First line therapy: interferon or analogues

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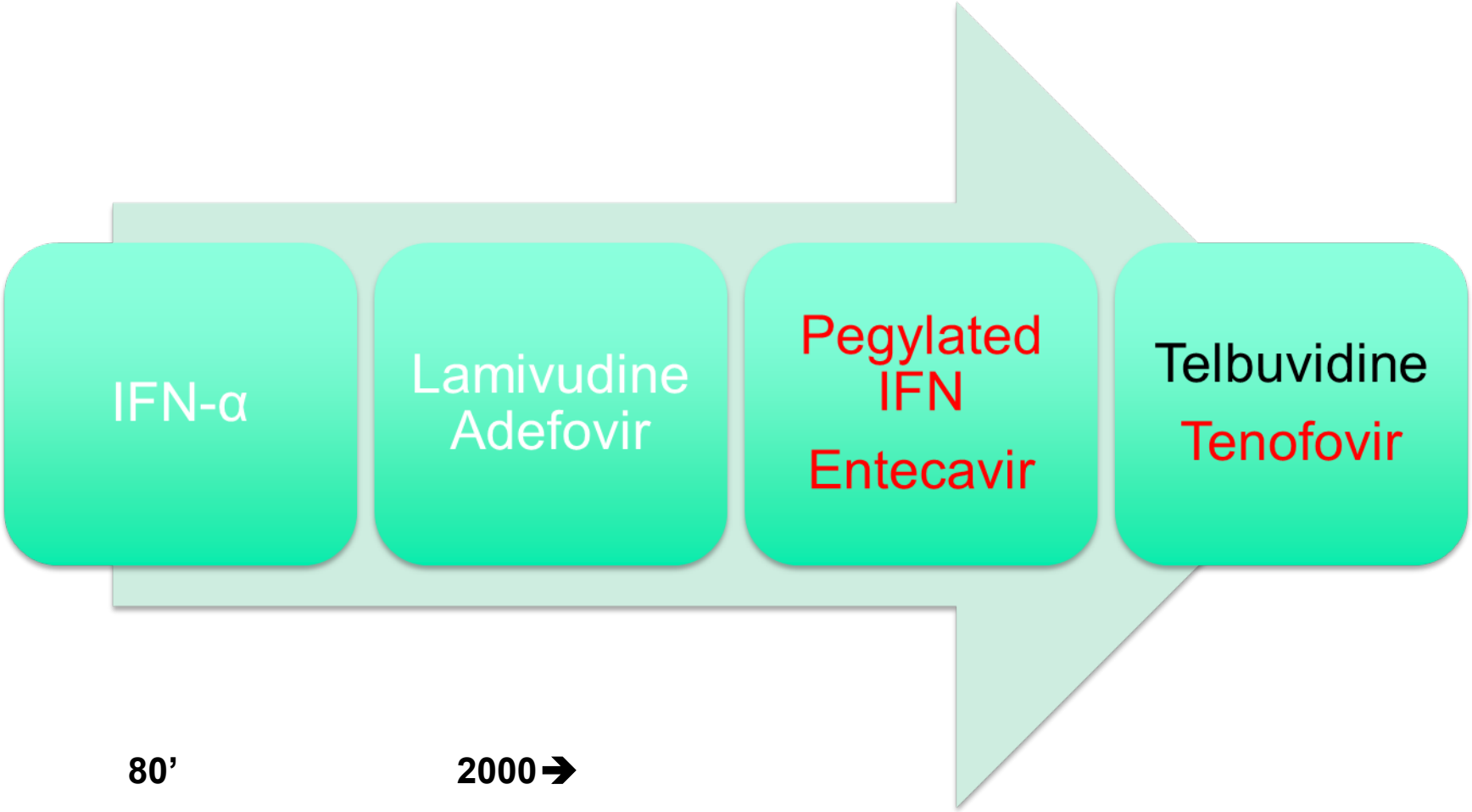
H+H Humanity & Health

5 years ago…..

- Limited long-term data
  - Tenofovir or Entecavir
  - Pegasys

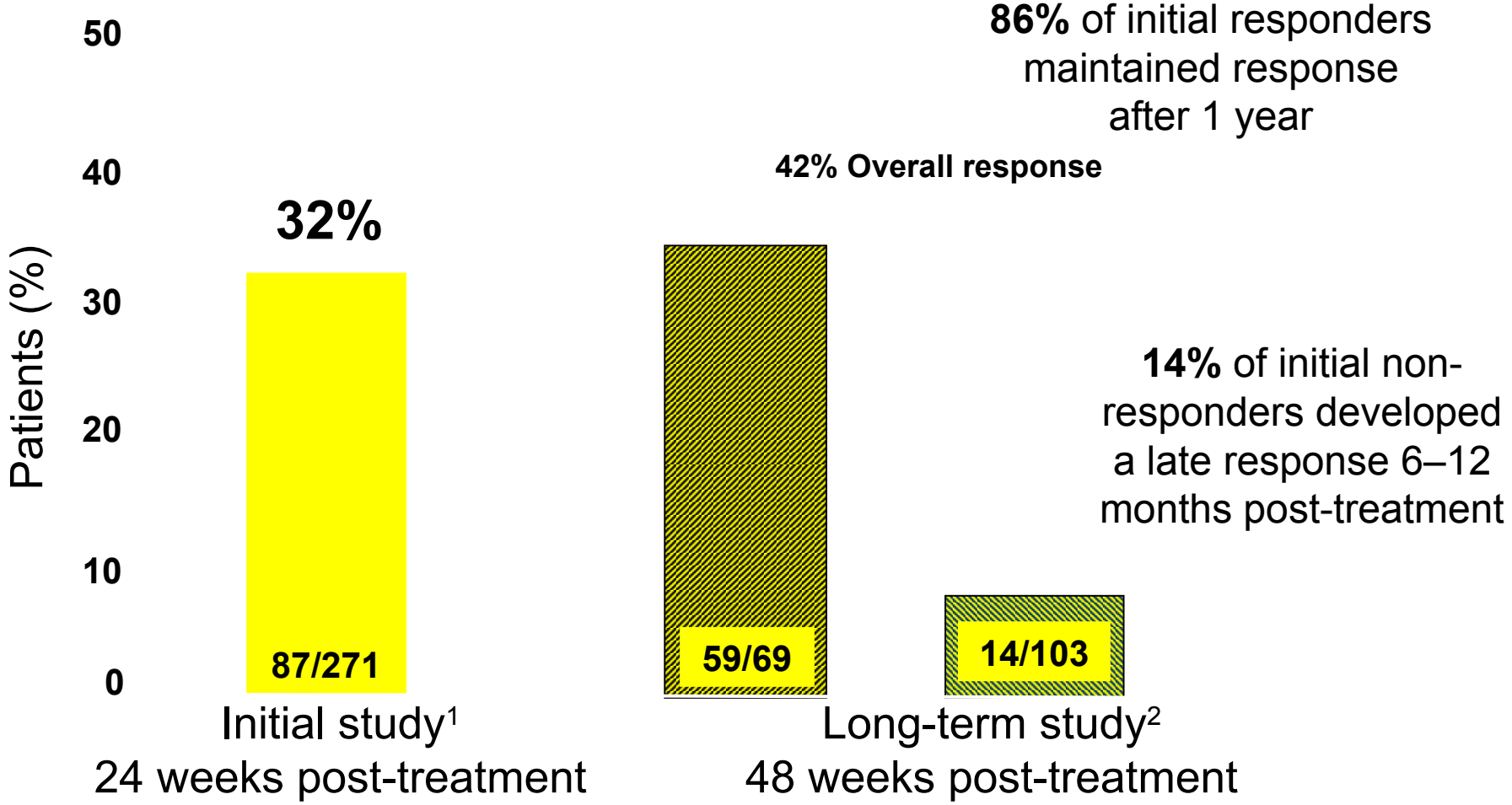
- Value of qHBsAg

Therapy of Chronic HBV infection



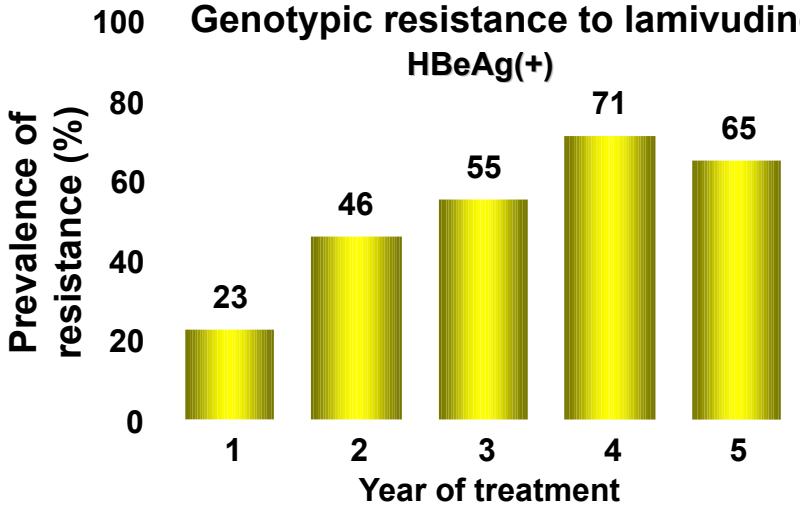
HBeAg Seroconversion
Long-term Roll-over Study: 1 Year Analysis

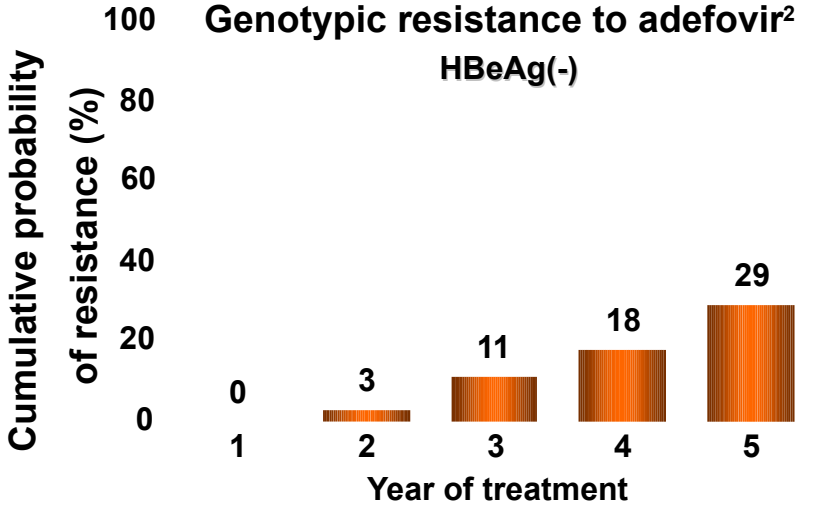
- 173 patients from the PEGASYS mono therapy arm entered the long-term study (63% of original study): 69 responders and 103 non responders

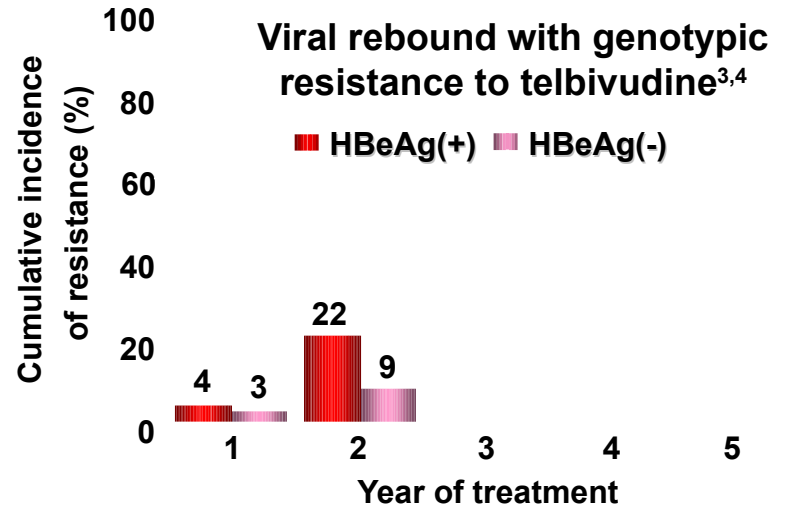


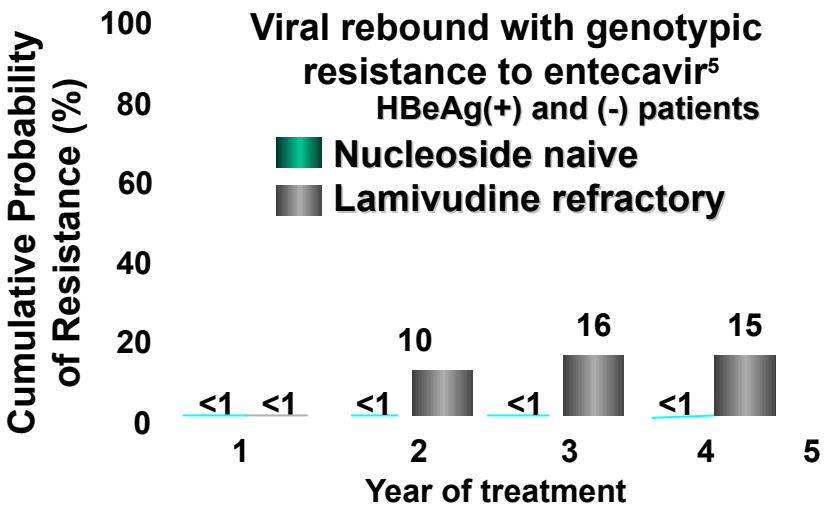
1. Lau et al. *N Engl J Med* 2005; 2. Lau et al. EASL 2006

Resistance Profiles of antiviral agents









1. Lok AS, et al. Gastroenterology. 2003;125:1714-22. 2. Borroto-Esoda K. J Hepatol. 2006;44(suppl 2):S179-80 (Poster 483). 3. Standrigg DN, et al. J Hepatol. 2006;44(suppl 2):S191 (Poster 514). 4. Lai CL, et al. Hepatology. 2006;44(4 suppl 1):222A (Oral 91). 5. Colonno et al. J Hepatol 2007;46(suppl 1):S293 (oral 781).

Predicted† and observed rates of HBeAg response 24 weeks post-treatment with pegylated interferon-α2a according to baseline ALT and HBV DNA*

	Predicted rates % [80% CI] / Observed rates % (n/n)		
	ALT High	ALT Med	ALT Low
HBV DNA ≤10.0 log	50% [40–61] 52% (13/25)	38% [31–45] 36% (22/61)	31% [24–39] 32% (18/56)
HBV DNA >10.0 log	29% [21–39] 28% (8/29)	20% [14–27] 22% (10/45)	16% [10–23] 12% (2/17)

*According to baseline levels of ALT and HBV DNA.
ALT: High >5 x ULN; Med >2–5 x ULN; Low ≤2 x ULN
†[80% Confidence Intervals]

Chow et al. *APASL* 2006

Optimising response in HBeAg-positive CHB through immune control

Peg-IFN

Short-term, finite duration (48 wks)

Long-term benefit in ~1/3 pts

HBsAg seroconversion achievable

No resistance

NAs

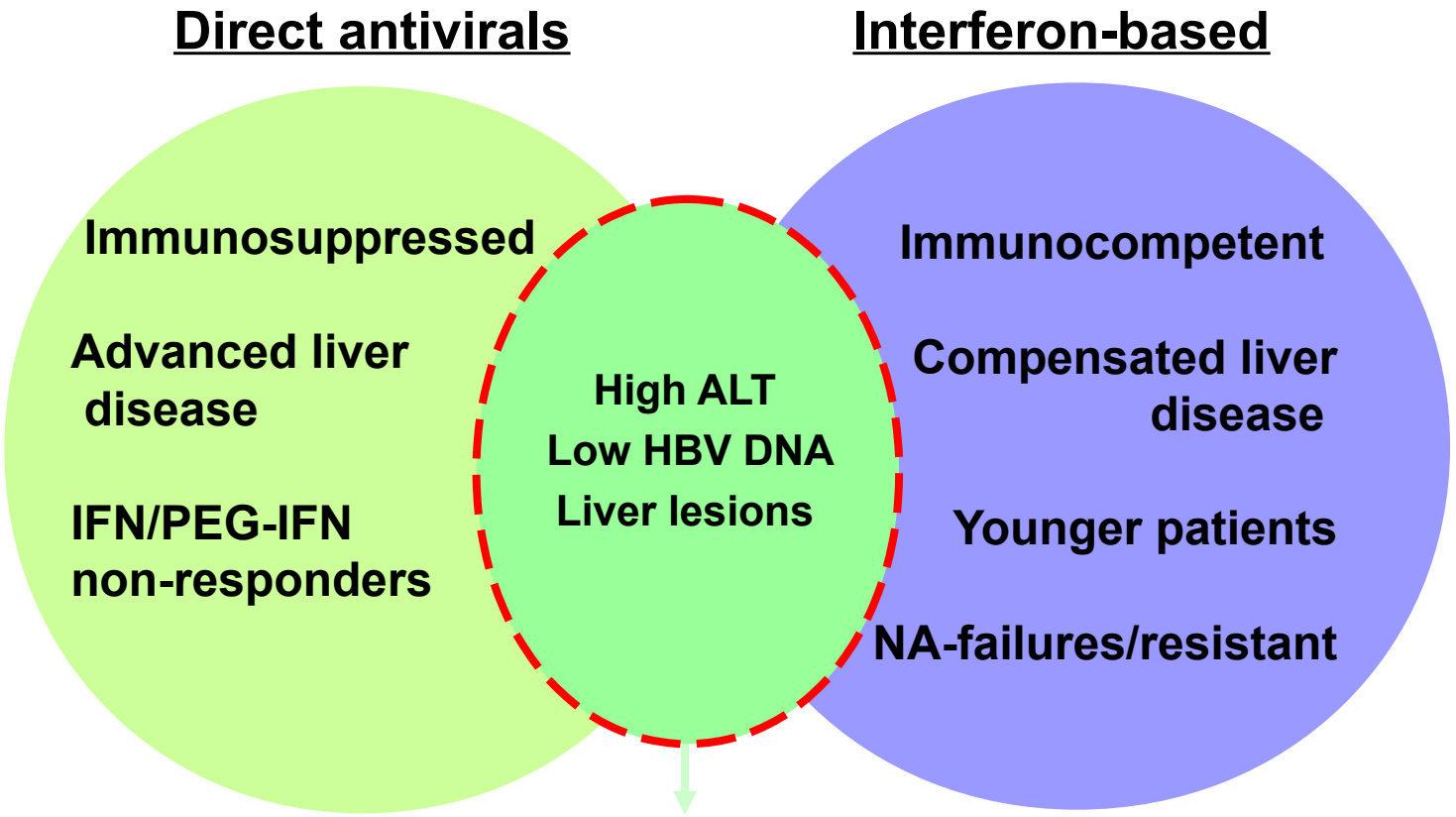
Long-term maintenance (years)

Risk of resistance, and cross-resistance – monitor closely

Use in combination?

For patients who do not respond or for whom IFN contraindicated we need to know how to use NAs appropriately

Who should be treated with what?



NA treatment should not be prescribed until the PATIENT understands that they CANNOT be stopped abruptly for any reason

2014

Long-term data

- Tenofovir or Entecavir
- Pegasys

- Value of qHBsAg

What to consider?

Cost-effectiveness

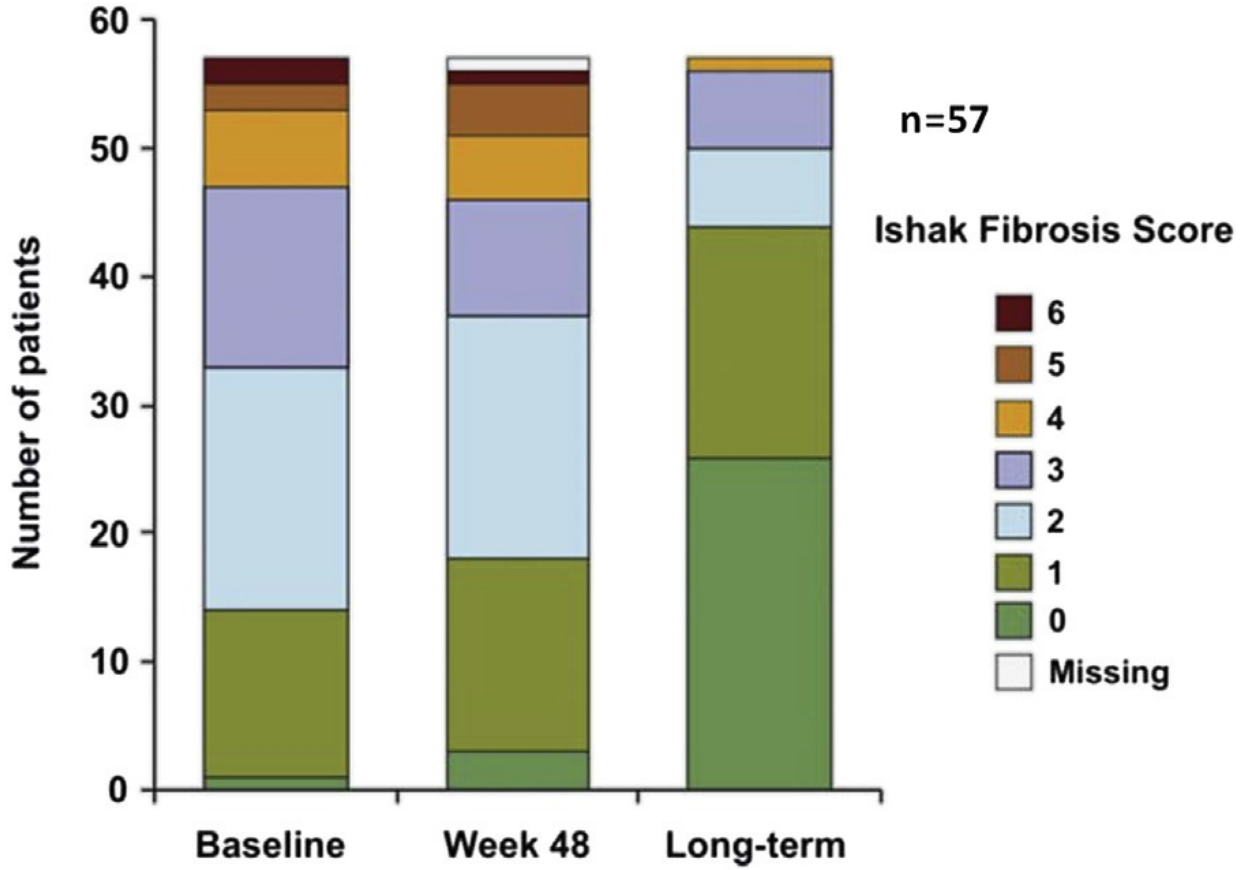
- Histological improvement
- Reduction of HCC
- HBsAg clearance
- Cost of drug and monitoring

Safety

- Tolerability
- Drug resistance

ETV

Distribution of Ishak fibrosis scores at the phase III baseline, after 48 weeks of ETV treatment, and at the time of long-term biopsy (median 6 years of ETV treatment)



Chang TT, Liaw YF, Wu SS, et al. Hepatology 2010;52(3):886–93.

HBsAg seroclearance after nucleoside analogue therapy in patients with chronic hepatitis B: clinical outcomes and durability

5409 CHB patients treated with lamivudine or entecavir

- **median follow-up period of 6 years (33 567 patient-years)**
- **110 achieved HBsAg seroclearance (0.33% annual seroclearance rate)**

- **Factors**
  - **Baseline alanine aminotransferase (ALT) level >5 times of ULN**
  - **HBeAg positivity**
  - **High HBV DNA level**
  - **Cirrhosis**

Kim GA et al Gut. 2013

Long-term continuous entecavir therapy in nucleos(t)ide-naïve CHB patients

- 474 nucleos(t)ide-naïve CHB patients (HBeAg-positive: 47%) on continuous entecavir treatment for 4 years
- Incremental increases were observed in the rates of undetectable HBV DNA, HBeAg seroclearance and seroconversion, and ALT normalization, reaching 96%, 42%, 38% and 93%, respectively, by the fourth year.
- Five patients experienced virological breakthrough including two (0.4%) who developed entecavir-resistance mutations.

Ono A, et al. J Hepatol. 2012;57(3):508-14.

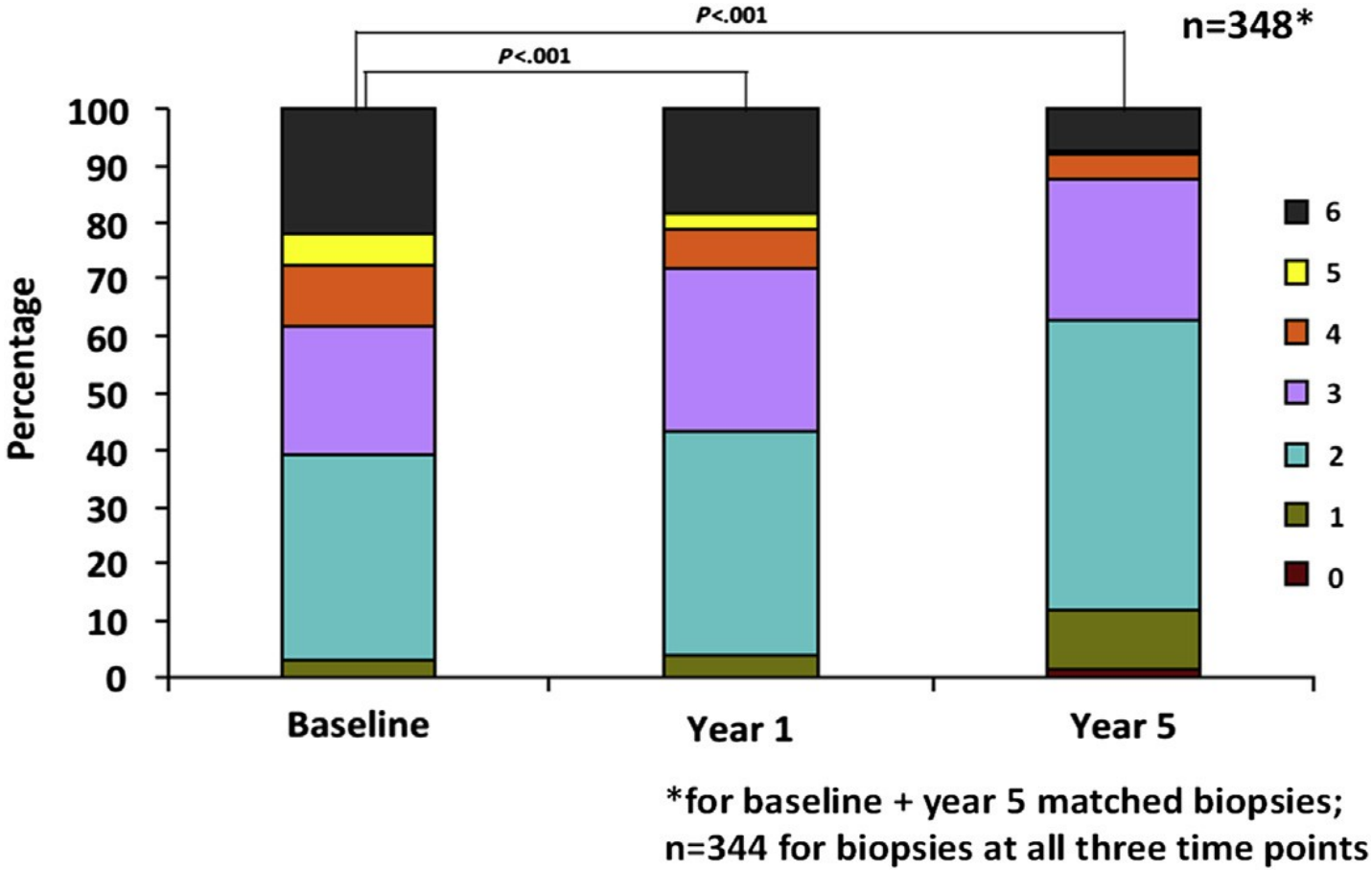
Changes of HBsAg in naive HBeAg-negative chronic hepatitis B patients under 4-year entecavir therapy

- 114 patients received entecavir for a median of 4.3years
- HBsAg levels decreased by a median of 0.03, 0.13, 0.17, 0.22, and 0.32 log10IU/ml at 6 months and 1, 2, 3, and 4years, respectively
- HBsAg loss occurred in 4/114 (3.5%) patients
  - 1/2, 3/21, and 0/91 patients with baseline HBsAg <100, 100-1000 and >1000IU/ml, respectively ($p<0.001$).

Papatheodoridis G. J Hepatol. 2014;60(1):62-8.

TDF

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study



Virological breakthrough occurred infrequently and was not due to resistance to TDF

Marcellin P, et al . Lancet 2013;381(9865):468–75

Therapy with tenofovir disoproxil fumarate for Chinese with HBeAg-negative chronic hepatitis B for up to 8 years-a real life experience

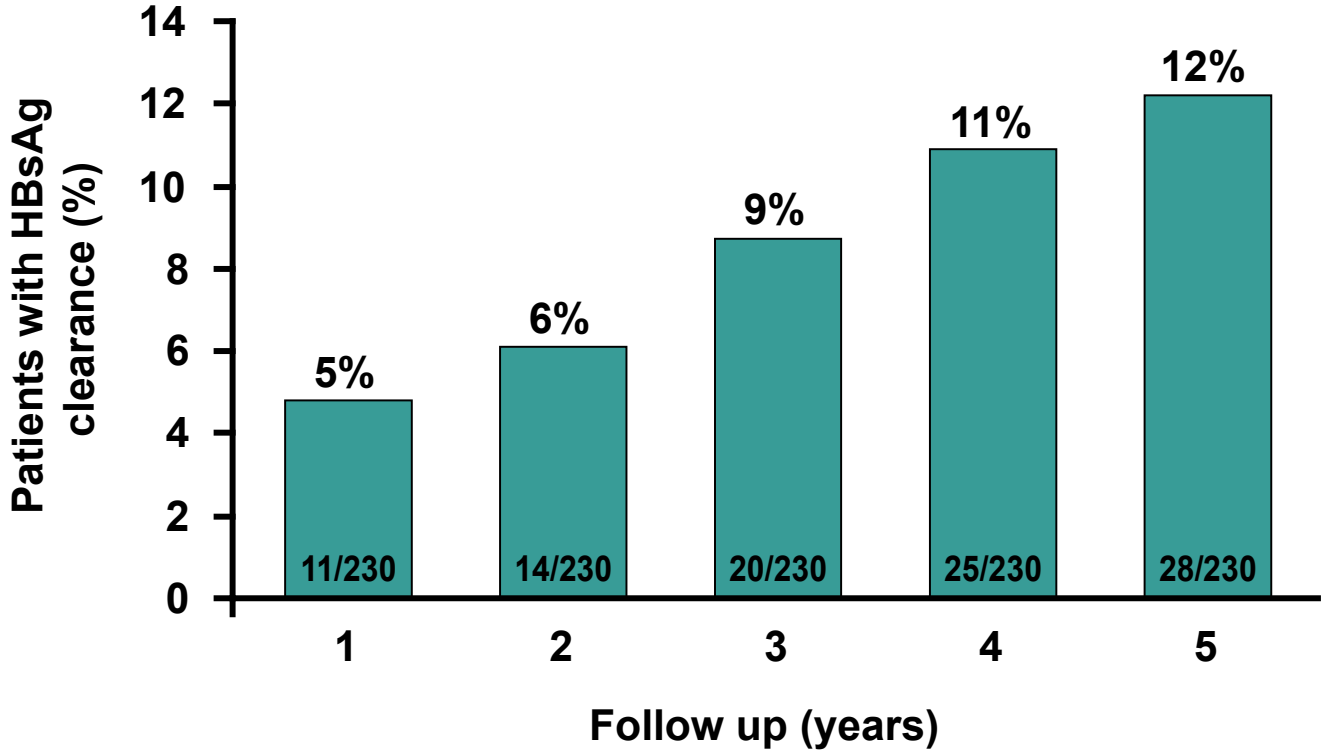
- 110 HBeAg- Chinese patients were treated with TDF for median duration of 33 (range: 24-102) months
- All patients remained HBsAg positive and none were taken off from DF therapy
- No amino acid substitutions in HBV DNA polymerase associated with resistance to TDF were detected
- LSM value significantly decreased after TDF therapy with a median change of LSM value/year was -0.8 (range: -8.5～5.9)
- Slight elevations in creatinine were confirmed in 1 (0.9%) patients

Dong Ji et al. APASL 2014

Peg-IFN

Hepatitis B surface antigen levels: association with 5-year response to peginterferon alfa-2a in hepatitis B e-antigen-negative patients

HBeAg-negative patients treated with PEGASYS (± lamivudine) in Phase 3 study



Marcellin P et al. Hepatol Int. 2013;7(1):88-97.

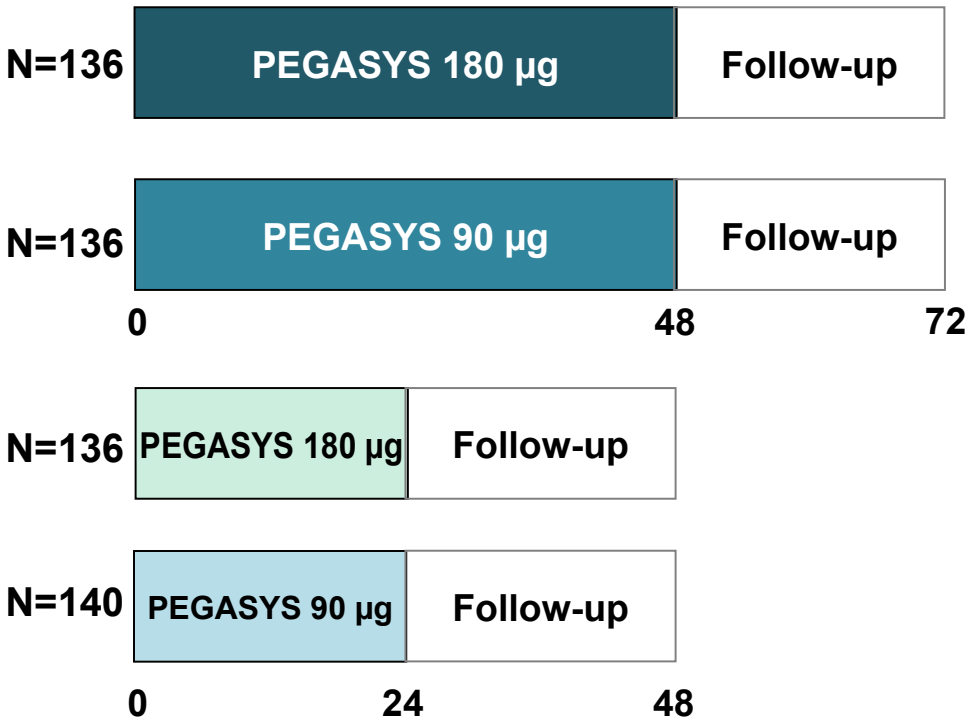
Hepatitis B surface antigen levels: association with 5-year response to pegIFN alfa-2a in HBeAg-negative patients

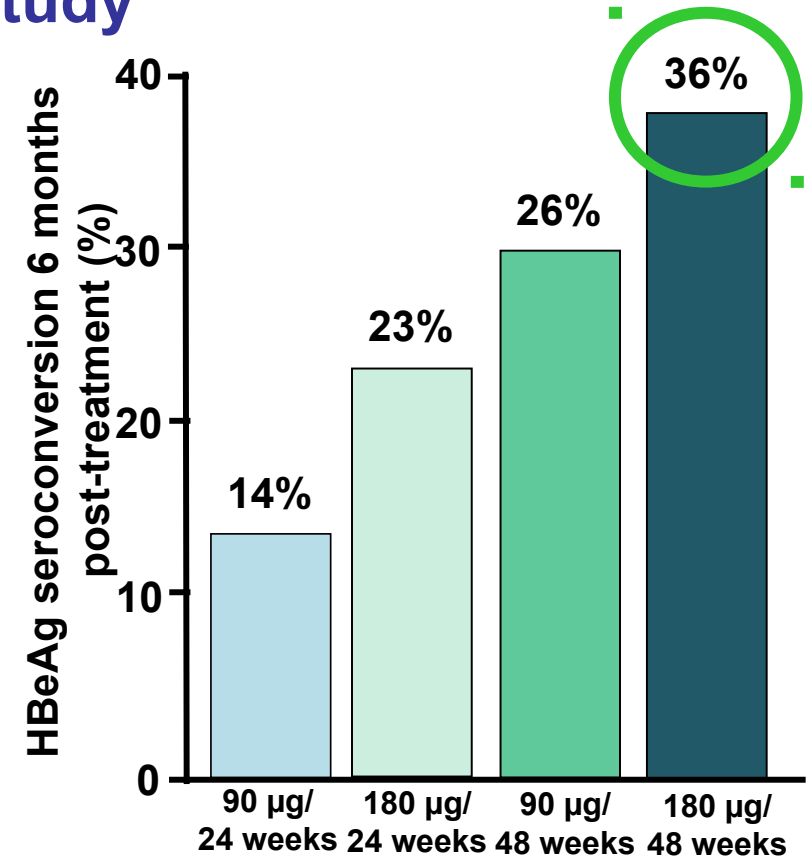
- HBsAg clearance with 5 years post-treatment
  - 12%
  - 22.6 and 22.4% in patients with ≥10% decline at weeks 12 and 24, respectively, compared with 7.5% ($p = 0.0161$) and 3.8% ($p < 0.0001$) in patients with <10% decline

Marcellin P et al. Hepatol Int. 2013;7(1):88-97.

PEGASYS in HBeAg-positive disease: Dose and duration are important

NEPTUNE study





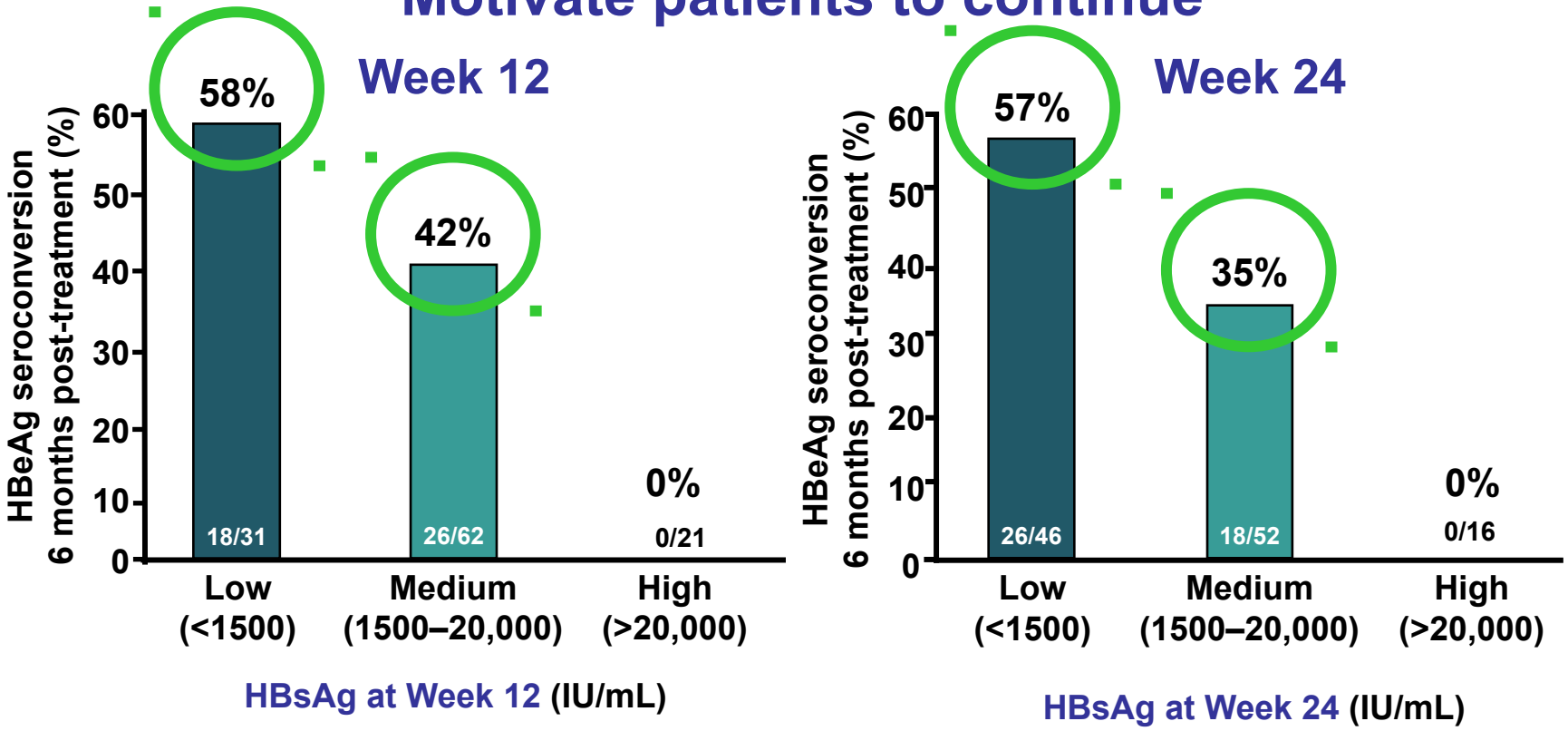
Highest sustained response with 180 µg and 48 weeks – confirms Phase 3 study

Liaw et al. Hepatology 2011

NEPTUNE: Confirms association of HBsAg level with response to PEGASYS

HBeAg-positive patients treated with PEGASYS for 48 weeks

Motivate patients to continue



HBsAg measured using Elecsys HBsAg II quant assay

Liaw et al. Hepatology 2011

Table 1. Negative predictive value for sustained virological response according to HBsAg level/decrease at week 12 and week 24 peginterferon therapy

			NPV	
Author (ref)	HBeAg	HBsAg	Week 12	Week 24
Chan (38)	Positive	<1 log decrease	na	85%
Lau (40)	Positive	<1500 IU/ml decrease	72%	76%
Gane (41)	Positive	>20 000 IU/ml	84%	na
Sonneveld (42)	Positive	Absence of decrease	97%	na
Piratvisuth (43)	Positive	Absence of decrease	82%	na
Liaw (2011)	Positive	<1500 IU/ml decrease	84%	85%
		>20 000 IU/ml	100%	100%
Moucari (52)	Negative	<0.5 log decrease	90%	97%
Rijckborst (57)	Negative	Absence of decrease	100%	na
Summary	e+/e−	Absence of decrease	72–100%	76–100%

Individualized treatment of HBeAg- CHB using pIFN as first-line and week-12 HBV DNA/HBsAg stopping rule: a cost-effectiveness analysis

Strategy

- **ETV/TDF**
- **PEG-IFN➔ ETV/TDF for either patients meeting the week-12 stopping rule* or week-48 null-responders/relapsers/CC**

Cost-effectiveness by Markov model

- **First-line PEG-IFN➔ NUCs**
  - **wk 12 HBV DNA/HBsAg stopping rule**
  - ❑ **wk-48 non-responders/relapsers**

***absence of a decline in HBsAg level combined with less than 2 log copies/mL decrease in HBV DNA level**

Iannazzo S et al. Antivir Ther. 2013;18(4):623-33.

Pegylated interferon results in higher serological, but not virological, response rates when compared to continuous entecavir

- 92 wks ETV (n=91) Vs 48 wks PEG-IFN (n=266)

- Finite PEG-IFN therapy
  - higher rates of HBeAg seroconversion (adjusted hazard ratio [HR] 3.16; P<0.001) and HBsAg clearance (HR 5.66; P=0.027)

- ETV
  - higher rates of HBV DNA undetectability (OR 31.14; P<0.001)

Sonneveld MJ et al. Antivir Ther. 2012;17(8):1605-8.

Summary

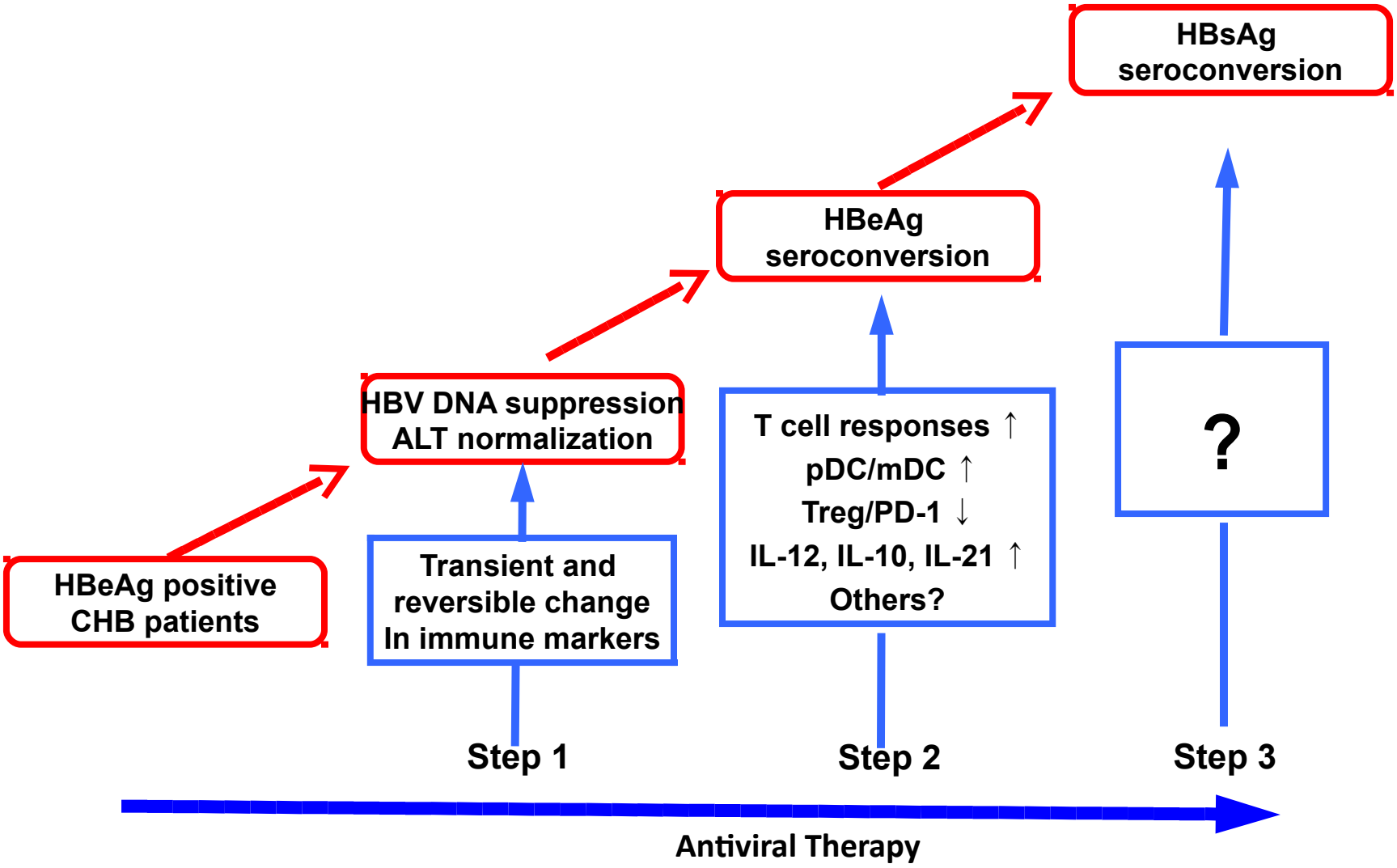
TDF or ETV

- Resistance-negligible
- Restoration of host immune control-low
  - Low HBeAg/HBsAg loss→Prolonged treatment

Peg-IFN

- Better patient selection-baseline parameters
- On therapy stopping rule

Immune markers correlated with HBeAg seroconversion



Lau GK et al J Hepatol 2012

Which strategy?

Best patients for PEG-IFN:

- Those preferring a finite course of therapy
- Younger patients
- Compensated disease

Which strategy?

Best patients for NAs:

- Patients cannot tolerate PEG-IFNs
- Those not responsive PEG-IFNs
- Decompensated disease

CHCF 2013

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