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Currently status of HBV therapy: efficacy and limitations

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Outline of the presentation

- Endpoints and goal of HBV therapy
- Peg-IFN, ETV, TDF as monotherapies
- PEG+IFN and NUC combination
- Long-term outcome: histology, ESLD, HCC and death
- Limitations of current therapies

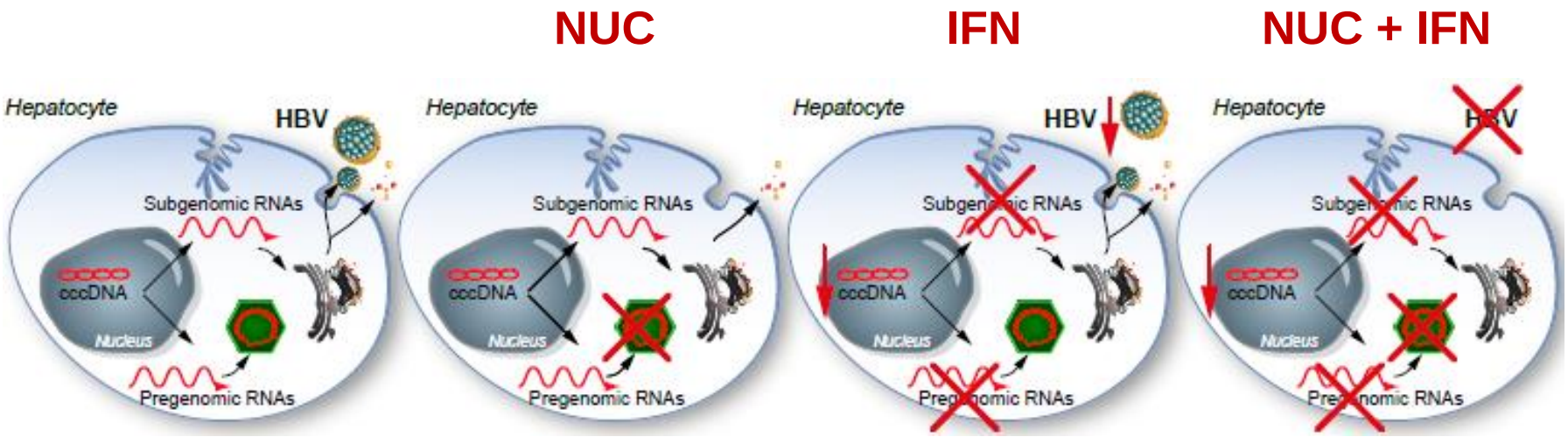
The decision to treat is historically based on phase of disease and risk of disease progression

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

What can we achieve with Peg-IFN alfa-2a in CHB?

- Treatment aims to enable patients to achieve inactive CHB with sustained immune control

Approximately 30% of patients respond to treatment with Peg-IFN alfa-2a[1,2]

- Peg-IFN alfa-2a treatment can also result in off-treatment immune control[2,3]
- Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:

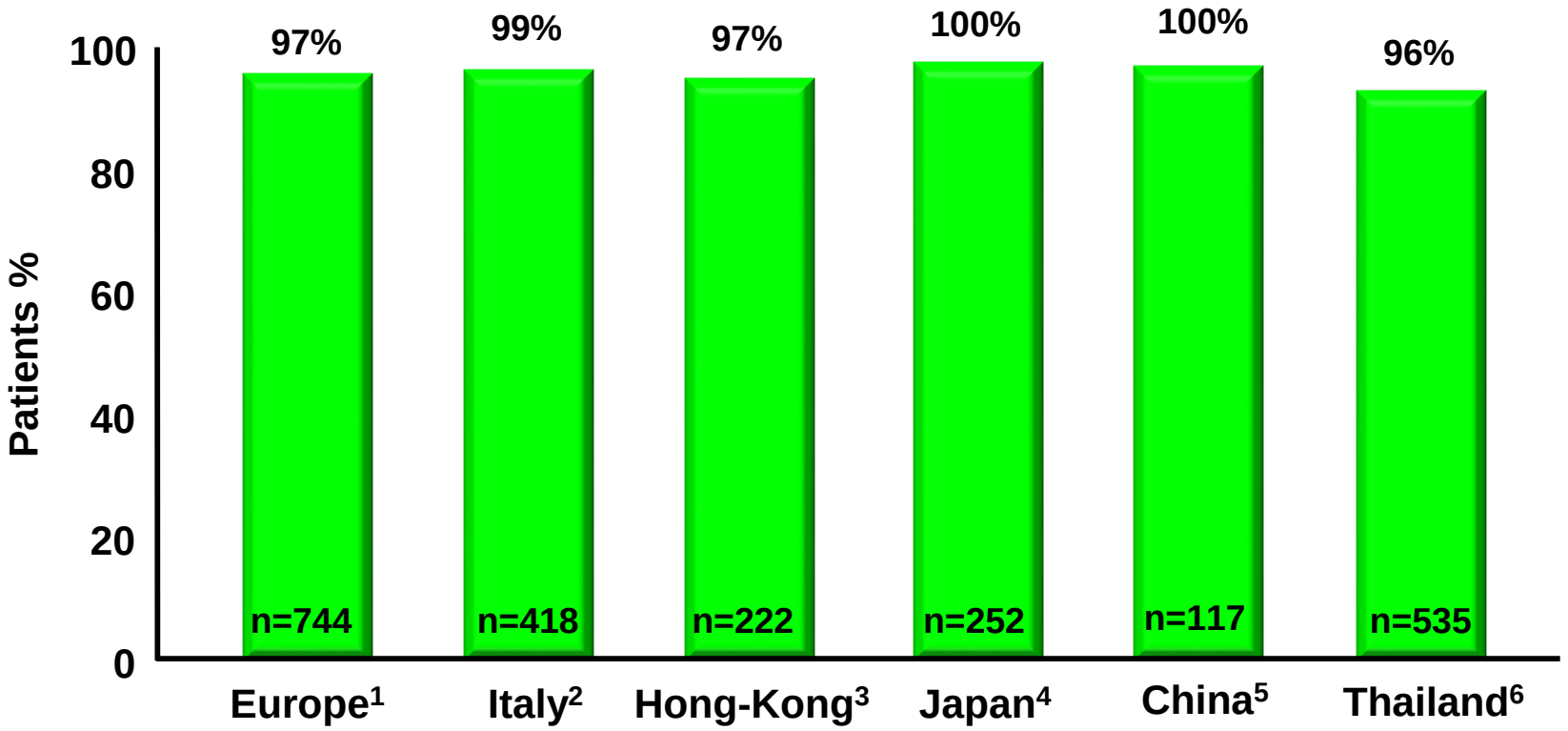
- Freedom from potentially life-long treatment[4]
- No long-term safety concerns[4]
- Decreased risk of cirrhosis and liver cancer[5,6]
- HBsAg clearance (clinical cure)[2]

1. Lau GK, et al. N Engl J Med 2005;352:2682–95; 2. Marcellin P, et al. Hepatol Int 2013;7:88–97 ; 3. Marcellin P, et al. Gastroenterology 2009;136:2169–79; 4. Perrillo RP, et al. Hepatology 2006;43:S182–93; 5. EASL HBV guidelines, J Hepatol 2012;57:167–85; 6. Liaw YF, et al. Antivir Ther 2010;15:25–33

How can we improve PEG-IFN efficacy ? Summary

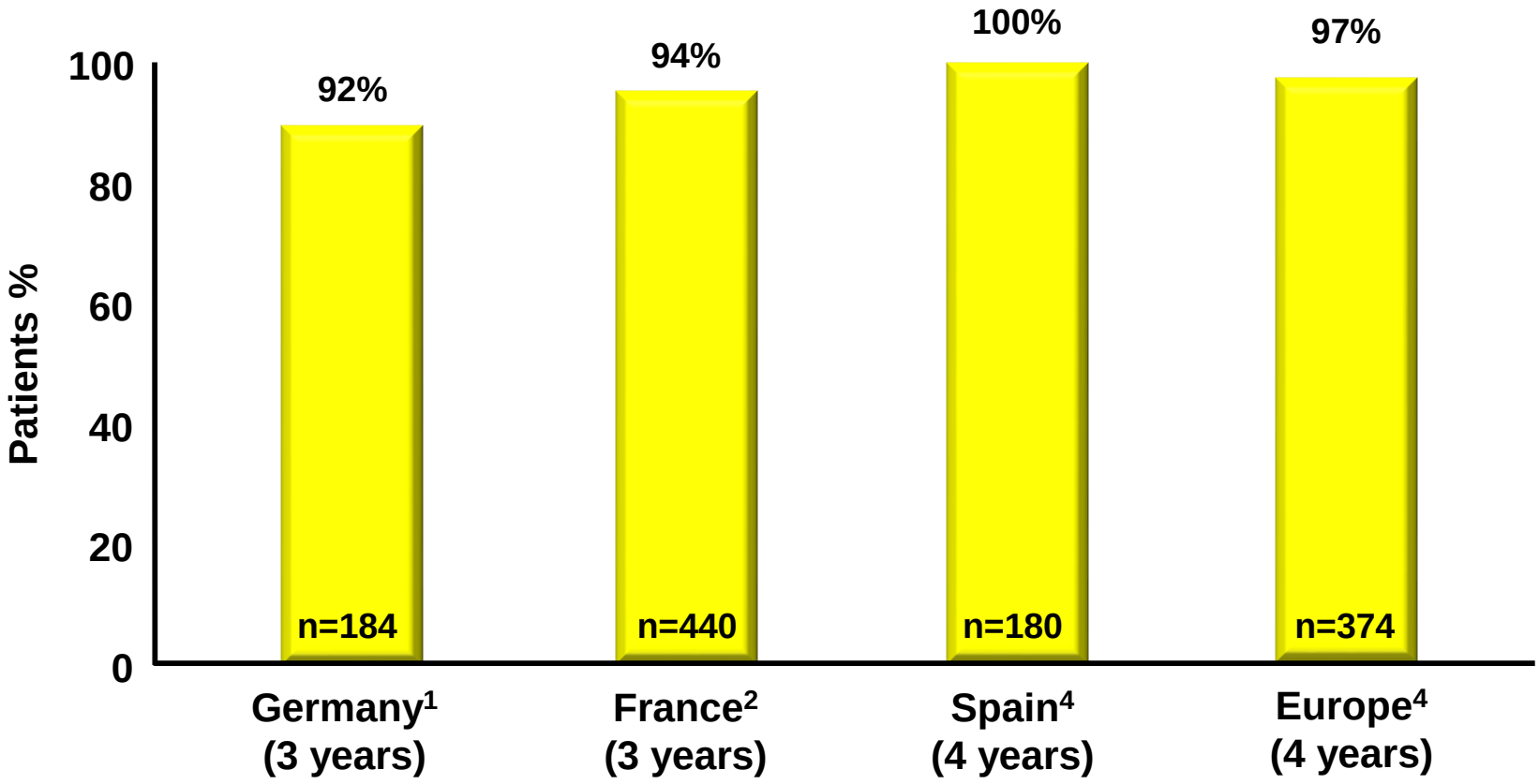
- Baseline predictive scores (4-5 variables) **(YES)**
- Baseline genetic predictors of HBsAg loss **(unclear)**
- Week 12-24 stopping rules based on HBsAg levels **(YES)**
- Extend duration of IFN to 96 wks for geno D **(YES)**
- NUC pretreatment for HBeAg pos pts **(NO)**
- *De-novo* PEG-IFN+TDF **(few patients, GT A ?)**

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

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

ETV or TDF therapy for CHB - Limitations

- Partial response in HVL patients (NUC-R ?)
- Safey issues in selected TDF treated patients
- Low HBeAg/HBsAg seroconversion rates
- Limited stopping rules (HBsAg seroconversion ?)
- Long duration of therapy
- Cost, compliance, resistance, safety > 8 years ??
- Young patients with mild liver disease

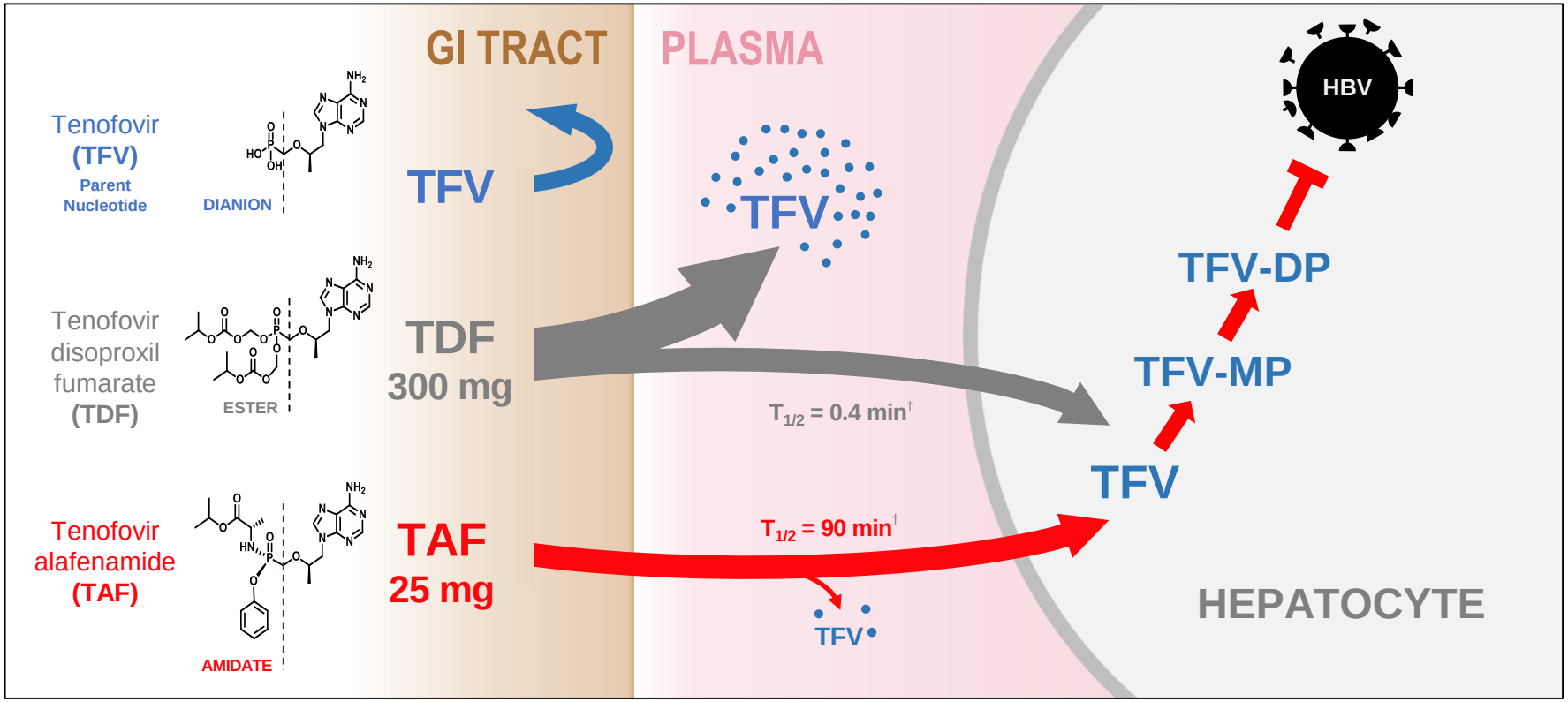
AP&T Alimentary Pharmacology and Therapeutics

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
- 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, longer duration of TDF ……
- Need for more research with more sensitive markers of tubular damage

Tenofovir Alafenamide (TAF)
Prodrug of TFV – Reduces Circulating TFV



- TAF is more stable in plasma compared with TDF[1-2]
- TAF 25 mg has 92% lower circulating plasma TFV levels compared to TDF 300mg[1]

† $T_{1/2}$ based on *in vitro* plasma data

1. Agarwal K, et al. *J Hepatology*. 2015; 62; 533-540
2. Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906.

Agarwal K et al. *J Hepatology* 2015; 62: 533-540
Murakami E et al. *Antimicrob. Agents Chemother*.13 Apr 2015 (ePub). doi:10.1128/AAC.00128-15.
Kearney BP, Flaherty JF, Shah J. *Clin Pharmacokinet*. 2004;43(9):595-612

TAF vs TDF in naive patients with CHB
A 48-week phase III study

(Authors' Conclusions)

- Treatment with TAF for 48 weeks demonstrated:
  - Non-inferior efficacy to TDF for the proportion with HBV DNA <29 IU/mL
  - Improved rates of ALT normalization
  - No resistance development in either treatment group
  - Rates of HBeAg loss and seroconversion similar to TDF in Study 110
- TAF was safe and well tolerated in HBeAg-neg and -pos patients
  - Treatment-emergent AEs similar to TDF
  - **Significantly less declines in hip and spine BMD** compared to TDF, with improved bone biomarkers
  - **Significantly smaller increases in sCr** (integrated safety analysis) and decreases in $eGFR_{CG}$ compared to TDF, with **improved markers of renal tubular function**

Buti M et al. Lancet Gastroenterol Hepatol 2016; Chan H et al, Lancet Gastroenterol Hepatol 2016

Combination of NUC and PEG-IFN ? A systematic review

- NUC to improve IFN response in <u>naive patients</u>
  - Sequential NUC to IFN **(NO)**
  - *De-novo* NUC + IFN combination **(few patients, GT A ?)**
- IFN to improve NUC response in <u>naive patients</u>
  - ″Early″ add-on IFN for HBeAg pos pts **(??)**
  - *De-novo* NUC + IFN combination **(few patients, GT A ?)**
- IFN to improve NUC response in <u>treated patients</u>
  - ″Switch″ NUC to IFN in HBeAg pos **(YES in few patients)**
  - ″Add-on″ IFN to NUC in HBeAg neg **(YES in few patients)**

Viganò M, Invernizzi F, Grossi G, Lampertico P. APT 2016

When to stop NUC therapy ?

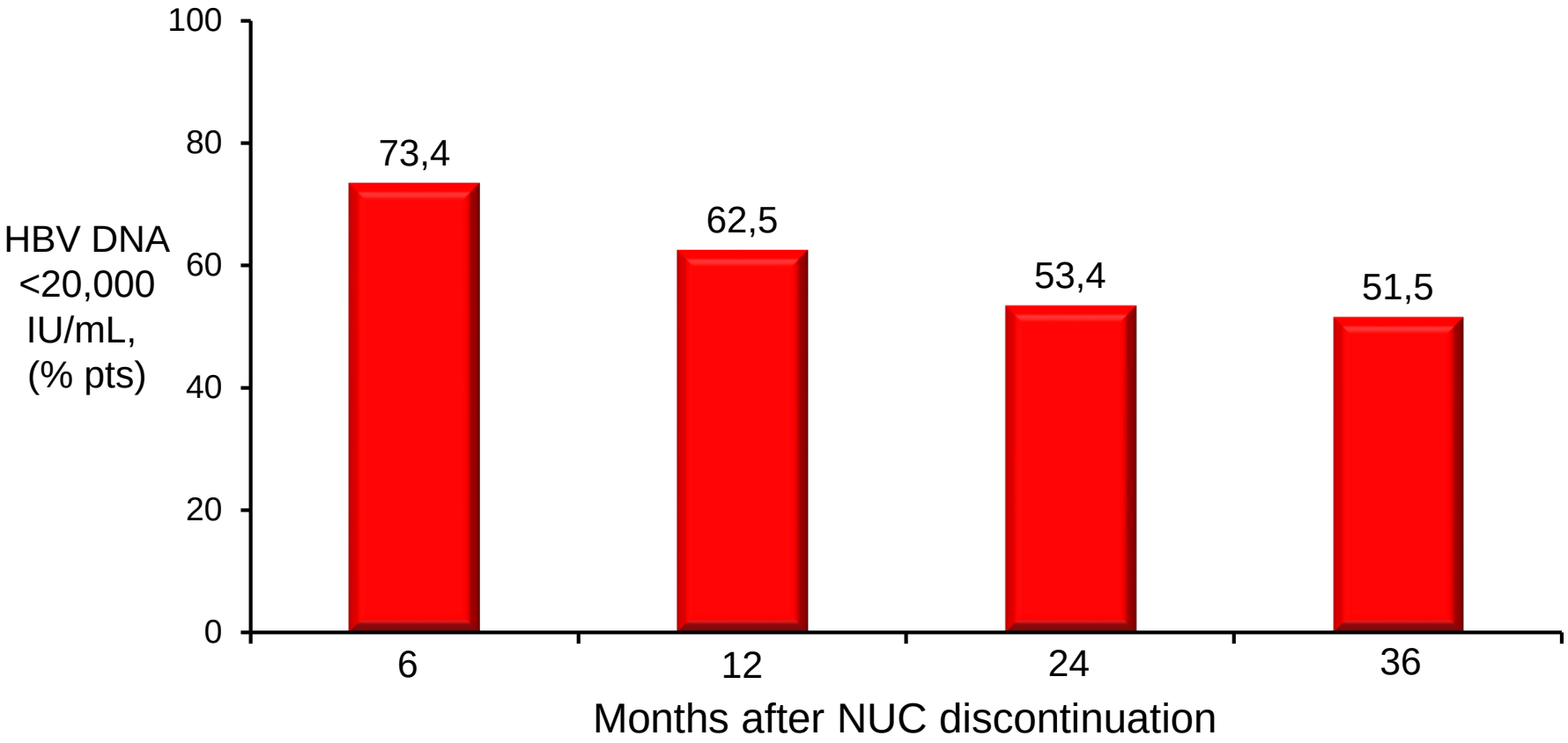
CHB Treatment Guidelines	EASL 2012 guidelines
HBeAg positive	A) confirmed anti-HBe seroconversion (and undectable HBV DNA) after at least 12 months of consolidation* **B) confirmed HBsAg loss and anti-HBs seroconversion**
HBeAg negative	**confirmed HBsAg loss and anti-HBs seroconversion**
Cirrhotics	**confirmed HBsAg loss and anti-HBs seroconversion**

*A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response

adapted from EASL HBV Guidelines, J Hepatol 2012; Reijnders JG and Janssen HL. Hepatology 2013, EASL Special HBV conference, J Hepatol 2015

Virological remission after NUC discontinuation in HBeAg pos CHB - A systematic review

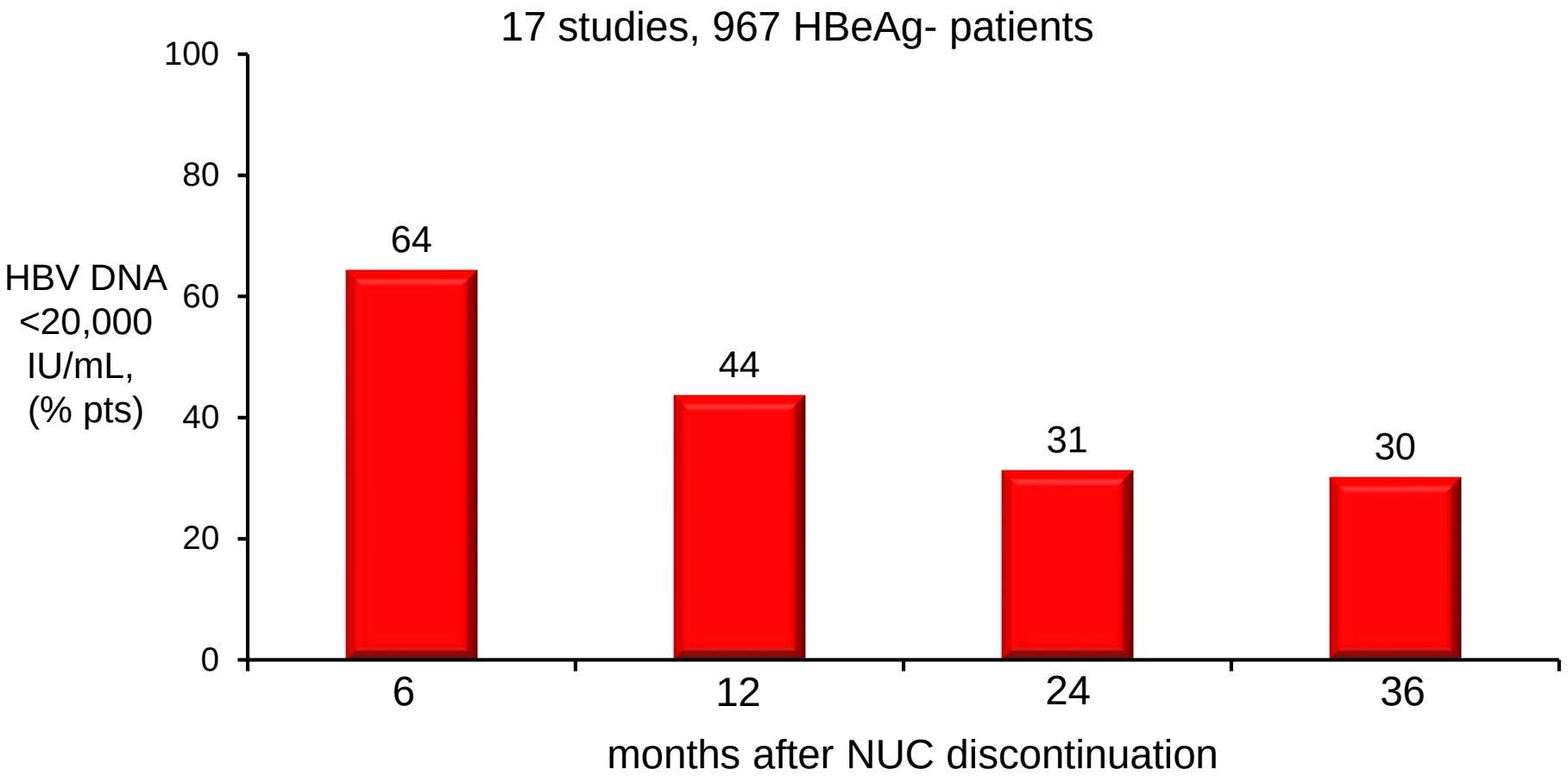
14 studies, 733 initially HBeAg+ patients



Pooled HBsAg loss: 1%; Durable biochemical remission: 76%

Papatheodoridis G. et al, Hepatology 2016

Virological remission after NUC discontinuation in HBeAg neg CHB - A systematic review



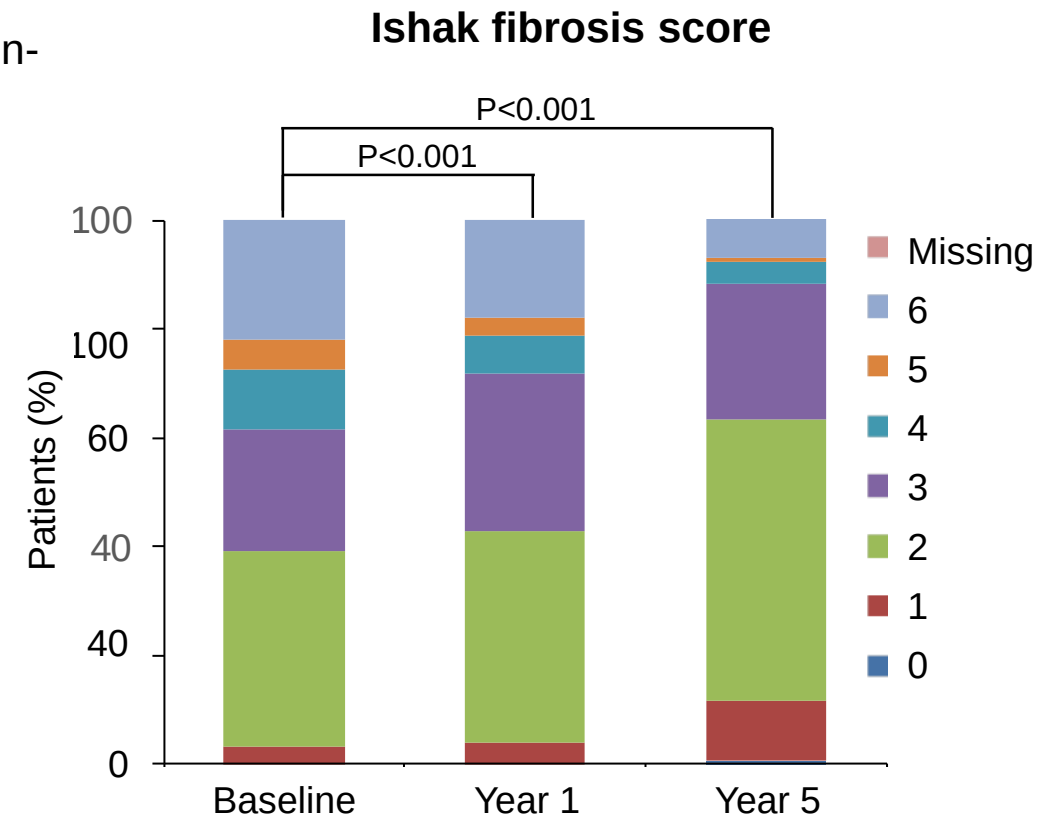
Pooled HBsAg loss: 1.7%; Durable biochemical remission: 57%

Papatheodoridis G. et al, Hepatology 2016

Long-term clinical benefits

5-year TDF treatment - Histological outcomes: liver fibrosis regression and cirrhosis reversal

- TDF vs ADV for 48 weeks then open-label TDF in HBeAg- and HBeAg+ patients (Studies 102 and 103)
  - N=348 had biopsies at baseline and Year 5
  - N=96 with cirrhosis
- 74% (71/96) had reversal of cirrhosis
- Only low BMI was associated with fibrosis regression at Year 5
- Baseline BMI, diabetes at baseline and on-treatment ALT level associated with cirrhosis reversal



Histologically evaluable patients in the long-term histology cohort; 344 patients had biopsies at baseline, Year 1 and Year 5;

Marcellin P, et al. Lancet 2013;381:468–75

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 Europe (5-6)

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

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

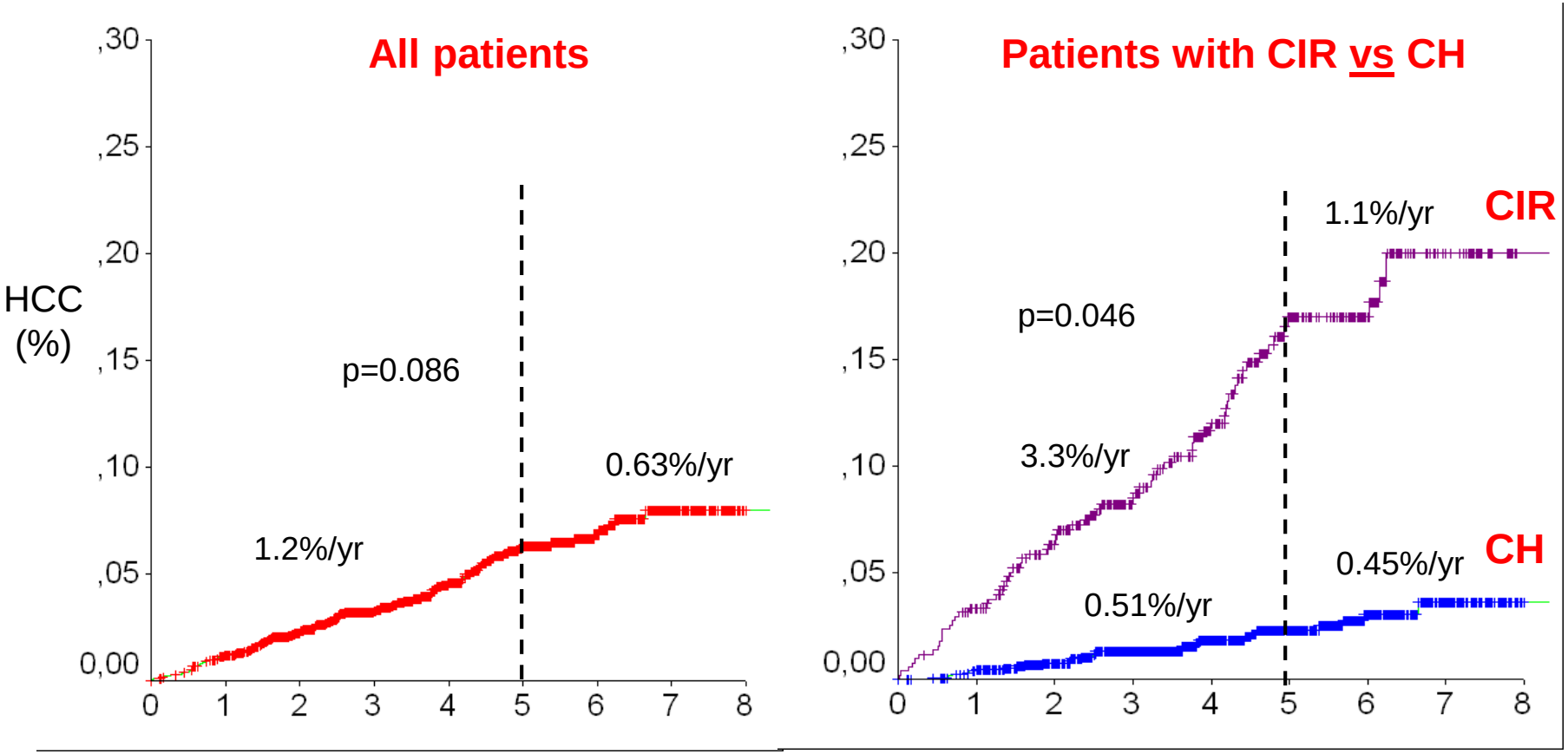
Long-term NUC and prevention of HCC
Propensity score studies from Asia and US

Author	Patients		Follow-up (yr)		% HCC at 5 yr		RR (95% C.I.)	P-value
	NUC+	NUC-	NUC+	NUC-	NUC+	NUC-		
Wu et al[1] (Taiwan)	21,595	21,595	3.4	5.2	7.3	22.7	**0.31 (0.27–0.53)**	<.001
Hosaka et al[2] (Japan)	316	316	3.3	7.6	3.7	13.7	**0.37 (0.15–0.91)**	.03
Kumada et al[3] (Japan)	117	117	12.3	11.6	2.7	11.3	**0.28 (0.13–0.62)**	.002
Gordon et al[4] (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.

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



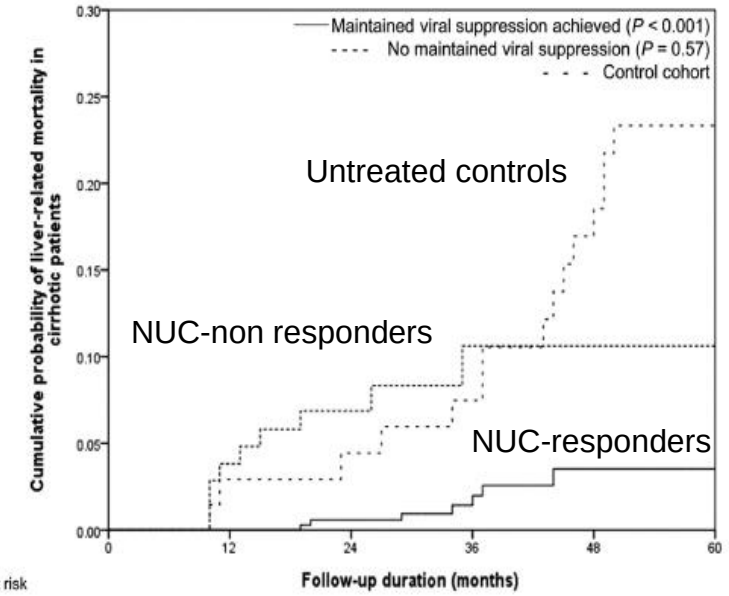
HCC beyond yr-5 associated only with older age (p=0.062) or age ≥55 at ETV/TDF onset (p=0.02)

Papatheodoridis G, Lampertico P et al. AASLD 2015

Survival

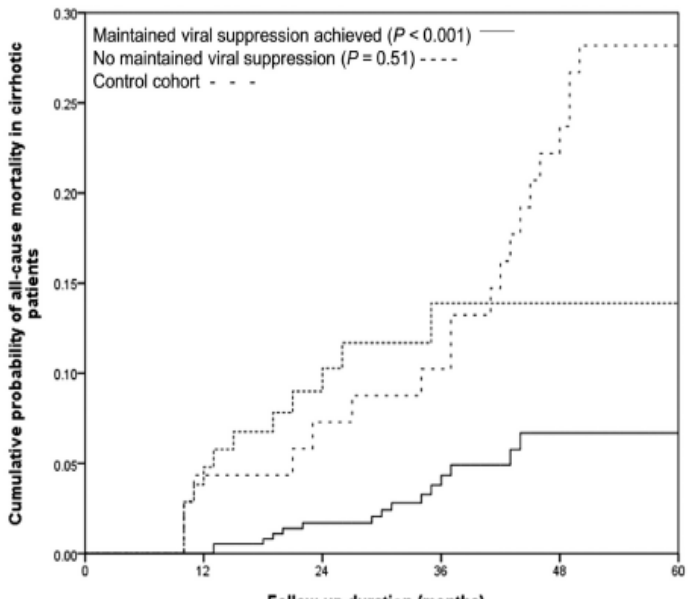
ETV treatment reduces deaths in HBV cirrhotics a retrospective study from Hong Kong

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

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

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

Current HBV treatments - Conclusions

- PEG-IFN for few patients, effective in some
- ETV/TDF for most CHB patients, very effective (>95%)
- IFN-NUC for selected patiets, TAF available in 2017
- Prevention of clinical decompensation, improvement of portal hypertension, HCC the only complication
- Excellent 5-yr overall and liver-related survival
- New strategies/drugs needed to reduce HCC (?) and to improve HBsAg loss rates