Hepatitis B Surface Antigen: Clinical Relevance

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HBsAg: Back to the Future?

- **Qualitative HBsAg:**
  - **Diagnostic Tool for HBV Infection**
  - **Prognostic Marker for Disease Resolution**

- **Quantitative HBsAg:**
  - **Reflect of the Natural History**
  - **Predictor of Sustained Response in IFN-Based Therapy**
  - **Guide to Optimize Treatment Duration with NUC**

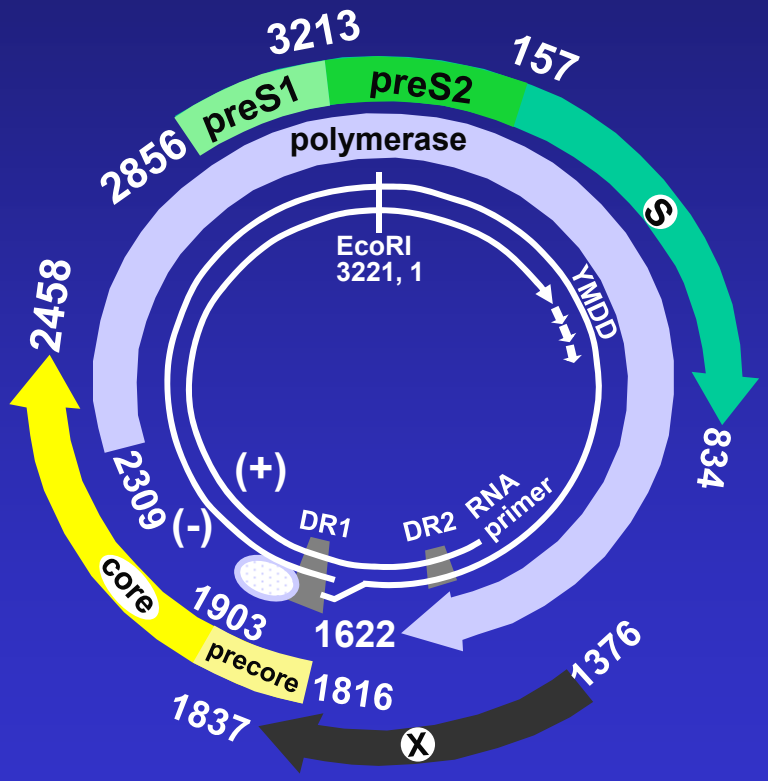
Moucari et al. Expert Rev Anti-infect Ther. 2009

Qualitative HBsAg: Diagnostic Tool for HBV Infection

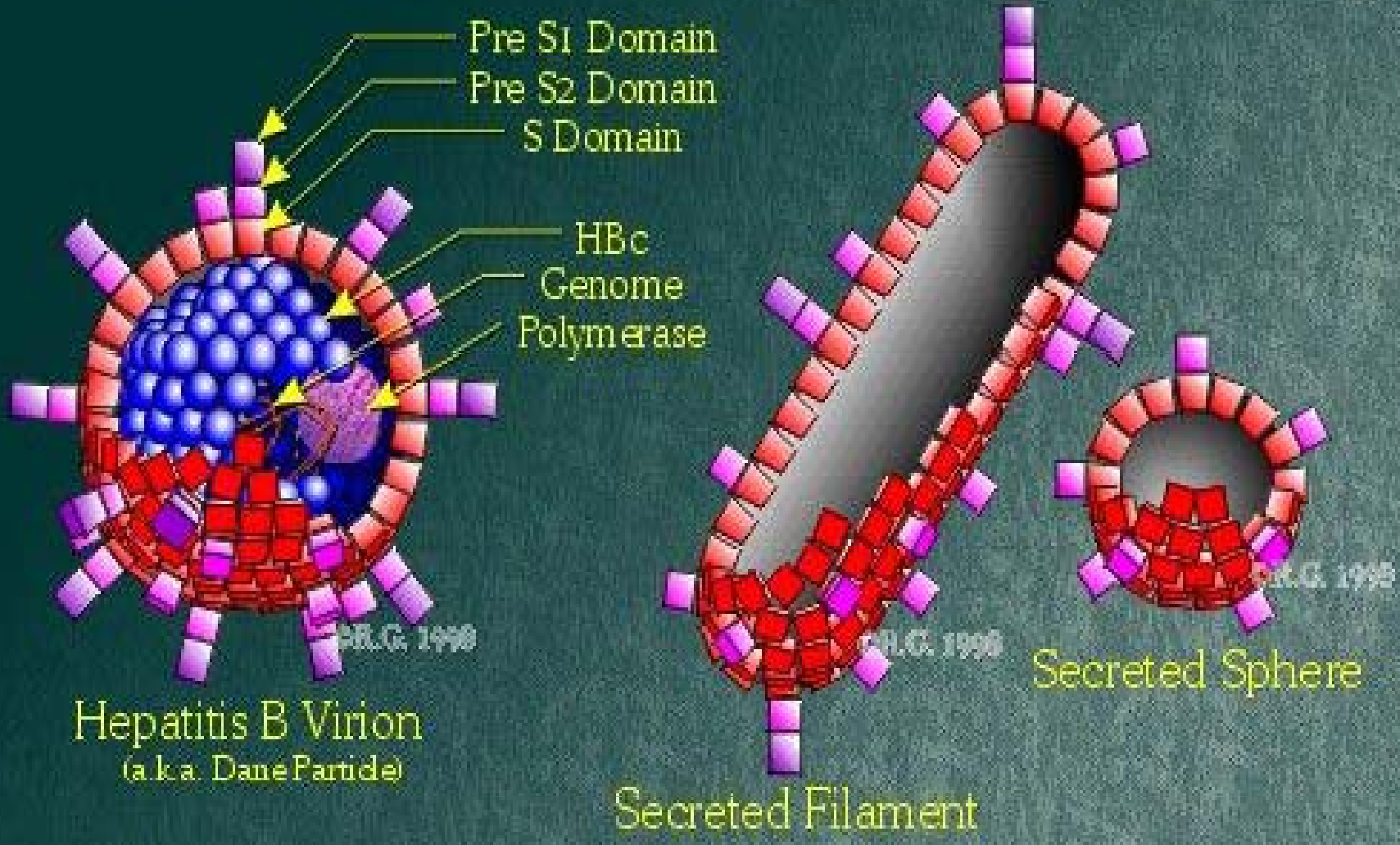
- HBsAg was the first hepatitis B virus (HBV) protein to be discovered
- “Australia antigen”, the Nobel prize discovery identifying HBV about 40 years ago
- Nowadays the fundamental diagnostic marker of HBV infection

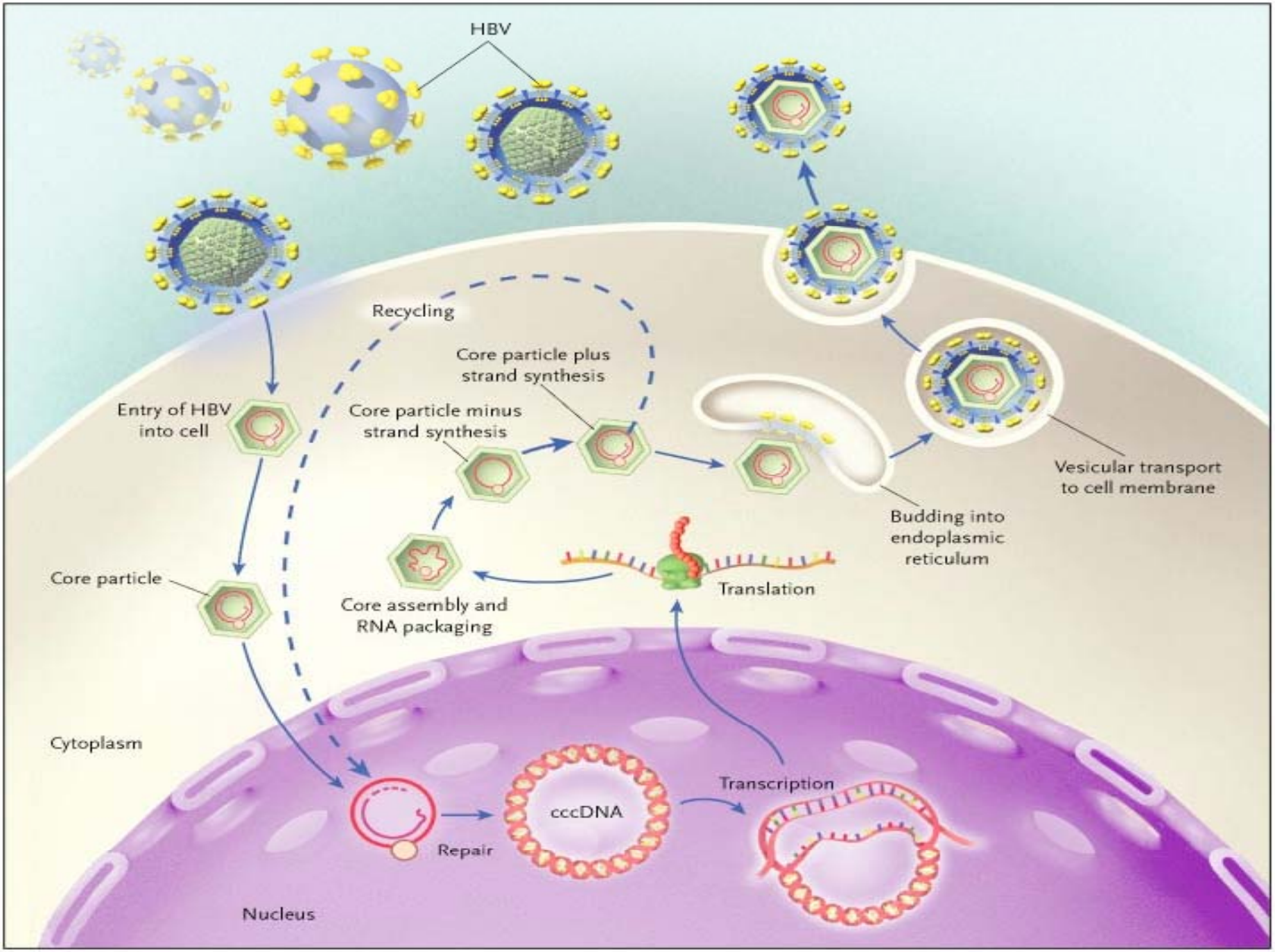
Blumberg et al. JAMA 1965

Hepatitis B Virus (HBV)



Hepatitis B Particle Types




HBV
Recycling
Core particle plus strand synthesis
Core particle minus strand synthesis
Entry of HBV into cell
Vesicular transport to cell membrane
Budding into endoplasmic reticulum
Core particle
Core assembly and RNA packaging
Translation
Cytoplasm
Transcription
cccDNA
Repair
Nucleus

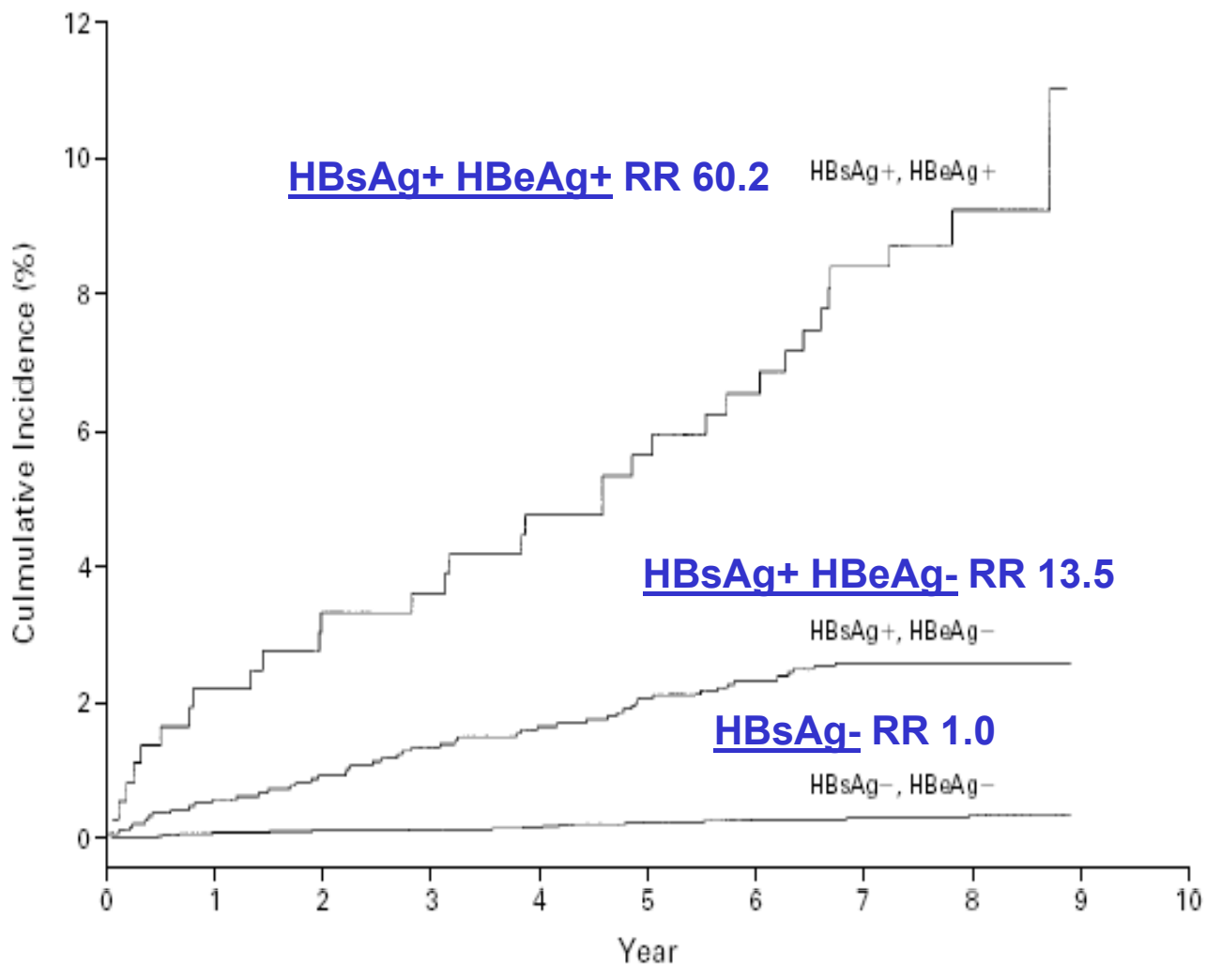
Qualitative HBsAg:
Prognostic Marker for Disease Resolution

As close to a clinical cure as we can expect to achieve in chronic hepatitis B

- Natural history shows real clinical benefit:
  - Reduced hepatic decompensation
  - Reduced HCC
  - Improved survival
- Molecular studies
  - Extremely low levels of cccDNA in patients who clear HBsAg

REVEAL study: Taiwan 1991–1992

Risk of HCC by HBV status

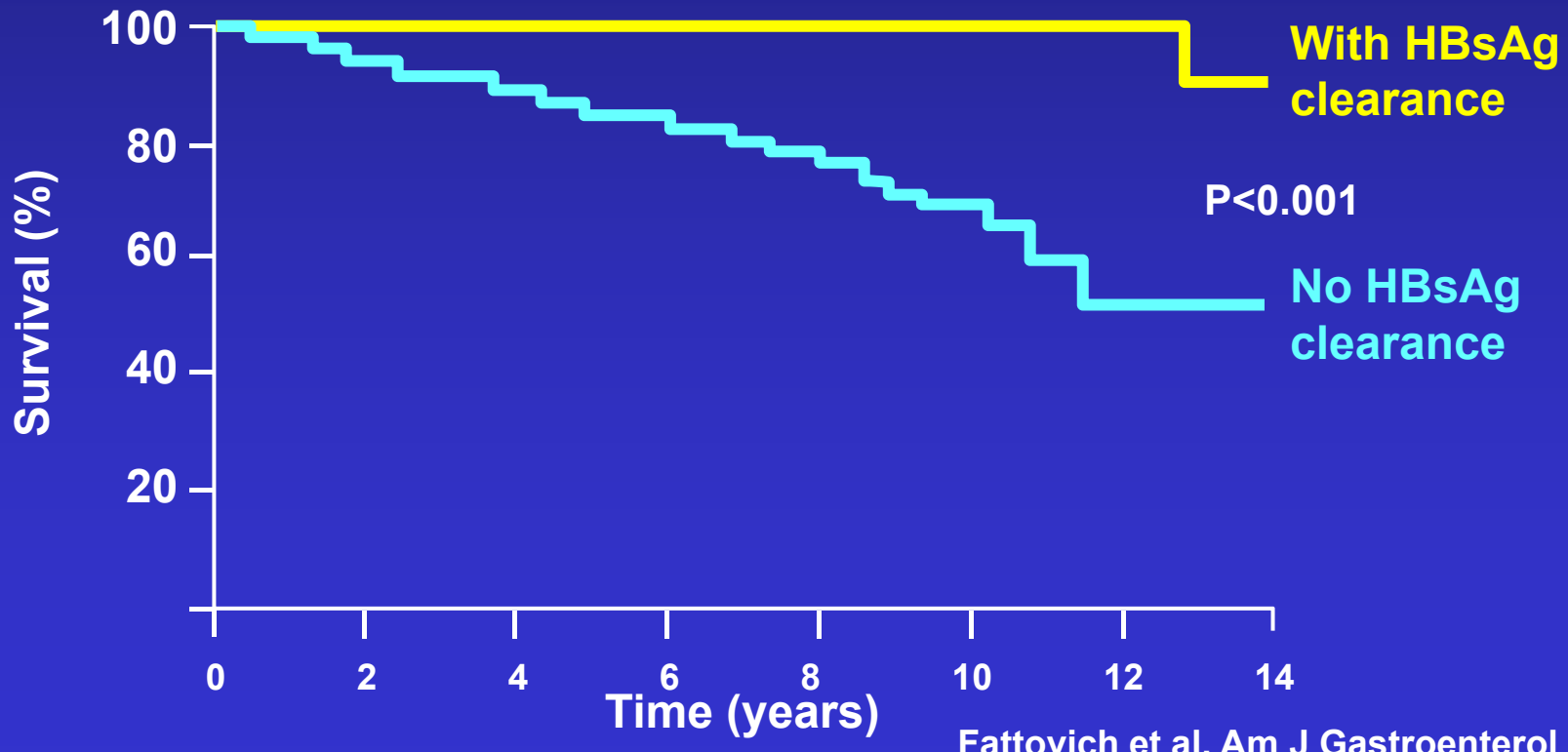


Yang et al. NEJM 2002

HBsAg Clearance – Improves Survival

Survival in patients with and without HBsAg seroconversion

Retrospective study of 309 cirrhotic patients over mean follow-up of 5.7 years



Fattovich et al. Am J Gastroenterol 1998

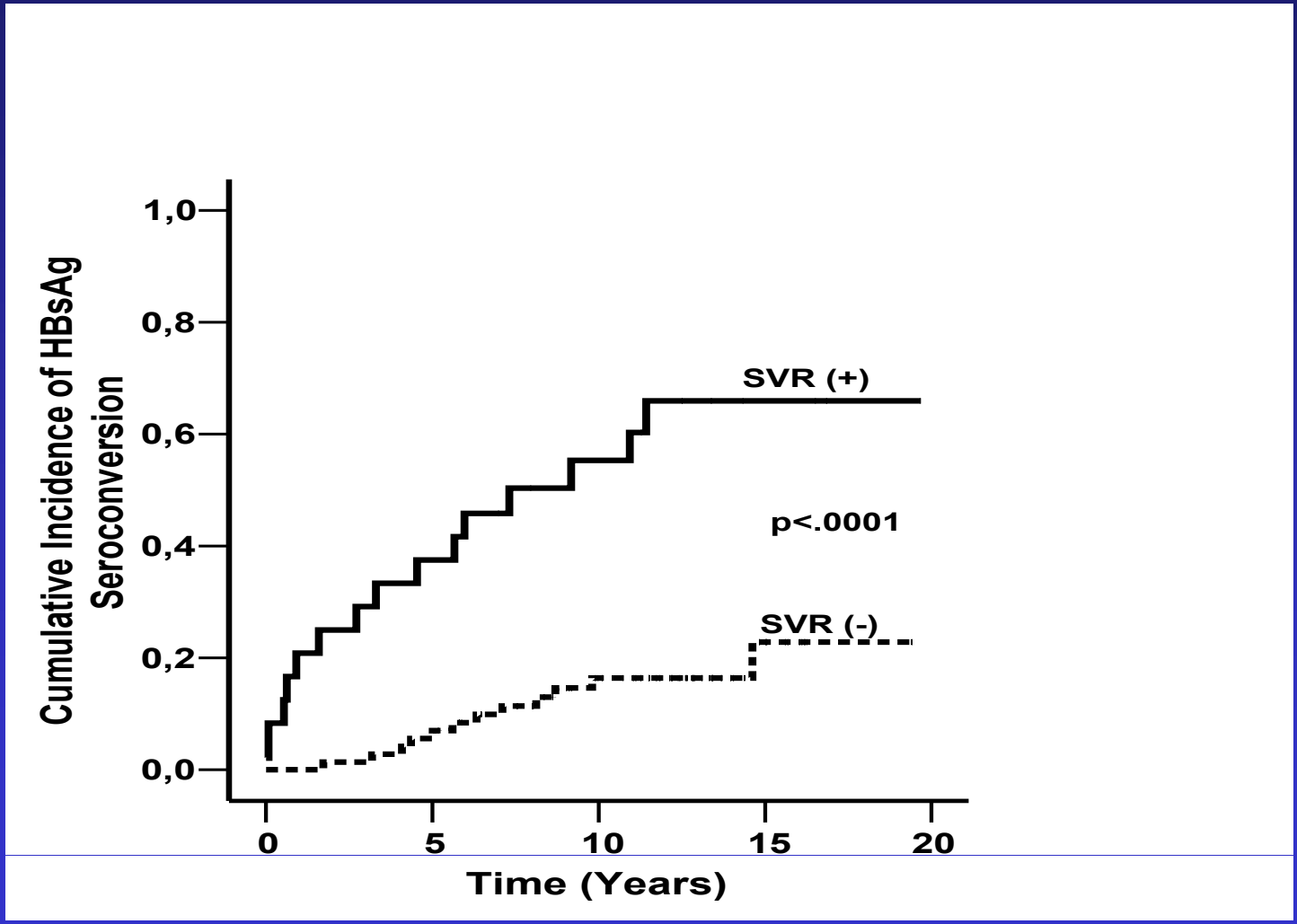
Guidelines
HBsAg clearance is the “Ideal endpoint”

- AASLD, EASL and APASL guidelines all acknowledge the importance of HBsAg clearance
  - Key role in the natural history of chronic HBV infection
- EASL guidelines (*J Hepatol* 2009)
  - “... is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome”

Spontaneous HBsAg Clearance in Untreated *inactive* CHB: 30-year Follow-up

Country	N	% with HBsAg cleared
Italy (Gut 2008;57:84)	40	45%
Taiwan (Hepatology 2007;45:1187)	1965	44.7%

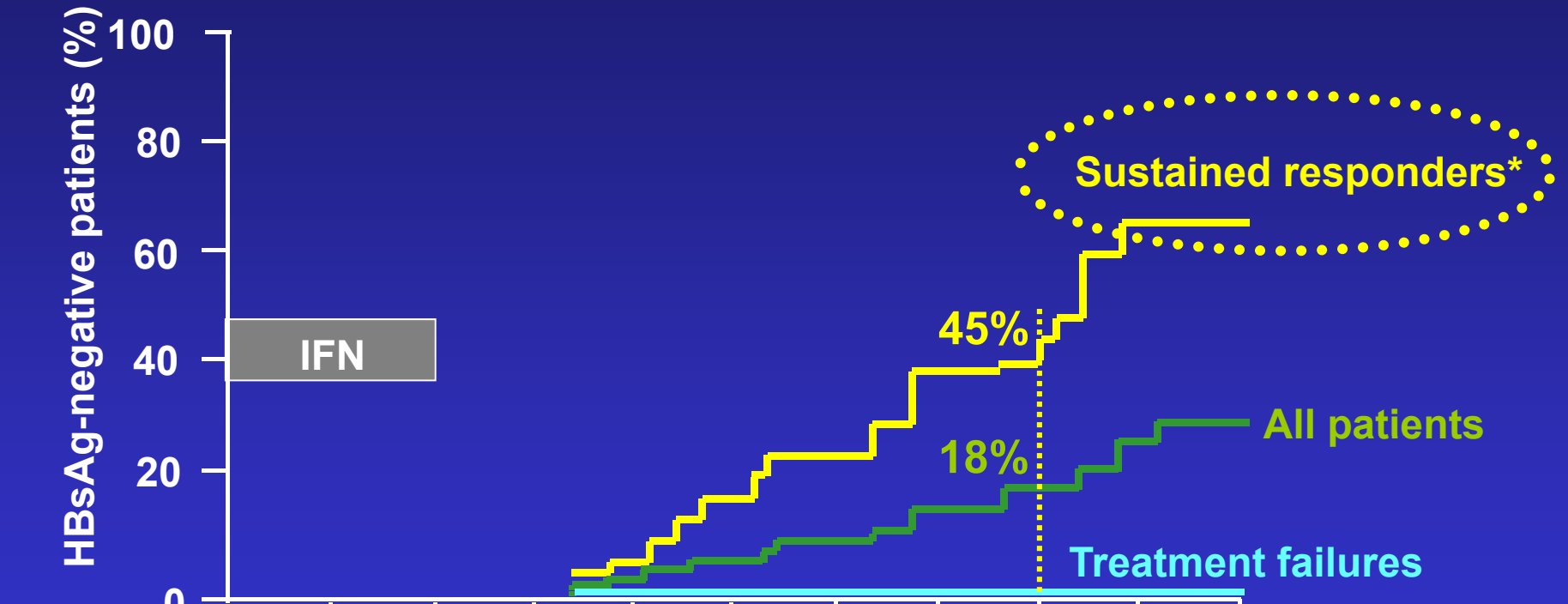
HBsAg Clearance Increases Over Time in Sustained Responders



Moucari et al. J Hepatol 2009

HBsAg Clearance Increases Over Time in Sustained Responders

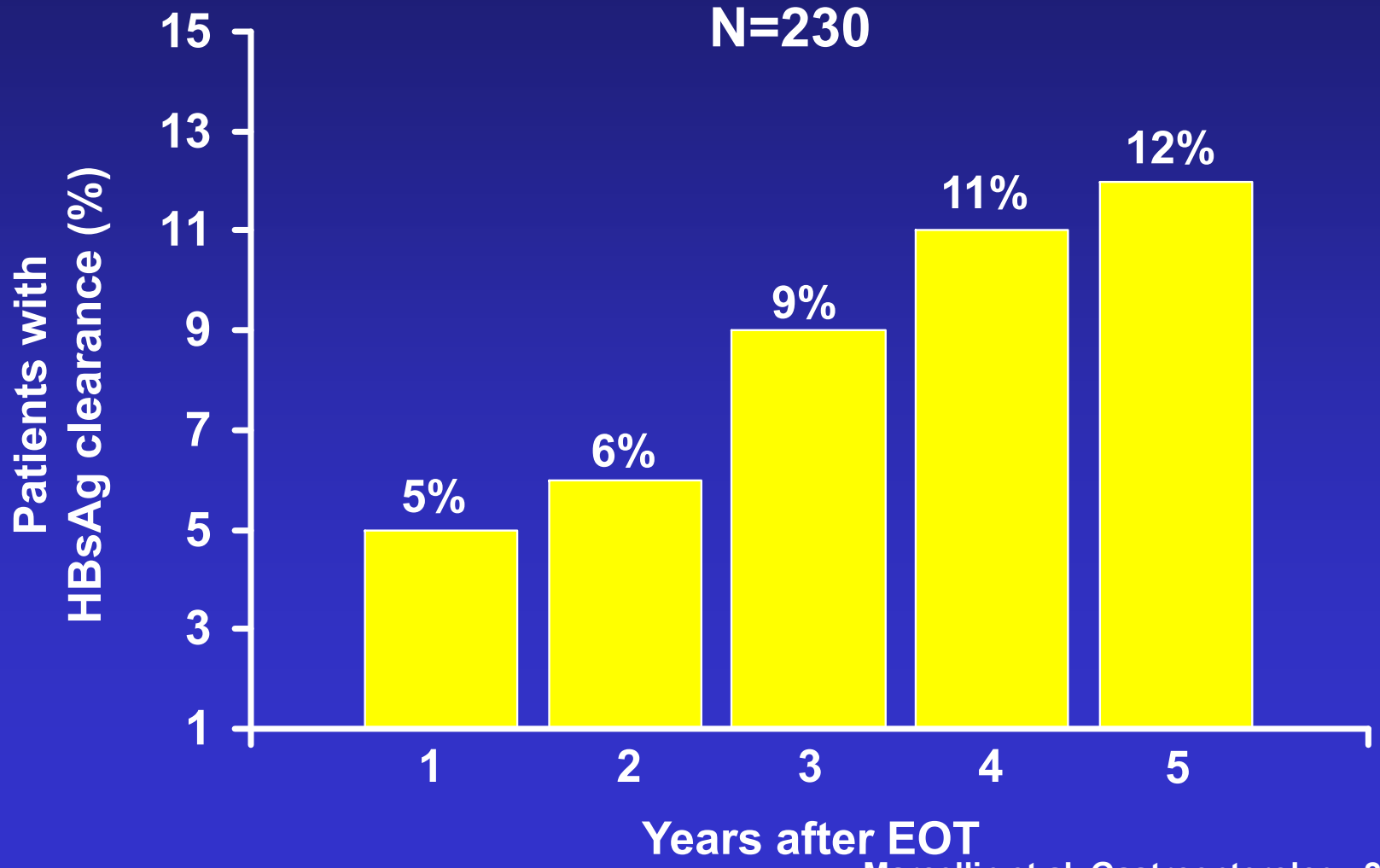
Population 92% genotype D



*ALT normal and HBV DNA undetectable <1pg/mL

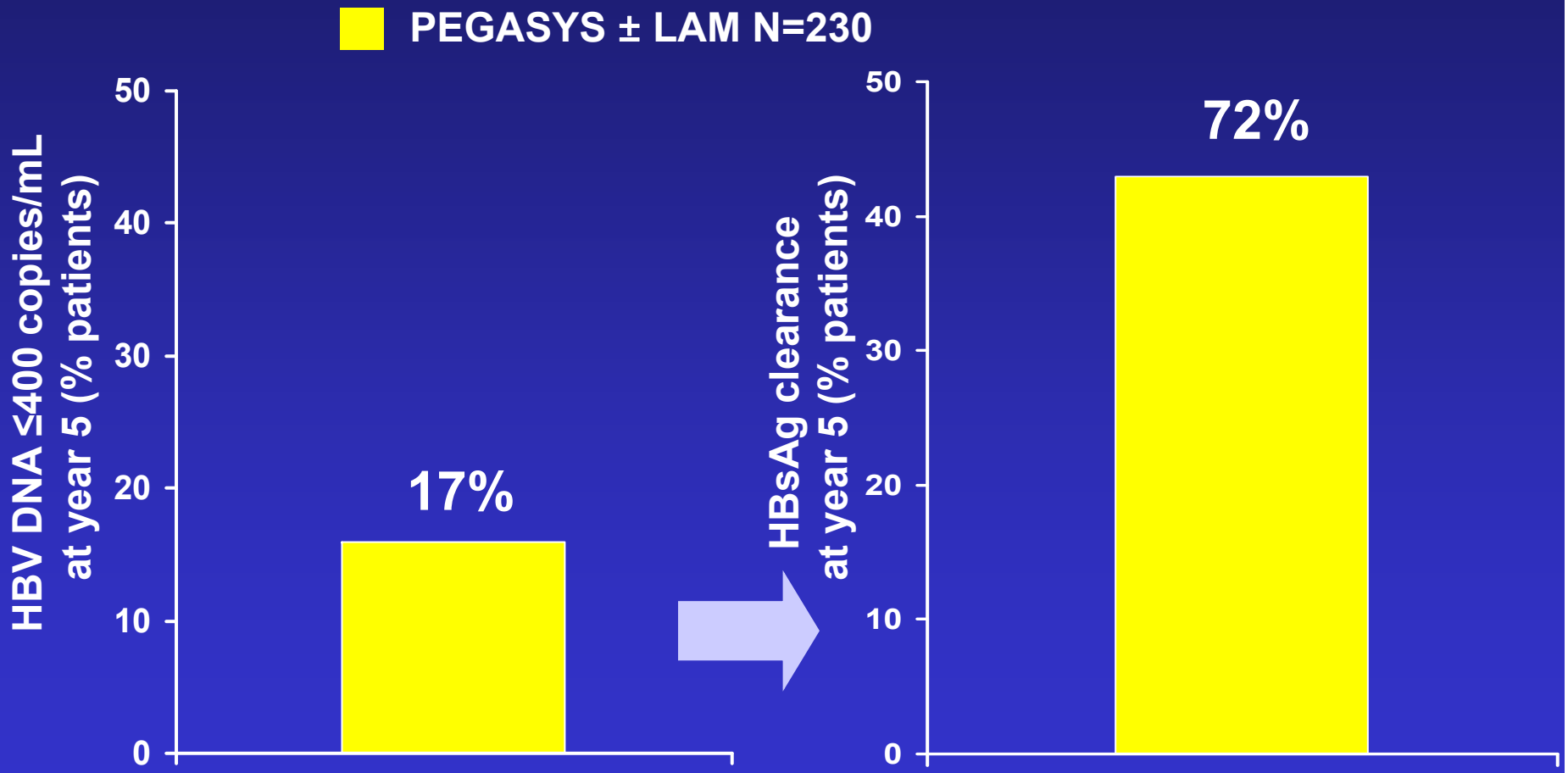
Lampertico et al. Hepatology 2003

HBsAg clearance rate continues to increase post-treatment with PEG-IFN (± LAM)



Marcellin et al. Gastroenterology 2009

High rate of HBsAg clearance in patients with HBV DNA ≤400 copies/mL at year 5



Marcellin et al. Gastroenterology 2009

How Can We Quantify HBsAg?

- Qualitative *screening* assays for HBsAg available universally
  - Commercial tests
    - **Architect – Abbott**
    - **Elecsys® II – Roche**
    - ADVIA Centaur HBsAg Assay – Bayer
    - Hepanostika HBsAg – Biomerieux
  - In-house assays widely used in some countries

Quantitative HBsAg assays: Architect HBsAg (QT)*

- Dynamic Range: 0–250.0 IU/mL (WHO)
  - Samples >250 IU/mL are diluted
  - Dilution factor used to automatically calculate the concentration of the sample
- Dual epitope capture format, detects all known HBsAg mutants

*Assay not commercially available in the US

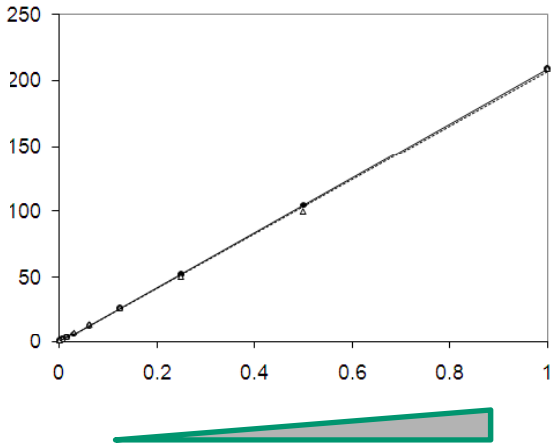
WHO: World Health Organization

Linearity across a broad range of concentrations – even at high levels

Analysis using Abbott Architect assay

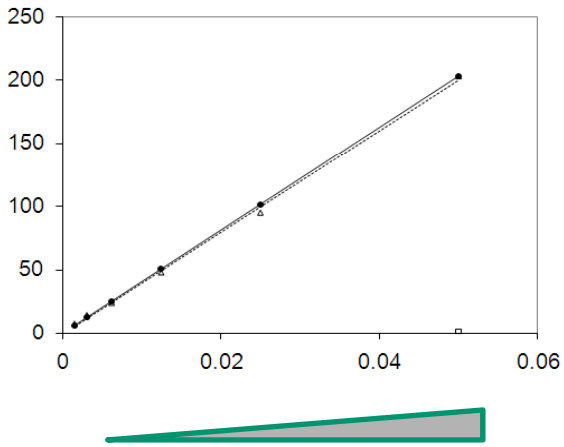
2-fold serial dilutions

0.05 − 250 IU/mL



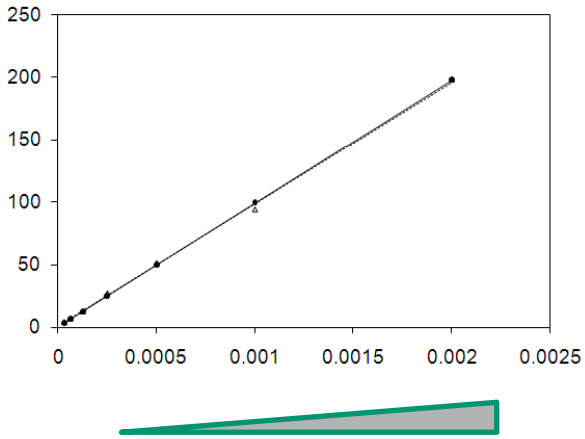
2-fold serial dilution after 20-fold pre-dilution

1 − 5000 IU/mL



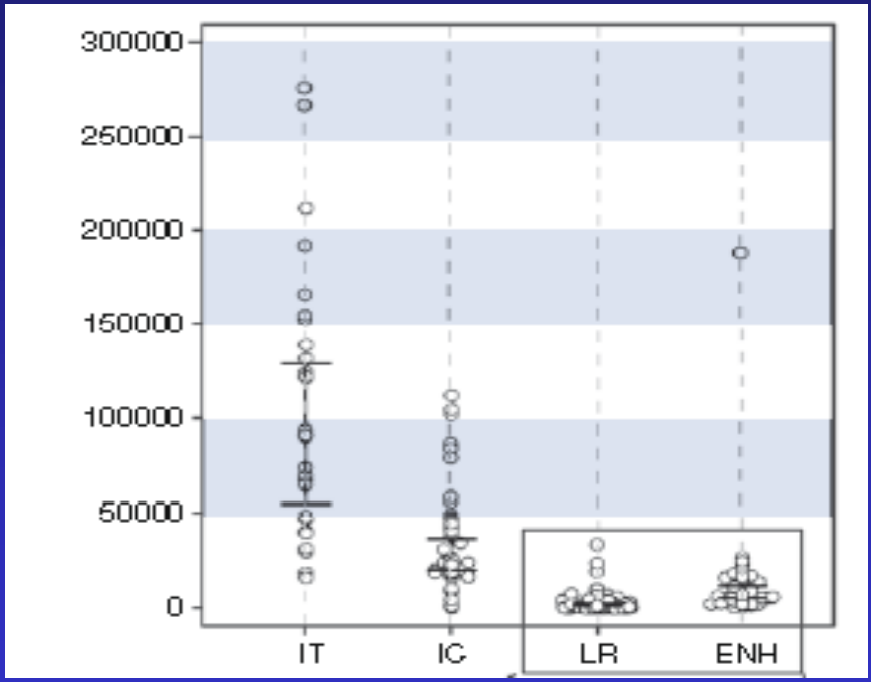
2-fold serial dilutions after 500-fold pre-dilution

25 − 125 000 IU/mL

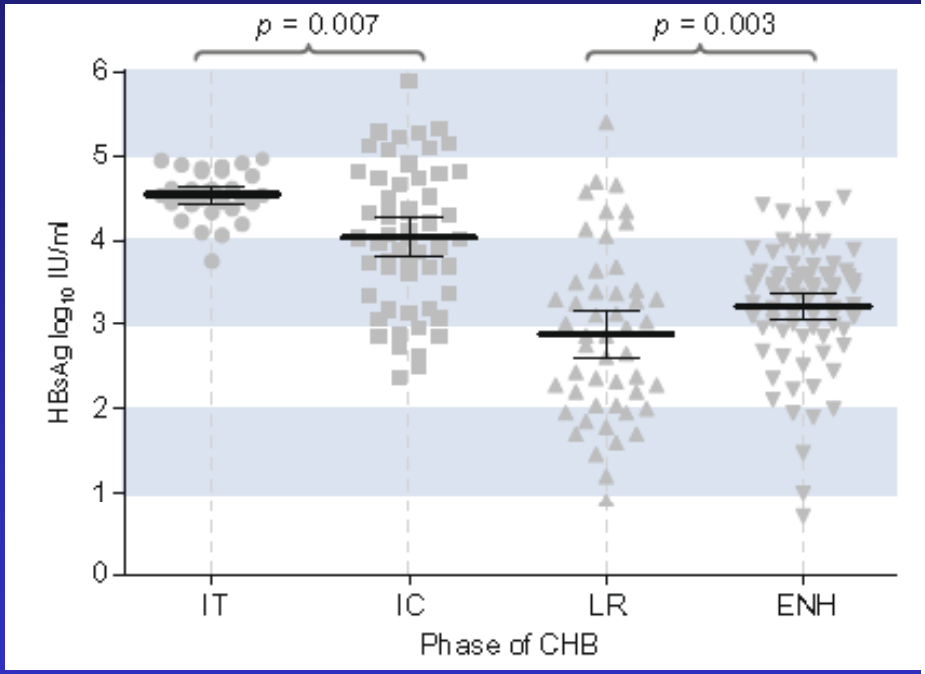


Mackiewicz & Moucari. submitted

Quantitative HBsAg: Reflect of the Natural History

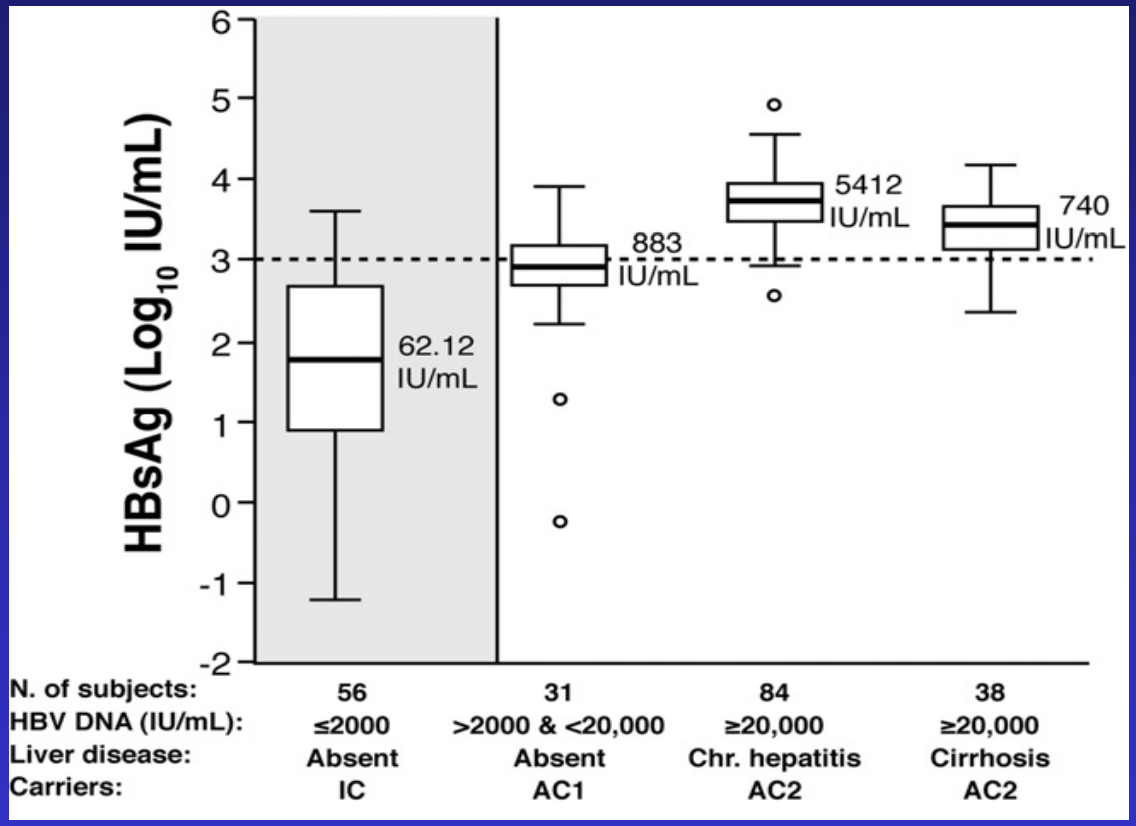


Jaroszewicz et al. J Hepatol 2010



Nguyen et al. J Hepatol 2010

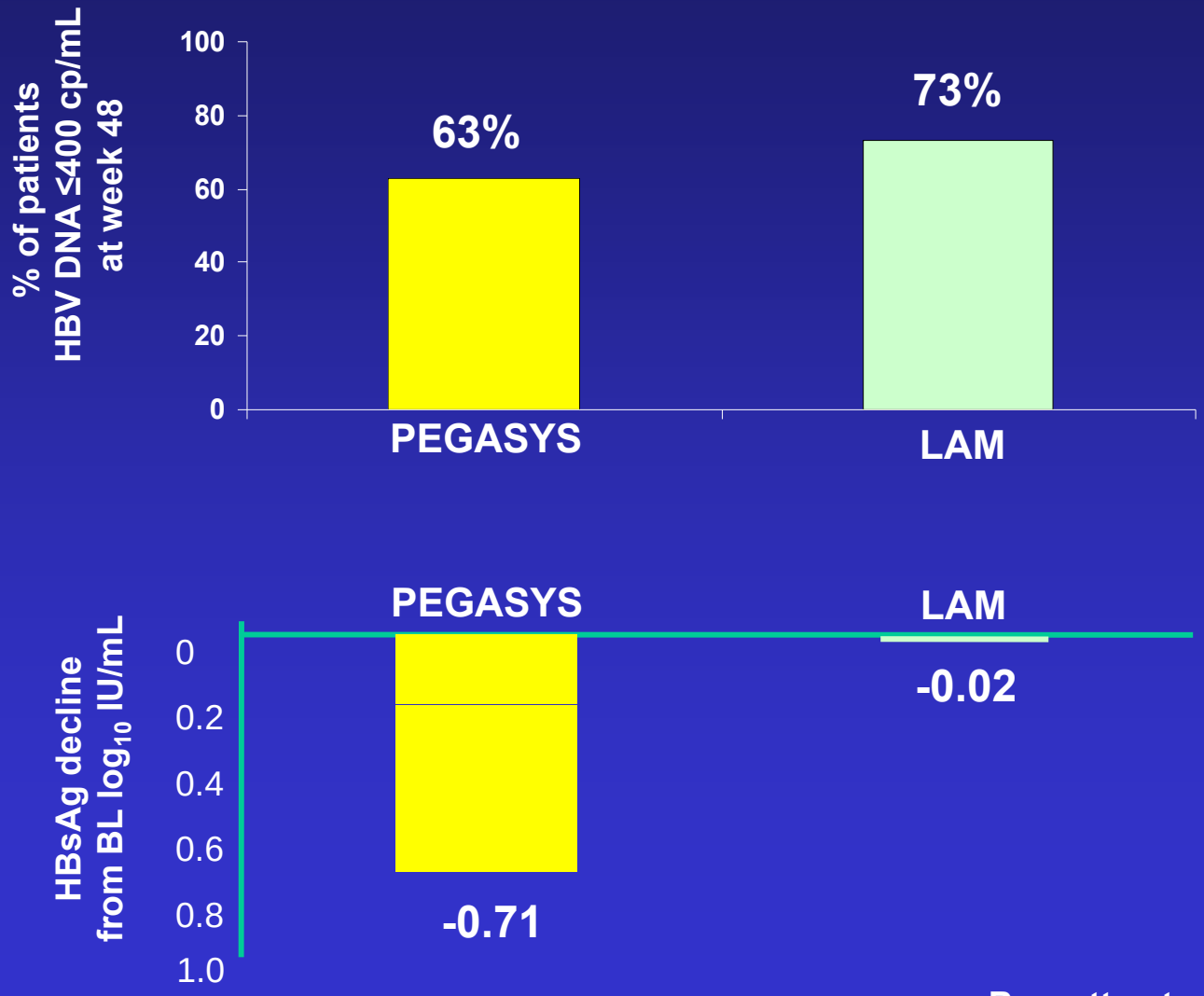
Quantitative HBsAg: Reflect of the Natural History



A combined single point quantification of HBsAg < 1000 IU/mL and HBV DNA < 2000 IU/mL identified IC with 94.3% diagnostic accuracy, 91.1% sensitivity, 95.4% specificity, 87.9% positive predictive value, 96.7% negative predictive value.

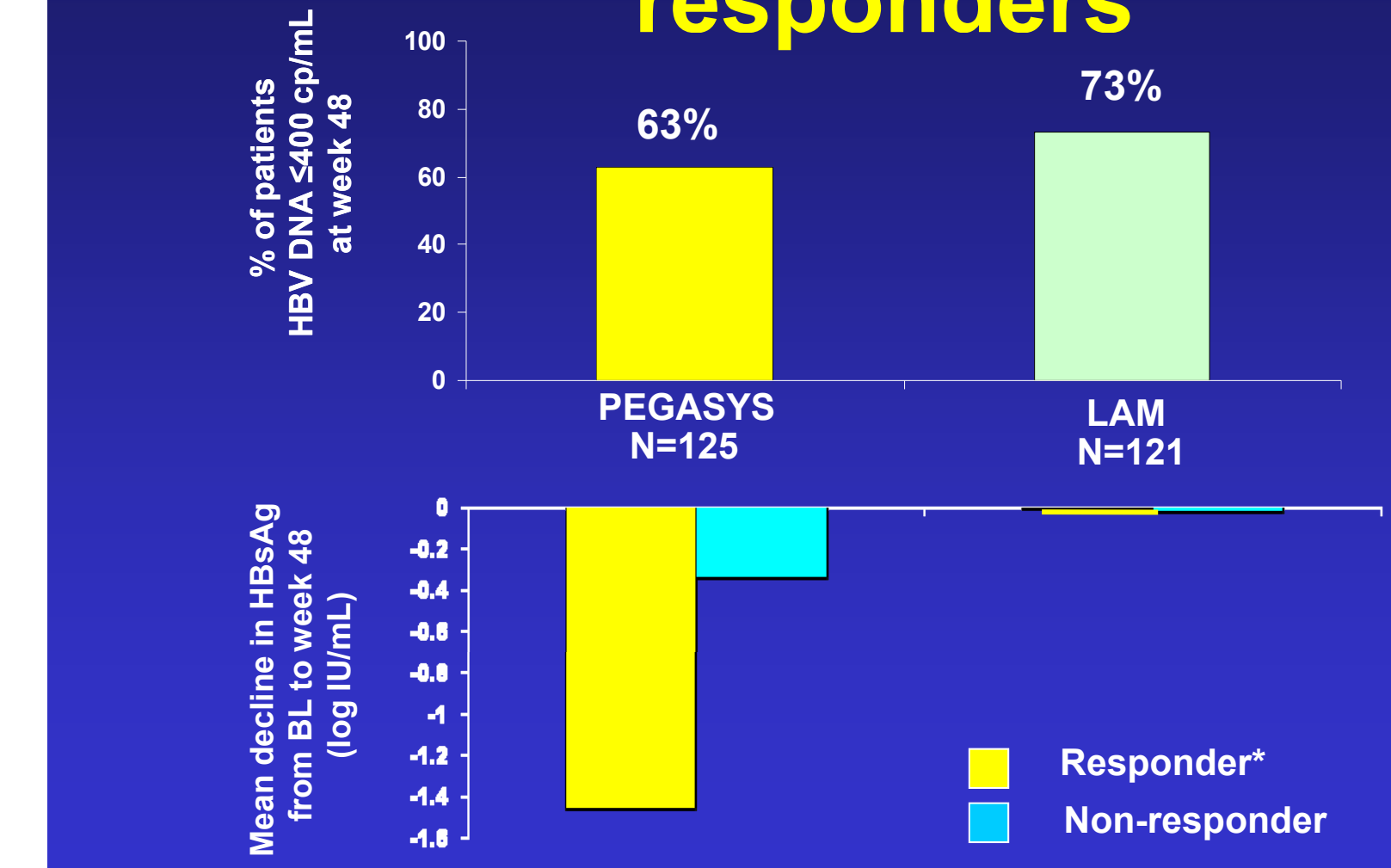
Brunetto et al. Gastroenterology 2010

Greater decline of HBsAg from BL to EOT with PEG-IFN vs. LAM



Brunetto et al. Hepatology 2009

Greater decline of HBsAg from BL to EOT in responders vs. non-responders



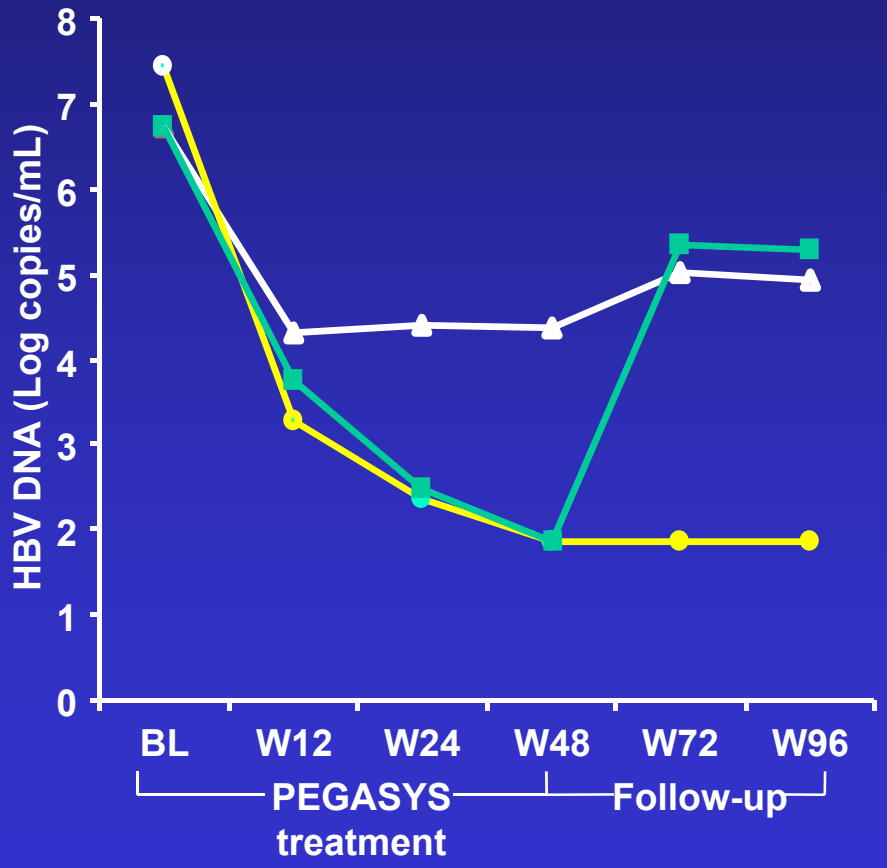
*HBV DNA ≤400 copies/mL at week 72

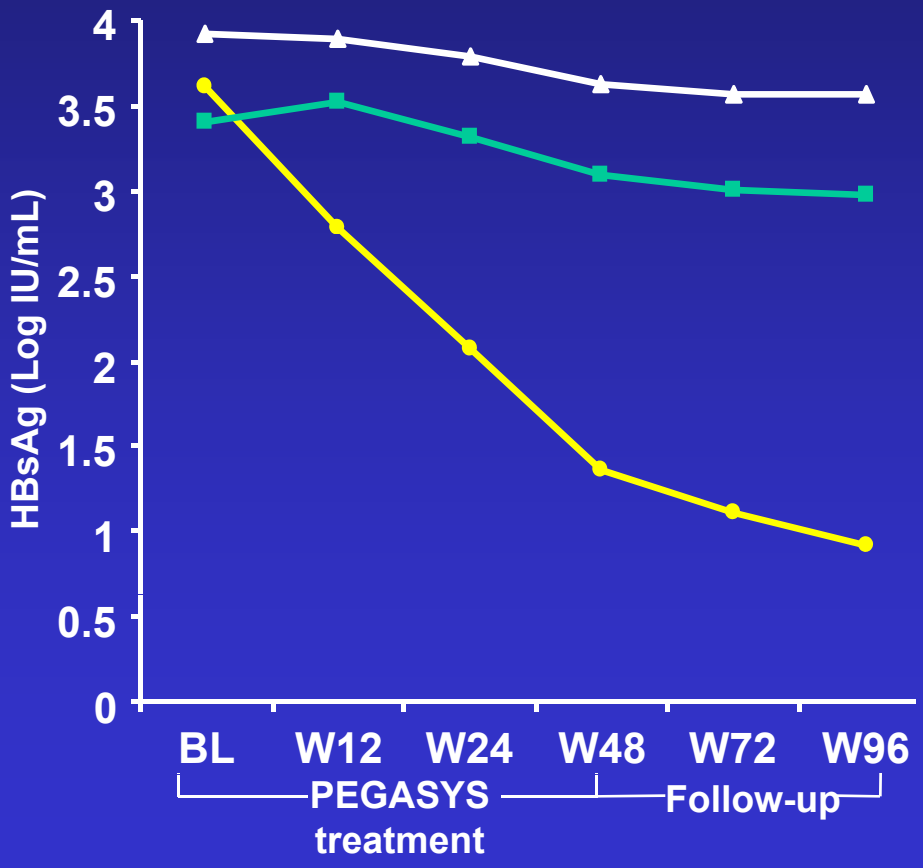
Brunetto et al. Hepatology 2009

HBsAg Decline: On Treatment

HBeAg-negative patients

Sustained responders* (N=12) **Non-Responders (N=18)** **Relapsers (N=18)**

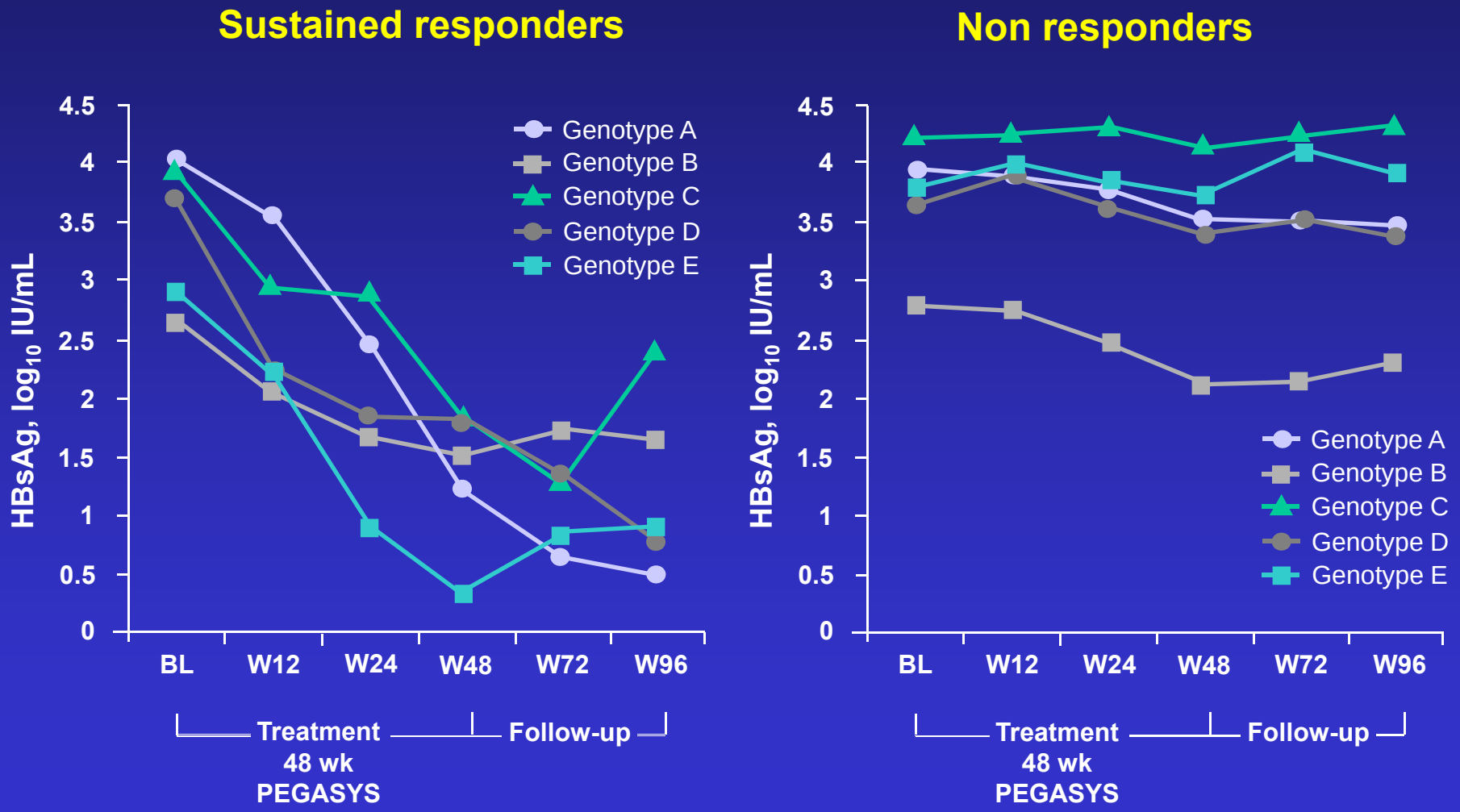




*HBV DNA undetectable by PCR 1 year post-treatment

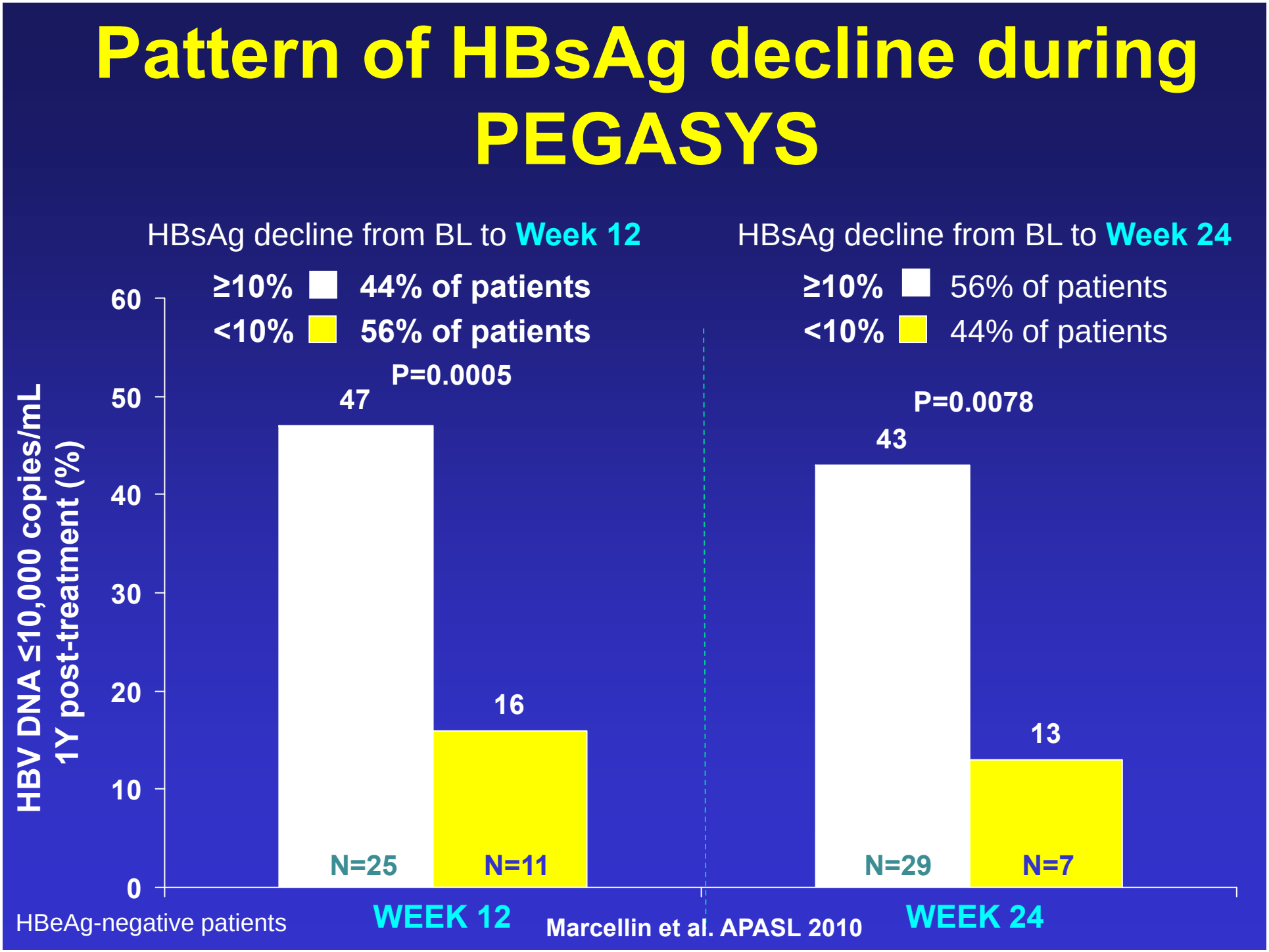
Moucari et al. Hepatology 2009

HBsAg Decline: Role of Genotypes

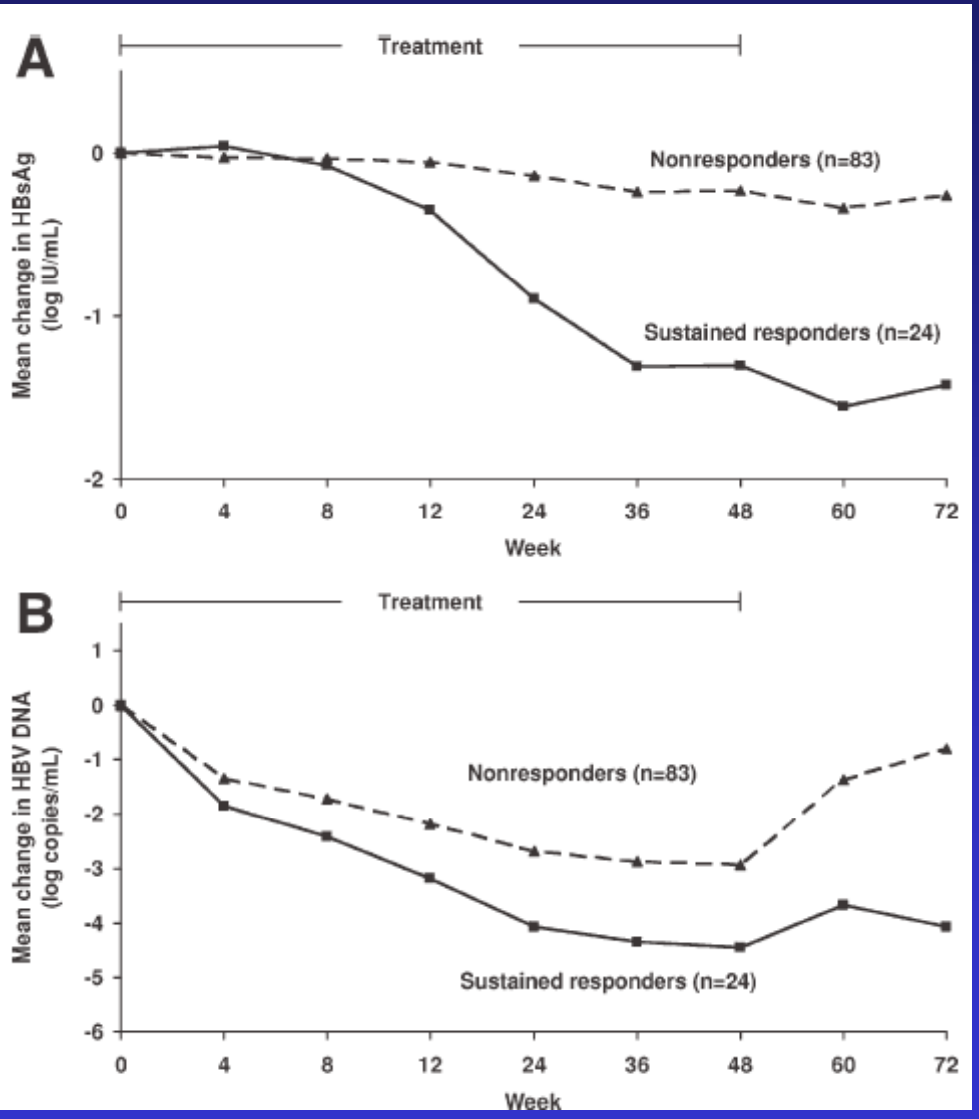


Moucari et al. Antiviral Therapy 2009

Pattern of HBsAg decline during PEGASYS



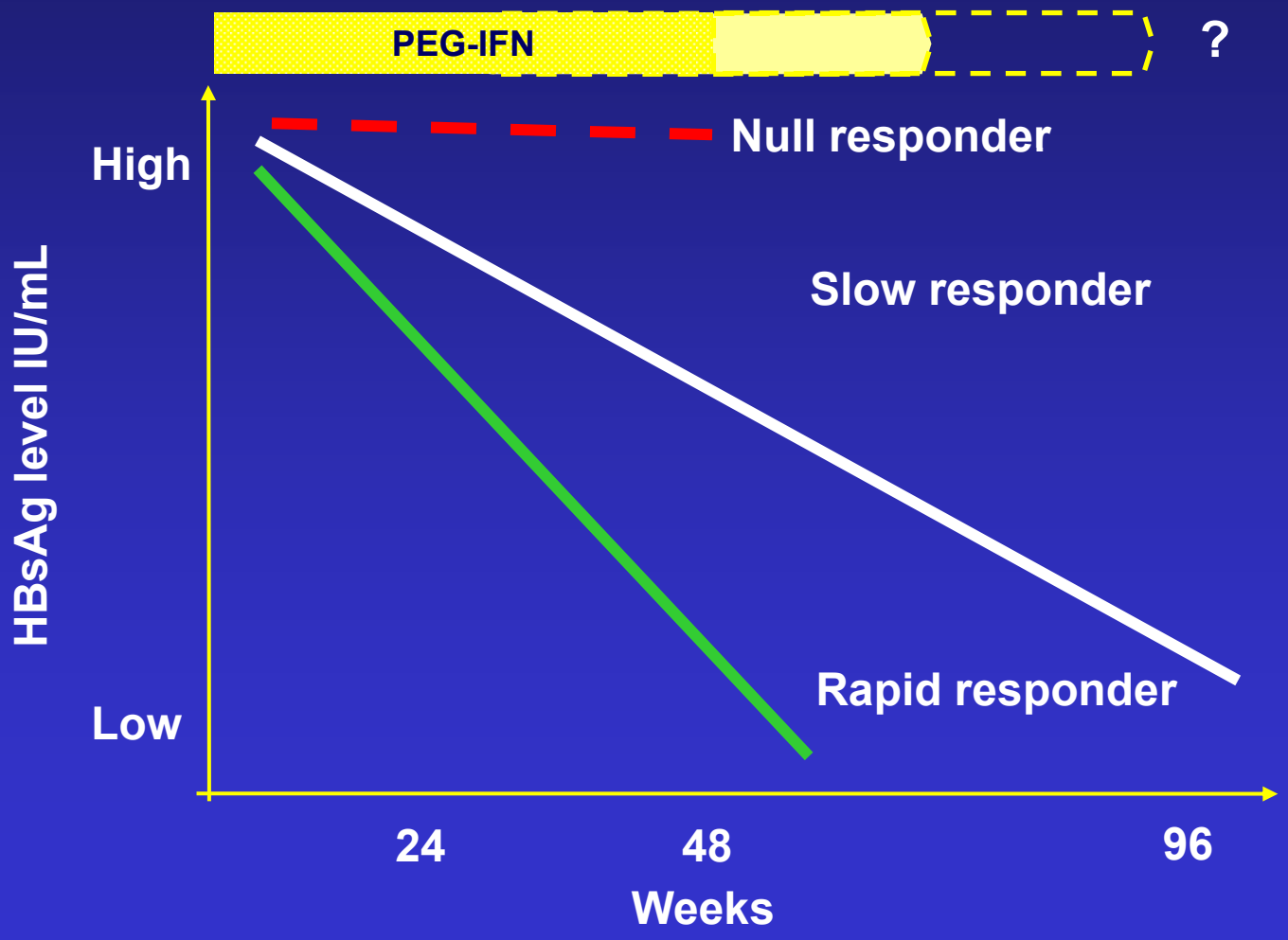
HBsAg & HBV DNA Decline: On Treatment



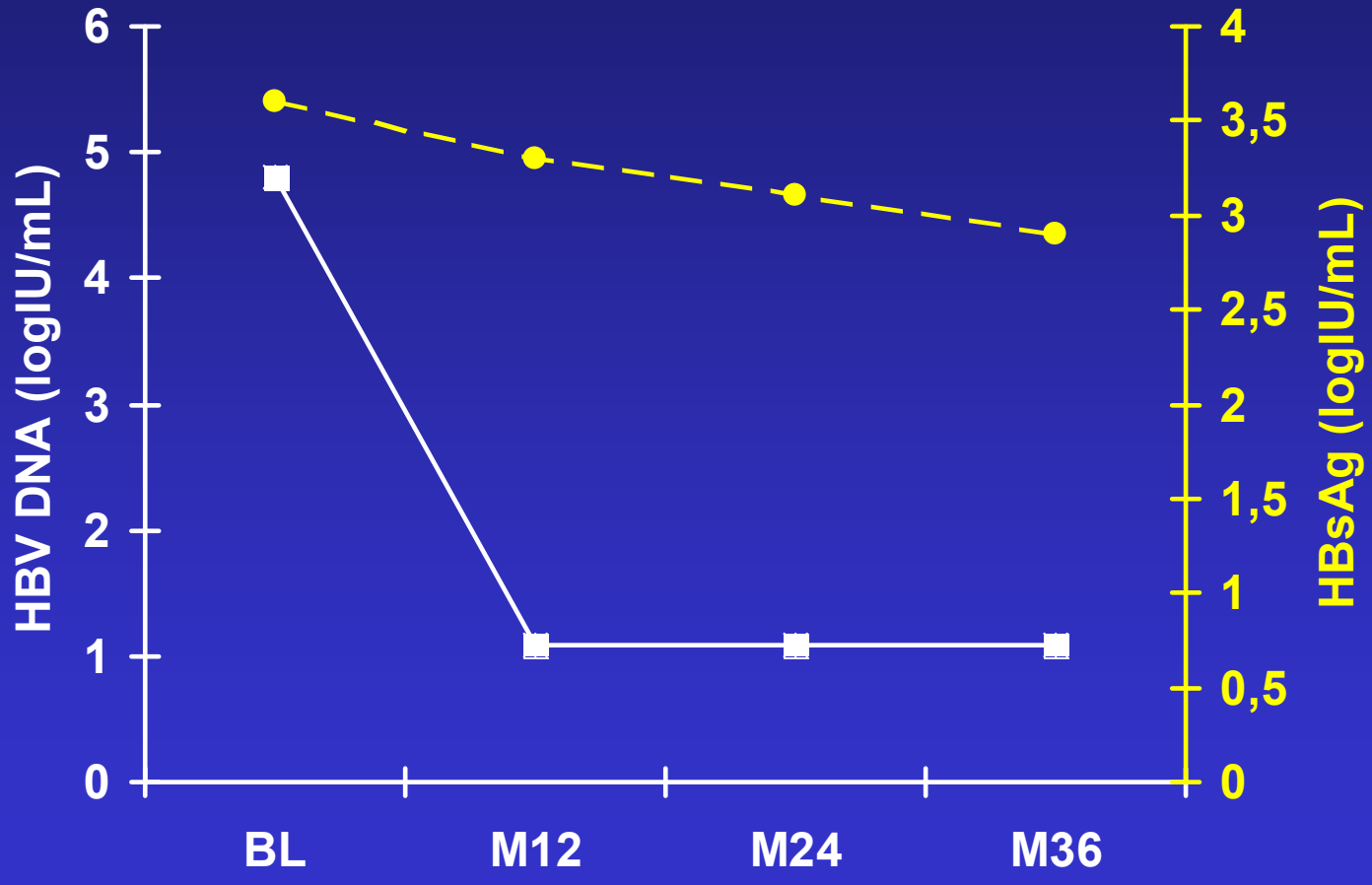
None of the 20 patients (20% of the study population) in whom a decrease in serum HBsAg levels was absent and whose HBV DNA levels declined less than 2 log copies/mL exhibited an SR (negative predictive value = 100%)

Rijckborst et al. Hepatology 2010

Monitoring HBsAg Decline

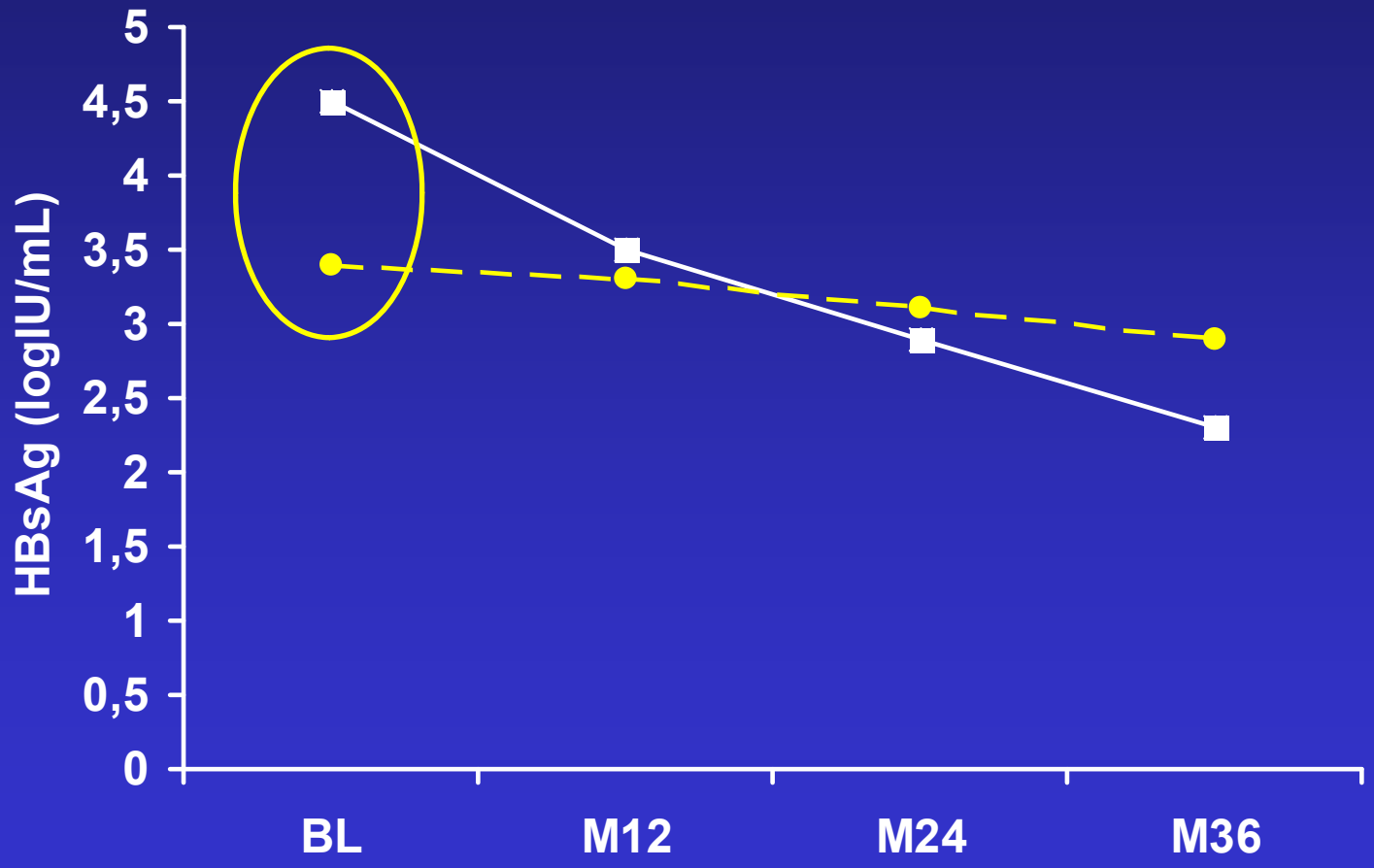


HBsAg Quantification in Patients Treated with NUCs



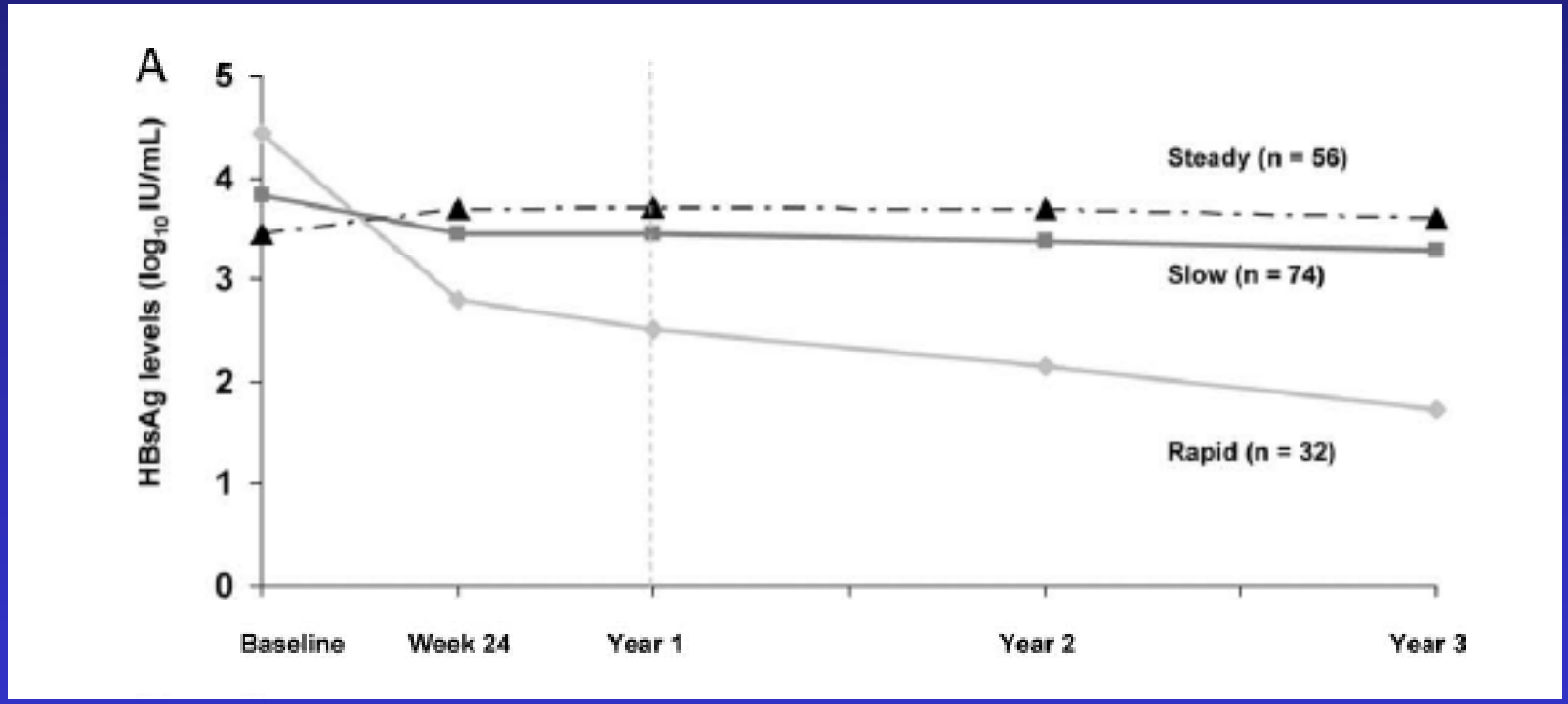
Moucari et al. AASLD 2009

HBsAg Quantification in Patients Treated with NUCs



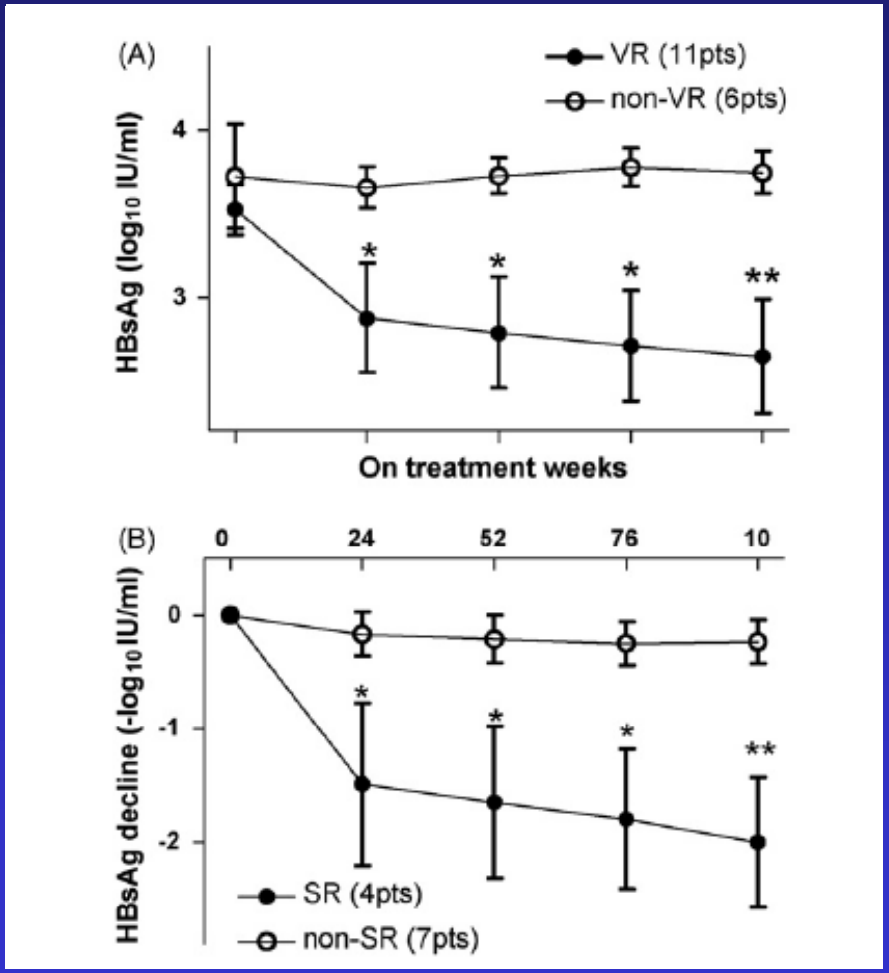
Moucari et al. AASLD 2009

HBsAg Quantification in Patients Treated with NUCs



Wursthorn et al. Hepatology 2010

HBsAg Decline: On Treatment (NUC)



HBsAg levels <2 log10 IU/ml at treatment week 104 were highly predictive of SR (i.e., HBV DNA <300 copies/ml, HBeAg seroconversion, ALT normalization) at 2 years off-treatment (positive predictive value [PPV], 93%; negative predictive value [NPV], 100%).

Cai et al. J Clin Virol 2010

CONCLUSION

- Qualitative serum HBsAg :
  - The hallmark of overt HBV infection
  - The closest to clinical cure outcome (clearance)

- Quantitative serum HBsAg :
  - Reflects the natural history of the disease
  - Predicts Response to IFN-based treatment
  - May Predict Response to NUC and help to tailor treatment duration