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HBsAg quantification to monitor patients

Michelle Martinot-Peignoux
Service d'Hépatologie Hôpital Beaujon
UMR 1149 inserm-Université Paris Diderot
Clichy-France

Inserm
Institut national
de la santé et de la recherche médicale

CRI
CENTRE de RECHERCHE
sur l'INFLAMMATION

HBsAg quantification is now a hot topic

Dev Biol Stand 1975;30:78-87
Standardized detection of hepatitis B surface antigen: determination of its serum concen
Gerlich W Thomseen R.

Digestion 1987;38(2)90-95
Detection of hepatitis B virus markers in sera of assymptomatic hepatits B sur
Hess G. Gerken G. MannsM, Meyer zum Büschenfelde K.-H.

Antiviral research 1994;23(34)251-257
Measurement of HBsAg to monitor hepatitis B patients treated with interferon
Jansen HL, Shalm SW.

Hepatology 2009;49:1151-1157
Early serum HBsAg drop: a strong predictor of sustained virological resp
Moucari R, Mackiewicz V, Lada O, Ripault MP, Castelnau C, Martinot-Peigno

Commercially available assays

1975 1987 1994 2011 2015

> 120 congress
> 500 articles in key journals

Significance of HBsAg in serum

The levels of serum HBsAg (qHBS):

- Reflect the balance between the virus and the host immune response.
- Dependent of the amount and transcriptional activity of cccDNA.
- *Increase*:
  - marker of new infection or reactivation
- *Decrease*
  - marker of efficient T cell immunity.

“ HBsAg ”

Natural History

Inactive carriers

Additional tool allowing to differentiate AgHBe negative patients with normal ALT and high risk of reactivation from inactive carriers.

The combination of HBsAg <1 000 IU/mL and HBV DNA ≤ 2 000 IU/mL allows identification of inactive carriers with 90% accuracy, 88% PPV

As effective as one year ALT follow-up

Brunetto et al. Gastroenterology 2010;139:483

Martinot-Peignoux et al. J Clin Virol 2013;58:401

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Identification of patients with high risk of reactivation that will benefit from therapy

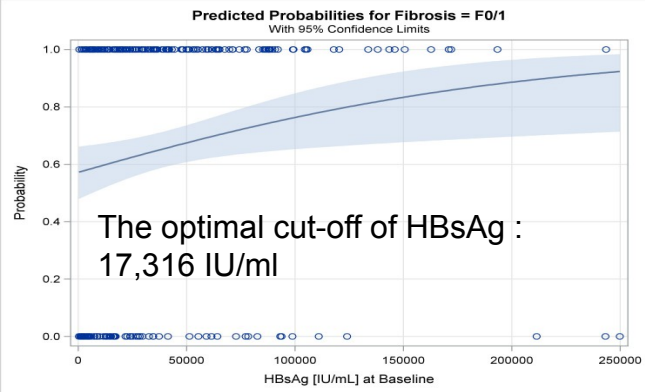
Brunetto et al. Gastroenterology 2010;139:483

Martinot-Peignoux et al. J Clin Virol 2013;58:401

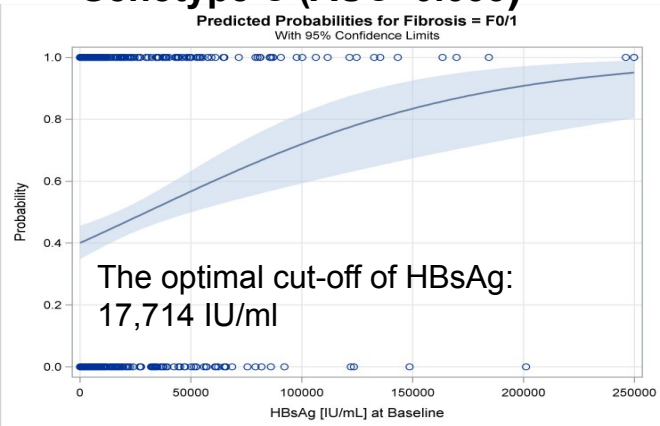
Prediction of fibrosis severity

HBeAg positive patients included in the Phase III (710) and NEPTUNE (465) trials.

Genotype B (AUC=0.683)



Genotype C (AUC=0.633)



Prediction score including
HBsAg ≤vs >17,500 IU/ml and Age < vs ≥ 30 years
created to reach accuracy:
85% identifying F0-F1; 95% identifying F0-F2

	Sensitivity	Specificity	PPV	NPV
F0-F1				
Phase III	39.5%	**87.7%**	**78.4%**	56.2%
Neptune	33.2%	**87.1%**	**75.9%**	51.6%
F0-F2				
Phase III	30.9%	**94.8%**	**96.8%**	21.0%
Neptune	27.3%	**95.5%**	**97.3%**	17.8%

Martinot-Peignoux et al. J Hepatol 2013;58:1089

Marcellin et al CGH 2014 on line

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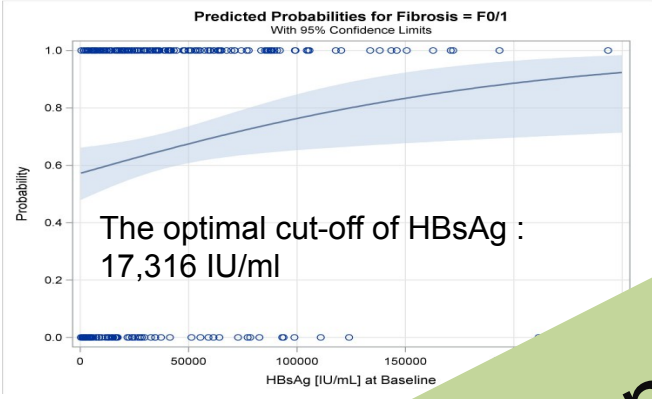
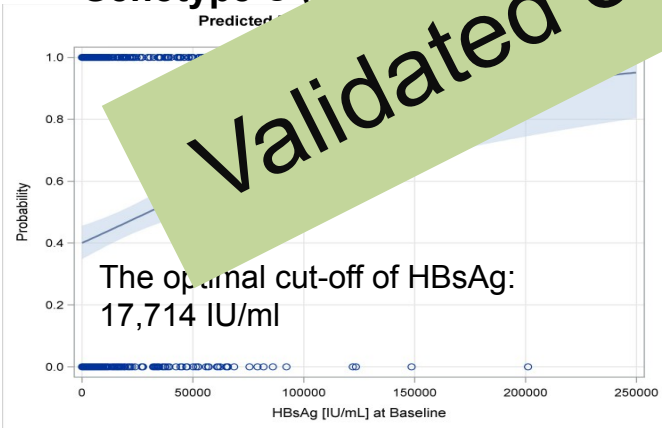


The optimal cut-off of HBsAg : 17,316 IU/ml

Genotype C (AU



The optimal cut-off of HBsAg: 17,714 IU/ml

Validated only for genotypes B and C

HBsAg [illegible] ding
[illegible] and Age < vs ≥ 30 years
[illegible] racy:
[illegible] 0-F 1; 95% identifying F0-F2

	Sensitivity	Specificity	PPV	NPV
F0-F1				
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Marcellin et al CGH 2014 on line

Prediction of outcome

The role of HBsAg levels in predicting clinical outcome of HBV carriers were widely investigated by 3 Taiwanese natural history studies

Study	Patients (n)	Phase	Follow-up (years)	Risk
REVEAL-HBV Lee et al . Hepatology 2013	3342	e + / e -	11,4	Minimal cirrhosis or HCC HBsAg < 1000 IU/ml HBV < 2 000 IU/ml OR(95%CI) 4.06(2.24-7.36)
ERADICATE-B Tseng et al . Gastroenterology 2012	2688	e + / e -	14,7	Minimal cirrhosis or HCC e – patients HBsAg < 1 000 IU/ml HBV DNA< 2 000 IU/ml OR(95%CI) 1.8(1.3-2.5)
SEARCH –B Tseng et al . Gastroenterology 2011	390	Early e -	7,4	HBs clearance at 6 years HBsAg < 100 IU/ml HBV DNA <200 IU/ml Accuracy 91%; NPV 99%

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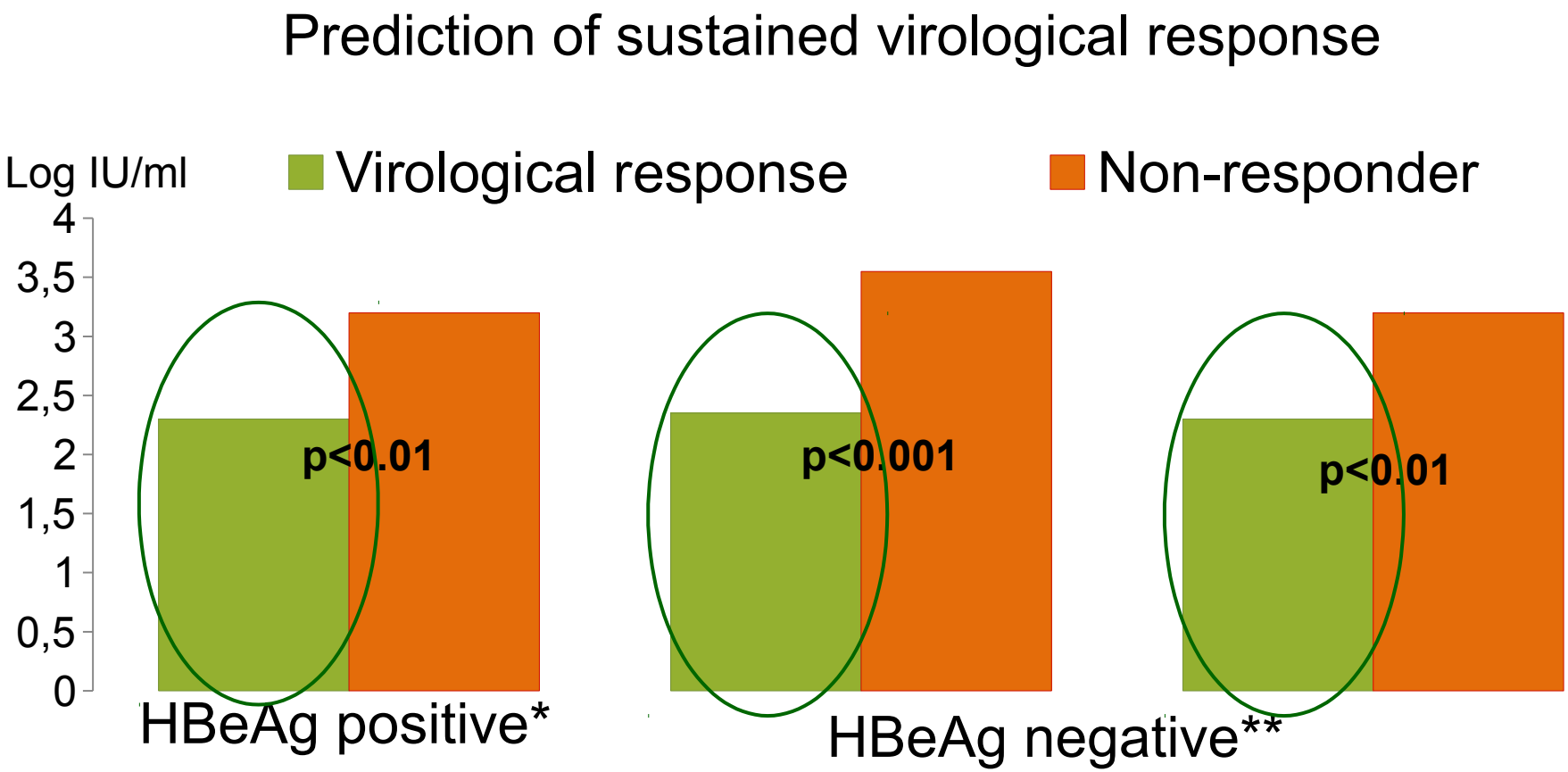
SEAR Tseng e Gastroen	90	Early e -	7,4	HBs clearance at 6 years HBsAg < 100 IU/ml HBV DNA <200 IU/ml Accuracy 91%; NPV 99%

Validated only for genotypes B and C

“ **HBsAg** ”

PEG-IFN therapy

Baseline HBsAg titer



*HBV DNA <2000 IU/ml + HBeAg negativation
6 months post-treatment

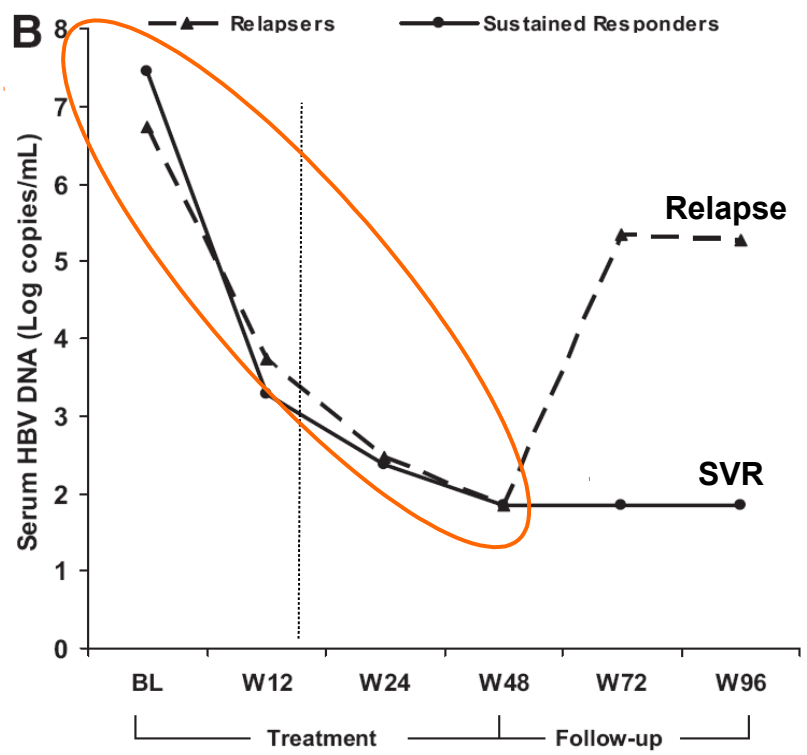
**HBV DNA <2000 IU/ml
6 months post-treatment

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

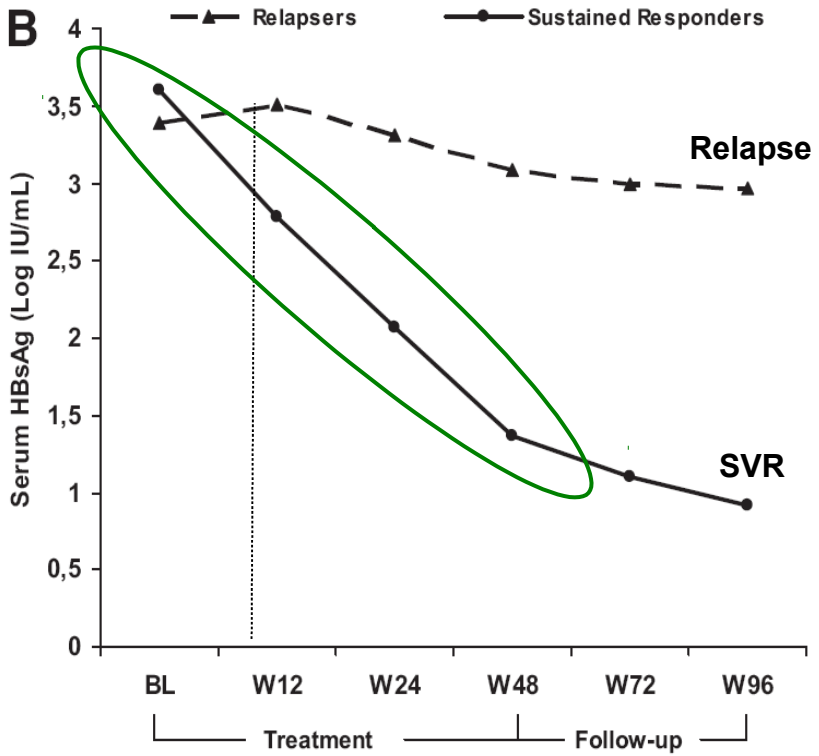
Piratvisuth T et al. Hepatol Int 2011
Takkenberg et al. Antiviral Therapy in Press.

On treatment kinetics

HBeAg negative patients receiving 48 weeks PEG-IFN



HBV DNA



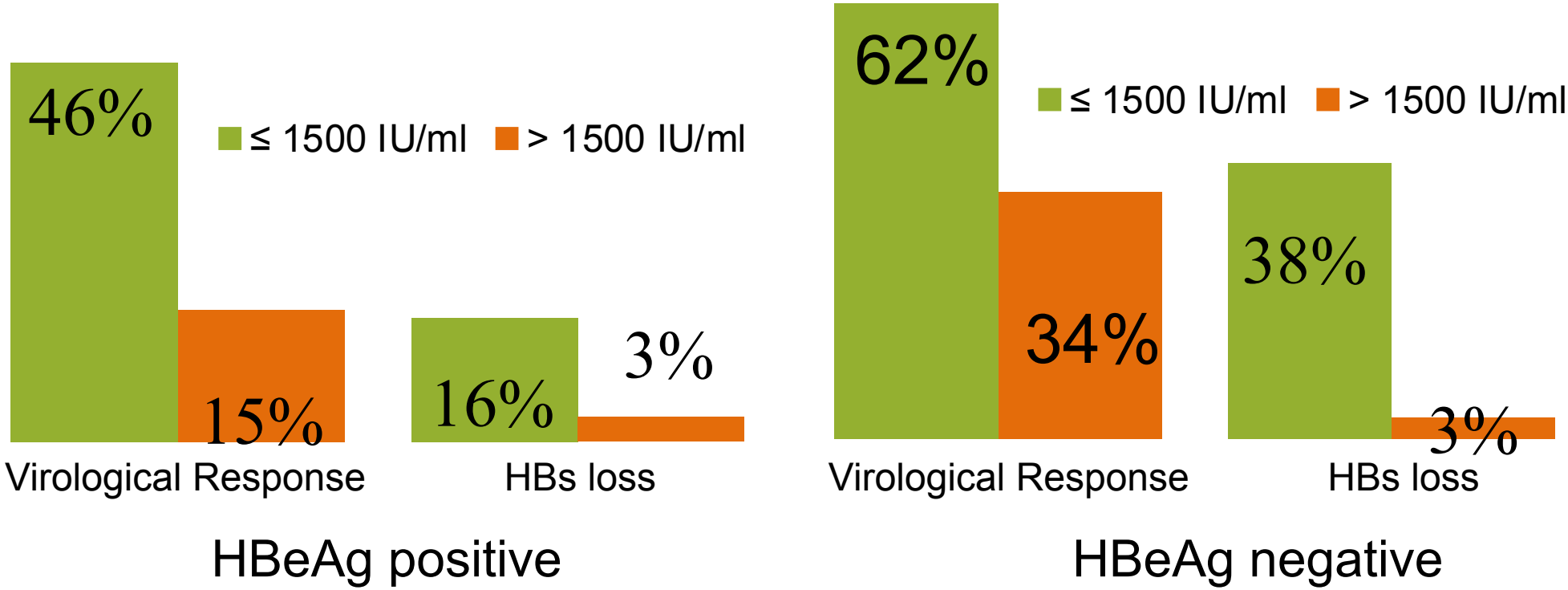
HBsAg

Moucari et al. Hepatology 2009;49:1151

During therapy (Week 12)

Real life S-Collate study

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

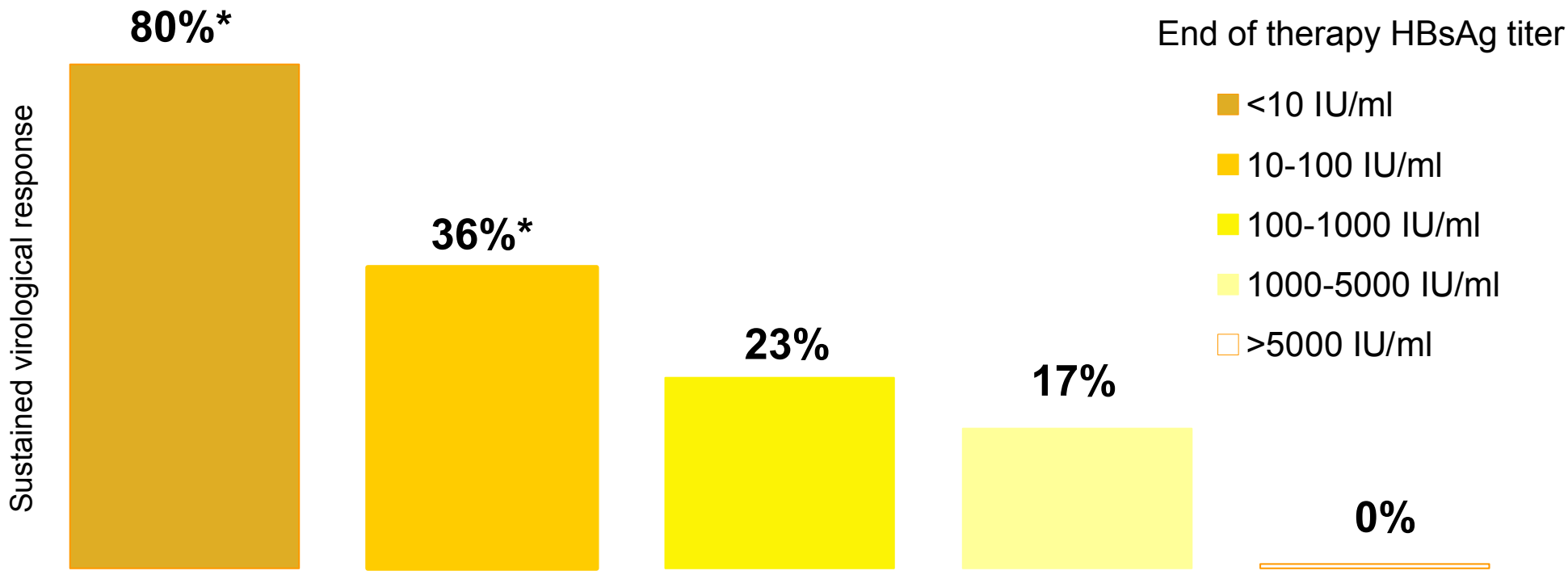


Marcellin et al. APASL 2013

When: end of therapy

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;49:1141

Conclusion PEG-IFN therapy

- Low baseline HBsAg level associated with response in both HBeAg positive-and-negative patients.
- Early HBsAg decline and level < 1 500 IU/ml at week 12 associated with probability of sustained virologic response and HBs loss.
    - Weeks 12 stopping rules:

treatment should be discontinued in the absence of any HBs decline combined with HBV DNA decline < 2log (NPVS 80-100%).

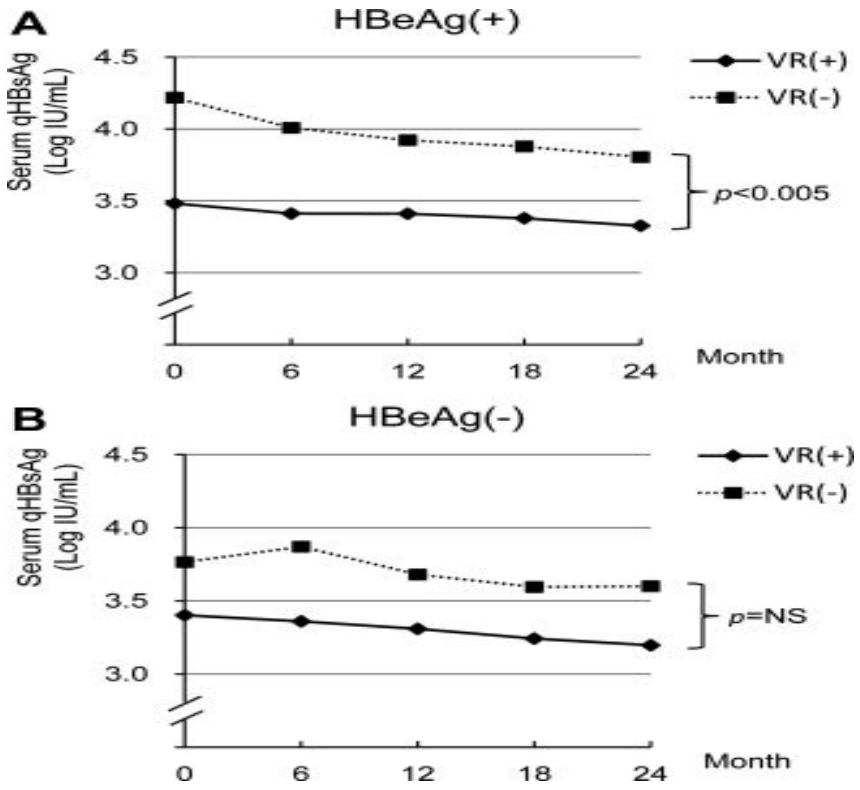
“ HBsAg ”

Oral therapy

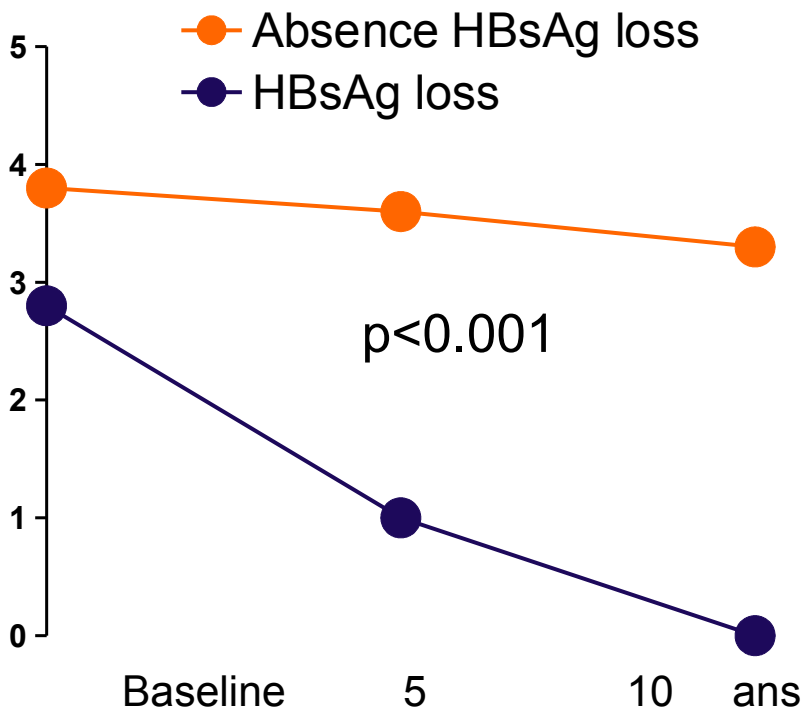
Baseline HBsAg titer

Prediction of virological response and HBsAg loss

Virological response



HBsAg loss



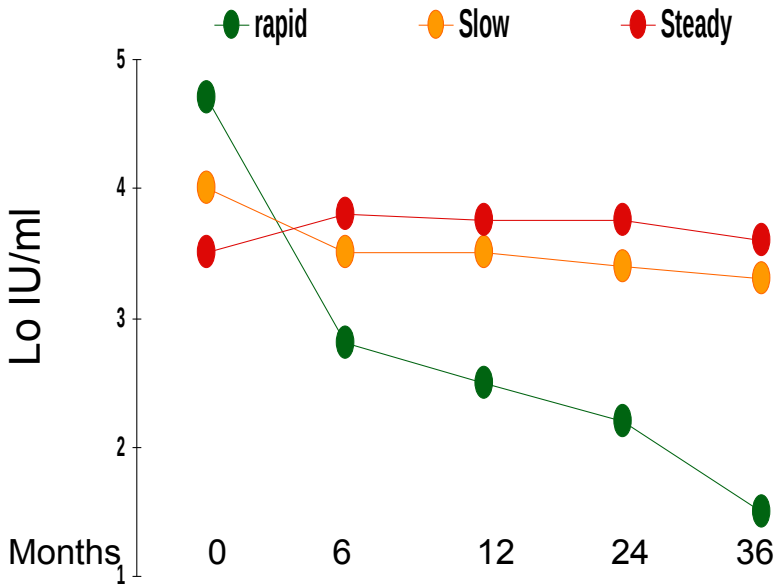
Lee ML. et al. Hepatology 2011

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

On treatment kinetics

HBsAg levels can help identify patients able to stop therapy

HBsAg decline patterns during therapy



Rapid decline associated with HBsAg clearence

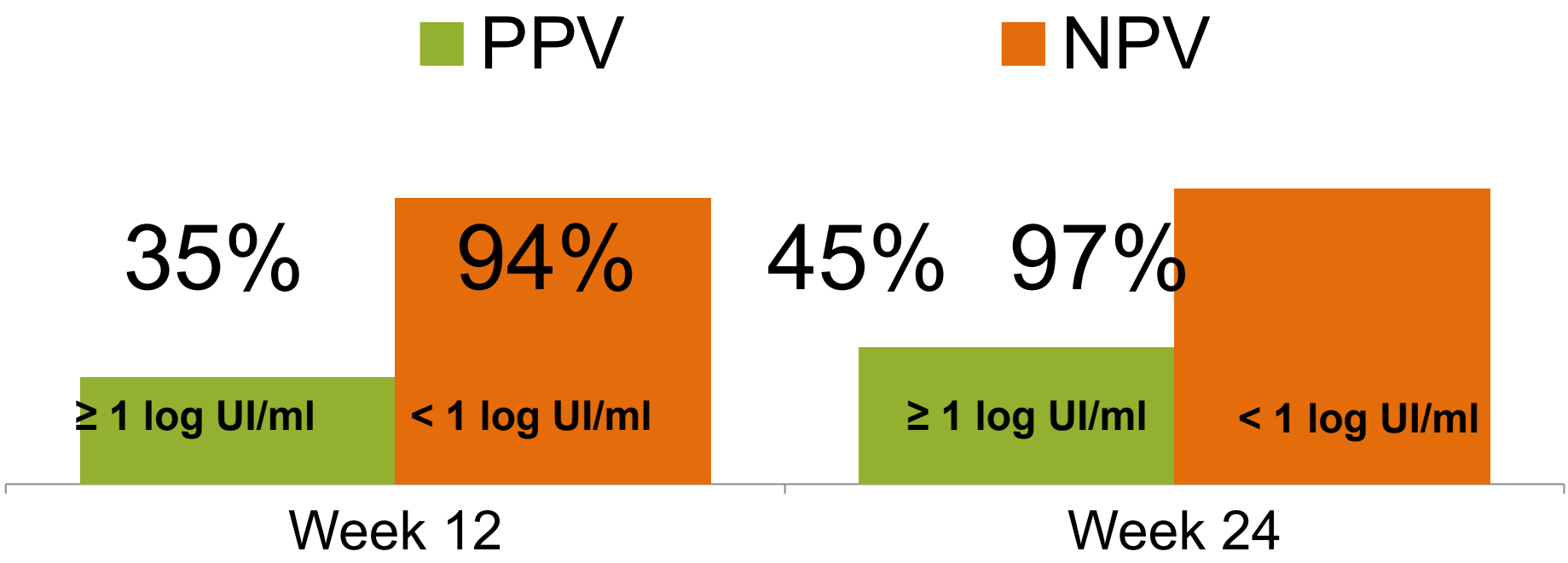
Decline year 1	Patients (162)	HBsAg clearance at 3 years
Rapid > 1 log	20% (32)	25%
Slow < 1 log	46% (74)	1.4%
Steady	34% (56)	0%

Patients with rapid decline who clear HBsAg may be able to stop therapy

Marcellin et al.N Engl J Med 2008 Wursthorn et al. Hepatology 2010 Heathcote et al. Gastroenterology 2011

During therapy

HBeAg positive patients receiving ADV and/or TDF (103 study)
Prediction of HBs loss



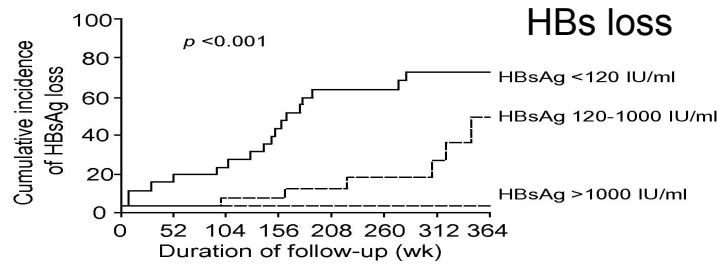
Marcellin et al. J Hepatol 2014;61:1228

Post-treatment outcome

HBsAg levels at treatment cessation predict HBV relapse and HBs loss

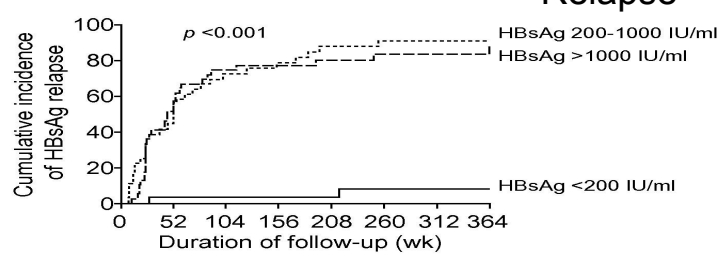
	On treatment decline	End of treatment	Accuracy
Chan et al. AVT 2011			
SVR	≥ 2 log IU/ml	≤ 2 log IU/ml	PPV 100%
Relapse	≤ 1 log IU/ml	> 2 log IU/ml	NPV 100%
Cai et al. JCV 2010			
SVR	≥ 1 log IU/ml	≤ 2 log IU/ml	PPV 79%
Relapse	< 1 log IU/ml	> 2 log IU/ml	NPV 86%
Liang et al. APT 2011			
SVR		≤ 2 log IU/ml	PPV 90%
Relapse		> 2 log IU/ml	NPV 70%

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

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

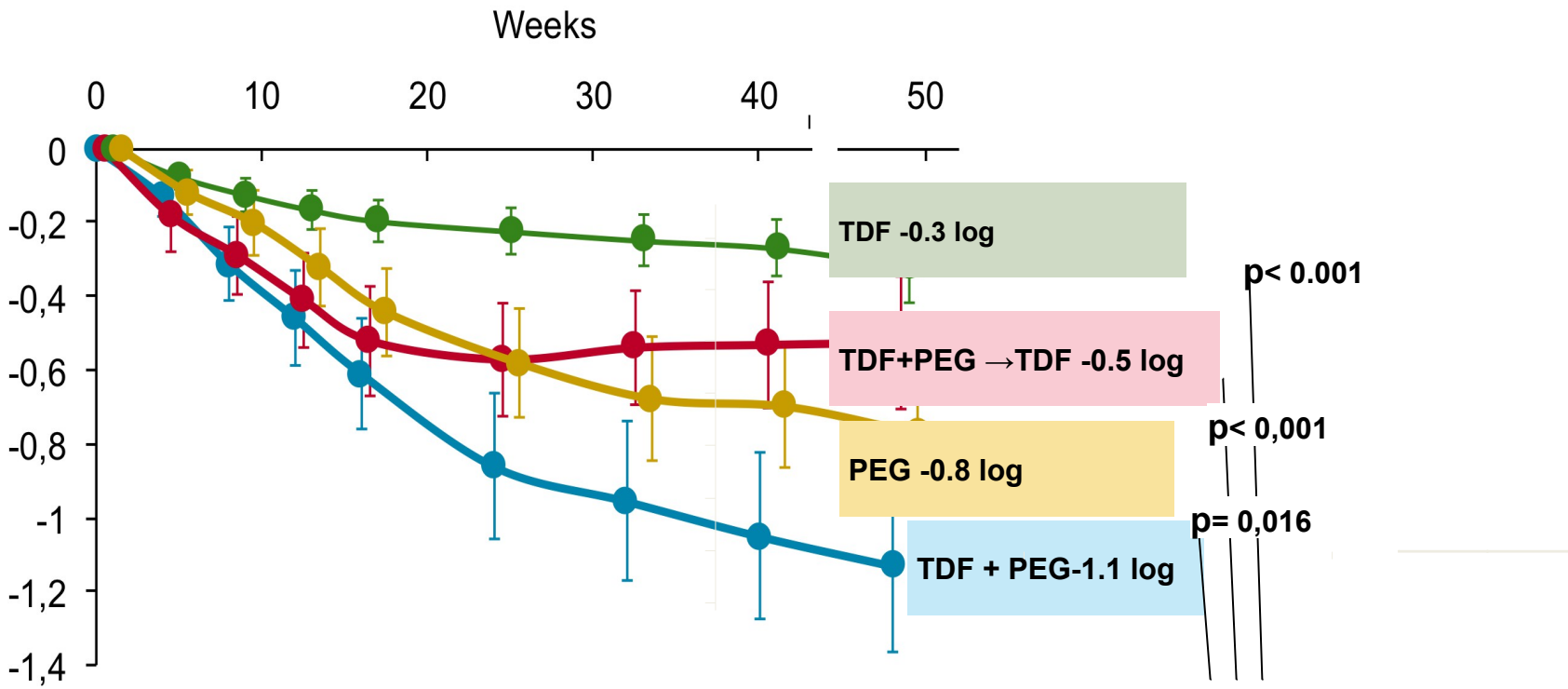
“ HBsAg ”

Combination therapy

Combinaison or Add-on

Controlled study 740 patients

HBeAg + or – ADN VHB > 2 000 UI/ml, Changes in HBsAg levels at week 48



HBsAg steeper decrease in patients receiving the combinaison TDF plus PEG-IFN

Marcellin P, France, AASLD 2014, Abs. 193

Conclusion oral therapy

- HBeAg positive patients

Low baseline HBsAg level, a rapid decrease (>1 log) associated with higher chance of HBs loss.

- HBeAg negative patients

Low end of treatment levels (< 100-500 IU/ml) associated with higher probability of sustained virologic response and HBs loss.

Summary

HBsAg quantification can complement HBV DNA to optimize the management of chronic hepatitis B patients

More data are needed, especially studies from western countries, to confirm these findings and the role of HBV genotypes.

There is needs for better definition of HBsAg decline and indentified time points with best predictive fit for response and likelihood of HBs loss.

Serum HBsAg titer in clinical setting:

Take home message

- ✓ Correlates with cccDNA in liver tissue
- ✓ Reflects immune control and clinical stages
- ✓ Identifies true inactive carriers
- ✓ Discriminates moderate from severe fibrosis
- ✓ Predictor of cirrhosis and HCC development
- ✓ PEG-IFN: early prediction of non-response

Take home message

HBsAg quantification in clinical setting:

- ✓ Correlates with cccDNA in liv
- ✓ Reflects immune cont inical stages
- ✓ Identifies true in arriers
- ✓ Discri moderate from advanced fibrosis
- tor of cirrhosis and HCC development
- PEG-IFN: early prediction of non-response
- ✓ NAs: allows treatment discontinuation ?

Needs to be confirmed for all HBV genotypes

References: HBsAg quantification to monitor patients

1. Martinot-Peignoux et al. J Clin. Virol. 2013;58:401
2. Martinot-Peignouxet al. J Hepatol. 2013;58:1089
3. Martcellin et al. CGH 2015 on line
4. Tseng et al. Gastroenterology 2012;142:1140
5. Moucari et al. Hepatology 2009;49:1151
6. Rijckborst et al. J Hepatol. 2012;56:1006
7. Marcellin et al. J Hepatol 2014;61:1228
8. Wursthorn et al. Hepatology 2010;52:1611
9. Chen et al. J Hepatol 2014;61:515
10. Martinot-Peignoux et al. Liver Intern. 2015;35(Suppl1):82