Using Hepatitis B Surface Antigen Quantification to the Management of Hepatitis B

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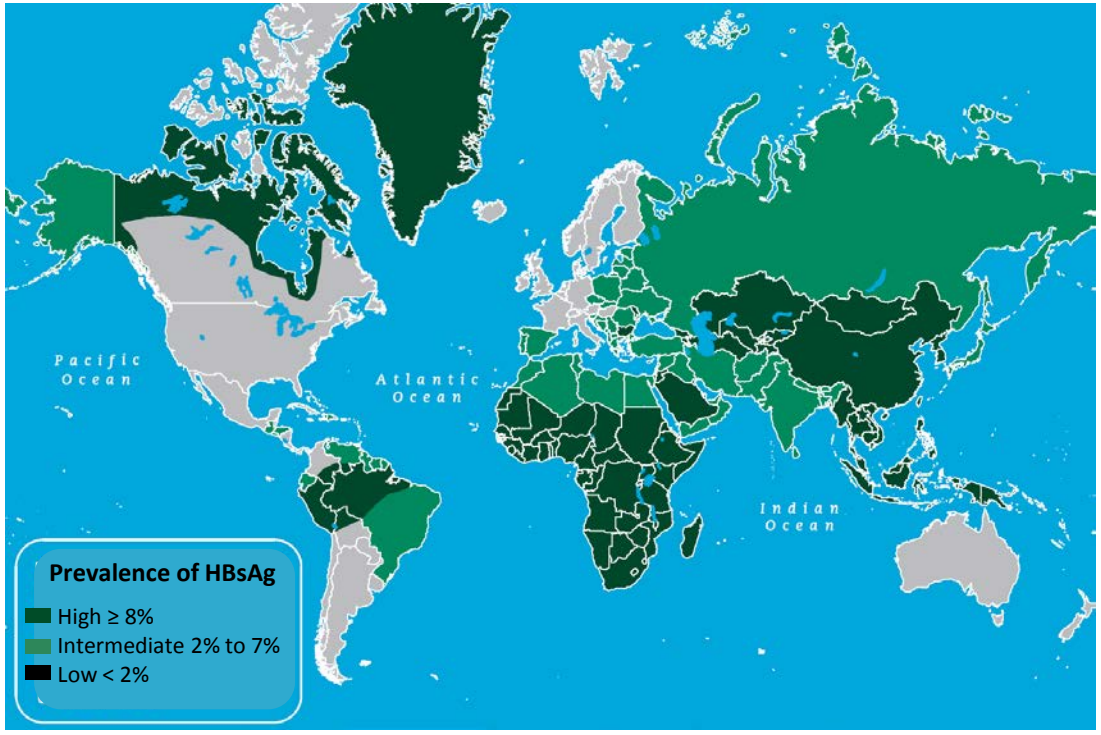
2012/05/19

Hepatitis B: Epidemiology

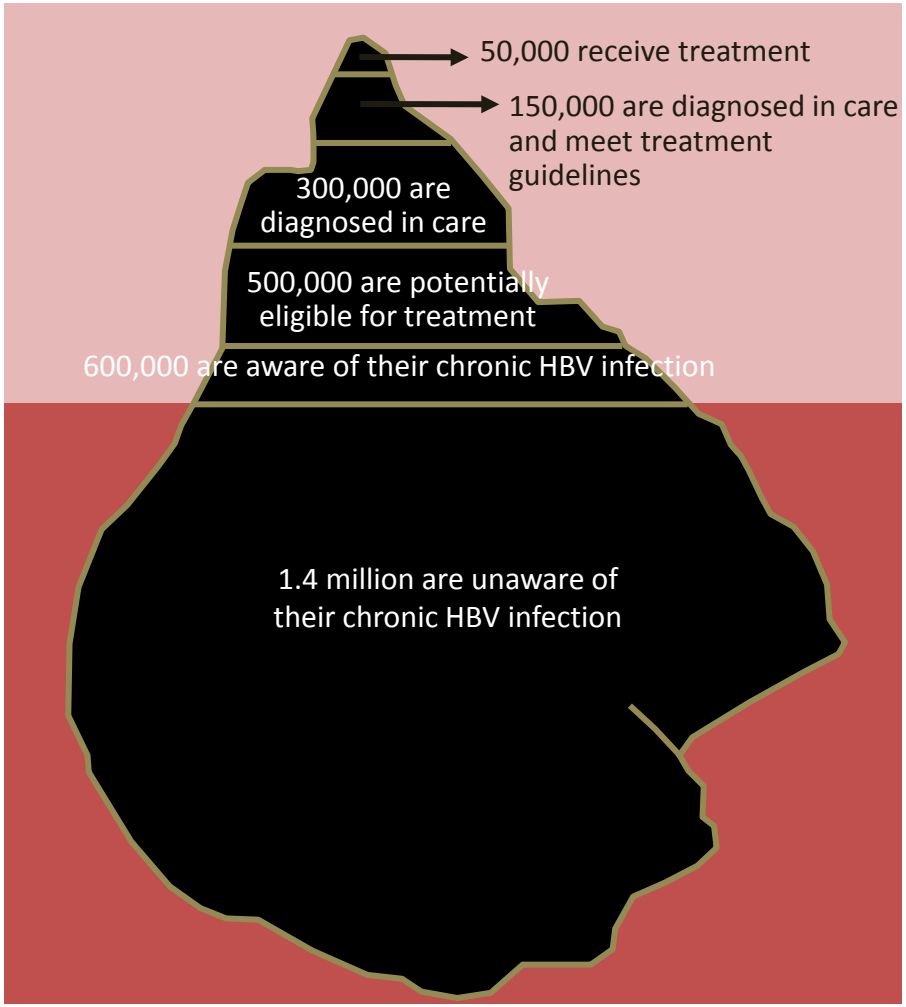


- 350 million people chronically infected
- 2 billion with evidence of past or present infection
- Country of origin is THE major risk factor

World Health Organization. Hepatitis B Fact Sheet. Centers for Disease Control and Prevention. CDC Health Information for International Travel 2012. New York: Oxford University Press; 2012.

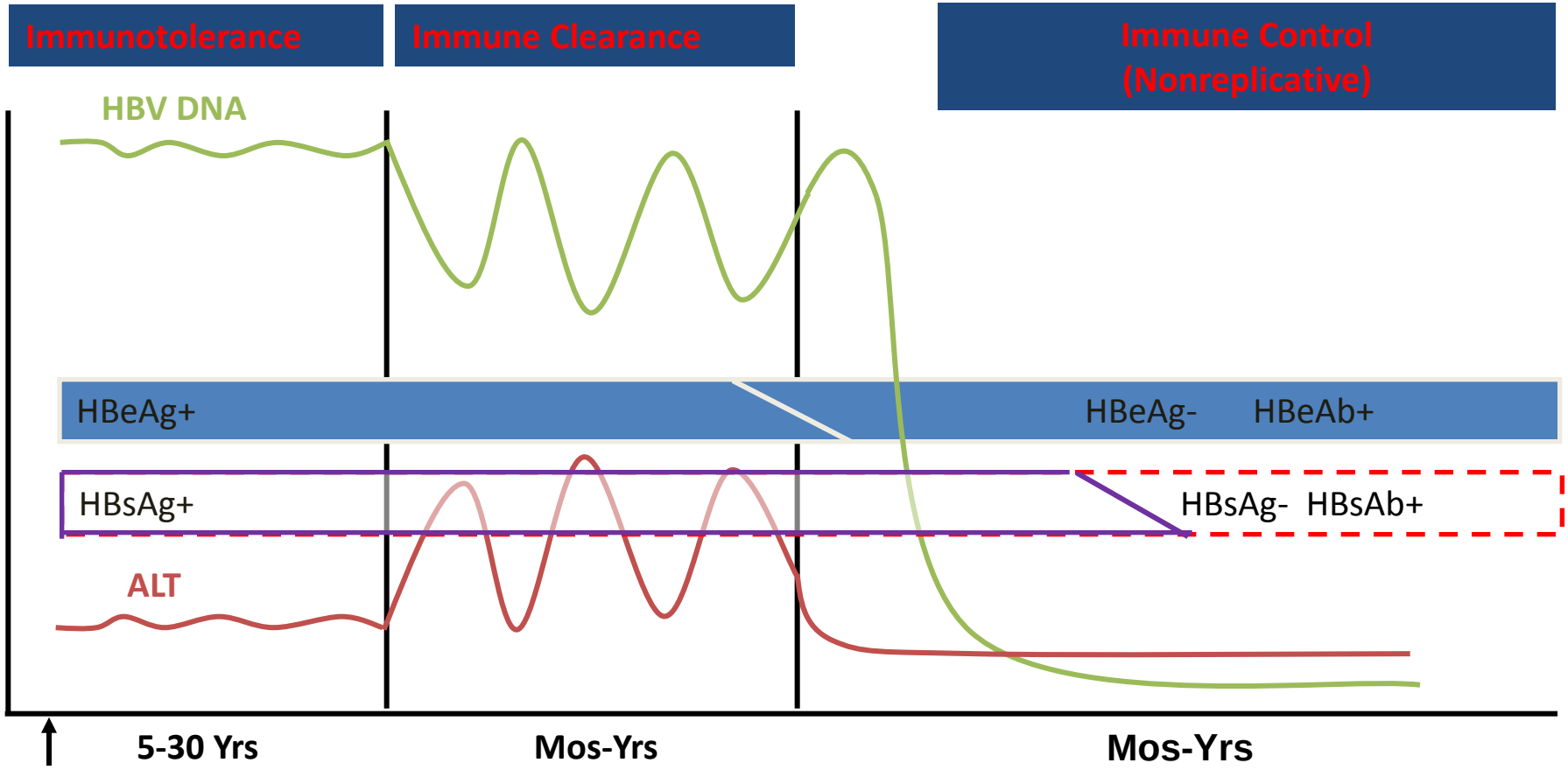
The HBV Iceberg

- Clinical populations are the tip of the iceberg
- Individuals in treatment are the tip of the tip
- Population-based studies allow us to look at the whole iceberg
  - Asia has been the place for these



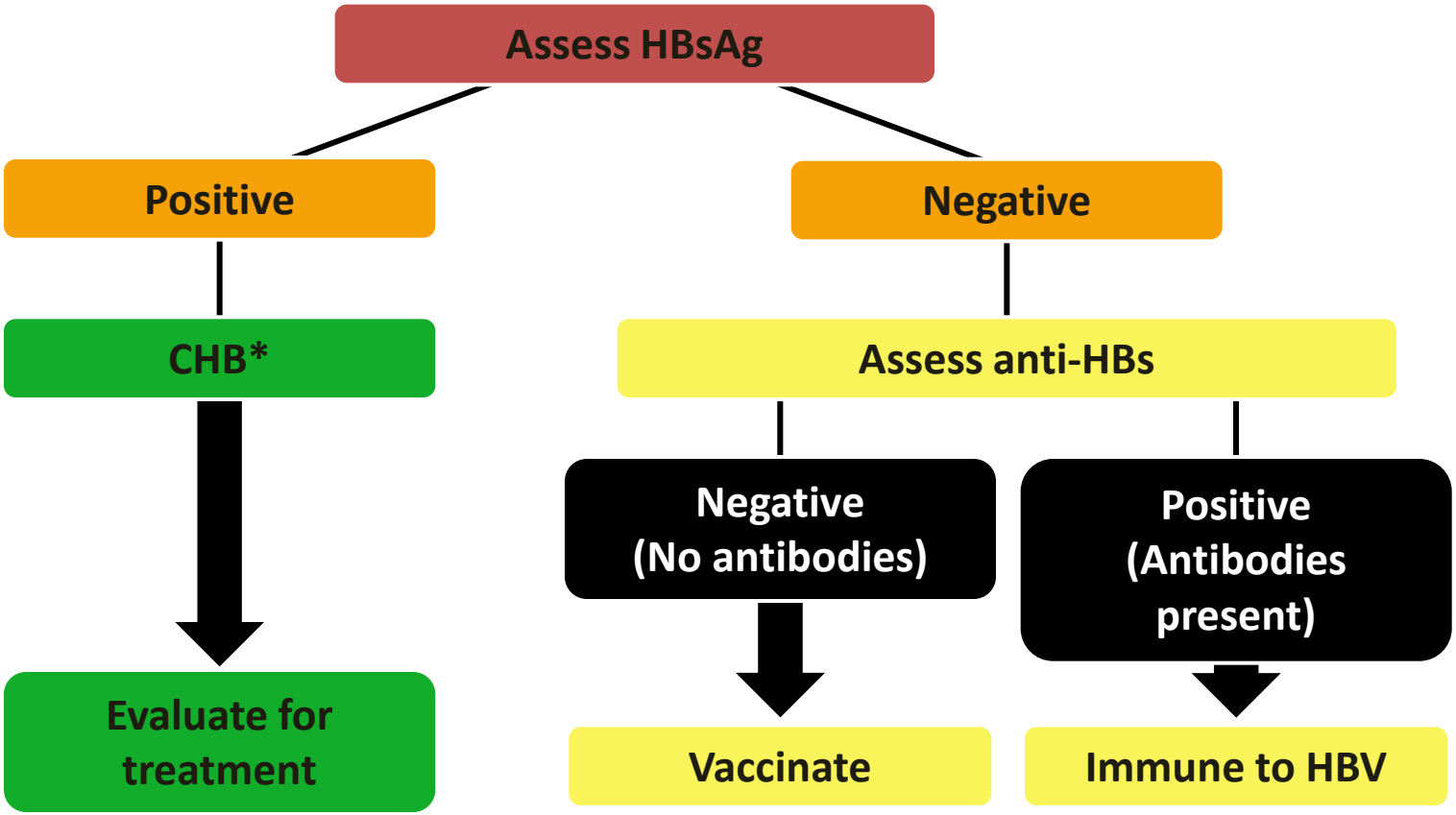
Cohen C, et al. J Viral Hepatitis. 2011;18:377-383. Graphic reproduced with permission.

Natural History of Chronic HBV Infection



Yim HJ, et al. Hepatology. 2006;43:S173-S181.

HBV Screening Algorithm



*Time from positive HBsAg test to diagnosis of CHB is 6 mos.

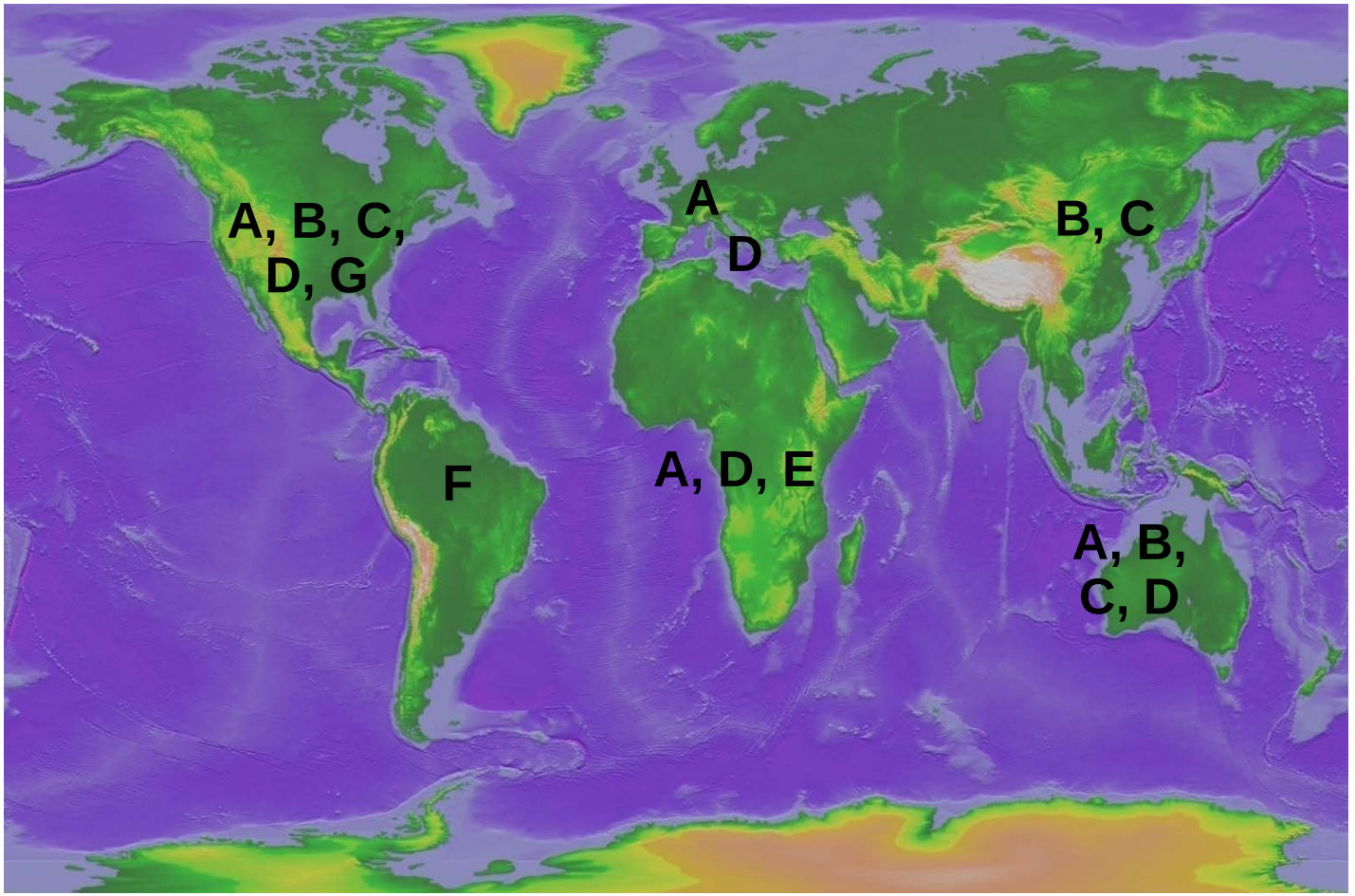
Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341.

Hepatitis B Serology: First Phase Testing

- AASLD guidelines recommend HBsAg and anti-HBs testing for all patients
  - HBsAg
    - Protein on surface of HBV detected during acute or chronic HBV infection
    - Presence indicates an individual is INFECTED OR INFECTIOUS
  - Anti-HBs
    - Presence indicates recovery and IMMUNITY from HBV infection
    - Also develops following vaccination against hepatitis B
- Total anti-HBc can be used as alternative; those testing positive should be tested for HBsAg and anti-HBs
  - Appears at the onset of symptoms in acute hepatitis and persists for life
  - Presence indicates EXPOSURE (previous or ongoing infection with HBV)

Lok AS, et al. Hepatology. 2009;50:661-662.

Geographic Distribution of HBV Genotypes



Liaw YF, et al. Liver Int. 2005;25:472-489. Chu CJ, et al. Gastroenterology. 2003;125:444-451.

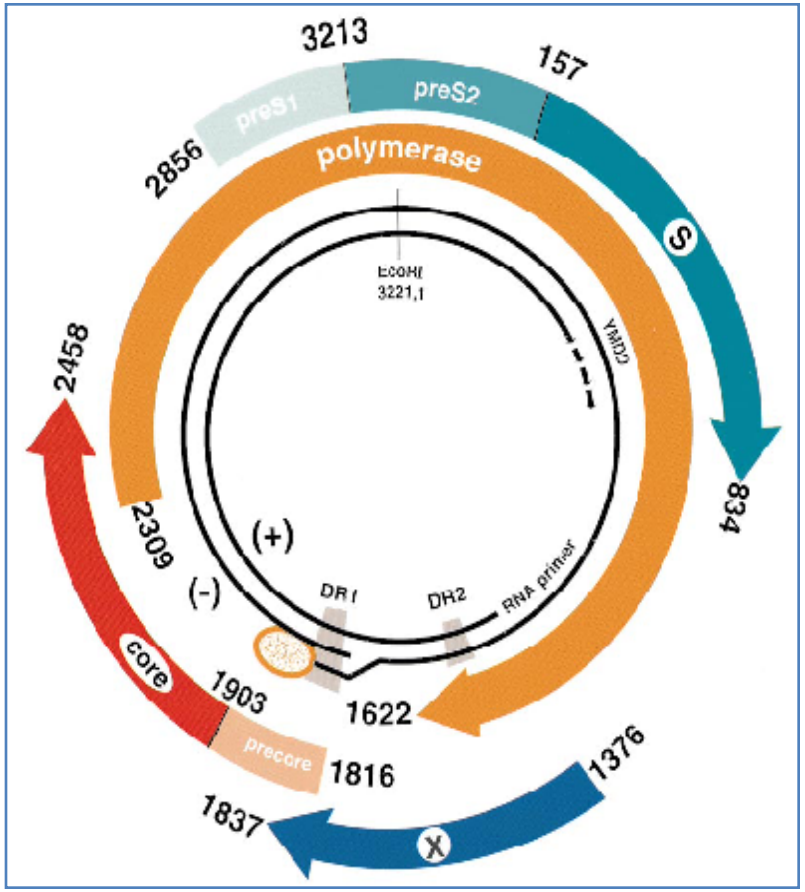
HBV Classified Into 10 Genotypes

Genotype	Geographic distribution
A	North America, northern Europe, India, and Africa
B and C	Asia
D	Southern Europe, Middle East, and India
E	West Africa and South Africa
F	Central and South America
G	United States and Europe
H	Central America and California
I	Vietnam
J	Japan

Fung SK, et al. 2004;40:790-792. Norder H, et al. Intervirology. 2004;47:289-309. Tuan Huy TT, et al. J Virol. 2008;82:5657-5663. Tatematsu K, et al. J Virol. 2009;83:10538-10547.

HBV Variants

- Wild type
  - Unmutated HBeAg-positive hepatitis
  - Mixed infection with
    - Basal core promoter mutations (44% of US patients)[1,2]
    - Precore mutations (27% of US patients)[2]
- Precore and core promoter mutations[3]
  - Eventually abolishes HBeAg production (HBeAg-negative CHB)
- Genotypes
- Treatment-induced mutations



1. Buckwold VE, et al. J Virol. 1996;70:5845-5851. 2. Chu CJ, et al. Gastroenterology. 2003;125:444-451.
3. Hunt CM, et al. Hepatology. 2000; 31:1037-1044.

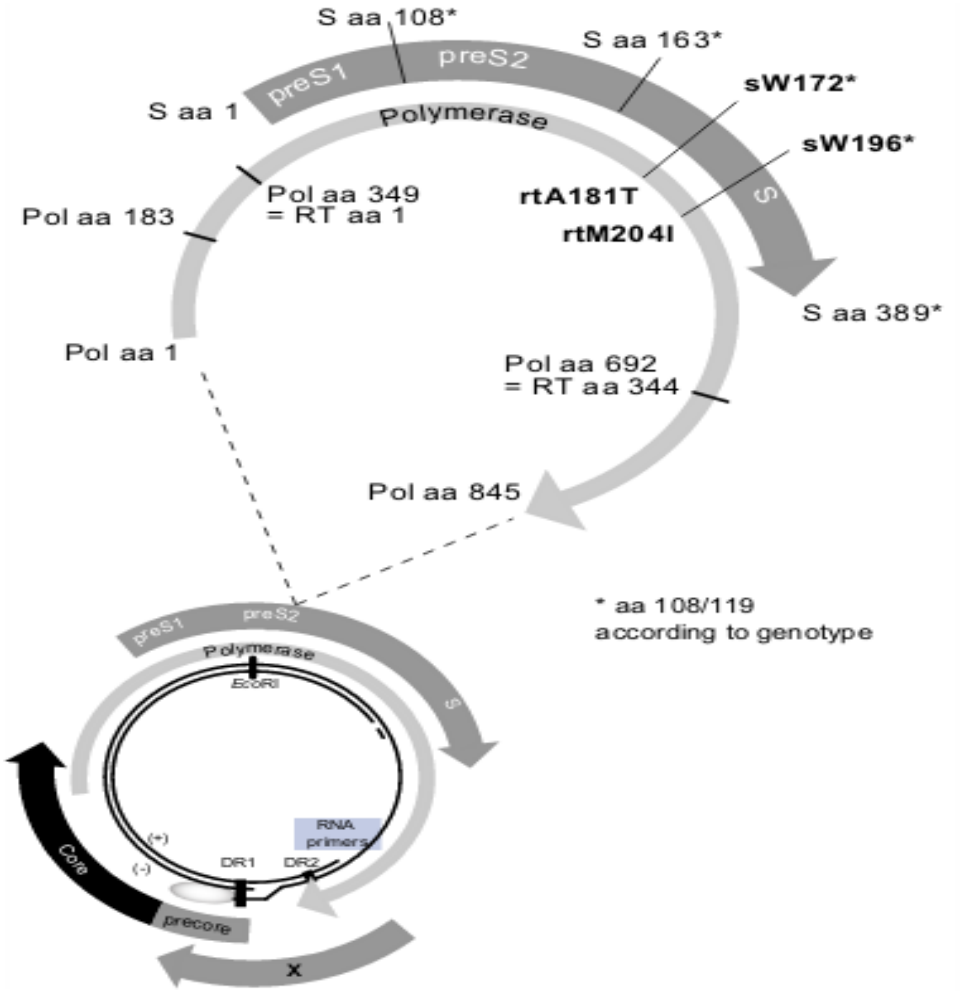


Fig. 1. The HBV open reading frames (ORF), highlighting the overlapping relationship between the envelope ORF and the HBV polymerase ORF.

J of Hepatology 2011;55:1121-1131

High Risk of Cirrhosis in Asians & Patients With Vertically Transmitted Disease

- The lifetime risk of cirrhosis or cancer in a person who is HBsAg positive is 20% to 30%
  - Risk is lower for women
  - Risk is highest for men

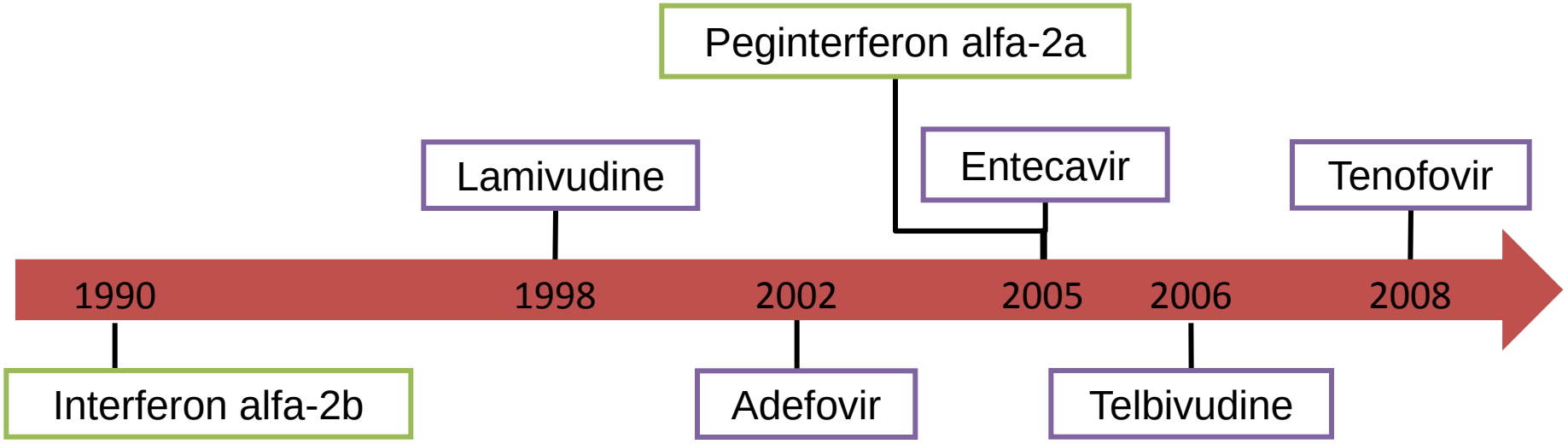
Fattovich G, et al. Am J Gastroenterol. 2002;97:2886-2895. Fattovich G, et al. Gastroenterology. 2004;11;27:S35-S50. McMahin BJ. Hepatology. 2009;49:S45-S55.

Why Test for HBV Genotype?

- Differences in natural history and treatment responsiveness
  - B is associated with less active disease, slower progression, and lower incidence of HCC than C
  - C has higher risk of HCC and cirrhosis
  - A and B respond better to IFN than C and D
  - F is associated with fulminant liver disease; rare

Lok AS, et al. Hepatology. 2009;50:661-662. EASL. J Hepatol. 2009;50:227-242.

HBV Treatment Landscape in 2010



HBV life cycle

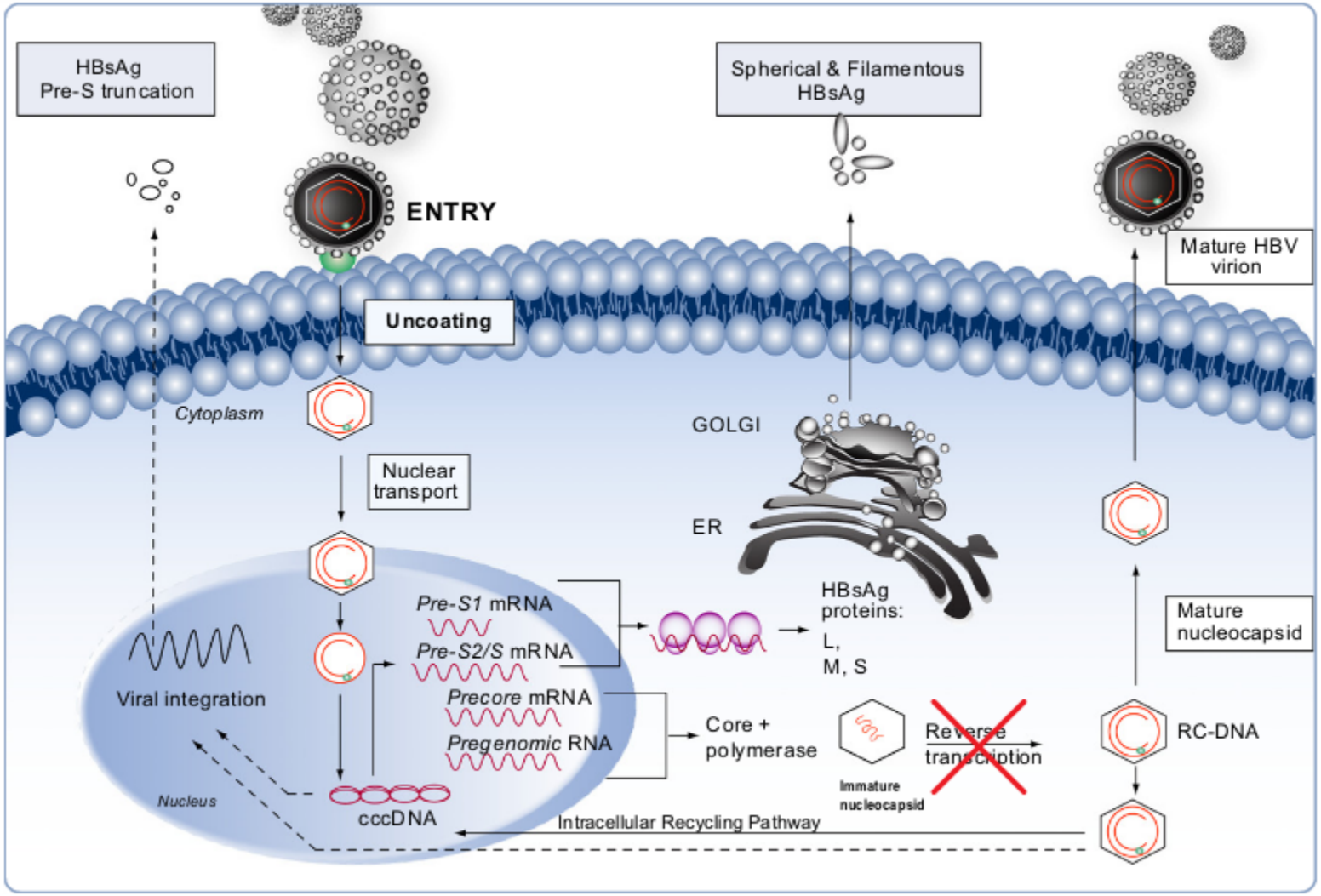


Fig. 2. HVB lifecycle. The lifecycle of HBV, highlighting: (i) the nuclear reservoir, covalently closed circular (ccc) DNA, which is the transcriptional template for the virus; (ii)

J of Hepatology 2011;55:1121-1131

Natural history : HBsAg level

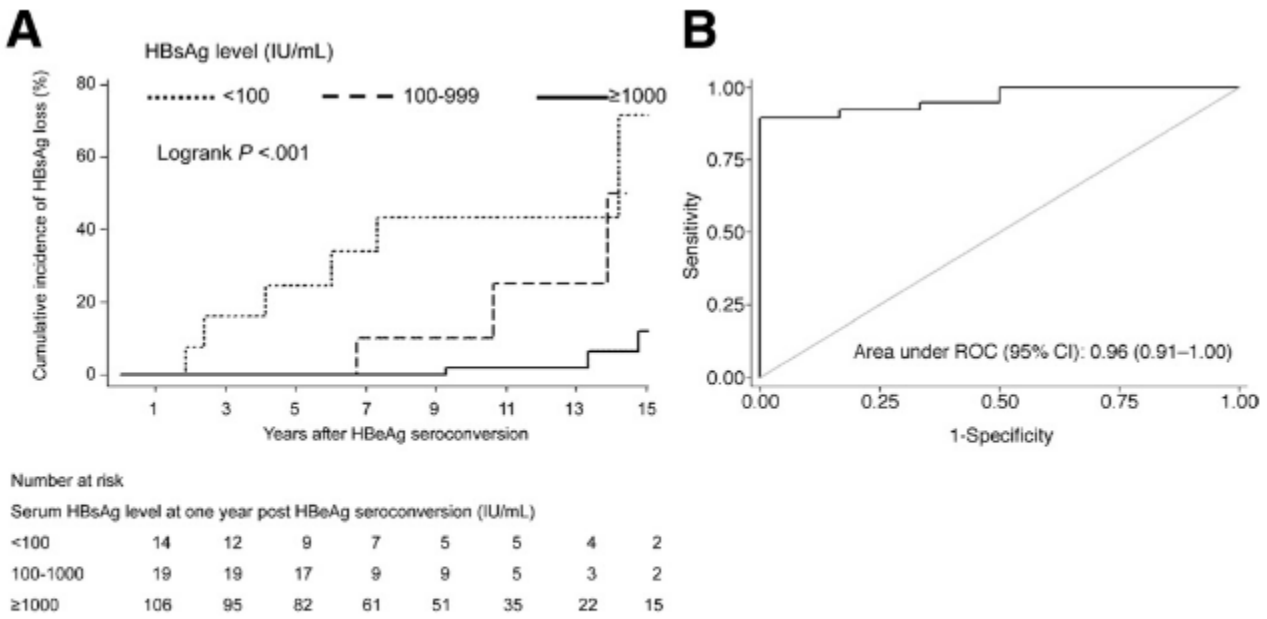
Serum Hepatitis B Surface Antigen Levels Predict Surface Antigen Loss in Hepatitis B e Antigen Seroconverters

Table 3. Univariate and Multivariate Analysis of Factors Associated With HBsAg Loss by Cox Proportional Hazards Regression Model

	Patient-years of follow-up	Annual incidence rate (per 100 patient-years)	Crude HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Sex						
Female	829.8	1.1	1.0		1.0	
Male	2060.7	0.4	0.4 (0.1–0.9)	.033	0.4 (0.1–1.2)	.111
Age at HBeAg seroconversion (*y*)						
Younger than 40	2617.5	0.6	1.0		1.0	
40 and older	273.0	1.1	2.5 (0.7–9.0)	.155	4.8 (1.1–21.1)	.040
Serum ALT level[a] (*U/L*)						
<40	2514.2	0.7	1.0		1.0	
40–79	376.4	0.3	0.4 (0.1–3.3)	.429	1.1 (0.1–9.4)	.902
Serum HBV DNA level[a] (*IU/mL*)						
≥2000	1200.9	0.1	1.0		1.0	
200–1999	604.3	0.7	6.0 (1.0–80.5)	.050	20.7 (2.0–211.1)	.010
<200	1085.4	1.2	14.6 (1.9–111.6)	.010	8.8 (1.1–75.0)	.046
Serum HBsAg level[a] (*IU/mL*)						
≥1000	2514.5	0.3	1.0		1.0	
100–999	260.4	1.2	4.4 (1.1–17.0)	.032	5.1 (1.1–23.8)	.041
<100	115.7	6.9	24.3 (8.7–67.5)	<.001	20.8 (5.7–76.7)	<.001
HBV genotype						
B	2176.3	0.5	1.0		1.0	
C	555.2	0.7	1.6 (0.5–5.1)	.442	2.3 (0.6–8.2)	.215
Undetermined[b]	158.2	1.9	3.4 (0.9–12.5)	.063	1.4 (0.3–6.3)	.653

Gastroenterololy 2011;141:517-525

HBsAg less than 100 IU/mL with a higher rate of HBsAg loss



Number at risk

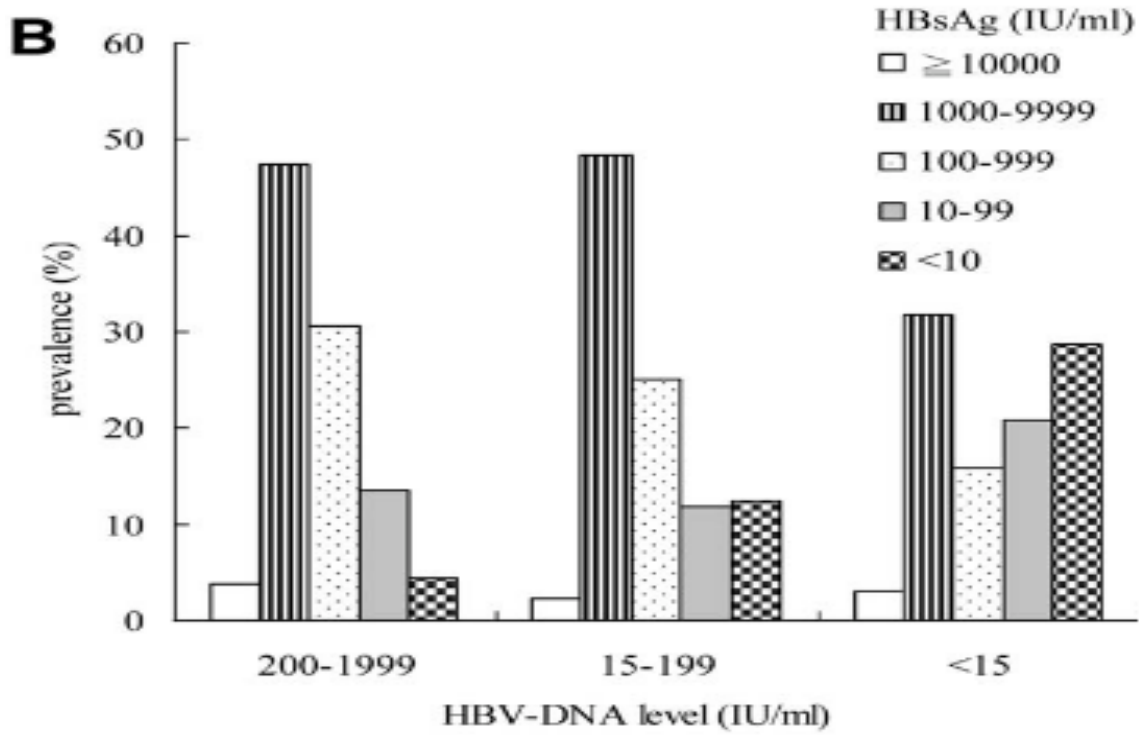
Serum HBsAg level at one year post HBeAg seroconversion (IU/mL)

<100	14	12	9	7	5	5	4	2
100-1000	19	19	17	9	9	5	3	2
≥1000	106	95	82	61	51	35	22	15

Figure 3. Serum HBsAg levels were associated with HBsAg loss in patients with HBV DNA levels <200 IU/mL. (*A*) A lower HBsAg level was associated with a higher cumulative incidence of HBsAg loss. (*B*) The ROC curve of serum HBsAg levels for the prediction of HBsAg loss within 6 years of follow-up.

Gastroenterololy 2011;141:517-525

Determinants of Spontaneous Surface Antigen Loss in Hepatitis B e Antigen–Negative Patients with a Low Viral Load



Hepatology 2012;55;68-76

HBsAg level less than 10 IU/mL is strong predictor of HBsAg loss

Table 2. Univariate and Multivariate Analysis of Factors Associated with HBsAg Loss by Cox Proportional Hazards Regression Model

Characteristic	P-yrs of Follow-Up	Annual Incidence Rate (per 100 P-yrs)	Crude HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Sex						
Female	3642.3	1.3	1.0	-	1.0	-
Male	4363.6	1.9	1.5 (1.1-2.2)	0.021	1.7 (1.2-2.5)	0.004
Age at enrollment (years)						
28-39	4558.3	1.4	1.0	-	1.0	-
40-49	2350.5	1.6	1.1 (0.7-1.6)	0.742	0.9 (0.6-1.3)	0.520
≥50	1097.1	2.5	1.9 (1.2-3.1)	0.004	1.3 (0.8-2.1)	0.214
Serum ALT level (U/L)						
≦40	6983.0	1.7	1.0	-	1.0	-
>40	1022.9	1.4	0.9 (0.5-1.5)	0.604	0.7 (0.4-1.2)	0.231
Serum HBV DNA level (IU/mL)						
15-1999	6916.3	1.5	1.0	-	1.0	-
<15	1089.6	2.5	1.7 (1.1-2.6)	0.013	1.0 (0.6-1.6)	0.972
Serum HBsAg level (IU/mL)						
≥1000	4102.3	0.7	1.0	-	1.0	-
100-999	2264.4	1.8	2.5 (1.6-4.0)	<0.001	2.6 (1.6-4.1)	<0.001
10-99	1110.2	1.9	2.8 (1.6-5.0)	<0.001	2.8 (1.6-5.0)	<0.001
<10	529.0	7.4	13.2 (8.1-21.5)	<0.001	13.2 (7.8-22.1)	<0.001

P-yrs, person-years.

Hepatology 2012;55;68-76

HBV DNA level less than 2000 IU/ml with HBsAg level less than 10 IU/ml related HBsAg loss

	Immune tolerance	Immune clearance	Inactive carrier state		HBsAg loss
			Detectable HBV-DNA	Undetectable HBV-DNA	
HBeAg/ Anti-HBe	HBeAg		Anti-HBe		Anti-HBe
ALT (U/L)	low	elevated	low		low
HBV-DNA level (IU/mL)	> 200,000	> 20,000	15-1999	<15	<15
HBsAg level (IU/mL)	> 10,000	>1000	10-10,000	<10,000	<0.05
% of HBsAg <10 IU/mL	<1%	<1%	**6.8%**	**28.7%**	

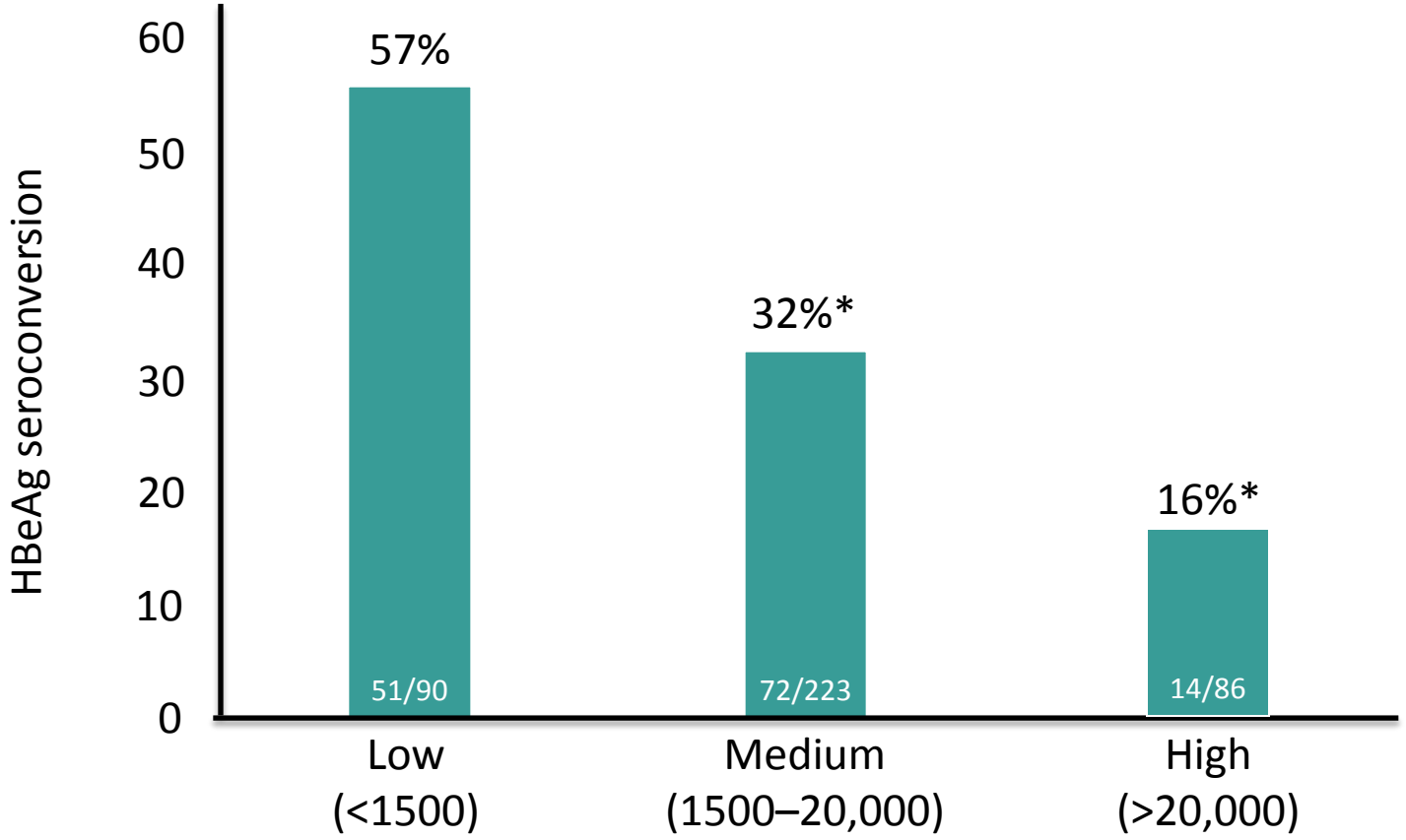
(7.0% per year)

Hepatology 2012;55;68-76

Peginterferon treatment

Lowest HBsAg levels at week 12 are associated with highest rate of sustained immune control

HBeAg-positive patients (N=399) treated with Peginterferon alfa-2a ± lamivudine

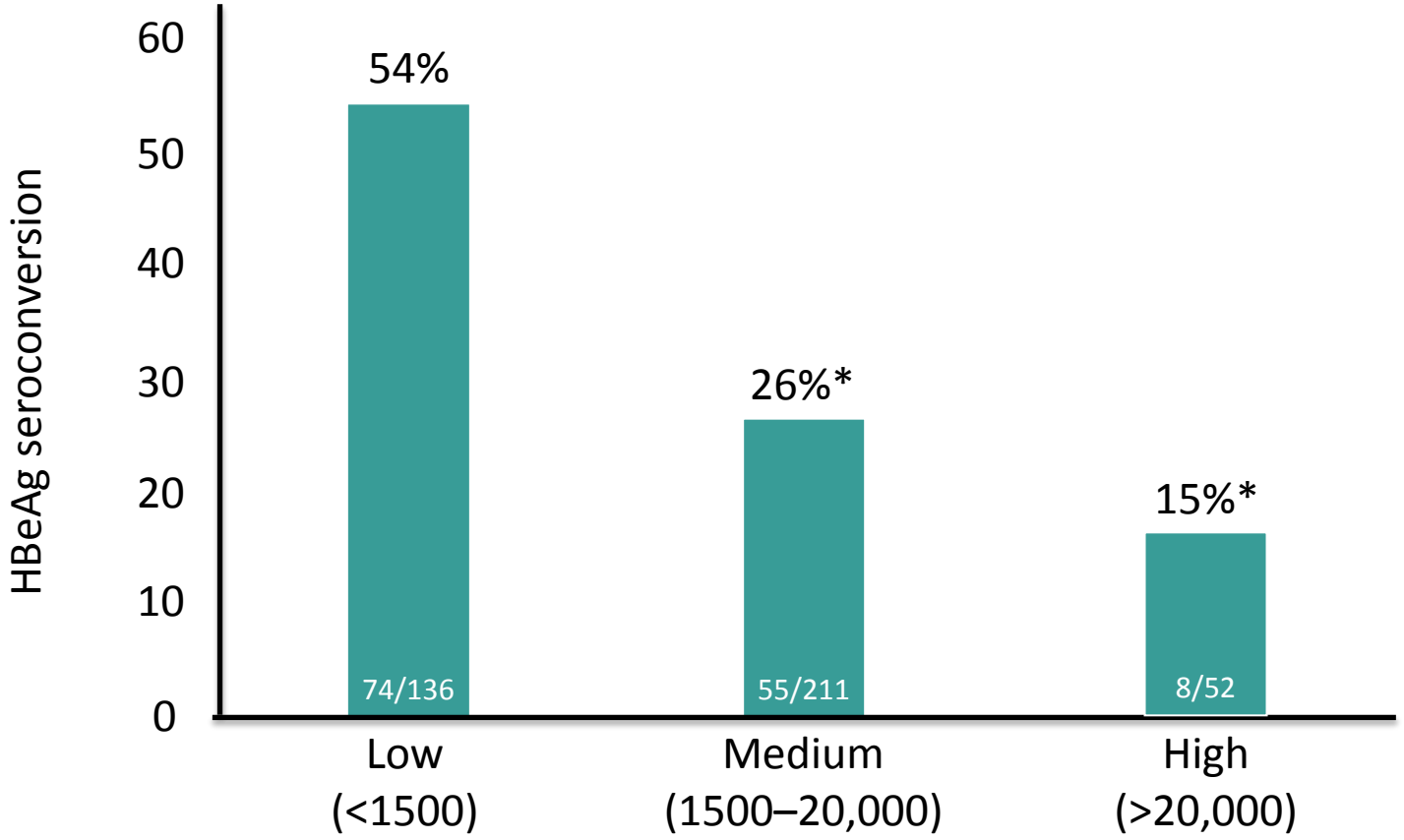


* P<0.0001 vs <1500 IU/mL

Piratvisuth et al. Hepatol Int. 2011 Jun 24. [Epub ahead of print]

Lowest HBsAg levels at week 24 are associated with highest rate of sustained immune control

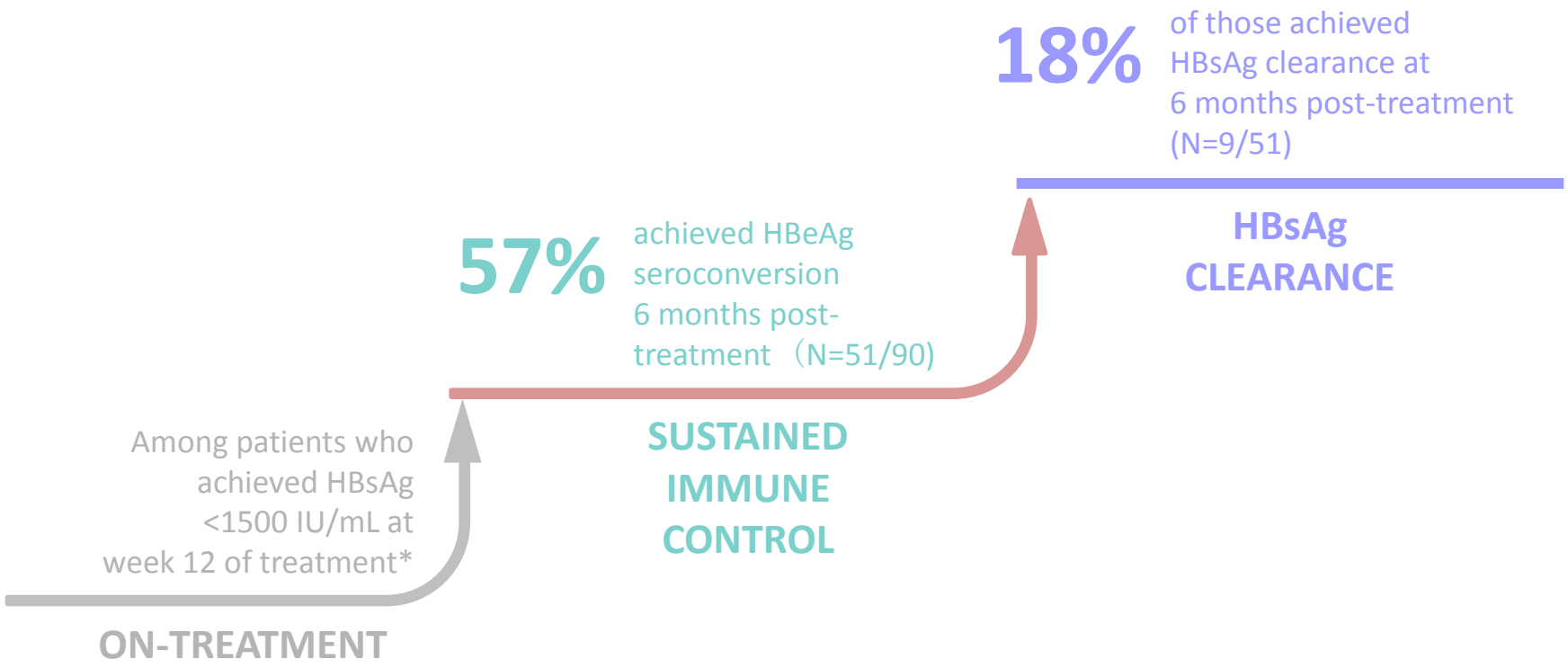
HBeAg-positive patients (N=399) treated with Peginterferon alfa-2a ± lamivudine



* P<0.0001 vs <1500 IU/mL

Piratvisuth et al. Hepatol Int. 2011 Jun 24. [Epub

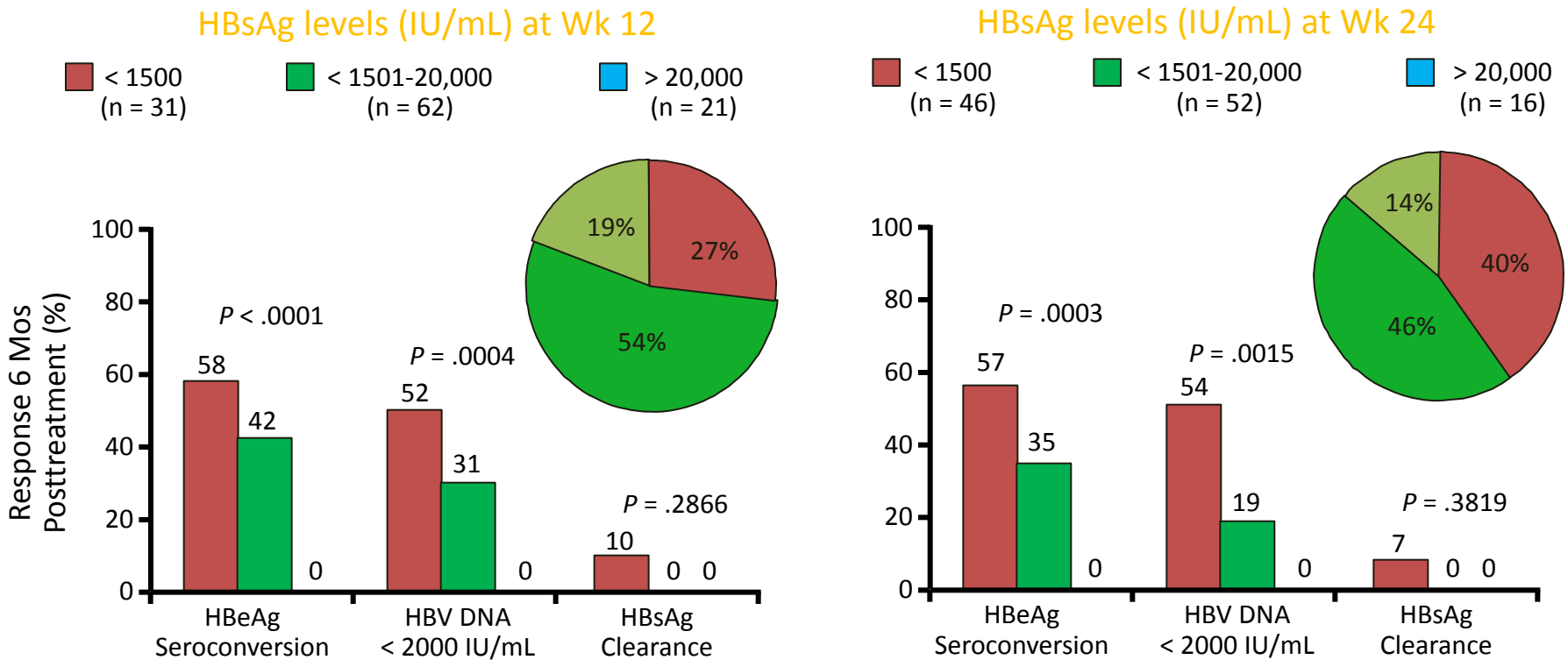
HBsAg decline at week 12 is an early sign of future HBsAg clearance



Piratvisuth et al. Hepatol Int. 2011 Jun 24. [Epub ahead of print]

NEPTUNE: On-Treatment HBsAg Level as Marker of Response to PegIFN

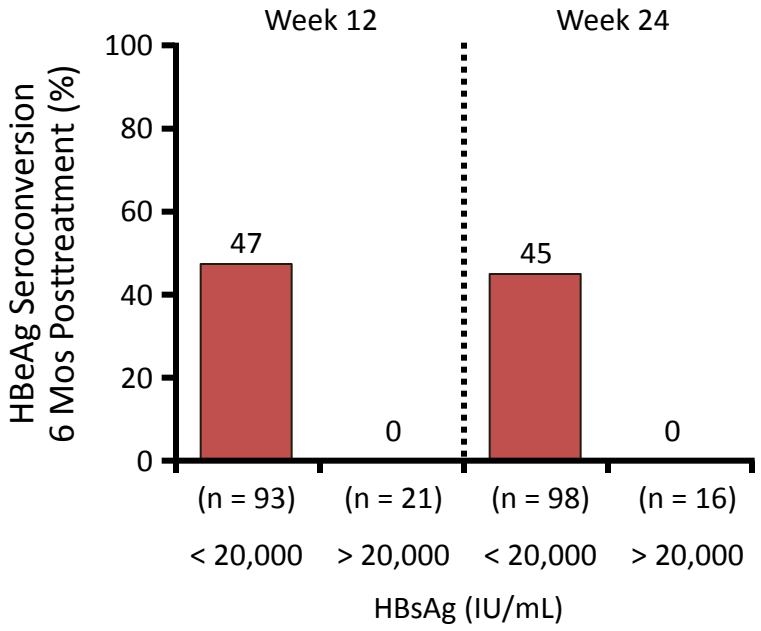
- HBeAg-positive patients: pegIFN alfa-2a 180 µg/wk for 48 wks
  - HBsAg analyzed at baseline and every 12 wks



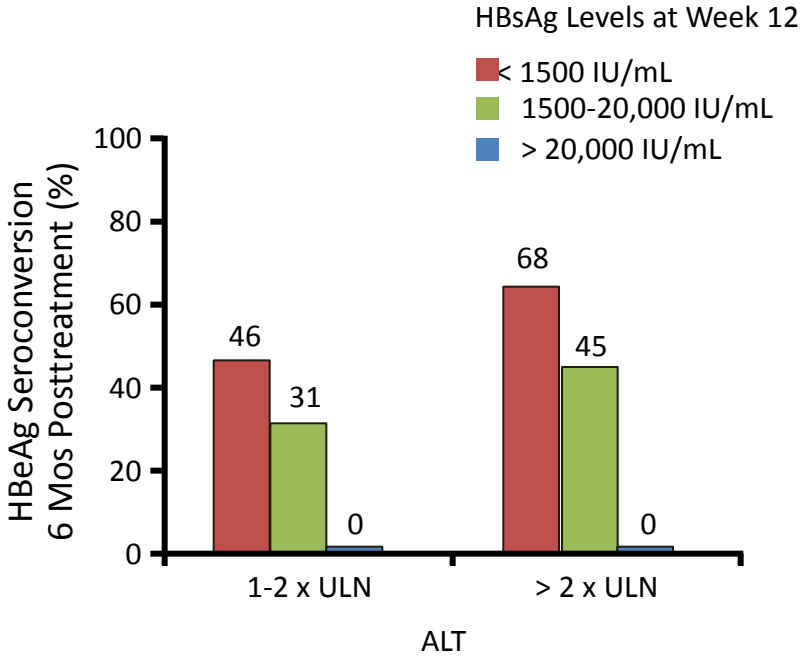
Gane E, et al. EASL 2011. Abstract 69. Graphic used with permission.

NEPTUNE: On-Treatment HBsAg as Marker of Response to PegIFN

- HBsAg < 20,000 IU/mL identified as key marker of response
- HBsAg > 20,000 IU/mL at Week 12 or 24 predicts lack of HBeAg seroconversion
  - Negative predictive value: 100%



- Combination of ALT level and HBsAg decline improves positive predictive value



Gane E, et al. EASL 2011. Abstract 69.

HBsAg level as predicted at week 12 and week 24

Review

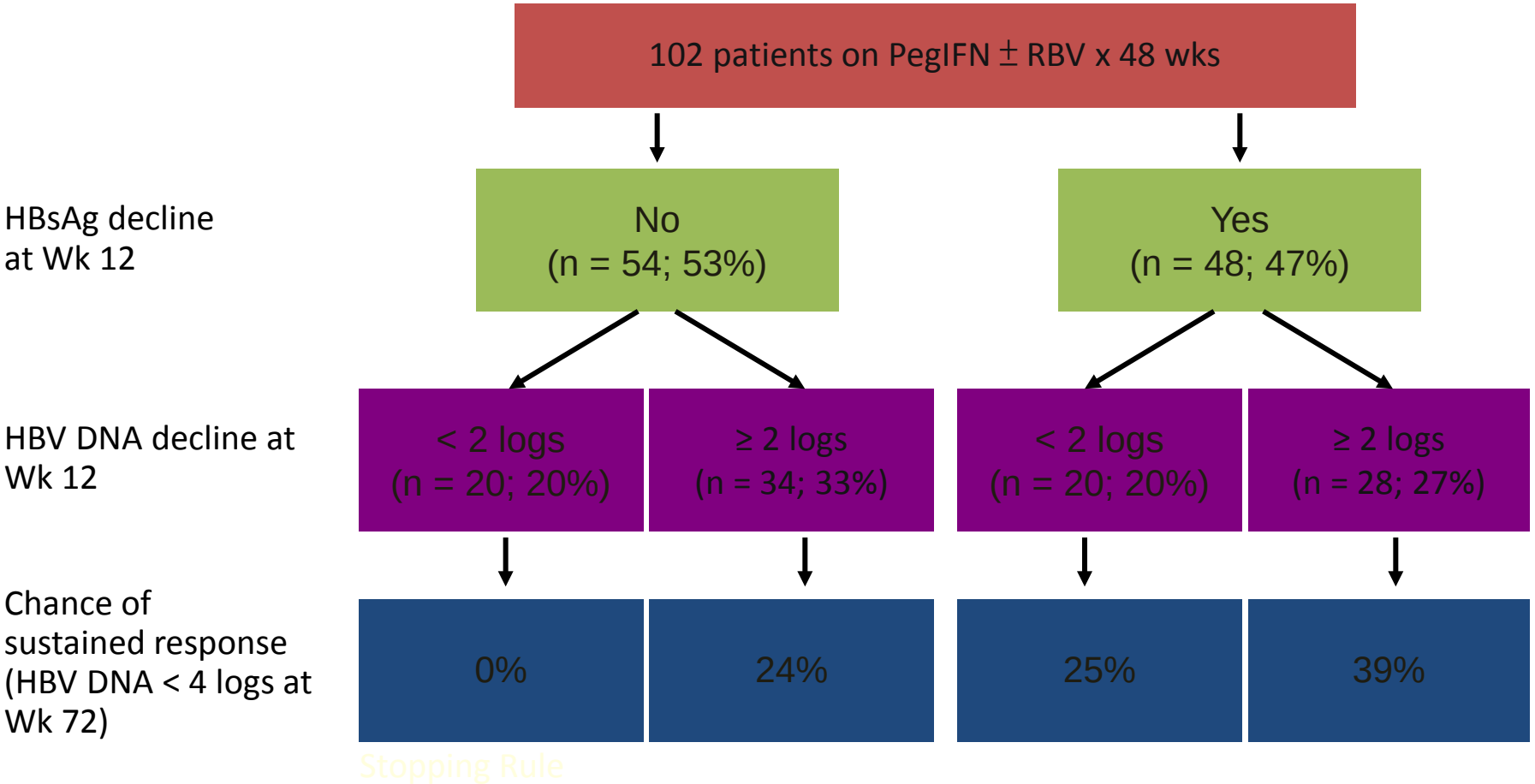
Table 1. Proportion of HBeAg-positive patients with sustained virological response (SVR) as predicted by serum HBsAg at week 12 and 24 of treatment. In general, poor HBsAg response at week 12 can predict non-responders and good HBsAg response at week 24 can predict good responders to peginterferon therapy.

			Prediction at week 12		Prediction at week 24	
Author	[Reference]	HBsAg	% patient	% SVR	% patient	% SVR
Sonneveld	[53]	No decline	31	3	25	8
Piratvisuth	[54]	No decline	24	18	NA	NA
Lau	[51]	>20,000 IU/ml	22	16	13	15
Gane	[52]	>20,000 IU/ml	18	0	14	0
Lau	[51]	<1500 IU/ml	23	57	34	54
Gane	[52]	<1500 IU/ml	27	58	40	57
Chan	[49]	<300 IU/ml	NA	NA	23	62
		<300 IU/ml and >1 log decline	NA	NA	13	75

NA = not available.

J of Hepatology 2011;55:1121-1131

Quantitative HBsAg and HBV DNA Predict SVR in HBeAg-Negative CHB on PegIFN



Rijckborst V, et al. Hepatology. 2010;52:454-461.

HBsAg decline : HBeAg-negative patient

Table 2. Prediction of treatment response by HBsAg decline at different phases of peginterferon therapy for HBeAg-negative chronic hepatitis B in the phase III trial of peginterferon alfa-2a [56,59].

Time (week)	HBsAg decline	n	Response (n, %)	Definition of response
12	≥10%	53	25 (47)	HBV DNA <4 log at year 1
	<10%	67	11 (16)	
	≥10%	53	12 (23)	HBsAg loss at year 5
	<10%	67	5 (7)	
24	≥10%	67	29 (43)	HBV DNA <4 log at year 1
	<10%	53	7 (13)	
	≥10%	67	15 (22)	HBsAg loss at year 5
	<10%	53	3 (4)	
48	>1 log	43	13 (30)	HBsAg loss at year 3
	≤1 log	155	4 (3)	

J of Hepatology 2011;55:1121-1131

CMUH ETV-Real Word Data

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2012/05/05

Predictors of Serum HBsAg Decline in Chronic Hepatitis B Patients Undergoing Entecavir Therapy

慢性B型肝炎病患接受貝樂克治療血清B型肝炎表面抗原濃度下降的預測因子

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Background

- On-treatment decline in quantitative serum hepatitis B surface antigen (qHBsAg) levels are predictors of therapeutic efficacy in chronic hepatitis B (CHB) patients treated with peginterferon

Aliment Pharmacol Ther 2012 ;35:458-68

Hepatology 2009;49:1141-1150

Hepatology 2009;49:1151-1157

- The decline in qHBsAg level and its predictors in CHB patients undergoing entecavir (ETV) therapy remain unclear

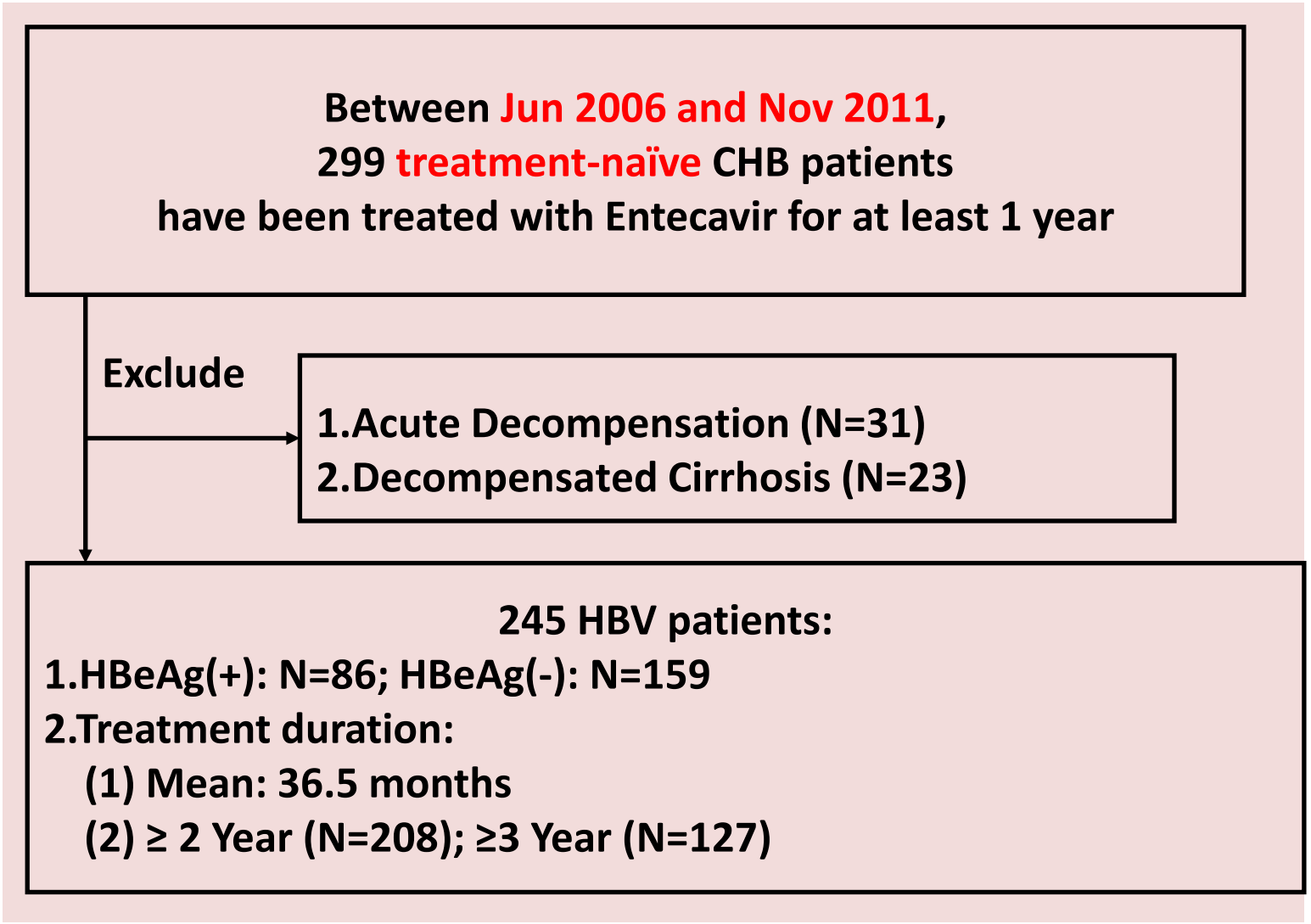
Hepatology 2011;53:1186-1193

Table 3 | Multivariate analysis of baseline and on-treatment factors associated with sustained response

Factors	OR	95% CI	*P* value
Baseline factors*			
HBsAg ≦2.71 vs.>2.71log$_{10}$IU/mL	3.5	(0.8, 15.2)	0.0952
HBV DNA ≦4.3 vs.>4.3log$_{10}$ copies/mL	7.0	(1.3, 36.2)	0.0203
On-treatment factors*			
HBsAg at week 12 ≦2.15 vs.>2.15log$_{10}$IU/mL	31.9	(4.8, 209.6)	0.0003
HBsAg at week 24 ≦2.05 vs.>2.05log$_{10}$IU/mL	8.8	(2.0, 38.0)	0.0035
HBsAg at week 48 ≦1.91 vs.>1.91log$_{10}$IU/mL	13.5	(2.8, 65.0)	0.0011

Aliment Pharmacol Ther 2012 ;35:458-68

Methods


Between Jun 2006 and Nov 2011,
299 treatment-naïve CHB patients
have been treated with Entecavir for at least 1 year
Exclude
1.Acute Decompensation (N=31)
2.Decompensated Cirrhosis (N=23)
245 HBV patients:
1.HBeAg(+): N=86; HBeAg(-): N=159
2.Treatment duration:
(1) Mean: 36.5 months
(2) ≥ 2 Year (N=208); ≥3 Year (N=127)

Factors associated with VR in CHB patients at year 1

	VR(-)	VR(+)	p^{uni}	p^{multi}	OR(95%CI)
Total patients	**N=24**	**N=221**			
HBeAg			<0.001	0.003	
-	5(20.8)	154(69.7)			7.491(1.948-28.813)
+	19(79.2)	67(30.3)			1.000
BL HBV DNA: Log_{10} copies/mL			<0.001		
<8	6(28.6)	167(77.0)			
≧8	15(71.4)	50(23.0)			
BL HBsAg: Log_{10} IU/mL			<0.001	0.024	
<3.7	7(35.0)	167(80.3)			3.429(1.180-9.968)
≥3.7	13(65.0)	41(19.7)			1.000
HBeAg(+)	**N=19**	**N=67**			
ALT: IU/L			0.041	0.005	
<110	14(73.7)	31(46.3)			1.000
≥110	5(26.3)	36(53.7)			7.275(1.817-29.126)[a]
BL HBsAg: Log_{10} IU/mL			0.043	0.005	
<3.7	5(29.4)	37(56.9)			6.520(1.738-24.455)[a]
≥3.7	12(70.6)	28(43.1)			1.000
BL HBV DNA: Log_{10} copies/mL			0.022	0.004	
<8	3(17.6)	31(48.4)			8.038(1.931-33.457)[b]
≥8	14(82.4)	33(51.6)			1.000
BL-3M HBsAg decline			0.023	0.006	
<10%	15(88.2)	35(57.4)			1.000
≥10%	2(11.8)	26(42.6)			10.118(1.966-52.079)[b]

Factors associated with HBeAg loss after 3 years of treatment

Median or N(%)	HBeAg loss (-) N=35	HBeAg loss (+) N=23	p –value
Genotype			0.030
B	23(65.7)	8(36.4)	
C	12(34.3)	14(63.6)	
PT: seconds prolonged	0.42	1.45	0.020
AFP: ng/mL			0.017
<8.0	25(80.6)	10(45.5)	
≧8.0	6(19.4)	12(54.5)	
BL HBV DNA: Log_{10} copies/mL	8.250	8.27	0.099
VR (6M)			0.028
-	21(60.0)	7(30.4)	
+	14(40.0)	16(69.6)	
HBsAg (6M): Log_{10} IU/mL			0.020
<2.8	3(8.8)	8(34.8)	
≧2.8	31(91.2)	15(65.2)	

Cox regression analysis of factors associated HBeAg loss

Variable	HR(95% CI)	p-value
Genotype (C)	3.141(1.226-8.004)	0.017
VR 6M (+)	2.572(1.025-6.457)	0.044
HBsAg 6M: (<2.8 Log_{10} IU/mL)	4.124(1.604-10.606)	0.003

Factors associated with HBsAg decline in HBeAg(+) patients (BL-3M)

Characteristics Median or N(%)	BL-3M <10% (N=50)	BL-3M ≧10% (N=28)	p-value
Age: year			0.026
<40	19(38.0)	18(64.3)	
≥40	31(62.0)	10(35.7)	
Genotype			0.019
B	21(42.9)	20(71.4)	
C	28(57.1)	8(28.6)	
Cirrhosis			<0.001
No	32(64.0)	28(100)	
Yes	18(36.0)	0(0)	
ALT: IU/L			<0.001
< 120	41(82.0)	5(17.9)	
≥120	9(18.0)	23(82.1)	
Total bilirubin: mg/dL	0.87	1.44	<0.001
AFP: ng/mL			0.004
<8	37(78.7)	13(46.4)	
≥8	10(21.3)	15(53.6)	
BL HBV DNA: Log_{10} copies/mL	7.90	8.47	0.011
BL HBsAg: Log_{10} IU/mL			0.059
<3.7	29(58.0)	10(35.7)	
≥3.7	21(42.0)	18(64.3)	

Multiple logistic regression analysis of factors associated HBsAg decline in HBeAg(+) patients

Variable	OR(95% CI)	p-value
AFP: ≥8 ng/mL	4.936(1.677-14.528)	0.004
BL HBsAg: ≥3.7 Log_{10} IU/mL	2.952(1.026-8.496)	0.044

Factors associated with HBsAg decline in HBeAg(-) patients (BL-12M)

Characteristics Median or N(%)	BL-12M<10% (N=112)	BL-12M≧10% (N=33)	p-value
ALT: IU/L			<0.001
<120	85(75.9)	12(36.4)	
≥120	27(24.1)	21(63.6)	
Inflammatory activity			0.004
0-1	59(69.4)	9(37.5)	
2-3	26(30.6)	15(62.5)	
Fibrosis stage			0.012
0-2	41(47.7)	19(76.0)	
3-4	45(52.3)	6(24.0)	
BL HBV DNA: Log_{10} copies/mL	5.86	6.56	0.003
BL HBsAg: Log_{10} IU/mL			<0.001
<3.7	108(96.4)	20(66.7)	
≥3.7	4(3.6)	10(33.3)	

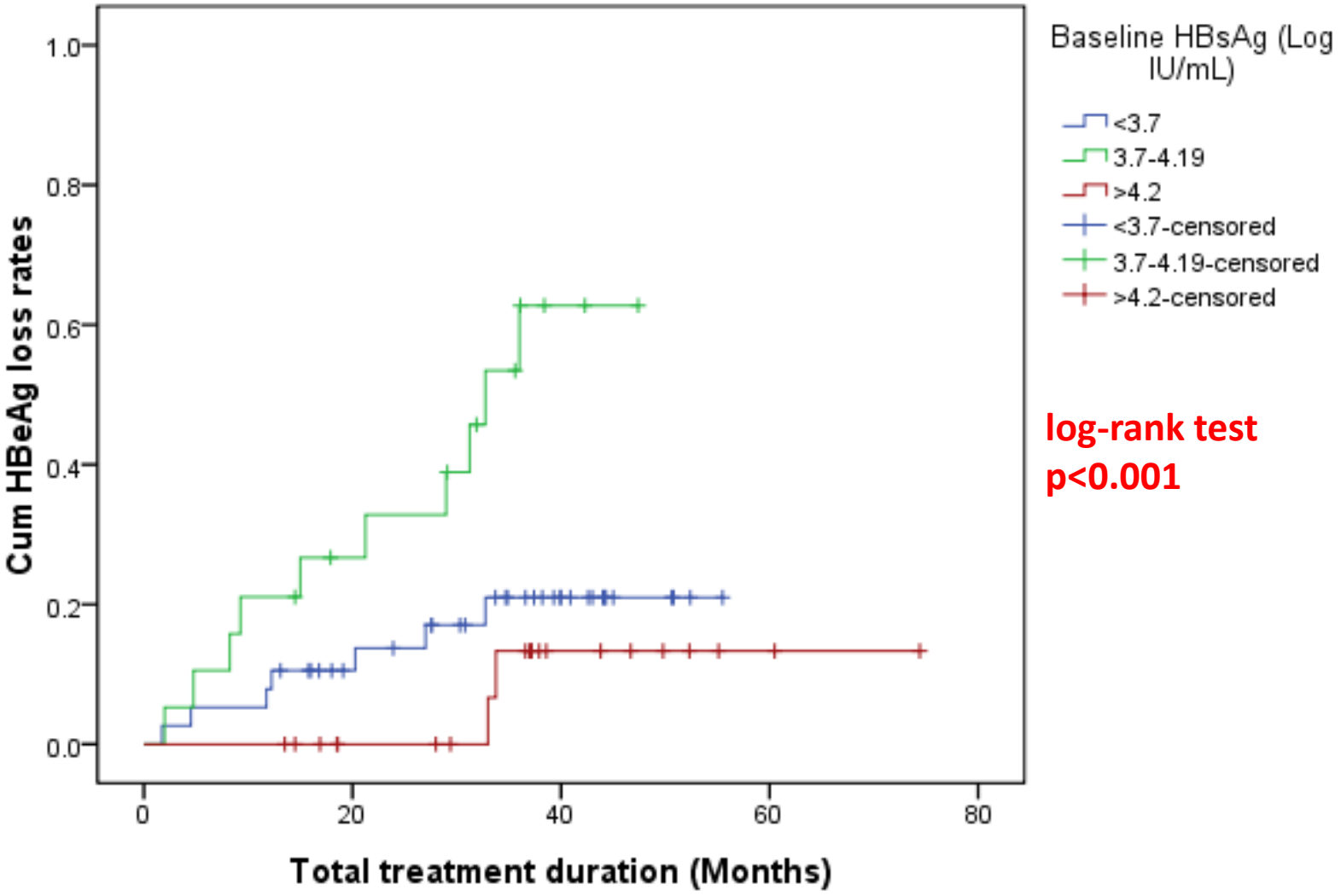
Multiple logistic regression analysis of factors associated HBsAg decline in HBeAg(-) patients

Variable	OR(95% CI)	p-value
ALT: ≥120 IU/L	4.980(1.964-12.629)	0.001
BL HBsAg: ≥3.7 Log_{10} IU/mL	12.018(3.149-45.869)	<0.001

Univariate and multivariate analyses of characteristics predicting serum HBsAg ≦2 Log_{10} IU/mL after three years therapy

	HBsAg>2	HBsAg≦2	p^{uni}	p^{multi}	OR(95%CI)
HBeAg(+)	45	4			
BL HBsAg: Log_{10} IU/mL	3.85	3.05	0.079	NA	
HBsAg BL-3M			0.019	NA	
<10%	26(66.7)	0(0)			
≧10%	13(33.3)	4(100)			
HBeAg(-)	67	20			
BL HBsAg: Log_{10} IU/mL	3.11	1.95	<0.001	<0.001	0.403 (0.273-0.594)
HBsAg BL-12M			<0.001	0.001	
<10%	52(85.2)	8(44.4)			1.000
≧10%	9(14.8)	10(55.6)			3.730(1.370-10.155)

Kaplan-Meier analysis of HBeAg clearance for HBeAg positive patients



log-rank test
p<0.001

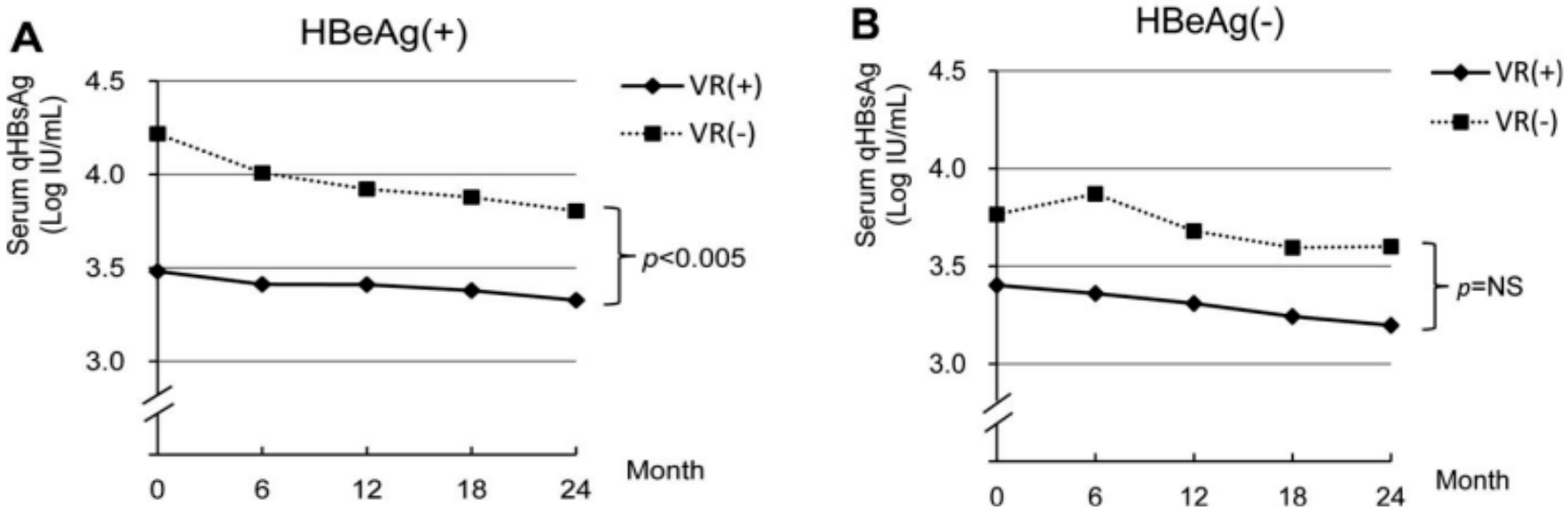
Factors Associated with VR in HBeAg(+) CHB Patients at Year 2

Table 2. Univariate and Multivariate Analyses and AUROC Values of Baseline Characteristics Predicting VR in HBeAg(+) Patients

Characteristic	VR(+) (n = 38)	VR(−) (n = 19)	Univariate *P* Value	Multivariate *P* Value	AUROC for VR
Age, years (mean ± SD)	46.3 ± 9.1	44.7 ± 8.5	0.531	–	–
Male sex [n (%)]	25 (65.8)	14 (73.7)	0.572	–	–
ALT, IU/L (mean ± SD)	91.5 ± 72.2	61.9 ± 36.0	0.099	0.013	0.619
HBV DNA, log copies/mL (mean ± SD)	6.68 ± 1.10	7.92 ± 1.14	<0.001	0.040	0.812
qHBsAg, log IU/mL (mean ± SD)	3.48 ± 0.65	4.22 ± 0.68	<0.001	0.033	0.823
qHBeAg, log PE IU/mL (mean ± SD)	1.11 ± 1.04	2.11 ± 0.65	<0.001	0.130	–

HEPATOLOGY, 2011 May;53(5):1486-93.

Serial values of HBsAg divided into VR(+) and VR(-) patients



HEPATOLOGY, 2011 May;53(5):1486-93.

Conclusions

- Baseline HBsAg level $< 3.7 \log_{10}$ IU/mL, and HBeAg negativity are predictors of VR at 1 year
- Genotype C, VR at 6 months, and HBsAg $< 2.8 \log_{10}$ IU/mL at 6 months are predictors of HBeAg loss after 3 years of treatment
- Baseline AFP ≥ 8 ng/mL and HBsAg $\geq 3.7 \log_{10}$ IU/mL are predictors of HBsAg decline ≥ 10% at 3 months for HBeAg-positive CHB
- Baseline ALT ≥ 120 IU/L and HBsAg $\geq 3.7 \log_{10}$ IU/mL are predictors of HBsAg decline ≥ 10% at 12 months for HBeAg-negative CHB

Conclusions

- Baseline HBsAg and decline of HBsAg are the predictors of achieving serum HBsAg $\leqq 2$ Log_{10} IU/mL after three years of therapy
- Patients with baseline HBsAg between Log_{10} 3.7 to 4.19 IU/mL have the highest cumulative rate of HBeAg loss at 3 years

Summary

- qHBsAg level predict HBsAg loss in nature course (HBsAg <100 IU/ML)
- qHBsAg level can predict the outcome of treatment during Peginterferon and NA treatment

謝謝聆聽