



The place of pegylated IFN in HBV therapeutic (clinical cases)

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Clinical case 1, AVT

16.02.2011

- Man, Caucasian, 34 years old, height 1.85 m, weight 86 kg (BMI 25.12 kg/m²).
- Route of transmission and duration of disease – unknown
- Anamnesis:
 - ✓ No IV drug use,
 - ✓ Mother is HBV infected.
 - ✓ He was operated on for melanoma at the age of 7 y.o. (1984)
 - ✓ HBs initial detection – 03.2010 (HBV 1550 IU/ml, ALT 52-84-62 IU/L).
 - ✓ No other diseases.
 - ✓ Athlete (amateur sports - running)
 - ✓ Just married

Clinical case 1, AVT

16.02.2011

- Man, Caucasian, 34 years old, height 1.85, weight 86 (BMI 25.12 kg/m²).
- HBs+, HBe-, antiHBe +, HCV -, HIV-, anti-HDV -, anti-HAV -.

Clinical case 1, AVT

16.02.2011

- Man, Caucasian, 34 years old, height 1.85, weight 86 (BMI 25.12 kg/m²).
- HBs+, HBe-, antiHBe +, HCV -, HIV-, anti-HDV -, anti-HAV -.
- Hematology: HGB 164 g/l, WBC 5.1x10⁹/L, PLT 270x10⁹/L.
- Blood chemistry:

ALT **43** U/L,

AST 26.1 U/L,

GGT **76.9** (10-60) U/L,

AP 91.9 (0-128) U/L,

bilirubin 19.14 µmol/L,

cholesterol **7.4** mmol/l,

glucose 5.13 mmol/L,

uric acid 356 µmol/L,

creatinin 85.4 µmol/L,

total protein 68.4 g/L,

albumin 52.9 g/L,

AFP 1.66 (0-16) IU/L.

- INR 0.95, PTT 13.3 sec (12-15 sec), PTI 111 (81-138%).

Clinical case 1, AVT, 34 y.o. man

- 16.02.2011: HBV DNA 173 500 IU/ml
- Abdominal ultrasound – normal
- LSM 8.6 kPa.

Clinical case 1, AVT, 34 y.o. man

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Treatment / follow-up options?

Working recommendations for Treatment Initiation in HBeAg-Negative Patients in 2011

	AASLD 2007 ^[1]	US Algorithm 2008 ^[2]	EASL 2009 ^[3]
HBV DNA, IU/mL	> 20,000 [‡]	> 2000	≥ 2000
ALT, x ULN*	1 to > 2	> 1	> 1
Disease stage/grade	Moderate/severe necroinflammation and/or significant fibrosis		
First-line therapy	ADV, [†] ETV, pegIFN	ETV, TDF, pegIFN	ETV, TDF, pegIFN

*Persistent (> 3-6 mos). [†]TDF not FDA approved at time of publication. [‡] Consider liver biopsy if > 2000 IU/mL and treat if moderate/severe inflammation and/or fibrosis found.

- Criteria for HBV DNA, ALT and disease stage/grade must all be met
 - If not, guidelines recommend monitoring and consideration of treatment based on individual's age, health status, and stage of infection/disease

1. Lok A, et al. Hepatology. 2007;45:507-539. 2. Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341. 3. EASL HBV Guidelines. Journal of Hepatology. 2009;50:227-242.

Current treatment options

	AASLD (2009)	APASL (2012)	EASL (2012)
Treatment candidacy			
HBV DNA (IU/mL)	≥ 20000	≥ 2000	> 20000
ALT	≥ 2 × ULN	≥ 2 × ULN	≥ 2 × ULN
Other criteria			Treat if, HBV DNA > 2000, ALT > ULN and moderate to severe inflammation on liver biopsy and/or at least moderate fibrosis.
Liver biopsy (or noninvasive markers of fibrosis) to consider if			
HBV DNA (IU/mL)	2000-20000	> 2000	> 2000
ALT	1-2 × ULN	1-2 × ULN	> ULN
Other criteria		≥ 40 yr old	
First-line treatment	PEG-IFN or Entecavir or Tenofovir	PEG-IFN or Entecavir or Tenofovir	PEG-IFN or Entecavir or Tenofovir
Duration of treatment			
IFN	12 mo	12 mo	12 mo
Oral	> 1 yr	Unknown/long-term	Unknown/long-term
Stopping treatment strategy for NA	Until HBsAg clearance	Until HBsAg clearance, may consider stopping if treated for at least 2 yr with undetectable HBV DNA on three separate occasions 6 mo apart.	Until HBsAg clearance.

Selecting Between Recommended First Line Nucleos(t)ide and Interferon Therapy

	Nucleos(t)ides		Interferon-Based Therapy	
Feature	Pro	Con	Pro	Con
Administration	Oral	Long term/indefinite	Finite duration	Subcutaneous
Antiviral activity	High			Low durable rates DNA suppression
Resistance	Very low resistance [†]		No	
Adverse events	Minimal	Rare renal tox with nucleotide		Substantial*
HBeAg loss and clearance	HBeAg loss ↑ over time	Lower rates vs IFN	Higher rates vs nucleos(t)ides	HBeAg loss ≠ HBV DNA suppression
HBsAg loss and clearance	Higher and earlier events [†]	Low rates	High rates (select populations)	Low rates in general patient groups
Other	Anti HIV (TDF)	May induce HIV resistance (TDF/ETV)	Anti HCV/HDV	

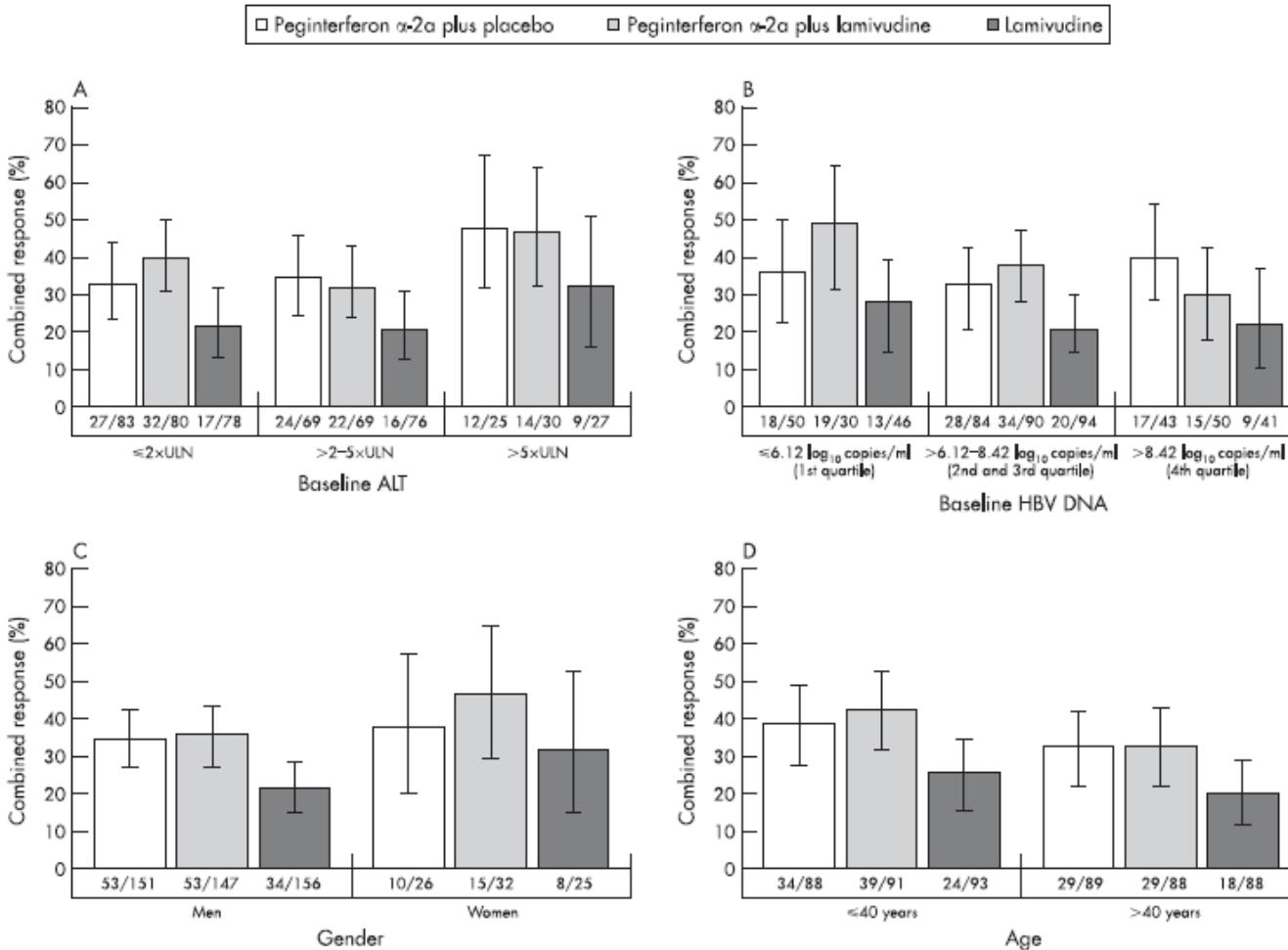
*Prolonged treatment not feasible. [†]Newer vs older nucleos(t)ides.

Clinical case 1, AVT, 34 y.o. man

- 16.02.2011: HBV DNA 173 500 IU/ml
- Abdominal ultrasound – normal
- LSM 8.6 kPa.

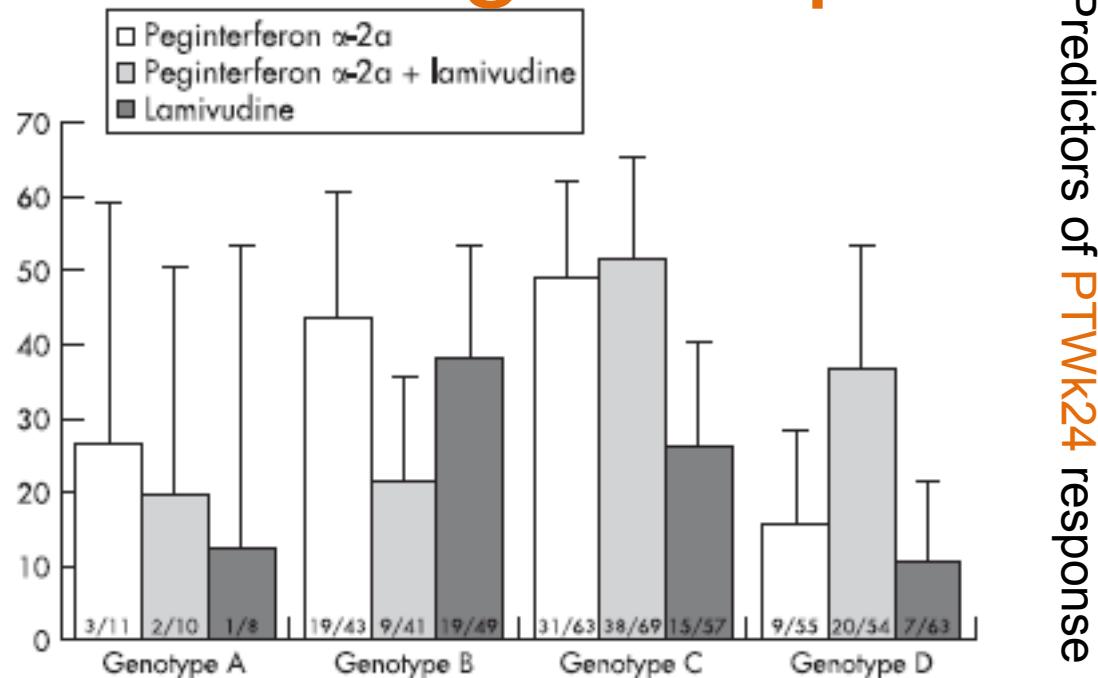
Additional testing?

Pre-treatment predictors of PegIFN efficacy in HBe- negative patients



Predictors of PTWk24 response

Pre-treatment predictors of PegIFN efficacy in HBe-negative patients



Pre-treatment predictors of PegIFN efficacy in HBe-negative patients

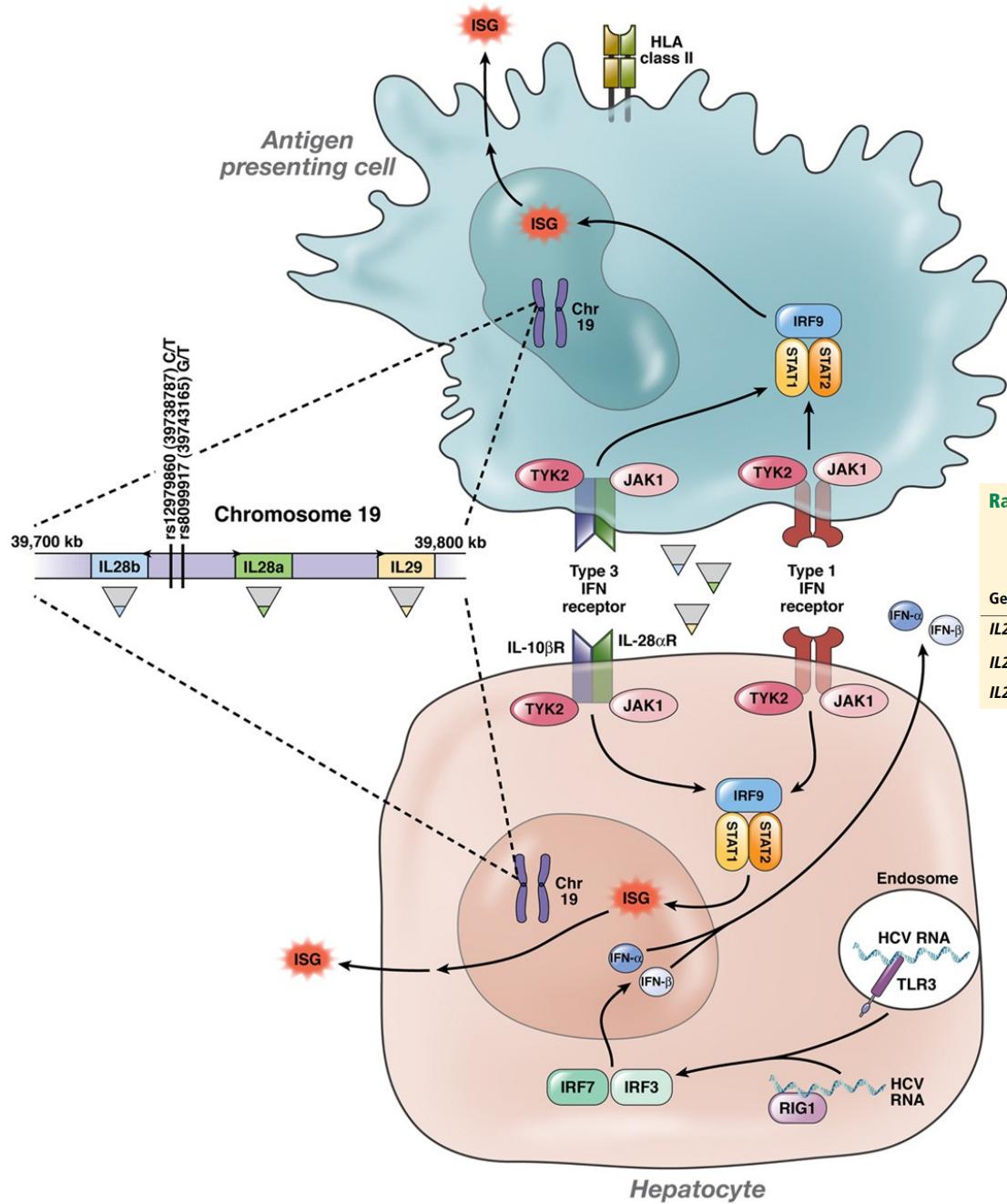
Pre-treatment factors and sustained combined response (normal ALT and HBV DNA ≤20000 cop/ml) at year 1 posttreatment follow-up

Factor	Odds ratio (95% CI)	p Value
Age (10 year increase)	0.80 (0.63 to 1.02)	0.0687
Gender (M v F)	0.68 (0.34 to 1.37)	0.2828
Weight (10 kg increase)	1.03 (0.81 to 1.30)	0.8271
ALT (baseline)	1.00 (1.00 to 1.00)	0.3970
Log ₁₀ HBV DNA (baseline)	1.06 (0.93 to 1.21)	0.3612
Genotype (A v D)	2.58 (0.73 to 9.20)	0.1432
Genotype (B v D)	3.69 (1.54 to 8.79)	0.0033
Genotype (C v D)	5.46 (2.46 to 12.1)	<0.0001
PEG-IFN α -2a v LAM	2.11 (1.11 to 4.01)	0.0223
PEG-IFN α -2a+LAM v LAM	2.16 (1.14 to 4.10)	0.0185

Clinical case 1, AVT, 34 y.o. man

- 16.02.2011: HBV DNA 173 500 IU/ml
- Abdominal ultrasound – normal
- LSM 8.6 kPa.
- **Genotype HBV –D**

Any other examination(s)?



Genotype	Sustained virologic response rates			
	Pegylated interferon + ribavirin	Protease inhibitor + pegylated interferon + ribavirin	Simeprevir + sofosbuvir + ribavirin	Sofosbuvir + ledipasvir
<i>IL28B</i> CC	78%	82%–90%	100%	100%
<i>IL28B</i> CT	38%	72%	100%	100%
<i>IL28B</i> TT	26%	57%	83%	98%

Pre-treatment predictors of PegIFN efficacy in HBe-negative patients

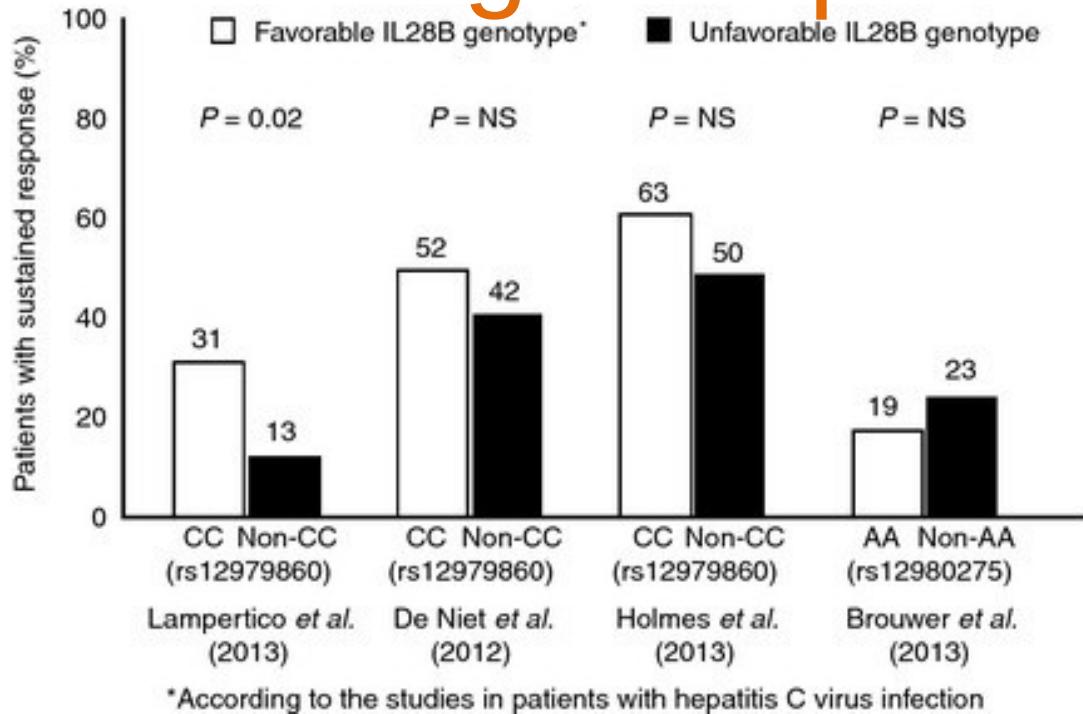
Rates of virological response to IFN therapy according to IL28B genotype

Response	CC (n = 48)	CT/TT (n = 53)	P Value
End-of-therapy virological response (%)	33 (69)	24 (45)	0.01
SVR (%)	15 (31)	7 (13)	0.02
HBsAg clearance (%)	14 (29)	7 (13)	0.04

Pre-treatment predictors of PegIFN efficacy in HBe-negative patients

Baseline Variable	SVR OR (95% CI); P Value		HBsAg Clearance OR (95% CI); P Value	
	Univariate	Multivariate	Univariate	Multivariate
Age, years	0.94 (0.89-0.99); 0.02	0.92 (0.87-0.98); 0.01	0.95 (0.90-1.00); 0.10	
Male	0.80 (0.23-2.80); 0.73		0.75 (0.21-2.61); 0.65	
Cirrhosis	0.75 (0.28-2.00); 0.57		1.06 (0.40-2.82); 0.89	
ALT levels, IU/L	1.00 (0.99-1.00); 0.16		1.00 (1.00-1.00); 0.02	1.00 (1.00-1.00); 0.03
HBV-DNA levels, log cp/mL	0.53 (0.34-0.84); 0.007	0.44 (0.27-0.74); 0.002	0.53 (0.33-0.84); 0.008	0.31 (0.15-0.62); 0.001
HBV genotype D	0.82 (0.15-4.38); 0.81		0.77 (0.14-4.12); 0.76	
IFN standard	1.76 (0.58-5.30); 0.31		3.41 (0.92-12.5); 0.06	
IFN treatment, months	1.07 (0.99-1.17); 0.08		1.16 (1.04-1.30); 0.008	1.20 (1.04-1.39); 0.01
Post-treatment follow-up, years	1.10 (1.00-1.21); 0.03		1.11 (1.01-1.22); 0.02	
CC genotype IL28B	2.98 (1.09-8.13); 0.03	3.72 (1.19-11.5); 0.02	2.70 (0.98-7.42); 0.04	3.63 (1.05-12.5); 0.04

Pre-treatment predictors of PegIFN efficacy in HBe-negative patients



Response rates of HBeAg-negative patients treated with (peg)-IFN according to different IFN-λ3 (IL28B) polymorphisms

Clinical case 1, AVT, 34 y.o. man

- 16.02.2011: HBV DNA 173 500 IU/ml
- Abdominal ultrasound – normal
- LSM 8.6 kPa.
- **Genotype HBV –D**
- **IL28B rs12979860 – C/T; rs8099917 – T/T**

PegIFN treatment initiation

Pro	Cons
ALT – 1.16 x ULN	HBV genotype D
HBV DNA – 173 500 IU/ml	IL28B rs12979860 - CT
Age – 34 y.o.	Gender – male
Specific demographics/social factors	

Clinical case 1, AVT, 34 y.o. man

Visit type	Baseline
DOV	27.04.2011
HBsAg	Positive
HBeAg	Negative
anti-HBe	Positive
HBV DNA quant, IU/ml	23525
HBs quant, IU/ml	3553
ALT, IU/ml	64
AST , IU/ml	34.5
GGT, IU/ml	
Bilirubin total µmol/l	23.42
Glucose, mmol/l	5.89
PTI, %	80
TSH, mIU/L	1.02
RBC, x10 ¹² /L	5.37
WBC x10 ⁹ /L	4,8
ANC x10 ⁹ /L	2.51
PLT, x10 ⁹ /L	307
HGB, g/L	160

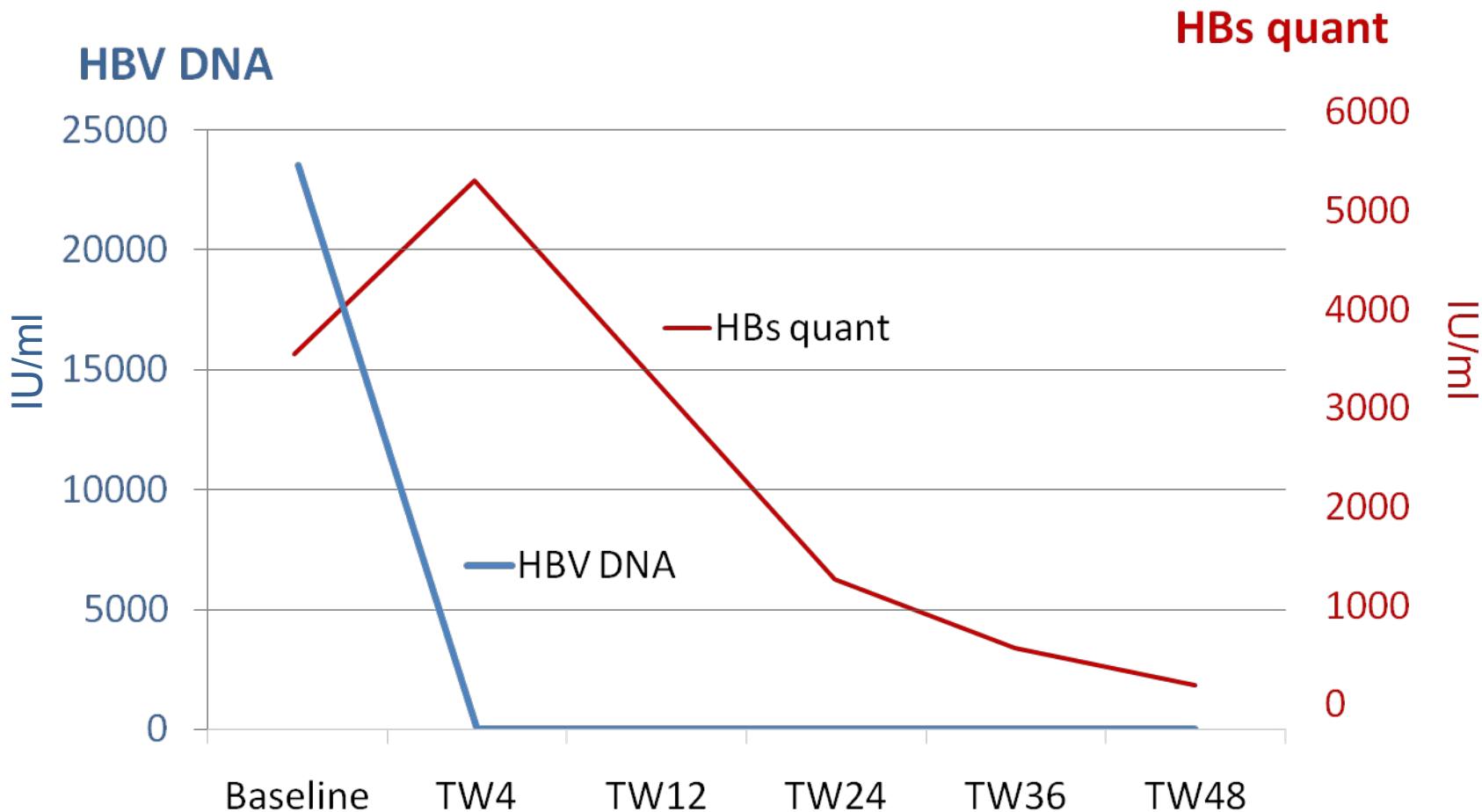
Clinical case 1, AVT, 34 y.o. man

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DOV	27.04.2011	25.05.2011	21.07.2011	14.10.2011	28.12.2011	26.03.2012
HBsAg	Positive					Positive
HBeAg	Negative			Negative		Negative
anti-HBe	Positive			Positive		Positive
HBV DNA quant, IU/ml	23525	not detected				
HBs quant, IU/ml	3553	5301		1278.8	574.9	204
ALT, IU/ml	64	52	40.8	80	57	52
AST , IU/ml	34.5	36	116.9	43.9	36.4	31,6
GGT, IU/ml		80.6	19.3	107.9	86.3	79.6
Bilirubin total μmol/l	23.42	13.32	42.55	10.27	12.64	9.09
Glucose, mmol/l	5.89	5.14	7.53	4.48	4.78	5.04
PTI, %	80					
TSH, mIU/L	1.02		0.94			0.98
RBC, x10 ¹² /L	5.37	5.79	5.47	5.91	5.9	5.44
WBC x10 ⁹ /L	4.8	3	5.47	3.4	5	3.1
ANC x10 ⁹ /L	2.51	2.23	2.22	1.71	2.96	1.29
PLT, x10 ⁹ /L	307	175	163	180	171	108
HGB, g/L	160	166	167	158	170	154

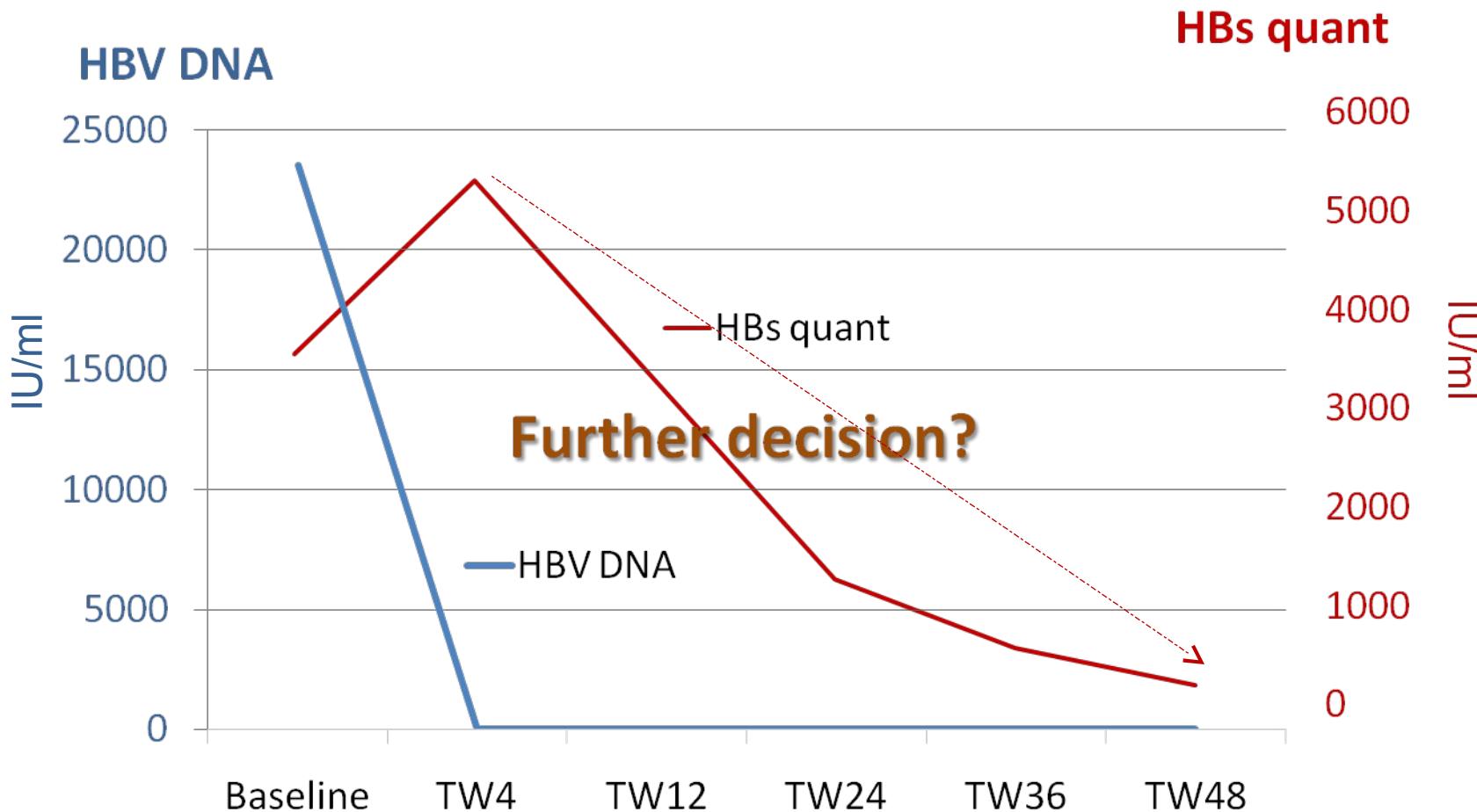
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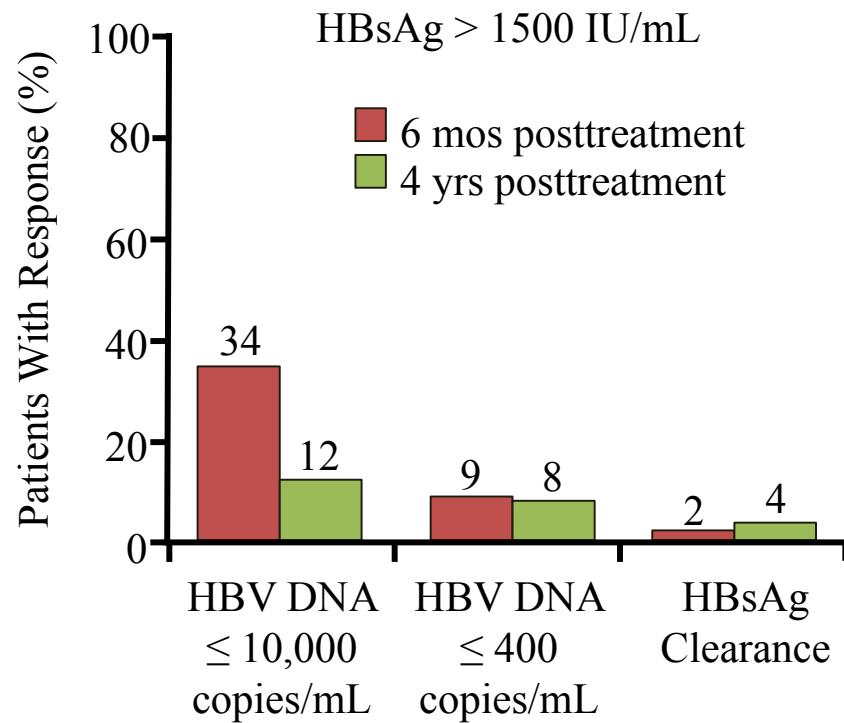
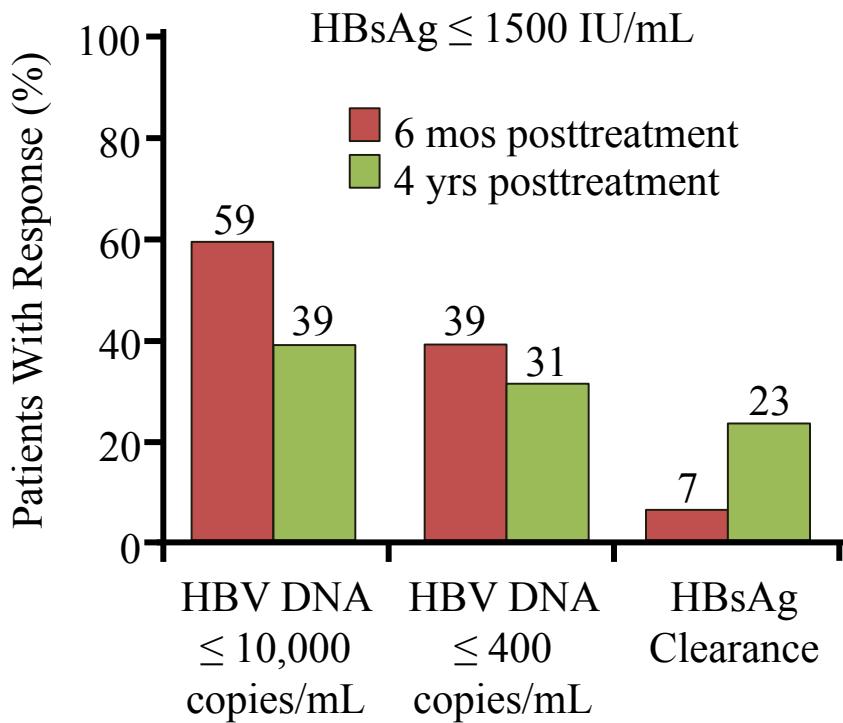
Clinical case 1, AVT, 34 y.o. man



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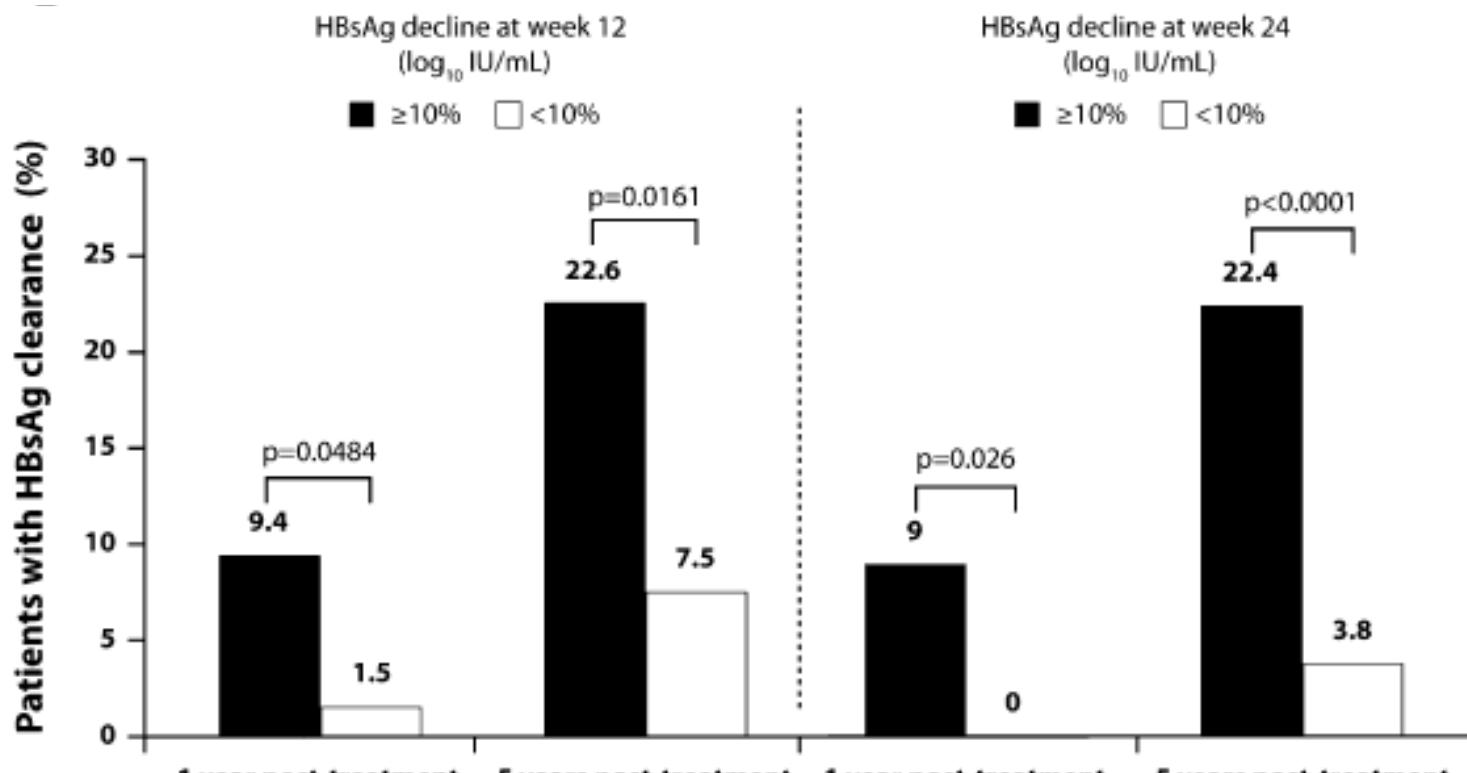


HBsAg Level as Predictor of Long-term Durability of PegIFN Response in HBeAg(-)



Predictive value of HBs at baseline and on-treatment

HBsAg $\leq 5,000$ IU/mL at baseline achieved the highest rates of response post-treatment, PPVs – 30% NPVs – 80%.



p-values: Mantel-Haenszel Chi-Square.

End-of-treatment HBs_e, HBV DNA and HBs clearance

Association Between End-of-Treatment Levels of HBsAg or HBV DNA and HBsAg Clearance 3 Years After Treatment

Parameter	Value	No. of Patients	Patients with HBsAg Loss 3 Years After Treatment,		P Value
			n (%)	Relative Risk	
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)		
	≤1.0	155	4 (2.6)	10.8 (3.7-31.8)	
HBV DNA level at week 48, copies/mL (n = 194)	≤400	161	15 (9)	3.1 (0.4-22.5)	NS
	>400	33	1 (3)		

Abbreviation: NS, not significant.

Clinical case 1, AVT, 34 y.o. man

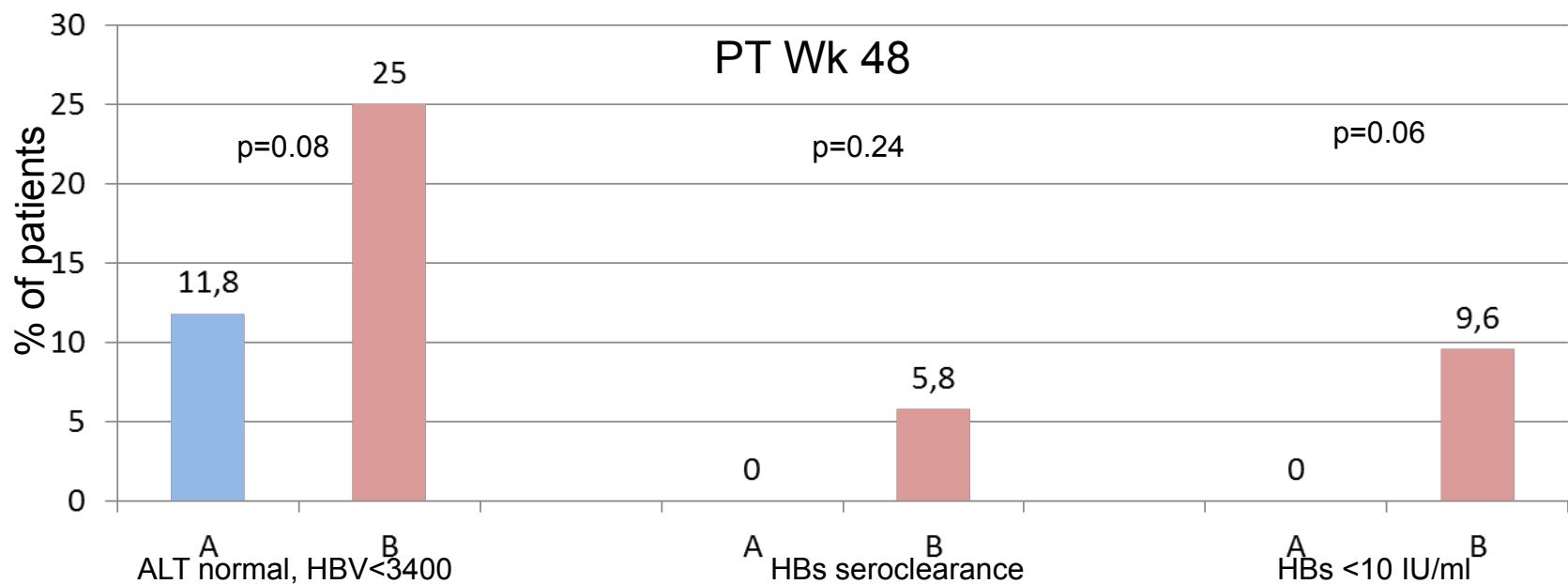
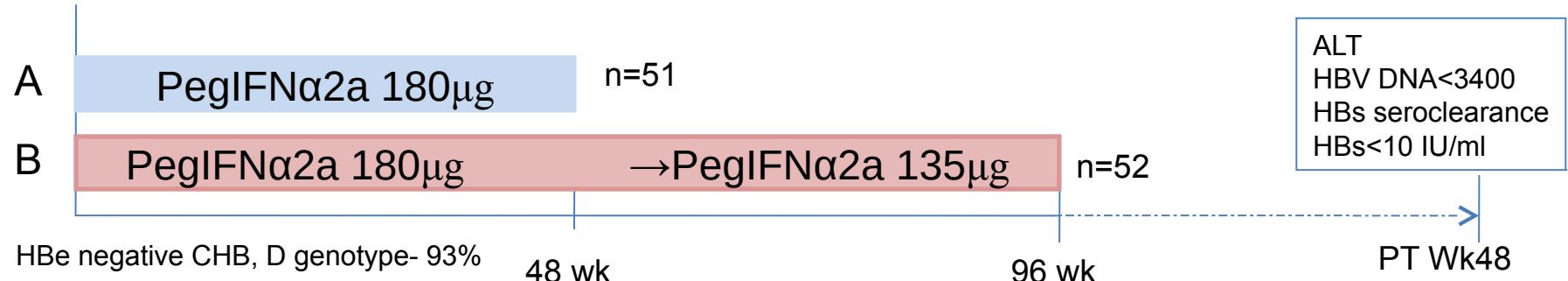
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DOV	27.04.2011	25.05.2011	21.07.2011	14.10.2011	28.12.2011	26.03.2012
HBsAg	Positive					Positive
HBeAg	Negative			Negative		Negative
anti-HBe	Positive			Positive		Positive
HBV genotype	D					
HBV DNA quant, IU/ml	23525	not detected				
HBs quant, IU/ml	3553	5301		1278.8	574.9	204
HBs change from basal lvl %log		No	ND	-35%	-83.8%	-94.3%

Clinical case 1, AVT, 34 y.o. man

Visit type	Baseline	TW 4	TW 12	TW 24	TW 36	TW 48
DOV	27.04.2011	25.05.2011	21.07.2011	14.10.2011	28.12.2011	26.03.2012
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HBs change from basal lvl %log		No	ND	-35%	-83.8%	-94.3%

Prolonged treatment?

Prolonged treatment HBe- CHB with PegIFN

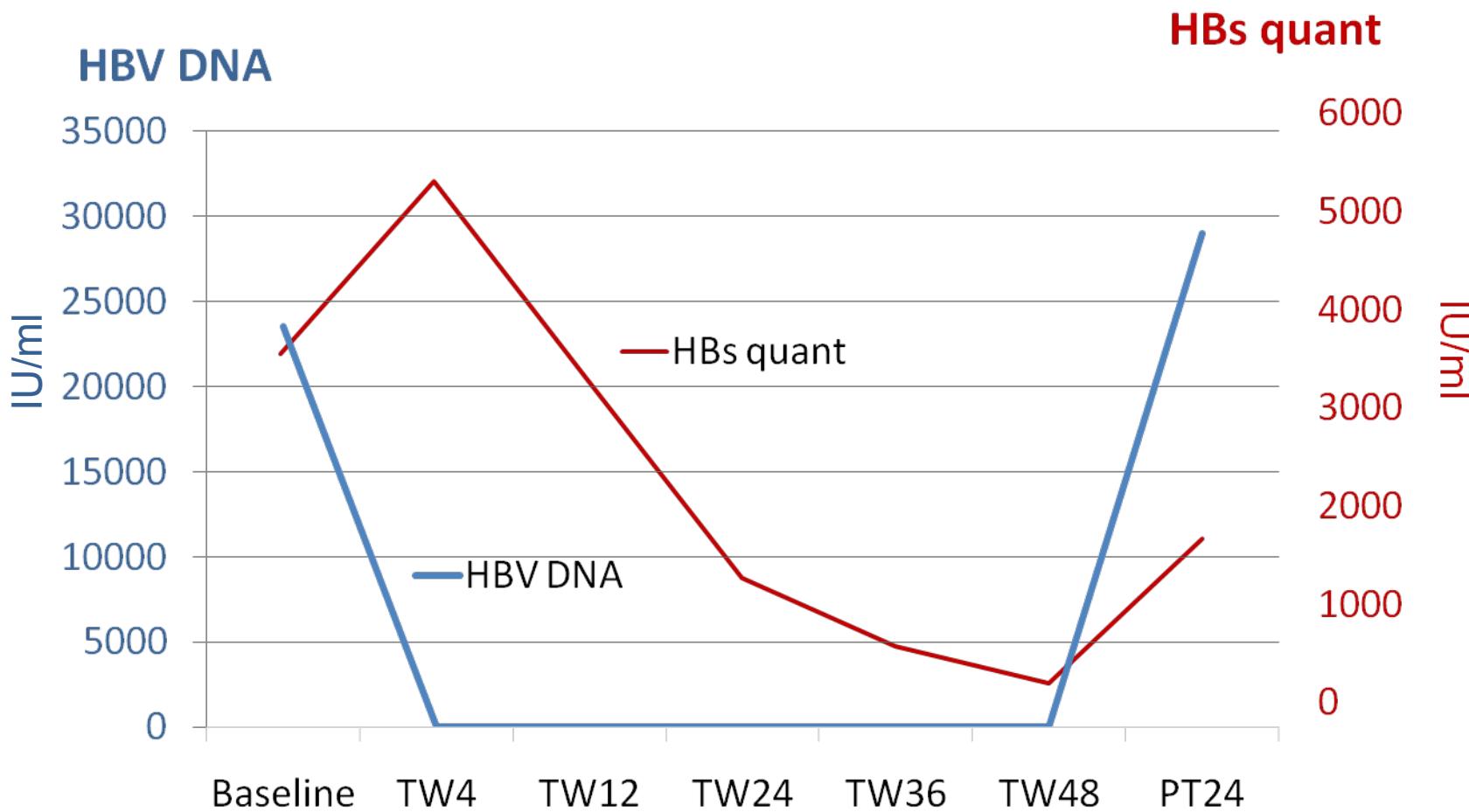


Clinical case 1, AVT, 34 y.o. man

Visit type	Baseline	TW 4	TW 12	TW 24	TW 36	TW 48	PT 24
DOV	27.04.2011	25.05.2011	21.07.2011	14.10.2011	28.12.2011	26.03.2012	19.09.2012
HBsAg	Positive					Positive	
HBeAg	Negative			Negative		Negative	
anti-HBe	Positive			Positive		Positive	
HBV DNA quant, IU/ml	23525	not detected	29000				
HBs quant, IU/ml	3553	5301		1278.8	574.9	204	1666
ALT, IU/ml	64	52	40.8	80	57	52	56
AST , IU/ml	34.5	36	116.9	43.9	36.4	31,6	42
GGT, IU/ml		80.6	19.3	107.9	86.3	79.6	53.1
Bilirubin total μmol/l	23.42	13.32	42.55	10.27	12.64	9.09	14.51
Glucose, mmol/l	5.89	5.14	7.53	4.48	4.78	5.04	5.37
PTI, %	80						
TSH, mIU/L	1.02		0.94			0.98	
RBC, x10 ¹² /L	5.37	5.79	5.47	5.91	5.9	5.44	5.35
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HGB, g/L	160	166	167	158	170	154	166

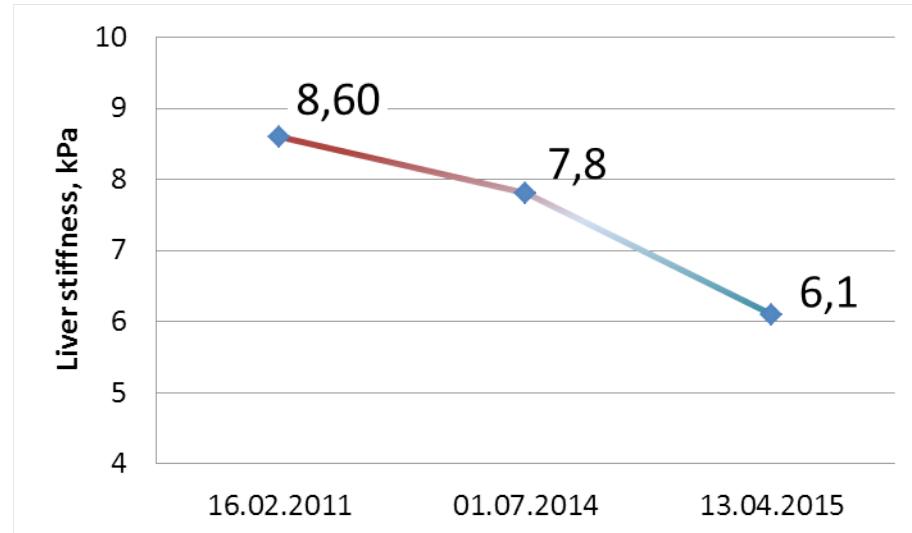
PegIFN-α2a 180 μg/week SC. Date of last dose 19.03.2012

Clinical case 1, AVT, 34 y.o. man



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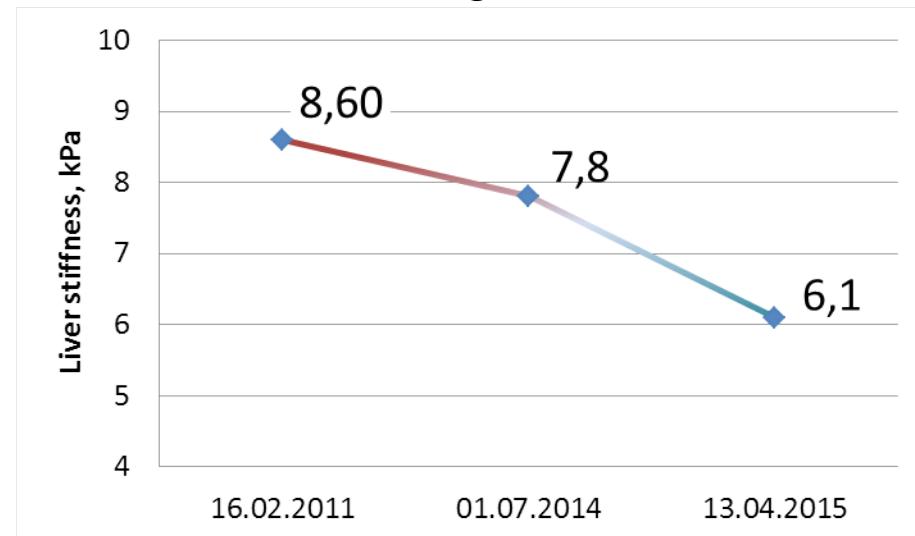
- Since 15.09.2012 patient receives Entecavir 1 mg/day with good compliance.
Concomitant medication: rosuvastatin 5 mg/day (due to ↑Cholesterol, LDLP↑)
- Persistently normal ALT, AST, HBs +, HBe-;
- Persistently negative HBV DNA.
- LSM 01.07.14 – 7.8 kPa (F2); LSM 13.04.15 – 6.1 kPa(F0-F1)
- **10.04.2015 anti-HBs 46 IU/ml, HBs +.**



Clinical case 1, AVT, 34 y.o.

man

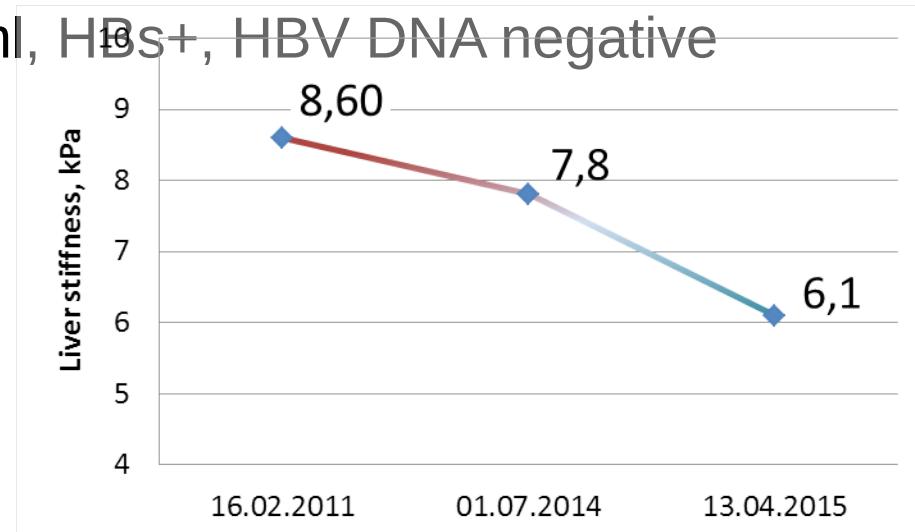
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- 20.08.2015 anti-HBs <3 IU/ml, HBs+, HBV DNA negative



Clinical case 1, AVT, 34 y.o.

man

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- LSM 01.07.14 – 7.8 kPa (F2); LSM 13.04.15 – 6.1 kPa(F0-F1)
- 10.04.2015 anti-HBs 46 IU/ml, HBs +.
- 20.08.2015 anti-HBs <3 IU/ml, HBs+, HBV DNA negative



Further treatment options?

Adding of PegIFN to a current nucleos(t)ide therapy

- 12 patients treated with NA, with undetectable HBV DNA level (9 pts HBe-).
- Added PegIFN as an individualized treatment.
- HBs clearance achieved in 2 (1 HBe-) pts at wk 40 or 32.
- Adding PegIFN to a stable course of NA may be promising
- Further larger studies are needed to obtain statistically powerful support

Clinical case 2

Clinical case 2, AAS, 38 y.o., man

- Referred in June, 13 as HCV patient
- In 2000 – IV drug use, jaundice, admitted to infectious diseases hospital, symptomatic treatment, IV drug users rehabilitation program 2001-2002.
- First examined in 2007: HCV Ab+, HBs+. ALT 189 IU/l, AST 154 IU/l, total bilirubin 19 µmol/l, HCV RNA +, HBV DNA-? HDV Ab+. Treatment considered, but postponed due to unknown reason.
- **21.04.11 (in infectious diseases hospital):**
 - Liver ultrasound - normal
 - Hematology – normal
 - Blood chemistry : bilirubin – 9µmol/l, ALT 155 IU/l, AST 70 IU/ml.
 - HBs+, HBV DNA -, HCV RNA +, genotype-? quantity? HIV Ab -.
 - Liver biopsy: 22 portal tracts, Knodell 4-1-4-3=12, METAVIR : A1 (PMN-3; LN-1)F2

27.04.11 started IFN α2a 9mln IU 3 times a week, 6 month.

PT HCV RNA negative achieved. HDV RNA – no data available.

Clinical case 2, AAS, 38 y.o., man

03.06.13 at the reference :

- Man, white/caucasian, DOB 28.05.1975.
- Denies IV drug use since 2001. Social drinking.
- General appearance, physical examination – normal.
- Height 172 cm, weight 80 kg, BMI 27.04 kg/m².
- Liver ultrasound - normal
- LSM 13.2 kPa (~F4).
- Anti HCV +, HCV RNA -, HBs+, HBV DNA 3467 IU/ml (10 400 copies/ml), HIV Ab -
- Anti HDV +, HDV RNA +
- ALT 35 IU/l, AST 23.1 IU/l, bilirubin 9.65 µmol/l, AP 53.7 IU/l, GGT 13.7 IU/l, cholesterol 4.34 mmol/l, creatinin 75 µmol/l, TP 76.8 g/l, albumin 47.1 g/l.
- PTI 75.6%, INR 1.1.

Clinical case 2, AAS, 38 y.o., man

03.06.13 at the reference :

- Man, white/caucasian, DOB 28.05.1975.
- Denies IV drug use since 2001. Social drinking.
- General appearance, physical examination – normal.
- Height 172 cm, weight 80 kg, BMI 27.04 kg/m².
- Liver ultrasound - normal
- **LSM 13.2 kPa (~F4).**
- Anti HCV +, HCV RNA -, HBs+, HBV DNA 3467 IU/ml (10 400 copies/ml), HIV Ab -
- Anti HDV +, HDV RNA +
- ALT 35 IU/l, AST 23.1 IU/l, bilirubin 9.65 µmol/l, AP 53.7 IU/l, GGT 13.7 IU/l, cholesterol 4.34 mmol/l, creatinin 75 µmol/l, TP 76.8 g/l, albumin 47.1 g/l.
- PTI 75.6%, INR 1.1 **Consider treatment?**

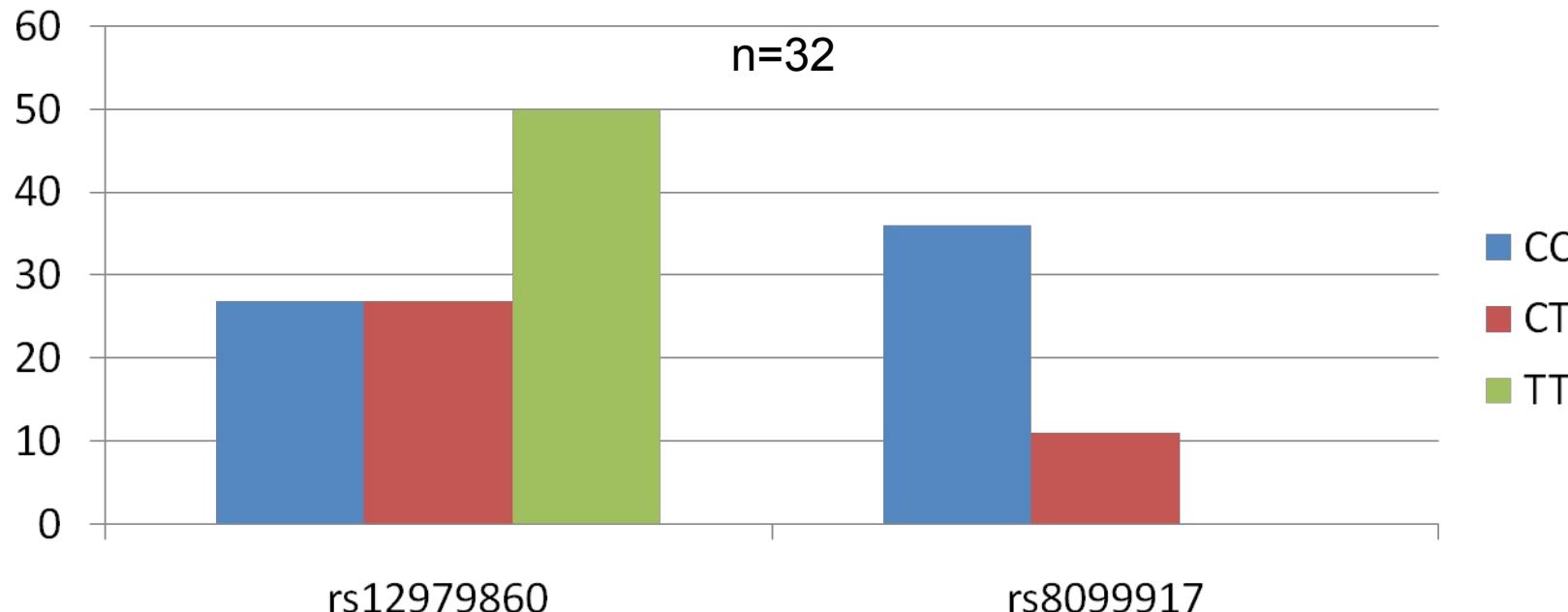
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Rates of sustained virologic response to IFN α therapy in HDV

	rs12979860			P value	rs8099917			P value
	CC	CT	TT		TT	TG	GG	
EoT response, n/total (%)	7/15 (47)	8/15 (53)	1/2 (50)	.94	12/22 (54)	4/9 (44)	0/1 (0)	.52
SVR, n/total (%)	4/15 (27)	4/15 (27)	1/2 (50)	.78	8/22 (36)	1/9 (11)	0/1 (0)	.30



HDV treatment predictors

- A negative HDV RNA at 6 months of treatment was the only predictor of SVR (OR = 20; 95% CI 2, 195; P = 0.01).
- Previous exposure to IFN treatment is a negative predictive factor

Clinical case 2, AAS, 38 y.o., man

- 10 JUN 2013 PegIFN α2b 120 µg/week was initiated.
- General tolerance – good

Clinical case 2, AAS, 38 y.o.,

man

Visit type	Baseline	TW 4	TW 12	TW 24	TW 36	TW 48	PT 34
DOV	03.06.13	08.07.13	02.09.13	18.11.13	10.02.14	05.05.14	25.12.14
HBsAg	Positive			Positive		Negative	Negative
HBeAg	Negative					Negative	Negative
anti-HBe	Positive			Positive		Positive	Negative
AntiHBs	Negative			Negative	7,76 (negative)		300 IU/ml
HBV DNA, IU/ml	3467	not detected	not detected	not detected	not detected	not detected	not detected
HDV RNA	+	+	Not detected	Not detected	Not detected	Not detected	Not detected
HBs quant, IU/ml							
ALT, IU/ml	35	120	231	133	140	126	13
AST, IU/ml	23.1	56.8	86.9	65.3	85.4	82.4	16.8
GGT, IU/ml	13.7	20.1	47.3	33.9		25.6	
Bilirubin total µmol/l	9.65	9.48	12.55	8.7		7.7	
INR	1.1	0.91	0.9	0.9			
TSH, mIU/L	0.95			2.13		2.91	
WBC x10 ⁹ /L	7.2	4.9	5.47	3.4	4.66	4.31	5.7
ANC x10 ⁹ /L	3.0	1.5	40.6	50.4	1.8	1.9	3.6
PLT, x10 ⁹ /L	202	106	163	180	112	125.9	251
HGB, g/L	149	146	167	158	141.3	136.3	154

07.04.14 (Wk 44): **HBs negative**, HBsAb <3.0IU/ml

Summary of PegIFN as HBV Therapy

- Advantages: finite duration of treatment, durable response in a subset of responding patients; lack of viral resistance development
- Disadvantages: administered by subcutaneous injections; associated with significant toxicities in most patients
- HBeAg and HBsAg seroconversion rates, tolerability, and likelihood of response to treatment vs nucleos(t)ides all play a role decision

Conclusions

Host factors:

Gender
Age
Genes affecting IFN response
BMI
Ethnicity
Nutrition
Previous treatment experience

Pathogen factors:

Genotype
Fitness
Mutations (?)

Environmental factors:

Access to different types of treatment
Family support during treatment

Conclusions

- PegIFN is the only finite treatment to offer a chance of SVR in CHB patients approved now.
- Current efficacy of <25% chances to be cured supported the need of identification of prognostic factors of favorable response.
- Further studies are needed to identify predictors of response and provide individualized treatment