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HBsAg: a tool to make decisions in HBV patients

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CHB: antiviral therapy

Peg-IFN used mainly in Chronic Hepatitis and early Cirrhosis

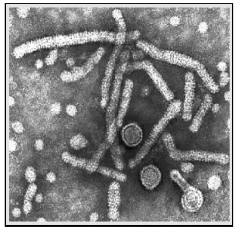
- transition from active to inactive infection in 20-40% of pts, with subsequent HBsAg clearance in about 50% of SVR
- reduction of liver disease progression rate (CHB to Cirrhosis, Cirrhosis to end stage liver disease and HCC)

NUCs used mainly in Cirrhosis

- HBV-DNA > 90% of pts after 3 years of treatment
- HBeAg to anti-HBe seroconversion in 40% of pts after 5 years
- HBsAg clearance in 3-10% of HBeAg pos cases, < 1%/year in HBeAg neg.
- histologic amelioration with regression of fibrosis
- reduction of liver disease progression to end stage complications

Lau et al. *AASLD* 2006; Buster E Gastro. 2008; Marcellin et al. EASL 2008; Brunetto MR, J Hep 2003; Sung et al. Ali Phl Ther 2008; Chang TT, et al. *N Engl J Med* 2006; Gish RG, et al. *Gastro.* 2007; Heathcote J, et al. AASLD 2010. Zoutendijk et al. J Infect Dis 2011; Wong et al, Hepatology 2013

Serum



HBV-DNA

Virions

replication

HBsAg

Virions + defective particles
(exceeding virions by a factor of 102-105)

replication

cccDNA transcription/
mRNAs translation

Serum HBV-DNA decline: reduction of replication

Serum HBsAg decline: reduction of the cccDNA amount or of the cccDNA transcription /mRNAs translation

Brunetto et al, J Hepatol 2010

HBV therapy: role of HBsAg quantification

Peg-IFN treatment

20-40% off therapy response after 1 year treatment

- to identify patients with poor change of response at baseline or early on treatment
- to increase the success rate by tailoring treatment according to the risk of relapse

A baseline prodictive tool for selecting HBeAg negative chronic hepatitis B patients who have a high probability of achieving sustained immune control with Peg-IFN

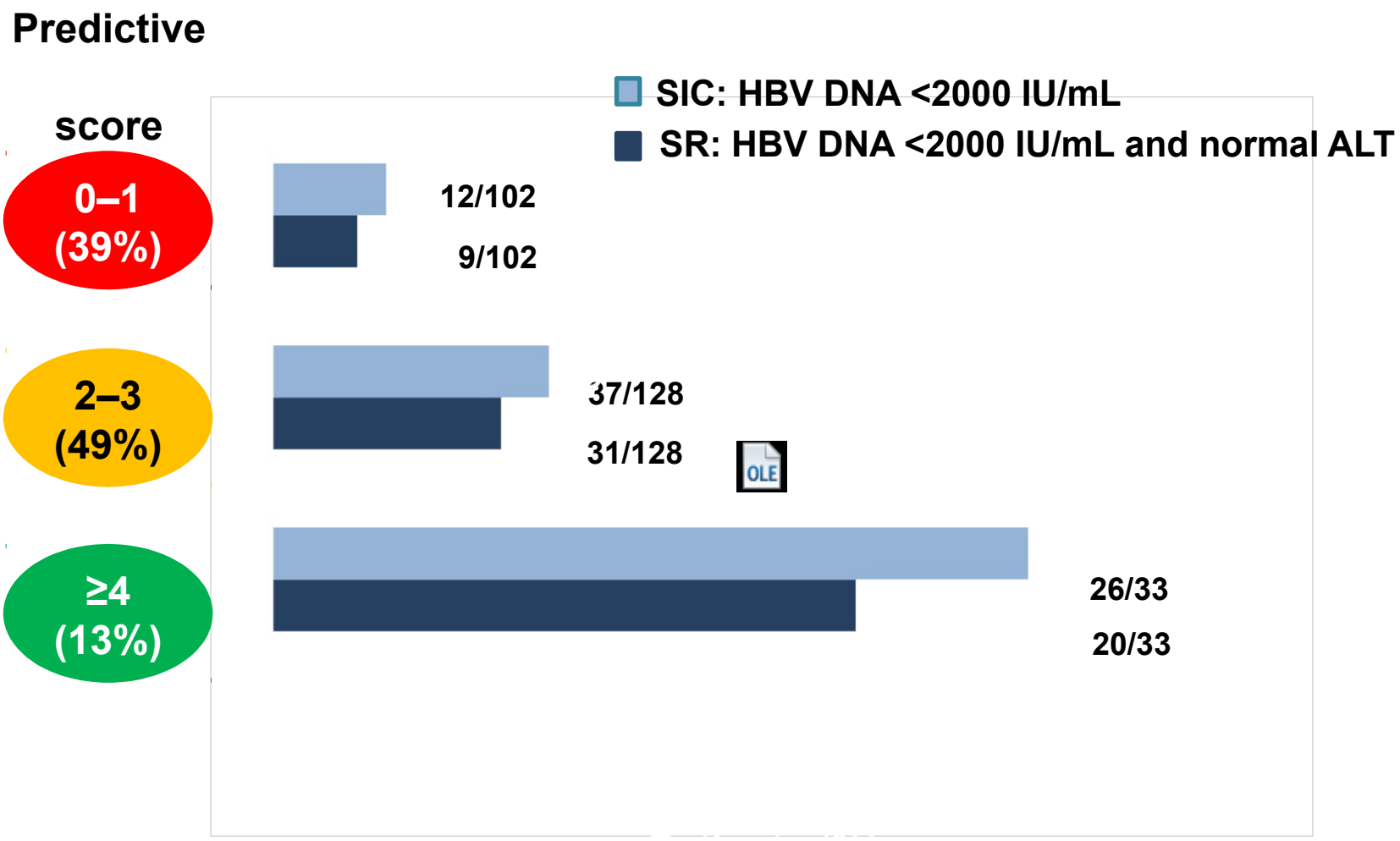
- 263 pts enrolled in Phase III (212) and Peg-B-Liver (51) trials
- 61% of Asian origin
- gen. A 5.7%, B 24.3%, C 35.4% and D 32.6%

Characteristic	Score
HBV genotype: C	1
Non-C	0
Age, years: >45	0
≥30–≤45	1
<30	2
HBsAg, IU/mL: ≥3500	0
≥1000–<3500	1
<1000	2
ALT ratio, x ULN: ≥5	1
<5	0

Chance of response	Prediction scores
Low	0–1
Moderate	2–3
High	≥4

Lampertico P et al, AASLD 2014

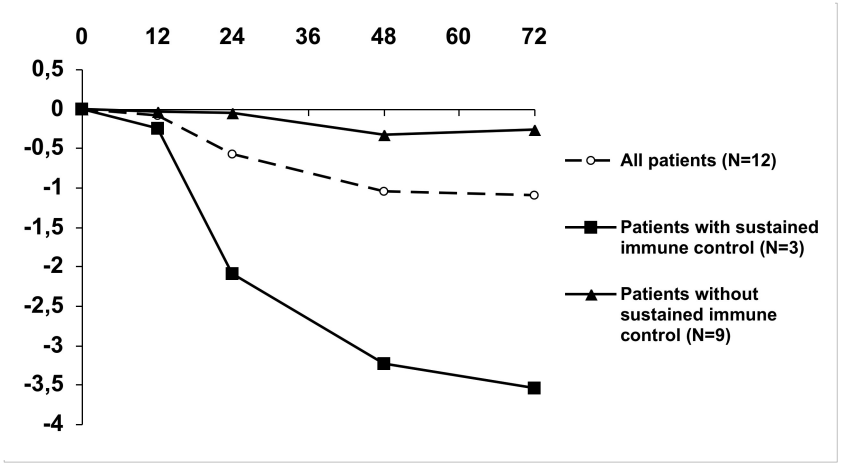
Sustained Immunological control (SIC) and Sustained Response (SR) rates by baseline score



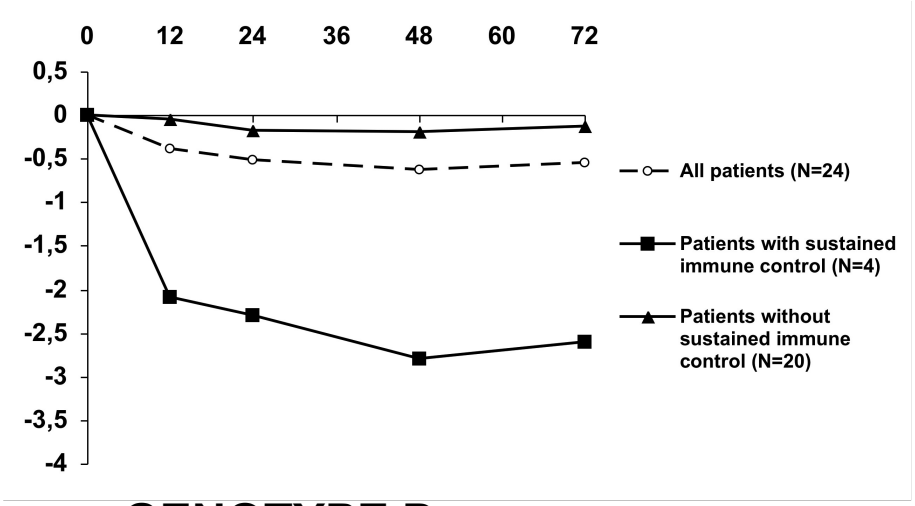
Lampertico P et al, AASLD 2014

HBeAg negative CHB: HBsAg decline on-treatment according to response 5 years post-treatment

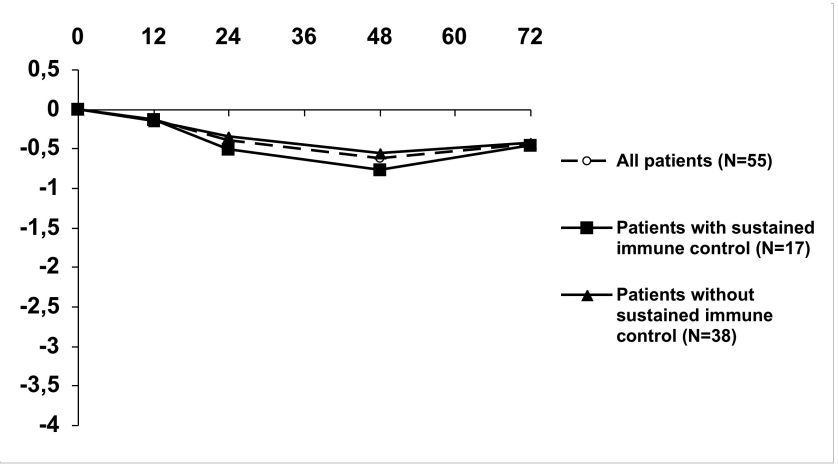
GENOTYPE A



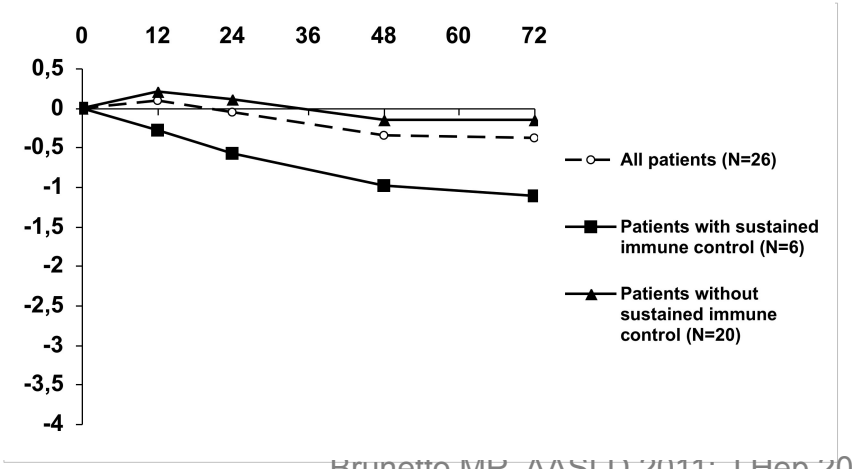
GENOTYPE B



GENOTYPE C



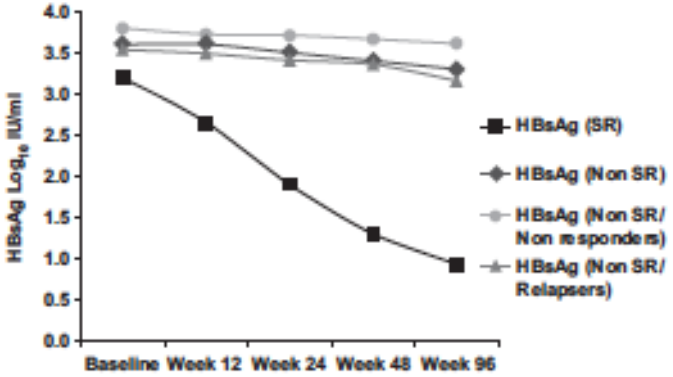
GENOTYPE D



Brunetto MR, AASLD 2011; J Hep 2013

Prediction of Sustained Response to Peg-IFN

On treatment HBsAg kinetics according to response

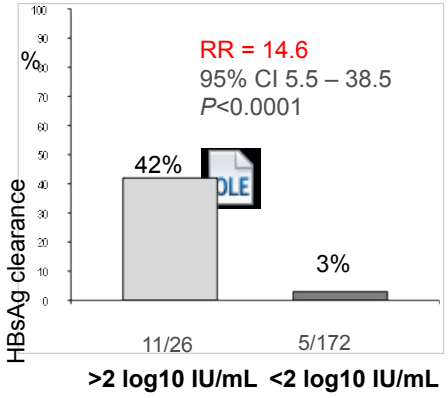


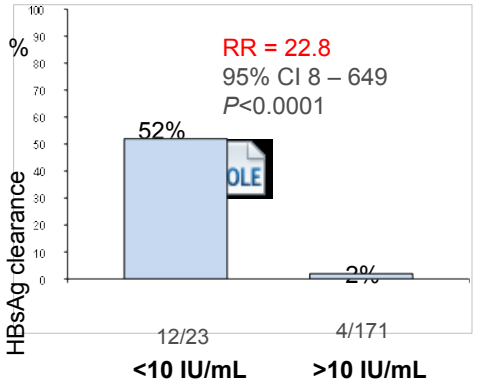
HBsAg decline ≥10% from **BL to w24** was significantly associated with SR: 81% vs 31%, OR 7.286, 95% CI 2.162-24.552, p=0.001

EOT HBsAg serum levels kinetics according to response

Genot. (n° pts)	HBsAg (IU/ml) EOT	5 years SVR
A	<400	PPV 75%
(13)	≥400	NPV 100%
B	<50	PPV 47%
(64)	≥50	NPV 100%
C	<75	PPV 70.6%
(91)	≥75	NPV 79.7
D	<1000	PPV 75.0%
(31)	≥1000	NPV 82.6%

3 years post-treatment HBsAg loss





Brunetto MR et al Hepatology 2009, Brunetto MR et al J Hepatol 2013; Goulis I et al , Liver inter, 2015

Prediction of Non Response to Peg-IFN

HBsAg serum levels kinetics during Peg-IFN vary according to HBV genotype

HBeAg positive CHB

At week 12: - absence of any decline gen. A (NPV 88%) or D (NPV 98%)

- HBsAg level >20,000 IU/ml gen. B (NPV 92%) or C (NPV 99%)

At week 24: - HBsAg >20,000 IU/ml nearly all patients failed to achieve response, irrespective of genotype (NPV 98%)

HBeAg negative CHB

At week 12: - absence of any HBsAg decline together with <2 log HBV-DNA decline in gen. D (NPV 100%) or in all genotype (validation cohort, NPV 95%)

The only patient who met the stopping rule but did achieve SVR was Caucasian with HBV genotype A

Brunetto MR, AASLD 2011; J Hep 2013; Rijckborst V et al, J Hepatol 2012; Sonneveld M J et al, AASLD 2012; Hepatology 2013

HBV therapy: role of HBsAg quantification

NUCs treatment

Viral suppression in > 90% of the pts after 3 y. treatment, but high relapse rates in case of treatment discontinuation

- to identify patients with high probability of sustained virologic response after treatment discontinuation
- to identify treatment strategies to achieve the control of HBV infection

Sustained virologic response after NUCs discontinuation

- **33 HBeAg negative CHB** pts, who discontinued **ADV** after 4-5 years, were followed up for 5.5 years: all pts had virological and 25 biochemical relapse
  - 18 of 33 (**55%**) achieved a **sustaiend biochemical and virological response** and 13 of 33 (**39%**) **cleared serum HBsAg**

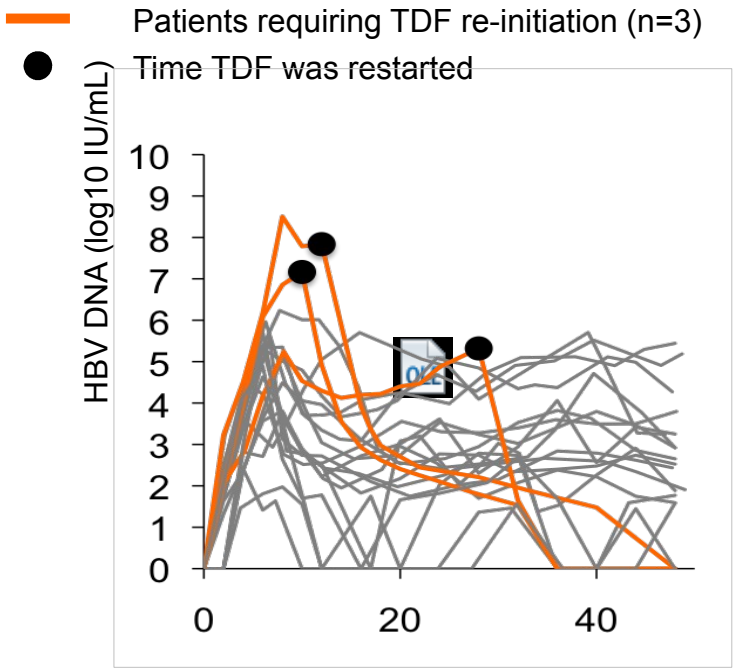
- **188 CHB pts** (105 HBeAg negative), all infected by genotypes B and C, treated with LMV for about 2 years (mean 89.3 ± 35.9 m), but who stopped LMV for at least 12 months
  - Cumulative incidence at year 6 after stopping LMV of **HBsAg loss** was **24%** and of **virologic response 34.1%**

A proportion of CHB patients treated with NUCs achieve a sustained control of HBV infection

Hadziyannis SJ et al Gastroenterology 2012; Chen C-H, J Hep 2014

HBV-DNA, ALT and HBsAg profiles after TDF discontinuation

42 HBeAg neg pts on TDF from ≥ 4 years were randomized to stop or stay on treatment: the **primary endpoint was HBsAg loss by Week 144**



- HBV DNA became detectable in 21/21 (100%) of TDF-Stop subjects
- HBV DNA up to W48:
  - Median: 5.32 log10 IU/mL
  - Min: 4.41 log10 IU/mL
  - Max: 8.50 log10 IU/mL
- **At W 48**
  - 89% (16/18) HBV DNA < 20.000 IU/mL
  - **78% (14/18) HBV DNA < 2.000 IU/mL**
- ★ **ALT** peaked at >2xULN in 12/21 TDF-Stop subjects (57%)
- ★ At W 48: 100% (18/18) ALT < 2xULN; **83% (15/18) ALT < ULN**

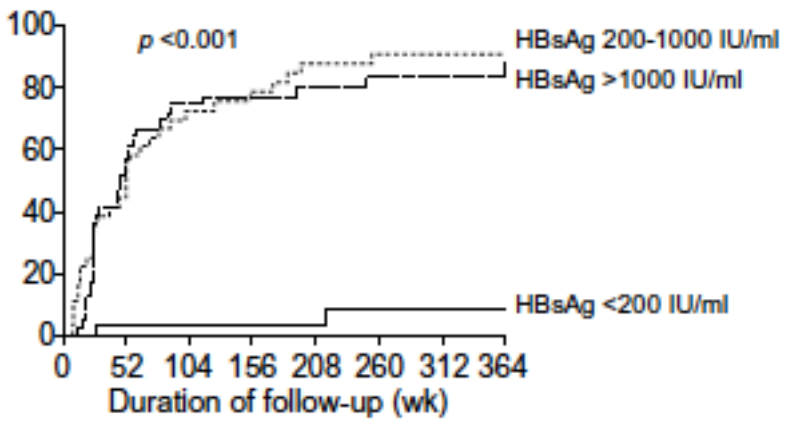
- ❖ **Stopping TDF was associated with a more profound decline in HBsAg levels** compared with continuous TDF (median 0.28 vs. 0.09 log10 reduction, respectively), 1.40 median log10 decline in TDF-Stop subjects with HBsAg <25,000 IU/mL at BL
- ❖ **HBsAg loss was observed in two subjects (9.5%) 48 weeks after TDF discontinuation**

T Berg et al., O0119 EASL 2015

The role of HBsAg quantification in predicting HBsAg loss and HBV relapse after discontinuation of LMV treatment

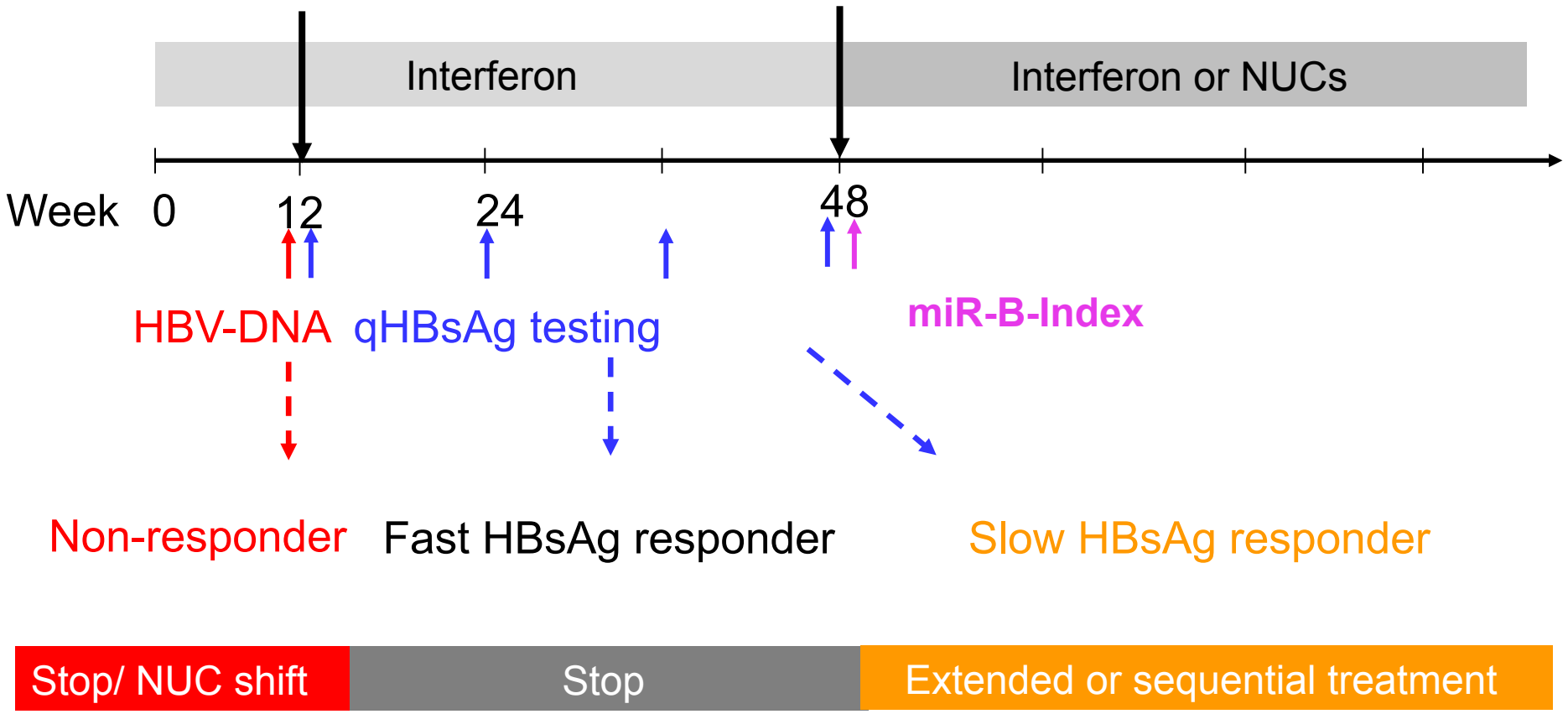
- **188 CHB pts** (105 HBeAg negative), all infected by genotypes **B** and **C**, treated with LMV for a mean 89.3 ± 35.9 m, but who stopped LMV for at least 12 months
- Cumulative incidence at year 6 after stopping LMV of **HBsAg loss was 24%** and of **HBV relapse 65.9%**
- At **EOT prediction of HBsAg** loss was
  - 55.6% for HBsAg levels of **300 IU/ml** in **HBeAg pos** pts
  - 79.2% for HBsAg levels **<120 IU/ml** in **HBeAg neg** pts
  - At **EOT** 93.3% **prediction of sustained virologic response** was achieved in HBeAg neg pts by HBsAg serum levels **< 200 IU/ml**

HBV relapse in HBeAg neg pts



Chen C-H, J Hep 2014

Towards treatment personalization in HBeAg negative CHB patients



Brunetto MR, *EASL-AASLD* 2008