

Clinical applications of HBsAg quantification

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Do you perform HBsAg quantification during the follow up of

- Interferon treatment
- NAs treatment

Clinical case

Female , 35 yrs, chinese

- ALT 126 IU/L (N=40)
- HBeAg (-)
- HBV DNA = 200 000 UI/mL
- HBsAg = 6050 UI/mL
- Liver biopsy: A2 F2

Clinical Case

	D0	M6	Y1	Y3	Y3.5	Y5	Y7
ALT UI/ml	166	62	40	40	38	29	32
HBs Ag UI/ml	6050	5880	6288	5900	120	0	0
HBVDNA UI/ml	200000	<20	<20	<20	<20	<20	<20

ENTECAVIR 0.5mg/D

PEG-IFN

INTERFERON

Aim for **OFF-TREATMENT**
immune control and
HBsAg clearance

SUSTAINED RESPONSE
through Immunomodulatory
and antiviral mode of action

FINITE therapy

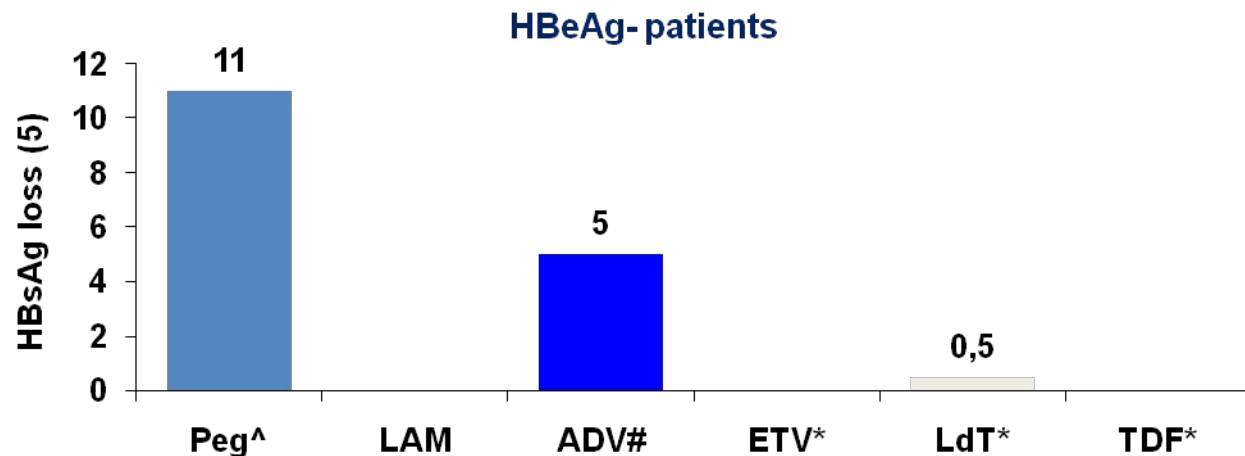
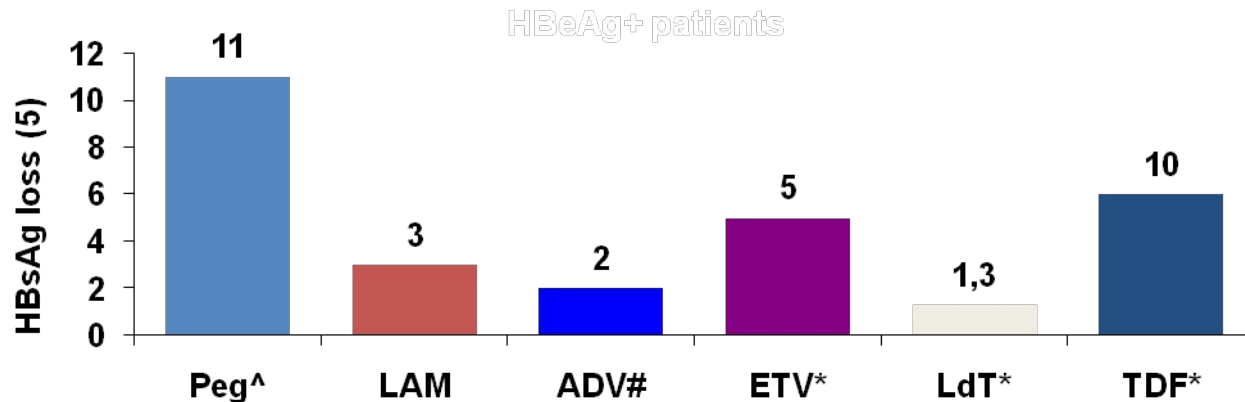
NAs

Aim for **ON-TREATMENT**
viral suppression

MAINTAINED suppression
through continued therapy

LONG-TERM therapy
(potentially life-long for some)

HBsAg loss after 1 and 2-5 ans of treatment



Peg = peginterferon

LAM = lamivudine

ADV = adefovir

ETV = entecavir

LdT = telbivudine

TDF = tenofovir

[^] 3-4 Years off Rx

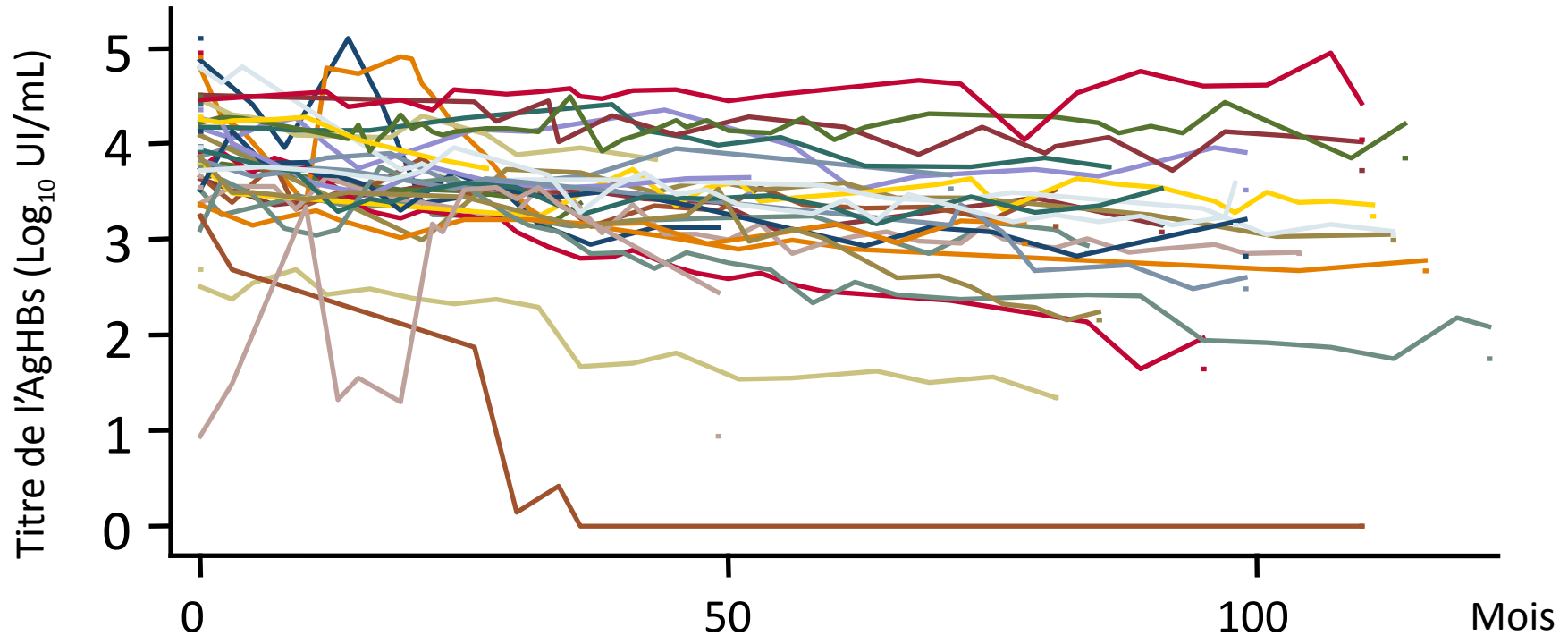
[#] 4-5 Years on Rx

1. Dienstag J, NEJM, 2008;359:1486-1500. 2. Buster EH, Gastro, 2008;135:459-467 3. Marcellin P, J Hepatol, 2008;48:suppl 2:S46. 4. Heathcote J, Hepatology, 2008;48(4)suppl1:376A. 5. Liaw Y, Gastro, 2009;136:486. 6. Heathcote J, EASL 2009

^{*} 2 Years on Rx

NAs

HBsAg decline in patients treated with NAs

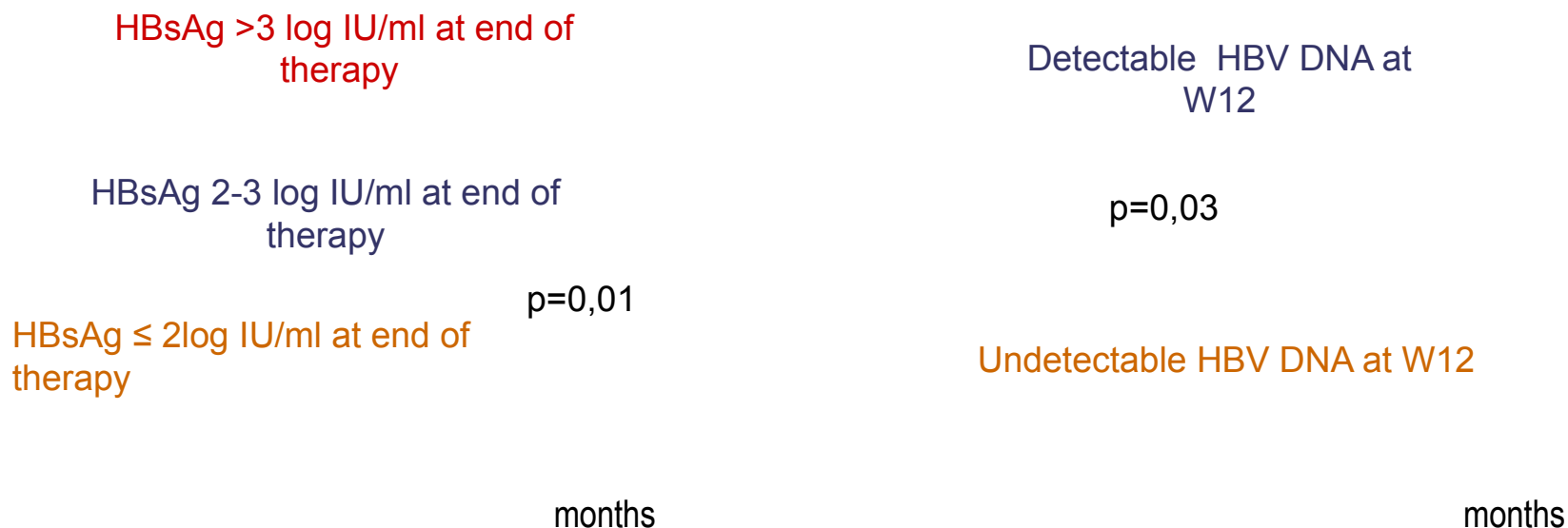


- Average decline/year 0.141 log₁₀
- Median time for HBs Ag loss = 52,1 years (Q1-Q3 : 24,5-117,6)

Prediction of outcome

Prediction of outcome after NUCs therapy discontinuation
(2 measurements with HBeAg or ADN negative)

Cumulative probability of virological relapse



HBsAg ≤ 2log IU/ml at treatment discontinuation is predictive of sustained response

- Define optimal HBsAg thresholds that enable treatment discontinuation with low risk of relapse

Off-Therapy Durability of Response to Entecavir in Hbe Ag negative chronic hepatitis Patients

- 95 patients (39 F4*) treated with ETV for 721 days (395- 1762) before discontinuation (APASL guidelines)
- Within 1year after stopping Relapse in 43 (45%) patients
23% vs. 53% according to

baseline HBVDNA < or >2X10⁵ UI/ML

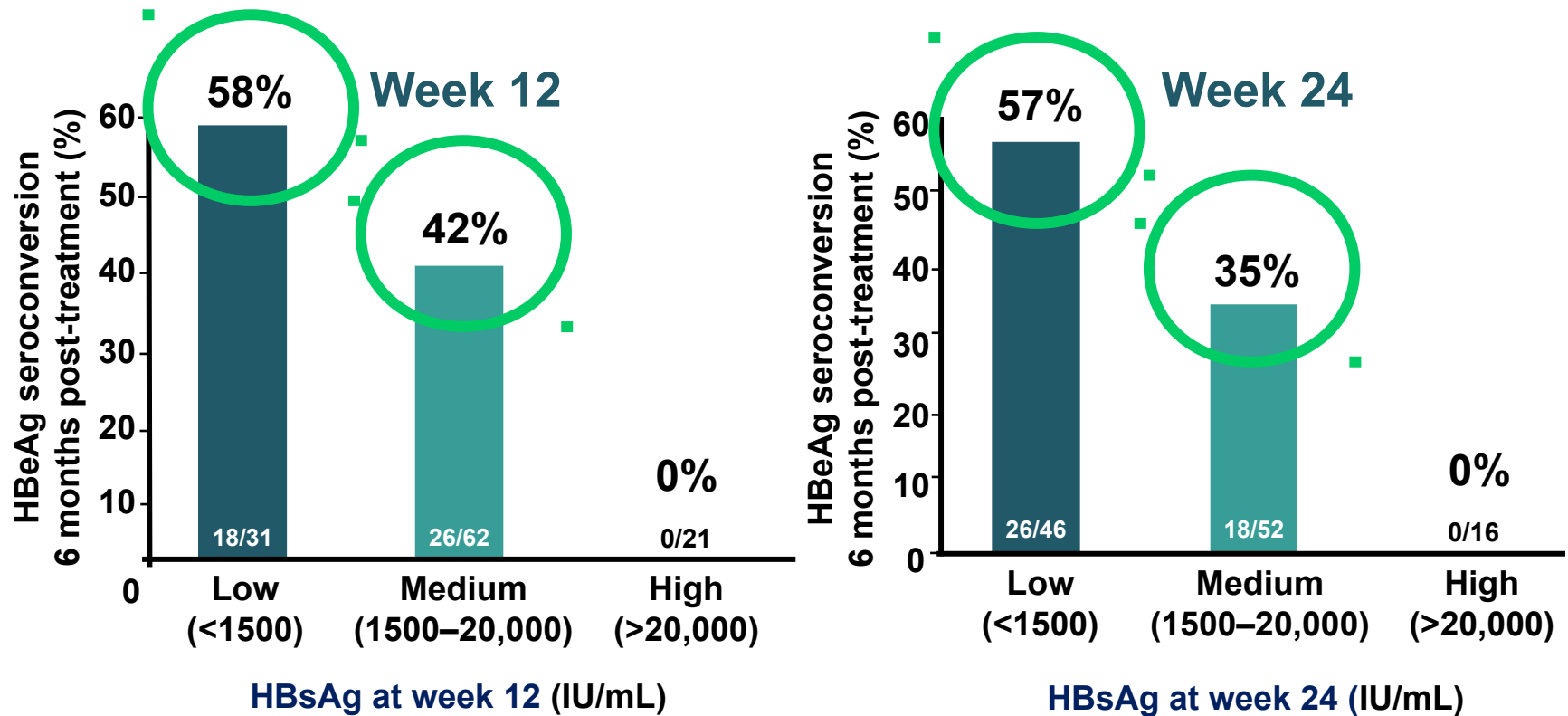
*1 decompensation

INTERFERON

Predicting response with HBsAg levels:
HBeAg-positive patients

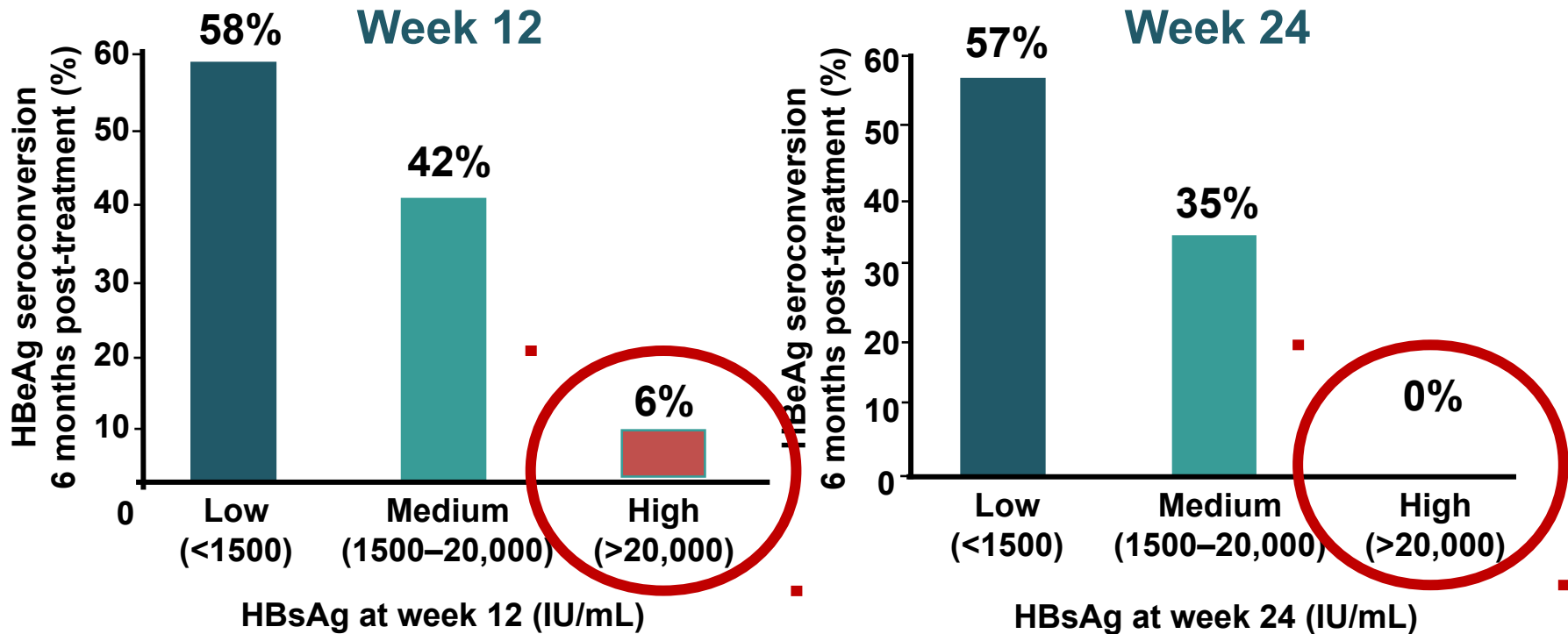
NEPTUNE confirms association of on-treatment HBsAg level with response to PEGASYS

HBeAg-positive patients treated with PEGASYS for 48 weeks



Motivate patients to continue

HBeAg-positive patients treated with PEGASYS for 48 weeks

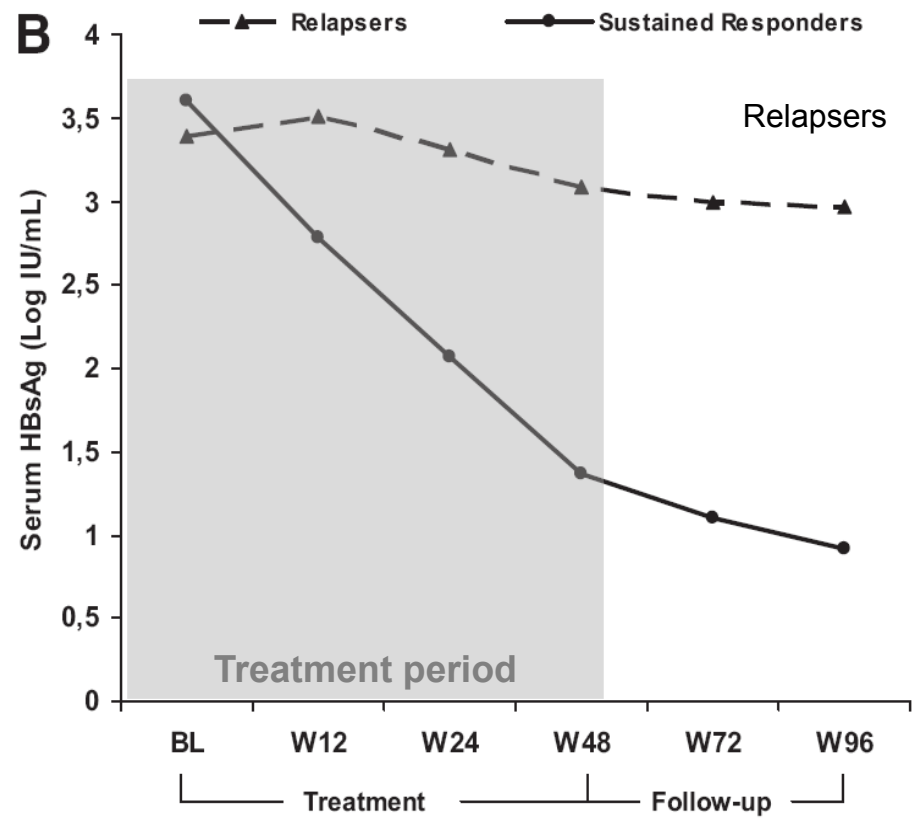
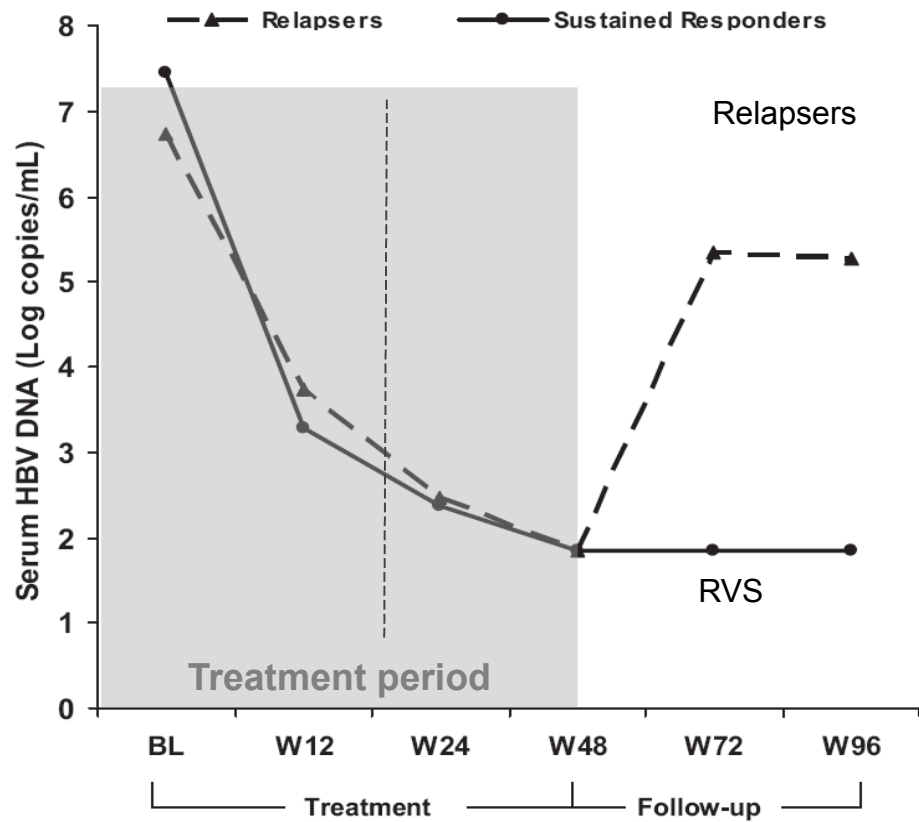


Potential early stopping rule

Predicting response with HBsAg decline:
HBeAg-negative patients

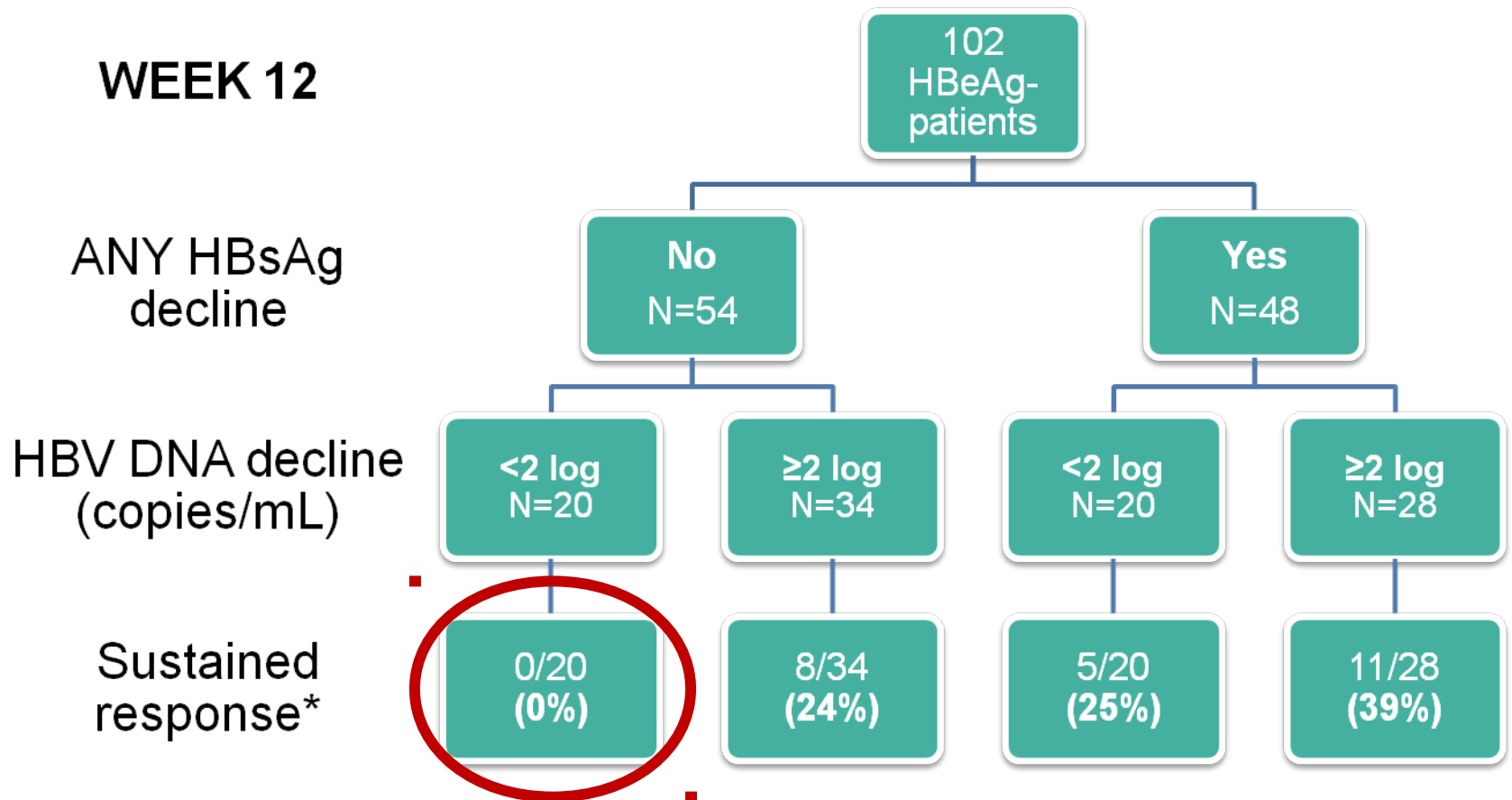
Early HBsAg kinetics between relapsers and responders

HBV DNA and HBsAg Kinetics



Combining HBsAg and HBV DNA decline for early identification of non-response

Analysis of 102 patients with available HBV DNA and HBsAg levels (80% genotype D)

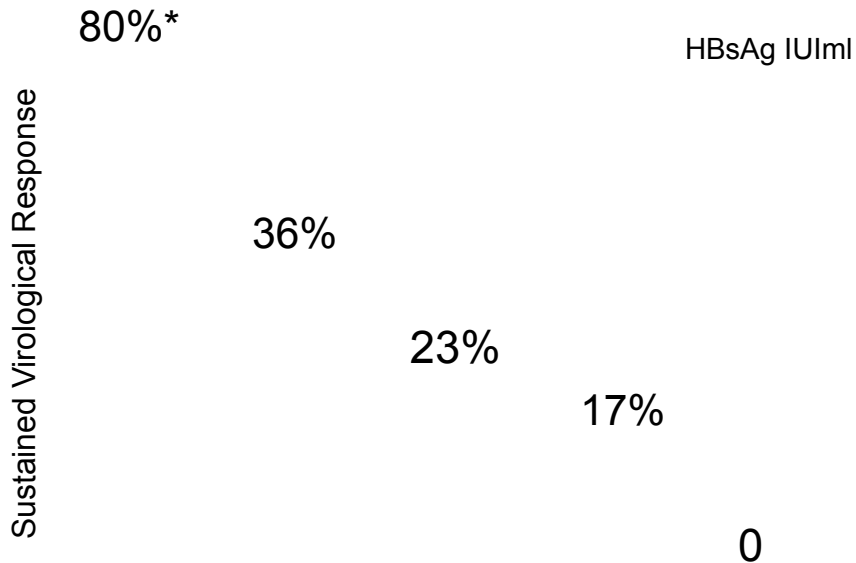


*HBV DNA <10,000 copies/mL and ALT normal 6 months post-treatment

Prediction at end of treatment

SVR and HBsAg loss

Week 48 HBsAg titer
Sustained Virological response



*52% HBsAg loss at 3 yers versus 2% if > 10 UI/ml

End of treatment HBsAg
threshold
Prediction of SVR

Genotype A	< 400 UI	PPV = 75% NPV = 100%
Genotype B	< 50 UI	PPV = 47% NPV = 100%
Genotype C	< 75 UI	PPV = 70% NPV = 80%
Genotype D	< 1000 UI	PPV = 75% NPV = 82 %

On-treatment kinetics of HBsAg serum
levels vary by HBV genotype

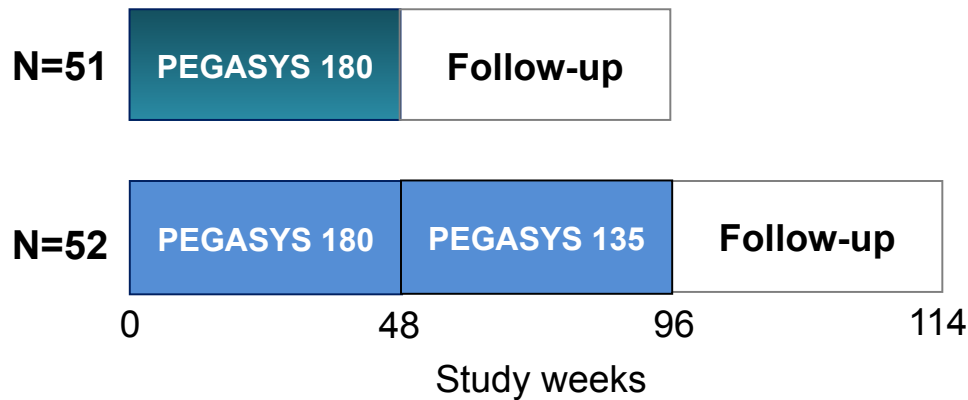
On-Treatment HBsAg as Marker of Response to PegIFN

120 HBeAg-patients treated with PEG-IFN α -2a during 48 sem

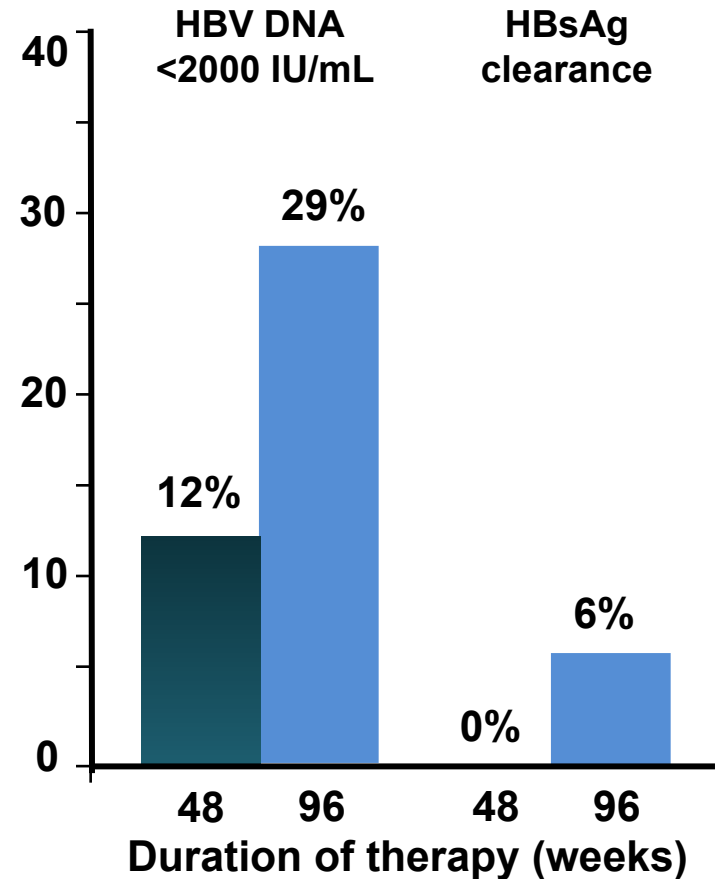
	Decline in HBsAg titers \geq 10 %		Percentage of patients	HBs Ag loss at 5 years (%)
	J0 à W24	W24 à 48		
Continious	yes	yes	51%	23%
Late	no	yes	16%	11%
Early	yes	no	5%	17%
Any decline	no	no	28%	0%

Extending duration of Pegasys treatment increase response rate in HBe negative patients: PegBeLiver study

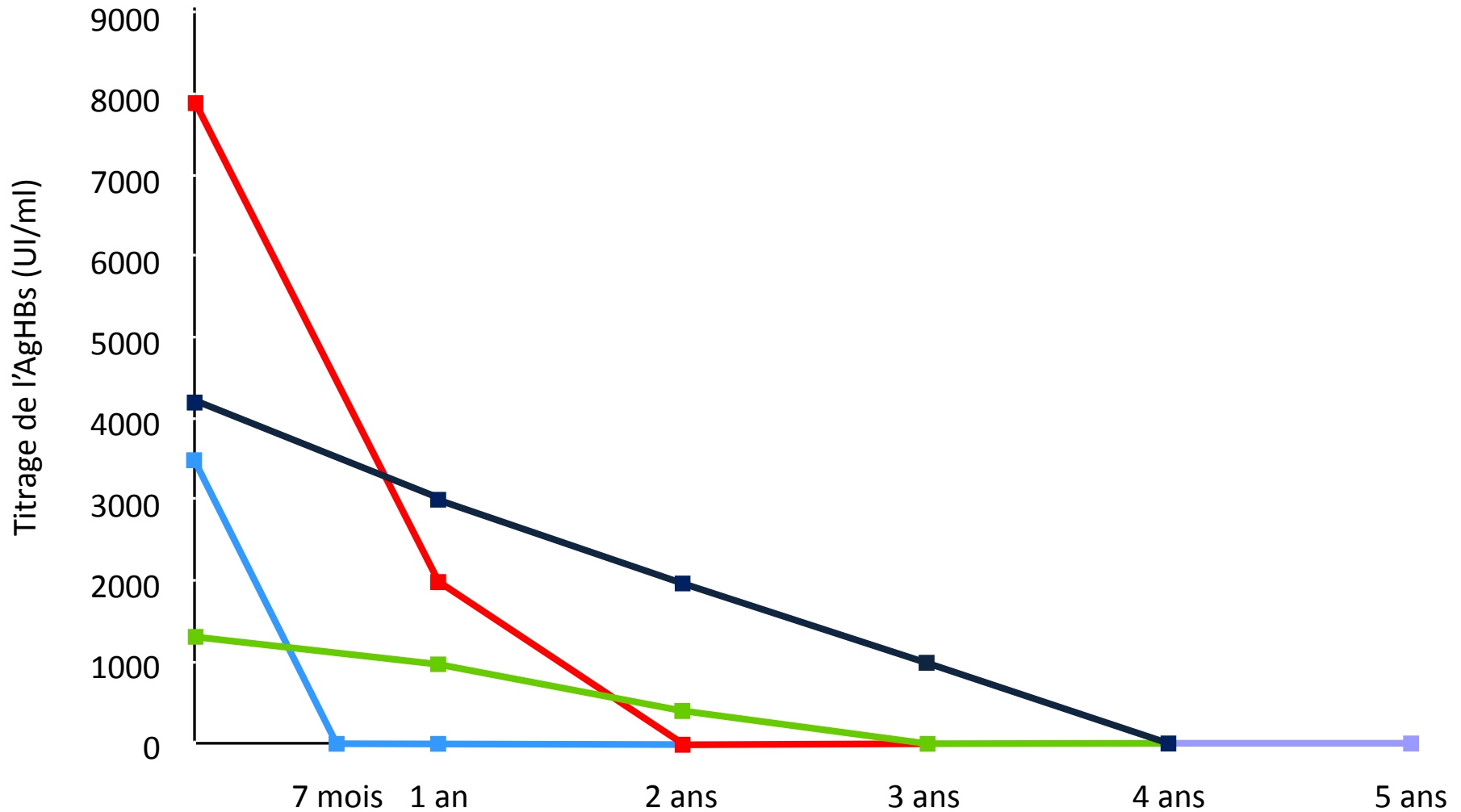
96% genotype D



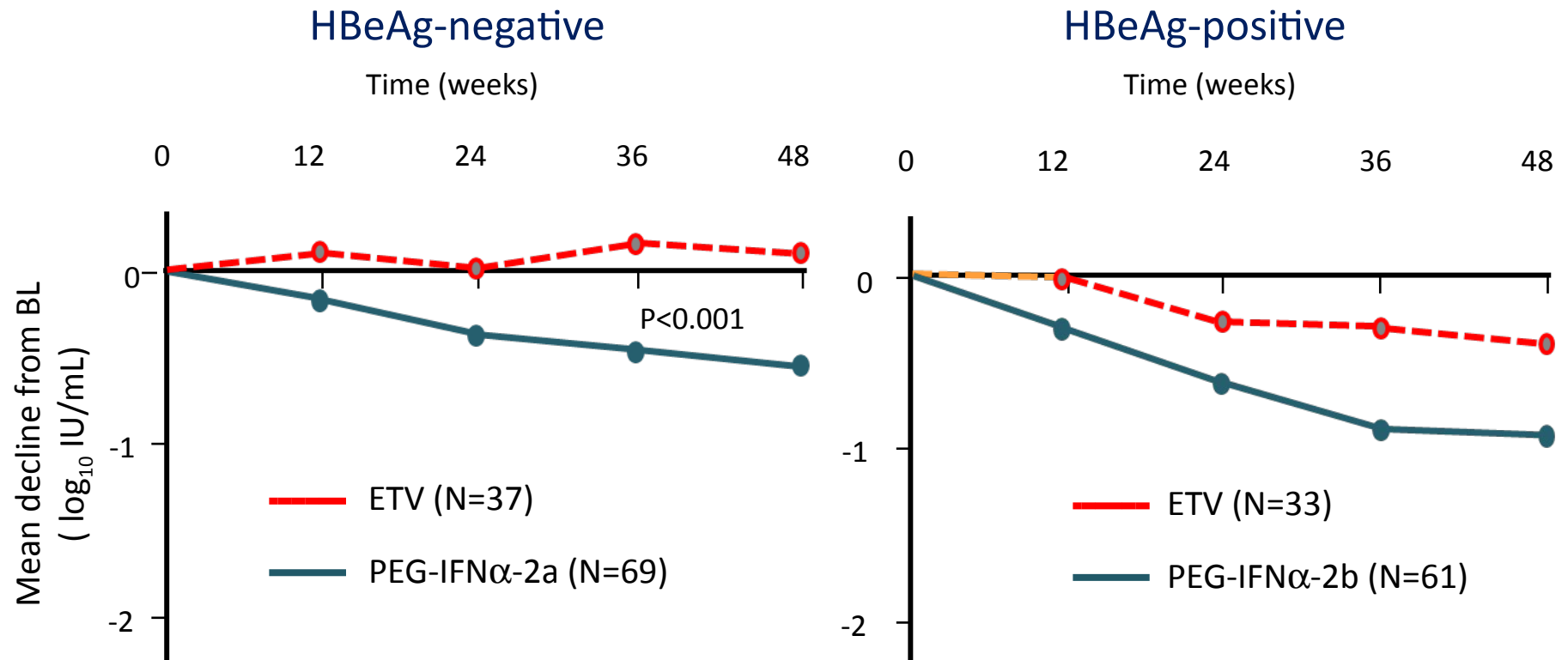
Patients with HBsAg <1000 IU/ml at week 48 had response rates of 25% vs 80%, depending on the treatment duration (48 vs. 96 weeks)



On-Treatment HBsAg as Marker of Optimal duration of PegIFN in patients with chronic hepatitis B+D

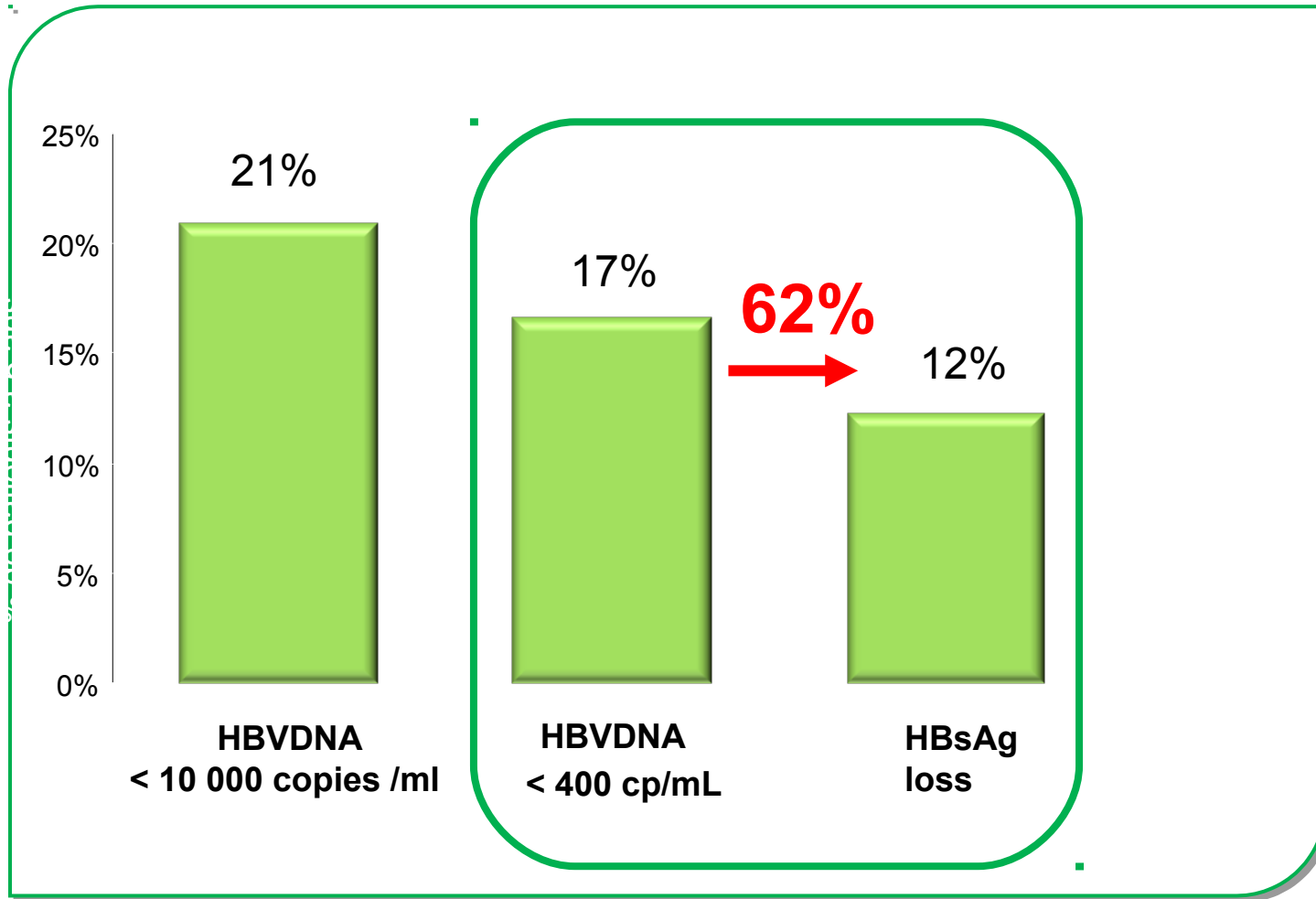


Overall decline in HBsAg is greater for PEG-IFN vs NAs



No significant decline of HBsAg with 1 year of ETV
in HBeAg-negative patients

PEGIFN 48 weeks : virological response at à 5 years



Reduction of HBV replication prolongs the early immunological response to IFN therapy

Marcellin P et al Hepatol Int .2013 ;7:88-97

Tan AT et al.J of Hepatol.2014; 60:54-61

Add-on of peg interferon to a stable nucleoside regimen led to loss of HBs Ag in chronic hepatitis HBe Ag negative patients



Denis Ouzan (1), Guillaume Pénaranda (2), Hélène Joly (1), Hacène Khiri (2), Philippe Halfon (2).

(1) Liver unit, Institut Arnauld-Tzanck, Saint-Laurent du Var; (2) Alphabio Laboratory, Marseille, FRANCE

10 HBe negative consecutive patients treated with NUCs during (3-7yrs)

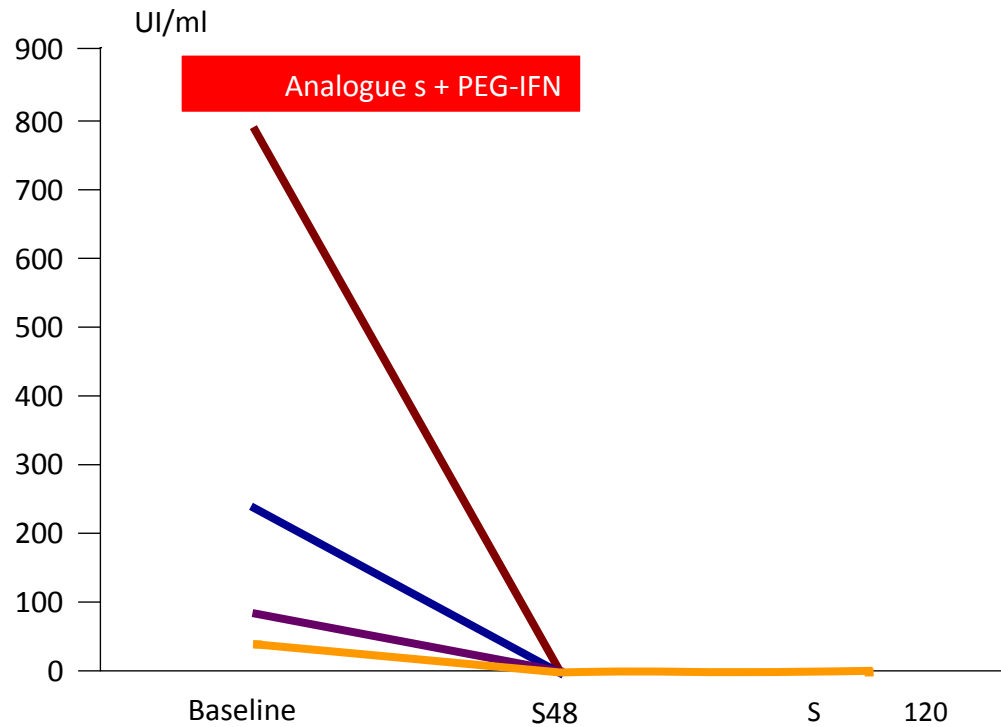
HBVDNA <20UI/ml in all patients since more than three years

These patients received additional peginterferon alpha2a treatment during 96 weeks

HBsAg titers (UI/ml) during add-on PEG IFN and 6 to 18 months later

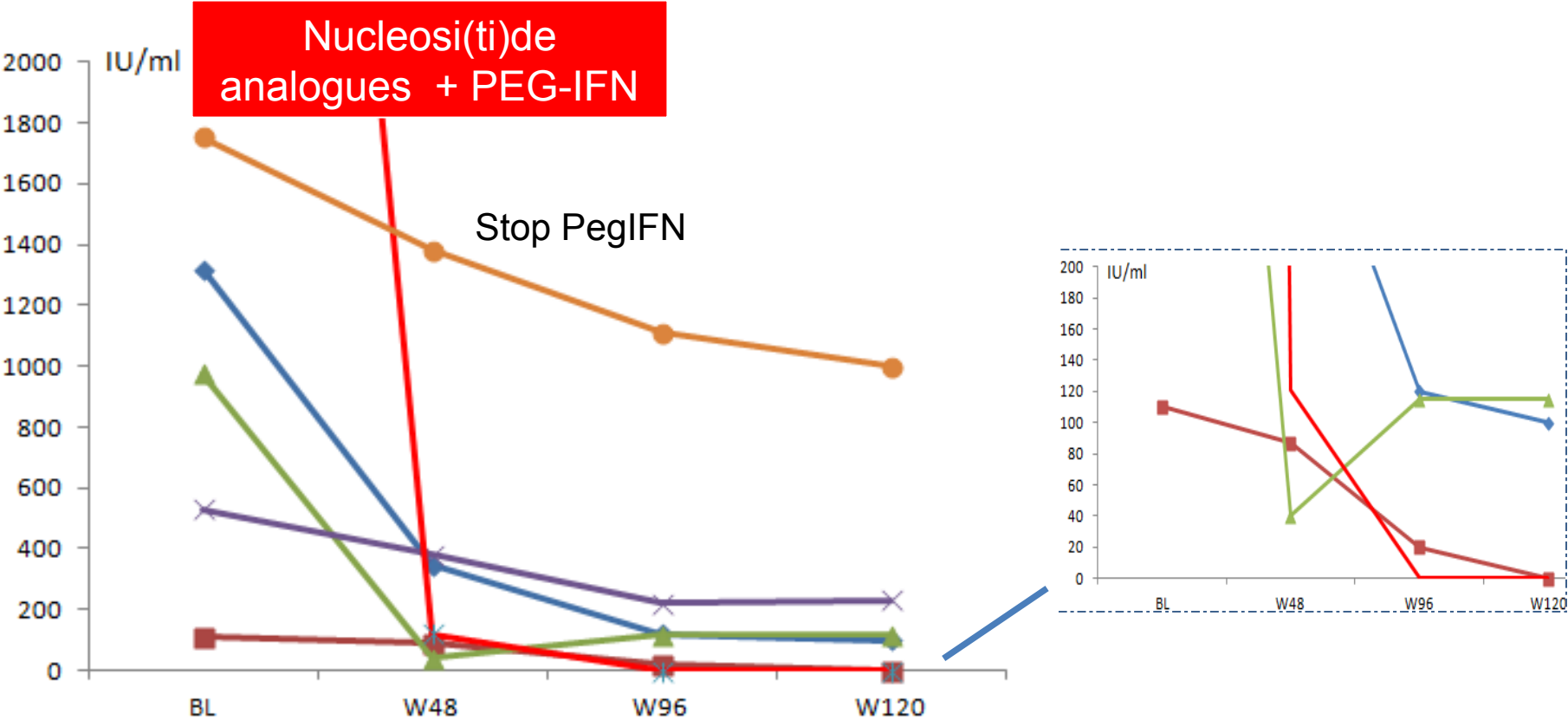
Metavir	NUCs treatment duration before PegIFN	J0	W48	W96	W120
A2F2	ADV (6 ans)	50	0	0	0
A2F3	LAM (8 ans)	123	0	0	0
A3F3	ADV (7 ans)	248	0	0	0
A1F1	ADV (6 ans)	789	0	0	0
A3F3	ADV+ETV (8 ans)	110	87	20	0
A2F2	ETV (3 ans)	6050	120	0	0
A2F4	ETV+ADV (6 ans)	530	380	120	130
A1F2	ADV+ETV (7 ans)	974	40	115	115
A1F1	LAM+TFV (3 ans)	1320	345	120	100
A2F4	LAM+ADV (8 ans)	1754	1380	1100	1000

HBs Ag titer decline in four patients who reached negative values at W48



➔ HBsAg loss in 4 patients : HBs Ag Séroconversion in 2 patients

HBs Ag titers decline in 6 patients who received (but one) Peg IFN treatment during 96 weeks



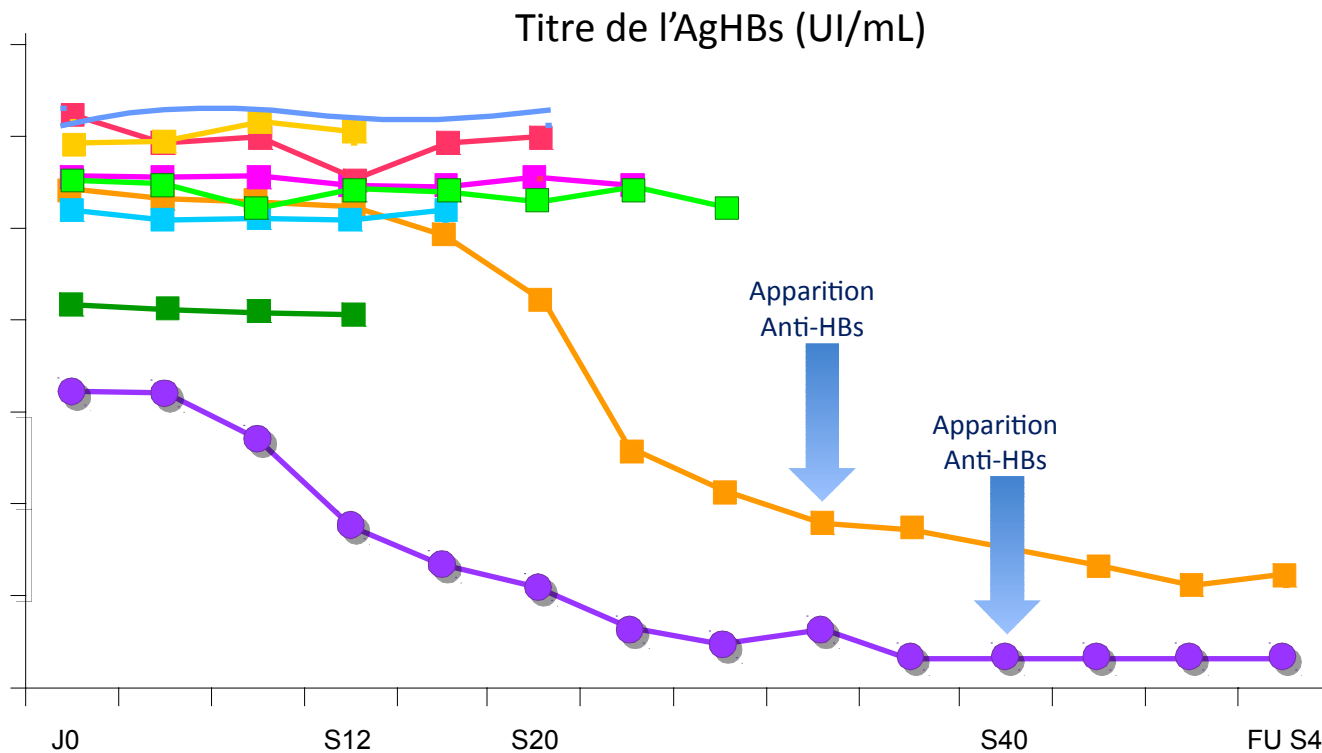
Add-on of peg interferon to a stable nucleoside regimen

- In patients, long term fully suppressed by NUCs, add-on of PegIFN, allows HBsAg loss in 6/10 patients.
- HBsAg titers decline constitute a useful tool which predicts the loss of HBsAg
- HBsAg titers decline may lead to define the optimal duration of IFN therapy.

Add-on of peg interferon to a stable nucleoside regimen

12 patients(HBeAg - : 9/12)

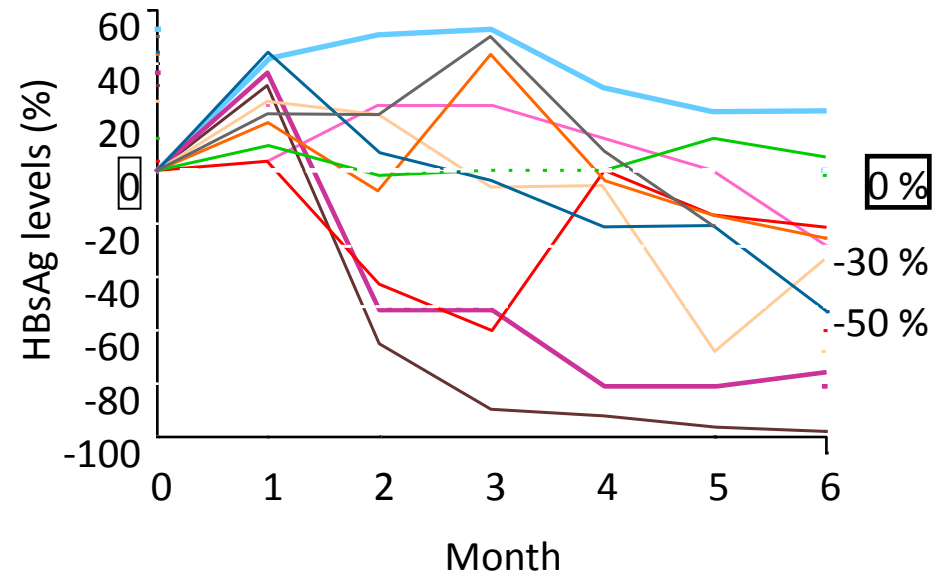
HBV DNA undetectable in all patients treated with NucS



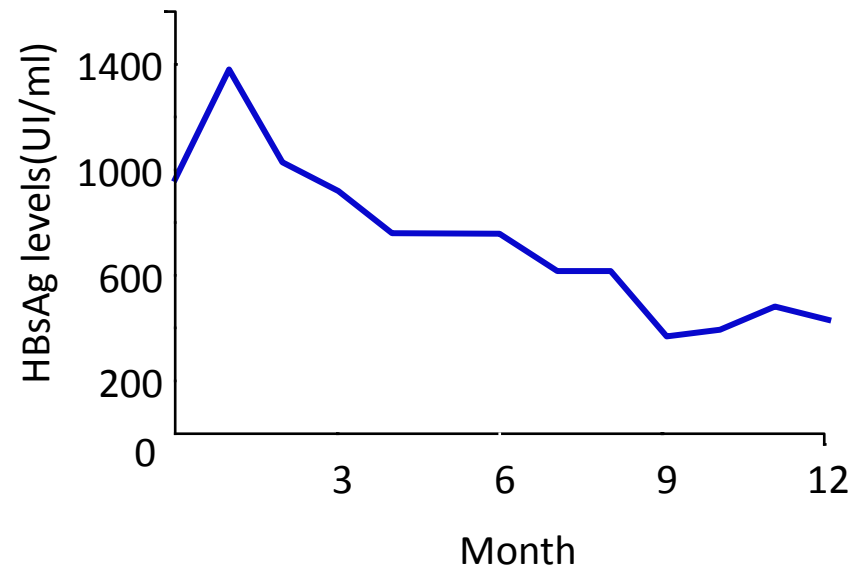
Add on PEGIFN improves HBs Ag kinetics in patients long term fully suppressed by NucS

- 12 patients(HBeAg - : 9/12)
- HBV DNA undetectable in all patients treated with NucS

HBsAg titers in 9 HBeAg-patients



HBsAg titers decrease in 5 patients HBeAg - treated more than 6 months



Add-on of peg interferon to a stable nucleoside regimen



30 centers

Pegasys 180 µg
48 weeks

Analogues 48
weeks

Analogues 96 weeks

Assesment of
HBsAg loss



NUCs

Randomisation



Analogues 144 weeks

≥ 1 an

*HBV DNA
undetectable

HBsAg quantification

- ✓ HBs Ag quantification has to be included in the follow up
of all patients treated for hepatitis B
- ✓ This assay together with HBVDNA predict treatment response, optimal duration of interferon treatment

HBsAg quantification

- ✓ A viral suppression can be provided today to all patients and it is the primary goal in clinical practice
- ✓ HBsAg loss became the next goal and depend of
 - HBs Ag quantification
 - Evaluation of new strategies : combination of antiviral and immune therapy

Review

**Hepatitis B surface antigen quantification:
Why and how to use it in 2011
A core group report**

Henry Lik-Yuen Chan, Alex Thompson, Michelle Martinot-Peignoux, Teerha Piratvisuth, Markus Cornberg, Maurizia Rossana Brunetto, Hans L. Tillmann,

Jia-Horng Kao, Ji-Dong Jia, Heiner Wedemeyer, Stephen Locarnini, Harry L.A. Janssen, Patrick Marcellin.

for the Good Practice in using HBsAg in Chronic Hepatitis B Study Group
(GPs-CHB Study Group)