Acute Decompensation Management of Hepatitis B patients

中國附醫消化內科
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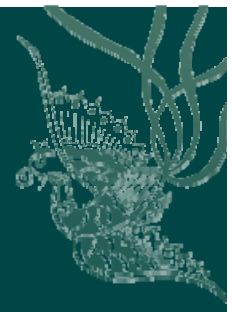
2012-2-23

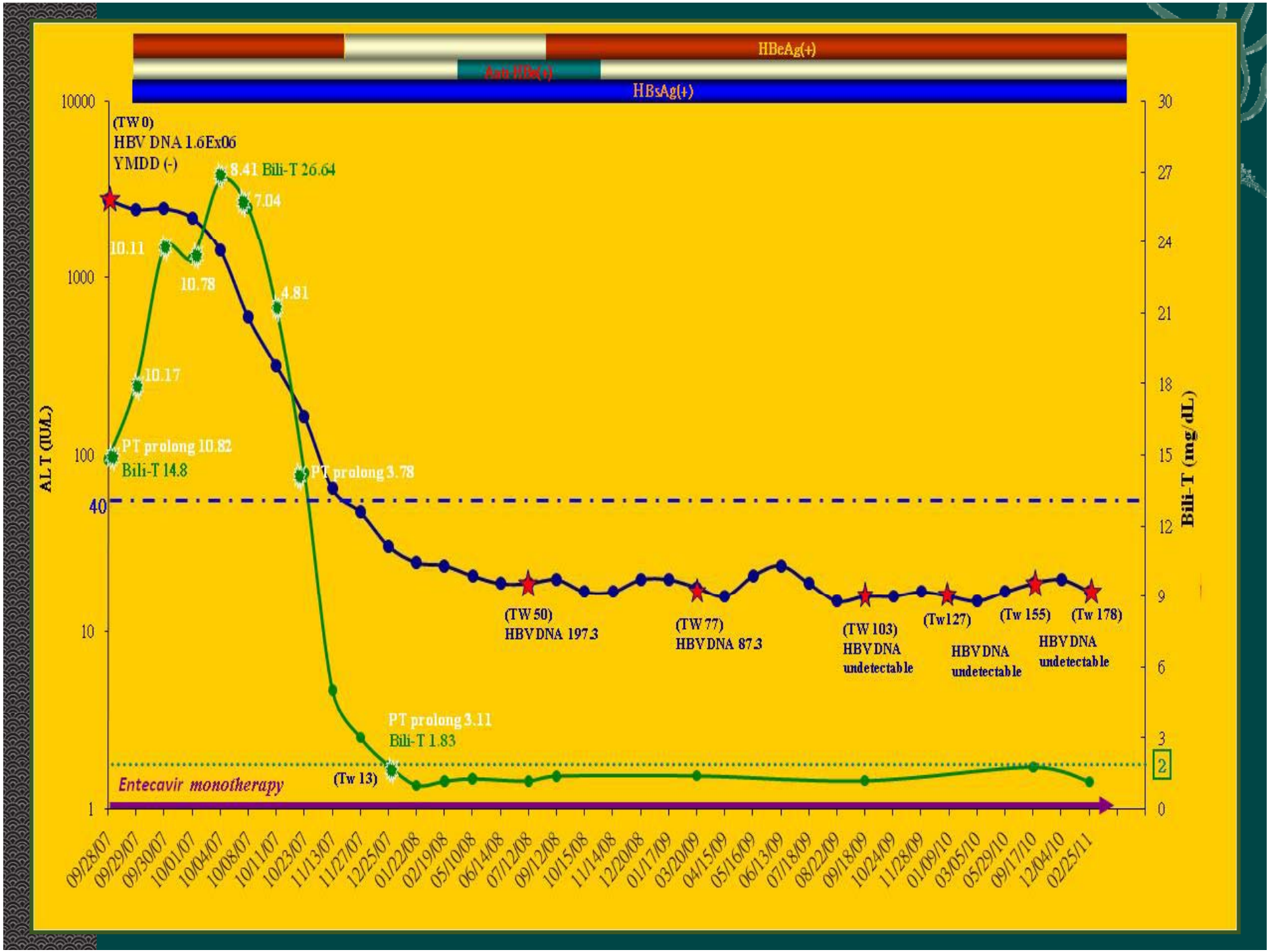
Case presentation (1)



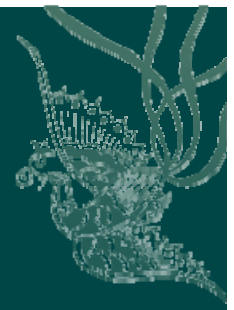
- 43 years old male
- Present illness: progressive jaundice for 2-3 days.
- Past history: hepatitis B for 10 years
- Family history: father and brother had DM, and hypertension
- Social alcohol consumption, smoking (-)

Case presentation

- Lab data:(2007-9-28) ALT:2802, AST:1507, Bili-T:14.80, bili-D:8.35, PT:21.26 (control 10.44 sec), INR:1.81, HBsAg(+), HCVAb (-), HBeAg (+), Anti-HBeAb (-), Anti-HBc IgM (+), HBV DNA:1.60 x 10^{6} copies/mL, genotype B.
- Echo: chronic liver parenchymal disease score 5


HBeAg(+)
Anti-HBe(+)
HBsAg(+)
(TW 0)
HBV DNA 1.6Ex06
YMDD (-)
8.41 Bili-T 26.64
7.04
10.11
10.78
4.81
10.17
PT prolong 10.82
Bili-T 14.8
PT prolong 3.78
(TW 50)
HBV DNA 197.3
(TW 77)
HBV DNA 87.3
(TW 103)
HBV DNA
undetectable
(Tw127)
HBV DNA
undetectable
(Tw 155)
HBV DNA
undetectable
(Tw 178)
PT prolong 3.11
Bili-T 1.83
(Tw 13)
Entecavir monotherapy
ALT (IU/L)
Bili-T (mg/dL)
10000
1000
100
40
10
1
30
27
24
21
18
15
12
9
6
3
2
0
09/28/07
09/29/07
09/30/07
10/01/07
10/04/07
10/08/07
10/11/07
10/23/07
11/13/07
11/27/07
12/25/07
01/22/08
02/19/08
05/10/08
06/14/08
07/12/08
09/12/08
10/15/08
11/14/08
12/20/08
01/17/09
03/20/09
04/15/09
05/16/09
06/13/09
07/18/09
08/22/09
09/18/09
10/24/09
11/28/09
01/09/10
03/05/10
05/29/10
09/17/10
12/04/10
02/25/11

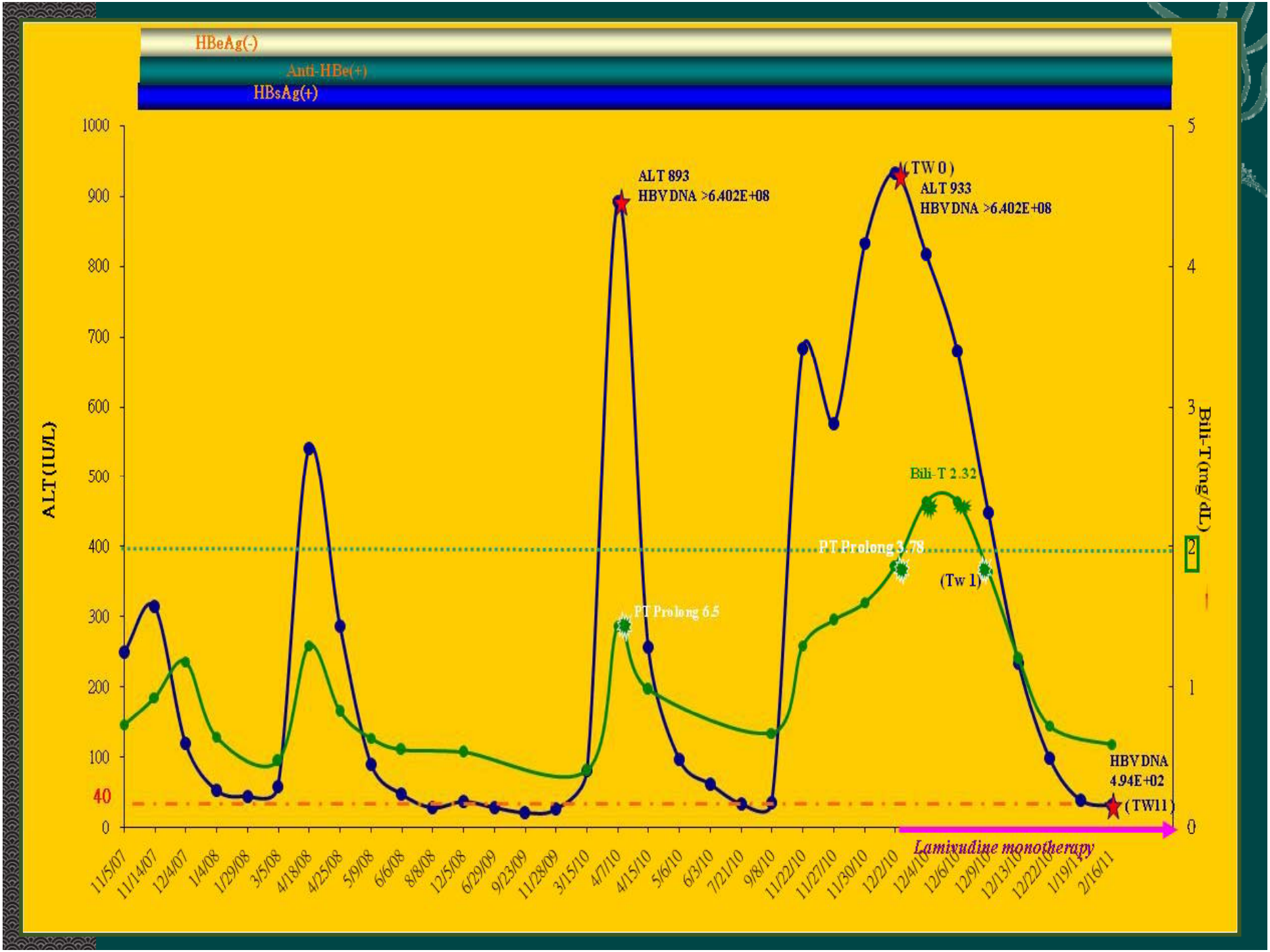
Case presentation (2)



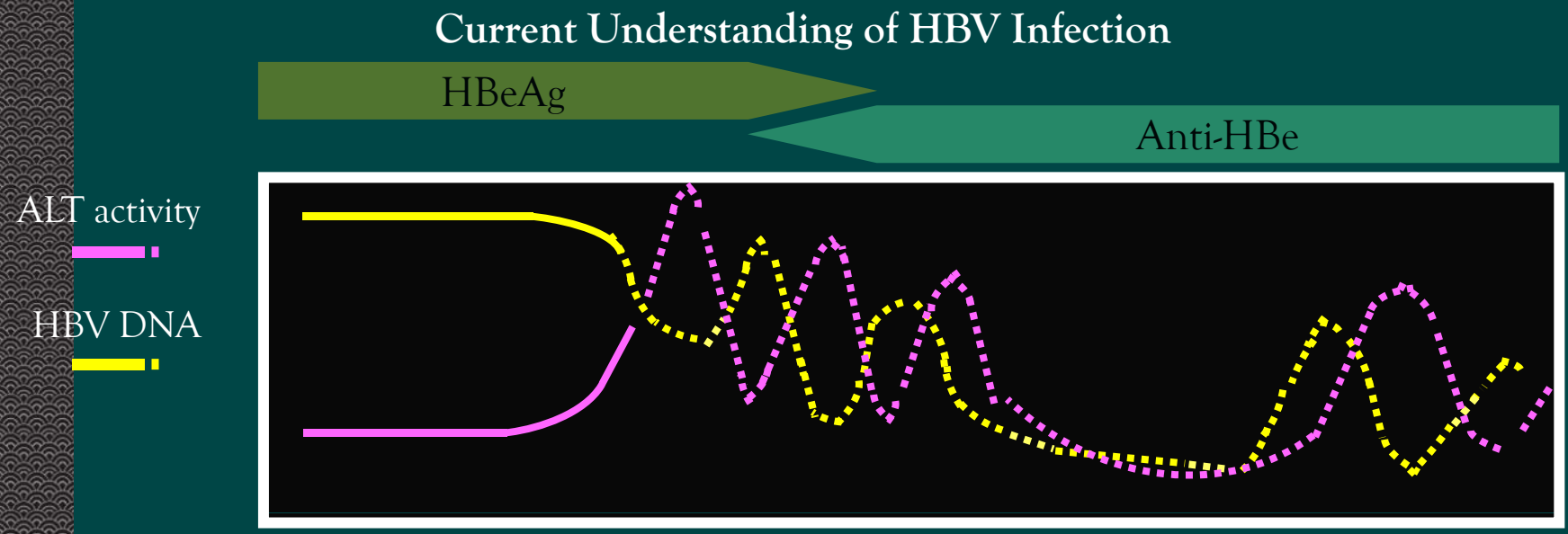
- 60 years old female
- Chief complaint: fatigue and poor appetite for one week
- Past history: hepatitis B for 20 years
- Family history: mother, five sisters and four brothers were hepatitis B carrier
- Alcohol consumption (-), smoking (-), Tattooing (30 years ago), Ear-piercing (30 years ago)

Case presentation (2)

- Lab data: (2010-1-39)ALT:932, AST:1076, Bili-T: 1.40, bili-D:0.4, PT:15.00 (control 11.34 sec), INR 1.34, HBsAg(+), HCVAb (-), HBeAg (-), Anti-HBeAb (+), HBV DNA>6.4 x 10^{8} copies/mL.
- Echo: chronic liver parenchymal disease score 6


HBeAg(-)
Anti-HBe(+)
HBsAg(+)
ALT (IU/L)
Bili-T(mg/dL)
1000
900
800
700
600
500
400
300
200
100
40
0
5
4
3
2
1
0
ALT 893
HBV DNA >6.402E+08
(TW 0)
ALT 933
HBV DNA >6.402E+08
Bili-T 2.32
PT Prolong 3.78
(Tw 1)
PT Prolong 6.5
HBV DNA
4.94E+02
(TW11)
Lamivudine monotherapy
11/5/07
11/14/07
12/4/07
1/4/08
1/29/08
3/5/08
4/18/08
4/25/08
5/9/08
6/6/08
8/8/08
12/5/08
6/29/09
9/23/09
11/28/09
3/15/10
4/7/10
4/15/10
5/6/10
6/3/10
7/21/10
9/8/10
11/22/10
11/27/10
11/30/10
12/2/10
12/4/10
12/6/10
12/9/10
12/13/10
12/22/10
1/19/11
2/16/11

4 Phases of Chronic HBV Infection

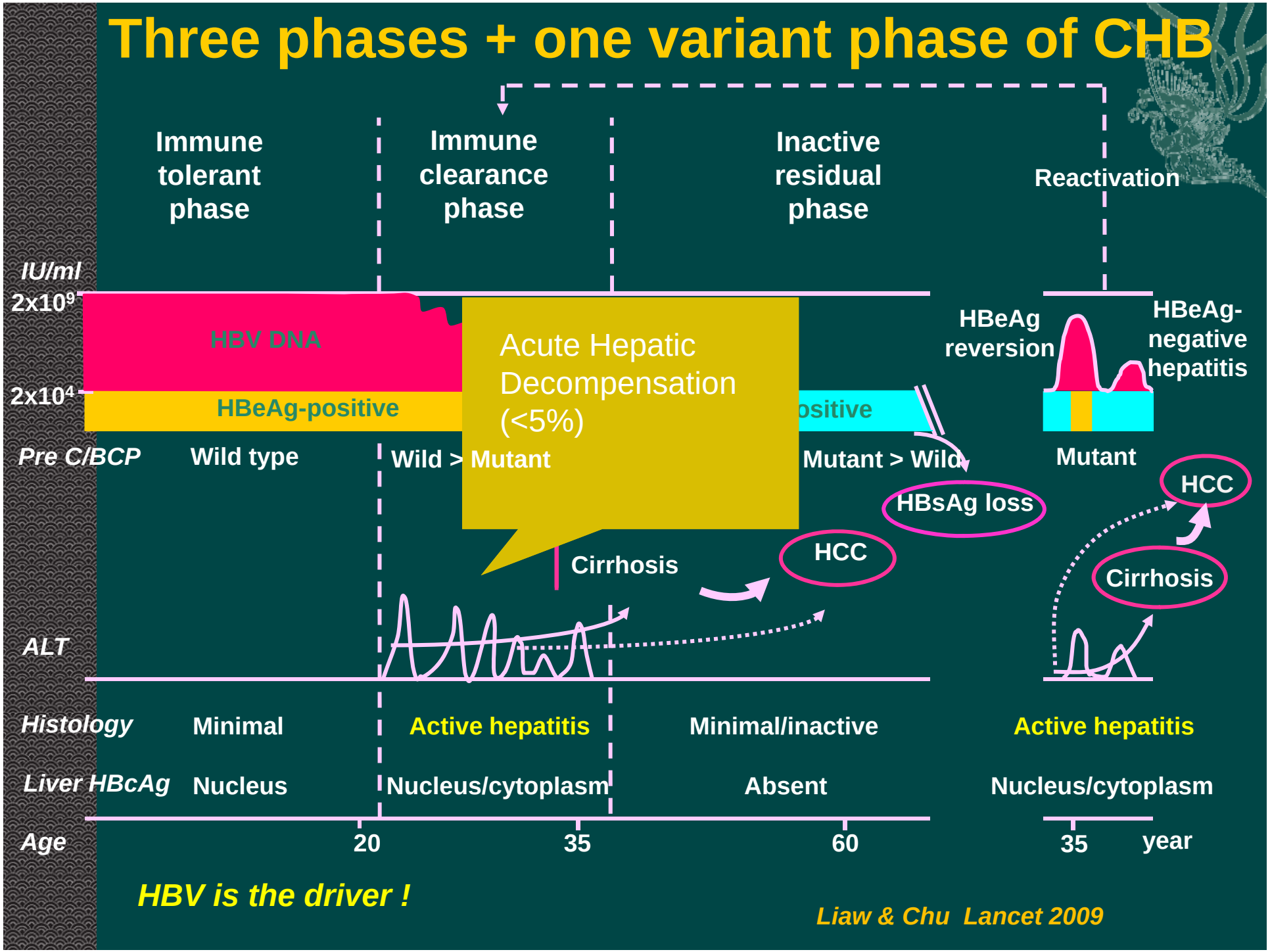


Phase	Immune Tolerant	Immune Clearance	Inactive Carrier State	Reactivation
Liver	Minimal inflammation and fibrosis	Chronic active inflammation	Mild hepatitis and minimal fibrosis	Active inflammation

Optimal treatment times

Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173-S181.

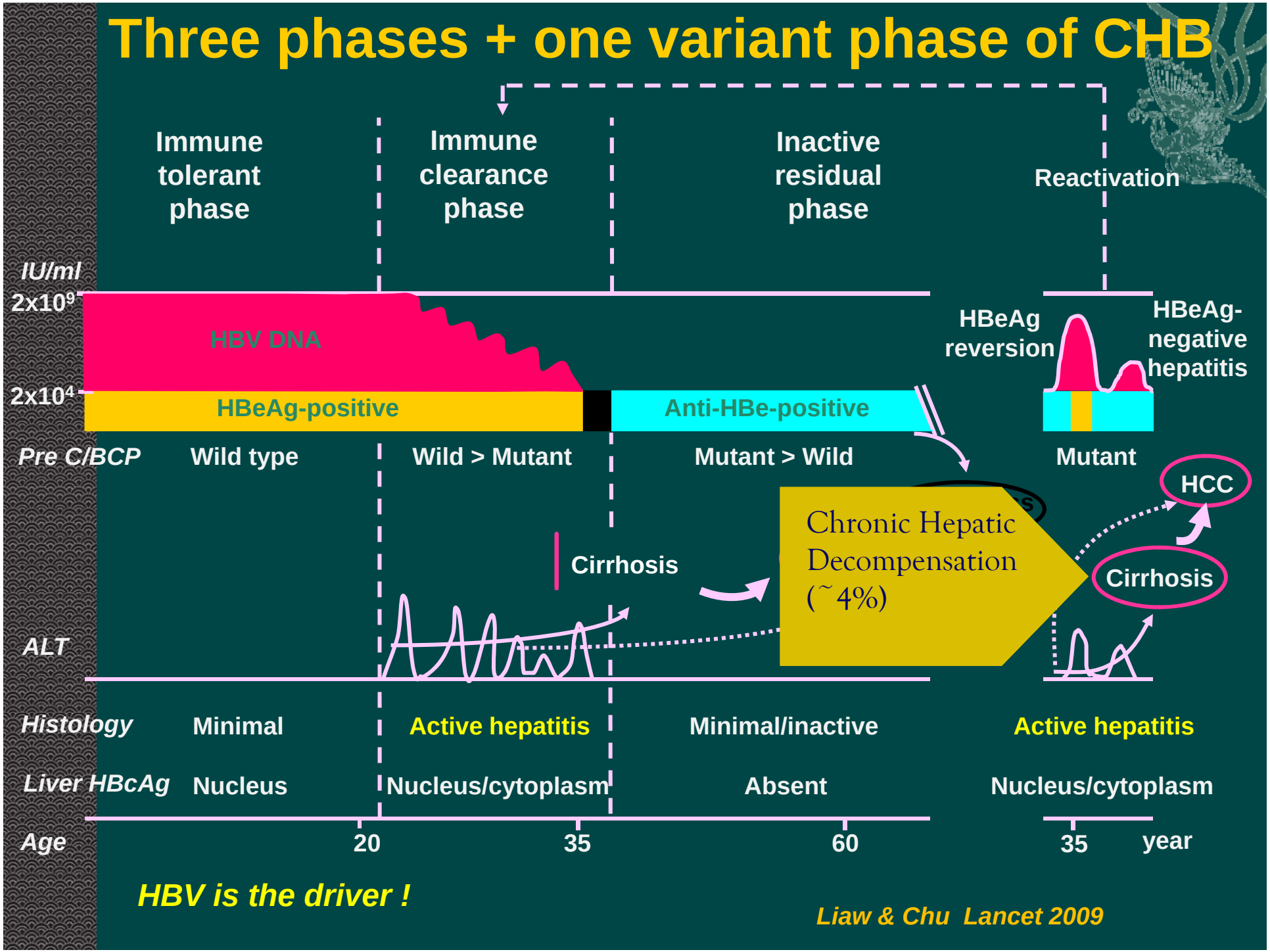
Three phases + one variant phase of CHB



HBV is the driver !

Liaw & Chu Lancet 2009

Three phases + one variant phase of CHB

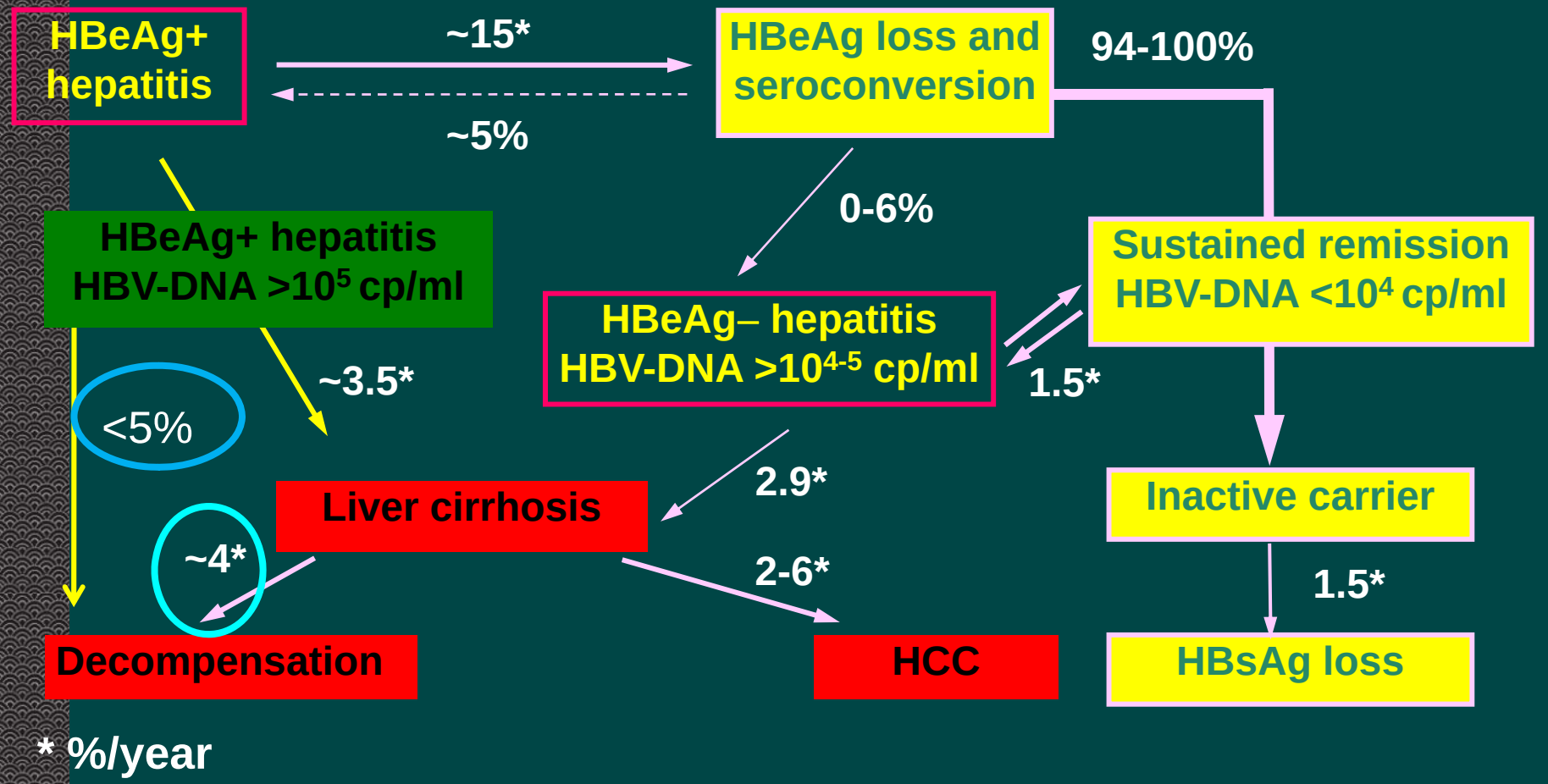


HBV is the driver !

Liaw & Chu Lancet 2009

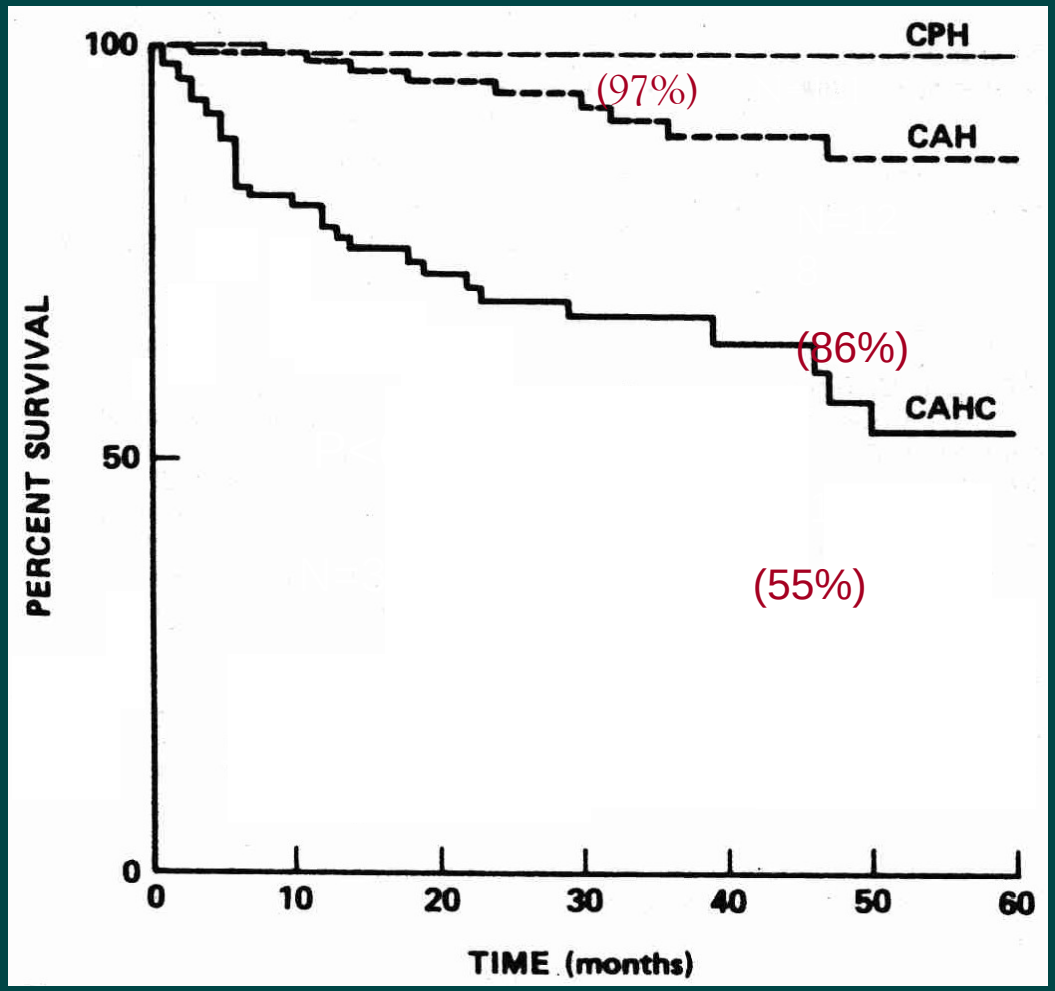
Spontaneous HBeAg seroconversion

A critical biologic "lock", leaks sometimes



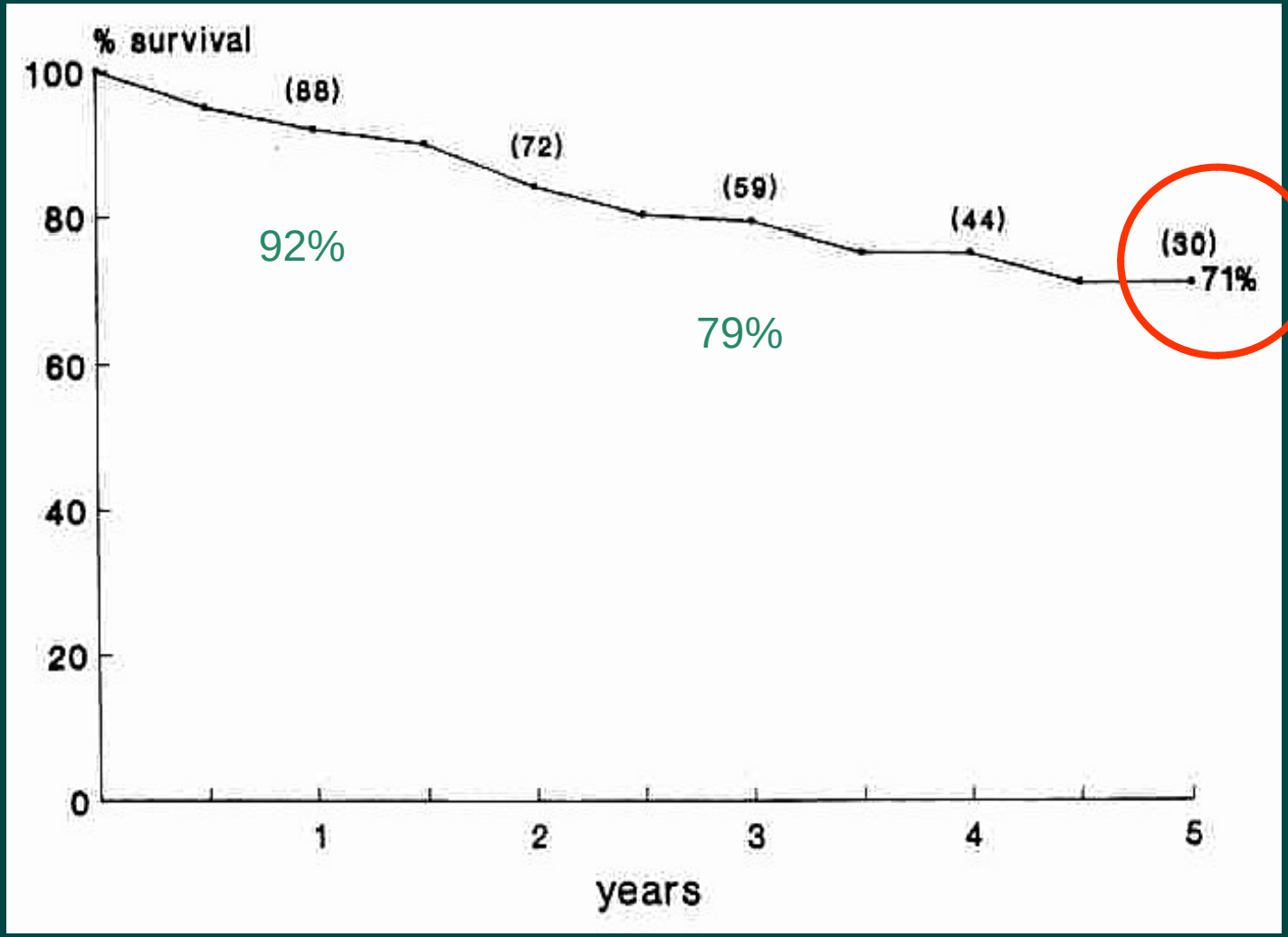
Hsu et al Hepatology 2002 Lin et al J Hepatol 2007 Chu et al AJM 2004; Hepatology 2007

5-yr Survival in Patients with Chronic Hepatitis B



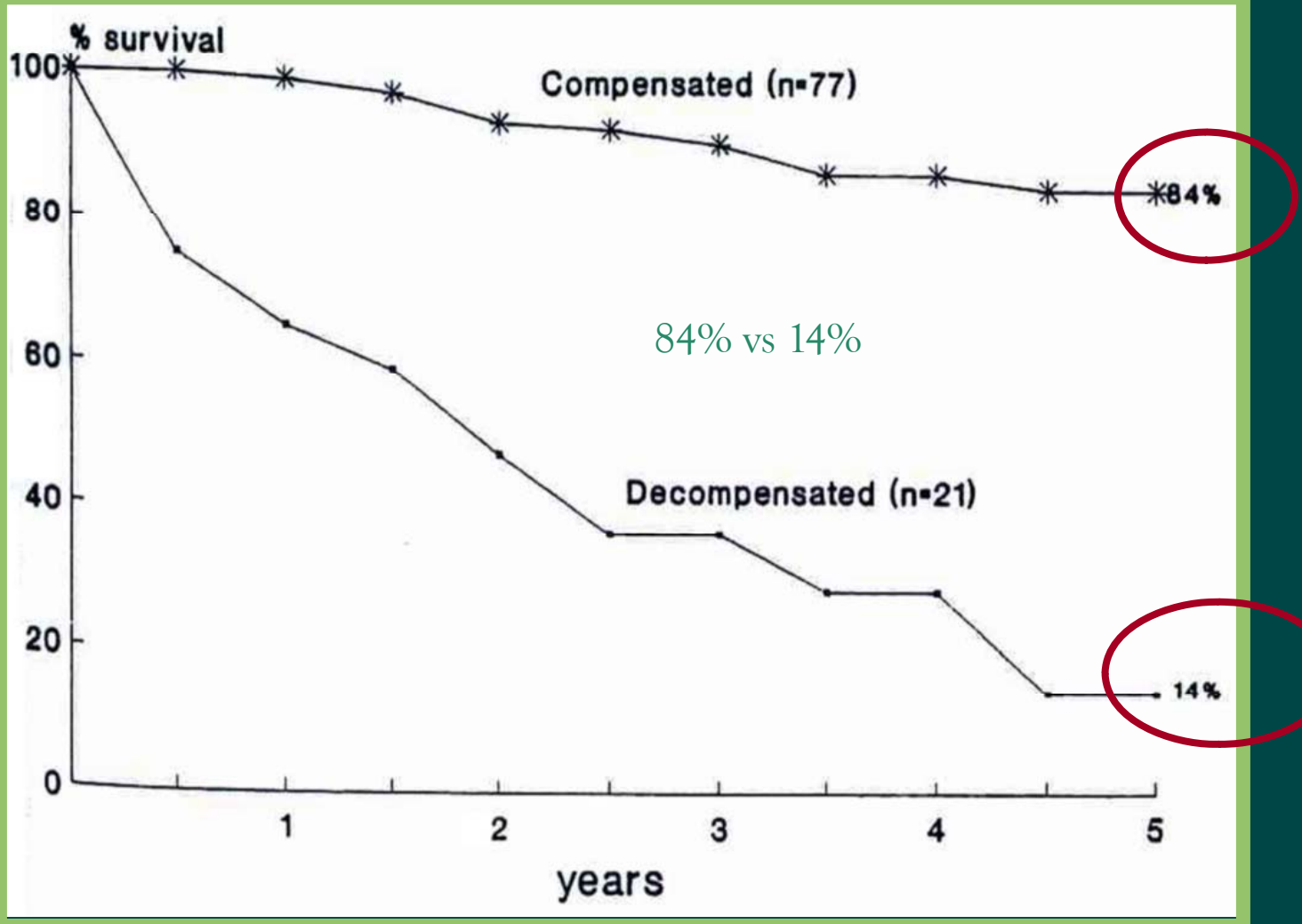
Weissberg et al. Ann Intern Med 1984

Survival of 98 patients with HBV related cirrhosis



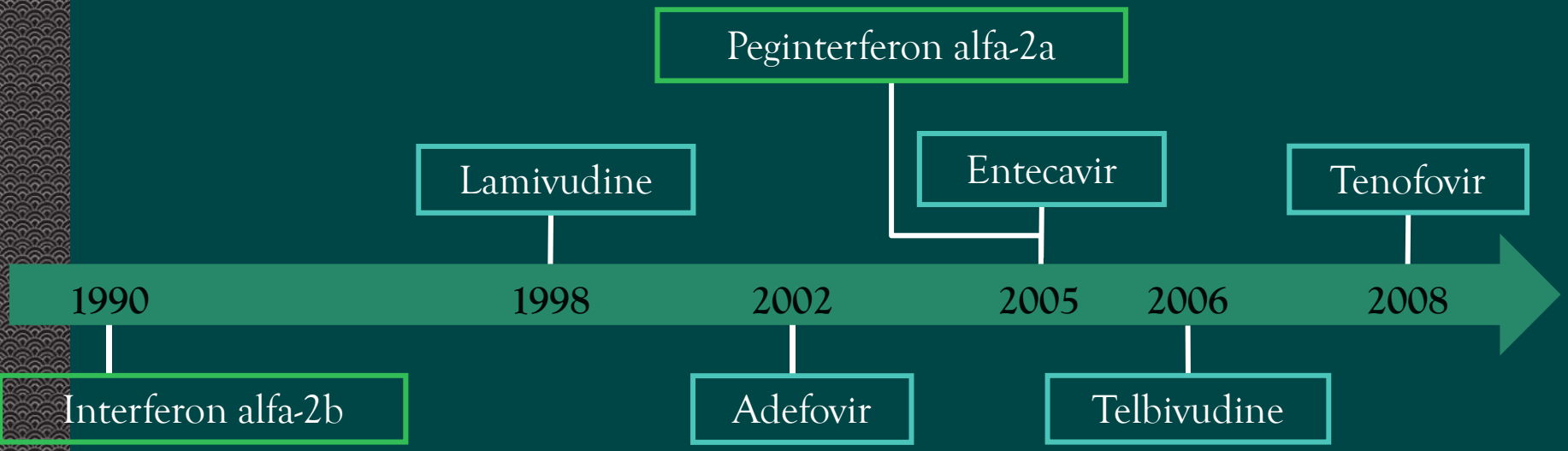
De Jongh et al. Gastroenterology 1992

Survival and Compensation



De Jongh et al. Gastroenterology 1992

HBV Treatment Landscape in 2011

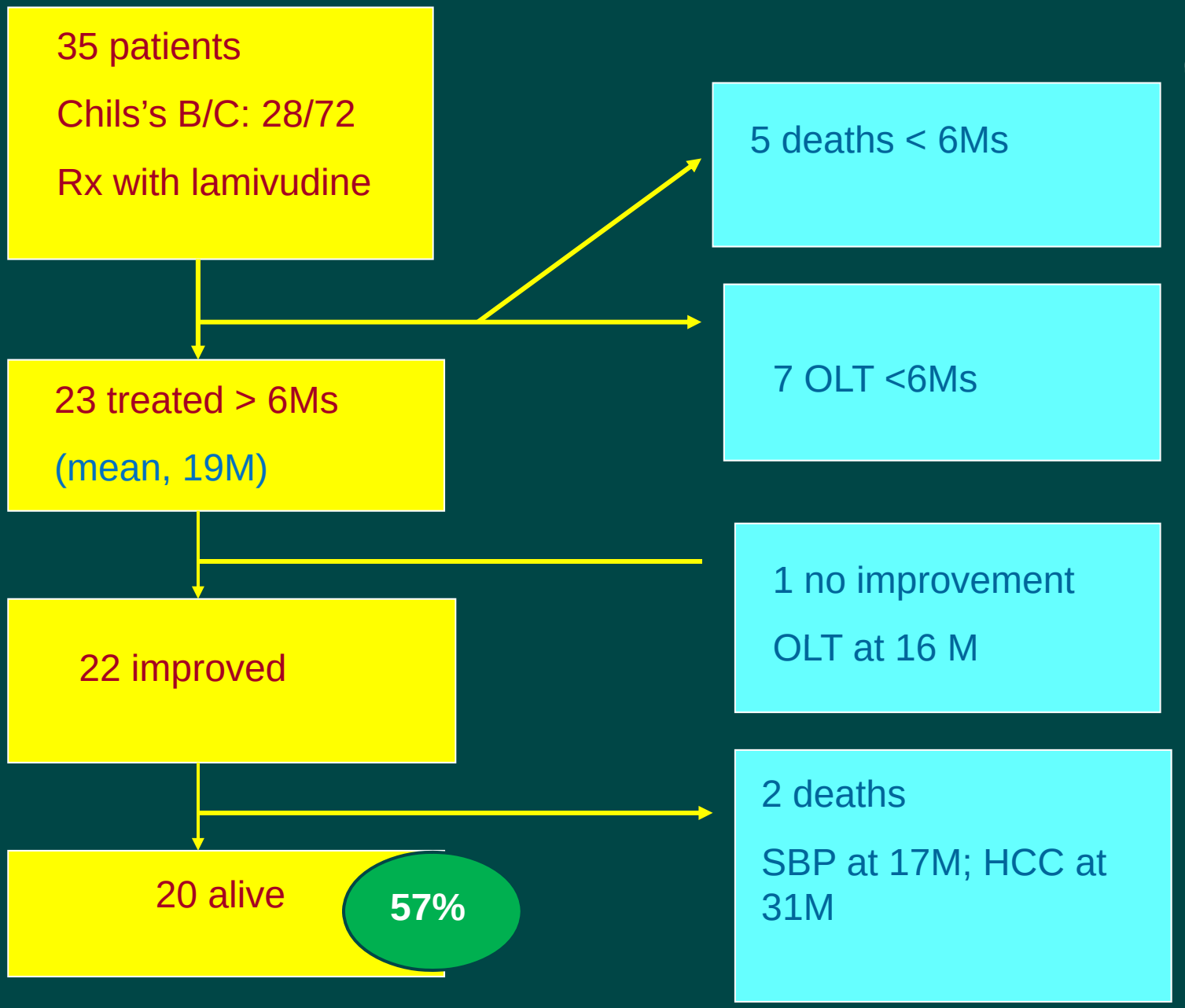


N=18; Child's B/C:78/22; Median Rx:18Ms

Parameter	Pre-treatment	Post-treatment	*p*
AST (IU/l)	130±67	72±21	<0.004
ALT (IU/l)	112±68	58±24	<0.009
S. albumin (g/dl)	3.33±0.4	3.57±0.4	NS
PT prolongation (s)	5.13±1.1	4.27±1.4	NS
S.bilirubin (mg/dl)	1.79±1.1	1.35±1	NS
Alfa-fetoprotein (ng/ml)	12.5±26	10.8±21	NS
Child's stage	14B,4C	7A, 8B, 3C	
Child-Pugh score	8.3±1.2	6.7±1.8	<0.013

AST: aspartate aminotransferase; ALT: alanine aminotransferase; NS: Not significant; PT: Prothrombin time.

Kapoor D et al. J Hepatol 2000



Villeneuve et al. Hepatology 2000

77 patients enrolled

39%

47 transplanted (Rx 38M)

30 not transplanted (Rx: 26 M)

5 treated < 12 weeks

3 withdrawn at week 1

42 > 12 weeks

27 treated > 1 week

3 deaths; 2 withdrawals

37 treated >52 weeks

22 treated > 52 weeks

Perrillo RP et al. Hepatology 2001

TABLE 2. Results of Virologic Testing in 37 Transplanted Patients Completing at Least 52 Weeks of Treatment Posttransplantation

	Day −1*	Week 52	Week 104	Week 156
All				
HBsAg (+)	34/34 (100)†	12/37 (32)	9/29 (31)	9/22 (41)
HBeAg (+)	15/34 (44)†	7/37 (19)	6/29 (21)	6/22 (27)
HBV DNA (+)	6/37 (16)	10/37 (27)	19/29 (66)	11/22 (50)
HBV DNA (+) at baseline‡ (n = 20)				
HBsAg (+)	18/18 (100)	9/20 (40)	9/18 (50)	9/15 (60)
HBeAg (+)	13/18 (72)	6/20 (30)	6/18 (33)	6/15 (40)
HBV DNA (+)	5/20 (25)	6/20 (30)	11/18 (61)	9/15 (60)
HBV DNA (−) at baseline (n = 17)				
HBsAg (+)	16/16 (100)	3/17 (18)	0/11 (0)	0/7 (0)
HBeAg (+)	2/16 (13)	1/17 (6)	0/11 (0)	0/7 (0)
HBV DNA (+)	1/17 (6)	4/17 (24)	8/11 (73)	2/7 (29)

*Day −1 represents day immediately preceding transplantation.
†HBsAg and HBeAg results not available in all patients.
‡Baseline represents value prior to initiation of lamivudine.

Perrillo RP et al. Hepatology 2001

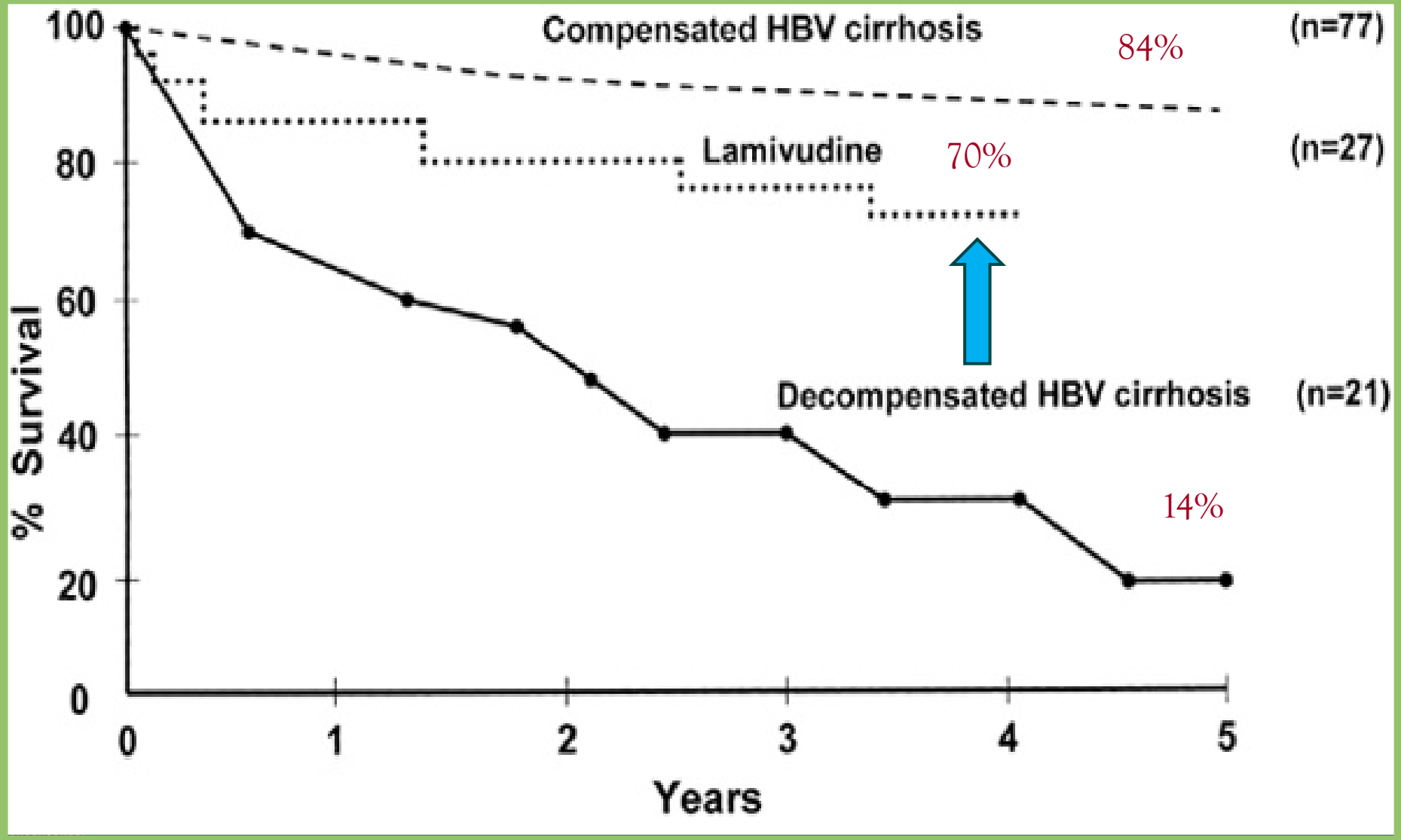
TABLE 3. Results of Virologic Testing in 27 Nontransplanted Patients

	Baseline (n = 27)	Week 52 (n = 22)	Week 104 (n = 17)
HBsAg (+)	27/27 (100)	5/5 (100)*	16/17 (94)
HBeAg (+)	20/27 (74)	2/6 (33)*	3/17 (18)
HBV DNA (+)	19/27 (70)	5/22 (23)	5/17 (29)

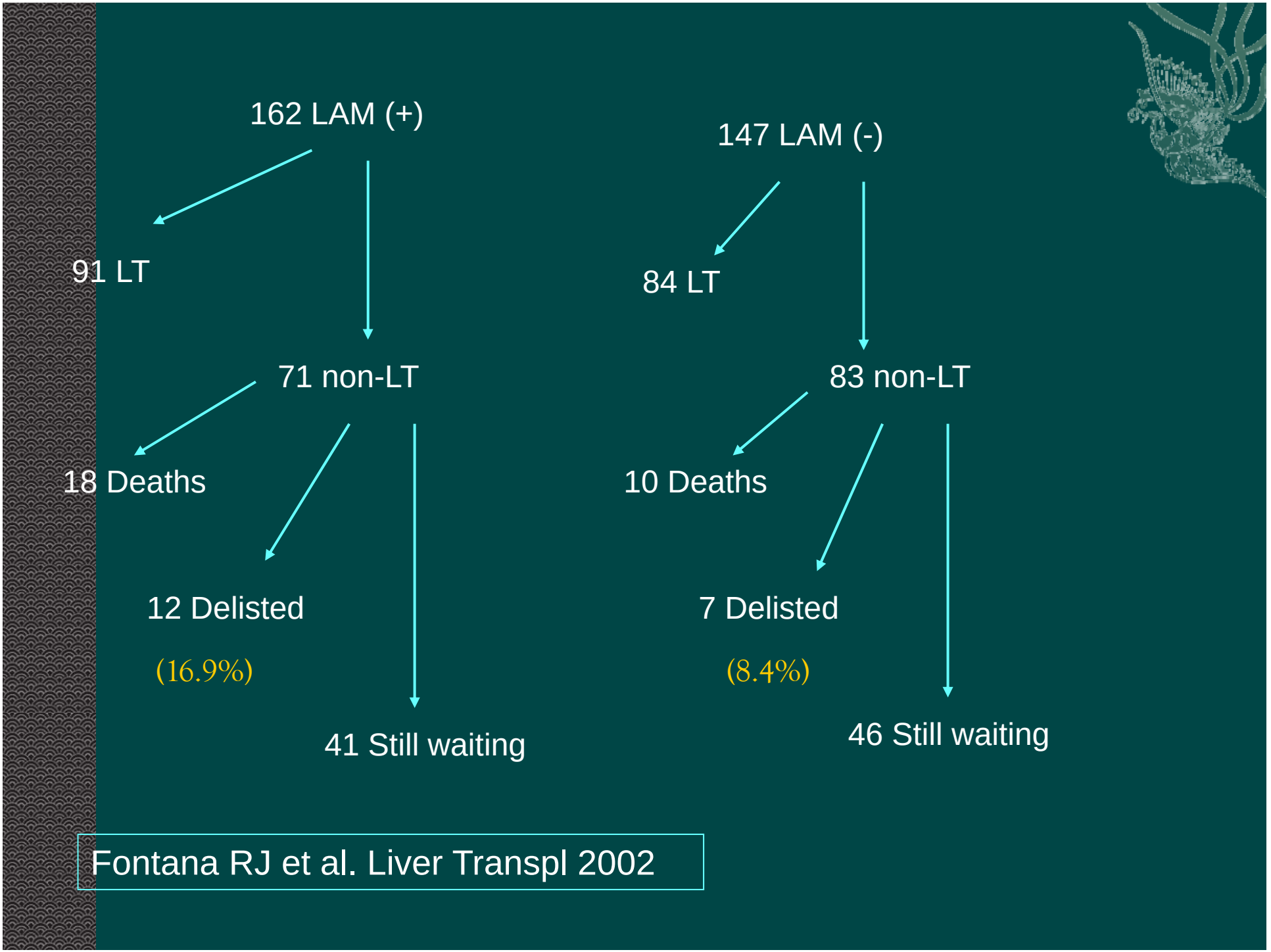
NOTE. Data does not include 3 patients who completed less than 1 week of lamivudine (see text for details).

*HBsAg and HBeAg results not available in all patients.

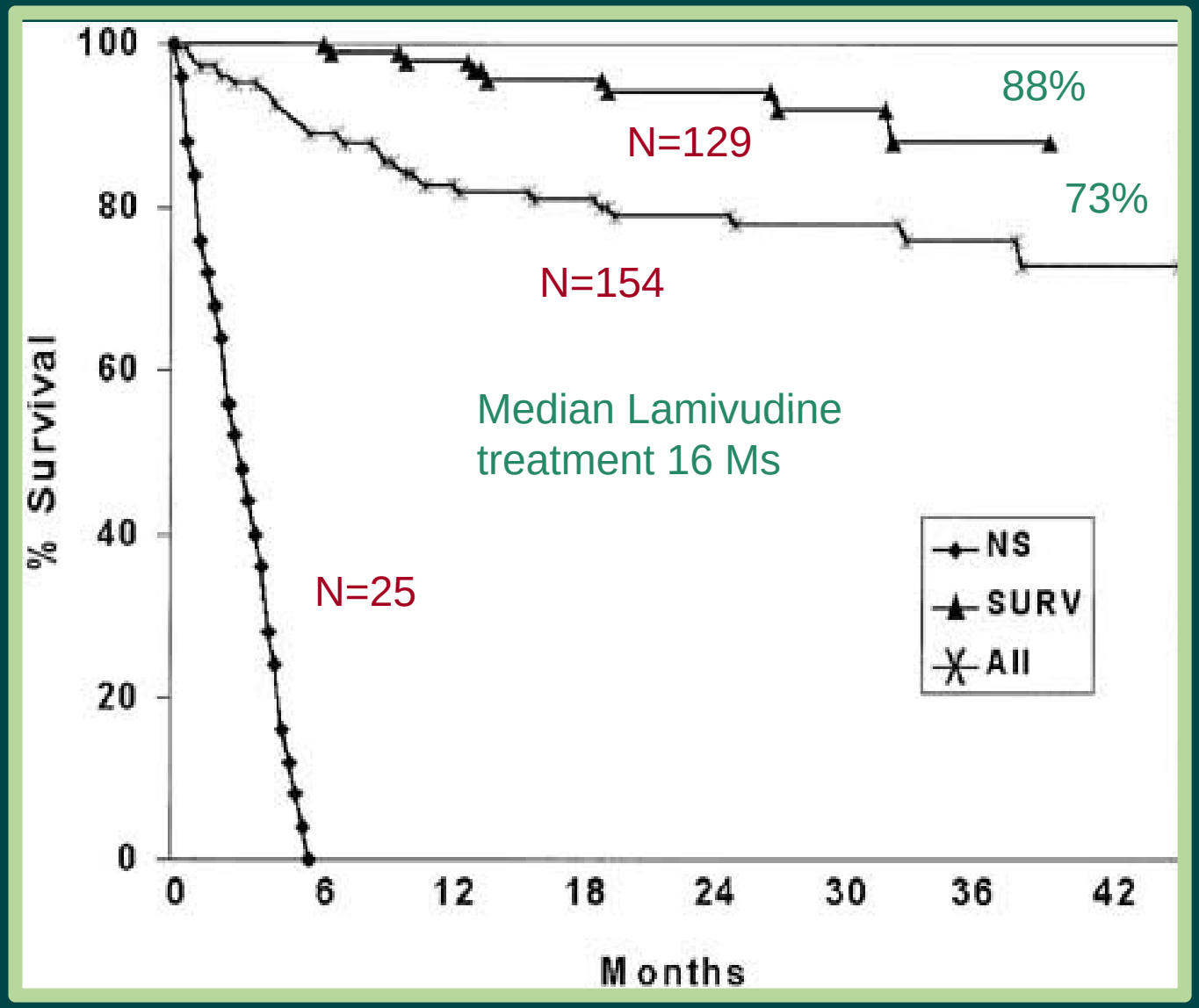
Perrillo RP et al. Hepatology 2001



Adapted from De Jongh et al.Gastroenterology 1992 and Perrillo et al. Hepatology 2001



Fontana RJ et al. Liver Transpl 2002



Fontana RJ et al. Gastroenterology 2002

Multivariate Cox Regression Model of Pretreatment Characteristics and 6-Month Mortality

Variable	SE of estimate	Risk Ratio (95% CI)	P value
Creatinine	0.311	5.23 (2.84-9.63)	0.0001
Bilirubin	0.084	1.69 (1.43-1.99)	0.0001
HBV DNA (+/-)	0.751	6.13 (1.41-26.76)	0.0158

Fontana RJ et al. Gastroenterology 2002

Studies of Lamivudine in Decompensated HBV Cirrhosis

Study	N	Child B/C	Median Follow-up (months)	%Viral Resistance	%Survival	% Transplantation
Uncontrolled, open label						
Yao FY et al. 2000 (UCSF)	13	0/100	15	7	100	15
Kapoor D et al. 2001(India)	18	78/22	18	17	100	0
Villeneuve et al. 2000 (Canada)	35	28/72	19	13	70	20
Perrillo RP et al. 2001(North America)	77	NA	26	21	96	61
Controlled, open label	23	0/100	13	10	100	35
Yao FY et al. 2001(UCSF)						
Fontana RJ et al. 2002 (North America)	162	NA	10	11	83	56

Severe Acute Exacerbation- Lamivudine vs Entecavir

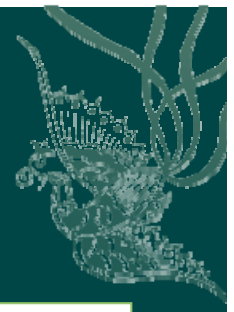


Table 2. Clinical outcomes of patients with severe acute exacerbation of chronic hepatitis B on entecavir and lamivudine treatment.

Outcome, n (%)	Entecavir (N = 36)	Lamivudine (N = 117)	*p*
Mortality			
Death within 30 days	4 (11)	2 (2)	0.028
Death between 30 days and 48 weeks	3 (8)	3 (3)	0.14
Mortality among cirrhotic patients			
Death within 30 days	0/5 (0)	1/25 (4)	1.0
Death between 30 days and 48 weeks	2/5 (40)	1/25 (4)	0.064
Cause of death (first 48 weeks)			
Liver failure	6 (17)	4 (3)	0.012
Other malignancies	1 (3)	1 (1)	0.42
Liver-related complications (first 48 weeks)			
Hepatic encephalopathy	6 (17)	4 (3)	0.012
Variceal bleeding	3 (8)	3 (3)	0.14
Ascites	4 (11)	2 (2)	0.028
Spontaneous bacterial peritonitis	0	1 (1)	1.0
Hepatorenal syndrome	2 (6)	2 (2)	0.24
Hospital stay (days)*	7 (1-35)	6 (1-62)	0.95

*Median (range).

Wong VW et al. J hepatol 2011;54:232-246

Severe Acute Exacerbation- Lamivudine vs Entecavir

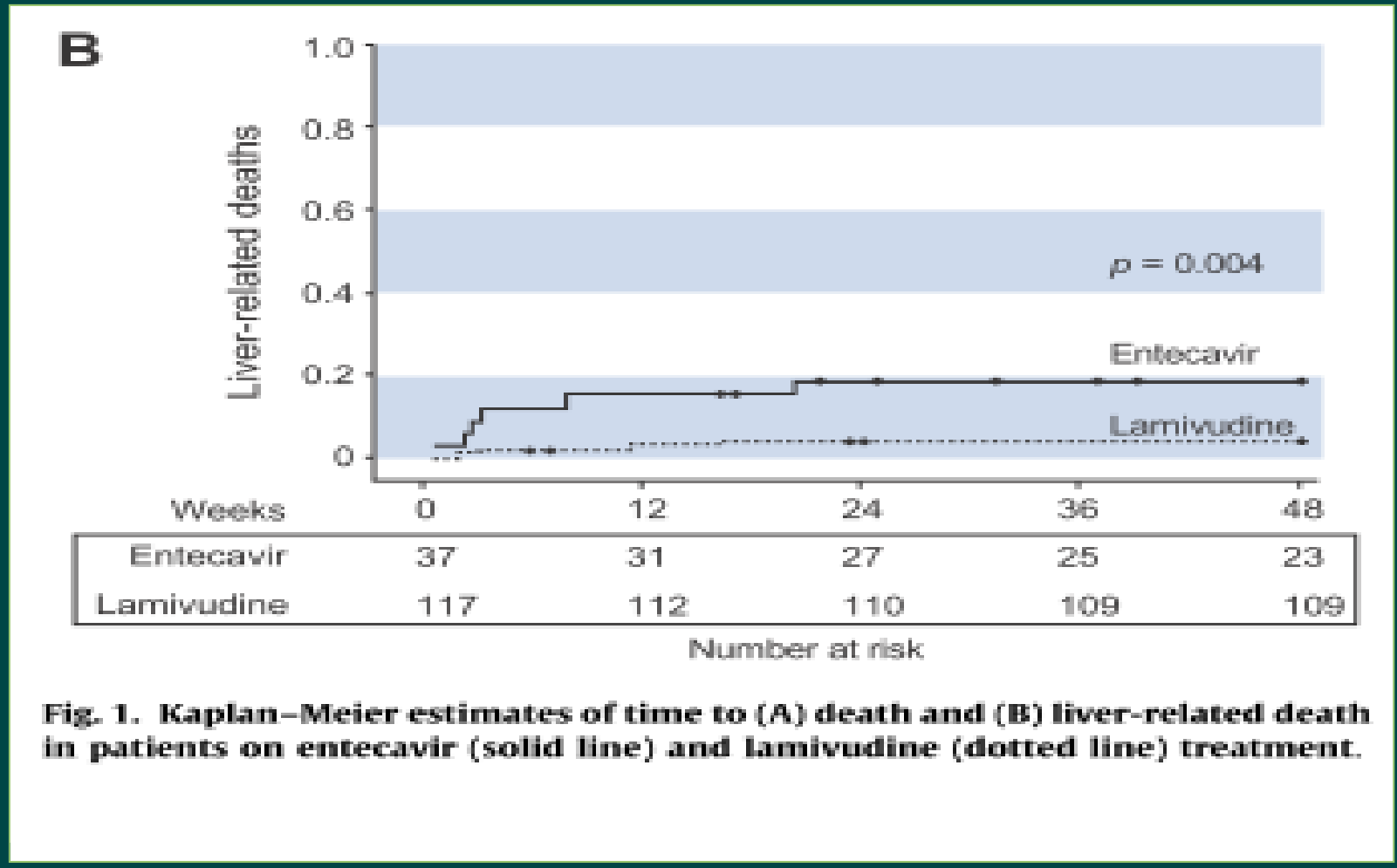


Fig. 1. Kaplan–Meier estimates of time to (A) death and (B) liver-related death in patients on entecavir (solid line) and lamivudine (dotted line) treatment.

Wong VW et al. J hepatol 2011;54:232-246

Severe Acute Exacerbation- Lamivudine vs Entecavir

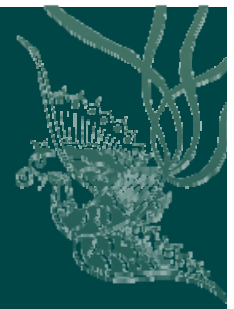


Table 4. Factors associated with overall and liver-related mortality at week 48.

Factors	Univariate			Multivariate		
	Hazard ratio	95% CI	*p*	Hazard ratio	95% CI	*p*
Overall mortality						
Age (years)	1.06	1.02-1.10	0.006	1.03	0.98-1.08	0.31
Male gender	0.39	0.12-1.29	0.12			
Baseline ALT (IU/L)	1.00	1.00-1.00	0.50			
Baseline bilirubin (μmol/L)	1.00	1.00-1.01	0.038	1.00	1.00-1.01	0.39
Baseline albumin (g/L)	0.95	0.86-1.05	0.28			
Baseline INR	5.9	3.1-11.3	<0.001	3.4	1.8-6.5	<0.001
Baseline HBeAg	0.11	0.014-0.85	0.034	0.18	0.020-1.5	0.12
Baseline HBV DNA (log copies/ml)	1.02	0.73-1.43	0.89			
Cirrhosis	2.1	0.64-7.0	0.22			
Antiviral therapy						
Lamivudine	Referent					
Entecavir	5.0	1.6-15.7	0.006	5.1	1.5-17.2	0.010
Time from presentation to starting antiviral drugs (days)	0.94	0.77-1.15	0.56			
Liver-related mortality						
Age (years)	1.07	1.02-1.12	0.004	1.05	1.00-1.11	0.058
Male gender	0.29	0.082-1.03	0.056			
Baseline ALT (IU/L)	1.00	1.00-1.00	0.58			
Baseline bilirubin (μmol/L)	1.00	1.00-1.01	0.038	1.00	1.00-1.01	0.56
Baseline albumin (g/L)	0.91	0.82-1.00	0.057			
Baseline INR	6.4	3.3-12.5	<0.001	4.2	2.1-8.5	<0.001
Baseline HBeAg	0.14	0.017-1.06	0.057			
Baseline HBV DNA (log copies/ml)	1.17	0.78-1.76	0.46			
Cirrhosis	2.8	0.79-9.9	0.11			
Antiviral therapy						
Lamivudine	Referent					
Entecavir	5.2	1.5-18.6	0.010	4.0	1.0-15.7	0.044
Time from presentation to starting antiviral drugs (days)	0.97	0.80-1.17	0.73			

ALT, alanine aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio.

Wong VW et al. J hepatol 2011;54:232-246

Entecavir versus lamivudine in the treatment of chronic hepatitis B patients with hepatic decompensation.

Hsu YC, Mo LR, Chang CY, Perng DS, Tseng CH, Lo GH, Tai CM, Lin CW, Hsu CC, Hsu CY, Huang SC, Lin JT.

Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung, Taiwan.

Antivir Ther 2011

Abstract

BACKGROUND:

Lamivudine has been widely used in chronic hepatitis B patients with hepatic decompensation, but its use is limited by drug resistance. This outcome research aimed to investigate the comparative efficacy and safety of entecavir versus lamivudine in decompensated patients.

METHODS:

Between November 2004 and February 2010, 126 consecutive treatment-naive patients received either entecavir (n=53) or lamivudine (n=73) for decompensated chronic hepatitis B. All patients presented with both hyperbilirubinaemia and coagulopathy. Primary outcome was mortality within 1 year; secondary outcomes included liver-related mortality, biochemical and virological response, and improvement of hepatic dysfunction.

RESULTS:

Both treatment groups were comparable in baseline characteristics. A total of 19 (35.8%) entecavir and 33 (45.2%) lamivudine receivers expired within 1 year, respectively (P=0.29, log rank test). Age (hazard ratio [HR] 1.04 per year, 95% CI 1.01, 1.06), cirrhosis (HR 2.07, 95% CI 1.02, 4.23), and international normalized ratio for prothrombin time (HR 1.44, 95% CI 1.20, 1.74) were independent baseline predictors for all-cause mortality. Antiviral therapy was also unrelated to liver-specific death. However, more patients taking entecavir tended to attain aminotransferase normalization (76.5% versus 52.5%; P=0.05) and viral DNA undetectability (100% versus 58.3%; P=0.06). Moreover, entecavir was associated with significantly greater reduction of the model for end-stage liver disease scores (median 10.0 versus 4.3; P=0.02). Overall, 3 (7.5%) lamivudine but no entecavir users acquired drug resistance in 1 year (P=0.25).

CONCLUSIONS:

Entecavir as compared with lamivudine is similar in the effect on short-term mortality but is associated with greater clinical improvement among chronic hepatitis survivors who recovered from hepatic decompensation.

Mexico, or India, but cases in the US without associated travel are beginning to be reported.[39] With acute viral hepatitis, as with many other etiologies of ALF, care is mainly supportive. Of note, the nucleoside analog lamivudine (and possibly other nucleos(t)ide analogues), used widely in the treatment of chronic hepatitis B, may be considered in patients with acute hepatitis B, although evidence of efficacy is equivocal.[40,41] Acute liver failure due to reactivation of

Hepatology 2011

HBV							HCV
1	2	3	4	5	6	7	8
HBsAg(+)	HBsAg(+)	HBsAg(+)>6M	HBsAg(+)>6M	HBsAg(+)>6M	有文件證明確係患者曾服用 Lamivudine、Entecavir0.5mg、Telbivudine **治療中**	HBsAg(+)	Anti-HCV(+)
PT≧3 或 Bil≧2mg/dl	1. 非肝臟移植 ALT>1X	HBeAg(+)>3M	HBeAg(+)>3M	HBeAg(−)>3M	**產生抗藥性時則治療中** HBV DNA≧1 log IU/ml	HBV DNA ≧2,000IU/mL	ALT>1X
	2. 肝臟移植 (可預防性使用)	ALT≧5X	2X≦ALT<5X	ALT≧2X (半年2次，間隔3個月)		肝組織切片 Metavir F4 或 超音波診斷為肝硬化併食道或胃靜脈曲張 或 超音波診斷為肝硬化併脾腫大	肝組織切片 中等纖維化(≧F1) 或 HCV RNA(+)
	3. 接受癌症化學治療中發作 (長期使用) 4. 化學治療前1週使用； (但此項療程僅至化學治療結束後6M)		肝組織切片 HBcAg(+) 或 HBV DNA ≧2,0000IU/mL	肝組織切片 HBcAg(+) 或 HBV DNA ≧2,000IU/mL			
Lamivudine 或 Entecavir 0.5mg 或 Telbivudine **療程** **12-36M** **若** 治療中e抗原陰轉可再治療**12M**	__限會診消化系專科醫師___	無肝功能代償不全	無肝功能代償不全； 無D型或C型肝炎合併感染	無肝功能代償不全； 無D型或C型肝炎合併感染			無肝功能代償不全
	Lamivudine 或 Entecavir 0.5mg 或 Telbivudine **長期使用**	Lamivudine (**療程 12-36M**) 或 Entecavir0.5mg (**療程 12-36M**) 或 Telbivudine (**療程 12-36M**) 或 長效 Peg-interferon alfa-2a (Pegasys): 1) HBeAg(+)**療程 6M** 2) HBeAg(−)**療程 12M** **若** 治療中e抗原陰轉可再治療**12M**			原藥物治療+ Adefovir **療程3年** 或 Entecavir 1mg (限Lamivudine產生抗藥性) **療程3年** 或 長效Peg-interferon alfa-2a (Pegasys) **療程12M**	Lamivudine 或 Entecavir0.5mg 或 Telbivudine **長期使用**	長效型干擾素 (Pegasys 或 eg-Intron) 併用 Ribavirin 療程 **6M**:RVR(+) 療程 **12M**: RVR(-)EVR(+) 療程 **4M**: RVR(-)EVR(-)


Thanks for your attention