Hepatitis B and Interferon

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- Assistance Publique – Hôpitaux de Paris, Service d'Hépatologie, Hôpital Cochin

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Disclosures

- Board: Gilead, Bristol-Myers Squibb
- Workshop or meeting invitation: Gilead, Bristol-Myers Squibb, Schering-Plough / MSD, Roche, Janssen, AbbVie, Mayoly-Spindler

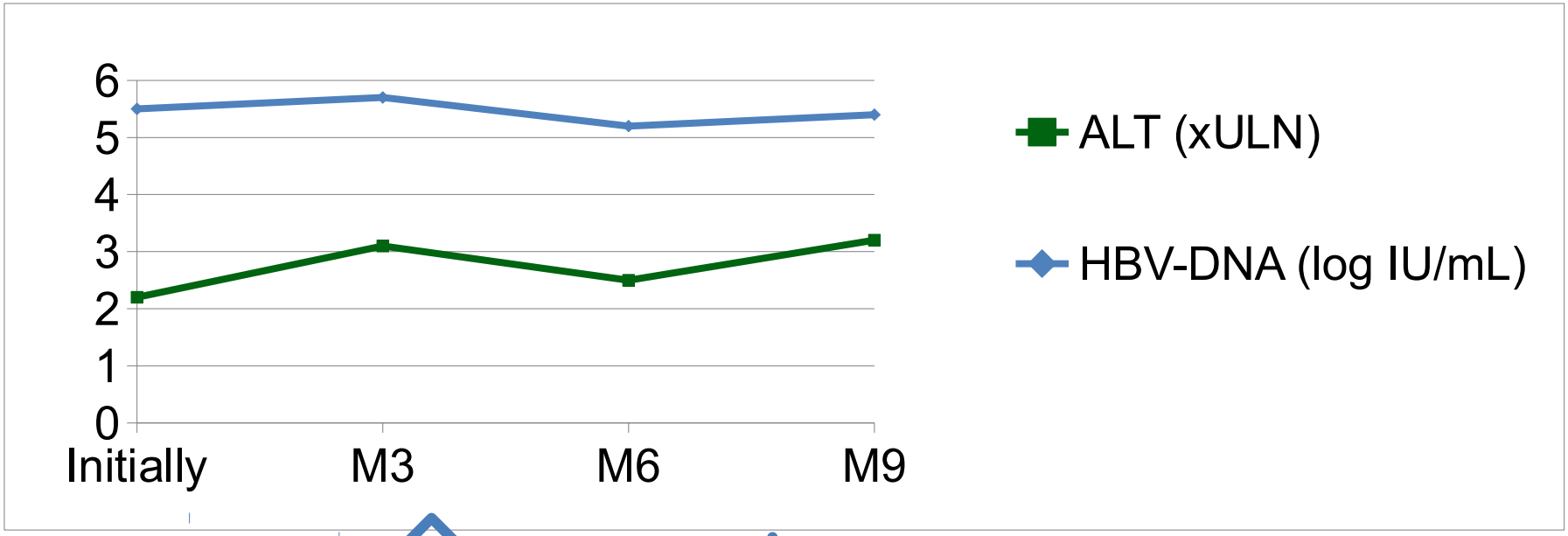
Mr H.

- Male 45 y.o., born in Cambodia
- Family screening (sister) ➔ HBsAg +
- No comorbidity, no medication, alcohol occasionally

- Normal physical examination; weight = 75 kg; height = 165 cm
- ASAT = 2.1 ULN; ALAT = 2.8 ULN; gGT = 2 ULN
- Total bilirubin and alkaline phosphat. N
- Platelets, INR and albumin = N. Creatinine and urine = N.
- HBeAg pos., HBV-DNA = 250.000 IU/mL
- HIV, HCV and HDV Ab. neg.
- Abdominal ultrasound: no dysmorphy, no sign of portal hypertension, liver and spleen size normal

ULN = upper limit of the normal

Mr H. (con't)



FibroScan® = 8,9 kPa
HBV genotype B

Wife: HBsAg –, antiHBs et antiHBc Ab +
Son: efficient vaccination
Sister followed for chronic hepatitis B
Parents in Cambodia

EASL Clinical Guidelines (J Hepatol 2012)

Patients with obviously active CHB: HBeAg-positive and HBeAg-negative patients with ALT above 2 times ULN and serum HBV DNA above 20,000 IU/ml may start treatment even without a liver biopsy (**B1**). In such patients, liver biopsy may provide additional useful information, but it does not usually change the decision for treatment. A non-invasive method for the estimation of the extent of fibrosis and most importantly to confirm or rule out cirrhosis is extremely useful in patients who start treatment without liver biopsy (**B1**).

➔ you decide to treat this patient

Question 1
You want to use PEG-IFNα2a for this patient What favorable baseline predictors of HBe-seroconversion for him?

A. ALT > 2 ULN
B. HBV-DNA < 8 log IU/mL
C. HBV genotype B (compared to D)
D. No predictors
E. All these factors

Response 1
You want to use PEG-IFNα2a for this patient What favorable baseline predictors of HBe-seroconversion for him?

A. ALT > 2 ULN

B. HBV-DNA < 8 log IU/mL

C. HBV genotype B (compared to D)

D. No predictors

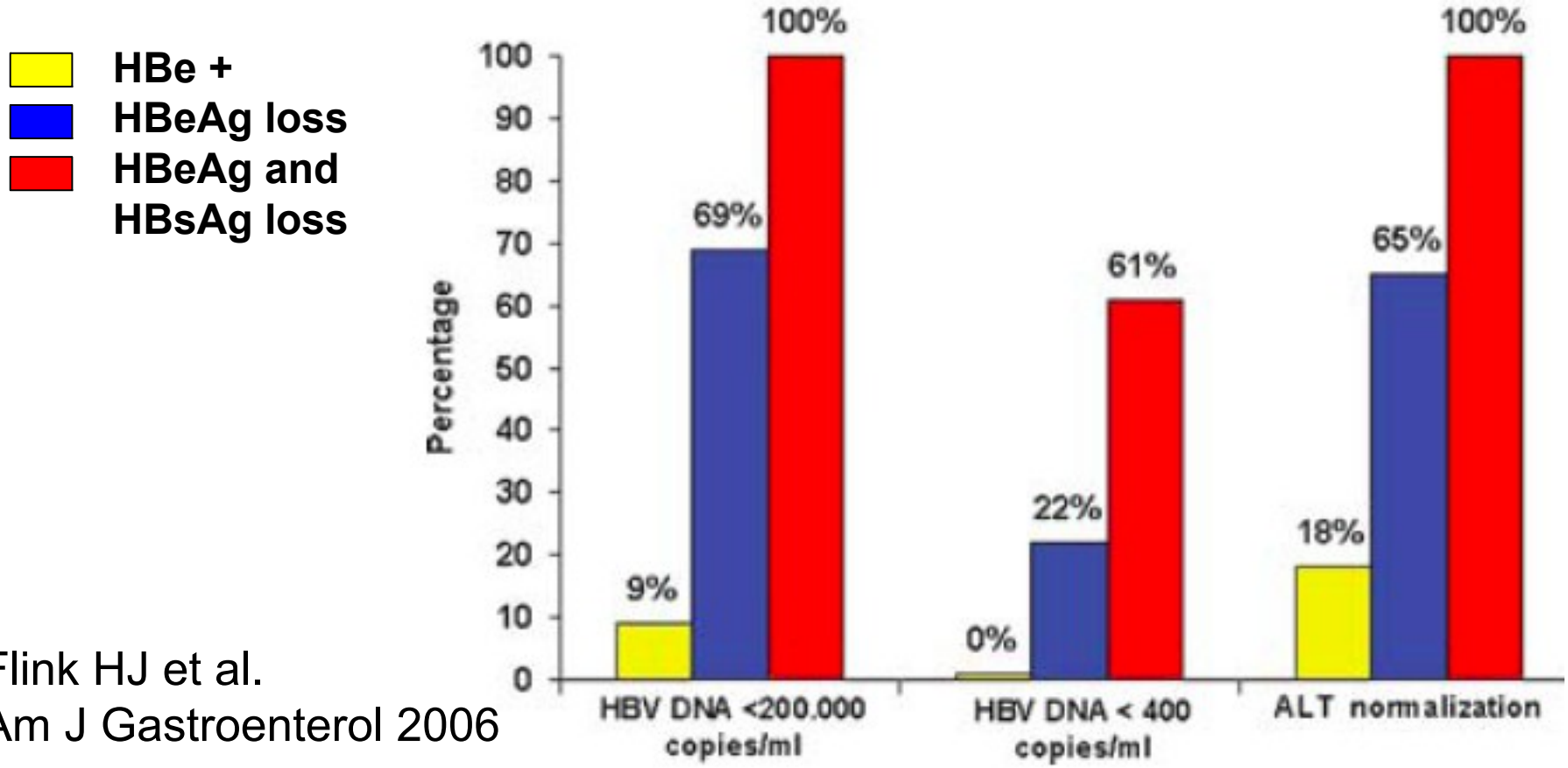
E. All these factors

EASL Clinical Guidelines (J Hepatol 2012)

In HBeAg-positive CHB, predictors of anti-HBe seroconversion are low viral load (HBV DNA below 2×10^8 IU/ml), high serum ALT levels (above 2–5 times ULN), HBV genotype and high activity scores on liver biopsy (at least A2) (**B2**). HBV genotypes A and B have been shown to be associated with higher rates of anti-HBe seroconversion and HBsAg loss than genotypes D and C, respectively, after treatment with PEG-IFN

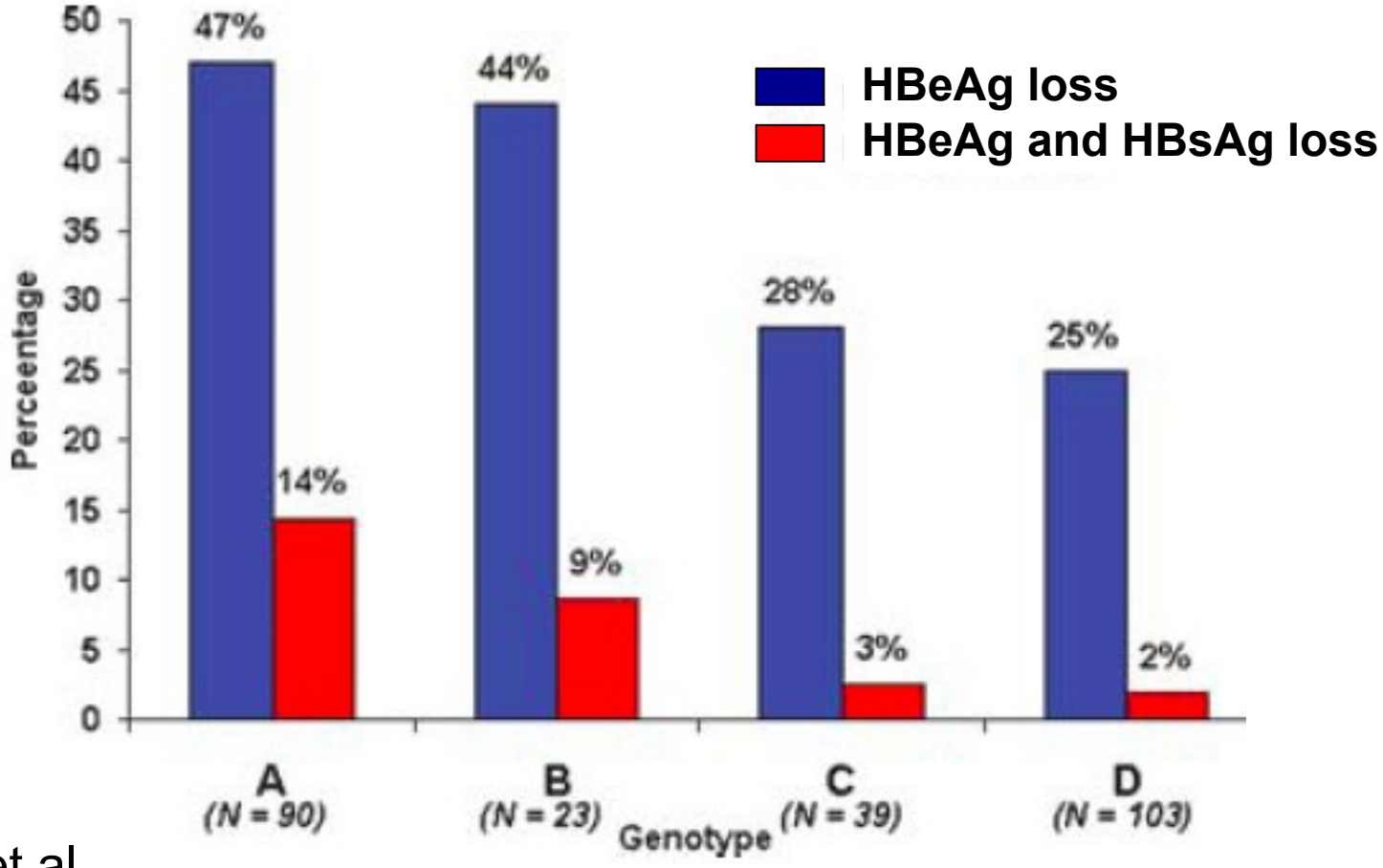
Virological and biological response to PEG-IFN

- 266 patients HBeAg + treated with PEG-IFNα2b (+/- Lamivudine) during 52 w
- Follow-up 26 w. post-treatment : 36% HBeAg loss and 7% HBsAg loss



Flink HJ et al.
Am J Gastroenterol 2006

Influence of HBV-genotype on virological response



Flink HJ et al.
Am J Gastroenterol 2006

Baseline factors associated with Sustained Response*

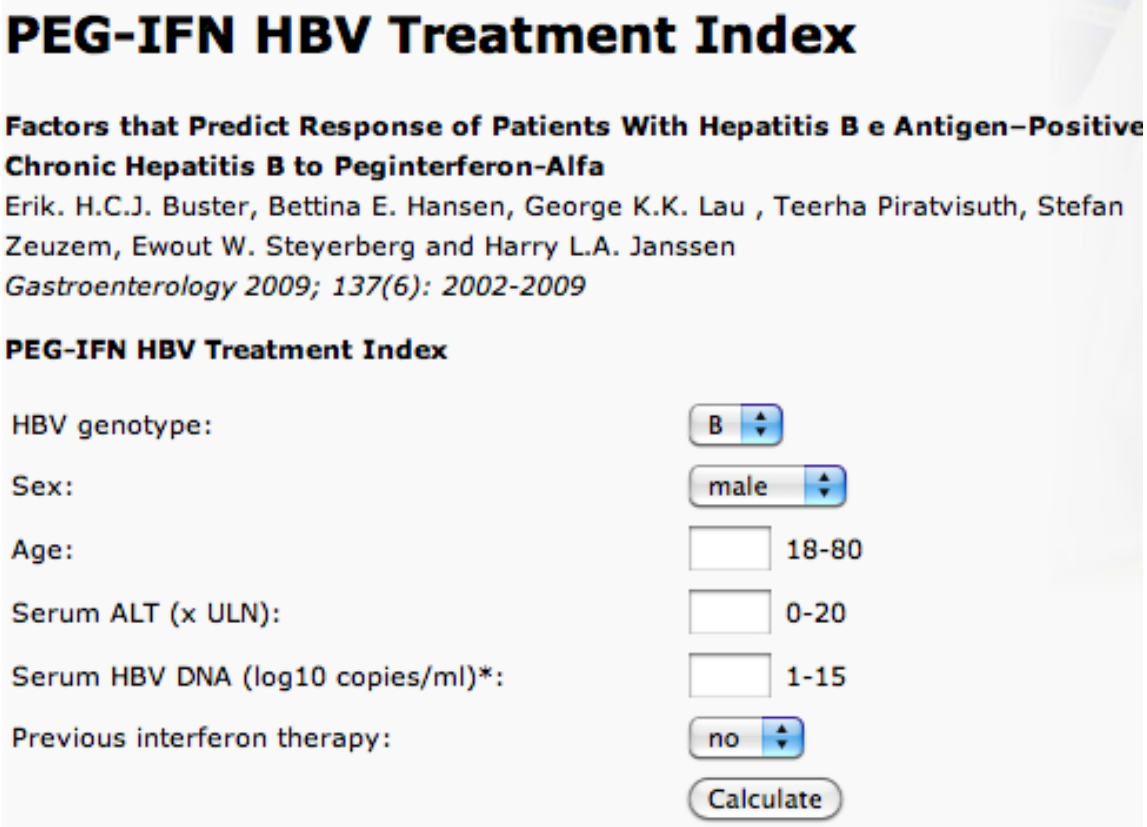
Characteristic	Sustained response[a] (n = 158)	No sustained response (n = 563)	OR	95% CI		P
				Lower	Upper	
Age, *y*	34.8 ± 11.4	32.4 ± 10.6	1.02	1.00	1.04	.01
Female sex	47 (29.7%)	120 (21.3%)	1.56	1.05	2.32	.03
Serum ALT level, × ULN	4.3 ± 3.0	3.9 ± 3.5	1.31	1.02	1.69	.03
HBV-DNA level, $\log_{10}$ *copies/mL*	9.4 ± 1.7	9.8 ± 1.8	0.85	0.77	0.95	.003
HBV genotype						<.001
A	42 (26.6%)	73 (13.0%)	1.00			
B	41 (25.9%)	125 (22.2%)	0.57	0.34	0.96	
C	67 (42.4%)	266 (47.2%)	0.44	0.28	0.70	
D	8 (5.1%)	99 (17.6%)	0.14	0.06	0.32	

Buster EH et al. Gastroenterology 2009

* SR: HBeAg loss and HBV-DNA < 4 log copies/mL, 6 months after treatment

Mr H. (con't)

http://www.liver-gi.nl/peg-ifn



PEG-IFN HBV Treatment Index

Factors that Predict Response of Patients With Hepatitis B e Antigen–Positive Chronic Hepatitis B to Peginterferon-Alfa

Erik. H.C.J. Buster, Bettina E. Hansen, George K.K. Lau , Teerha Piratvisuth, Stefan Zeuzem, Ewout W. Steyerberg and Harry L.A. Janssen

Gastroenterology 2009; 137(6): 2002-2009

PEG-IFN HBV Treatment Index

HBV genotype:	B
Sex:	male
Age:	18-80
Serum ALT (x ULN):	0-20
Serum HBV DNA (log10 copies/ml)*:	1-15
Previous interferon therapy:	no
	Calculate

For Mr H. estimated Sustained Response*: 29%

Buster EH et al. Gastroenterology 2009

* SR: HBeAg loss and HBV-DNA < 4 log copies/mL, 6 months after treatment

Question 2
Is baseline qHBsAg in this patient could be useful for prediction of PEG-IFN response?

A. Yes

B. No

Response 2
Is baseline qHBsAg in this patient could be useful for prediction of PEG-IFN response?

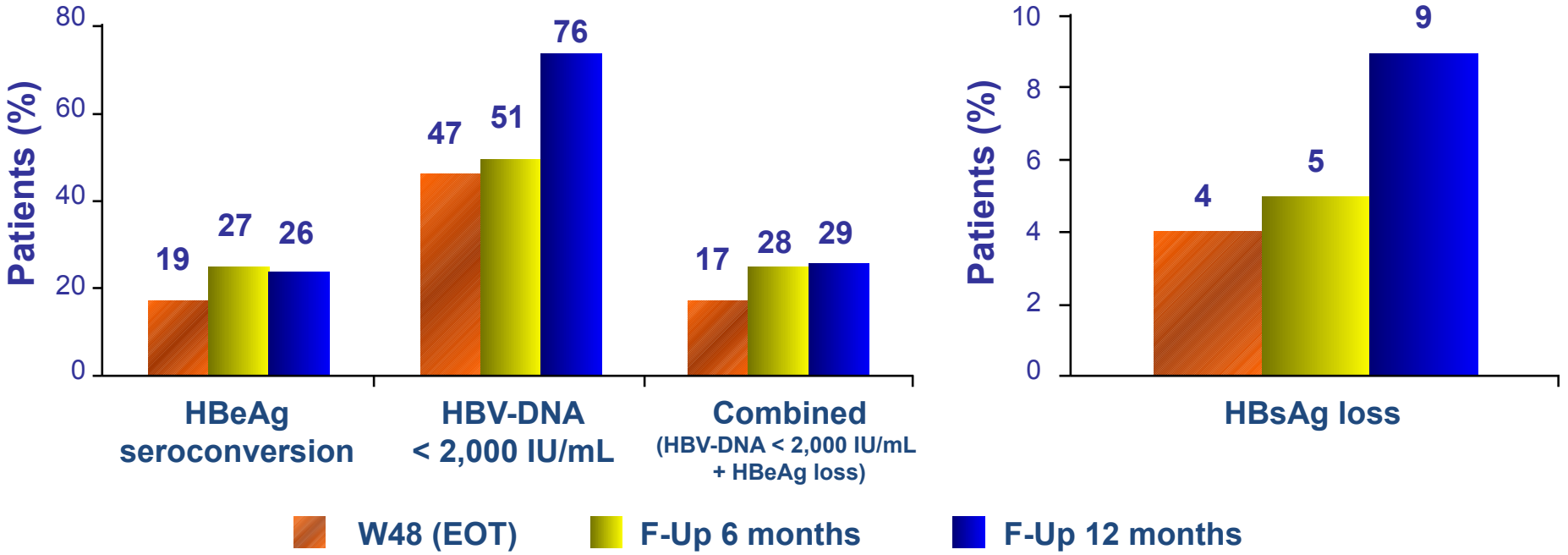
A. Yes

B. No

Results from S-COLLATE study (1)

- 1,849 patients included ➔ May 2013, treatment 48 weeks of PEG-IFNα-2a
- 612 patients included in Europe (182 HBeAg + and 430 HBeAg –)

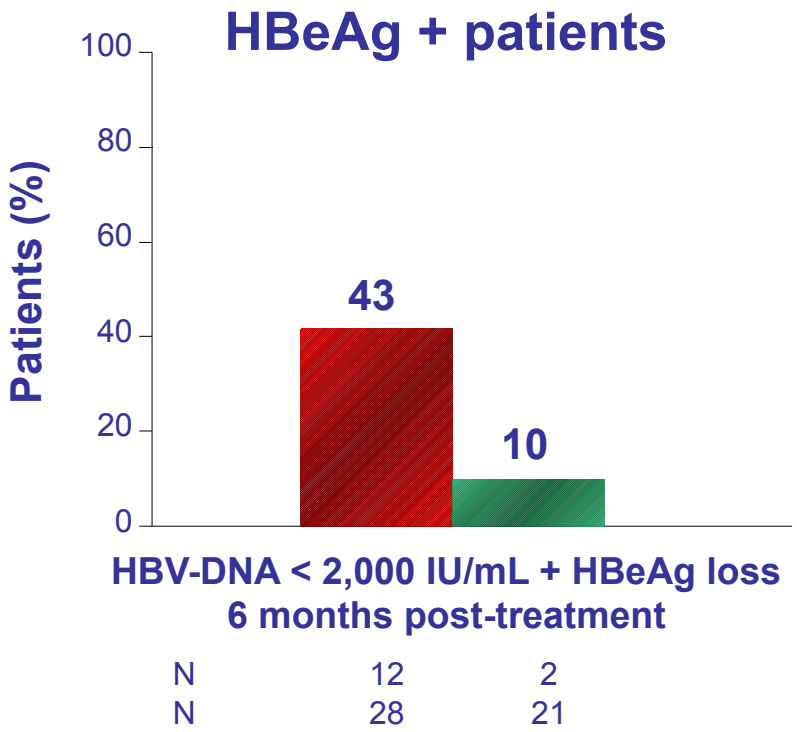
Response in HBeAg + patients



Marcellin P et al. AASLD 2013, Abs. 939

Results from S-COLLATE study (2)

Baseline qHBsAg is predictive of virologic response



qHBsAg < 20,000 IU/mL at inclusion

qHBsAg ≥ 20,000 IU/mL at inclusion

Independent predictive factor?

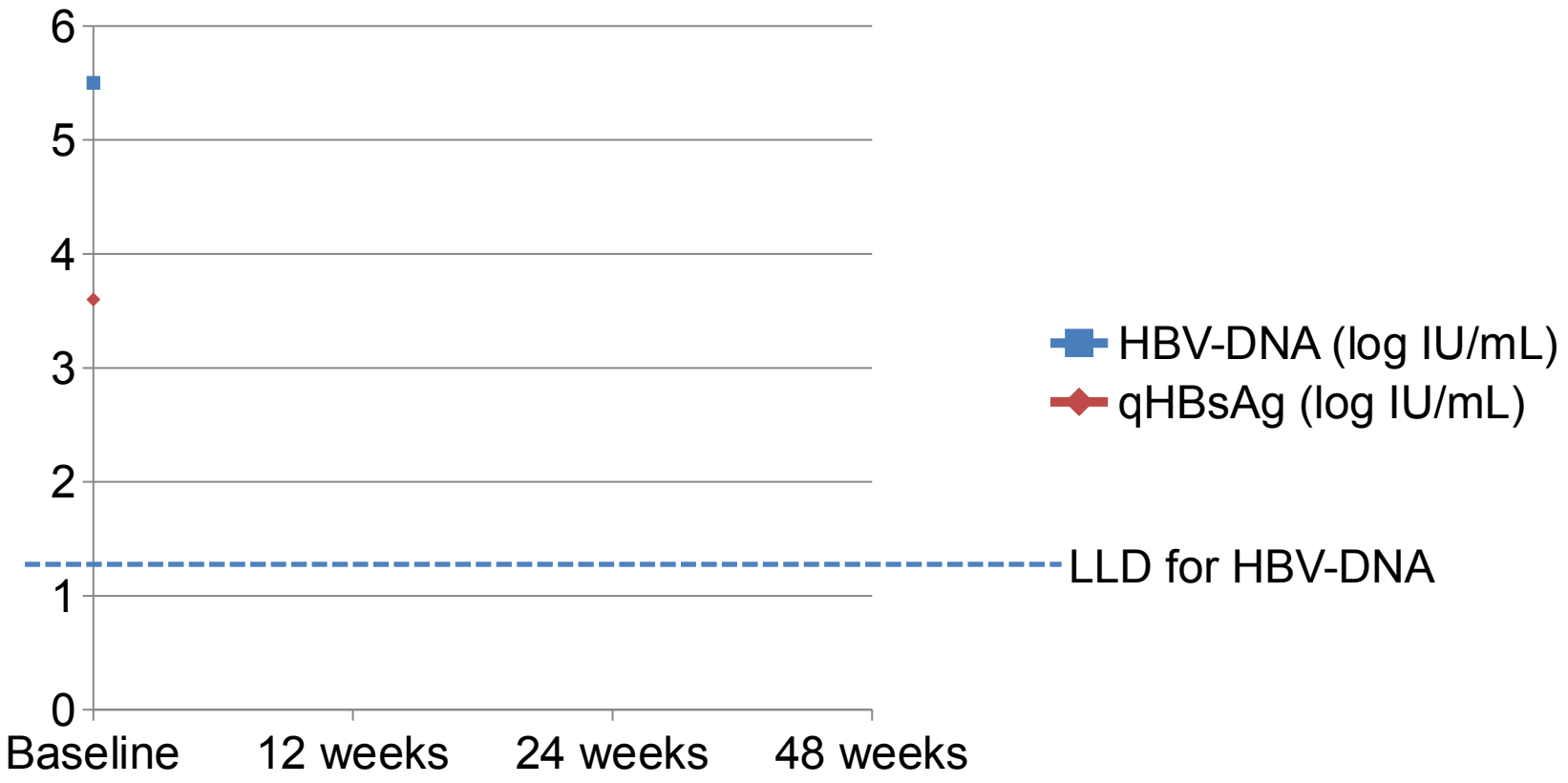
Marcellin P et al. AASLD 2013, Abs. 939

Mr H. (con't)

- At initiation of treatment:
  - HBV-DNA = 5.5 log IU/mL (≈ 320,000 IU/mL)
  - qHBsAg = 3.6 log IU/mL (≈ 4,000 IU/mL)

- A treatment with PEG-IFNα-2a (180 µg/w SC) was introduced and planned for 48 weeks

Mr H. (con't)
Treatment with PEG-IFNα-2a



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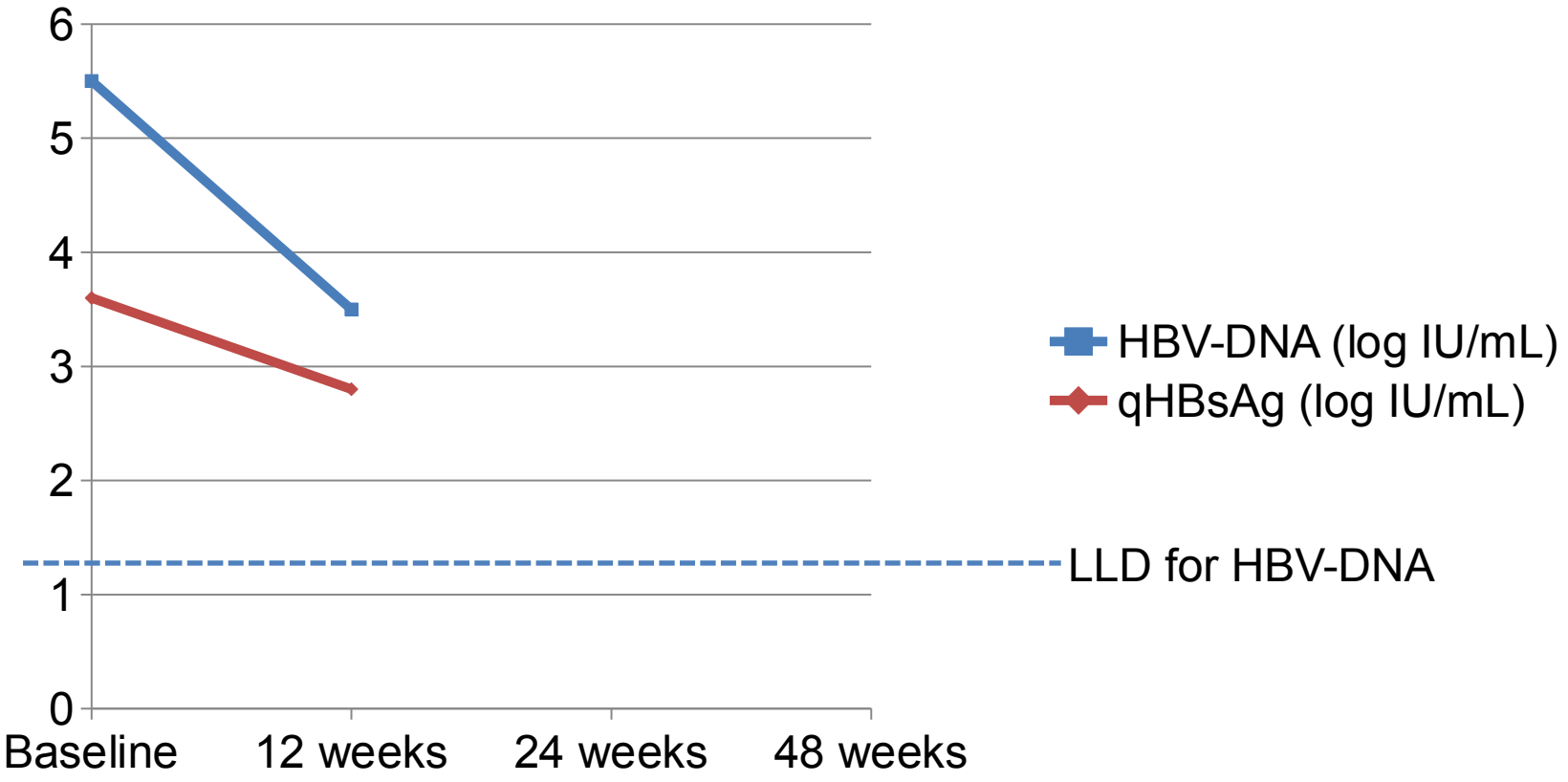
Treatment with PEG-IFNα-2a



Question 3
At 12 weeks of PEG-IFN

A. I stop the treatment since the patient still has HBV-DNA > 2.000 UI/mL at W12
B. I continue the treatment since the patient has a decrease of HBV-DNA
C. I continue the treatment since the patient has a decrease of qHBsAg
D. I continue the treatment since it was to soon to have predictive factors

Response 3
At 12 weeks of PEG-IFN

A. I stop the treatment since the patient still has HBV-DNA > 2.000 UI/mL at W12

B. I continue the treatment since the patient has a decrease of HBV-DNA

C. I continue the treatment since the patient has a decrease of qHBsAg

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EASL Clinical Guidelines (J Hepatol 2012)

In HBeAg-positive and HBeAg-negative patients, the ideal end point is sustained off-therapy HBsAg loss, with or even without seroconversion to anti-HBs. This is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome (**A1**).

EASL Clinical Guidelines (J Hepatol 2012)

Virological response on IFN/PEG-IFN therapy

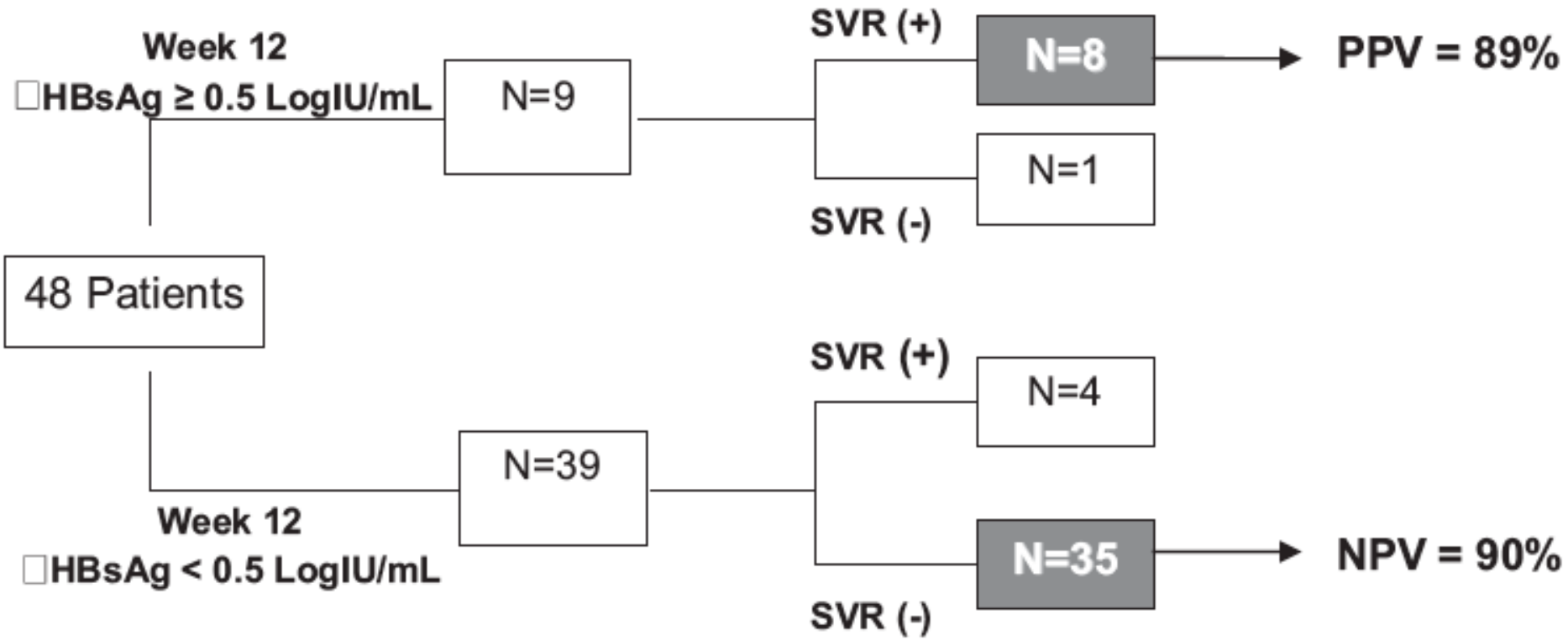
- Primary non-response has not been well established.
- Virological response is defined as an HBV DNA concentration of less than 2000 IU/ml. It is usually evaluated at 6 months and at the end of therapy as well as at 6 and 12 months after the end of therapy.
- Sustained off-treatment virological response is defined as HBV DNA levels below 2000 IU/ml for at least 12 months after the end of therapy.

Serological response for HBeAg applies only to patients with HBeAg-positive CHB and is defined as HBeAg loss and seroconversion to anti-HBe.

Decrease in qHBsAg at W12

- Important factor for management of IFN-based therapy in HBV patients
- We have stopping rules
- But different rules depending on
  - Different selected population
  - HBeAg + or –
  - HBV genotype
  - Definition of response

AgHBe – patients / Caucasian patients



SVR = undetectable HBV-DNA 24 weeks post-treatment

Moucari R et al. Hepatology 2009

AgHBe + patients / Caucasian patients

Predictive value of any qHBsAg decline on IFN-therapy

	Response Week 78*				HBsAg Loss Week 78			
	No	Yes	PPV	NPV	No	Yes	PPV	NPV
Any decline, week 12 Yes	104	35	25%	–	122	17	12%	–
No	61	2	–	97%	63	0	–	100%
Any decline, week 24 Yes	122	36	23%	–	140	18	11%	–
No	47	4	–	92%	51	0	–	100%

*Response is defined as HBeAg loss and HBV DNA < 10,000 copies/mL.

Sonneveld MJ et al. Hepatology 2010

AgHBe + patients / Asian patients

	qHBs (IU/mL)	PPV of HBe seroconversion 6 months post-treatment	
W12	< 1,500	> 55 %	
	> 20,000		0 – 15 %
W24	< 1,500	> 55 %	
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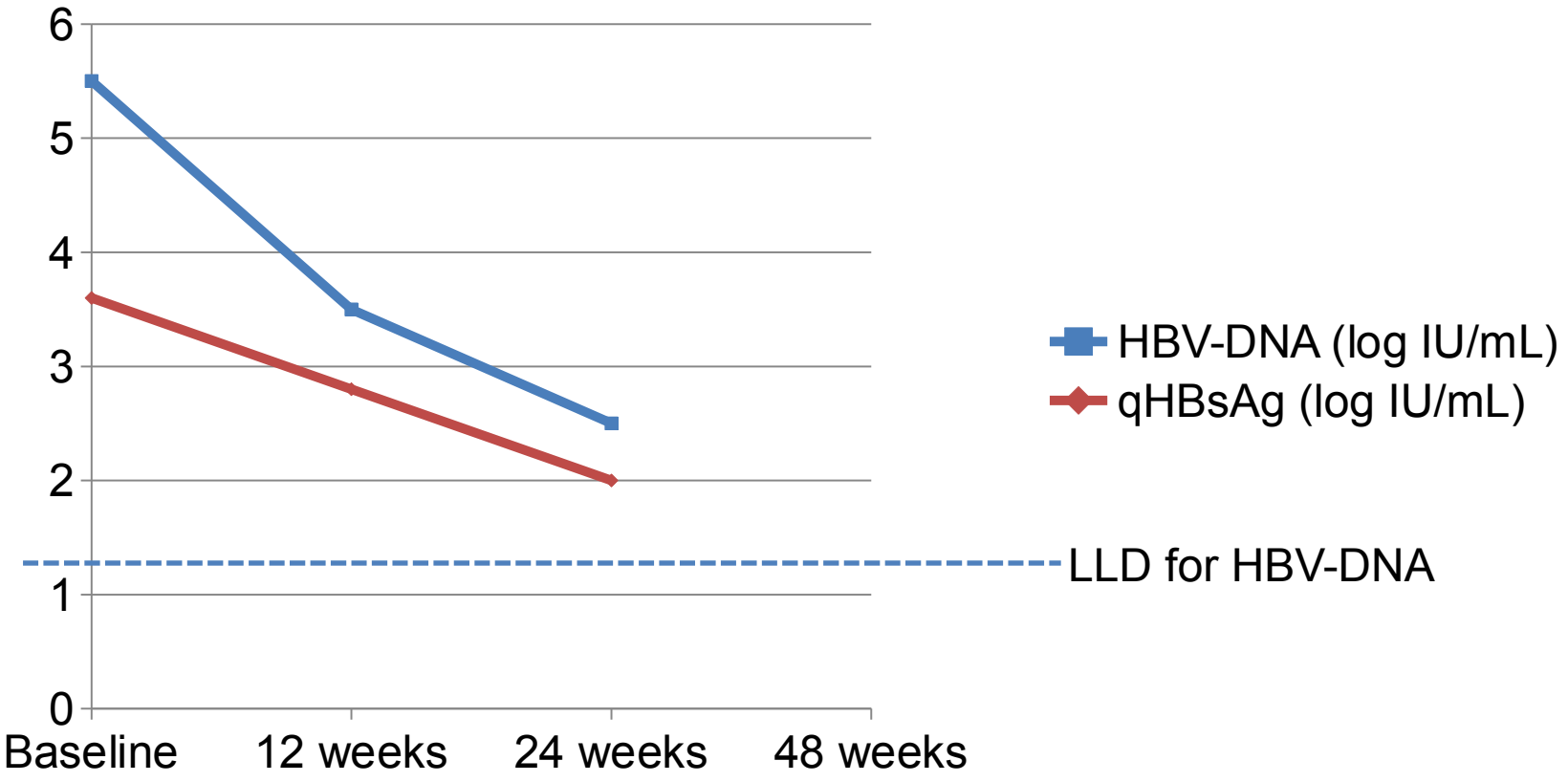
Gane E et al. EASL 2011
Piratvisuth T et al. Hepatol Int 2010

Mr H. (con't)
Treatment with PEG-IFNα-2a



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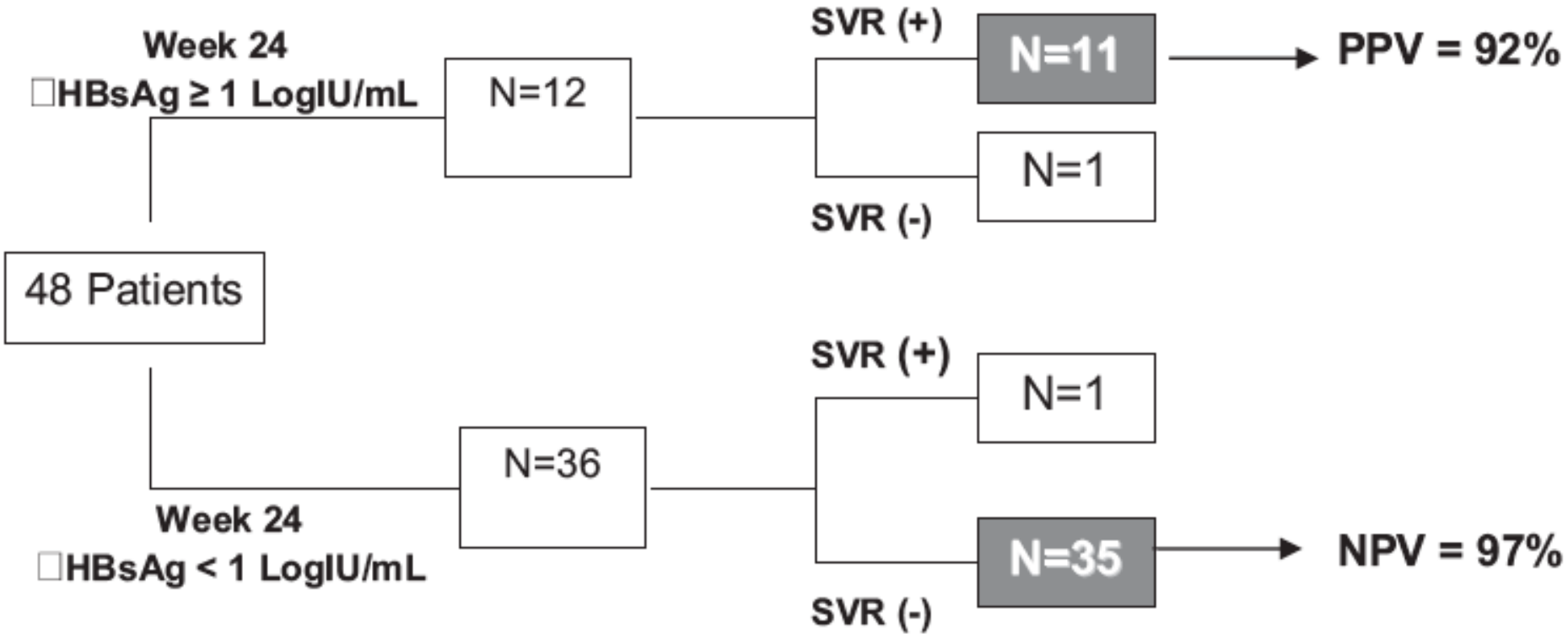

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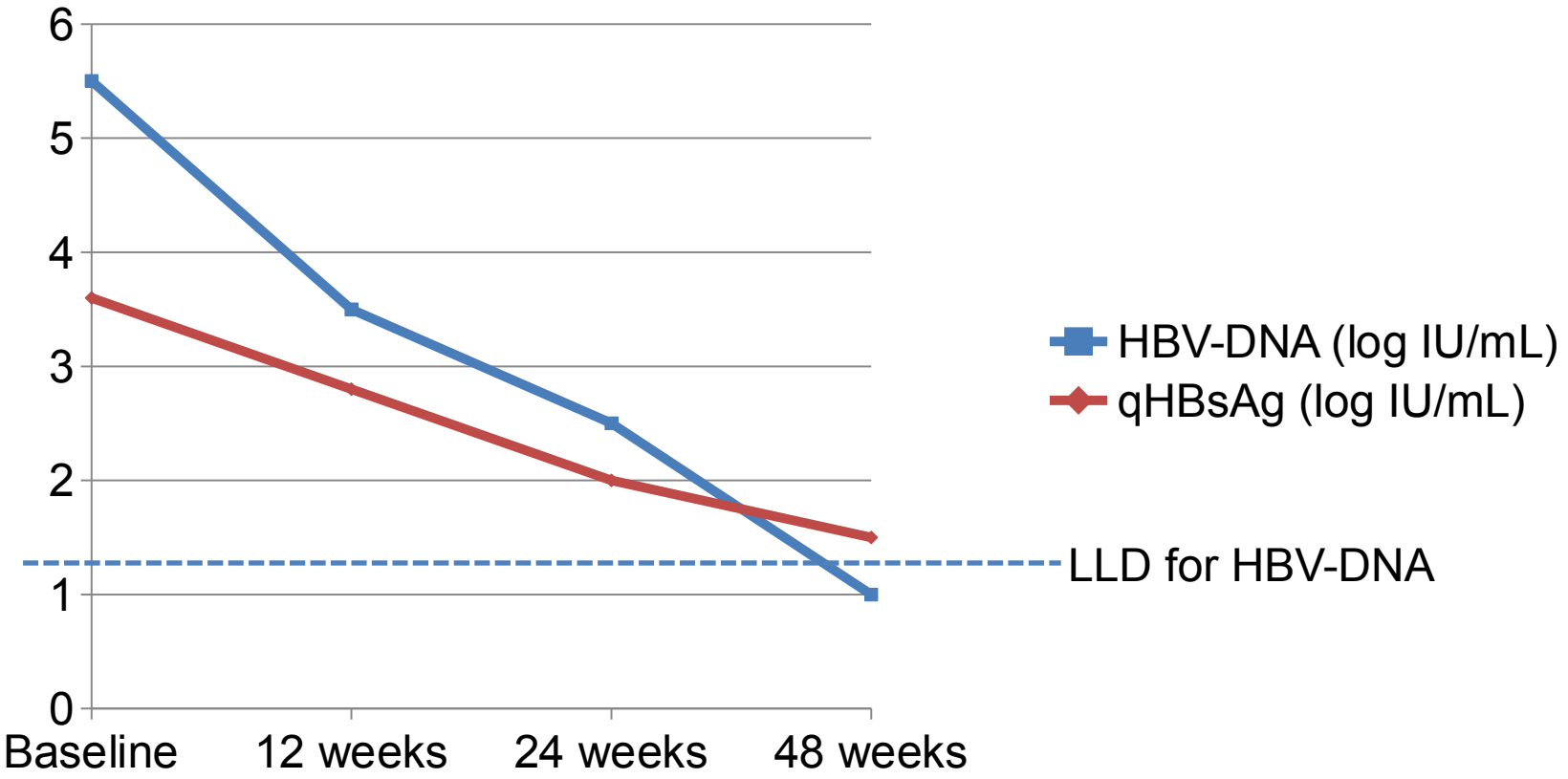
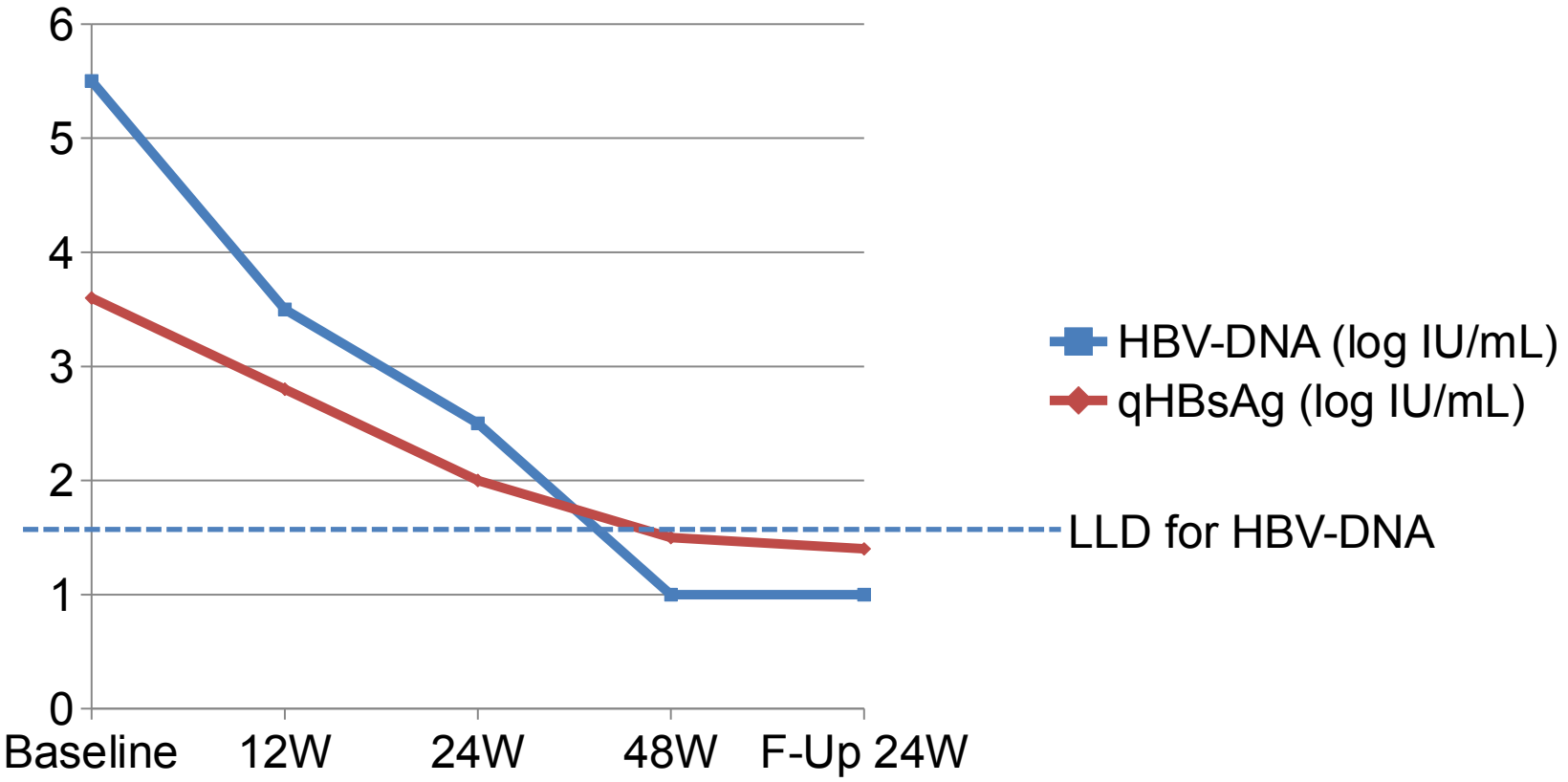


Mr H. (con't)
Follow-up after PEG-IFNα-2a



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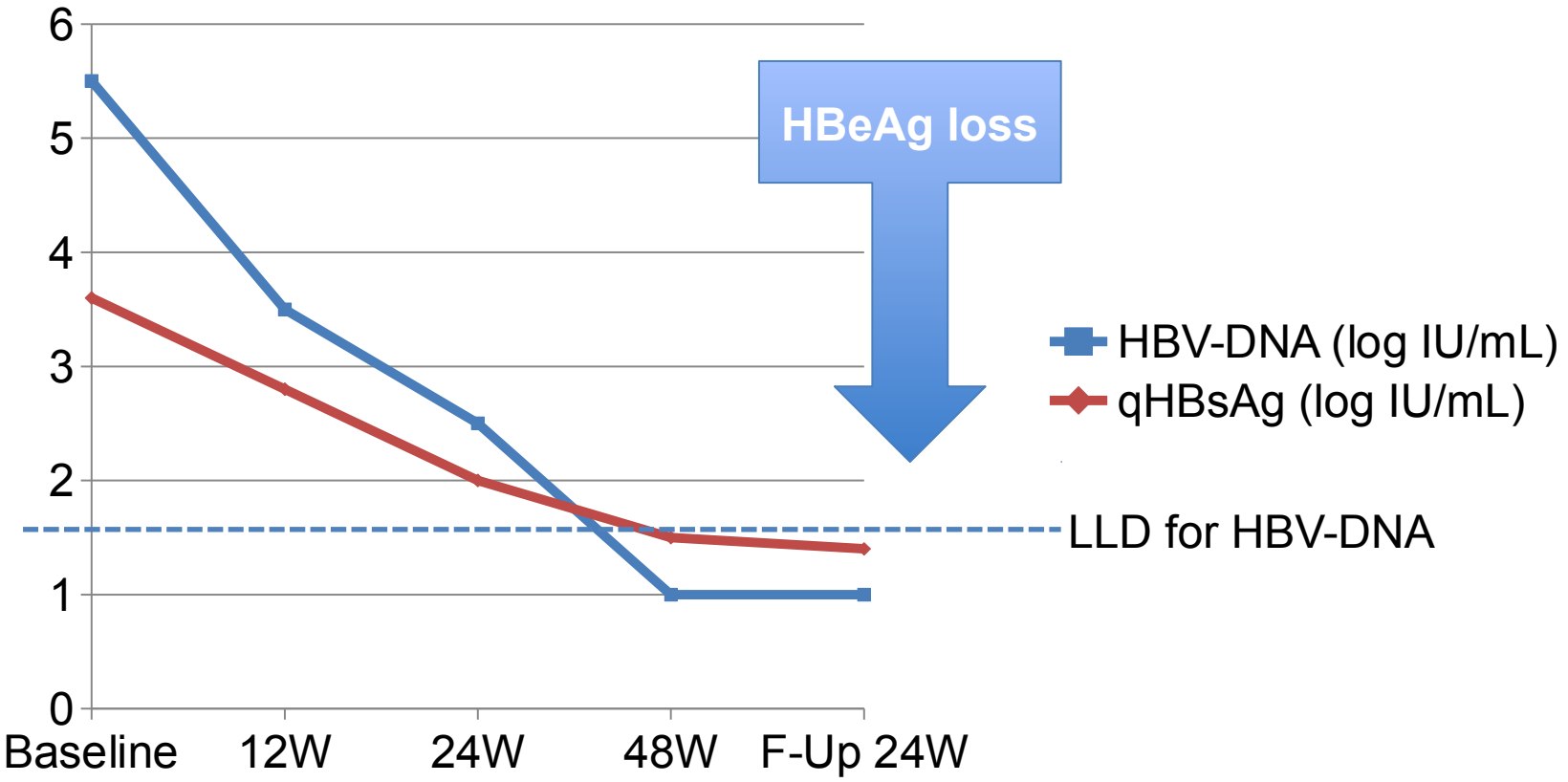

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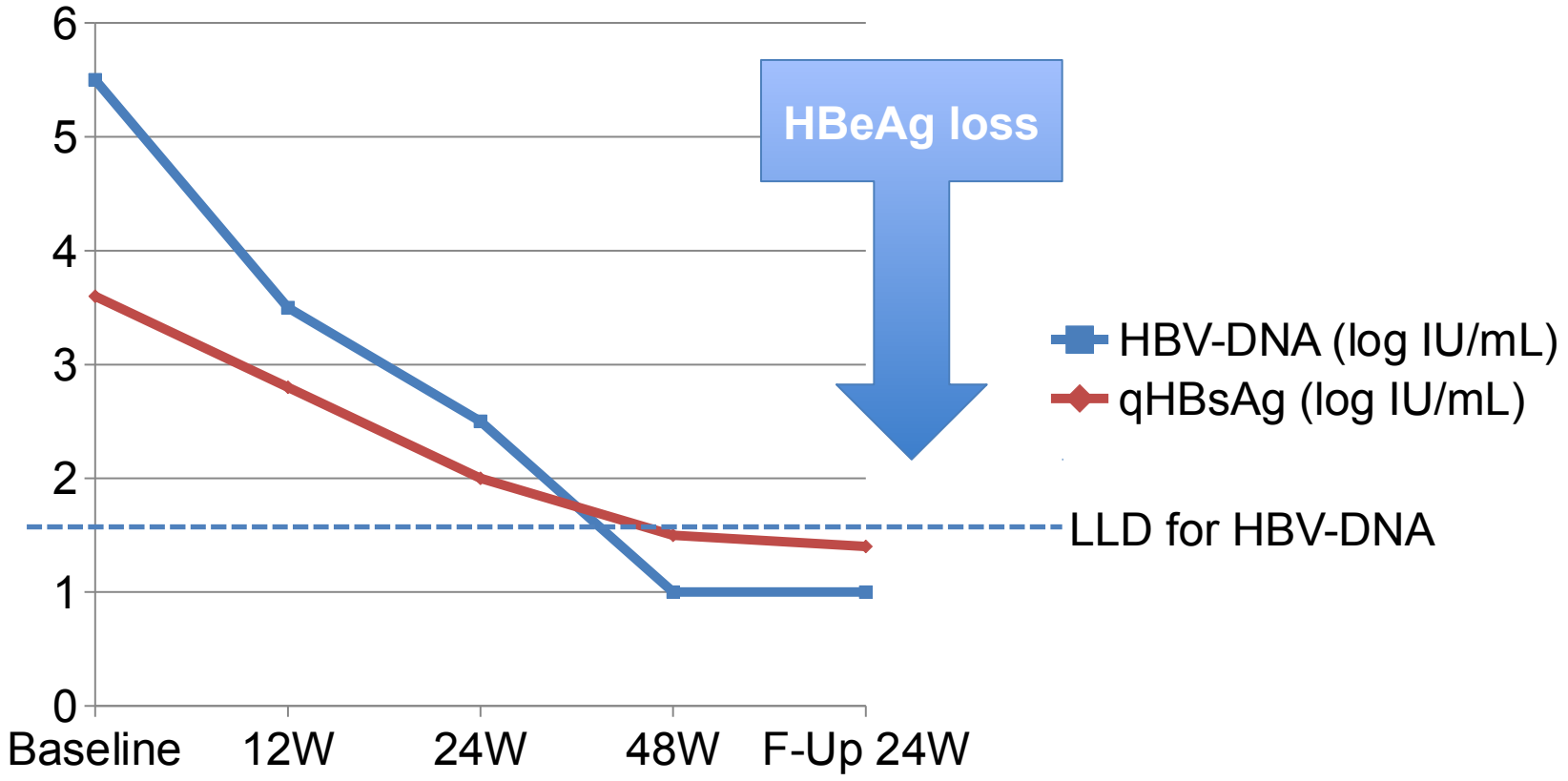


We are waiting for HBe seroconversion then HBsAg loss then HBs seroconversion…

qHBsAg decline during IFN-therapy Long-term predictive value

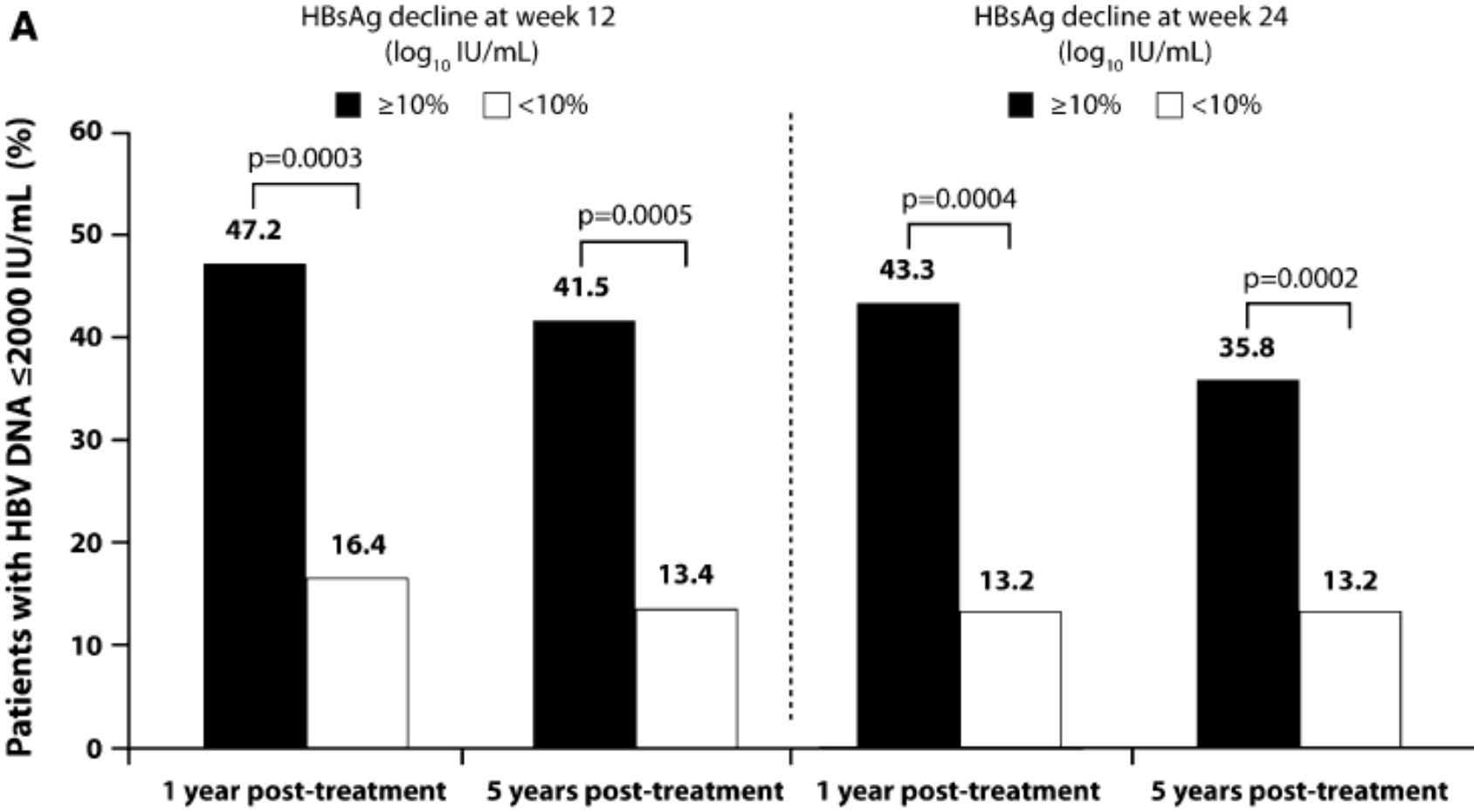
Association between end-of-treatment decline of qHBsAg or HBV-DNA level and HBsAg loss at 3 years in HBeAg – patients

Parameter	Value	No. of Patients	Patients with HBsAg Loss 3 Years After Treatment, n (%)	Relative Risk	*P* Value
HBsAg level at week 48, IU/mL (n = 194)	≤10	23	12 (52)	22.8 (8-649)	<0.0001
	>10	171	4 (2.3)		
Decline in HBsAg from baseline to week 48, $\log_{10}$ IU/mL (n = 198)	>2.0	26	11 (42.3)	14.6 (5.5-38.5)	<0.0001
	≤2.0	172	5 (2.9)		
	>1.0	43	13 (30)	10.8 (3.7-31.8)	<0.0001
	≤1.0	155	4 (2.6)		

Brunetto MR et al. Hepatology 2009

qHBsAg decline during IFN-therapy
Long-term predictive value

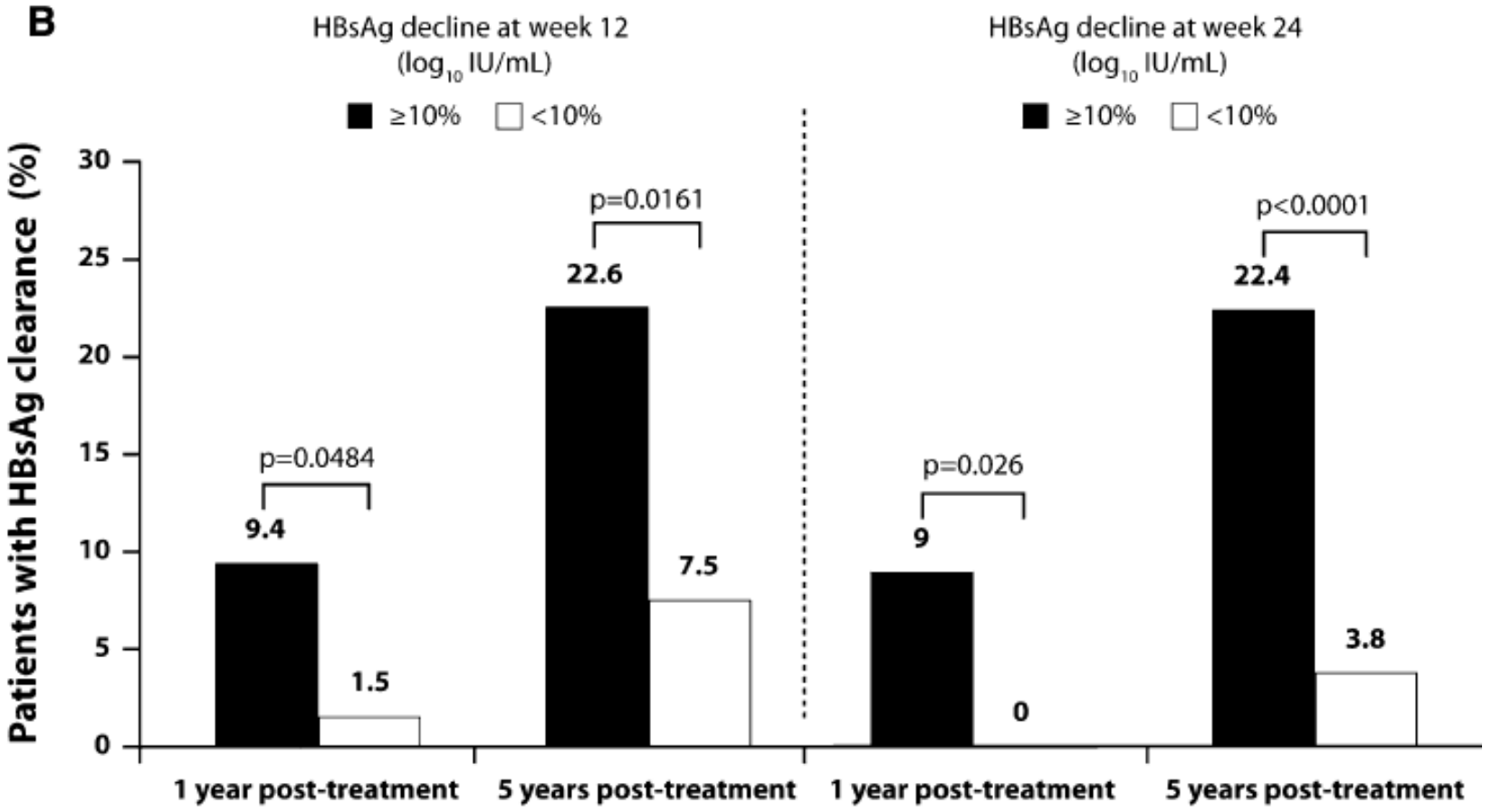
Long-term HBV-DNA response in HBeAg negative patients



Marcellin P et al. Hepatol Int 2013

qHBsAg decline during IFN-therapy
Long-term predictive value

Long-term HBsAg loss in HBeAg negative patients



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Conclusion

- Baseline qHBsAg is a predictive factor of response to IFN-therapy. Its role for initial choice between IFN and analogue therapy has to be evaluated.
- On-treatment qHBsAg is a predictive factor of short and probably long-term efficacy of IFN therapy in HBV
- No decline or qHBsAg > 20,000 IU/mL at 12 or 24 weeks on IFN therapy ➔ stop IFN and switch to analogue