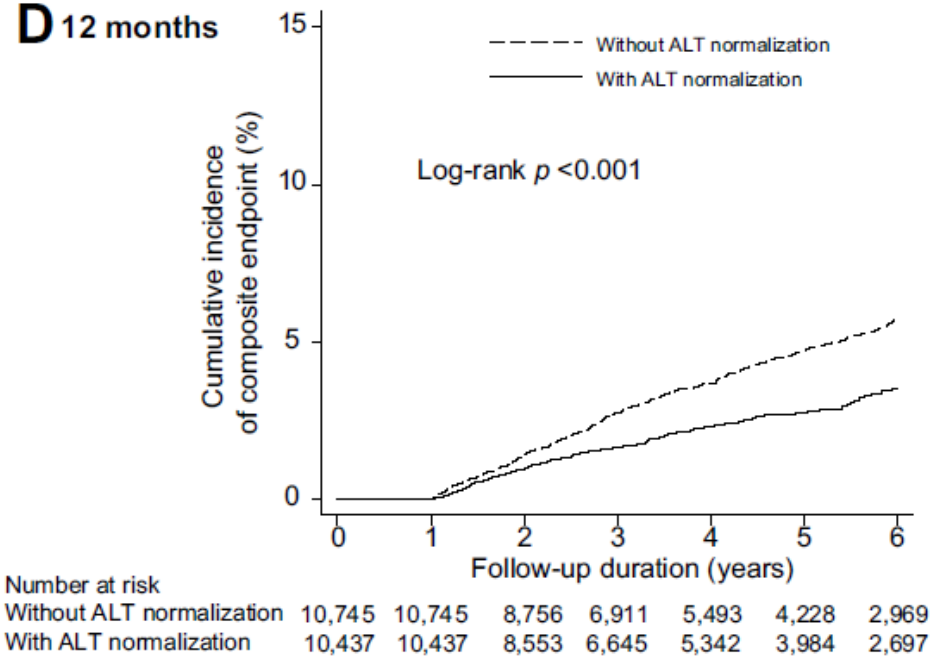
AASLD 2018 criteria ULN: males ≤ 35 U/L, females ≤ 25 U/L

Chan, AASLD 2018, 0381

Normal on-treatment ALT during antiviral therapy is associated with a lower risk of hepatic events in patients with chronic hepatitis B

Cumulative incidence of combined HCC or Hepatic Event in 21,182 CHB patients followed for 4±1.7 yrs





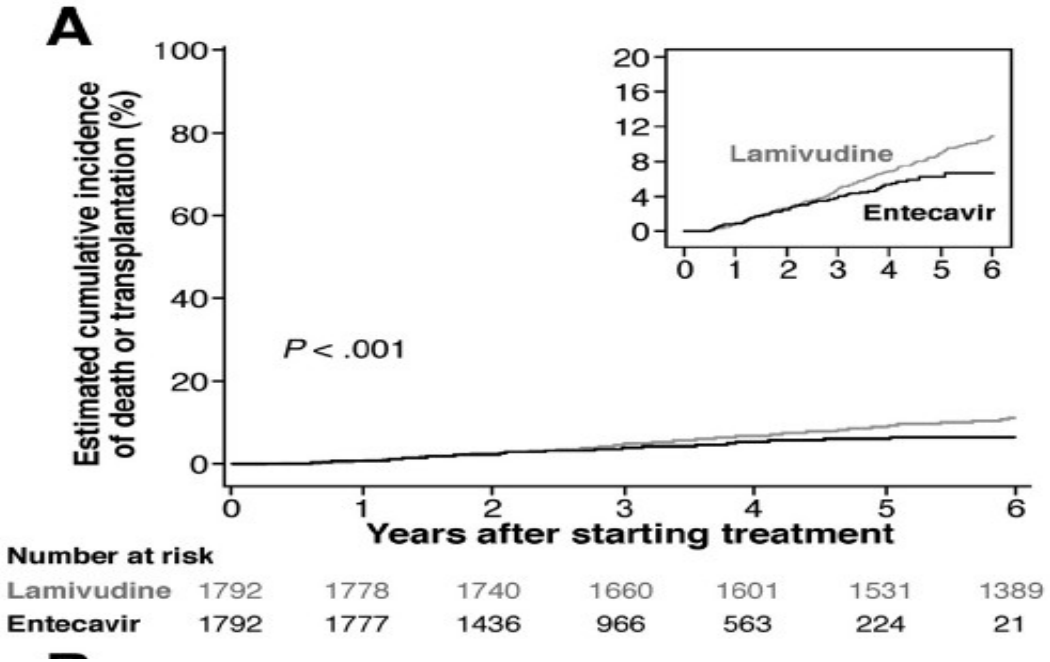
Cumulative incidence of composite endpoint at 6 years (%) (95% CI)	3 months	6 months	9 months	12 months
Without ALT normalization	4.76 (4.34-5.21)	5.24 (4.76-5.77)	5.57 (5.04-6.16)	5.70 (5.15-6.32)
With ALT normalization	4.27 (3.54-5.15)	3.60 (3.07-4.21)	3.44 (2.98-3.97)	3.51 (3.06-4.02)

Wong G L-H et al. J Hepatol 2018; 69:793-802

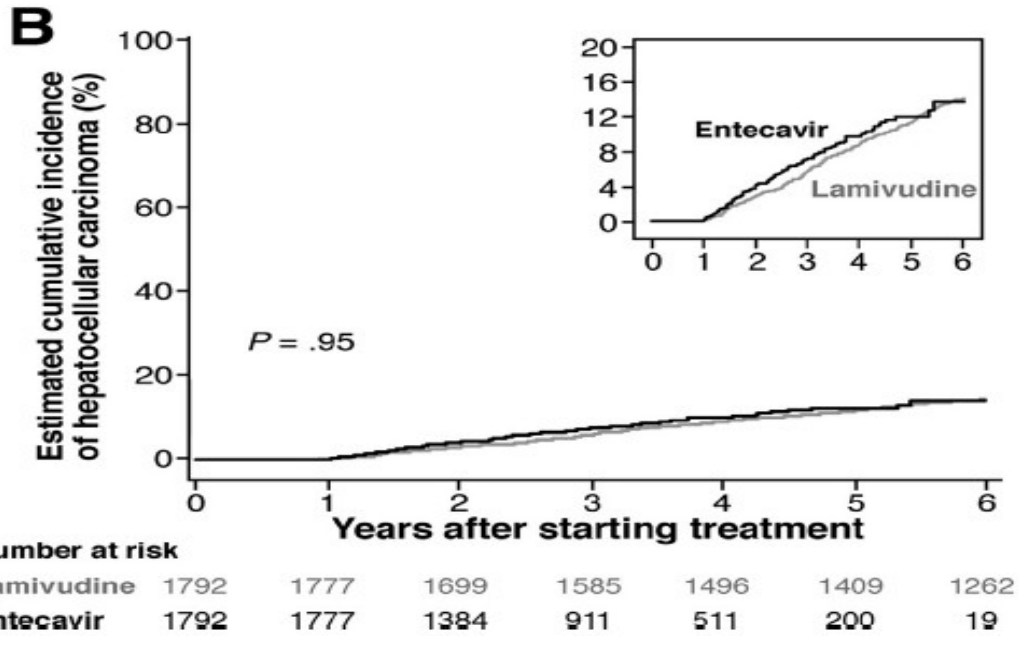
Mortality, liver transplantation, and hepatocellular carcinoma among patients with chronic hepatitis B treated with entecavir vs lamivudine

Retrospective analysis on the clinical outcomes of 5374 consecutive CHB adult patients treated with ETV (n=2000) or LAM (n=3374) between 11/1/1999 and 12/31/2011

Death or Liver Transplantation



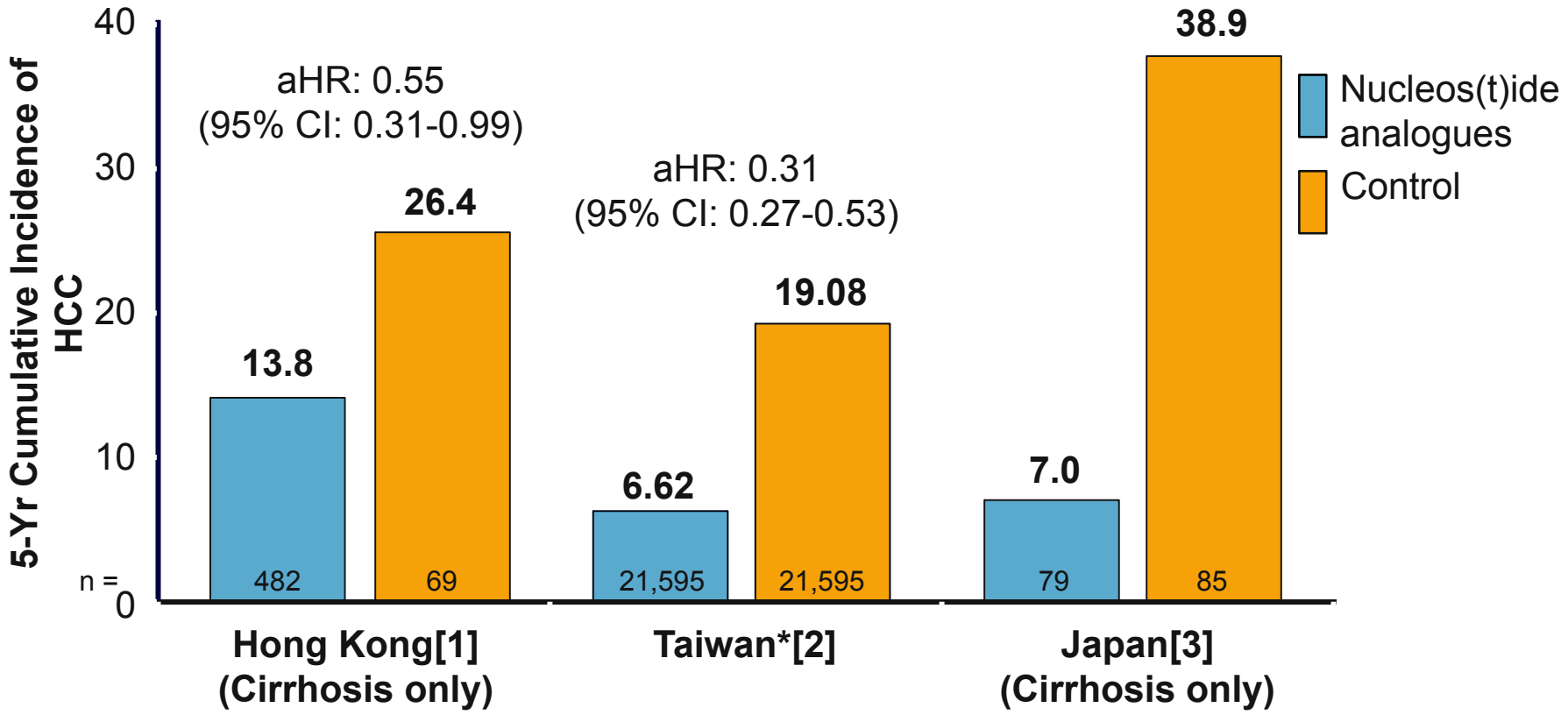
Hepatocelullar Carcinoma



ETV was associated with lower risk of death or transplantation than LAM, but no difference in HCC risk

Lim et al. *Gastroenterology* 2014;147:152-161

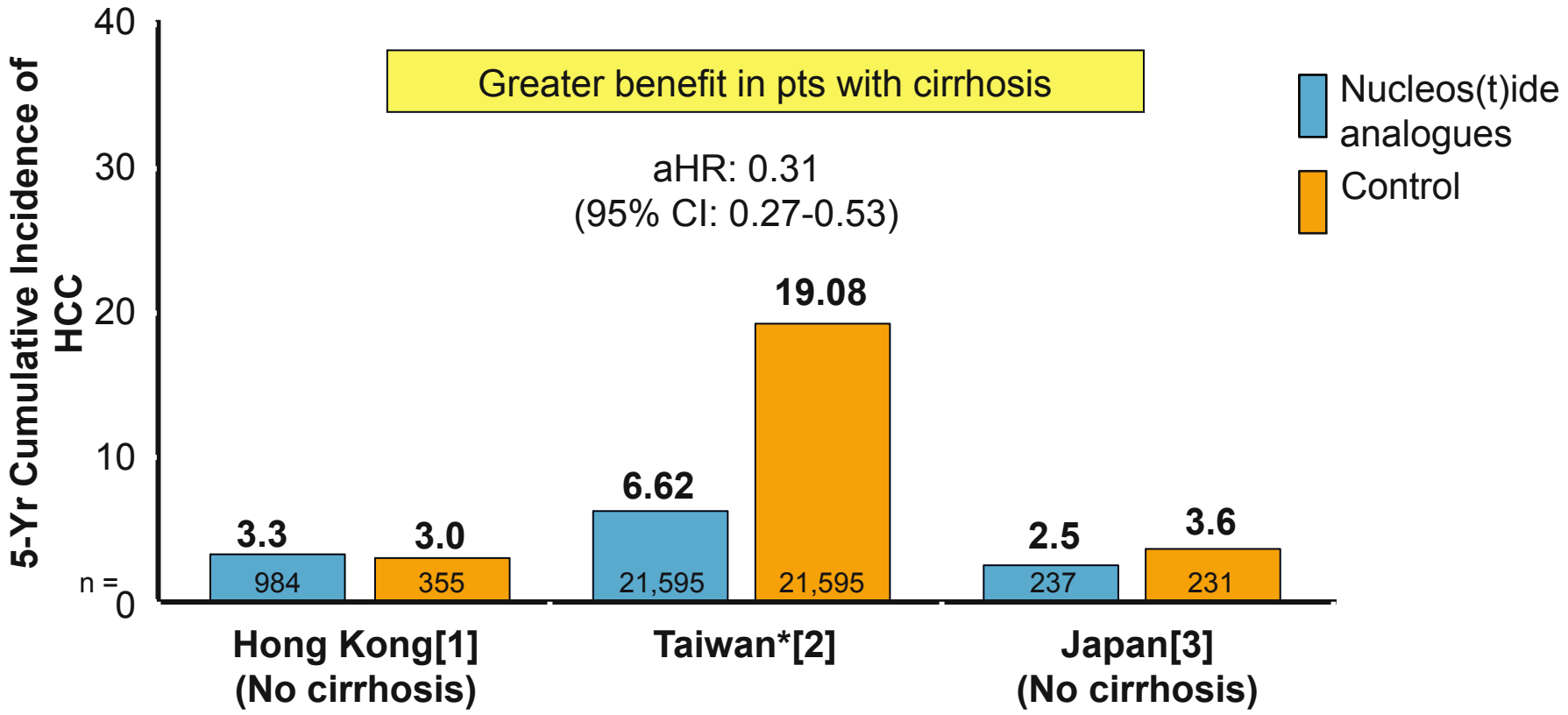
HCC Incidence in Pts With Chronic HBV Infection



*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.

HCC Incidence in Pts With Chronic HBV Infection but Without Cirrhosis



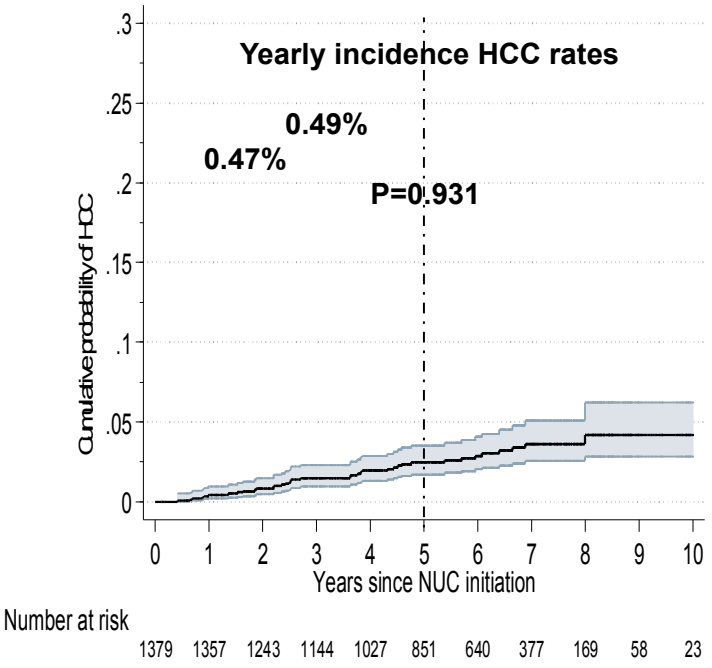
*Incidence rates include cirrhotic pts (13.6% of pts had cirrhosis at baseline) and noncirrhotic pts.

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.

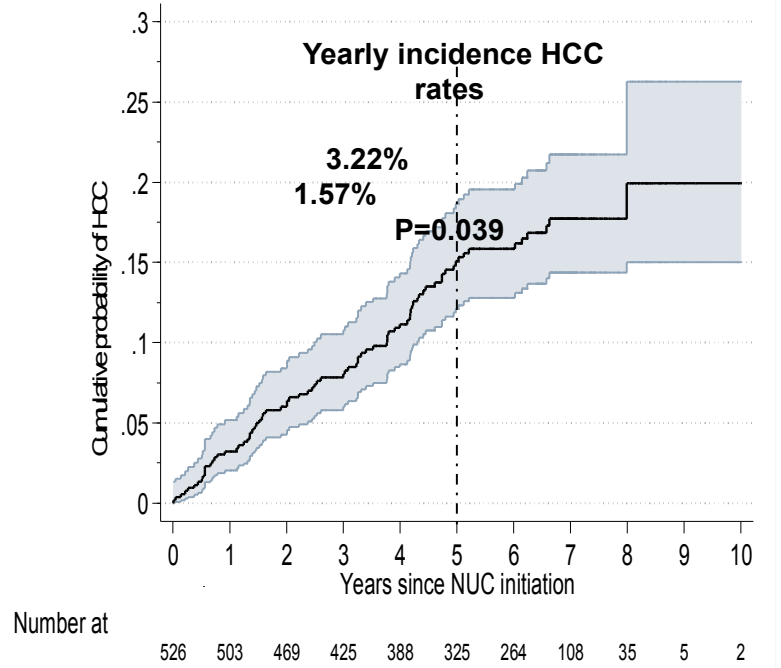
The PAGE-B study: HCC in ETV/TDF treated pts beyond year 5

1951 patients on ETV/TDF for 72 months

Chronic hepatitis



Compensated cirrhosis

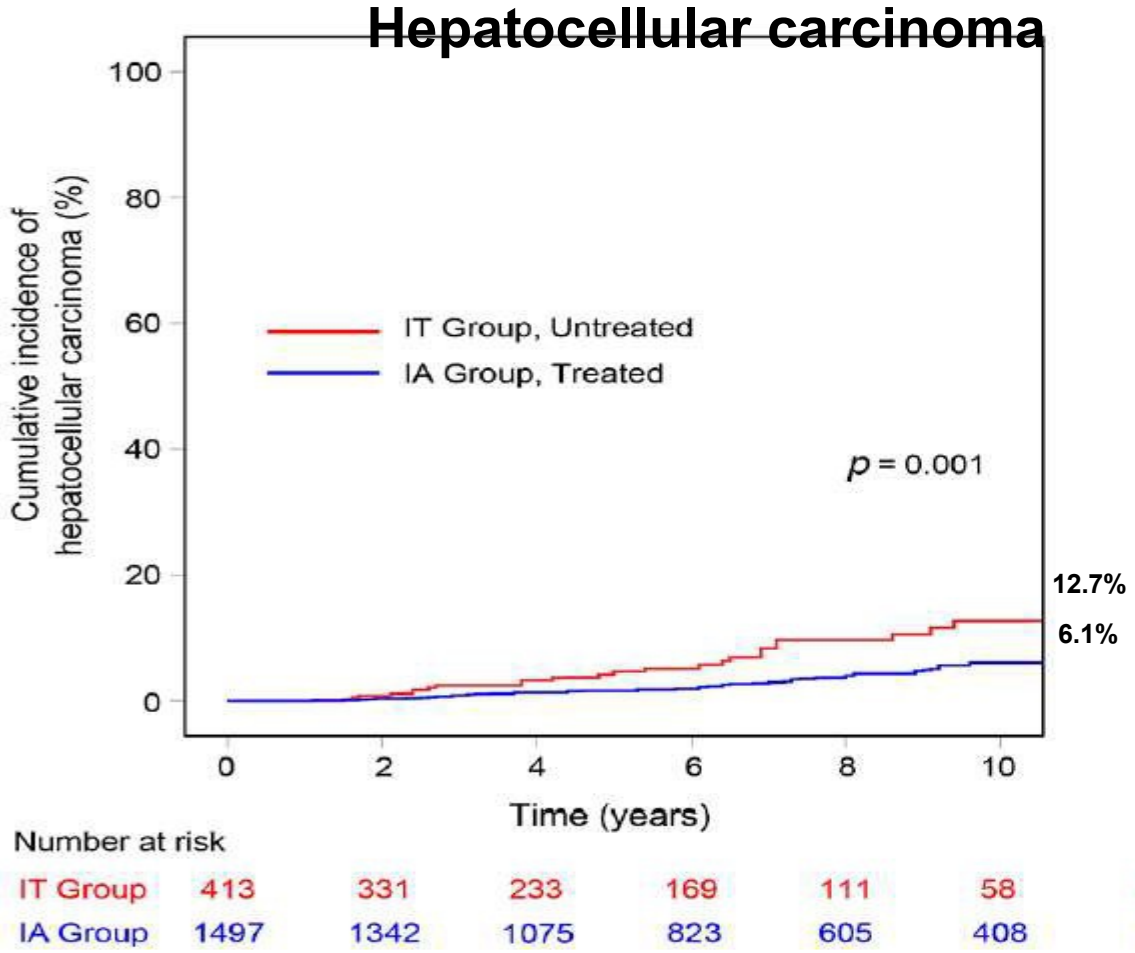


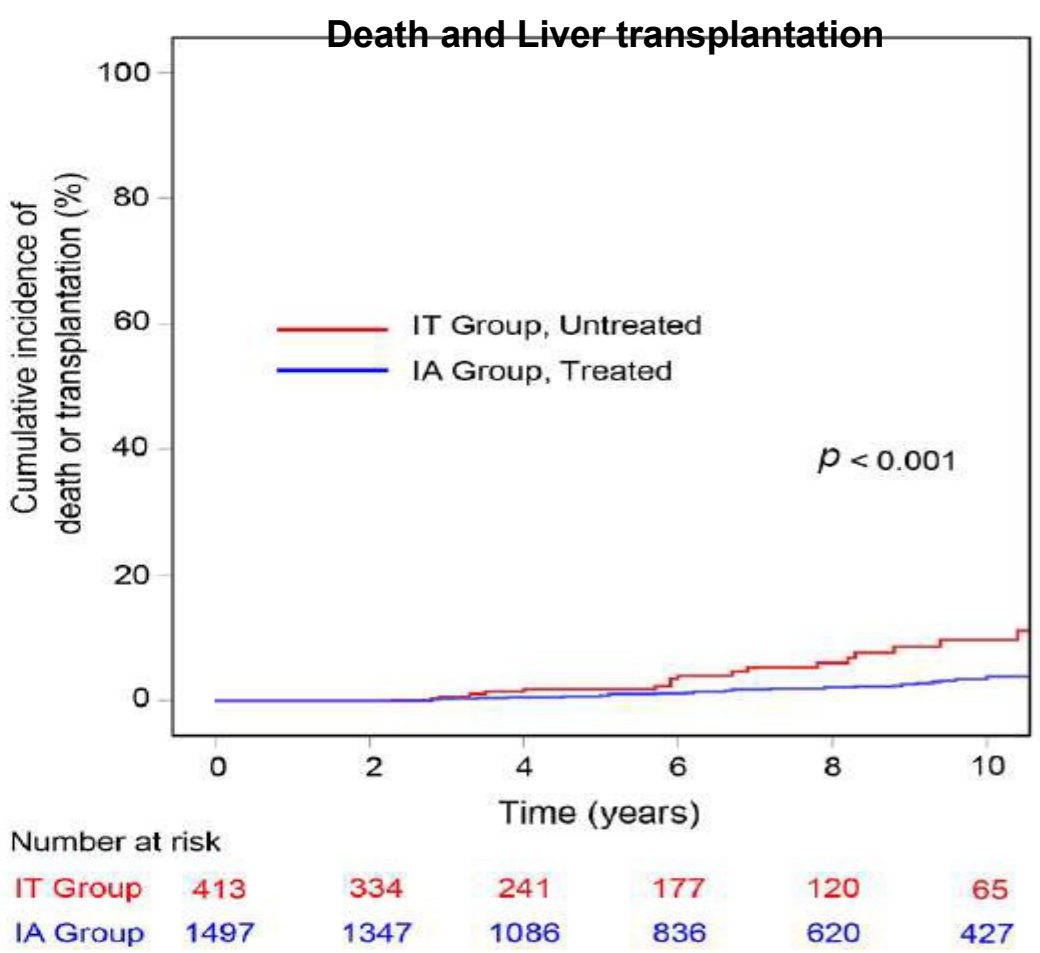
- **The HCC risk decreases after the first 5 yrs of ETV/TDF therapy in patients with compensated cirrhosis at baseline but not in those with Chronic Hepatitis**
- **Older age, especially ≥50 yrs, and lower platelets represent the main risk factors for late HCC development.**

Papatheodoridis G, et al. Hepatology 2017;66:1444-1453

Benefits of Achievement of viral suppression in patients with Chronic HBV Infection ????

Incidences of HCC and death or transplantation in the Immuno Tolerant phase vs Immuno Active patients A retrospective study in Korea





IT-phase: Immunotolerant; IA-phase: immunoactive CHB

Kim G A et al, Gut 2018;67:945-952.

Safety of Nucleos(t)ide Analogues

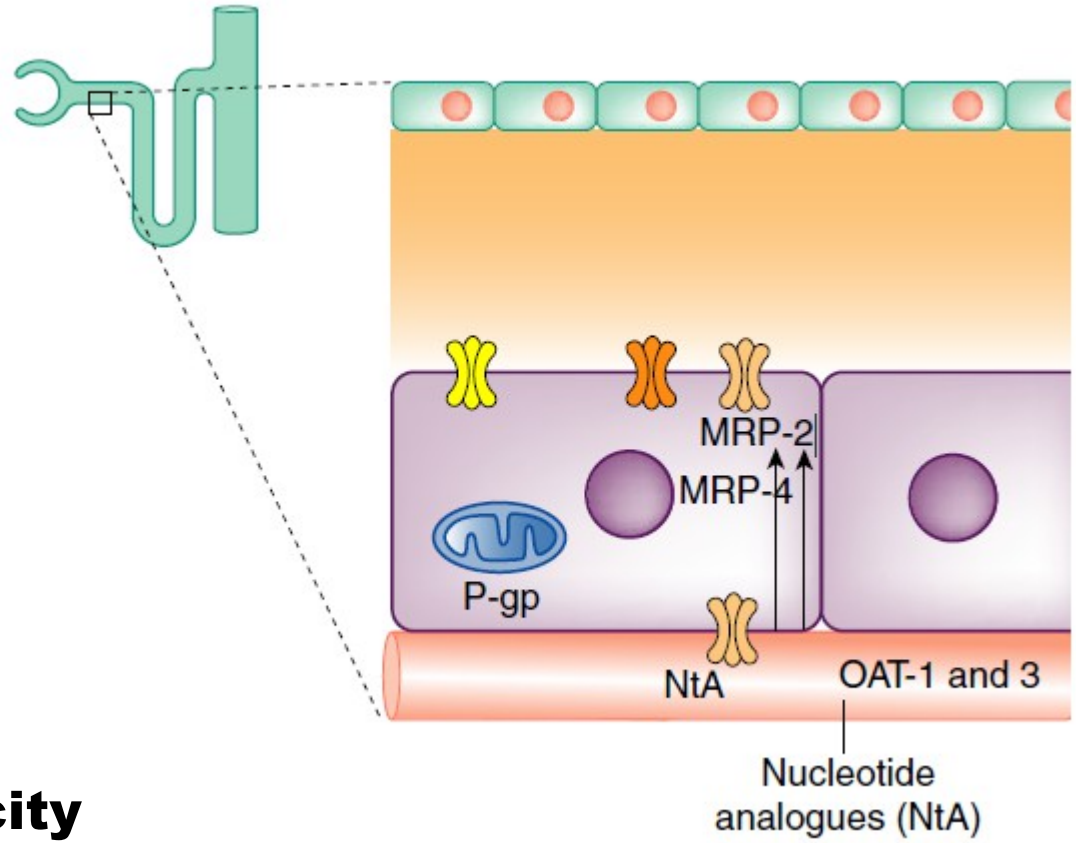
- Renal
- Bone
- Cancer
- Pregnancy

Renal Safety

Chronic HBV infection increase the risk of chronic kidney disease

All NAs are renally excreted. Need to be adjusted to GFR

ADV and TDF have been associated with a small risk of nephrotoxicity (Increase creatinine 3% vs 1% at yr 5)



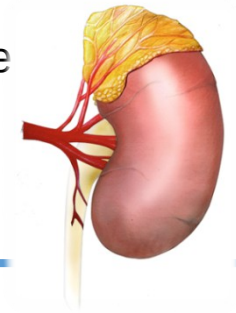
Mechanisms of NA-associated Nephrotoxicity

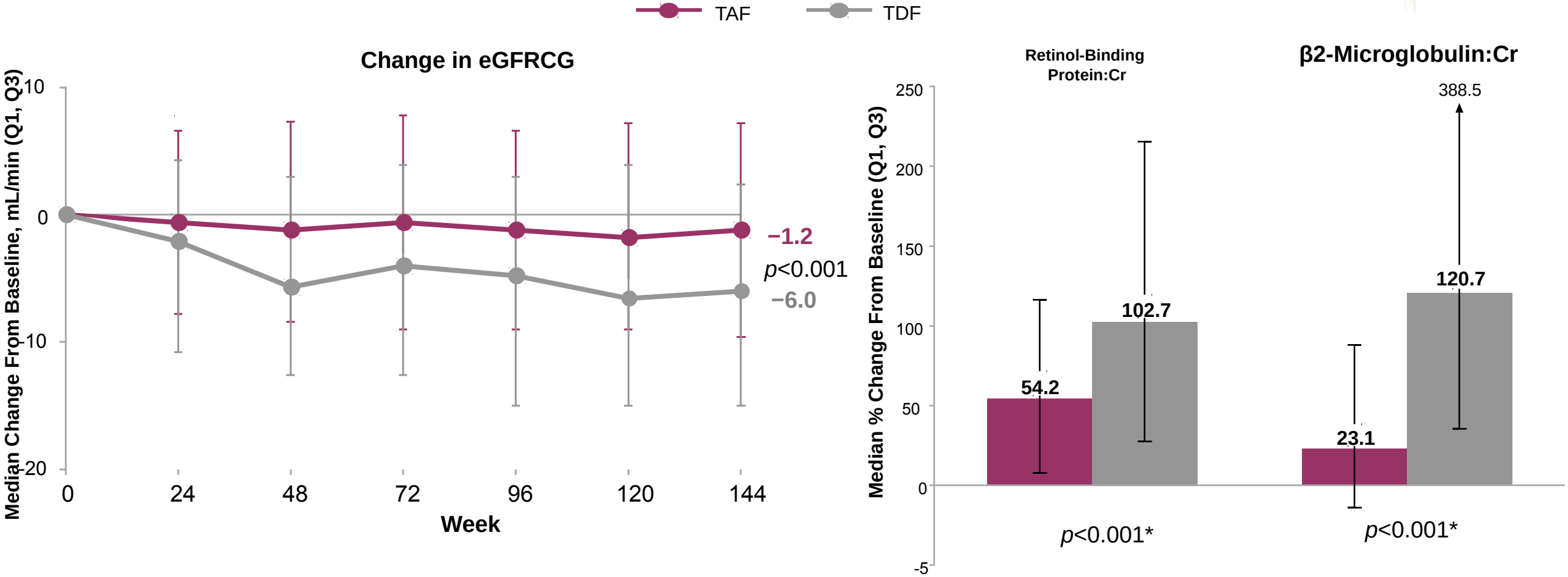
ADV and TDF are substrates of organic anion transporter (OAT)-1 and OAT-3; they are excreted by multidrug resistance protein (MRP)-4.

ADV and TDF would be actively transported by MRP-4 to the proximal tubule; when MRP-4 is saturated, ADV and TDF may accumulate in the intracellular environment leading to tubular damage

Rodriguez-Novoa S, et al. Clin Infect Dis. 2009;48:e108-e116.

Renal Safety
Change in Renal Parameters Over 144 Weeks



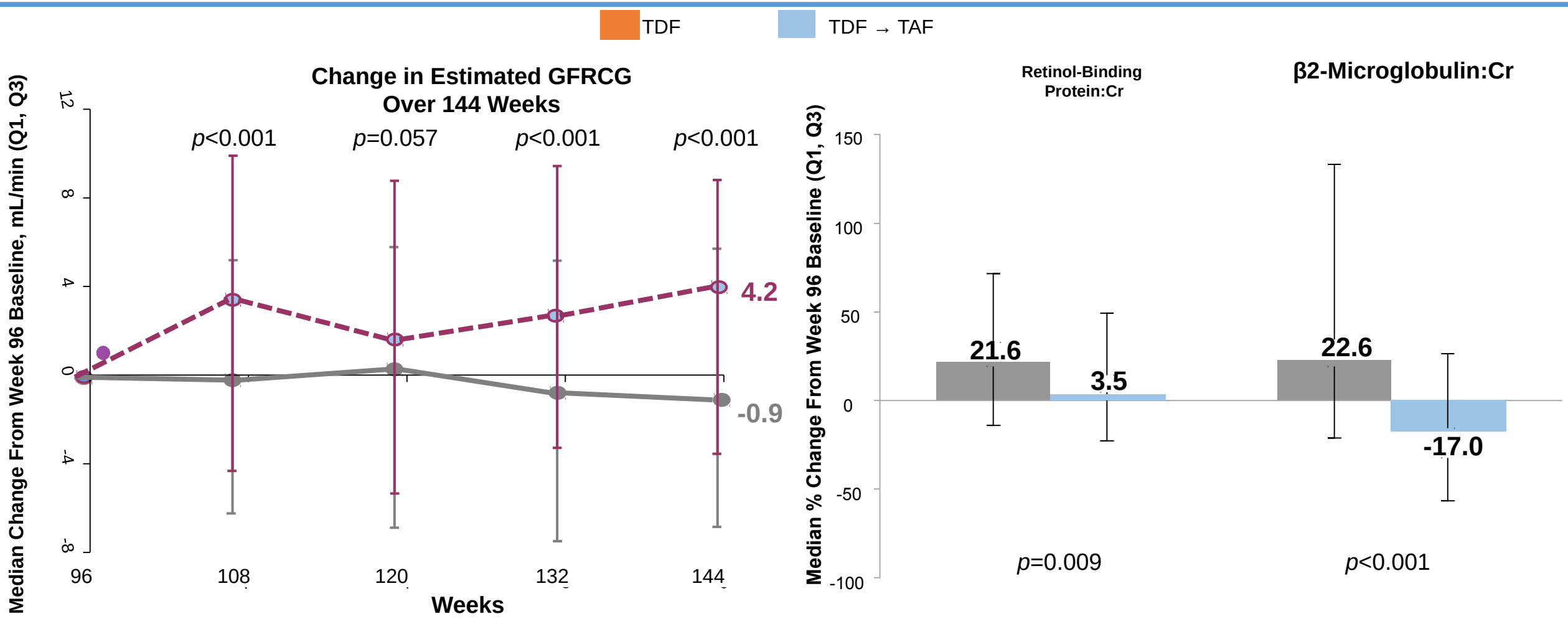


There were significantly smaller decreases in eGFRCG and smaller changes in proximal tubular markers with TAF compared to TDF at Week 144

*From 2-sided Wilcoxon rank-sum test

Chan, AASLD 2018, 0381

Change in Renal Parameters after switch from TDF to TAF



48 wks after switch from TDF to TAF significant improvements in eGFRCG and in markers of renal tubular function were observed

Seto, AASLD 2018, 0404

Bone Safety

- CHB by itself also affects the skeletal system
- Vitamin D deficiency was found in 35-82% of Chinese CHB patient
- Asian patients are particularly at risk of bone problems in view of low body-mass
- Bone safety closely related with renal Aes
  - Related to nucleoside analogue effect on renal proximal tubular and phosphaturia
  - Real-life data demonstrated increased risk of hip fracture in patients received adefovir but not TDF

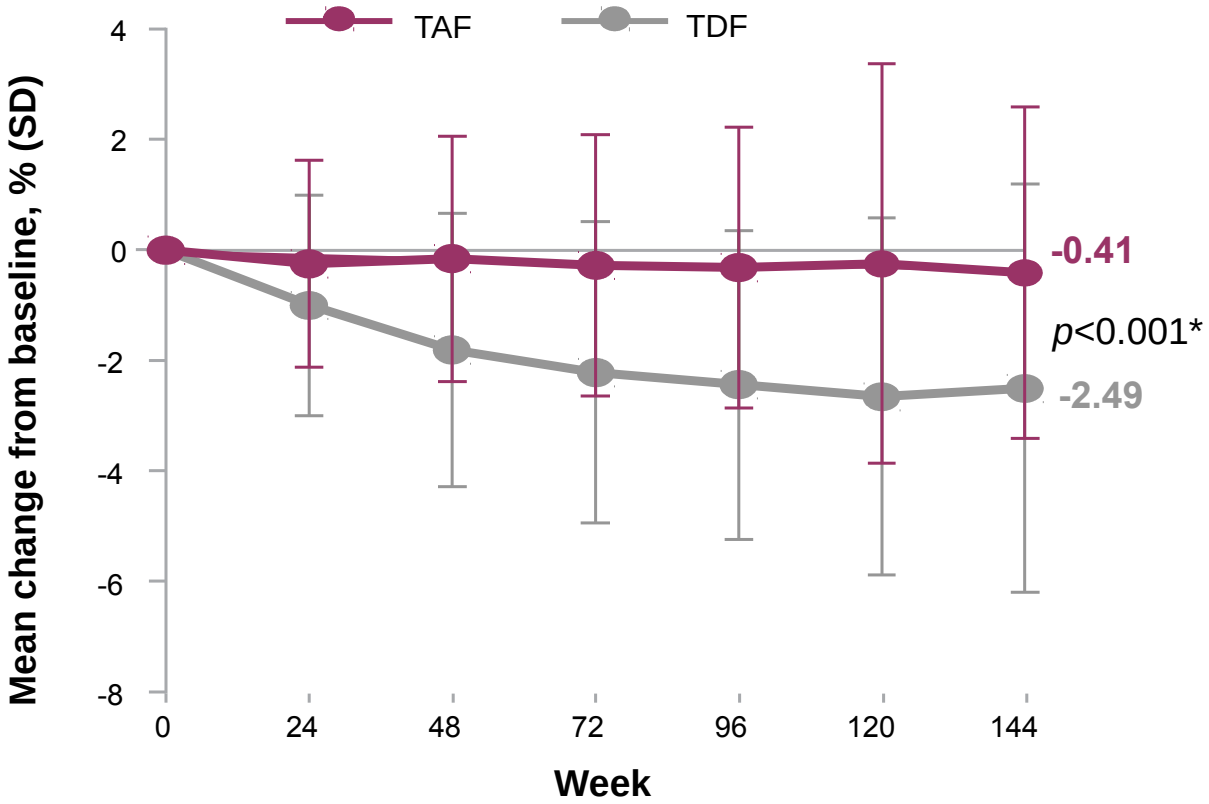
Rouillard S, et al.Hepatology. 2001;33: 301-307. Wong GL, et hepatitis B. Clin Gastroenterol Hepatol. 2015;13:783-790 e1. Chan HL, et al. J Hepatol. 2015;63:1086-1092

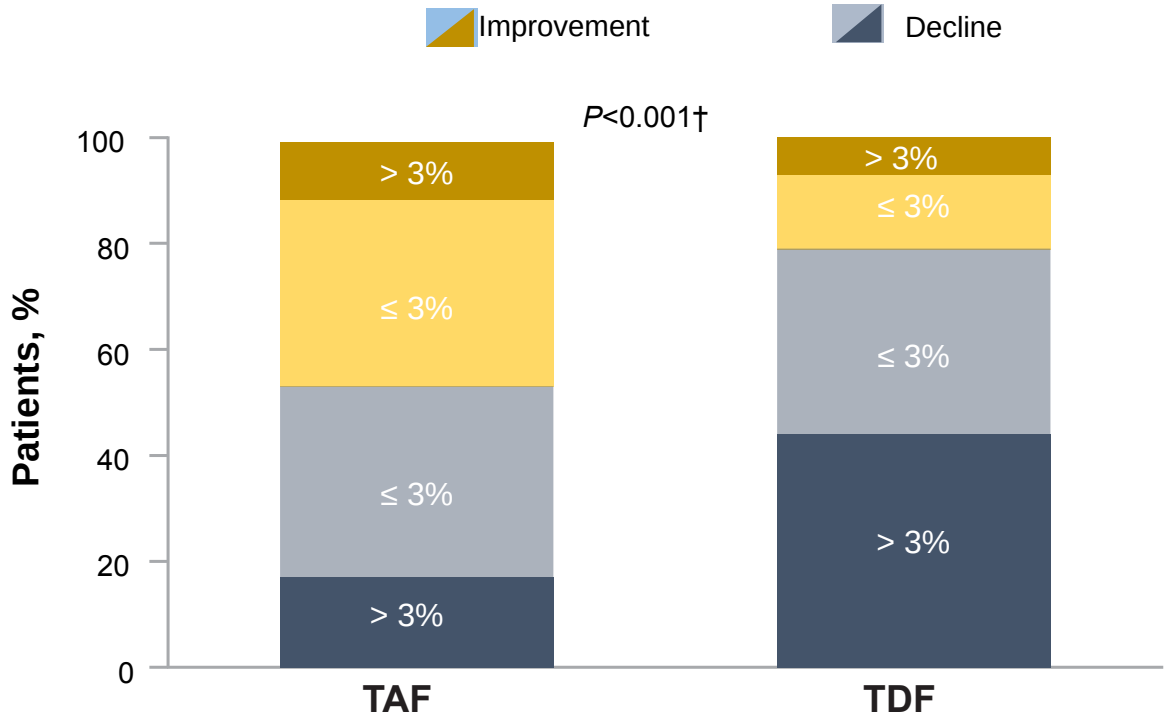
Study 108 and 110 Pooled Analysis: TAF vs TDF at 144 Weeks

TAF vs. TDF for HBV: Bone Mineral Density

Changes in Bone Mineral Density (BMD) in Patients Over 144

Hip





There were significantly less declines in hip BMD in patients on TAF compared to TDF

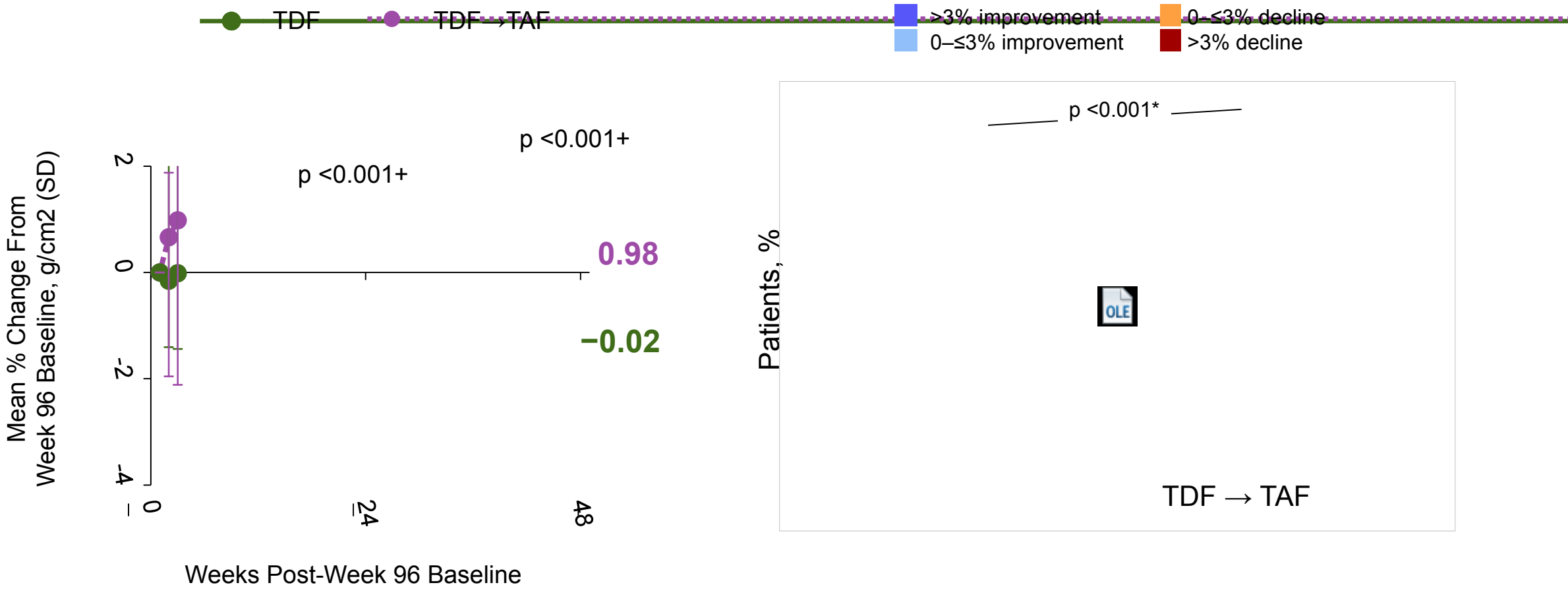
The proportion of TAF patients with hip BMD improvement was significantly higher when compared to TDF

*From analysis of variance model including treatment as fixed effect

† From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

Chan, AASLD 2018, 0381

Changes in Hip BMD From Week 96 Baseline to Week 144



- Greater proportions of TAF vs TDF patients showed improvements in BMD at Week 144

+From analysis of variance model including treatment as a fixed effect.
*From Cochran-Mantel-Haenszel test for ordinal data (row mean scores differ statistic was used).

EASL Clinical Practice Guidelines on the management of HBV infection

Indications for selecting TAF or ETV over TDF

Age >60 years

Bone disease
Chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis

Renal alteration
(eGFR <60 min/mL/1.73 m2; albuminuria; low phosphate; haemodialysis)

- ETV dose adjusted if eGFR <50 mL/min
- No dose adjustment of TAF is required in adults or adolescents* with estimated CrCl ≥15 mL/min
  or in patients with CrCl <15 mL/min who are receiving haemodialysis

TAF preferred to ETV in patients with previous NA exposure

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017

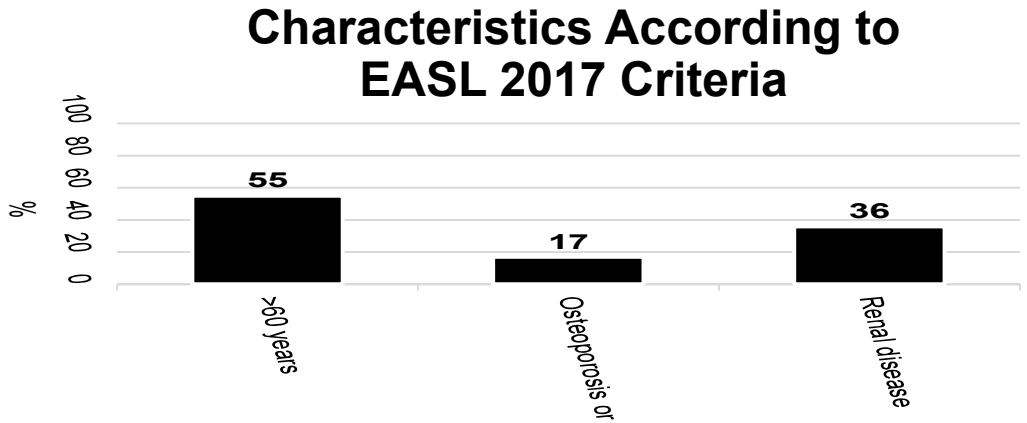
Validation of EASL 2017 Clinical Practice Guidelines for Switching HBV Patients Treated with TDF to ETV or TAF

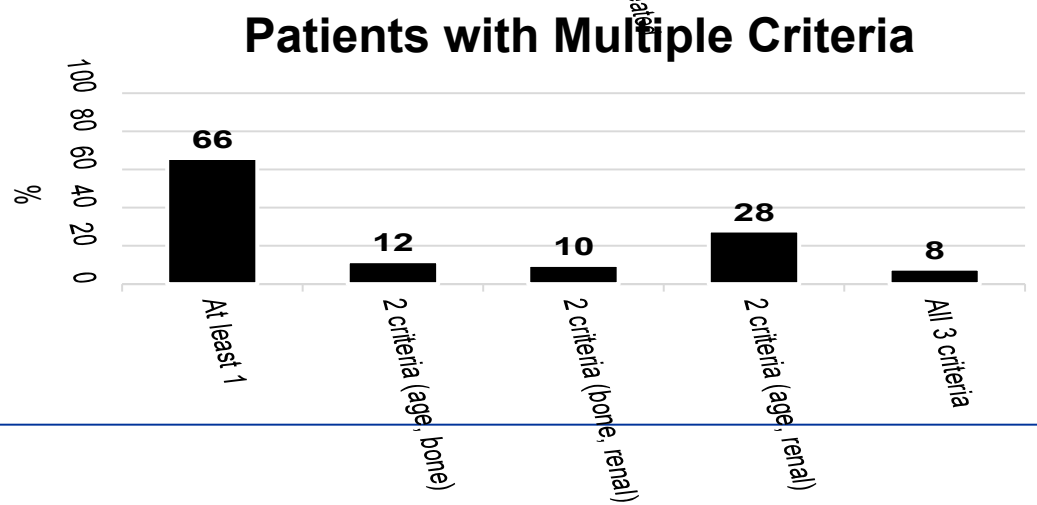
Cross-sectional study of patients treated with TDF in two EU centers that should be considered for TAF or ETV switch according to EASL Guidelines*

Patient Characteristics

	[redacted]
Age, years (range)	62 (18-91)
Caucasian, %	92
HBeAg-negative, %	92
GT 3, %	77
Male, %	75
Cirrhosis, %	40
Diabetes, %	10
BMI, kg/m2	25 (16-46)
Undetectable HBV DNA, %	95
Normal ALT, %	91
Previous LAM or ADV, %	53

A significant proportion of CHB patients on long-term TDF fulfill the EASL 2017 recommendations to switch to ETV or TAF





Loglio, AASLD 2018, 269

Cancer Risk

Concerns about the effect of antiviral treatment on the risks of non-liver cancers
Entecavir at high doses shows potential carcinogenic effect in some early animal studies.

A population-based study of 44,494 subjects in Hong Kong showed that NA-treated patients had similar risks of various common malignancies when compared to untreated patients

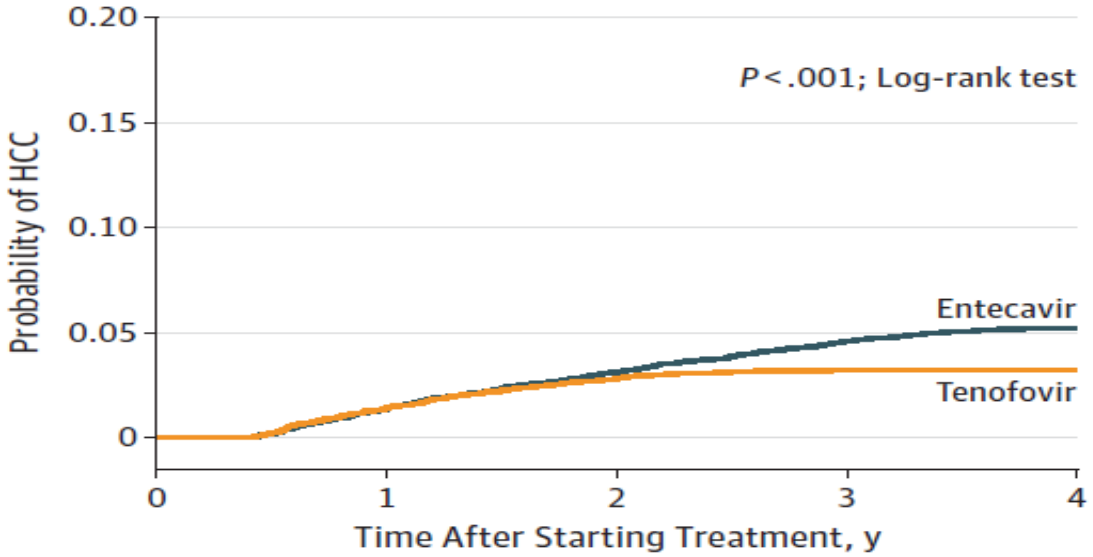
	All	Male	Female	Entecavir[a]
All malignancies	1.01 (0.82-1.25)	0.98 (0.81-1.19)	1.31 (0.92-1.87)	1.07 (0.65-1.75)
HCC	0.90 (0.69-1.16)	0.90 (0.71-1.14)	1.17 (0.71-1.93)	1.48 (0.77-2.86)
Colorectal cancer	2.17 (1.08-4.36)	1.80 (0.82-3.96)	5.78 (1.81-18.42)[b]	2.43 (0.52-11.27)
Lung and pleural cancers	0.82 (0.52-1.31)	0.74 (0.43-1.27)	0.79 (0.29-2.12)	1.38 (0.39-4.88)
Urinary and renal malignancies	1.04 (0.38-2.81)	0.96 (0.35-2.62)	N.A.	N.A.
Cervical cancer	N.A.	N.A.	7.33 (1.72-31.17)	N.A.
Breast cancer	1.37 (0.44-4.28)	N.A.	2.02 (0.65-6.30)	N.A.
Lymphoma	1.63 (0.65-4.08)	1.46 (0.50-4.29)	2.50 (0.57-10.95)	N.A.

Wong G et al. . Aliment Pharmacol Ther. 2017;45:1213-1224.

Risk of Hepatocellular Carcinoma in Patients Treated with Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study

Outcomes in Propensity Score-Matched Nationwide Cohort

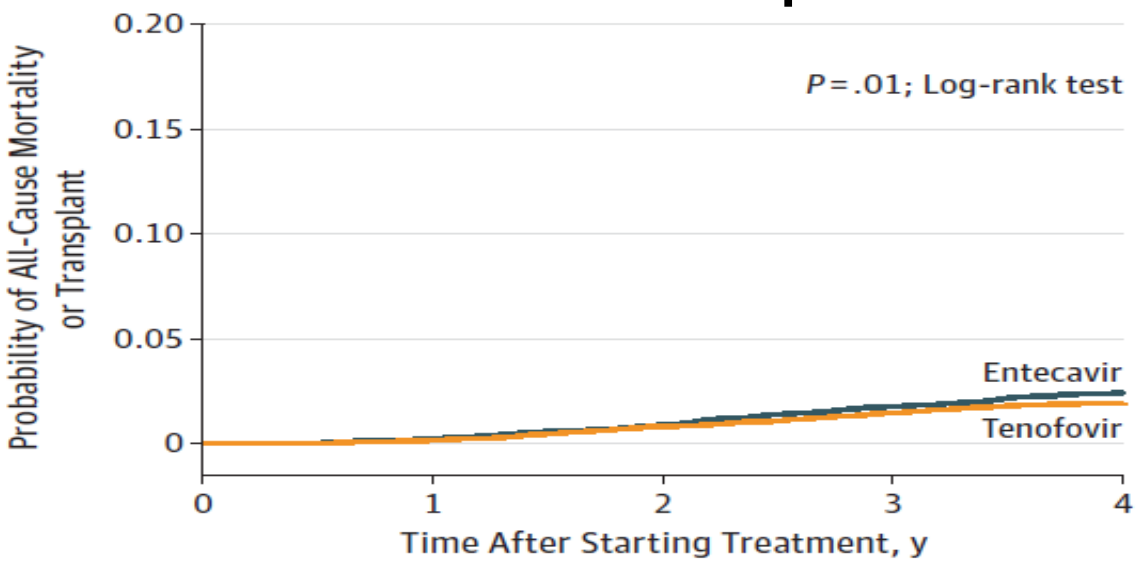
HCC



No. at risk					
Entecavir	10923	10762	10542	10342	10246
Tenofovir	10923	10763	10574	10490	10458

	Eventsn	Events/100 patient-years	HR	*P*-value
ETV	567	1.07	Reference	<0.001
TDF	350	0.66	0.62 (0.54-0.70)	

Death or Transplant



No. at risk					
Entecavir	10923	10897	10826	10728	10657
Tenofovir	10923	10904	10834	10764	10714

	Events n	Events/100 patient-years	HR	*P*-value
ETV	266	0.49	Reference	0.01
TDF	210	0.39	0.79 (0.66-0.94)	

Choi J et al. JAMA Oncol 2018

Safety in pregnancy and breastfeeding

- HBV is endemic in many Asian and African countries with high birth rates

	Crosses placenta	Breast milk excretion	Animal studies	Human studies—pregnancy	Human studies—breastfeeding
Lamivudine	Yes	Yes	Embryonic loss (rabbits) at doses comparable to clinical doses in humans	No increased risk for birth defects	No data
Adefovir	Unknown	Unknown	Embryo toxicity (rats) at doses comparable to 23 times human exposure	No data	No data
Telbivudine	Yes	Yes	No impaired fertility No harmful effects to foetal development	No increased risk for infant adverse events	No data
Entecavir	Unknown	Yes	Foetal malformations (rabbits) at doses comparable to 883 times in humans.	No data	No data
Tenofovir disoproxil fumarate	Yes	Yes	No impaired fertility No harmful effects to pregnancy or foetal development	No increased risk for birth defects	Infant growth not affected up to 2 y
Tenofovir alafenamide	Yes	Unknown	No impaired fertility No harmful effects to foetal development	No data	No data

Wong GL, et al. .Aliment Pharmacol Ther. 2018;47:730-737

Summary

- Long-term NAs therapy can:
  - Suppress HBV DNA
  - Reduce inflammation and fibrosis
  - Reduce the risk of HCC and liver-related events
  - Reduce liver related mortality

- Safety in long term therapy should be considered. TAF and ETV are recommended over TDF for patients with risk of renal and bone diseases