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Virologic and serologic markers for the management of chronic hepatitis B patients

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sur l'INFLAMMATION

HBV serologic and virologic testing are critical to disease prevention and treatment decision:

- providing data contributing to a better understanding of natural history
- helping to determine appropriate treatment monitoring strategy and efficacy.

HBV Markers

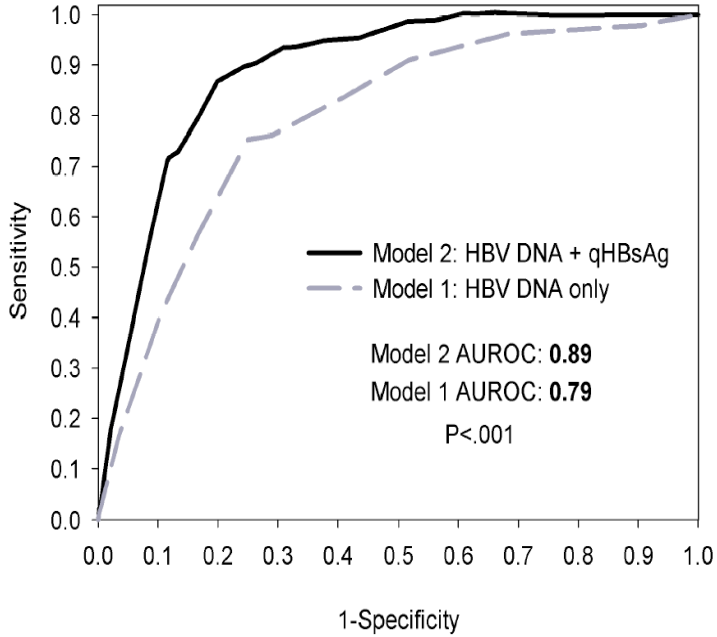
- ✓ Hepatitis B surface antigen (HBsAg)
  qualitative: diagnosis
  quantitative: outcome, treatment monitoring
- ✓ Hepatitis B e antigen (HBeAg)
  differentiate wild type (+) from mutant (-)
  - HBV mutants: fibrosis, HCC
  - HBV DNA: measure level of viral replication outcome, treatment monitoring
    - Viral genotype: 8 genotypes A to H outcome, treatment decision.

Natural History

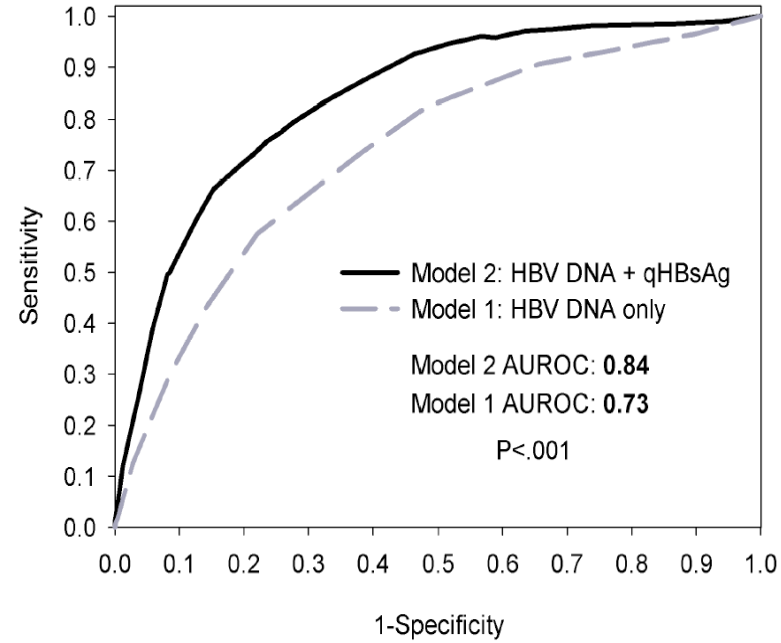
Prediction of HBsAg loss

Combination of HBsAg and HBV DNA

2491 HBeAg negative genotype B or C



5 years



10 years

HBV DNA < 2000 IU/ml and HBsAg < 100 IU/ml

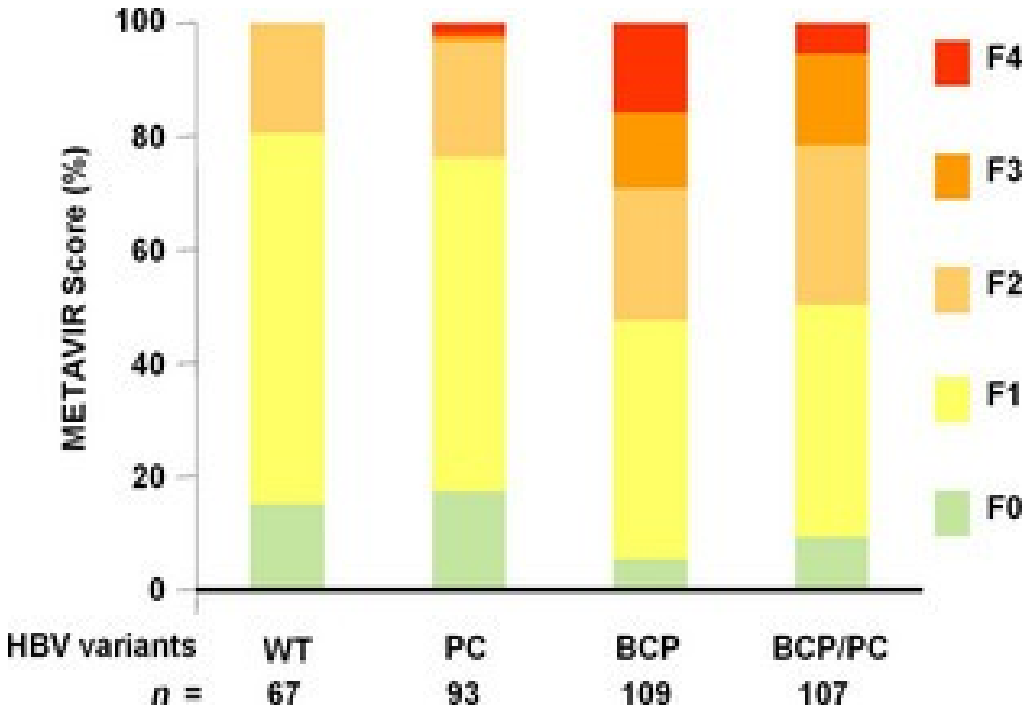
Tseng et al. Hepatology 2012
Seto et al.; Hepatology 2012

Liu J. et al. J Hepatol.2013

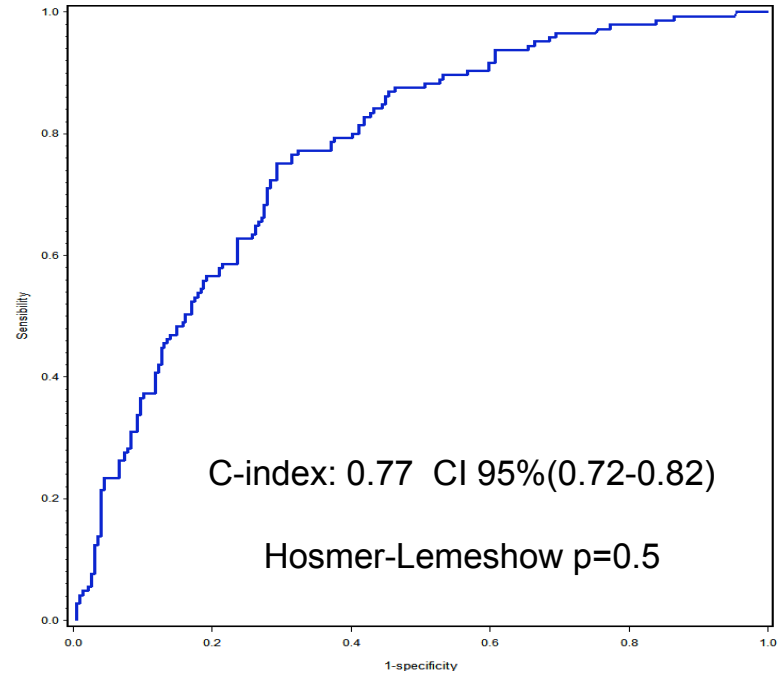
HBV variants

374 HBeAg positive/negative patients genotype A to E

Distribution of fibrosis stages according to HBV variants



Diagnosis of significant fibrosis (Age + HBV DNA* + ALT + HBV mutant**)

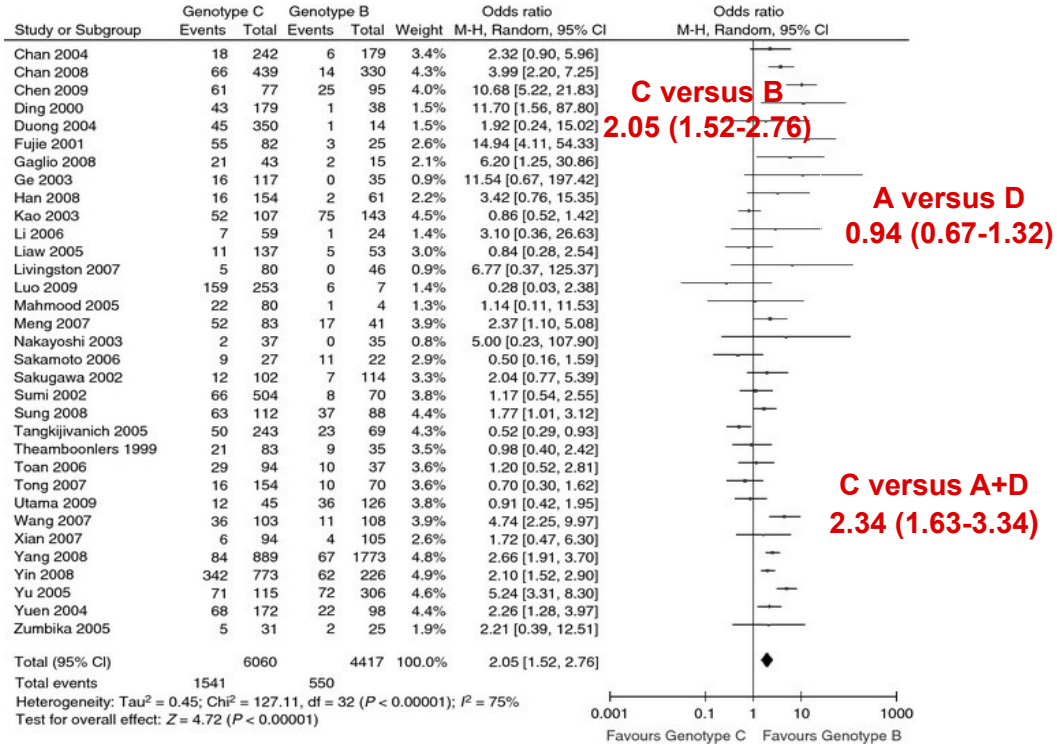


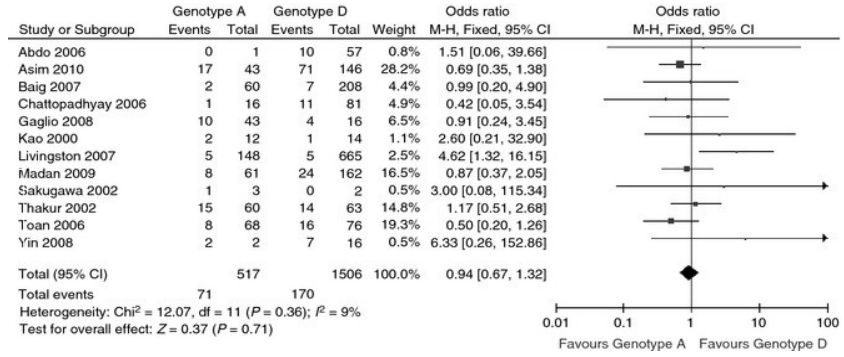
* >4.301 log IU/ml ** A1762T/G1764A

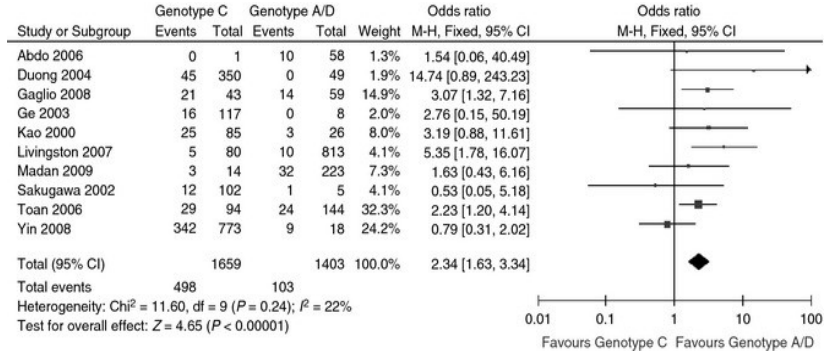
Lapalus et al. Liver Intern 2015

Prediction of HCC

Meta-analysis on the risk of HCC among the 4 major genotypes







Genotype C is associated with a higher risk of hepatocellular carcinoma than genotypes A, B or D (p>0.001)

Wong GLH et al. Aliment Pharmacol Ther. 2013

Prediction of HCC

Baseline Viral Load, HBsAg levels and HBV mutants are Major Factors Determining the Fate of the Liver

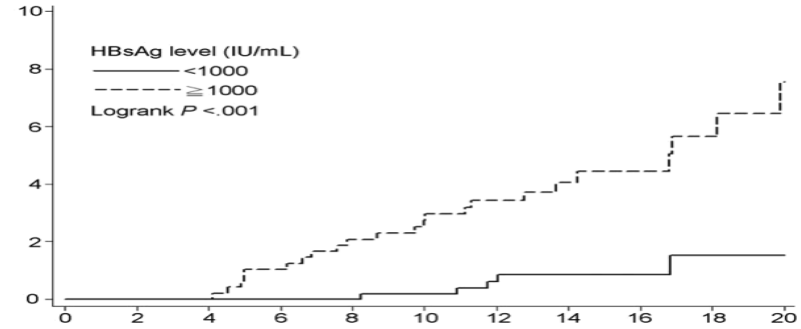
820 HBe positive/negative patients120 months of follow-up
5 and 10 years prevalence HCC 4.4% and 6.3%

Risk score of baseline HCC predictors
Gender, HBV DNA, HBV mutant, cirrhosis.

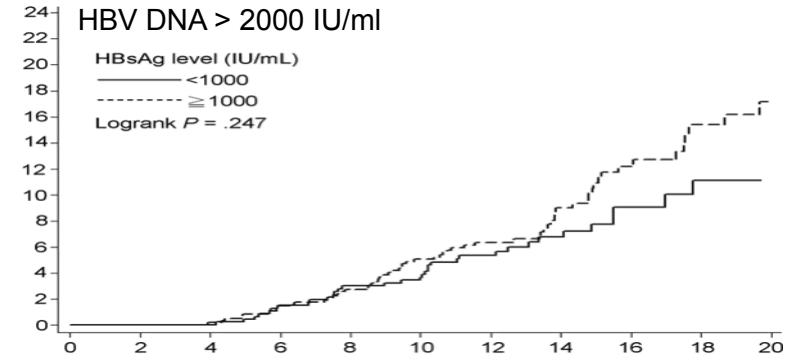
Male	2.98 (1.15-7.78)	0.025
Higher HBV- DNA (>4 log)	**1.28 (1.04-1.58)**	**0.02**
Core Promoter Mutant (A1762T/G1764A)	**3.66 (1.42-9.47)**	**0.007**
Cirrhosis	7.31 (3.76-14.27)	0.001

Cumulative incidence of HCC

HBV DNA ≤ 2000 IU/ml



HBV DNA > 2000 IU/ml



Yuen et al J Hepatol 2009
Yang HI et al. Lancet Oncol 2011

Tseng et al. Hepatology 2013.
Tseng et al. Gastroenterology 2012

Assessment of Inactive carriage

HBeAg negative patients with quarterly normal ALT for one year

Combination HBsAg <1000 IU/ml + DNA< 2000 IU/ml

Identification of true inactive carriers

Sensitivity	91%
Specificity	95.4%
PPV	87.9%
NPV	96.7%

As effective as one year serum ALT follow-up

Brunetto et al. Gastroenterology 2010;139:483

Martinot-Peignoux et al. J Clin Virol 2013

Therapy monitoring

The ultimate goal of therapy is to stop the progression of liver disease preventing the onset of complications

Surrogate end points are:

Biochemical ALT normalization
Virological suppression of HBV DNA
Serological loss of HBeAg with or without seroconversion
loss of HBsAg with or without seroconversion

Two categories of drugs are available:

- finite treatment duration
  pegylated interferon (PegIFN)
- life long treatment duration
  specific nucleoside or tide (NAs) HBV inhibitors
  (mainly entecavir and tenofovir)

✓ PegIFN therapy

One third of the HBeAg positive/negative patients respond with high probability of HBsAg seroconversion.

- NAs therapy

Profound HBV DNA suppression with no or slow HBsAg decline, rarity of HBsAg seroclearance

Identifying patients with high probability of response, before or early on therapy, to personalize treatment, is a pressing issue.

Marcellin et al. N Engl J Med 2008 Moucari et al. J Hepatol 2009 Chevaliez et al. J Hepatol 2013

Treatment predictors

Important tools for the management of therapy

Demographic: ethnicity, age, gender, duration ….

Biochemical: ALT, AST, γGT,…..

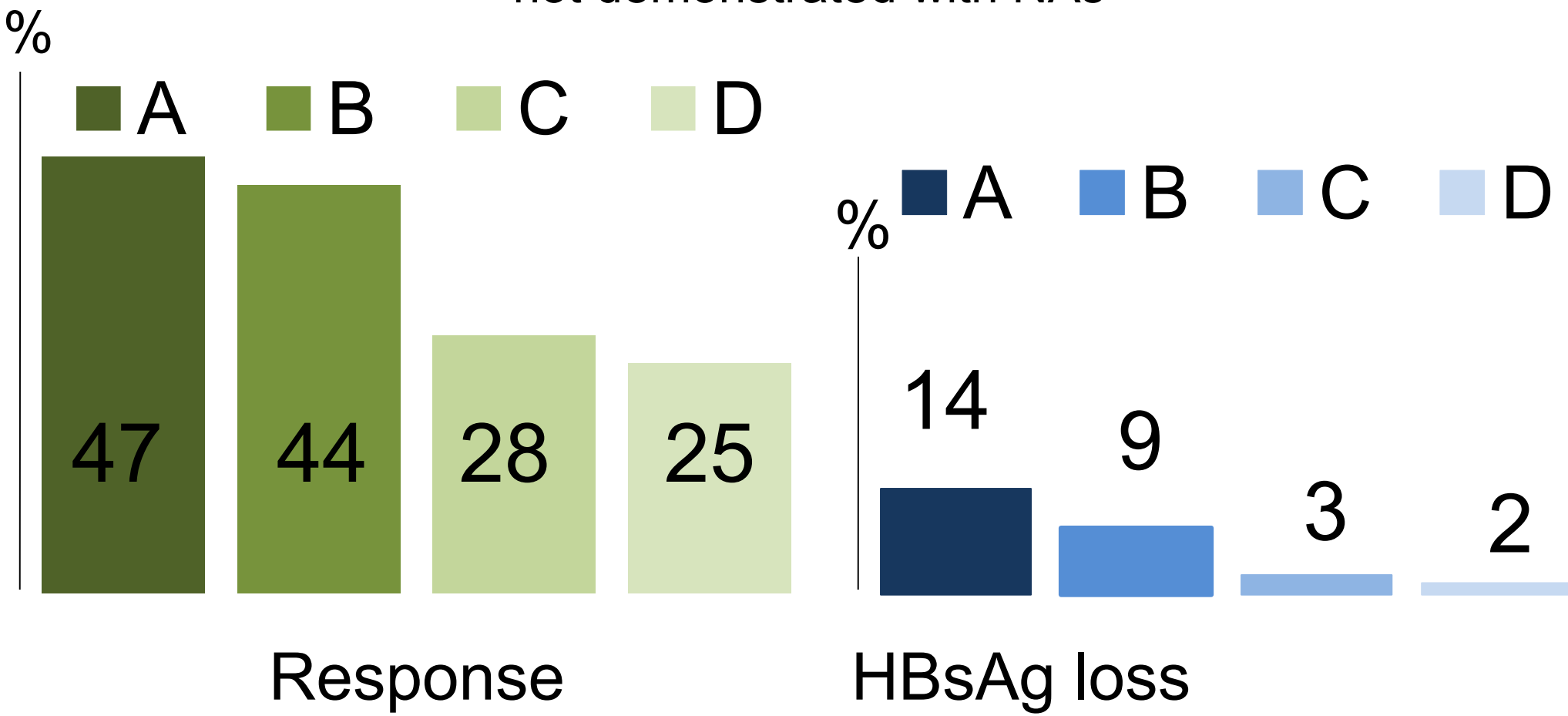
Histological: Necroinflammation grade, fibrosis stage

Serologic: HBeAg status, HBsAg level

Virologic: HBV DNA, HBV genotype, IL 28B…..

HBV genotypes

Prediction of response and HBs loss with PegIFN, not demonstrated with NAs



Janssen et al. Lancet 2005

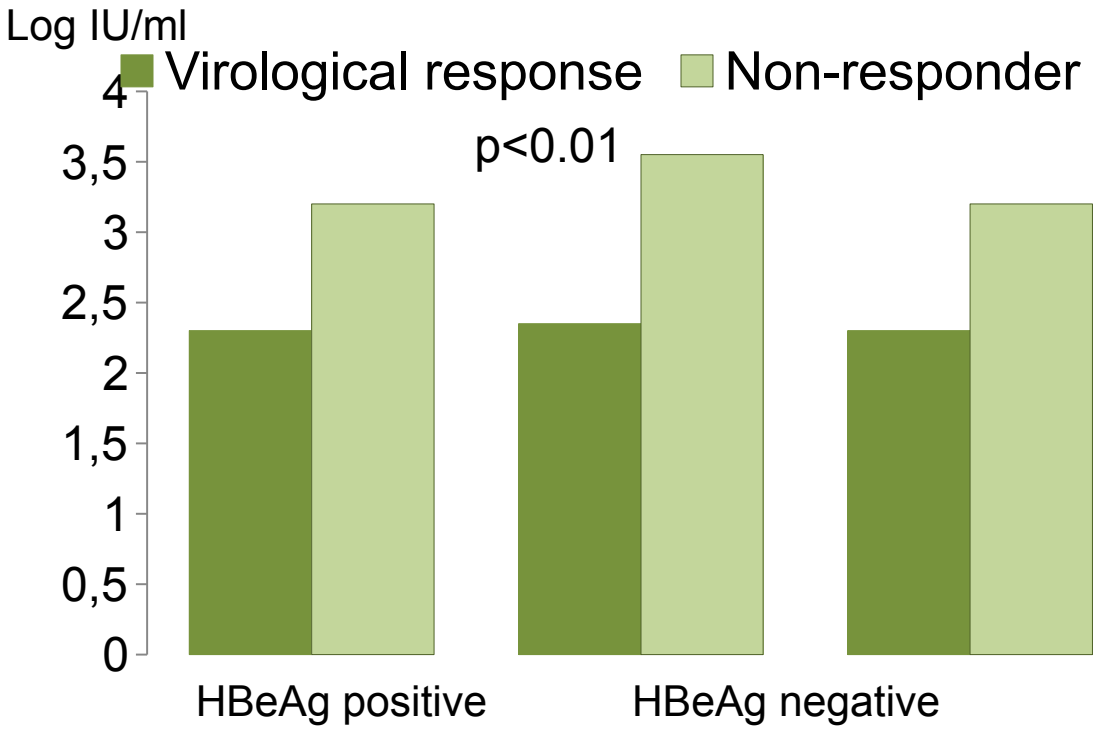
Flink et al Am J Gastroenterol. 2006

Raimondi et al. J Hepatol 2010

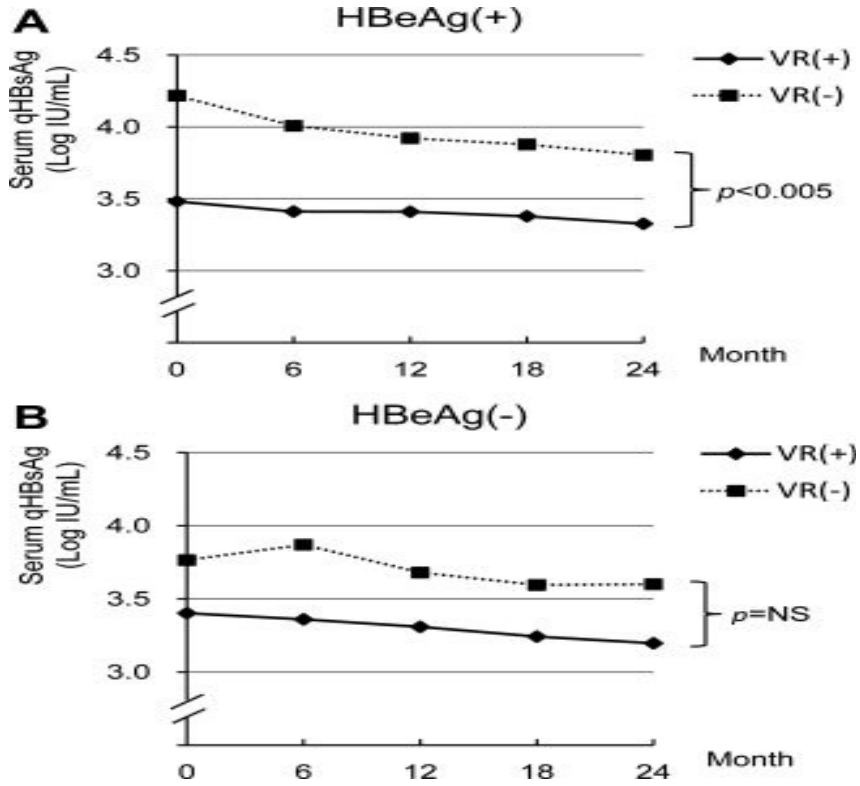
Baseline HBsAg titer

Prediction of sustained virologic response

Pegylated interferon



Entecavir



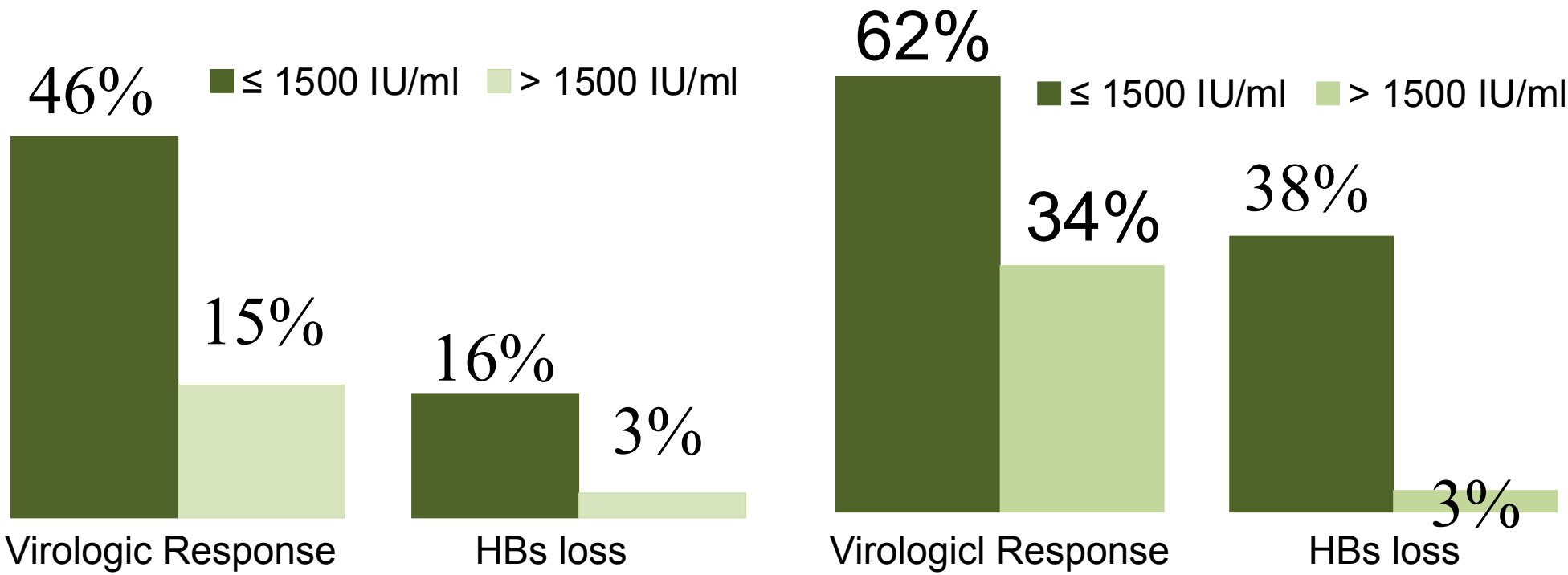
Tangkijvanich et al. J Clin Virol 2009
Marcellin et al. AASLD 2013

Lee ML. et al. Hepatology 2011

During therapy (Week 12)

Real life S-Collate study

Low on-treatment HBsAg levels associated with higher SVR and HBsAg loss rates

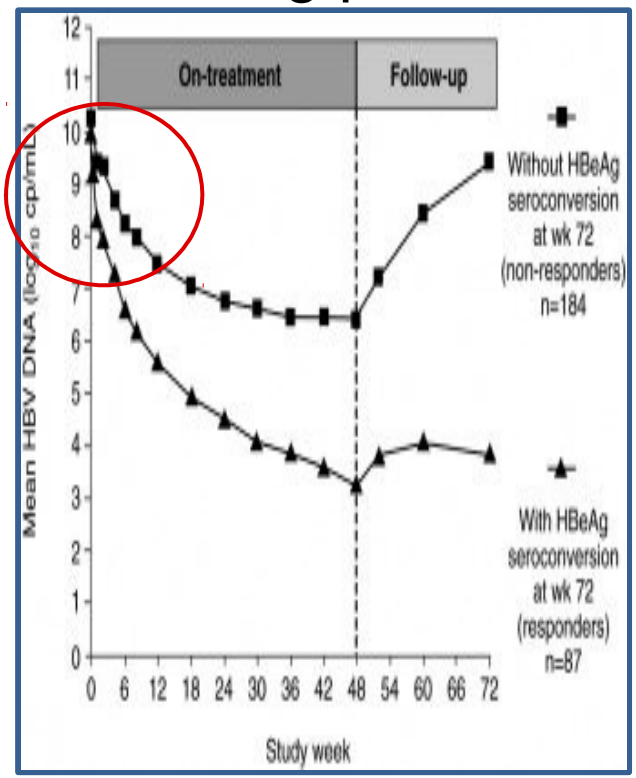


Marcellin et al. APASL 2013

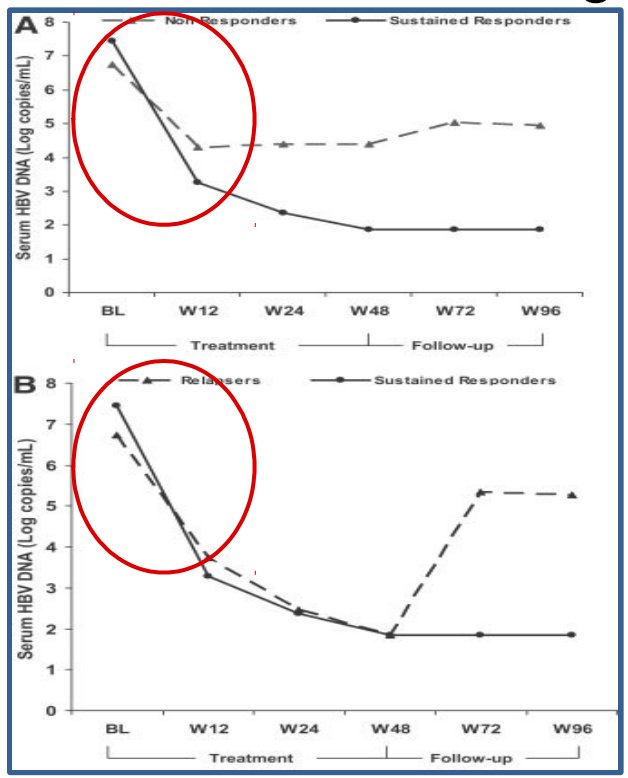
On treatment kinetics PegIFN

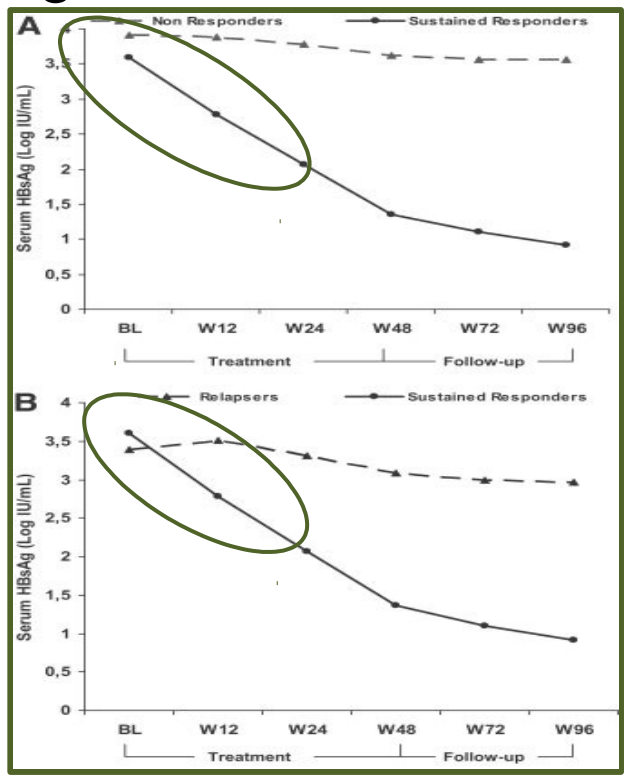
HBV DNA and HBsAg

HBeAg positive



HBeAg negative





HBV DNA

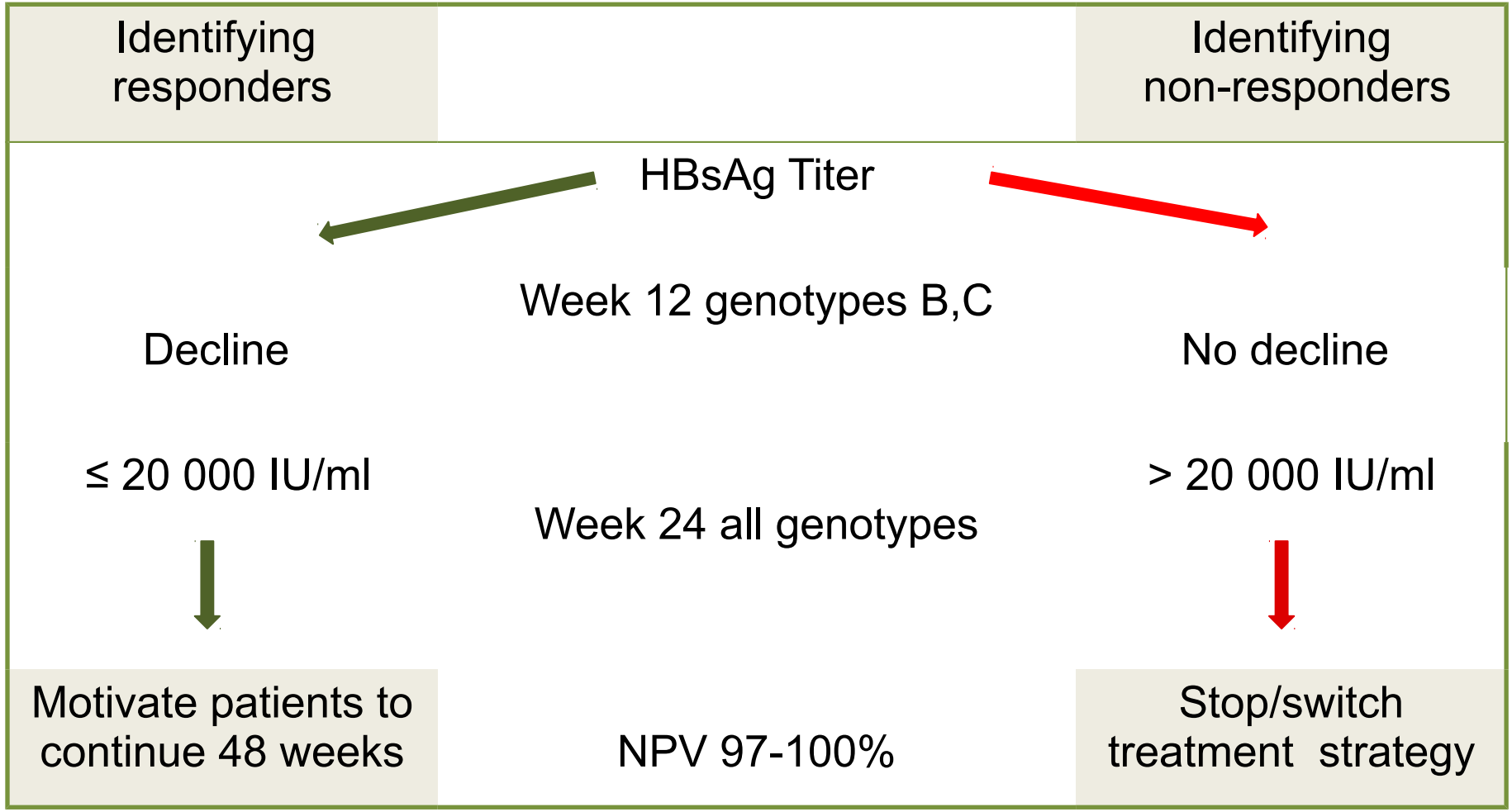
HBsAg

Fried et al. Hepatology 2008

Moucari et al. Hepatology 2008

Response guide monitoring: PegIFN

HBeAg positive patients

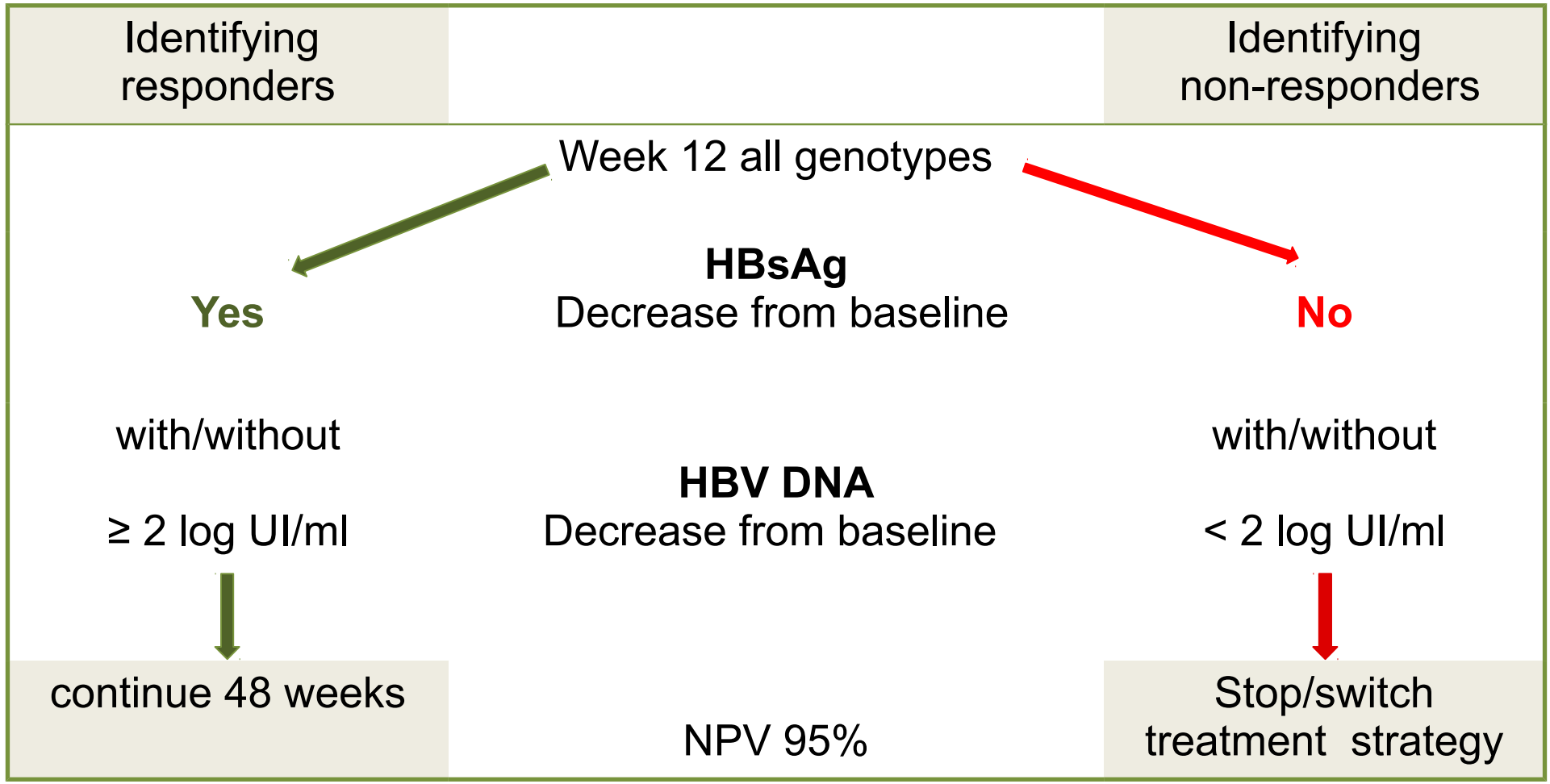


Sonneveld et al Hepatology 2010

Sonneveld et al Hepatology 2013

Response guide monitoring: PegIFN

HBeAg negative patients



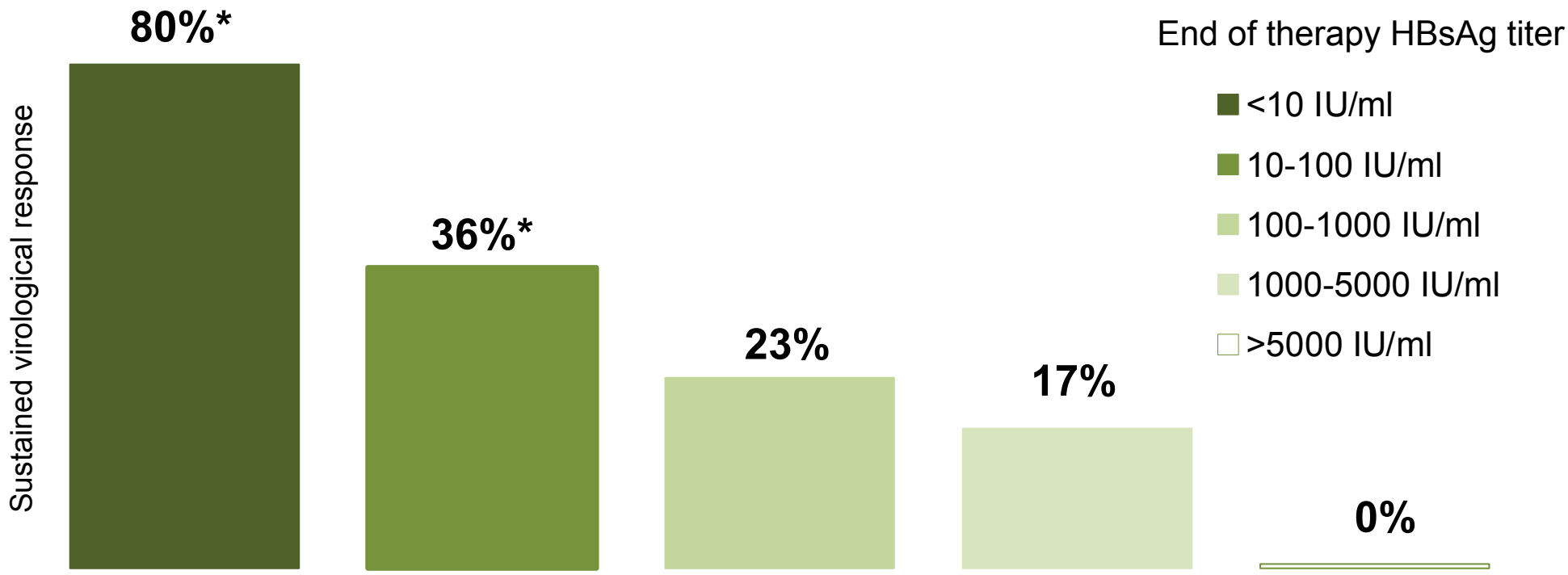
Rijckborst et al. Hepatology 2010

Rijckborst et al. J Hepatol 2012

Post-treatment outcome: PegIFN

HBeAg negative genotype D patients

End of treatment HBsAg level predictive of SVR and HBs loss



*** At year 3 post-treatment HBsAg: <10 IU/ml 52% HBs loss; > 10 IU/ml ≤2% AgHBs loss**

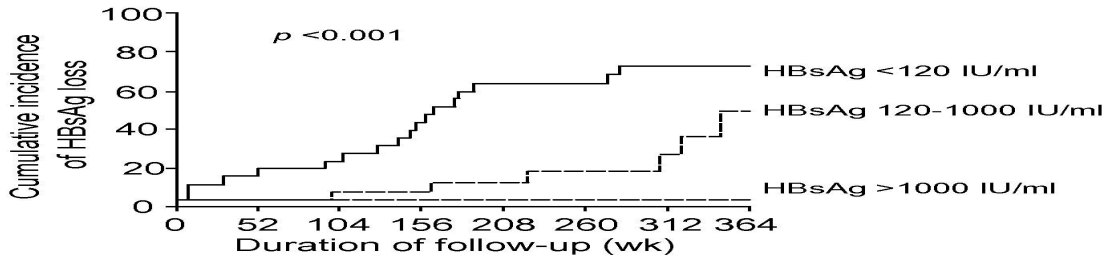
Brunetto et al. Hepatology 2009

Post-treatment outcome: NAs

HBsAg levels at treatment cessation predict HBV relapse and HBs loss

HBs loss

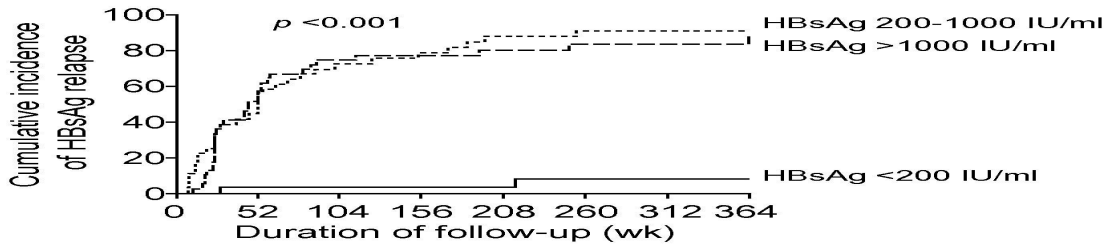
A



No. at risk HBsAg								
<120 IU/ml	24	20	19	14	9	8	4	4
120-1000 IU/ml	42	31	24	20	16	10	8	4
>1000 IU/ml	39	35	26	21	17	14	8	2

Relapse

B

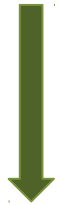


No. at risk HBsAg								
<200 IU/ml	30	29	28	25	20	16	10	9
200-1000 IU/ml	36	19	9	7	4	3	3	1
>1000 IU/ml	39	19	10	8	7	5	2	1

Chen CH J Hepatol 2014;61:515

Post-treatment: NAs

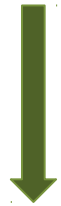
Strategy for treatment cessation and follow-up



Consider cessation

NAs >2 years with 12 to 18 months consolidation

Especially if HBsAg< 200 IU/ml



Off therapy follow-up

HBV DNA every 3 months for 1-2 years

ALT monthly (4 months) every 3-6 months for 1-2 years

Chang ML. et al Aliment Pharmacol Ther 2015

Take home messages (1)

Natural History

- ✓ Combination HBV DNA (< 2000 IU/ml) and HBsAg (<100 IU/ml)prediction of HBs loss at 5 years.
- ✓ High viral load (> 2000 IU/ml) and BCP mutant associated with higher risk of HCC development independently from HBsAg titer.
- ✓ Genotype C associated with higher risk of HCC development.
- ✓ Combination of HBV DNA <2000 IU/mL and HBsAg <1000 IU/mL robust predictor of inactive carrier status.

Take home messages (2)

Patients treated with PegIFN

- ✓ Genotypes A and B respond better than C and D
- ✓ Treatment should be discontinued at week 12:

HBeAg positive: HBsAg > 20 000 IU/ml genotypes B and C

HBeAg negative: no HBsAg decline or < 2 log HBV DNA decrease.

- ✓ Treatment should be discontinued at week 24

HBeAg positive HBsAg > 20 000 IU/ml all genotypes

Patients treated with NAs

- ✓ With an appropriate stopping rule (undetectable HBV DNA and HBsAg <200 IU/ml) and proper off-therapy monitoring, cessation of therapy is a feasible alternative to indefinite treatment strategy.

Perspectives

- ✓ Decisional algorithms based on:

Baseline

HBV genotype, HBsAg and HBV DNA cut-off

On treatment

HBsAg and HBV DNA cut-off or kinetics

leading to personalized medicine are needed.

- ✓ Well identified cut-offs remain to be determine with clinical trials