31 January 2017

Long-term impact of antiviral therapy with nucleot(s)ide analogues (NUC)

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Financial disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, MSD, ARROWHEAD, ALNYLAM

Outline of the presentation

- Endpoints of NUC therapy
- Long-term virological responses
- Safety issues (TAF)
- Clinical decompensation, HCC
- Survival

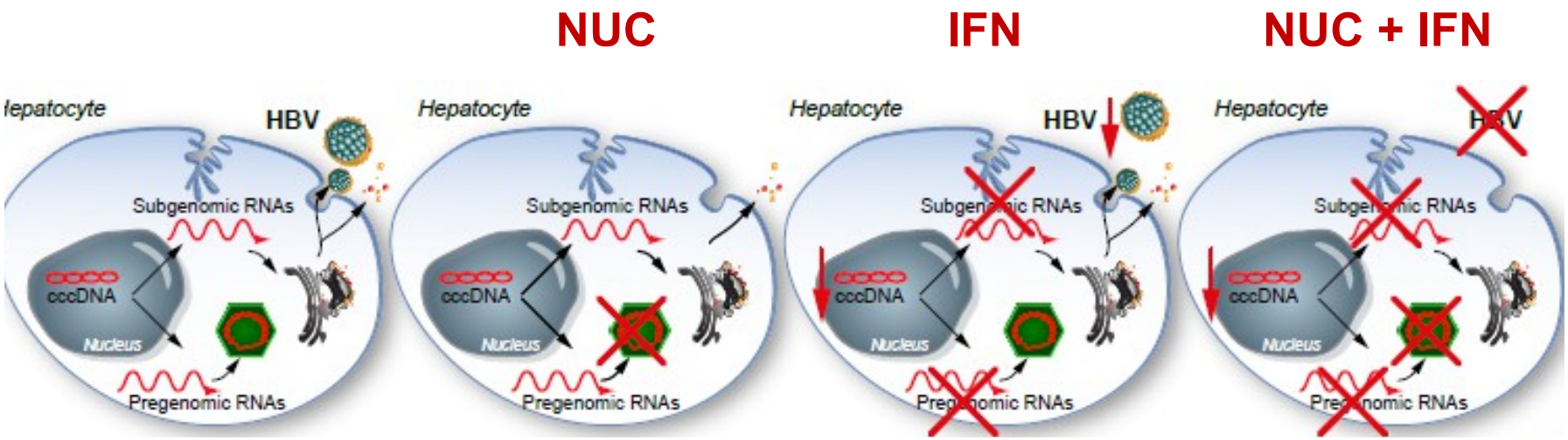
The decision to treat is historically based on phase of disease and risk of disease progression

Phase	Immune tolerant	HBeAg-positive CHB	Inactive carrier	HBeAg-negative CHB
HBeAg status	Positive	Positive	Negative	Negative
HBV DNA	Very high >200,000 IU/mL	>2000 IU/mL	<2000 IU/mL	>2000 IU/mL (fluctuating)
ALT	Normal	Elevated	Normal	Elevated (fluctuating)
Liver histology	Normal or mild inflammation and limited fibrosis	Inflammation and fibrosis: degree varies	Normal or mild inflammation	Inflammation and fibrosis: degree varies
Disease progression	Low	**Moderate to high**	No, very low	**Moderate to high**
Treatment	Not indicated*	**Indicated**	Not indicated	**Indicated**

**** Treatment indicated in some patients***

EASL HBV Guidelines, J Hepatol 2012;57:167–185; EASL special HBV conference, J Hepatol 2015;63:1238–1253

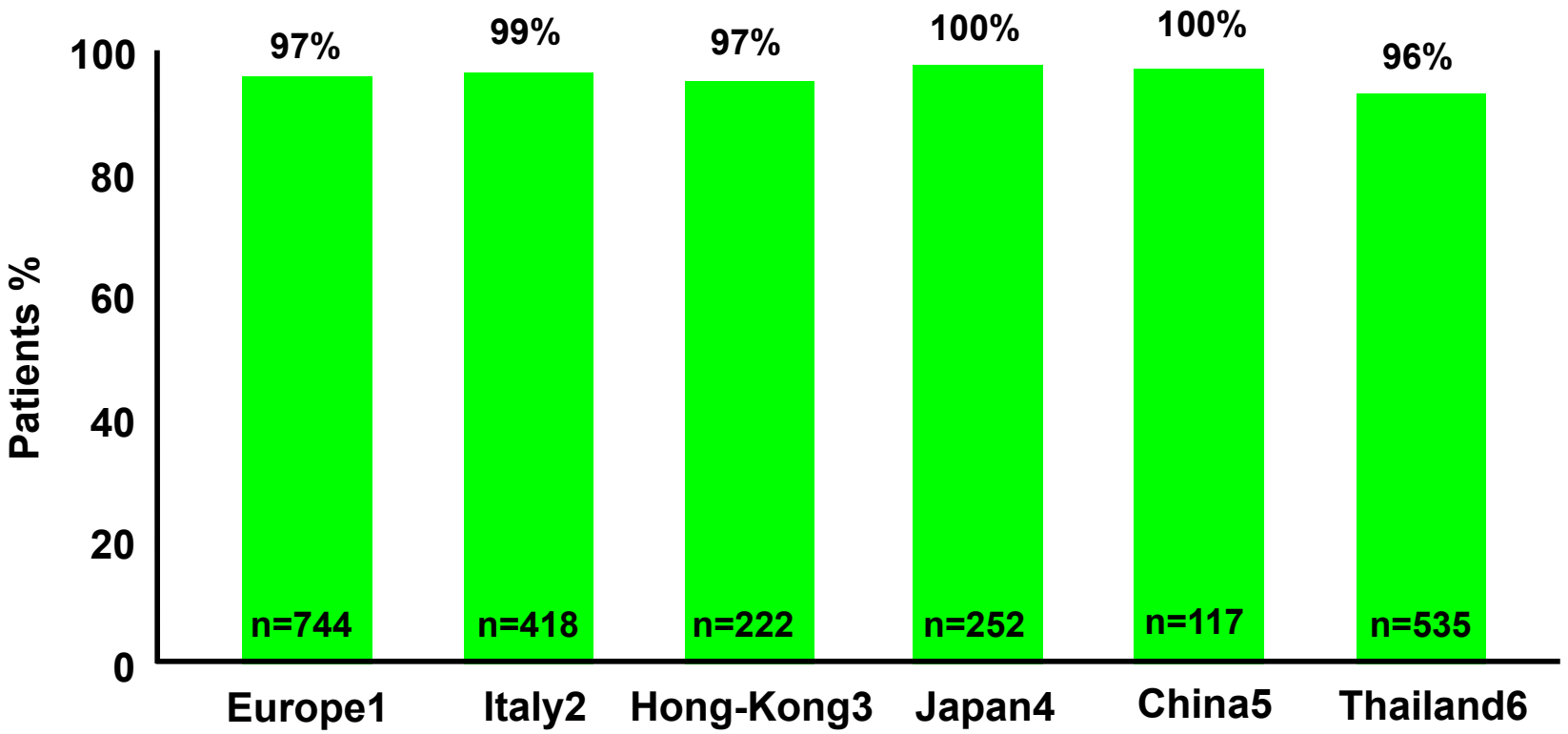
PEG-IFN and NUC have different mechanisms of action



Studies in patients and humanized mice indicate that combination treatments suppressing both HBV replication (NUCs) and cccDNA transcription (IFNα) may trigger significant antigen decline (HBe and HBs) – combination needs to be done in a smart way

Adapted from Thimme & Dandri, J Hepatol 2012;58:205-9

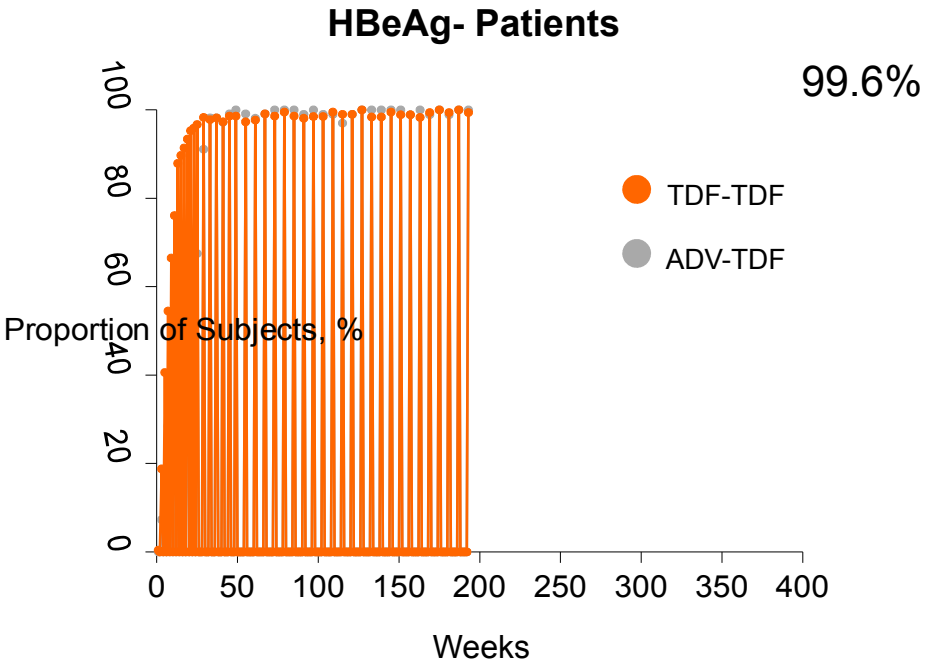
5 years ETV for real life, naive CHB patients
Virological summary

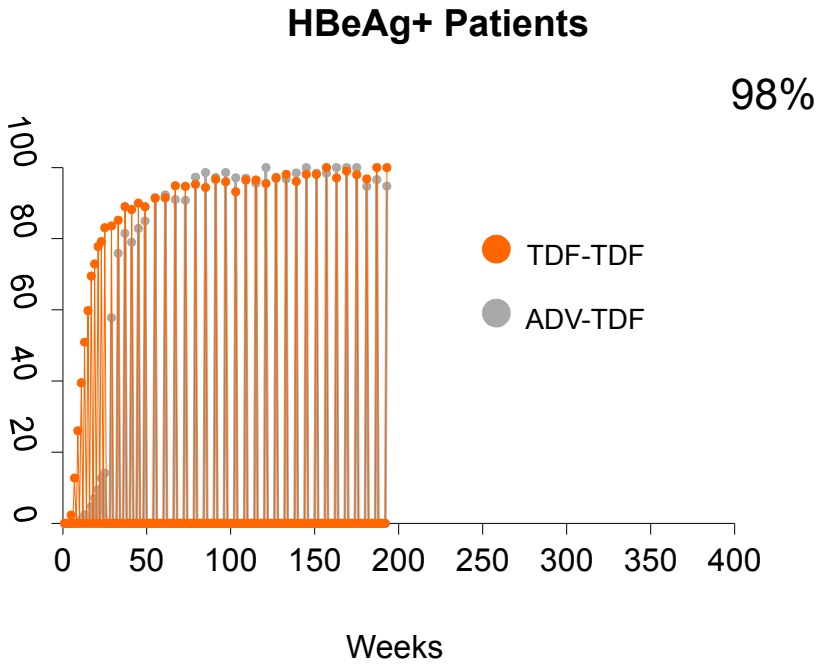


1)Arends P, et al Gut. 2014 in press 2) Lampertico P, et al. J Hepatol 2013;58:S306. 3) Seto WK, et al J Gastroenterol Hepatol 2014;29:1028-34. 4)Ono A, et al J Hepatol 2012;57:508–14. 5)Luo J, et al, Int J Med Sci 2013;10:427-433. 6)Tanwandee T, et al. Hepatology 2013;58:672A

Studies 102/103

TDF Efficacy Results at Year 8 - HBV DNA <69 IU/mL (Observed)



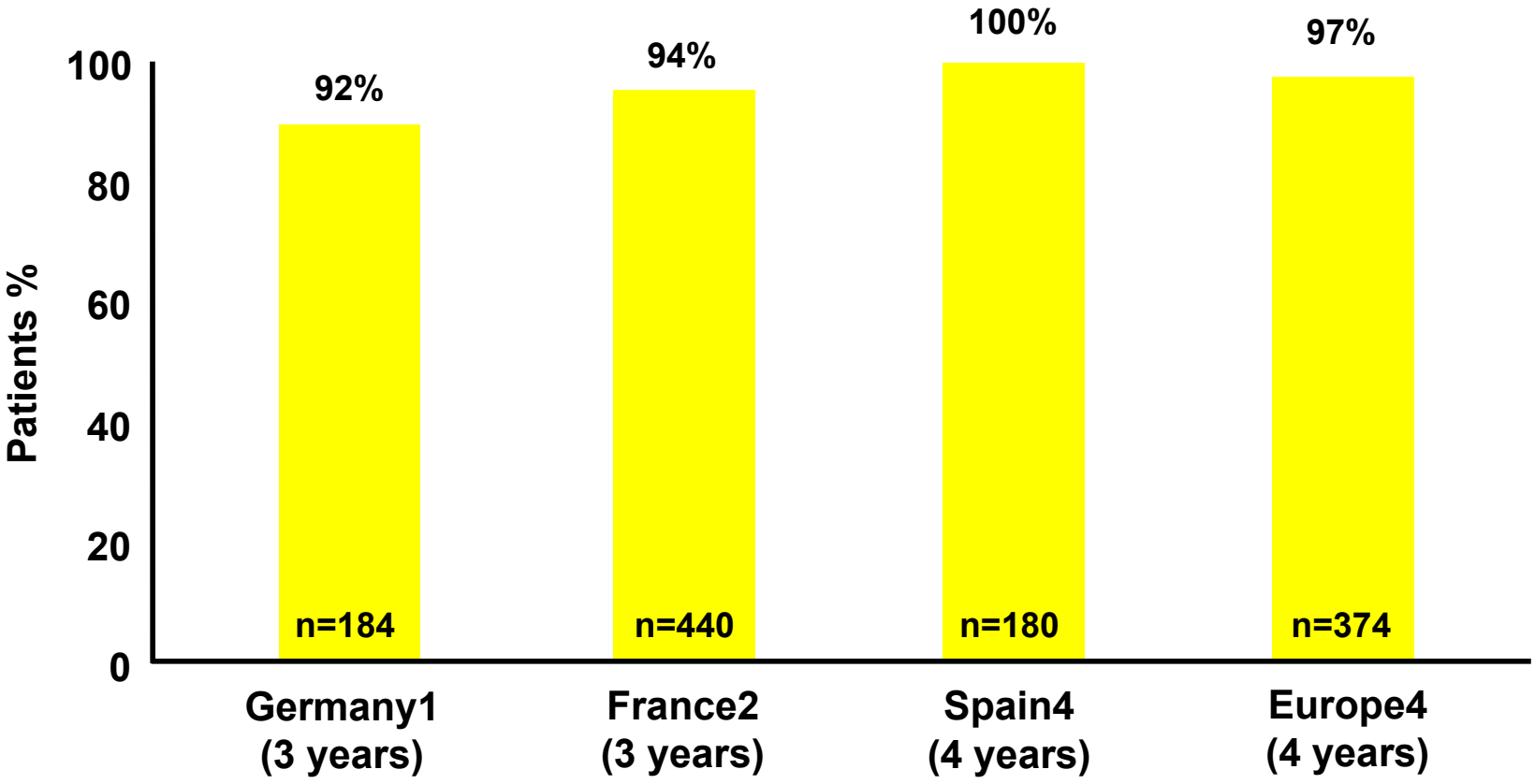


	HBeAg-	HBeAg+
HBeAg loss / seroconversion†	NA	47/31%
HBsAg lossa/seroconversion (KM%) ‡	1.1/0.7%	12.9/10.3%

*Missing/addition of FTC = failure (LTE-TDF)

Marcellin, AASLD, 2014, Oral #229

3-4 years TDF for real life, naive CHB patients Virological summary



1)Petersen J, et al. J Hepatol 2014;O122. 2) Pageaux GP, et al. J Hepatol 2014; P1061. 3) Tabernero D,et al J Hepatol 2014;P1058. 4) Lampertico P, et al Hepatology 2013:58:A933

AP&T Alimentary Pharmacology and Therapeutics

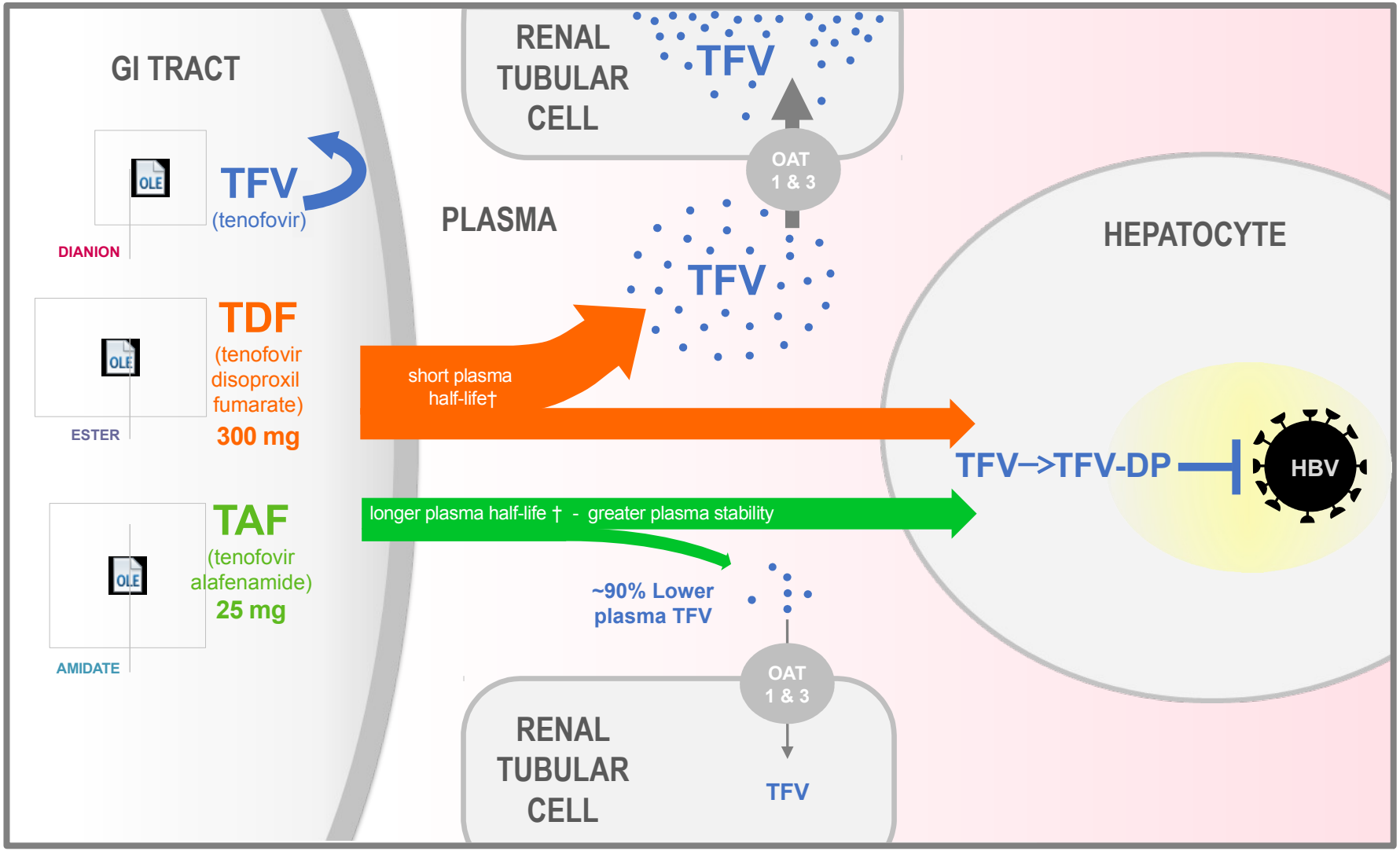
Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients

P. Lampertico*, H. L. Y. Chan†, H. L. A. Janssen‡, S. I. Strasser§, R. Schindler¶ & T. Berg**

- Registration studies (8 years) showed minimal renal events on TDF (~2%)
- Real-life studies with TDF showed controversial results
- 8 cases of TDF-induced Fanconi syndrome have been described
- Higher risk of TDF renal toxicity in older patients, previously exposed to ADV, with comorbidities……
- Need for more research with more sensitive markers of tubular damage
- The best management of the few cases with renal toxicity unclear (TAF or ETV ?)

‡

Tenofovir alafenamide (TAF) – A Novel Prodrug of Tenofovir



† T1/2 based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 90 minutes.

Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

Study 108 and 110: Phase 3 CHB Studies

Efficacy and Safety for TAF compared to TDF for CHB Through Week 72

	TAF (N = 866)	TDF (N = 432)	P Value
HBV DNA <29 IU/mL, HBeAg -	93%	92%	0.84
HBV DNA <29 IU/mL, HBeAg+	72%	72%	0.78
Resistance (Week 48)	0%	0%	—
ALT normalisation, Central Lab*	76%	68%	<0.05
ALT normalisation, AASLD Criteria†	49%	39%	<0.005
Mean changes in eGFRCG, mL/min	-0.8	-3.8	<0.001
Median % change in β2M:Cr	-3.5%	38%	<0.001
Mean % changes in Hip BMD	-0.29%	-2.43%	<0.001
Mean % changes in Spine BMD	-0.60%	-2.52%	<0.001

* ≤34 and ≤43 U/L for females and males, respectively, aged <69 y, and ≤32 and ≤35 U/L, respectively, aged >69 y
† <19 and <30 U/L for females and males, respectively
Agarwal et al. AASLD 2016, P1844; Chan et al. AASLD 2016, P1843; Fung et al. AASLD 2016, P1852; Seto et al. AASLD 2016, O67

Clinical benefits

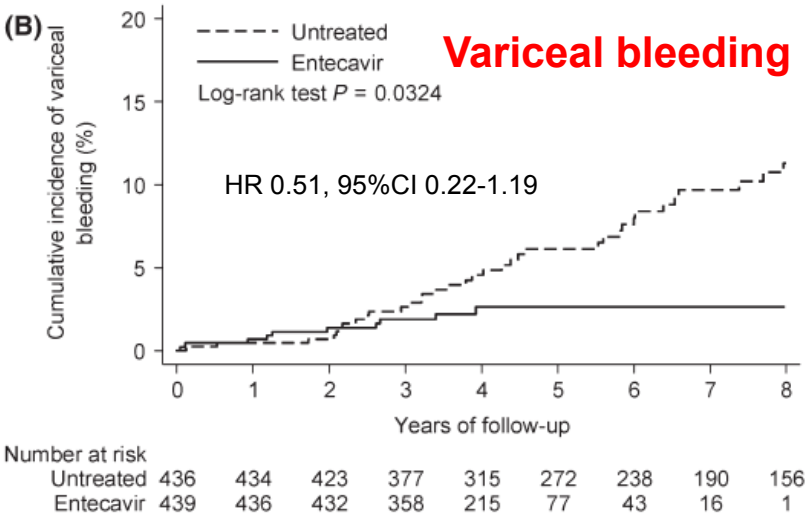
Does long-term NUC therapy prevent decompensation in cirrhotics?

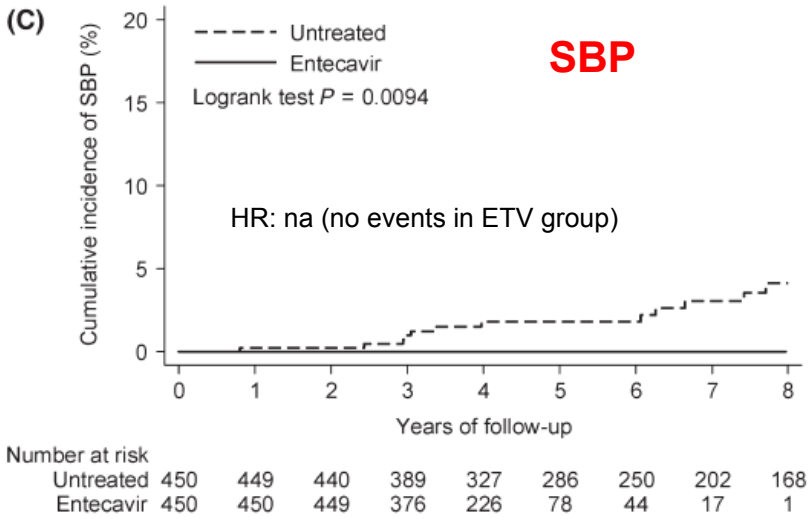
- ETV: 3-5 years real life cohort studies in Europe and Asia 1-4
- TDF: 3-4 years real life cohort studies in Europe5-6

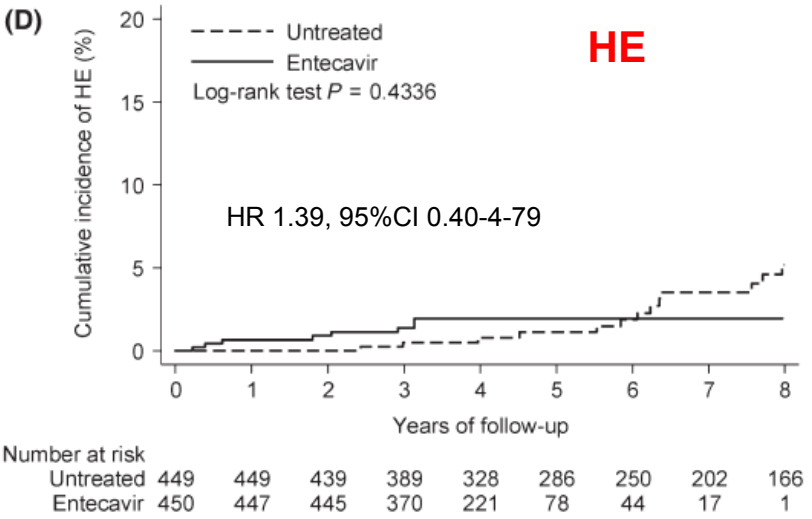
Decompensation is fully prevented in ETV or TDF treated compensated cirrhotics (if HBV in the only aetiology !)

1. Wong GL, et al, Hepatology 2013; 2. Zoutendijk R, et al, Gut 2013; 3.Lampertico P, et al, EASL 2013; 4; Lim et al, Gastroenterology 2014; 5.Lampertico P, et al, AASLD 2013; 6. Papatheodoridis G et al, AASLD 2013

Cumulative incidence of liver events in ETV and untreated cirrhotics after PS matching from Taiwan







Su TH et al, Liver Int 2016;36(12):1755-1764. doi: 10.1111/liv.13253

HCC in HBV: a challenging issue

- Complex pathogenesis (single cell event)
- Multiple risk factors (host, virus, interactions)
- Long time elapsed between first cell committed and diagnosis
- Study design (RCT, retrospective, prospective, cohort..)
- Patient selection (with or without cirrhosis, NUC-naïve….)
- Controls (????, all cirrhotics treated since 1996 !!)
- Duration of therapy (> 5 years ETV/TDF….)
- Competitive causes of liver-related death

Long-term NUC and prevention of HCC
Propensity score studies from Asia and US

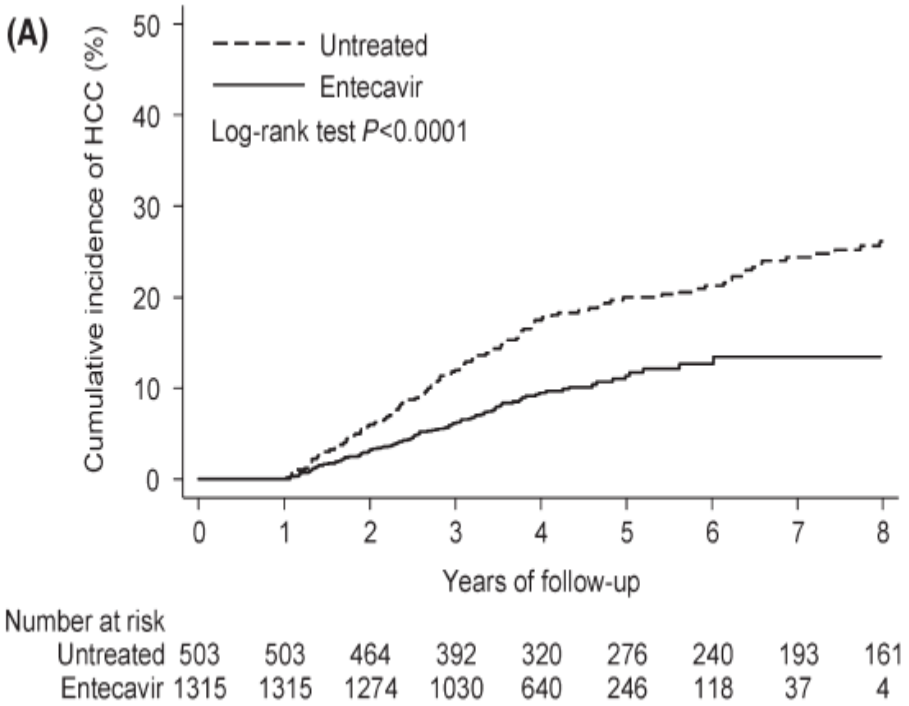
Author	Patients		Follow-up (yr)		% HCC at 5 yr		RR (95% C.I.)	P-value
	NUC+	NUC-	NUC+	NUC-	NUC+	NUC-		
Wu et al1 (Taiwan)	21,595	21,595	3.4	5.2	7.3	22.7	**0.31 (0.27–0.53)**	<.001
Hosaka et al2 (Japan)	316	316	3.3	7.6	3.7	13.7	**0.37 (0.15–0.91)**	.03
Kumada et al3 (Japan)	117	117	12.3	11.6	2.7	11.3	**0.28 (0.13–0.62)**	.002
Gordon et al4 (United States)	820	1,851	5.2	5.2	n.a.	n.a.	**0.48 (0.27–0.86)**	<.01

n.a. = not available

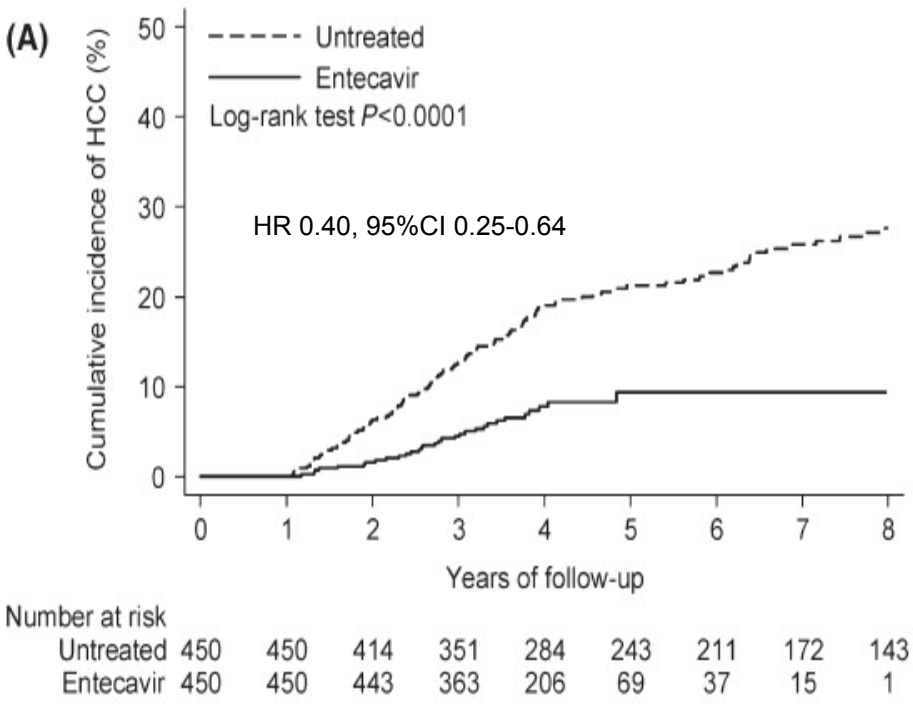
1. Wu CY et al, Gastroenterology 2014;147:143–151. 2. Hosaka T, Hepatology 2013;58:98–107. 3. Kumada T et al, J Hepatol 2013;58:427–433. 4. Gordon SC et al, Clin Gastroenterol Hepatol 2014;12:885–893.

HCC in ETV and untreated cirrhotics before and after Propensity Score (PS) matching from Taiwan

Before PS matching



After PS matching



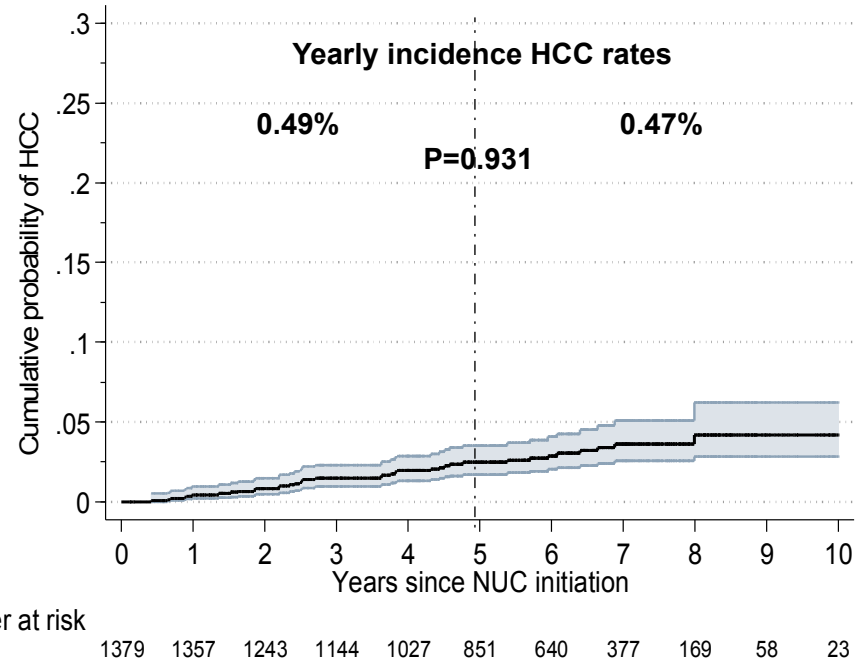
HCC predictors: older age, male gender, HBeAg positivity, AFP level ≥7 ng/mL before ETV, and 1-year virological response.

Su TH et al, Liver Int 2016;36(12):1755-1764. doi: 10.1111/liv.13253

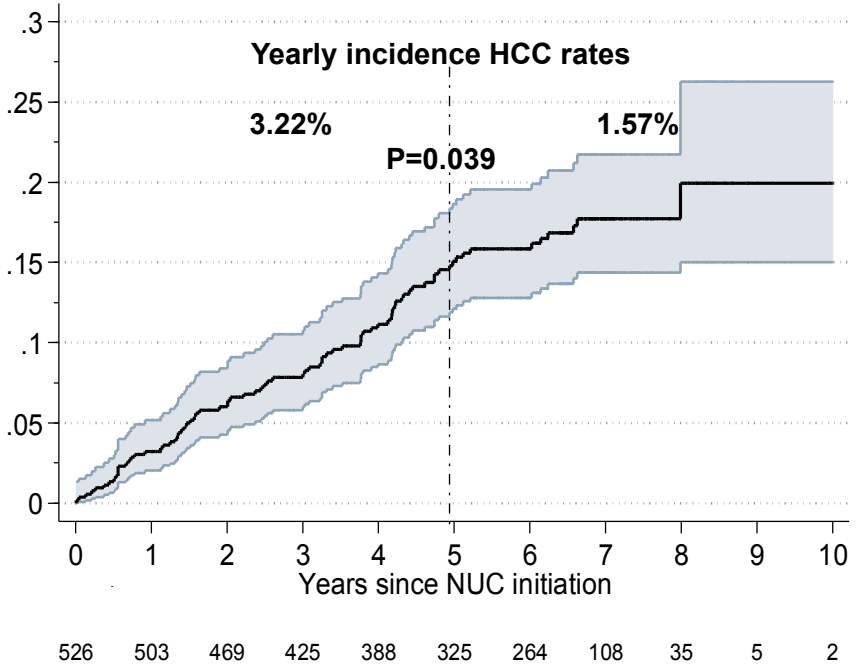
The PAGE-B study
HCC in ETV/TDF treated pts beyond year 5

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 CH.**
- **Older age, especially ≥50 yrs, and lower platelets represent the main risk factors for late HCC development.**

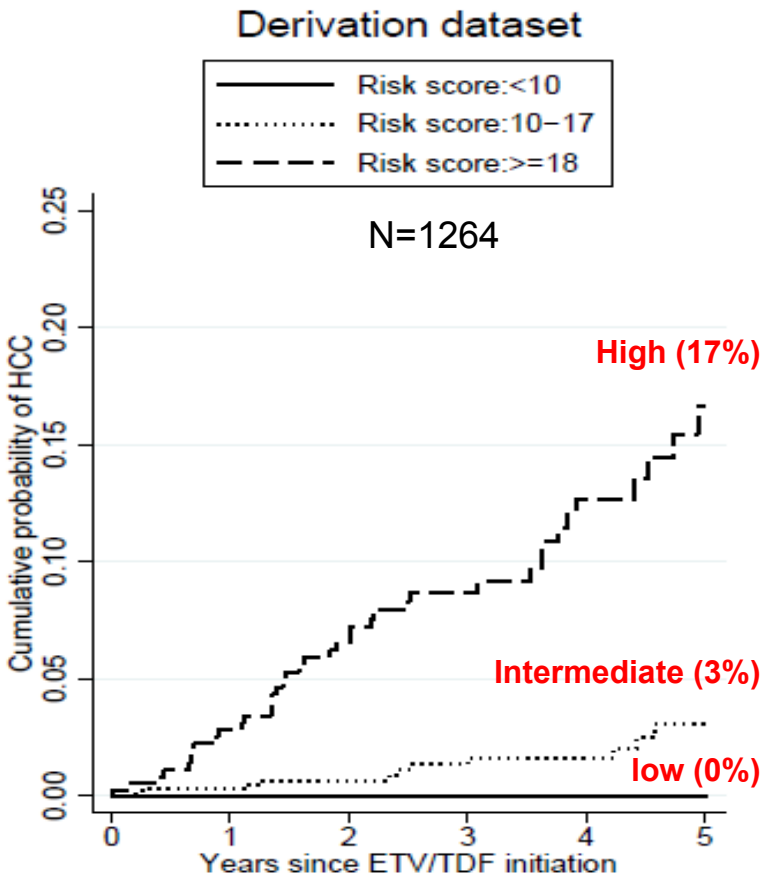
Papatheodoridis G, Lampertico P et al. AASLD 2016

HCC risk scores in untreated HBV patients
Baseline predictors

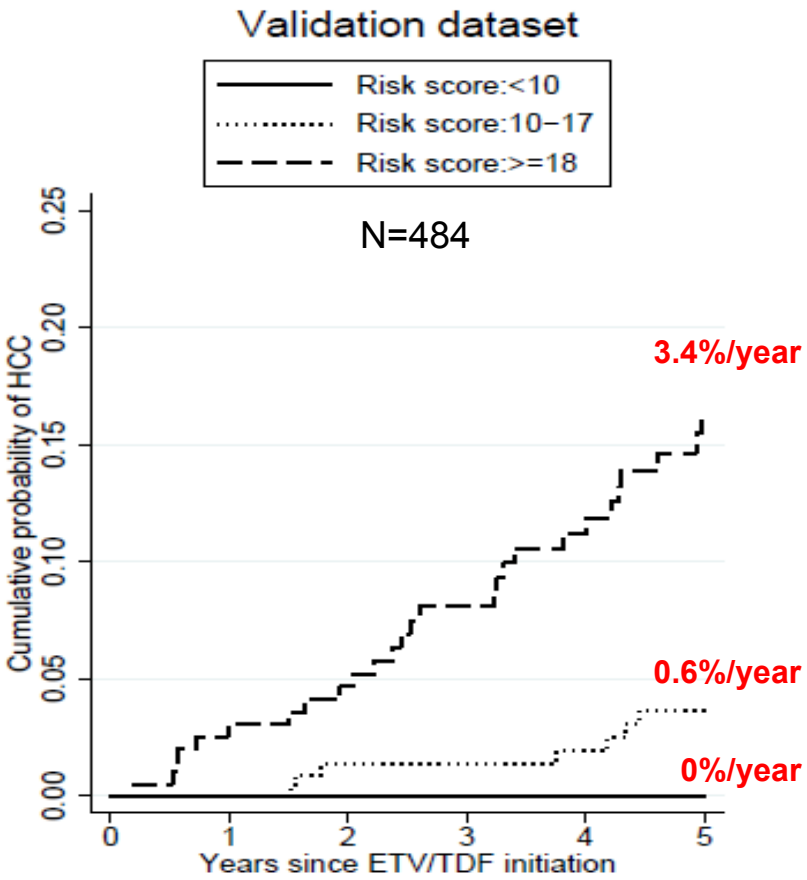
Risk score	Patients	Cirrhosis	Variables	Performance at 5 years
GAG-HCC (52)	820 hospital-based Hong-Kong	15%	Male, age, HBV-DNA, cirrhosis	Optimal cutoff=82 PPV 21% NPV 98%
CU-HCC (54)	1005 and 424 hospital-based Hong-Kong	38% and 16%	Age, albumin, bilirubin, HBV-DNA, cirrhosis	Optimal cutoff=5 PPV 14% NPV 98%
REACH-B (56)	3584 and 1505 Taiwan and Korea	0% and 18%	Male, age, ALT, HBeAg +, HBV DNA	By score: ≤11: <3.4% =12: ~5% ≥13: >8%
REVEAL (57)	2227 and 1113 Taiwan	0%	Age, sex, ALT, family history, composite HBV markers	AUROC 0.89
LSM-HCC (79)	1035 and 529 Hong-Kong	32% and 31%	Age, albumin, HBV-DNA, Fibroscan	Optimal cutoff=11 PPV 8% NPV 100%

Wong V and Janssen H, J Hepatol 2015

The PAGE-B study
5-year HCC according to the PAGE-B risk score



Patients: 25%, 47%, 28%
Cirrhosis: 4%, 18%, 41%



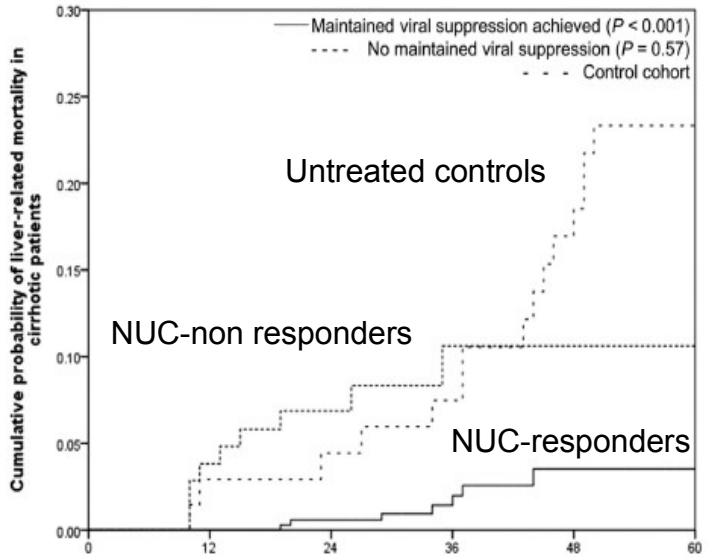
Patients: 11%, 48%, 41%
Cirrhosis: 15%, 41%, 66%

Papatheodoridis G, Lampertico P et al, J Hepatol 2016

Survival

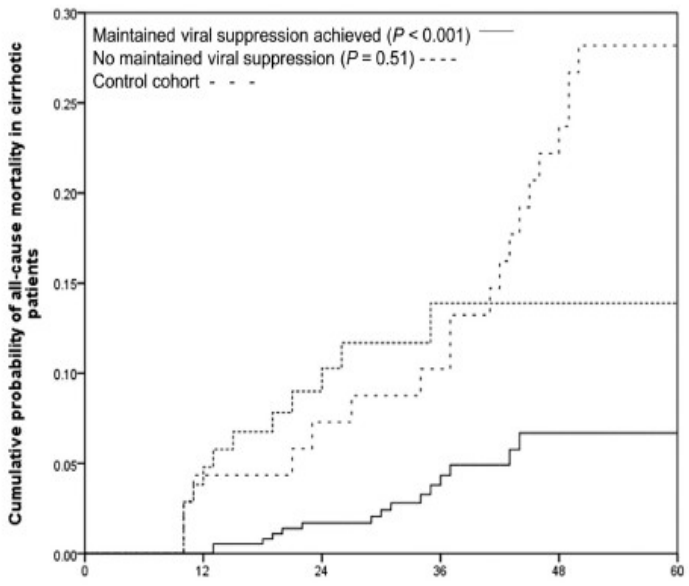
ETV treatment reduces deaths in HBV cirrhotics a retrospective study from Hong Kong

Liver-related mortality



Patients at risk						
Control cohort	69	66	63	61	52	48
Maintained viral suppression	377	374	312	178	80	21
No maintained viral suppression	105	99	71	36	13	2

All-cause mortality



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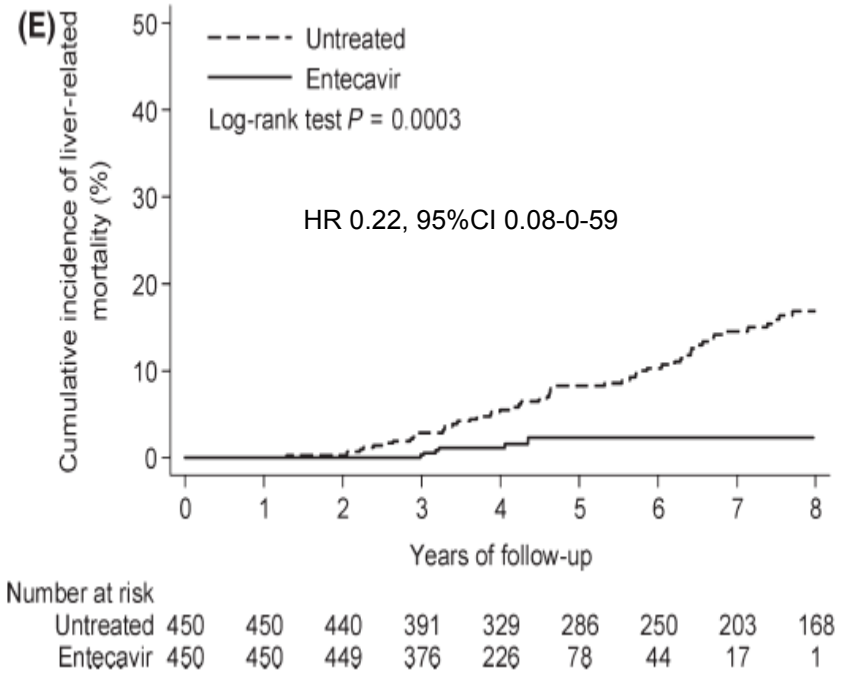
No maintained viral suppression	105	99	71	36	13	2

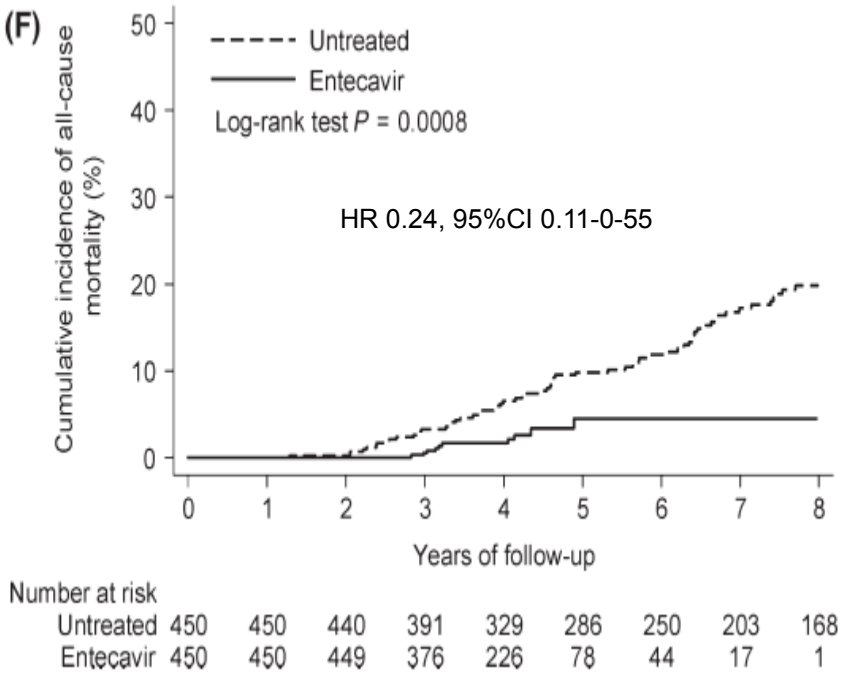
Wong et al, Hepatology 2013;58:1537-1547

Cumulative incidence of mortality in ETV and untreated cirrhotics after propensity-score matching from Taiwan

Liver related mortality*



All causes mortality*



*Including liver transplantation

Su TH et al, Liver Int 2016;36(12):1755-1764. doi: 10.1111/liv.13253

The PAGE-B study
Causes of deaths in ETV/TDF treated patients

1851 patients on ETV/TDF for 72 months

Outcome	Total (N=1815)	No cirrhosis* (n=1269)	Cirrhosis* (n=503)	*P value
Liver unrelated deaths	33 (1.8%)	17 (1.3%)	14 (2.8%)	0.059
Liver related deaths	21 (1.2%)	4 (0.3%)	15 (3.0%)	<0.001
- in patients with HCC	16/85 (18.8%)	4/26 (15.4%)	10/57 (17.5%)	1.000
- in patients without HCC	5/1730 (0.3%)	0/1243 (0%)	5/446 (1.1%)	0.001

- The 5-yr survival of Caucasian CHB patients treated with ETV/TDF is excellent (**>95%**)
- A **significant proportion of deaths** comes from liver unrelated causes.
- **HCC development is a major factor** affecting the overall mortality and the only factor affecting liver related mortality in such patients.

Papatheodoridis G, Lampertico P et al, EASL 2015 and AASLD 2016

Long-term benefit of NUC treatment - Conclusions

- ETV/TDF: high long-term viral suppression rates (>95%)
- No major safety problems, some issues in selected TDF treated patients (TAF available shortly)
- Prevention of clinical decompensation, improvement of portal hypertension
- HCC the only complication (HCC risk scores ?)
- Excellent 5-yr overall and liver-related survival
- New strategies/drugs needed to reduce HCC (?) and to improve HBsAg loss rates (shorten therapy)

Thank you !