# HBsAg quantification
# *"Useful for the indication and follow-up of therapy"*

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# Agenda

- ✓ Introduction
- ✓ HBsAg quantification
  - Why ?
  - When ?
  - Take home message
  - The future

# Treatment strategies

Treatment goals as defined by EASL guidelines 2012

- Sustained HBV DNA suppression, histologic improvement and HBsAg loss.

Two treatment strategies recommended:

✓ **Pegylated interferon** (PEG-IFN): immune control and HBsAg clearance with 48 weeks therapy.

✓**Nucleos(t)ide analogues** (NAs): viral suppression with unlimited treatment duration.

Journal of Hepatology 2012

# The present: PEG-IFN therapy

HBsAg titer in combination with HBV DNA enables on-treatment adjustments.

Absence of decline combined with HBV DNA decline < 2 log IU/ml at week 12 is highly predictive of no response.

NPV 80-100%

Lau GK et al. Liver Int 2009 Brunetto MR et al. Hepatology 2009 Moucari R et al. Hepatology 2009 Sonneveld MJ et al. Hepatology 2010 Chan HL et al. Aliment Pharmacol Ther 2010 Liaw YF. Hepatology 2011 Piratvisuth T et al. Hepatol Int 2011

# The present: NAs therapy

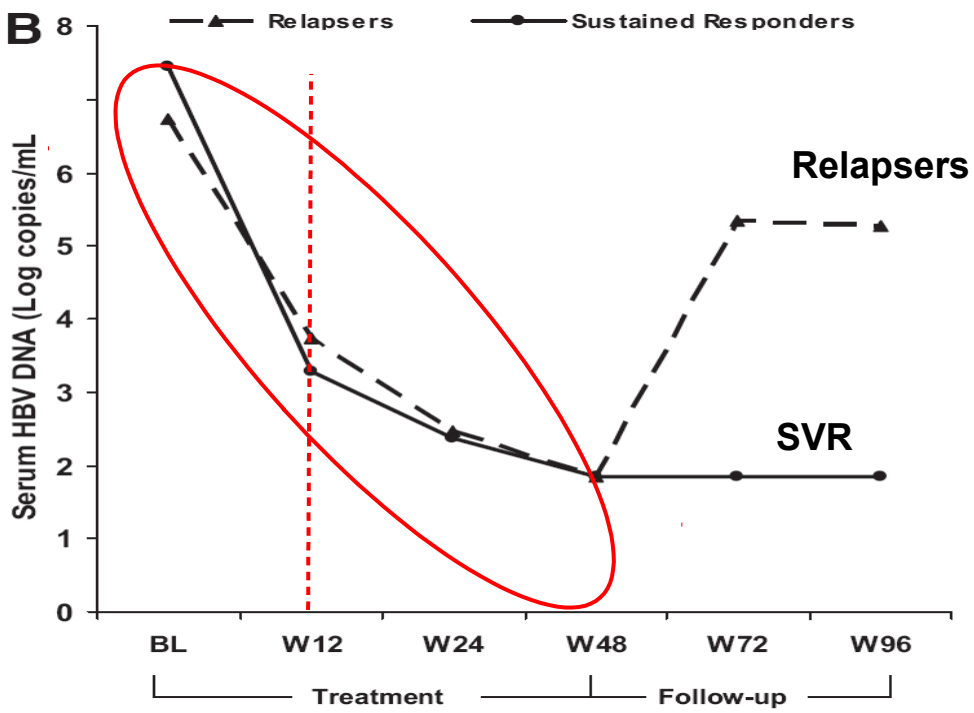
- Decline is lower than with PEG-IFN, more pronounced in HBe positive than in HBe negative patients.
- Low baseline titer and decline during the 24 first weeks of therapy predictive of HBe and HBs loss .


Wursthorn K et al. Hepatology 2010
Shouval D et al. J Hepatol 2013
Boglione L. et al. Liver International 2013
Reijinders JGP et l. J Hepatol 2011
Tseng TC et al. J Gastroenterol 2013
Papatheodoridis G. et al . J Hepatol 2013
Chevaliez S et al. J Hepatol 2013

# Why quantify HBsAg?

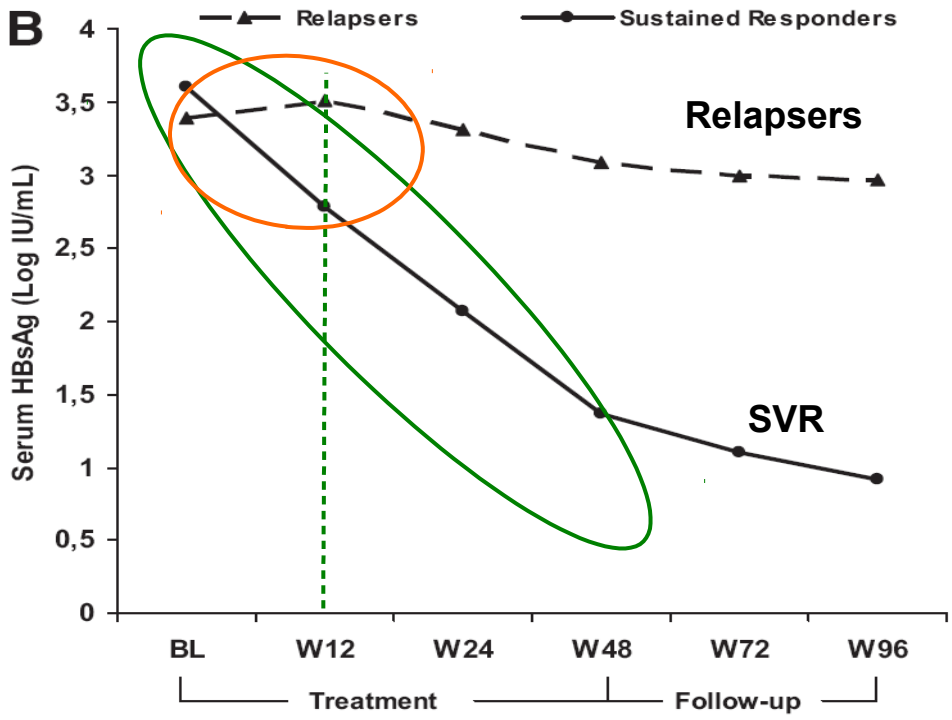
## Pegylated Interferon Therapy

### HBV DNA kinetics




Moucari M et al. Hepatology 2009

### HBsAg kinetics

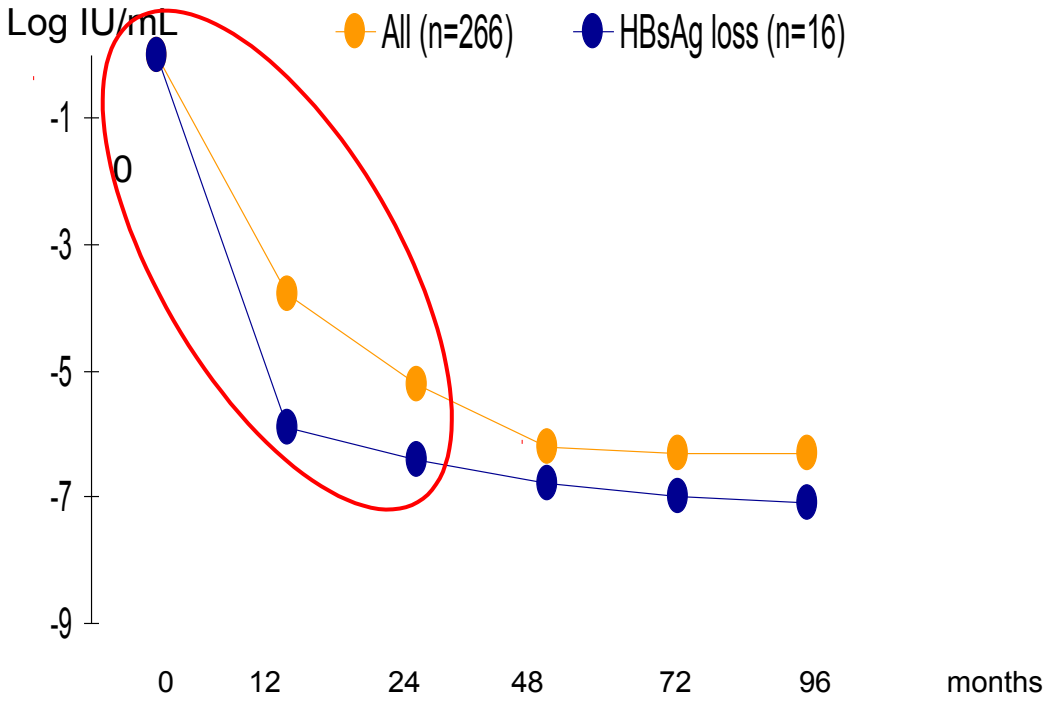



Brunetto MR et al. Hepatology 2009

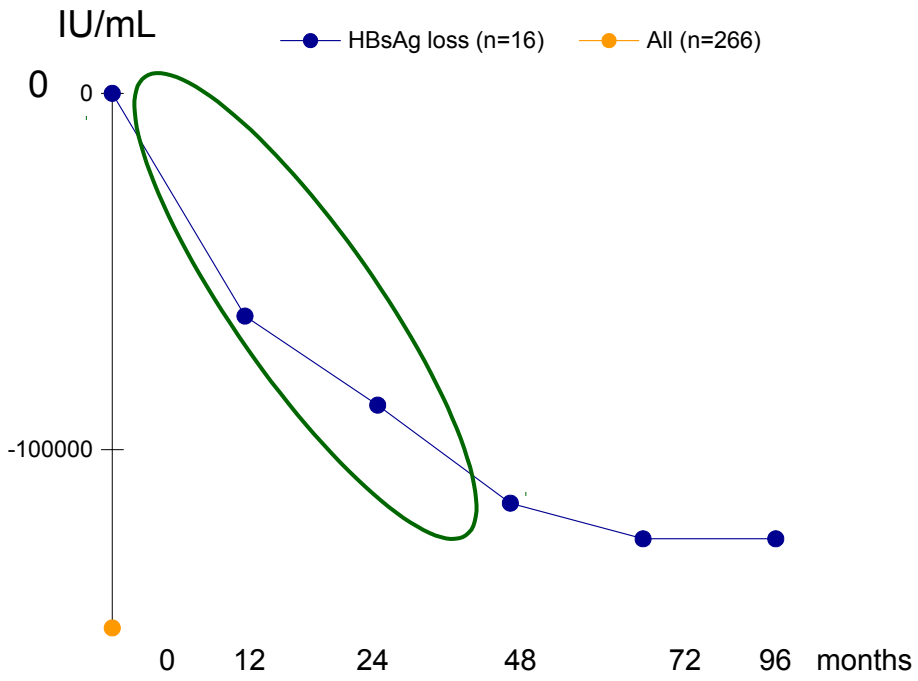
# Why quantify HBsAg?

## Nucleos(t)ides therapy

**HBV DNA Kinetics during therapy**



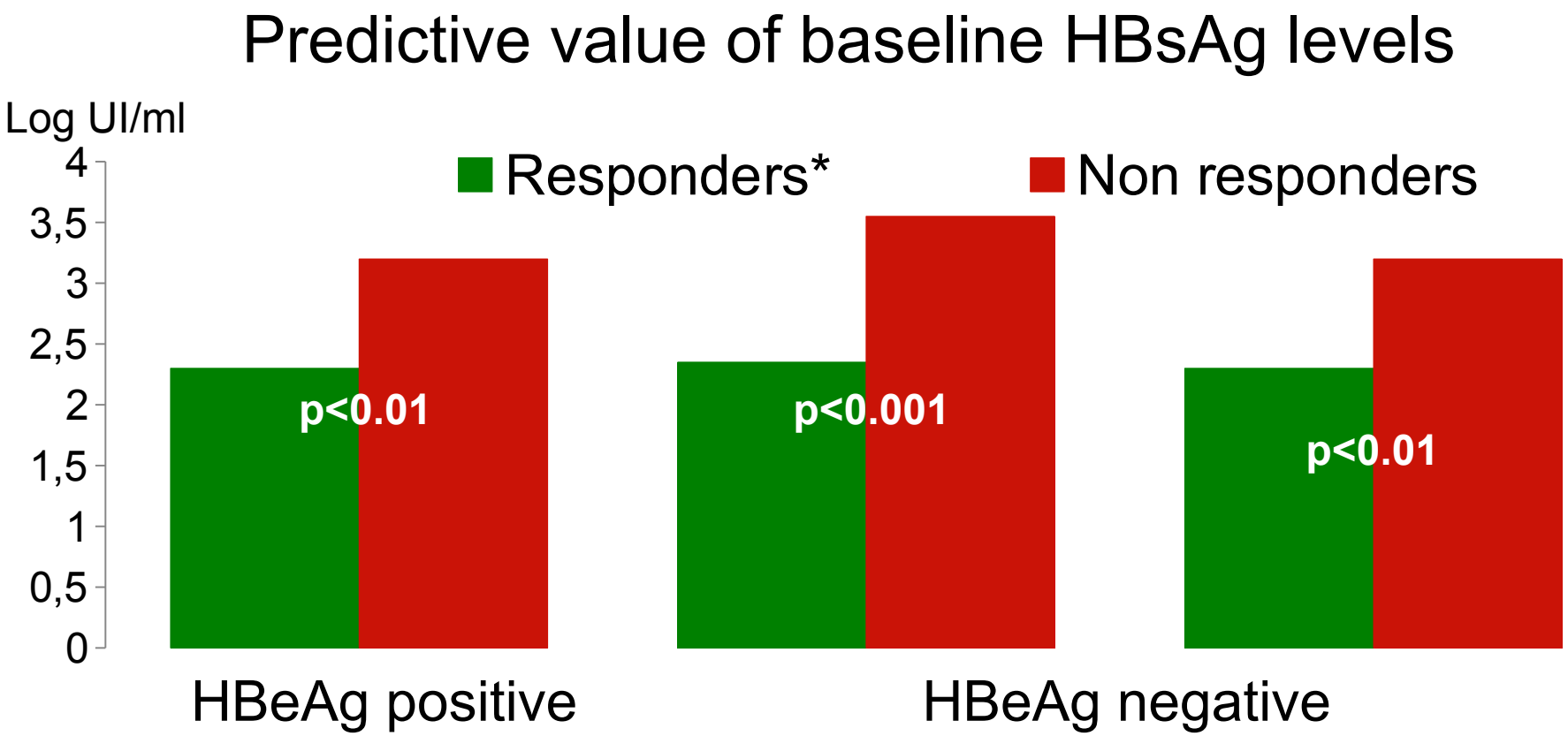

**HBsAg Kinetics during therapy**




Piratvisuth T t al. APASL 2010
Marcellin P et al.N Engl J Med 2008

Gane et al. EASL 2011
Heathcote J et al. Gastroenterology 2011

# When: Baseline (PEG-IFN)




*ADN VHB <2000 IU/ml +HBeAg loss
6 months post-treatment

*ADN VHB <2000 IU/ml
6 months post-treatment

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

Piratvisuth T et al. Hepatol Int 2011
Takkenberg et al. Antiviral Therapy in Press.

# Prédiction: Initiation du traitement

48 weeks PEG-IFN +TDF
Prediction of baseline HBsAg titer

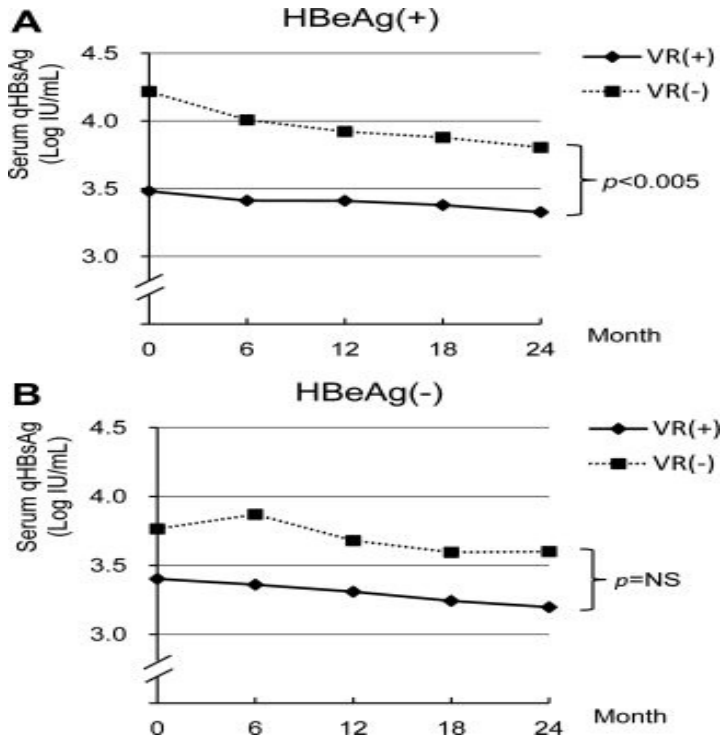
| **HBsAg (UI/ml)** | **≤ 1500** | **> 1500** | **≤ 2000** | **> 2000** |
|---|---|---|---|---|
| SVR | 45% | 21% | **44%** | 20% |
| HBsAg loss | 27% | 12% | **36%** | 5% |

Marcellin et al. AASLD 2013

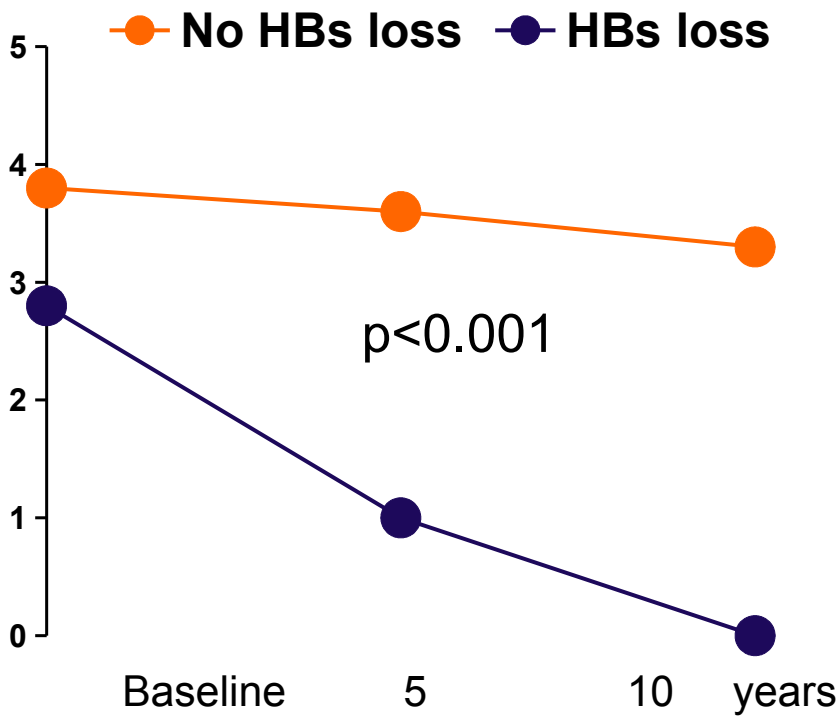
# When: Baseline (NAs)

## Baseline HBsAg level

### Virologic response




### HBsAg loss

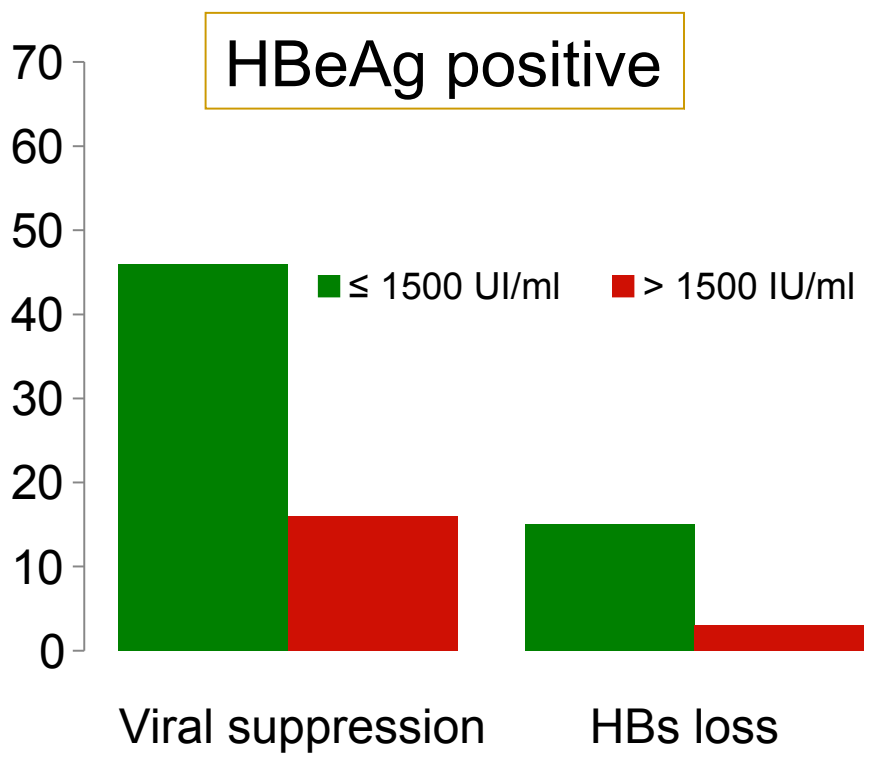


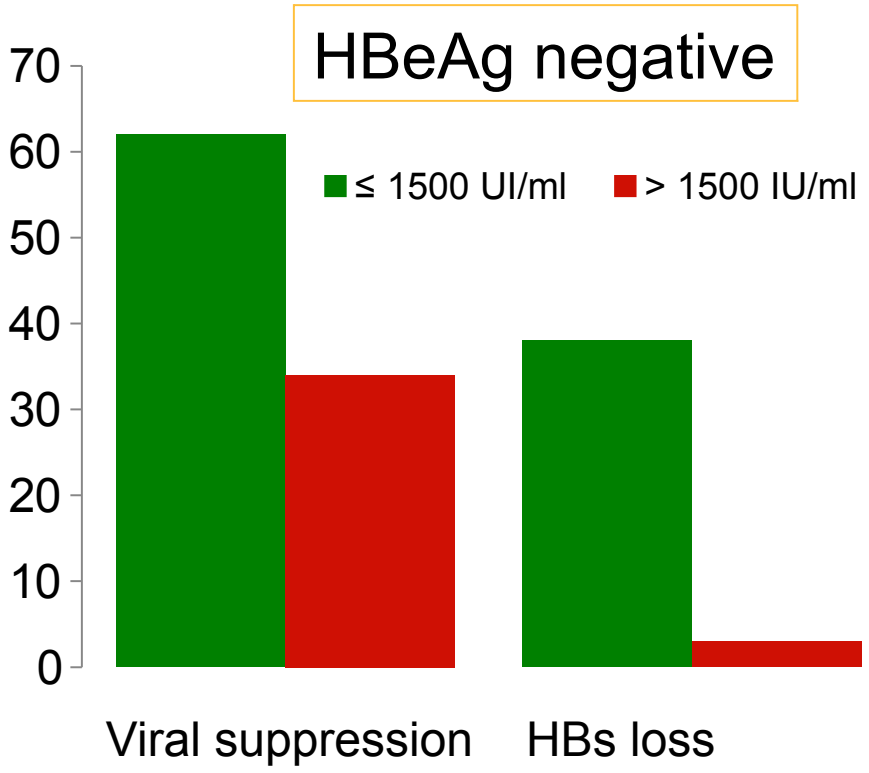

Lee ML. et al. Hepatology 2011

Seto WK. et al. J Hepatol 2013 and Hepatology 2013

# When: during therapy (PEG-IFN)

## Real-world S-Collate study
## Predictive value of HBsAg levels at week 12




Marcellin et al. APASL 2013

# When: during therapy (PEG-IFN)

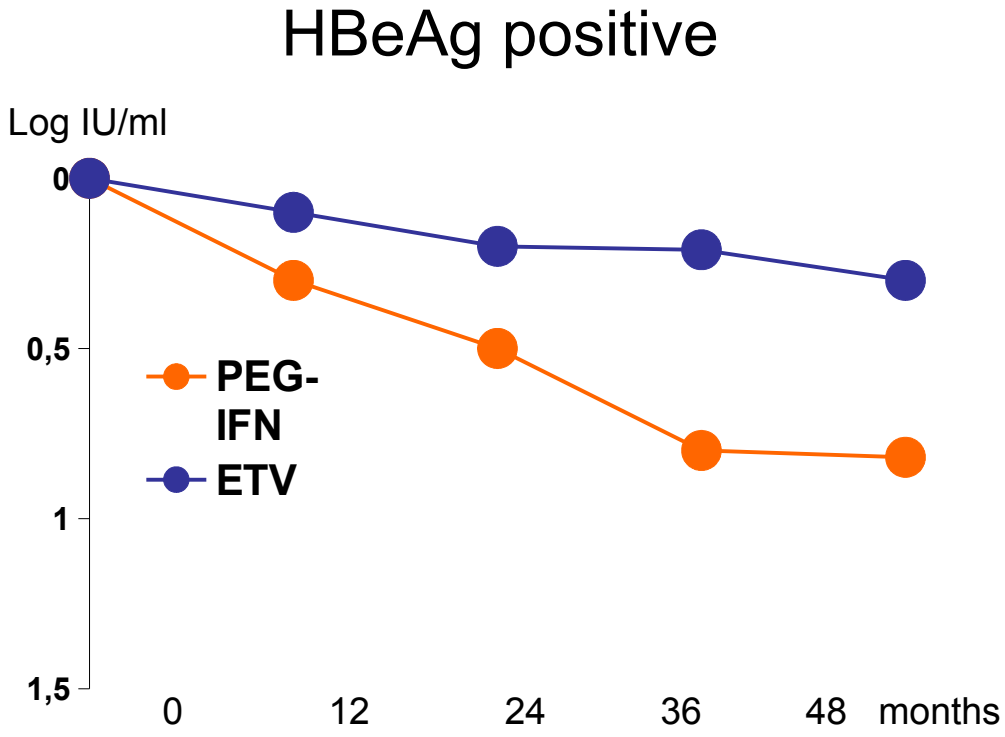
## Week twelve stopping rule

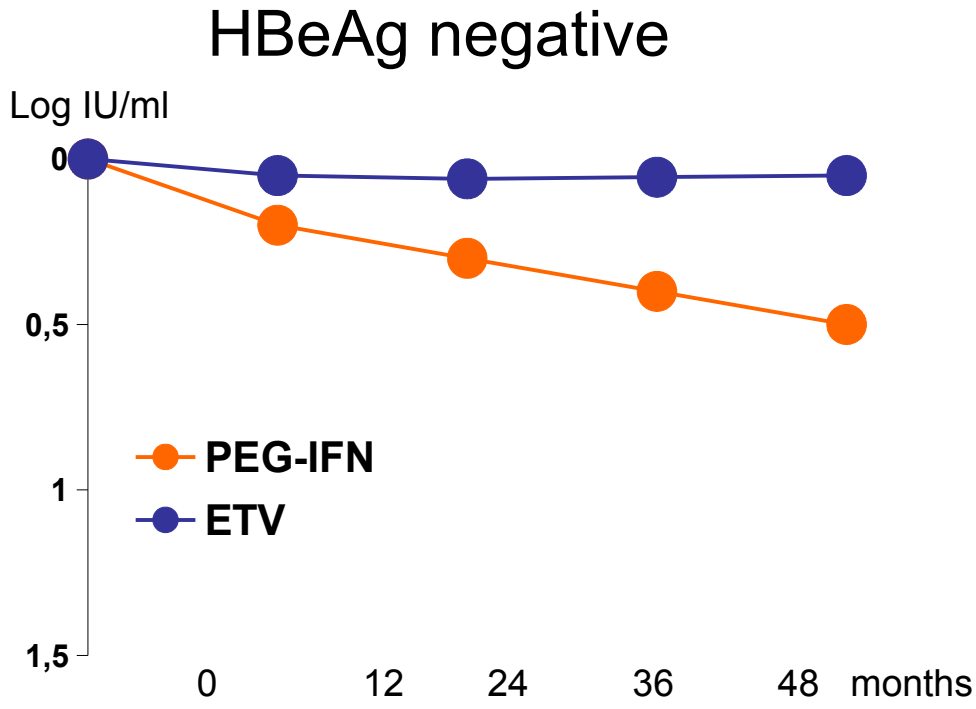
| | | SVR |
|---|---|---|
| HBsAg decline **NO** | HBV DNA decline < 2 log | **0%** |
| | HBV DNA decline ≥ 2 log | 24% |
| HBsAg decline **YES** | HBV DNA decline < 2 log | 25% |
| | HBV DNA decline ≥ 2 log | **39%** |

Rijckborst V et al. Hepatology 2010

# When: during therapy

## HBsAg kinetics in HBeAg + /- patients
## 48 weeks PEG-IFN or Entecavir

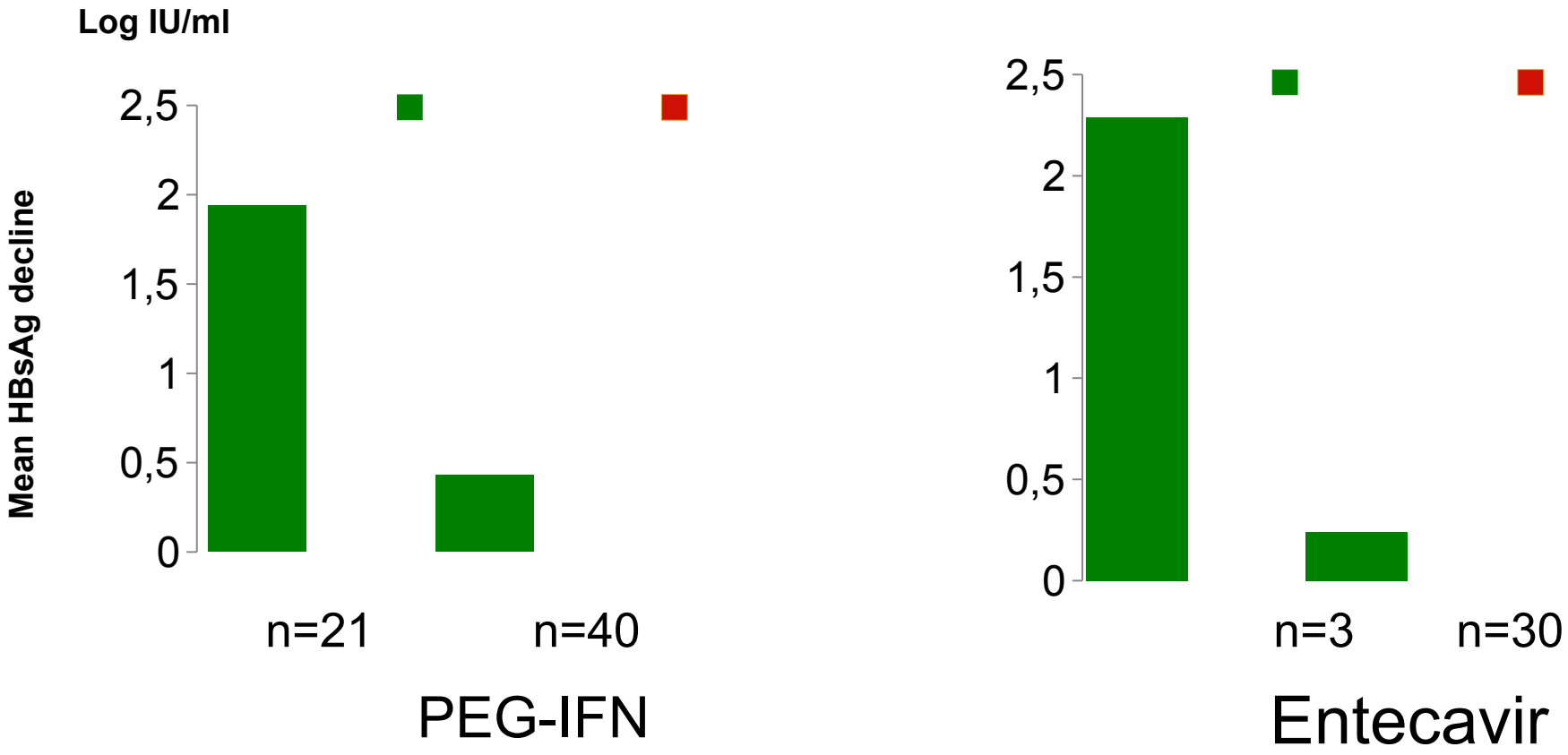



Reijinders JGP et al. J Hepatol 2011;54:449

# When: during therapy

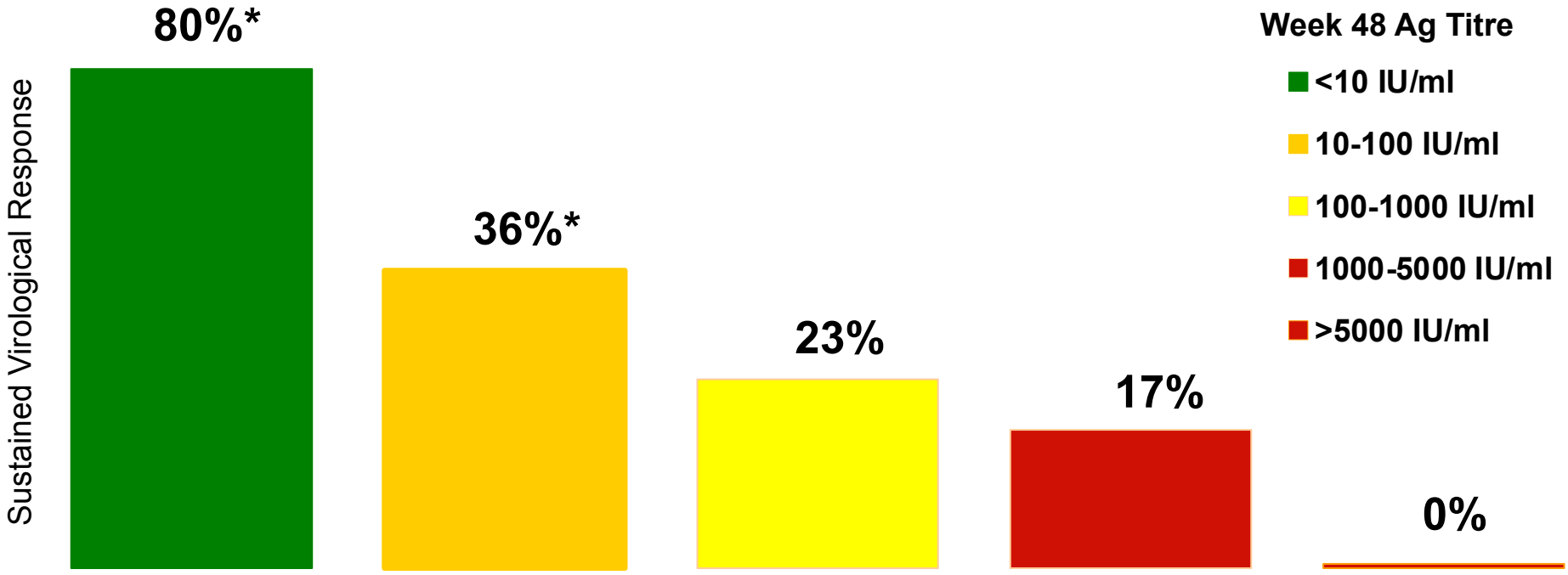
## Predictive value of HBsAg decrease
## HBeAg + /- patients 48 weeks PEG-IFN or Entecavir




Reijinders JGP et al. J Hepatol 2011;54:449

# When: end of treatment (PEG-IFN)

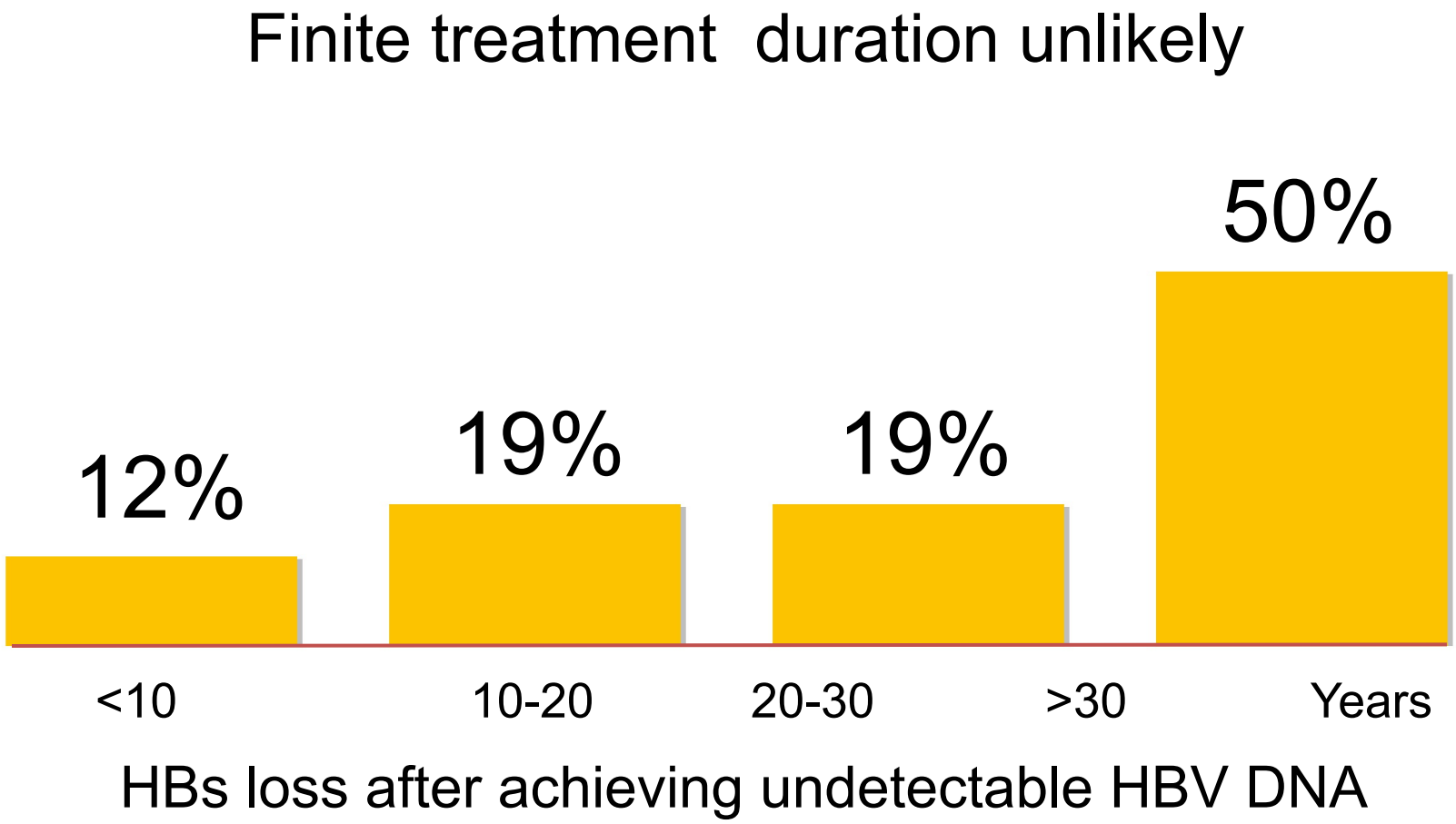
SVR and HBsAg loss
according to end of treatment HBsAg levels




*** At 3 years :HBsAg <10 IU/ml 52% HBsAg loss and HBsAg > 10 UI/m: 2% HBsAg loss**

Brunetto MR et al. Hepatology 2009

# When: ending therapy (NAs)

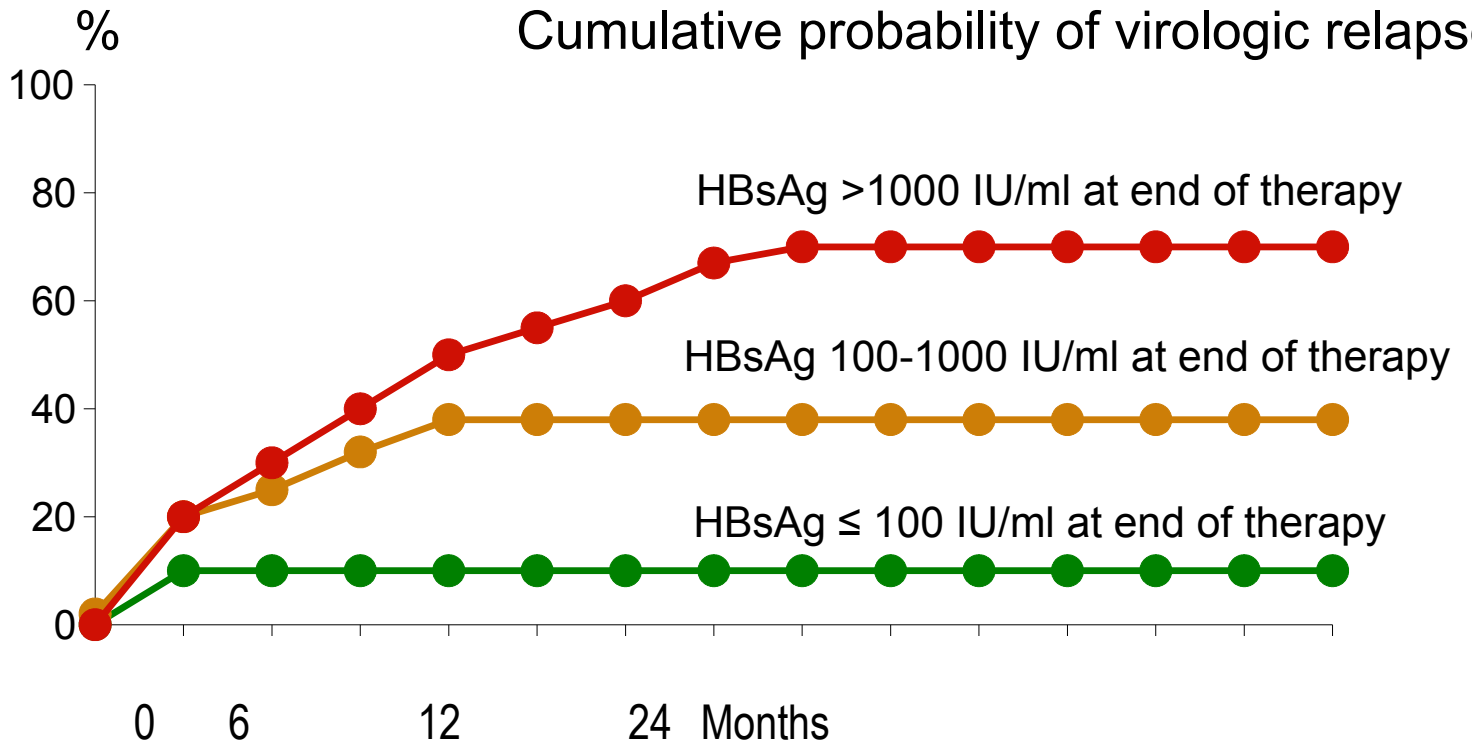



Zoutendijk R et al. JID 2011;204:415

Chevaliez S et al. J Hepatol 2013

# When: end of therapy (NAs)

## Prediction of outcome after NAs therapy discontinuation (APASL guidelines)

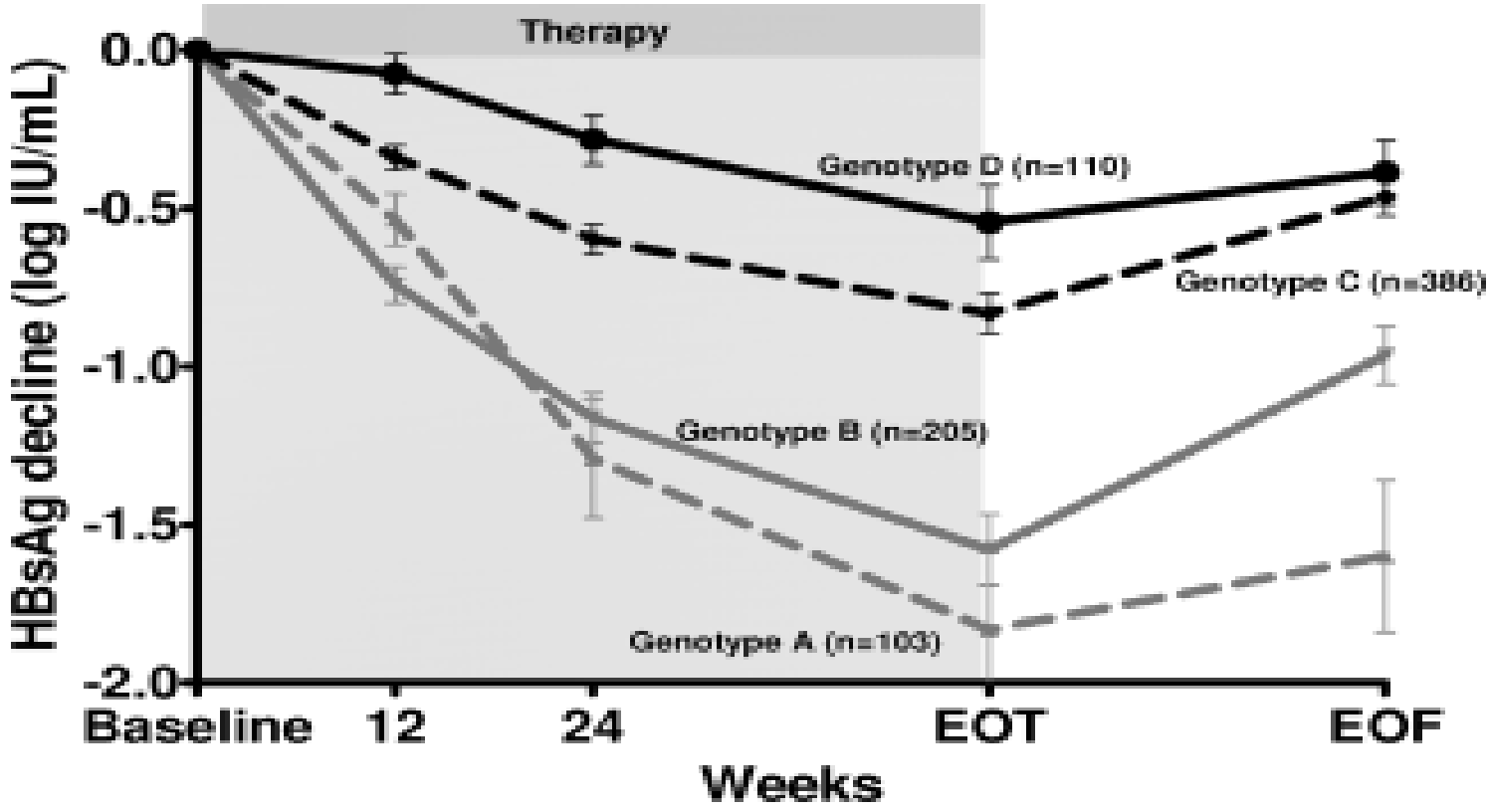



Liaw YF et al. Hepatol Int 2008L

Liang Y. AP&T 2011

# HBsAg and HBV genotypes (PEG-IFN)

Changes in serum HBsAg from baseline during therapy according to HBV genotypes



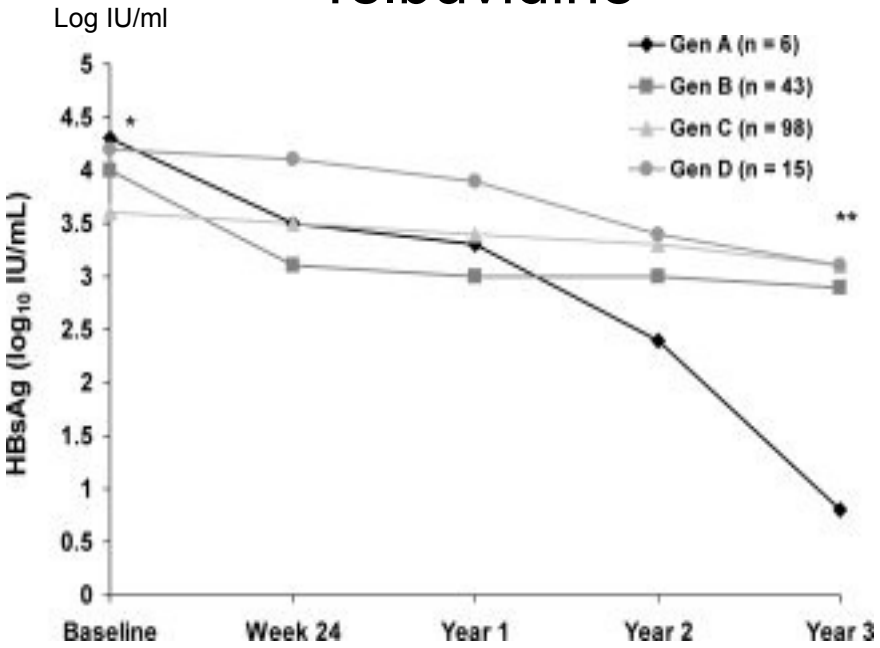

Brunetto MR et al J Hepatol 2013

Sonneveld MJ et al. Hepatology 2013

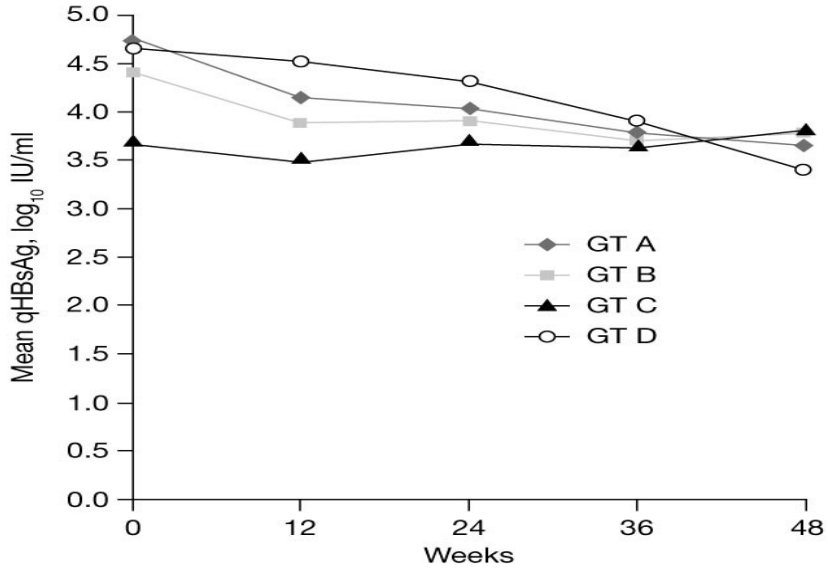
# HBsAg and HBV genotypes (NAs)

## Effect of genotypes on HBsAg kinetics

### Telbuvidine




### Entecavir




| Number of patients | | | | | |
|---|---|---|---|---|---|
| GT A | 36 | 34 | 33 | 35 | 31 |
| GT B | 19 | 19 | 17 | 16 | 16 |
| GT C | 12 | 11 | 12 | 10 | 9 |
| GT D | 11 | 10 | 10 | 11 | 10 |

Wursthorn K et al. Hepatology 2010

Marcellin P et al AASLD 2013

Gish R. et al. Antiviral Therapy 2013

# The present: summary (1)

HBsAg kinetics during the 24 first weeks of Pegylated-interferon or nucleos(t)ides therapy, is highly predictive of HBeAg and HBsAg loss, independently from HBV genotypes.

# The present: summary (2)

- qHBsAg can complement HBV DNA levels to optimize the management of chronic hepatitis B patients.
- More data are needed, especially studies from Western countries to confirm these findings, mainly observed in Asian patients, and the role of HBV genotypes.
- There is needs for better definition of specific degree of HBsAg decline and identified time points with the best predictive fit for sustained virilogical response and evaluating the likelihood of HBsAg seroconversion.

# Take home message

The better use of this new tool is likely serial measurements of HBsAg concentration

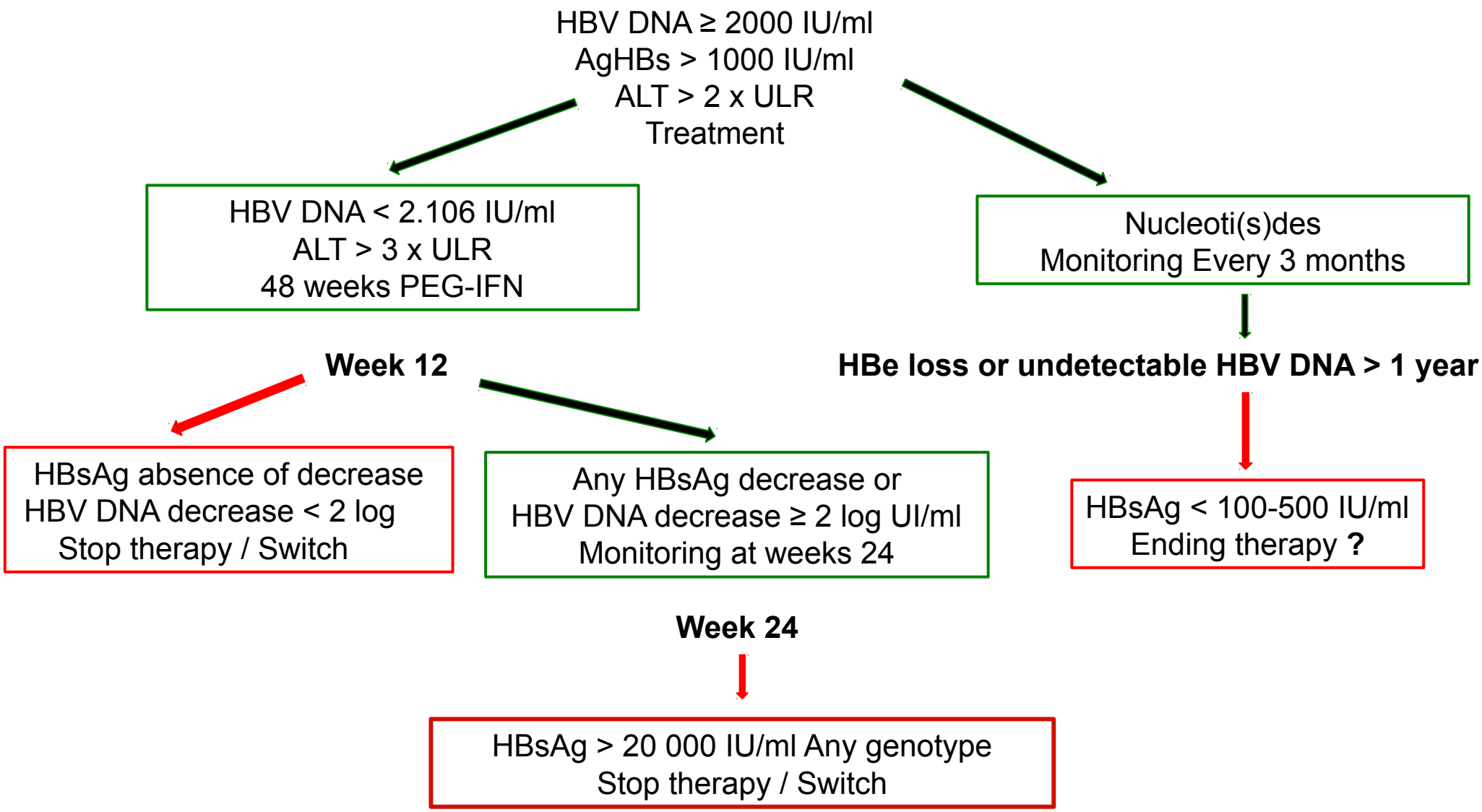
**PEG-IFN therapy**

Baseline, weeks 12 and 24 to identify patients with high probability of non-response and switch.

**NAs therapy**

Baseline, week 24 to identify patients with high probability of HBeAg and HBsAg loss, before ending therapy to identify patients without risk of relapse.

# Take home message



# The Future (1)

**Individualized treatment strategy for HBeAg negative: First line PEG-IFN and week 12 stopping rule**

The cost effectiveness of the management of HBeAg negative chronic hepatitis B could be improved significantly by a shift toward a response guide first line therapy with PEG-IFN followed by a switch to NAs in patients meeting the week-12 HBV-DNA / HBsAg stopping rule.

Iannazzo S et al. Systematic review of all English articles from 2004-2012. Antiviral Therapty 2013

# The future (2)

- ✓ Decisional algorithms based on HBsAg and HBV DNA kinetics will be added to AASLD, EASL, APASL guidelines.
- ✓ Stopping rules validated according to HBsAg level and on treatment decrease, genotype specific, will be applied to the PEG-IFN treatment, whatever the HBe status.
- ✓ HBsAg thresholds, probably genotype specific, will be identified and will allow to end NAs treatment without risk of relapses.