Terapia dell'epatite cronica B: paradigmi attuali e possibili scenari futuri

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Main goal of treatment of chronic hepatitis B

Suppress HBV replication

↓

Induce remission of liver disease before liver cirrhosis and HCC have developed

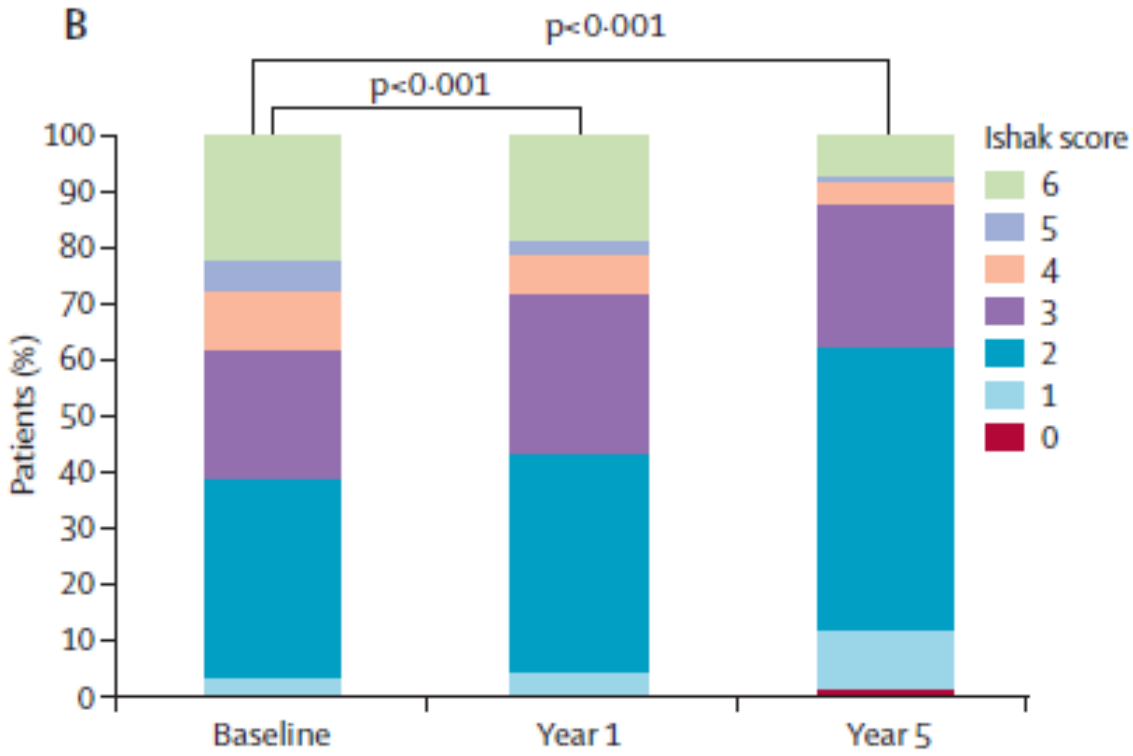
Goals and Benefits of Hepatitis B Treatment

- Prevention of long-term negative clinical outcomes (eg, cirrhosis, liver transplantation, HCC, death) by durable suppression of HBV DNA
- Primary endpoint
  - Sustained decrease in serum HBV DNA level to undetectable
- Secondary endpoints
  - Decrease or normalize serum ALT
  - Improve liver histology
  - Induce HBeAg loss or seroconversion in HBeAg-positive disease
  - Induce HBsAg loss or seroconversion
- Treatment is often long term or lifelong, particularly in HBeAg-negative patients

Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study

Patrick Marcellin, Edward Gane, Maria Buti, Nezam Afdhal, William Sievert, Ira M Jacobson, Mary Kay Washington, George Germanidis, John F Flaherty, Raul Aguilar Schall, Jeffrey D Bornstein, Kathryn M Kitrinos, G Mani Subramanian, John G McHutchison, E Jenny Heathcote

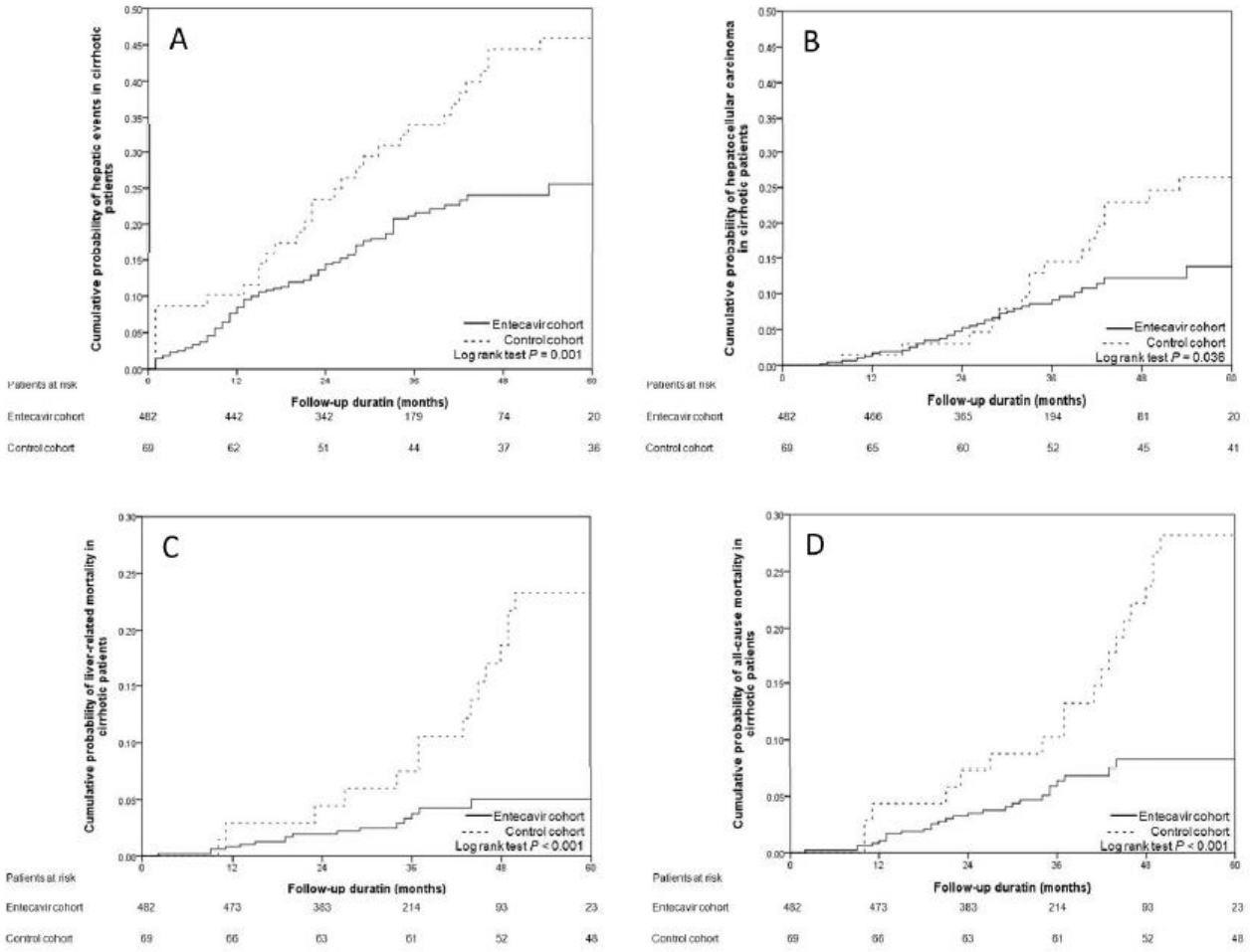
348 patients (HBeAg and anti-Hbe) treated for 240 weeks with two liver biopsy



Lancet 2013

Entecavir Treatment Reduces Hepatic Events and Deaths in Chronic Hepatitis B Patients with Liver Cirrhosis

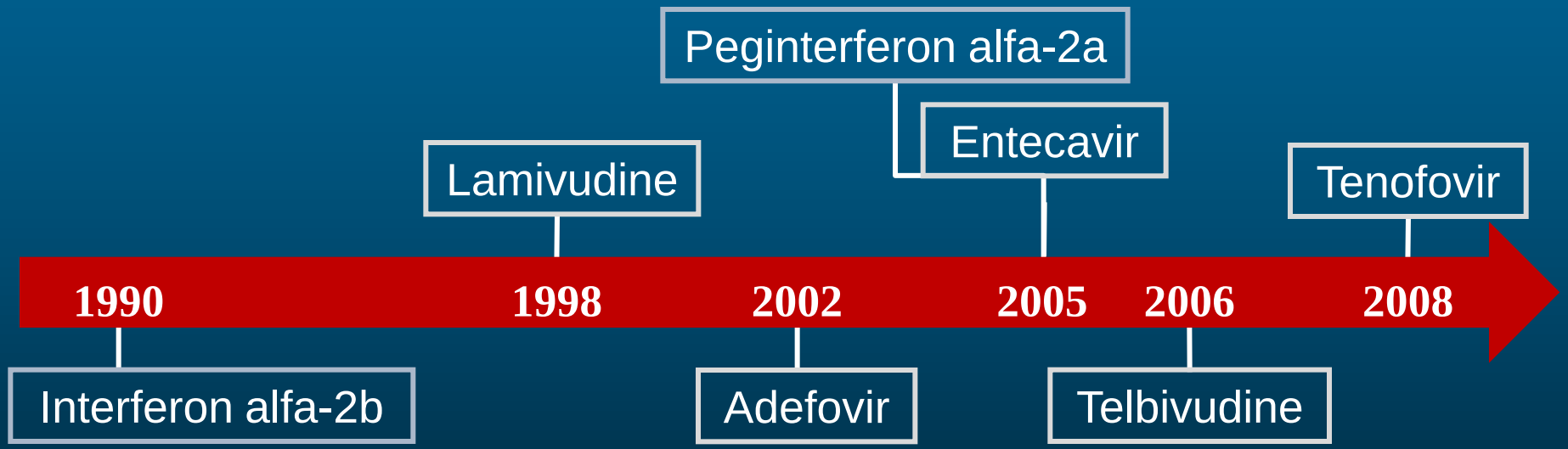
1,446 Entecavir treated patients (follow-up 36±13 months) and 424 treatment-naive patients (follow-up 114±31 months)



Kaplan-Meier analysis of cumulative of (A) hepatic events, (B) hepatocellular carcinoma, (C) liver-related mortality and (D) all-cause mortality among cirrhotic patients of entecavir and control cohort

Wong GLH, Hepatology 2013, In press

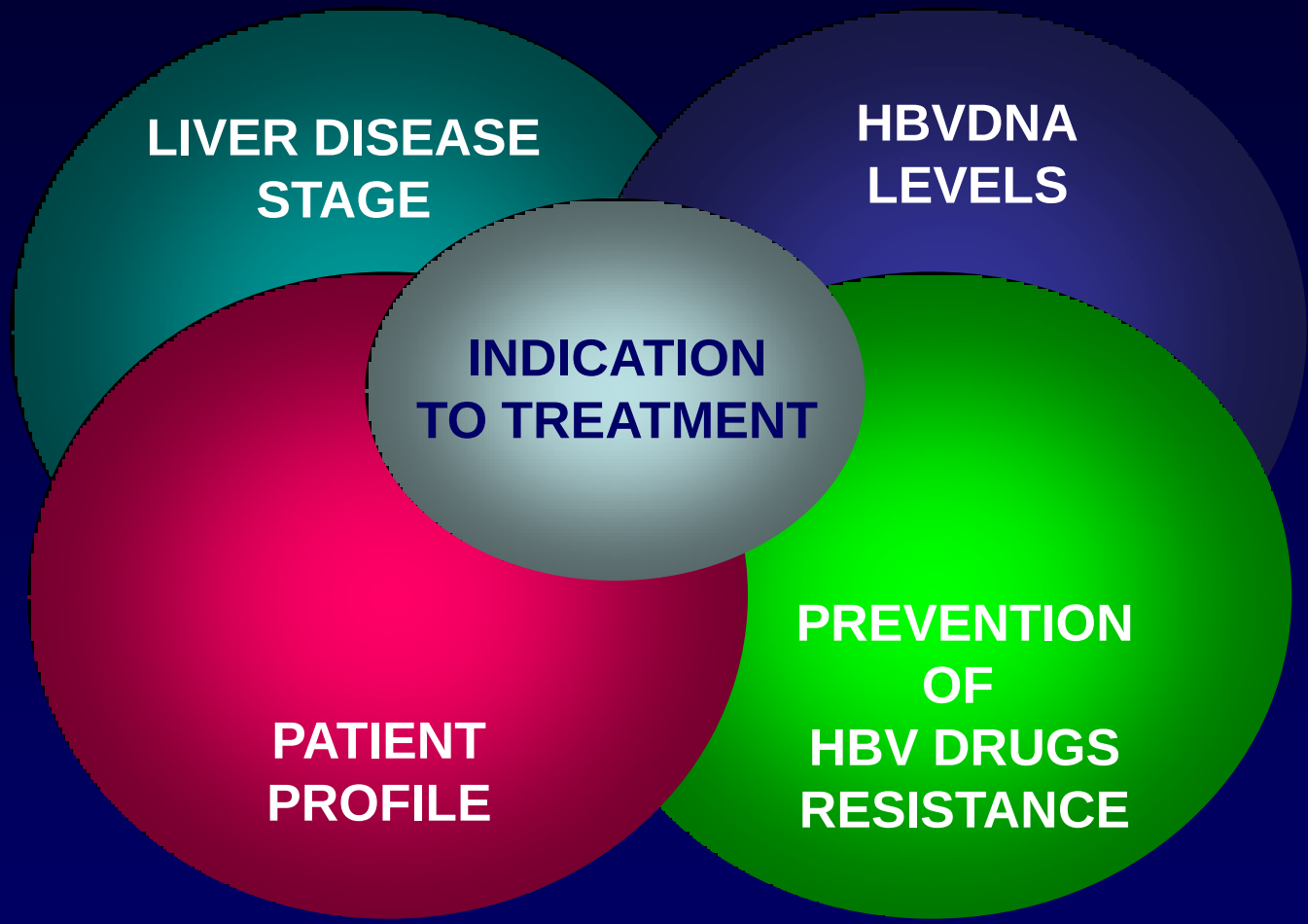
HBV Treatment Landscape in 2014



Terapia Epatite Cronica B

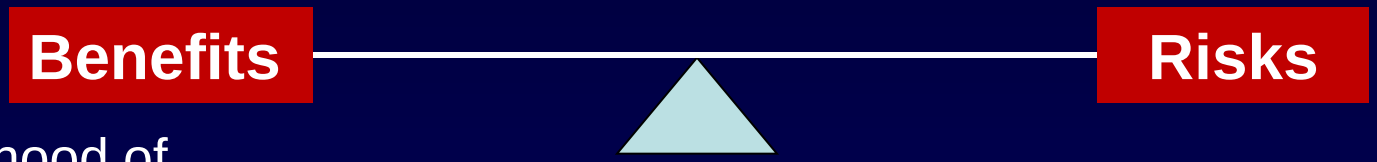
- **Indicazione**
- Opzioni terapeutiche
- Scelta della migliore opzione terapeutica
- Monitoraggio della risposta terapeutica
- Possibili scenari futuri

Indication to Treatment is an Integrated Decision



G. Carosi, M Rizzetto. Dig Liv Dis 2008

When to Start HBV Treatment?



Likelihood of
- Adverse outcome without treatment
- Long-lasting response

Patient's age and preference
Costs

Adverse effects
Drug resistance

Likelihood of adverse outcome without treatment

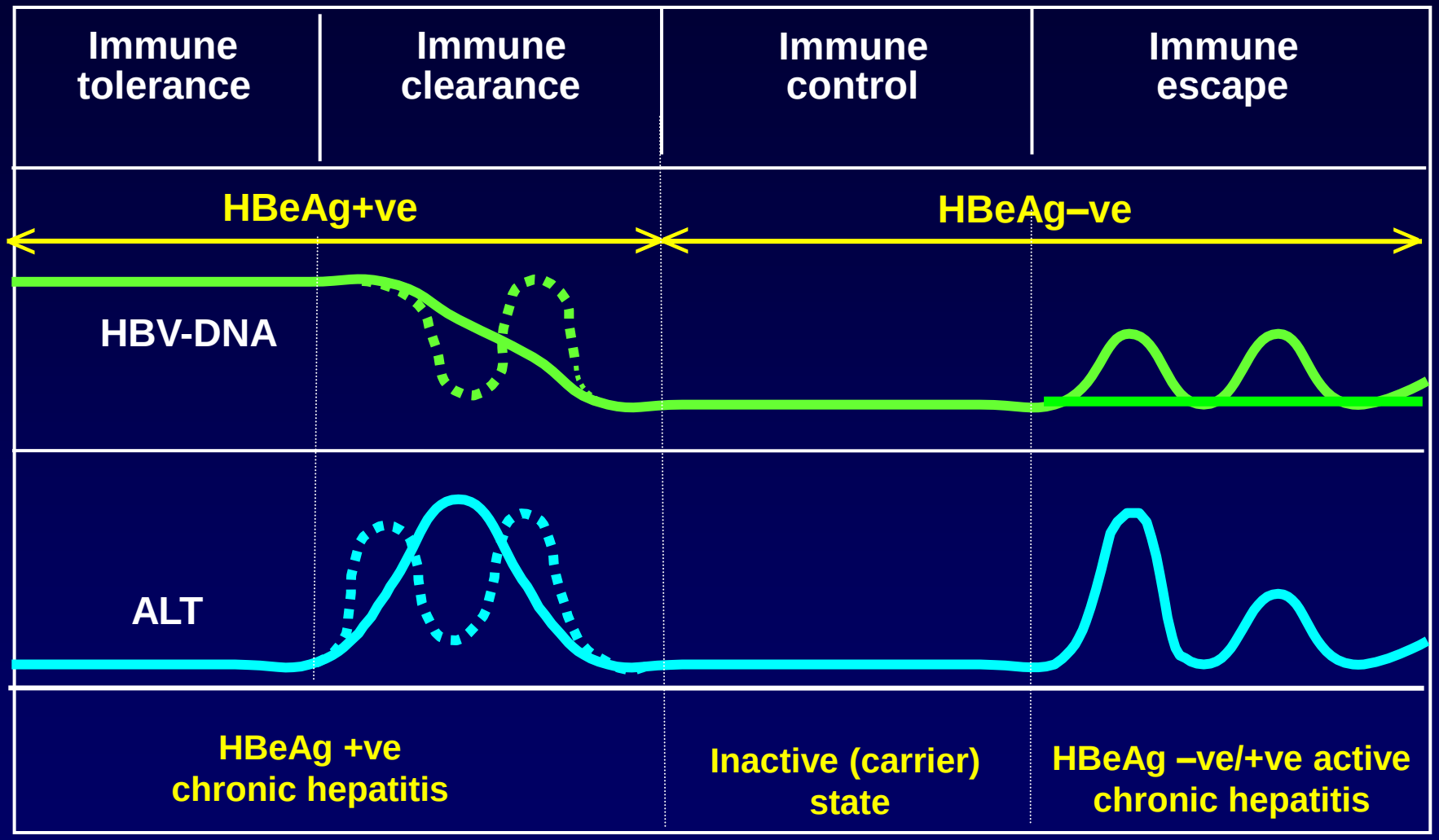
Activity and stage of liver disease at presentation

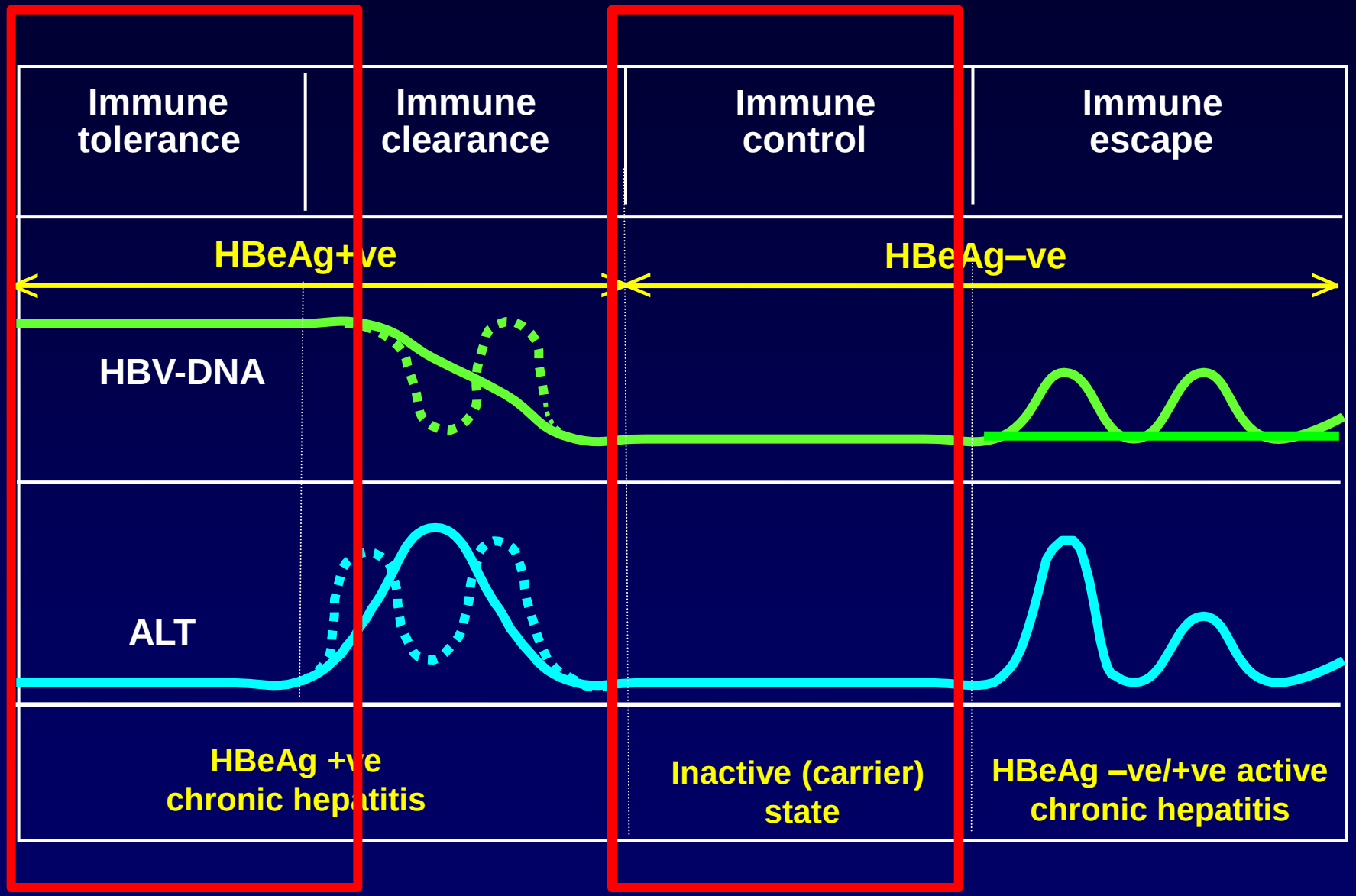
Risk of cirrhosis/HCC in the next 10-20 yrs

Likelihood of long-term benefit with treatment

Who Should Be Treated?

- Not a question of who to treat, but when: treat now or monitor and treat later when indicated
- All HBV carriers are potential treatment candidates
- A patient who is not a treatment candidate now can be a treatment candidate in the future
  - Changes in HBV replication status and/or activity/stage of liver disease
  - Availability of new or improved treatments


Immune tolerance
Immune clearance
Immune control
Immune escape
HBeAg+ve
HBeAg–ve
HBV-DNA
ALT
HBeAg +ve chronic hepatitis
Inactive (carrier) state
HBeAg –ve/+ve active chronic hepatitis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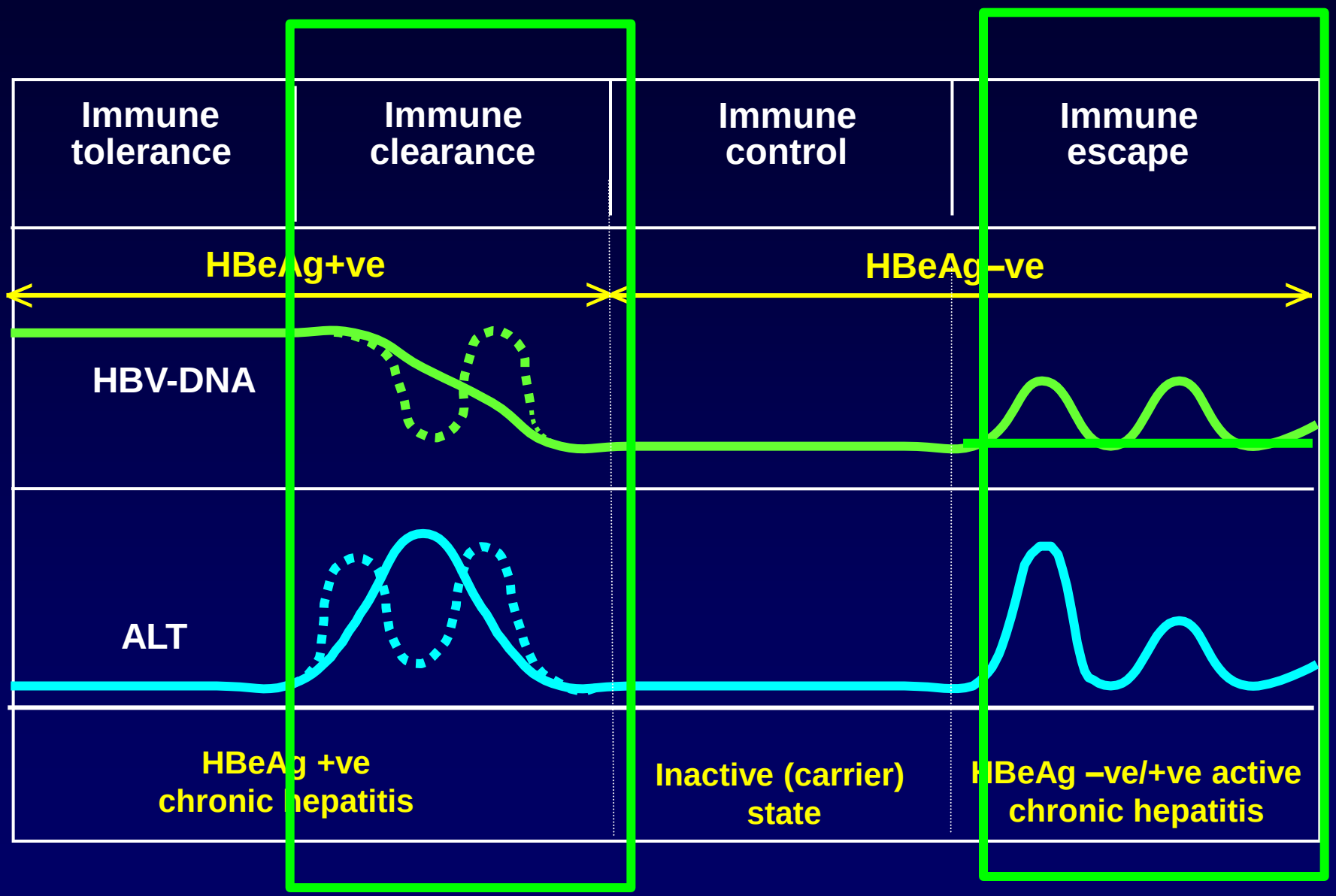
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Determining Treatment Candidacy for Chronic Hepatitis B: Guidelines

Guidelines	HBeAg Positive		HBeAg Negative	
	HBV DNA, IU/mL	ALT	HBV DNA, IU/mL	ALT
AASLD 2009[1]	> 20,000	> 2 x ULN or positive biopsy*	≥ 20,000	≥ 2 x ULN or positive biopsy*
EASL 2012[2]	> 2000	> ULN	> 2000	> ULN
APASL 2008[3]	≥ 20,000	> 2 x ULN	≥ 2000	> 2 x ULN
NIH Consensus Conference 2009[4]	> 20,000	> 2 x ULN or positive biopsy*	≥ 20,000	≥ 2 x ULN or positive biopsy*

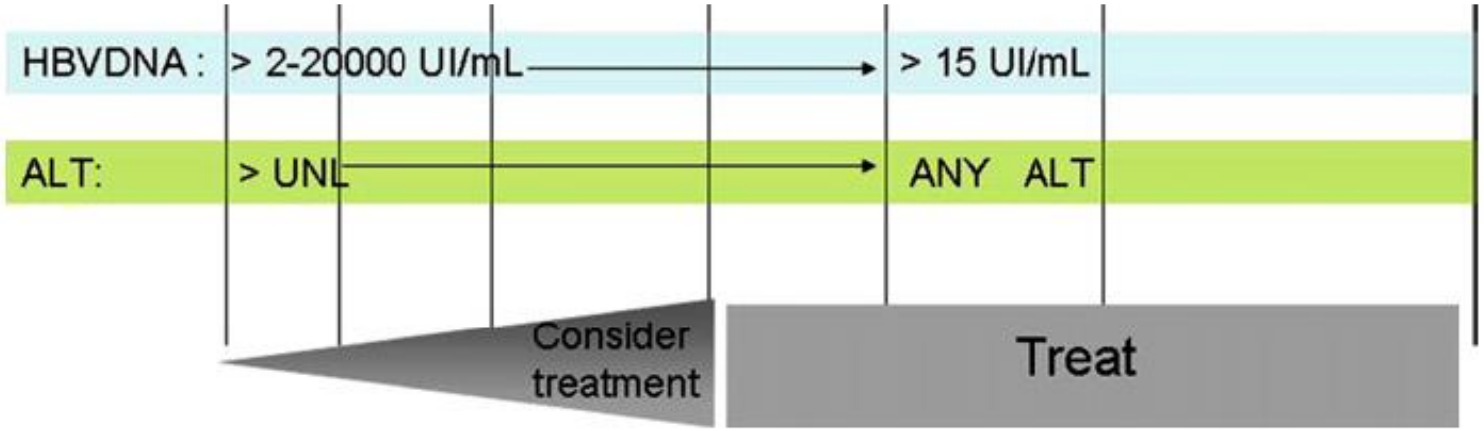
*Moderate/severe inflammation or significant fibrosis.

- Expert guidelines also published with recommendations specific for HBV management in US[5] and more recently for Asian Americans[6]
  - Some key differences between these guidelines

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. EASL. J Hepatol. 2009;50:227-242. 3. Liaw YF, et al. Hepatol Int. 2008;3:263-283. 4. Degerekin B, et al. Hepatology. 2009;S129-S137. 5. Keeffe EB, et al. Clin Gastroenterol Hepatol. 2008;6:1315-1341. 6. Tong MJ, et al. Dig Dis Sci. 2011;56:3143-3162.

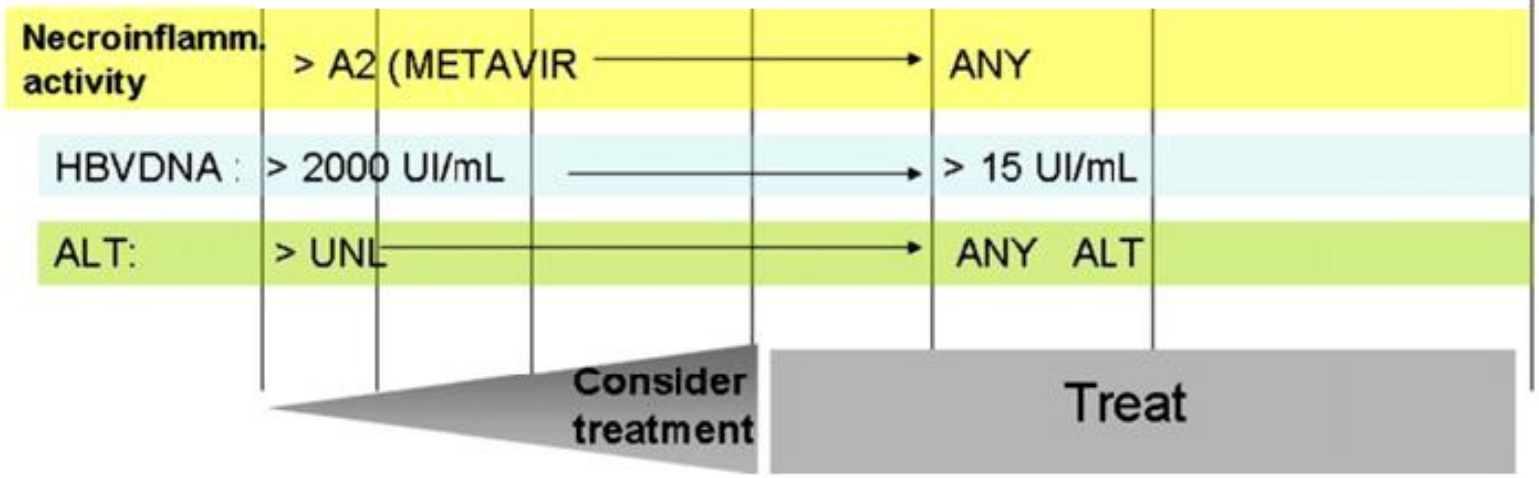
"Paradigma di Stresa" pazienti con epatite cronica HBeAg positiva con o senza cirrosi

	Hepatitis				Cirrhosis	Decompensated cirrhosis
Fibrosis	No	Mild	Moderate	Severe		
METAVIR Ishak's	F0 S0	F1 S 1-2	F2 S3	F3 S4	F4 S5-6	



"Paradigma di Stresa" pazienti con epatite cronica HBeAg negativa con o senza cirrosi

	Hepatitis				Cirrhosis	Decompensated cirrhosis
Fibrosis	No	Mild	Moderate	Severe		
METAVIR	F0	F1	F2	F3	F4	
Ishak's	S0	S 1-2	S3	S4	S5-6	



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Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection
- Entecavir
- Tenofovir

EASL. J Hepatol. 2009;50:227-242. Liaw YF, et al. Hepatol Int. 2008;2:263-283.
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Treatment of chronic hepatitis B

Finite Curative treatment: aimed to control HBV infection and to cure chronic hepatitis by a time limited treatment

Indefinite Suppressive treatment: aimed to obtain and maintain a long lasting inhibition of viral replication with control of disease activity by a continous antiviral treatment

Treatment of HBV chronic hepatitis

- HBeAg positive chronic hepatitis
- HBeAg negative chronic hepatitis

END – POINTS OF THERAPY

- HBeAg-positive and negative patients:
  - Sustained HBsAg loss, with or without seroconversion to anti-HBs (ideal end-point)
- HBeAg-positive patients
  - Durable HBe seroconversion (satisfactory endpoint)
- HBeAg-positive patients who do not achieve HBe seroconversion and HBeAg-negative patients:
  - Maintained undetectable HBV DNA level with NUCs
  - Sustained undetectable HBV DNA level after IFN therapy (next most desirable end-point)

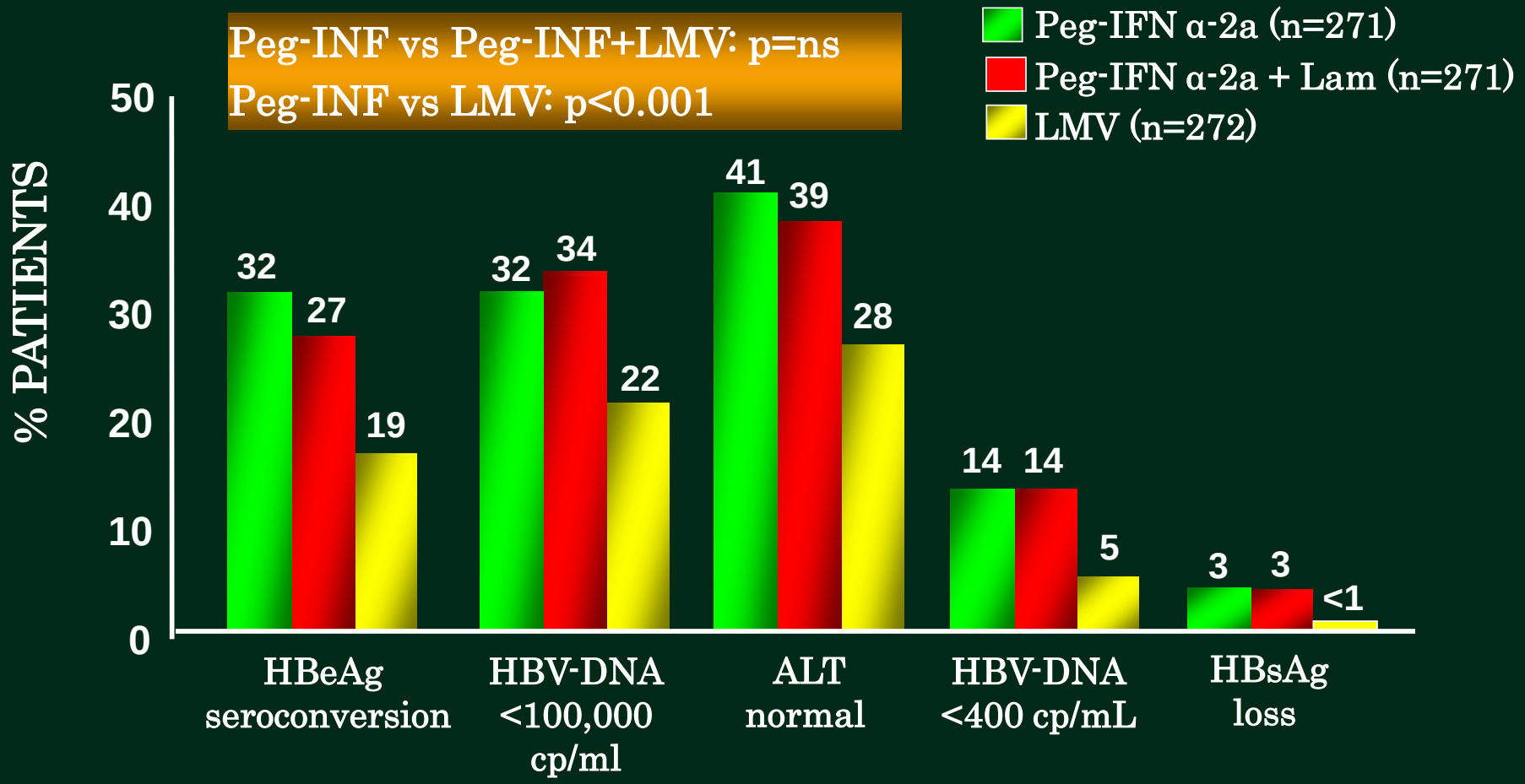
EASL Clinical Practice Guidelines, J Hepatol 2012

Treatment of HBV chronic hepatitis

- HBeAg positive chronic hepatitis
- HBeAg negative chronic hepatitis

A RCT of 48 wk Peg-IFN α-2a ± LMV vs LMV
HBeAg positive patients

End of Follow-up Response (24 wks post-Rx)



Lau et al, NEJM 2005

Response-Guided PegIFN-Based Therapy in HBeAg-Positive Patients

- Pooled analysis of 3 global randomized studies (N = 803)[1]
  - Phase III study of pegIFN[2]
  - HBV 99-01 study[3]
  - Neptune study[4]
- Response observed in
  - 23% with HBeAg loss with HBV DNA < 2000 IU/mL (n = 182)
  - 5% with HBsAg loss at 6 mos posttreatment (n = 39)
- HBsAg levels at Wks 12 and 24 predicted response to therapy
- HBV genotypic–specific stopping rules proposed
  - Low response rates if HBsAg > 20,000 IU/mL at Wk 24 in all genotypes

1. Sonneveld MJ, et al. AASLD 2012. Abstract 23. 2. Lau GK, et al. N Engl J Med. 2005;352:2682-2695.
3. Janssen HL, et al. Lancet. 2005;365:123-129. 4. Liaw YF, et al. Hepatology. 2011;54:1591-1599.

Trattamento con Peg-IFN
-fattori prognostici-

HBeAg+

Fattori pre-treatment

- **ALT> 5 ULN**
- **HBV DNA UI< 6 LOG**
- **genotipo A o B**
- **Severa attività necro-infiammatoria**

Fattori on-treatment

- **Calo livelli di HBsAg**

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Entecavir Treatment for up to 5 Years in Patients with Hepatitis B e Antigen–Positive Chronic Hepatitis B

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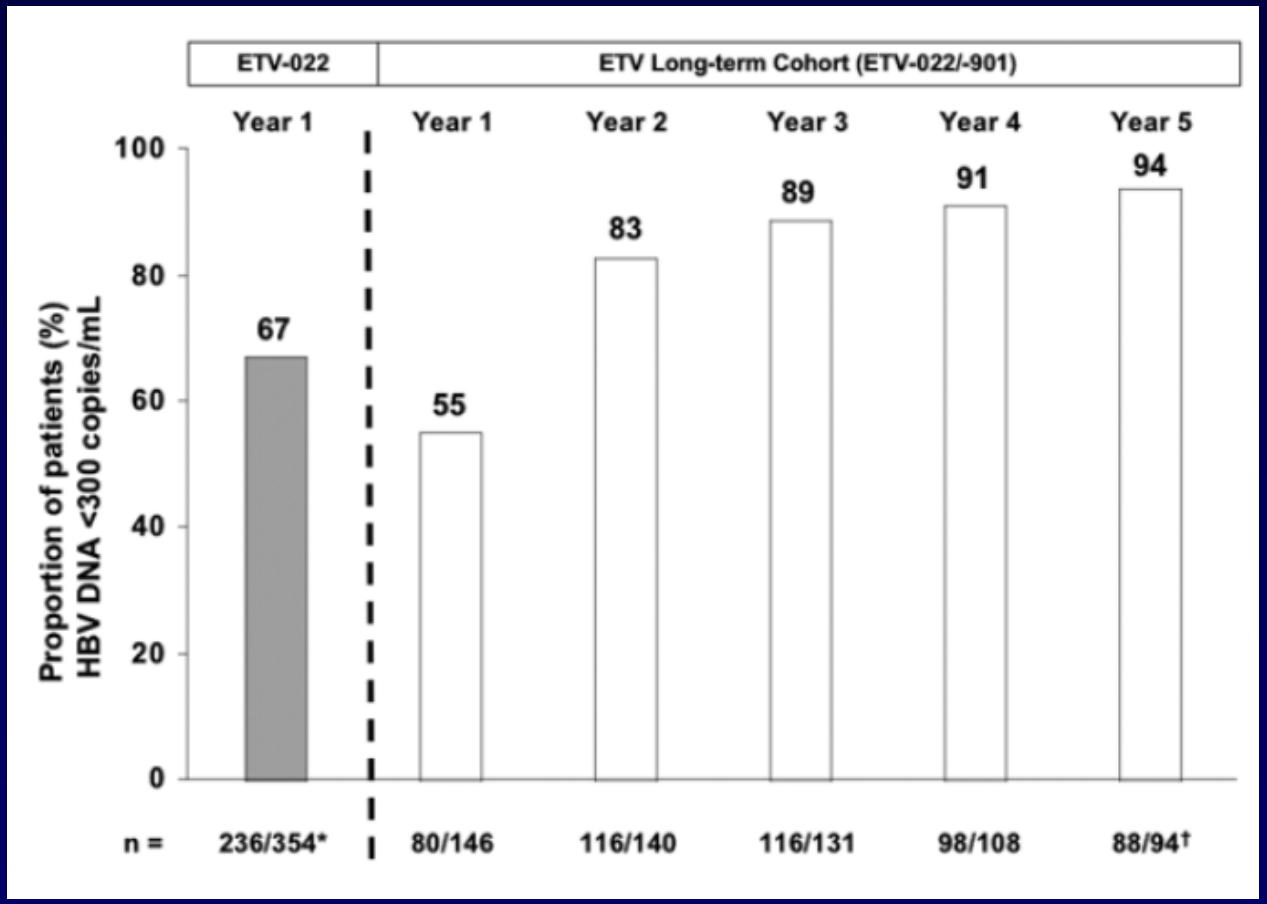
183 HBeAg positive patients treated with entecavir for 5 years.



Hepatology 2010

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183 HBeAg positive patients treated with entecavir for 5 years.

Serological end-points

33/141 (23%) patients achieved HBeAg seroconversion

2/145 (1.4%) patients achieved HBsAg seroconversion

Hepatology 2010

Efficacy of Tenofovir Disoproxil Fumarate at 240 Weeks in Patients With Chronic Hepatitis B With High Baseline Viral Load

Stuart C. Gordon,[1] Zahary Krastev,[2] Andrzej Horban,[3] Jörg Petersen,[4] Jan Sperl,[5] Phillip Dinh,[6] Eduardo B. Martins,[6] Leland J. Yee,[6] John F. Flaherty,[6] Kathryn M. Kitrinos,[6] Vinod K. Rustgi,[7] and Patrick Marcellin[8]

Antiviral response after 240 weeks of tenofovir in 129 patients with CHB who had baseline high viral load (>9log10 cps/mL) and in 512 without

Table 1. Baseline Clinical and Demographic Characteristics

	HVL* (n = 129)	Non-HVL* (n = 512)	*P* Value†
Median (IQR) age, years	31 (23, 39)	43 (33, 50)	<0.001
Sex, n (%)			
Male	96 (74.4)	377 (73.6)	0.856
Female	33 (25.6)	135 (26.4)	
Median (IQR) HBV DNA, $\log_{10}$ copies/mL	9.52 (9.25, 9.73)	7.34 (6.23, 8.29)	<0.001
HBeAg positive at baseline, n (%)	118 (91.5)	148 (28.9)	<0.001
Anti-HBeAg positive at baseline, n (%)	13 (10.2)	375 (73.2)	<0.001
Previous LAM/FTC experience > 12 weeks, n (%)	6 (4.7)	69 (13.5)	0.005
No. (%) with cirrhosis (Ishak 5/6)	24 (18.6)	128 (25.2)	0.148
HBV genotype (%)			
A	28 (22.0)	75 (15.0)	0.292
B	12 (9.4)	62 (12.4)	
C	19 (15.0)	93 (18.6)	
D	62 (48.8)	253 (50.5)	
Other‡	6 (4.7)	18 (3.6)	

Hepatology 2013

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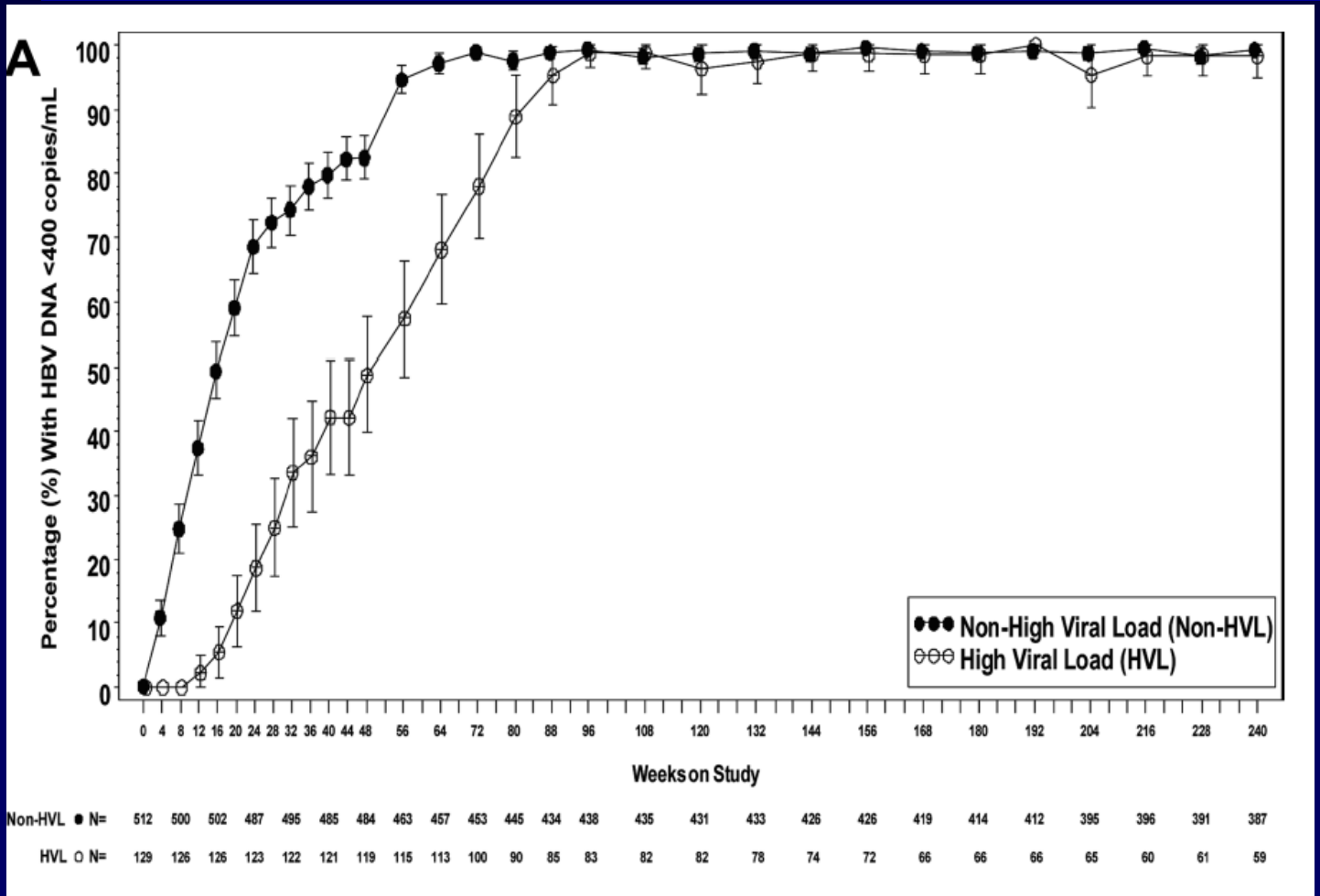

Hepatology 2013

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A RCT of 48 wk Peg-IFN α-2a ± LMV vs LMV
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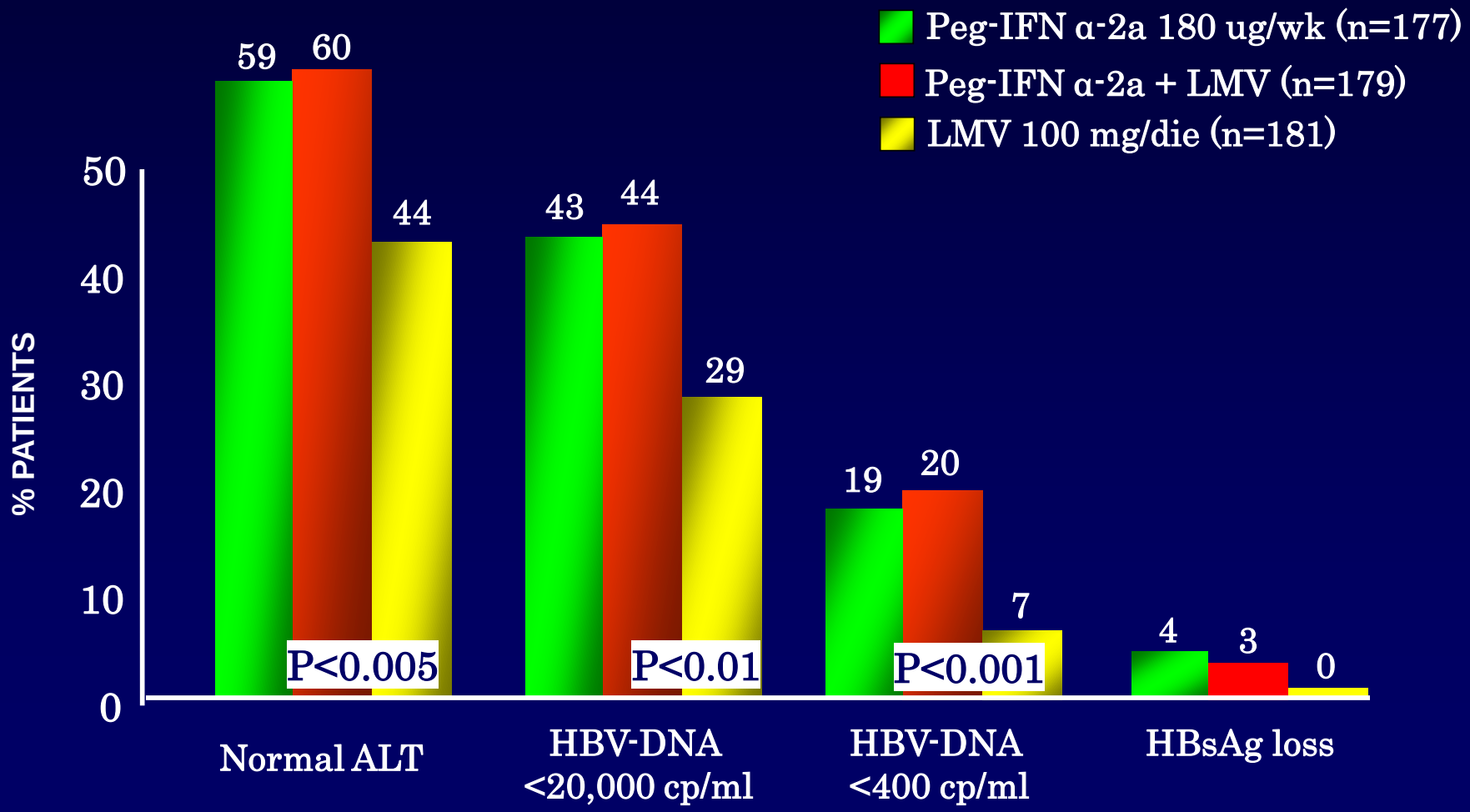
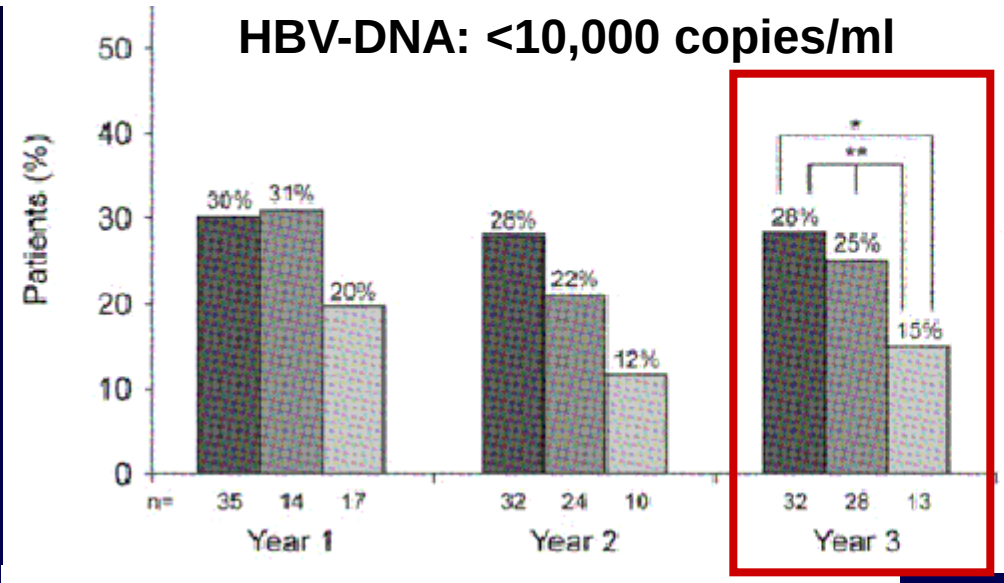


Marcellin et al, NEJM 2004

Sustained Response of Hepatitis B e Antigen-Negative Patients 3 Years After Treatment with Peginterferon Alfa-2a

PATRICK MARCELLIN,* FERRUCCIO BONINO,‡ GEORGE K. K. LAU,§ PATRIZIA FARCI,|| CIHAN YURDAYDIN,¶ TEERHA PIRATVISUTH,# RUI JIN,** SELIM GUREL,‡‡ ZHI-MENG LU,§§ JIAN WU,|||| MATEI POPESCU,¶¶ and STEPHANOS HADZIYANNIS,## for the Peginterferon alfa-2a in HBeAg-negative Chronic Hepatitis B Study Group

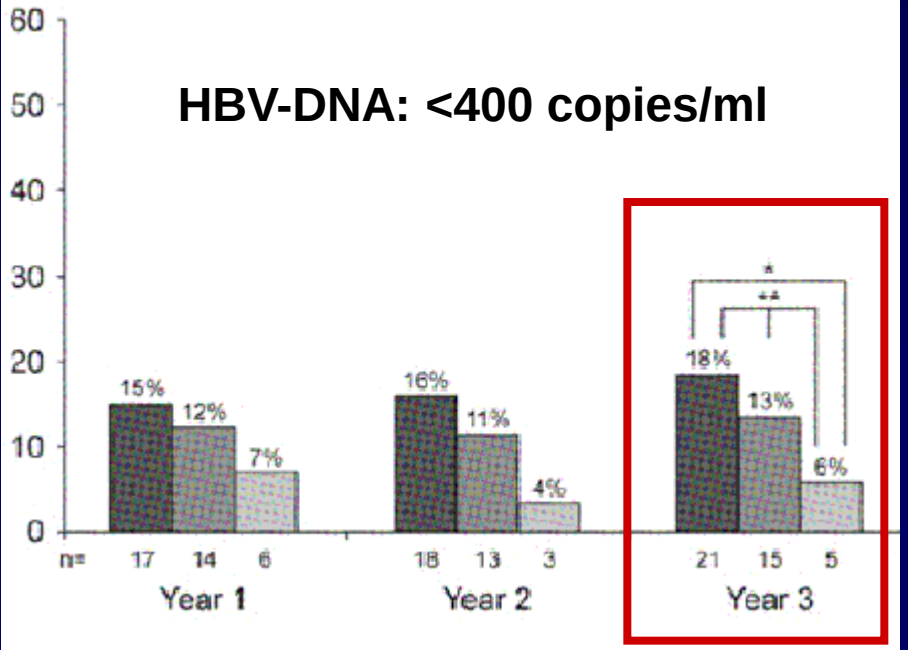
HBV-DNA: <10,000 copies/ml



Peginterferon alfa-2a (n=116)
Peginterferon alfa-2a + lamivudine (n=114)
Lamivudine (n=85)

*P = .0415 for Peginterferon alfa-2a vs lamivudine
**P = .0505 for Peginterferon alfa-2a ± lamivudine vs lamivudine

HBV-DNA: <400 copies/ml



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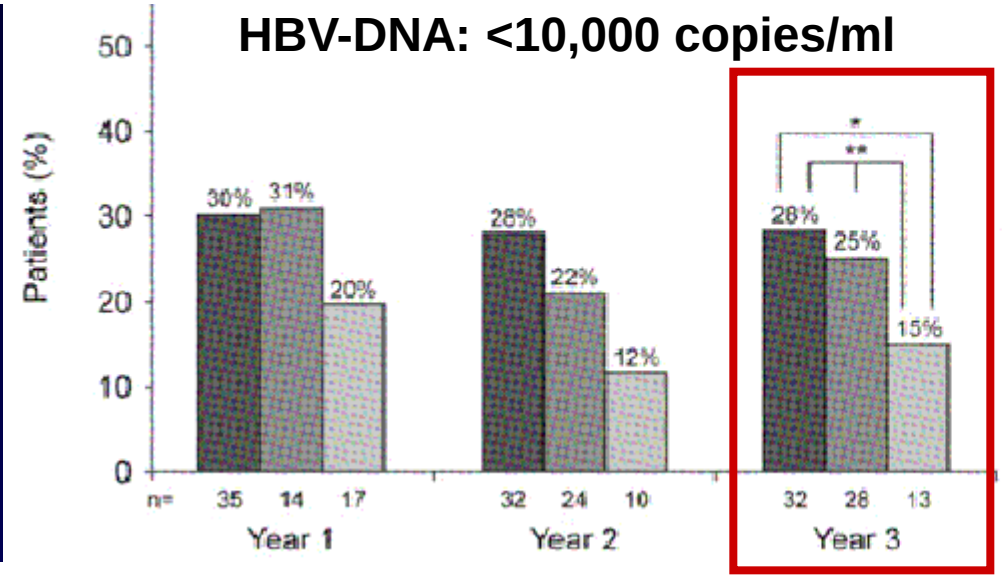

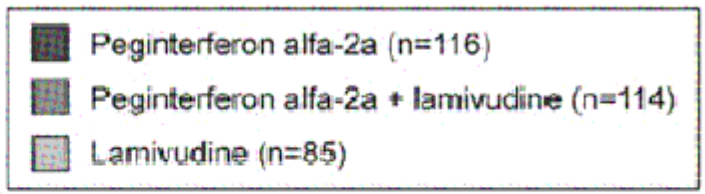

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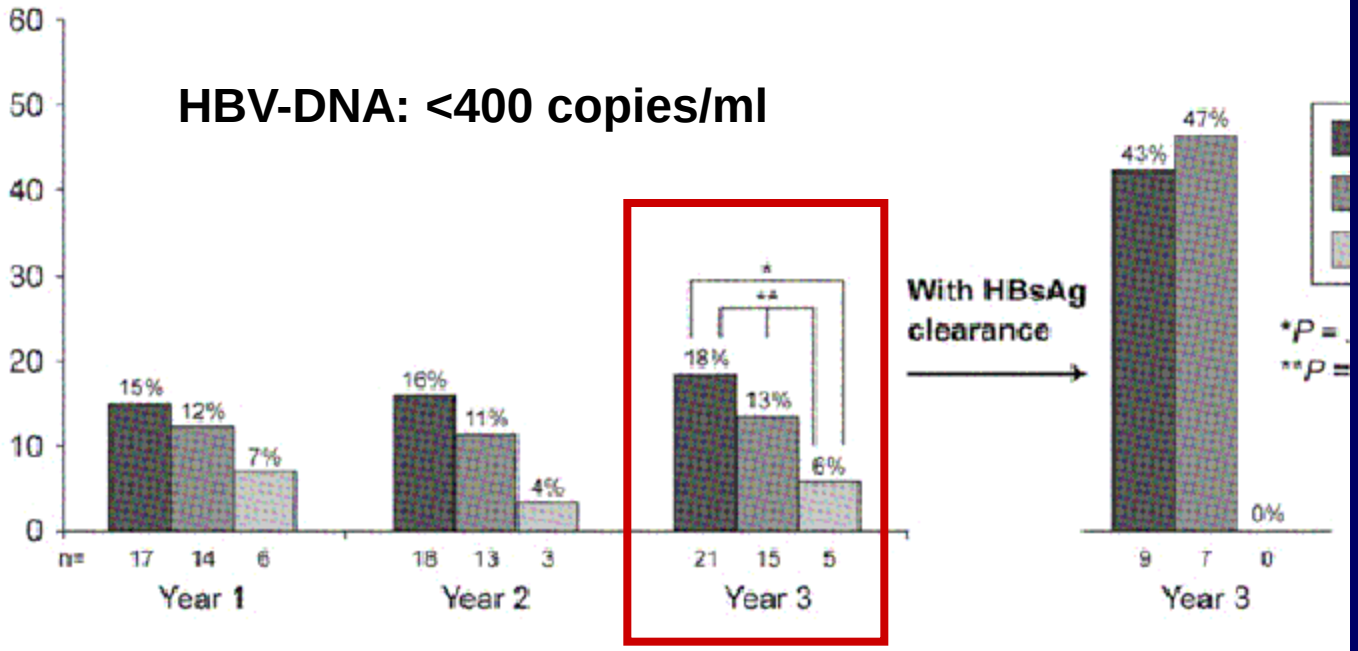

Gastroenterology 2009

Randomised study comparing 48 and 96 weeks peginterferon α-2a therapy in genotype D HBeAg-negative chronic hepatitis B

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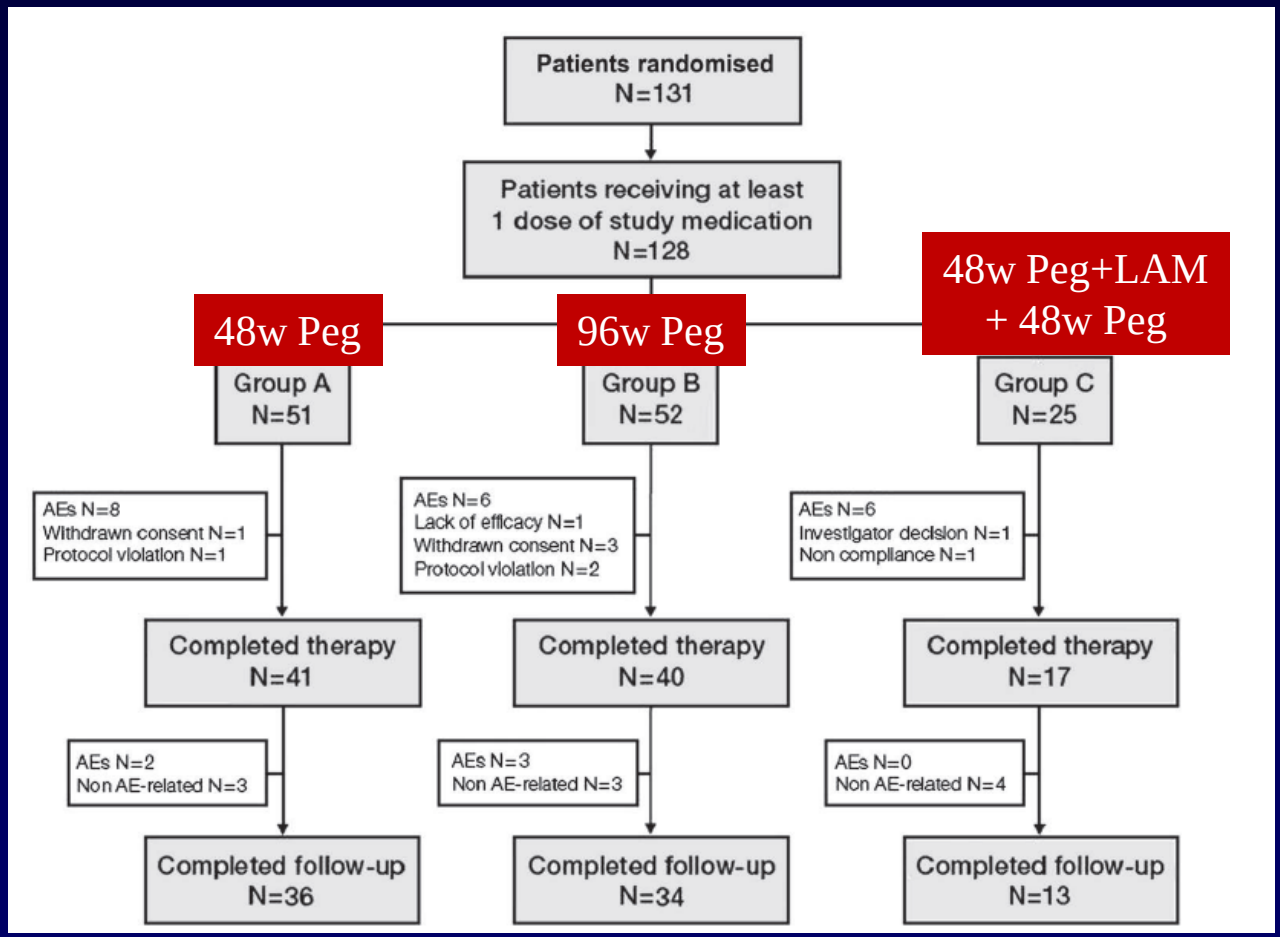

Gut 2013

Table 3 Intention-to-treat analysis of the response rates at the end of 48-week post-treatment follow-up

Outcomes, n (%)	48-week PegIFN (group A, N=51)	96-week PegIFN (group B, N=52)	PegIFN + lamivudine (group C, N=25)	p Value* (A vs B)
HBV DNA <3400 IU/ml + ALT normalisation	6 (11.8)	13 (25.0)	5 (20.0)	0.0834†
HBV DNA <20 000 IU/ml + ALT normalisation	10 (19.6)	15 (28.9)	6 (24.0)	0.2742†
ALT normalisation	18 (35.3)	18 (34.6)	9 (36.00)	0.9424†
HBV DNA <20 000 IU/ml	12 (23.5)	20 (38.5)	6 (24.0)	0.1016†
HBV DNA <3400 IU/ml	6 (11.8)	16 (30.8)	5 (20.0)	0.0186†
HBV DNA <2000 IU/ml	6 (11.8)	15 (28.8)	5 (20.0)	0.0314†
HBV DNA <6 IU/ml§	1 (2.0)	4 (7.7)	2 (8.0)	0.3627‡
HBsAg <10 IU/ml	0 (0.0)	5 (9.6%)	0 (0.0)	0.0565‡
HBsAg clearance	0 (0.0)	3 (5.8)	0 (0.0)	0.2427‡

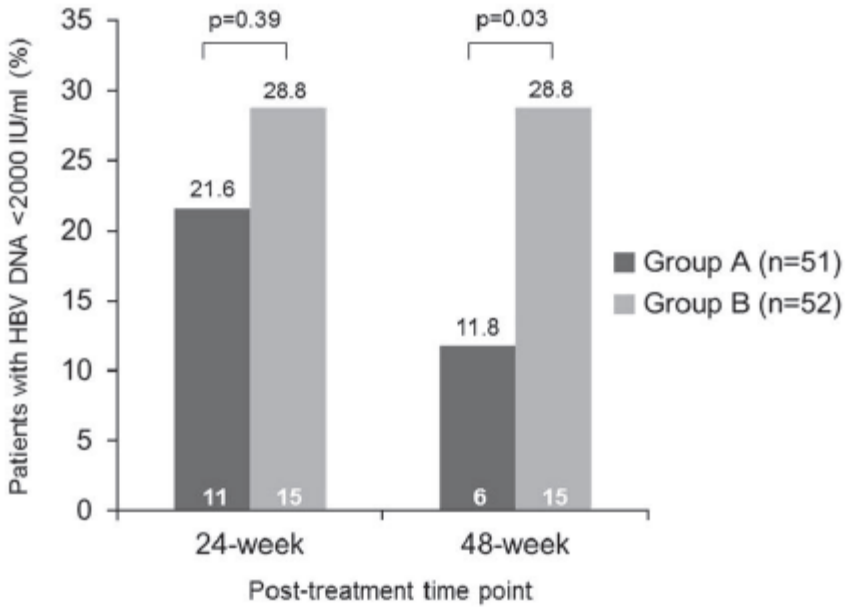

Figure 3 Virological response rates (HBV DNA <2000 IU/ml) after 24 or 48 weeks of post-treatment follow-up in patients treated for 48 (group A) or 96 (Group B) weeks with pegylated interferon α2a (intention-to-treat analysis).

Gut 2013

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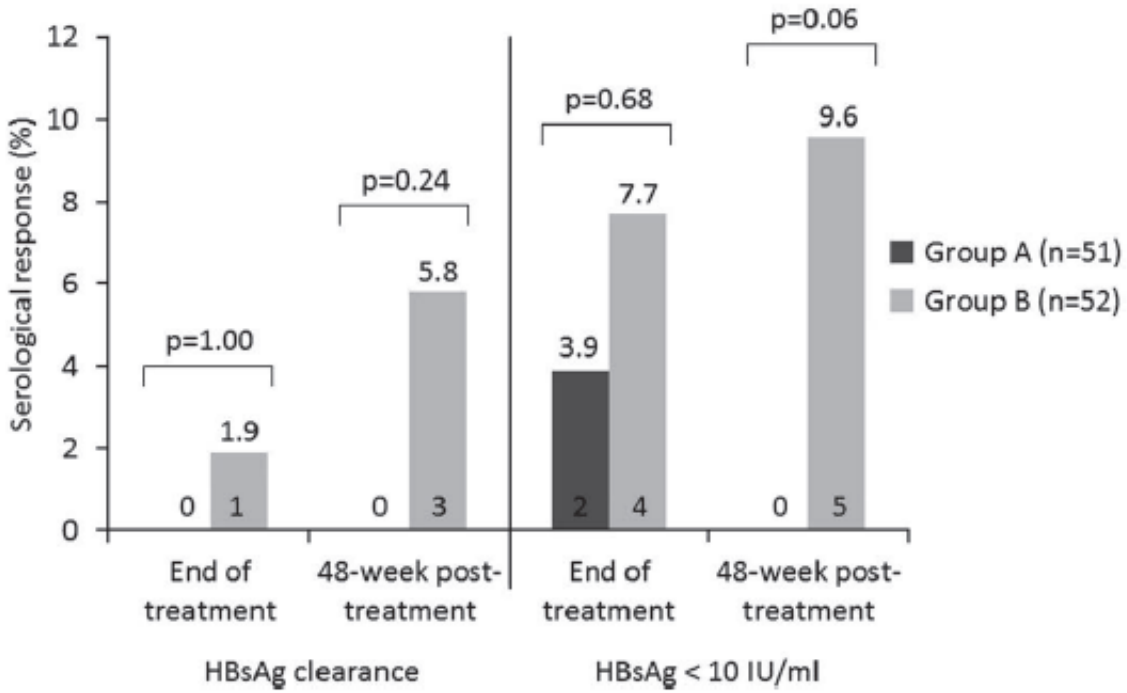


Figure 4 HBsAg response rates at the end of treatment and 48 weeks post-treatment in patients treated for 48 (group A) or 96 (Group B) weeks with pegylated interferon α2a (intention-to-treat analysis).

Gut 2013

Trattamento con Peg-IFN

-fattori prognostici-

Predicting response to peginterferon α-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B

F Bonino, P Marcellin, G K K Lau, S Hadziyannis, R Jin, T Piratvisuth, G Germanidis, C Yurdaydin, M Diago, S Gurel, M-Y Lai, M R Brunetto, P Farci, M Popescu, P McCloud, for the Peginterferon Alfa-2a HBeAg-Negative Chronic Hepatitis B Study Group

518 patients treated with Peg-IFN a-2a +/-LAM or with LAM alone.
Response: ALT normalisation and HBV DNA< 20 000 copies/ml 24 week after treatment

Table 1 Logistic regression analysis on pre-treatment factors and sustained combined response*

Pre-treatment factor†	Comparison	Odds ratio‡ (95% CI)	p Value
Age	10 year decrease	1.26 (1.0 to 1.5)	0.018
Gender	Female v male	1.93 (1.1 to 3.4)	0.022
Body weight	10 kg increase	1.10 (0.9 to 1.3)	0.273
Baseline ALT	1 $\log_{10}$ unit (IU/l) increase	3.69 (1.7 to 8.1)	0.001
HBV DNA	1 $\log_{10}$ unit (copies/ml) decrease	1.28 (1.1 to 1.4)	<0.001
HBV genotype			<0.001
	A v B	0.42 (0.1 to 1.2)	0.097
	A v C	0.33 (0.1 to 0.9)	0.030
	A v D	0.97 (0.3 to 2.7)	0.958
	B v C	0.79 (0.5 to 1.3)	0.344
	B v D	2.31 (1.3 to 4.2)	0.006
	C v D	2.9 (1.7 to 5.0)	<0.001
Treatment	PEG-IFNα-2a v LAM	1.84 (1.1 to 3.0)	0.014
	PEG-IFNα-2a+LAM v LAM	2.19 (1.3 to 3.6)	0.002
	PEG-IFNα-2a v PEG-IFNα-2a+LAM	1.19 (0.8 to 1.9)	0.460
Treatment by HBV genotype interaction	–	–	0.018

GUT 2007

Hepatitis B Virus Surface Antigen Levels: A Guide to Sustained Response to peginterferon alfa-2a in HBeAg-Negative Chronic Hepatitis B

Maurizia Rossana Brunetto,[1] Francesco Moriconi,[1] Ferruccio Bonino,[2] George K. K. Lau,[3] Patrizia Farci,[4] Cihan Yurdaydin,[5] Teerha Piratvisuth,[6] Kangxian Luo,[7] Yuming Wang,[8] Stephanos Hadziyannis,[9] Eva Wolf,[10] Philip McCloud,[11] Richard Batrla,[12] and Patrick Marcellin[13]

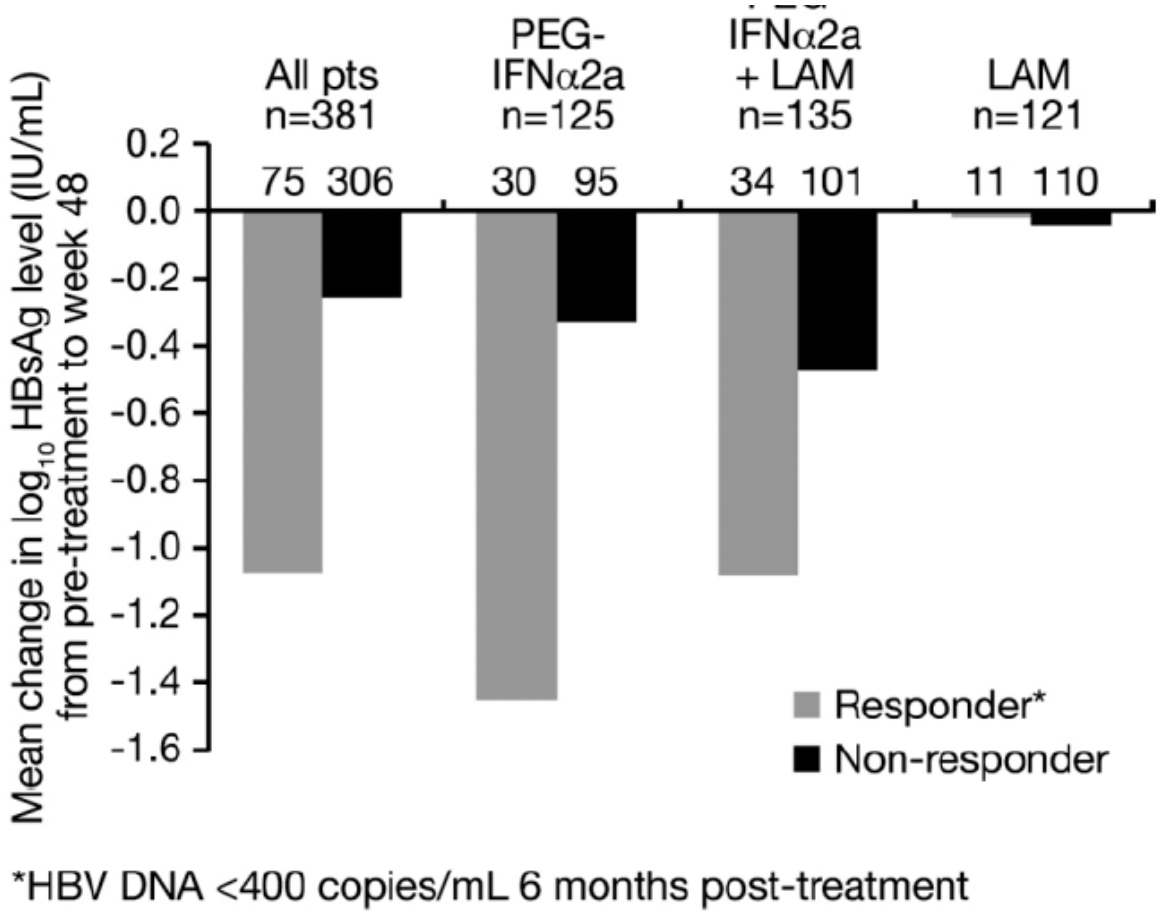


Fig. 4. Decline in HBsAg from pretreatment to end of treatment according to virological response and treatment group.

Hepatology 2009

Hepatitis B Virus Surface Antigen Levels: A Guide to Sustained Response to peginterferon alfa-2a in HBeAg-Negative Chronic Hepatitis B

Maurizia Rossana Brunetto,[1] Francesco Moriconi,[1] Ferruccio Bonino,[2] George K. K. Lau,[3] Patrizia Farci,[4] Cihan Yurdaydin,[5] Teerha Piratvisuth,[6] Kangxian Luo,[7] Yuming Wang,[8] Stephanos Hadziyannis,[9] Eva Wolf,[10] Philip McCloud,[11] Richard Batrla,[12] and Patrick Marcellin[13]

Table 2. 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, 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)		
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.

Hepatology 2009

IL28B Polymorphisms Predict Interferon-Related Hepatitis B Surface Antigen Seroclearance in Genotype D Hepatitis B e Antigen–Negative Patients With Chronic Hepatitis B

Pietro Lampertico,[1] Mauro Viganò,[1] Cristina Cheroni,[2] Floriana Facchetti,[1] Federica Invernizzi,[1] Vincenza Valveri,[2] Roberta Soffredini,[1] Sergio Abrignani,[2] Raffaele De Francesco,[2] and Massimo Colombo[1]

Hepatology 2013

101 HBeAg-negative patients with CHB followed up for a median of 11 years (range, 1-17) after a median of 23 months (range, 10-48) of IFN-alpha therapy
Post-treatment response: HBsAg clearance

Table 3. 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

Trattamento con Peg-IFN
-fattori prognostici-

HBeAg-

Fattori pre-treatment

- **ALT aumentate**
- **HBV DNA UI< 6 LOG**
- **genotipo A o B**
- **Severa attività necro-infiammatoria**
- **IL28B CC**

Fattori on-treatment

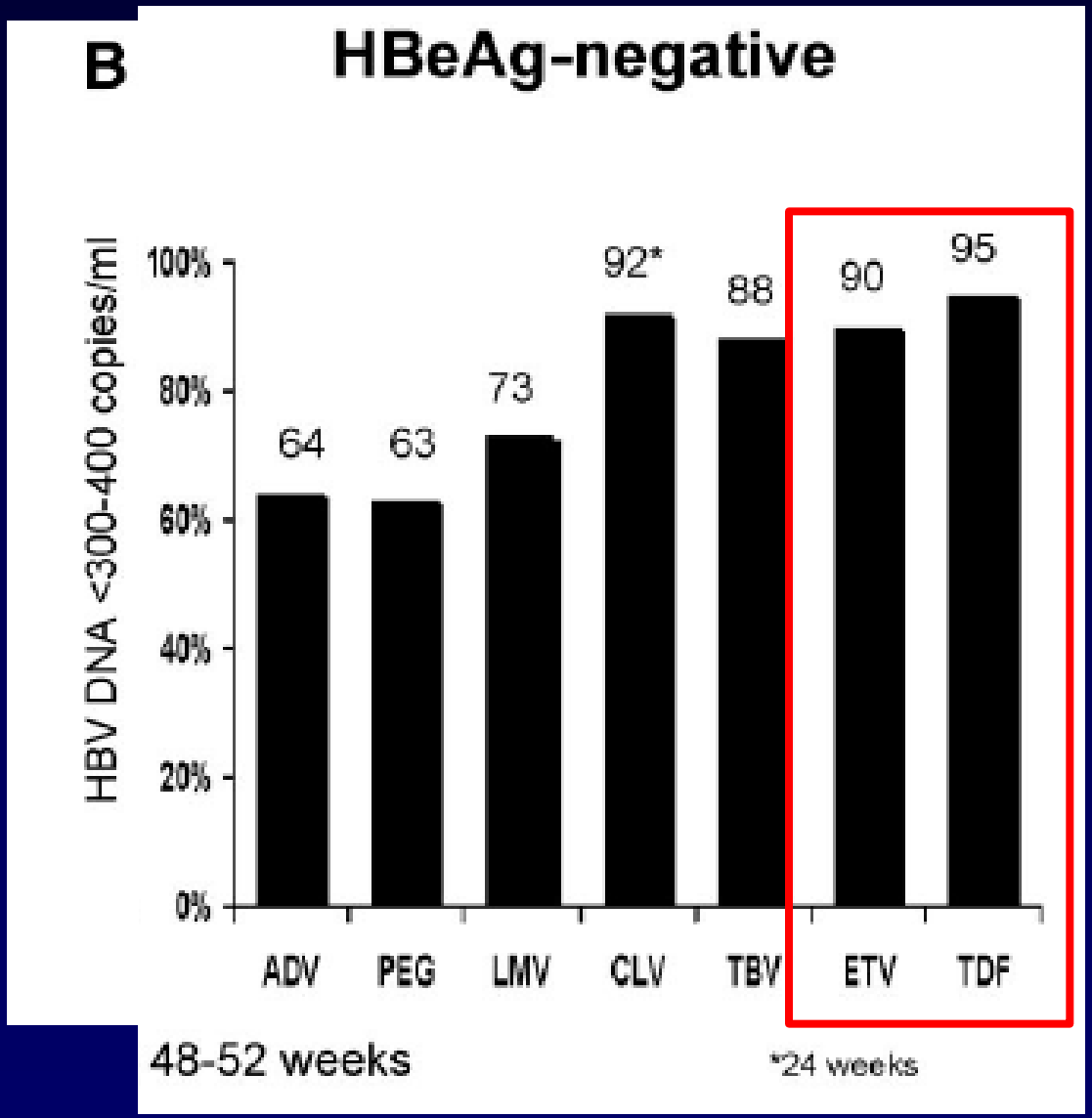
- **Calo livelli di HBsAg**

Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection
- Entecavir
- Tenofovir

EASL. J Hepatol. 2009;50:227-242. Liaw YF, et al. Hepatol Int. 2008;2:263-283.
Lok AS, et al. Hepatology. 2009;50:661-662.

Treatment with NUC in HBeAg negative patients

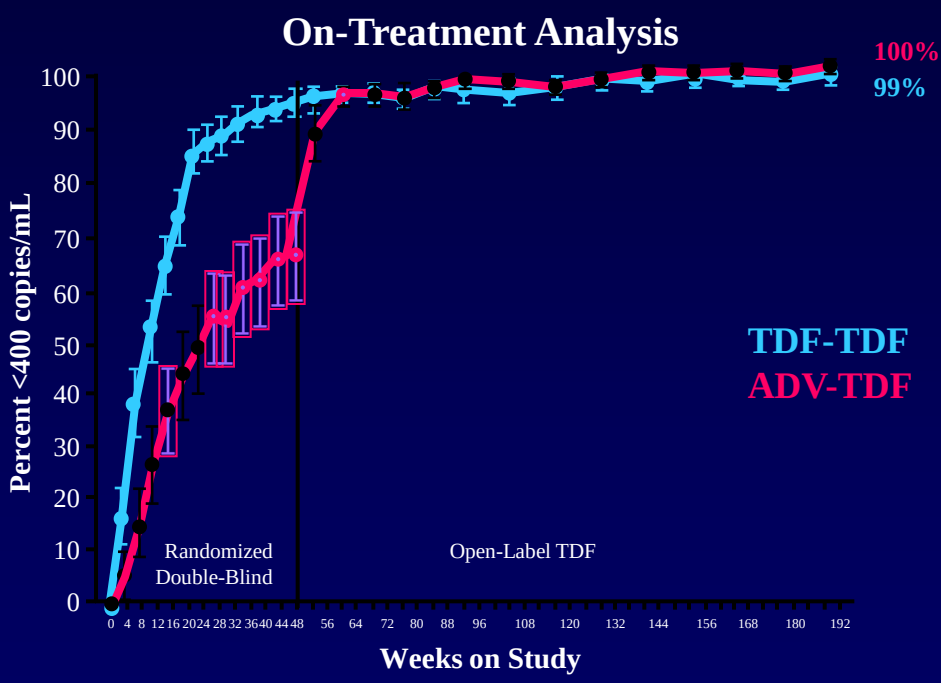


4 Years of TDF : HBeAg NEGATIVE Pts (Study GS-102)

Patients Entering Year 4 had Similar Baseline Characteristics to Patients Originally Randomized

	Randomized Treatment		Patients Entering Year 4	
	TDF (n=250)	ADV (n=125)	TDF-TDF (n=218)	ADV-TDF (n=109)
Mean Age (years)	44	43	45	44
Race				
Caucasian	64%	65%	67%	67%
Asian	25%	24%	24%	23%
Male	77%	78%	80%	78%
Prior Lamivudine Experience	17%	18%	18%	19%
Mean HBV DNA (log_{10} copies/mL)	6.86	6.98	6.86	7.00
Mean ALT (U/L)	128	164	131	171
Mean Knodell Necroinflammatory Score	7.8	7.8	7.8	7.9
Mean Knodell Fibrosis Score	2.3	2.4	2.4	2.3
Knodell fibrosis score= 4 (Cirrhosis)	19%	20%	20%	18%
Viral Genotype				
A	12%	11%	13%	12%
B	9%	14%	9%	14%
C	12%	10%	11%	9%
D	64%	63%	64%	62%

HBV DNA Remains Suppressed with up to 4 Yrs of TDF



ITT (192w):HBeAg NEG
TDF-TDF 85% *vs* ADV-TDF 87%

Marcellin P, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 476.

Entecavir in HBeAg negative CHB in real life

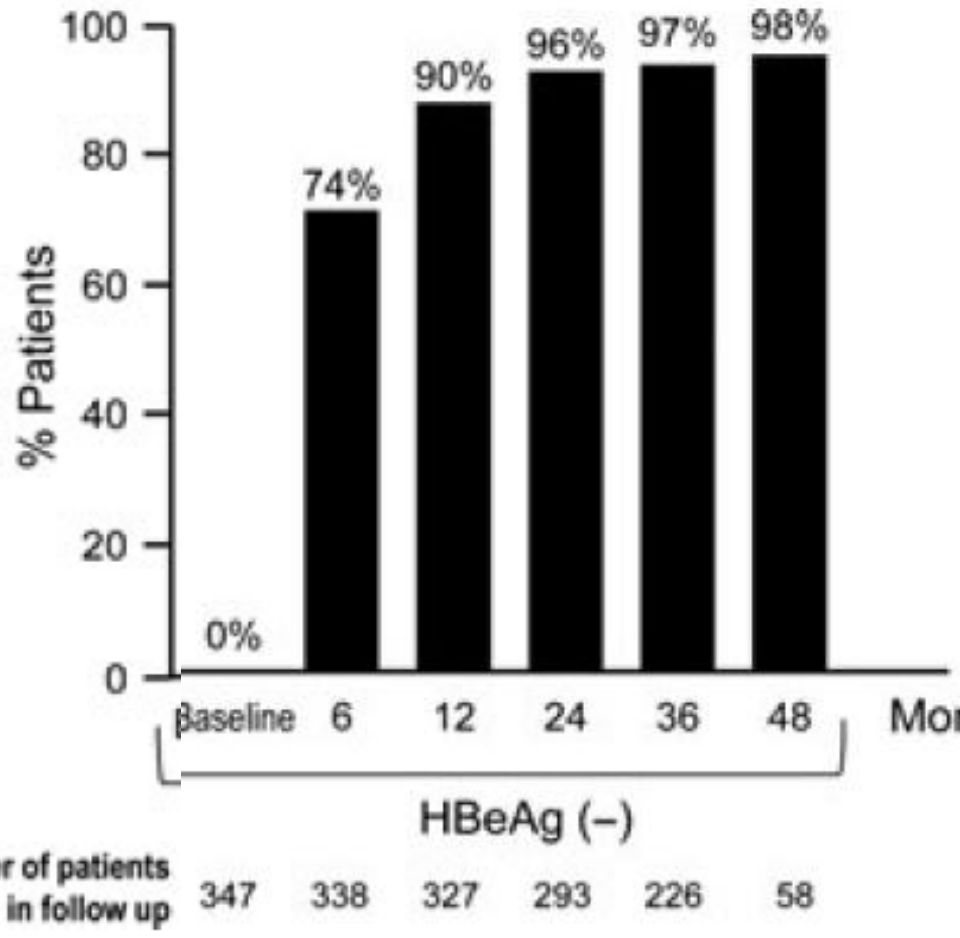
Characteristic, *n* (%)*	Italian cohort	Hong Kong cohort
Reference	[27]	[28]
N	418	222
Age, years (SD or range)	58 (18–82)§	47 (21–77)§
Male	316 (76)	157 (71)
Race		
White	NR	NR
Asian		
Black		
Other		
Region		
Europe	Italy	Hong Kong
North America		
South America		
Australia and Asia		
Genotype D	84/93 (90)	NR
HBeAg(−)	347 (83)	132 (59)
HBV DNA, $\log_{10}$ IU/mL*	6.0 (1.5–9)§	7.1 (4.0–>8.8)§
ALT, IU/L*	92 (11–2241)§	92 (17–2168)§
Cirrhosis	202 (49)	0

Lampertico P, Hepatology 2011
Seto WK, J Hepatol 2011

Entecavir in HBeAg negative CHB in real life

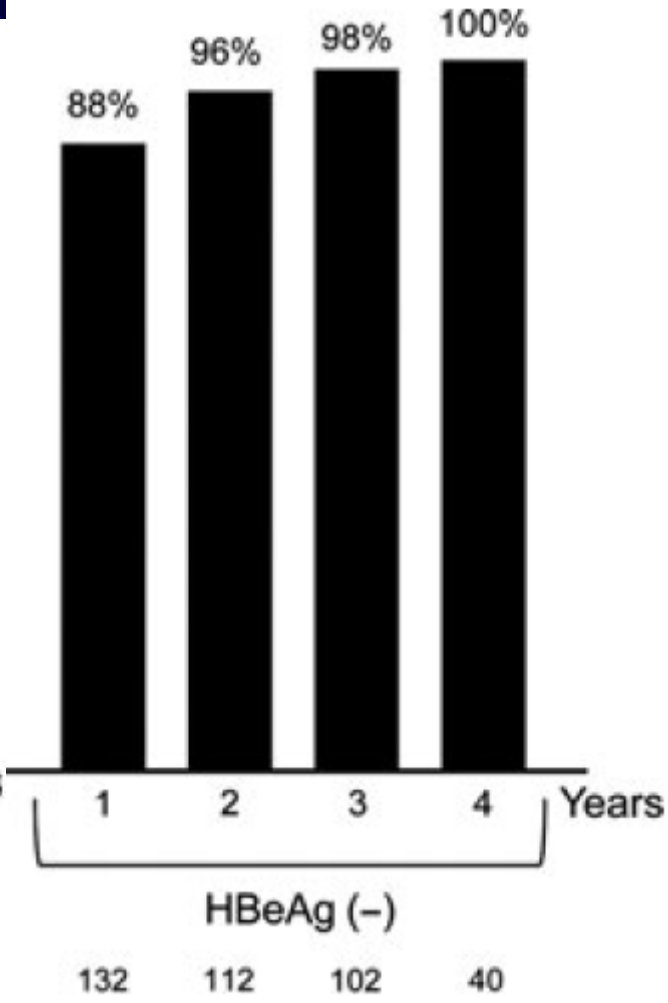
Lampertico P, Hepatology 2011

Italian cohort



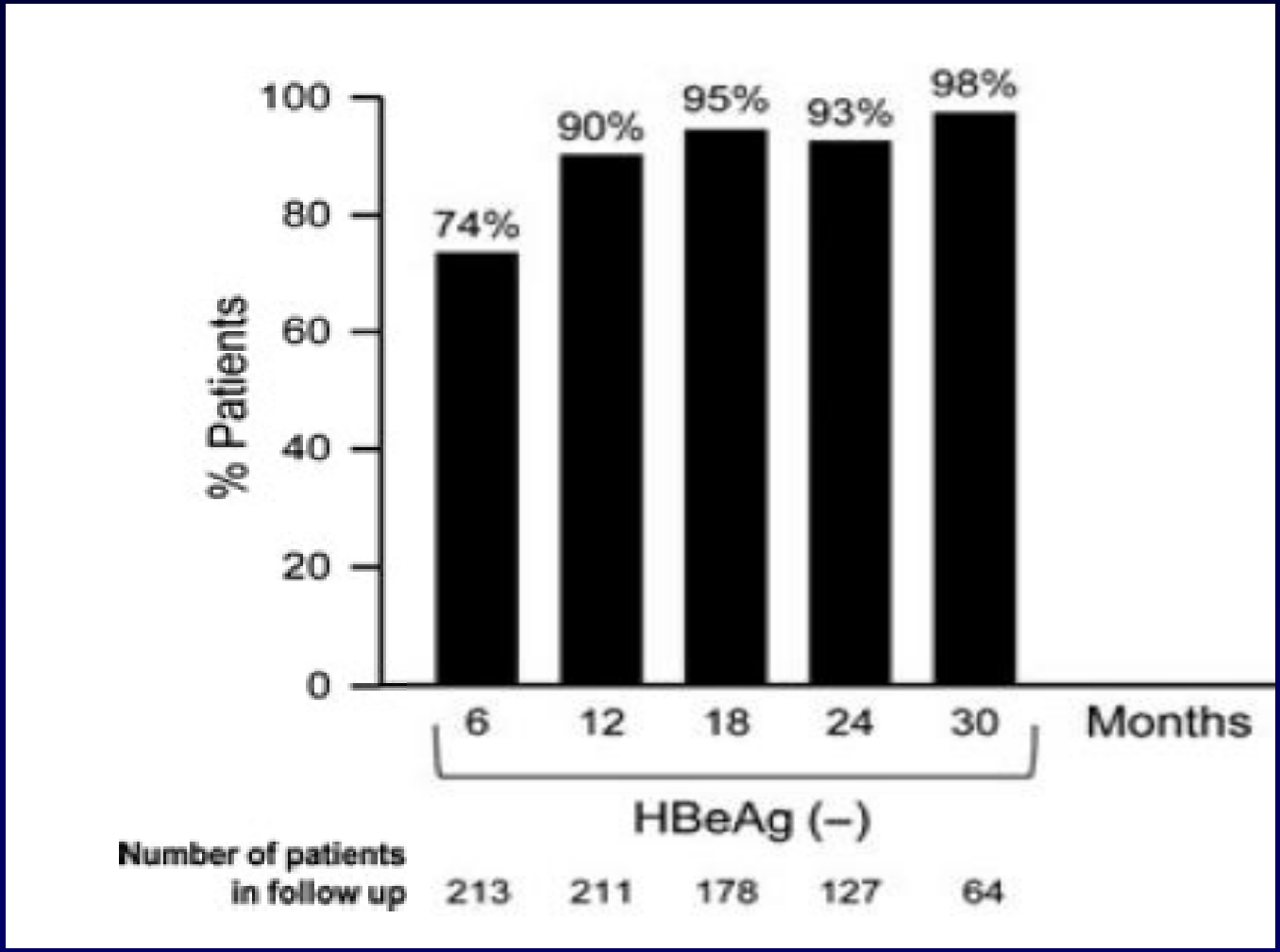
Seto WK, J Hepatol 2011

Hong Kong cohort



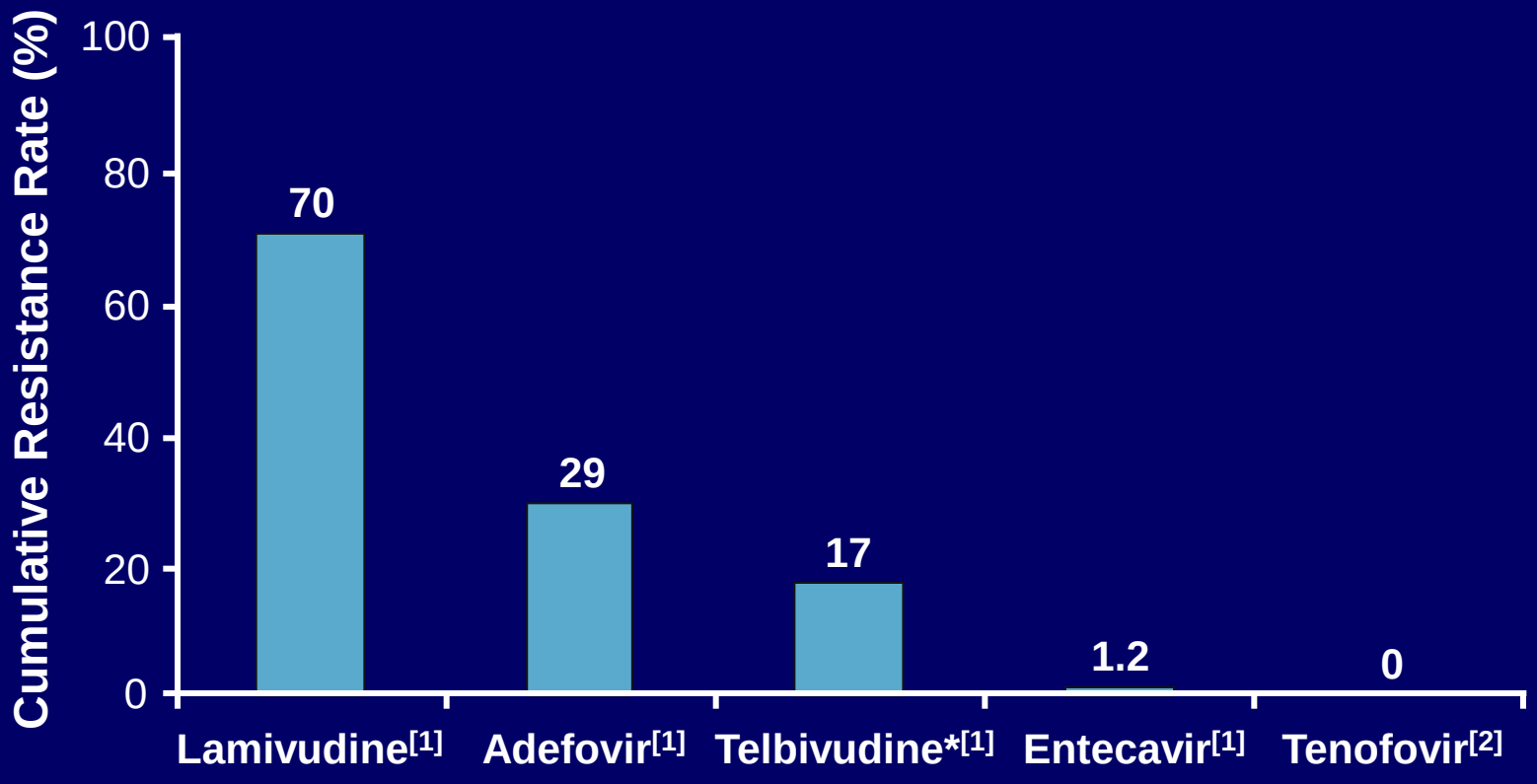
Tenofovir in HBeAg negative CHB in real life

302 HBeAg negative European patients treated with tenofovir



Lampertico P, Hepatology 2011

5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients



*Telbivudine rate determined at Yr 2.

1. EASL. J Hepatol. 2009;50:227-242. 2. Marcellin P, et al. AASLD 2011. Abstract 1375.

No Detectable Resistance to Tenofovir Disoproxil Fumarate After 6 Years of Therapy in Patients With Chronic Hepatitis B

Kathryn M. Kitrinos,[1] Amoreena Corsa,[1] Yang Liu,[1] John Flaherty,[1] Andrea Snow-Lampart,[1] Patrick Marcellin,[2] Katyna Borroto-Esoda,[1] and Michael D. Miller[1]

347 HBeAg negative and 238 HBeAg positive patients receiving tenofovir in an open-label, long- term extension of two phase 3 studies

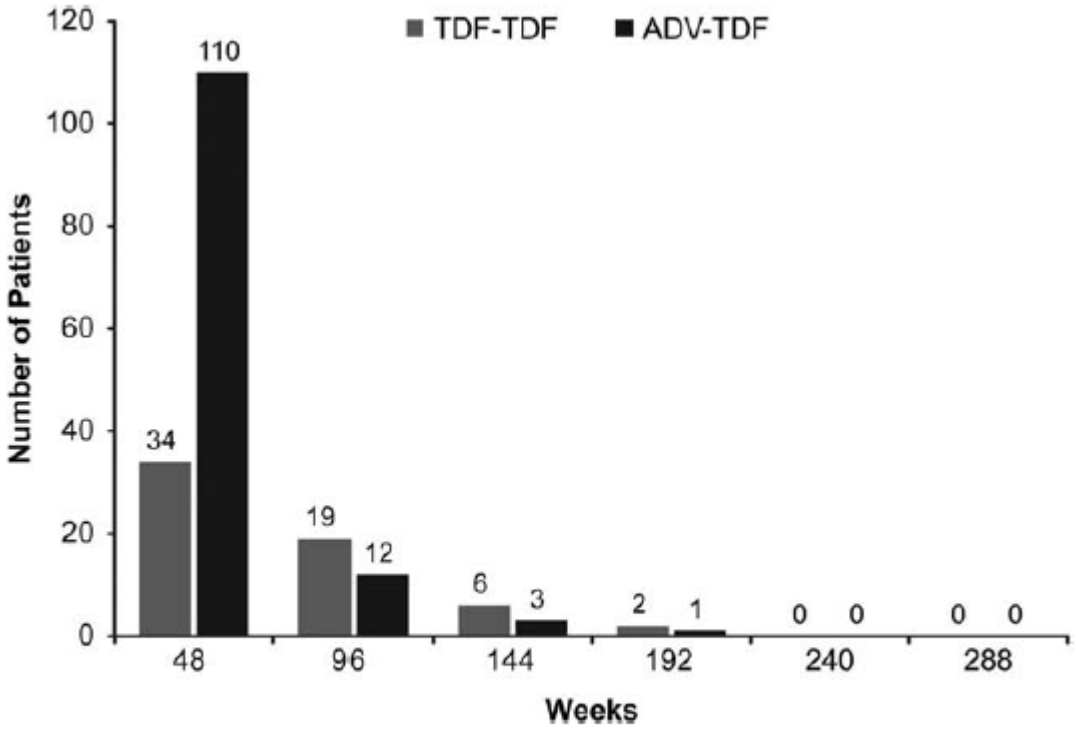


Fig. 5. Number of patients with persistent viremia (HBV DNA ≥400 copies/mL) at the end of each 48-week year of the study.

Hepatology 2014

Terapia Epatite Cronica B

- Indicazione
- Opzioni terapeutiche
- **Scelta della migliore opzione terapeutica**
- Monitoraggio della risposta terapeutica
- Possibili scenari futuri

PegIFN vs Nucleos(t)ide Analogues

PegIFN		Nucleos(t)ide Analogues	
Pro	**Con**	**Pro**	**Con**
▪ Finite course of therapy ▪ No resistance ▪ Higher rate of HBeAg loss in 1 yr ▪ Higher rate of HBsAg loss with short duration therapy*	▪ SQ administration ▪ Frequent AEs ▪ Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed	▪ PO administration ▪ Infrequent AEs ▪ Safe at all stages of disease, including decompensated cirrhosis† ▪ Safe in immuno-compromised populations ▪ Selected drugs probably safe in pregnancy	▪ Need for long-term or indefinite therapy ▪ Potential for drug resistance

*Particularly for HBeAg-positive patients with genotype A infection.

†Recent case report of lactic acidosis in severe liver failure.

Lok AS, et al. Hepatology. 2007;45:507-539. Lok AS, et al. Hepatology. 2009;50:661-662. Lok AS. Hepatology. 2010;52:743-747. Buster EH, et al. Gastroenterology. 2008;135:459-467. Lange CM, et al. Hepatology. 2009;50:2001-2006.

When to Consider PegIFN

- Favorable predictors of response[1,2]
  - Low HBV DNA*
  - High ALT*
  - Genotype A or B > C or D[3-5]
  - Not advanced disease
- Specific patient demographics[1,2]
  - Generally young people
  - Young women wanting pregnancy in near future
  - Absence of comorbidities
- Patient preference[1,2]
- Concomitant HCV infection

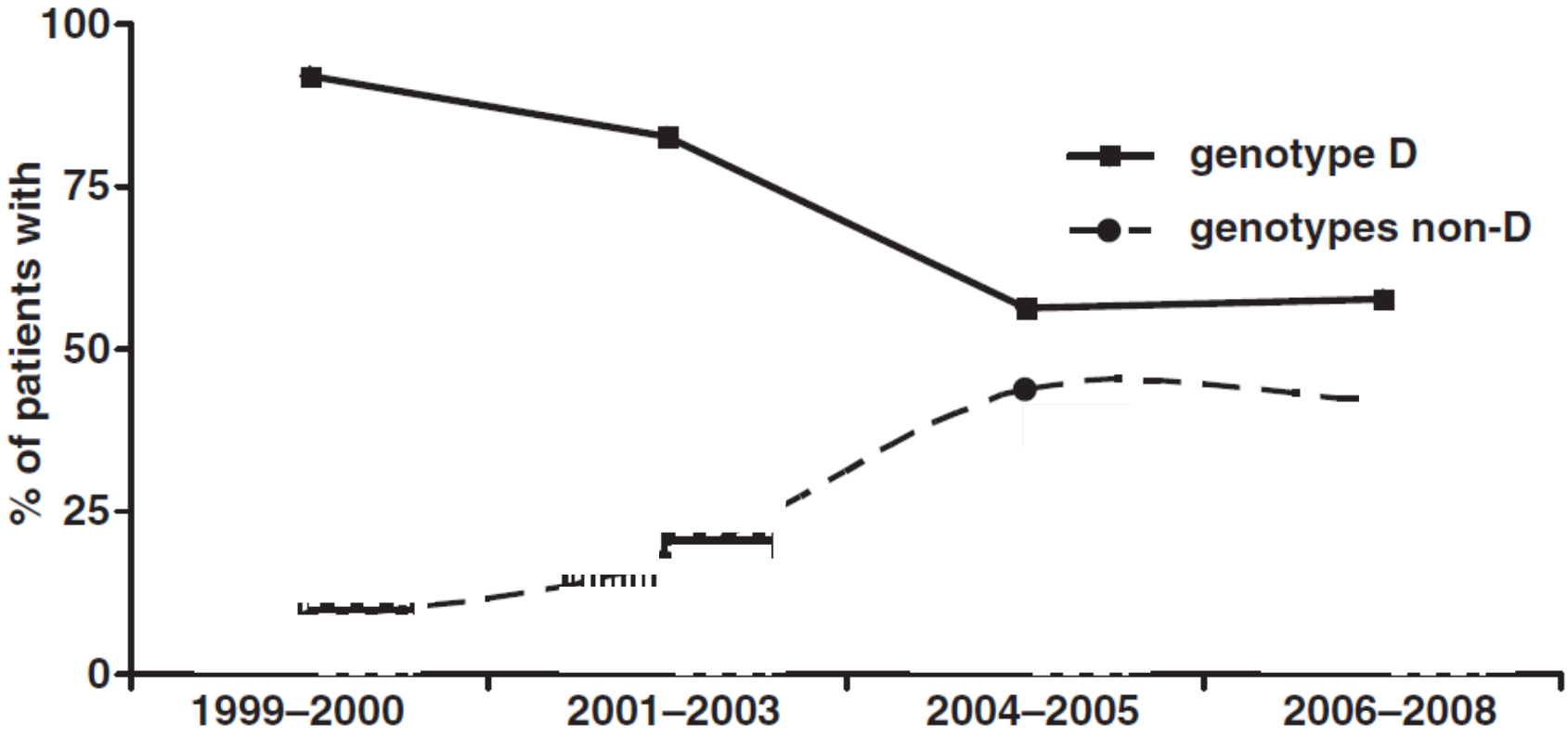
*Also predictive of response to nucleos(t)ide analogues.

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. Lok AS. Hepatology. 2010;52:743-747. 3. Janssen HL, et al, Lancet. 2005;365;123-129. 4. Lau GK, et al. N Engl J Med. 2005;352:2682-2695. 5. Flink HJ, et al. Am J Gastroenterol. 2006;101:297-303.

Journal of Viral Hepatitis, 2009 doi:10.1111/j.1365-2893.2009.01201.x

Factors affecting the changes in molecular epidemiology of acute hepatitis B in a Southern Italian area

N. Coppola,[1] A. Masiello,[1] G. Tonziello,[1] R. Pisapia,[1] M. Pisaturo,[1] C. Sagnelli,[1,2] V. Messina,[2] V. Iodice[1] and E. Sagnelli[1,2] [1]*Department of Public Medicine, Section of Infectious Diseases, 2nd University of, Naples; and* [2]*Division of Infectious Diseases, Azienda Ospedaliera Sant'Anna e San Sebastiano di Caserta, Caserta, Italy*



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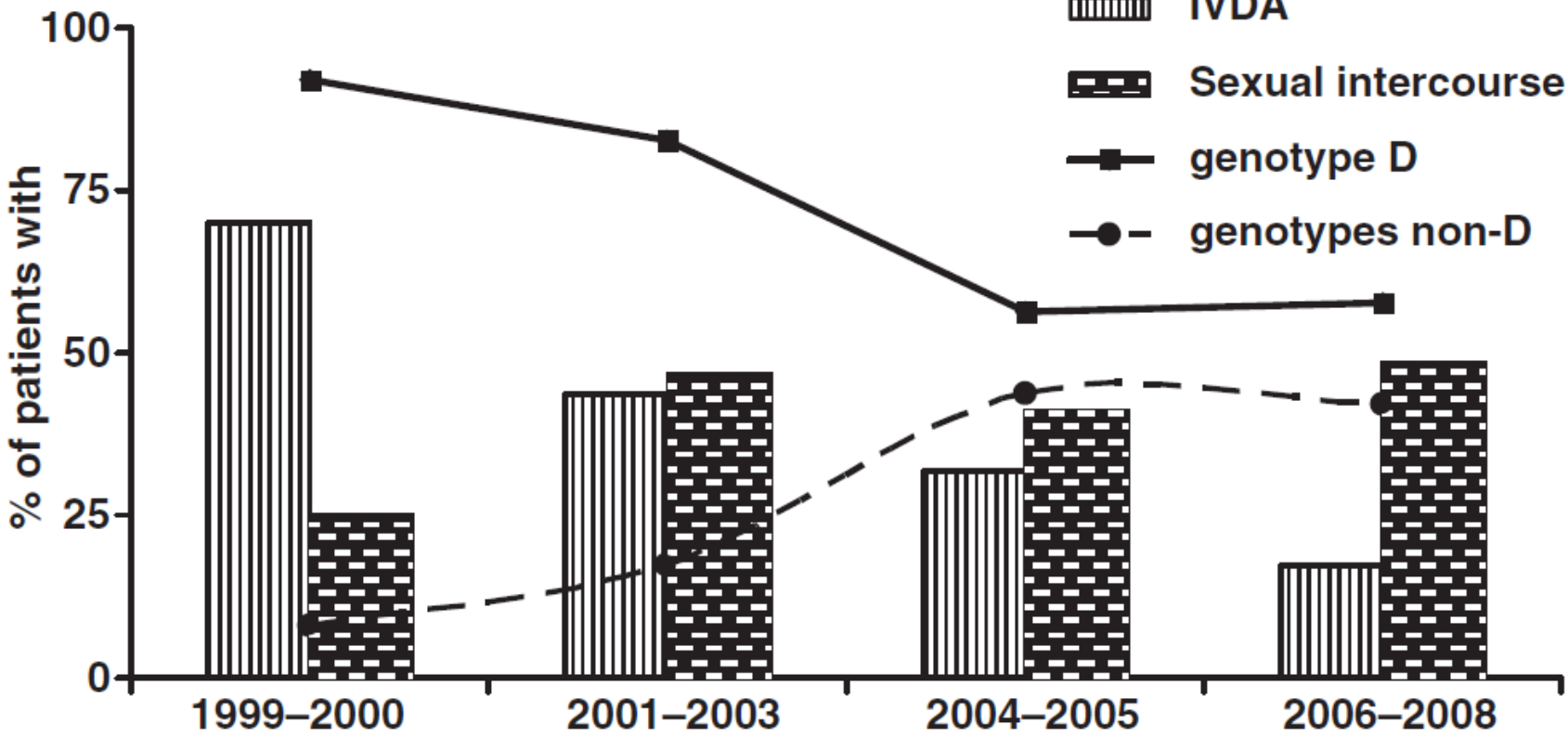
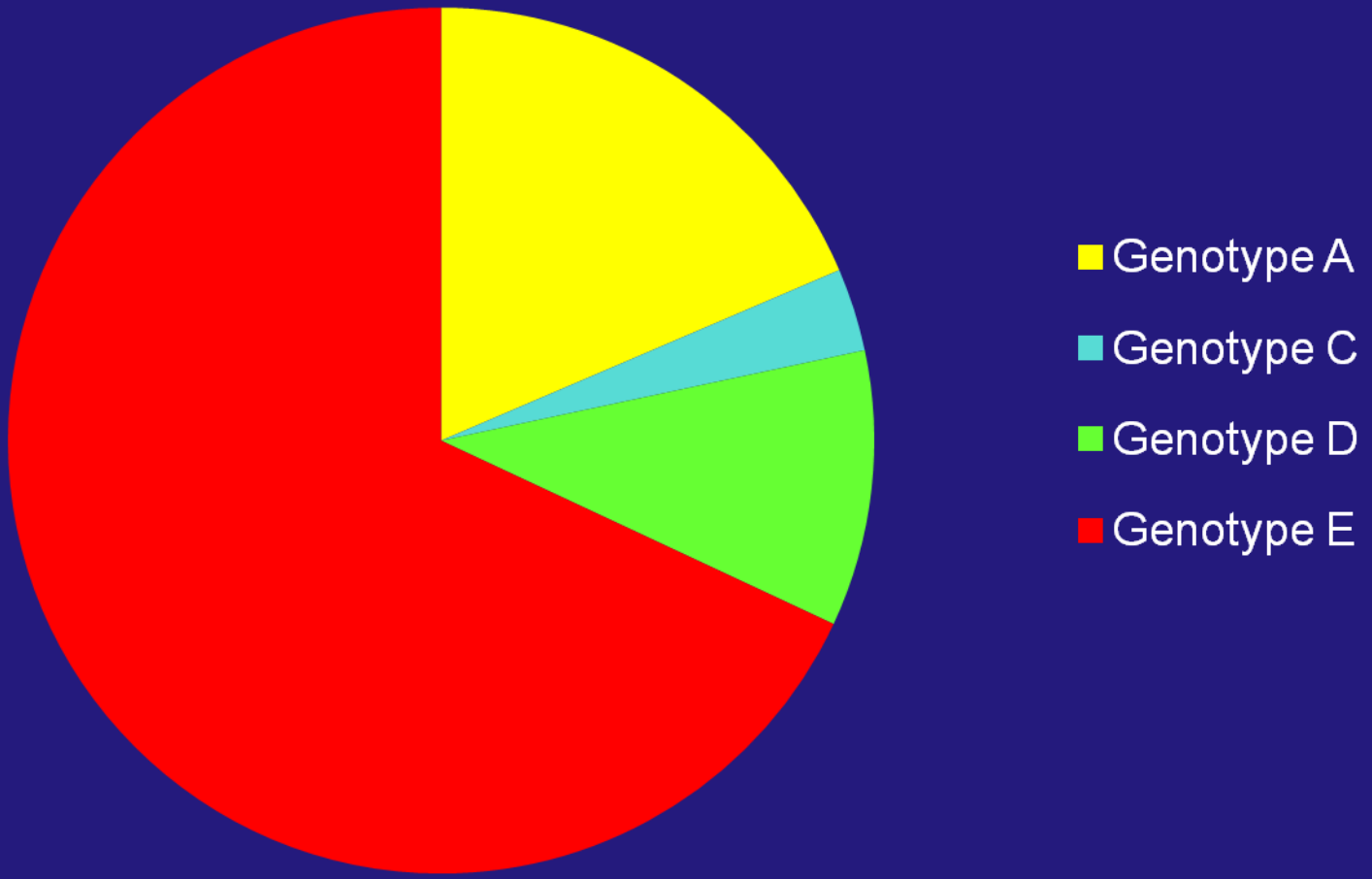
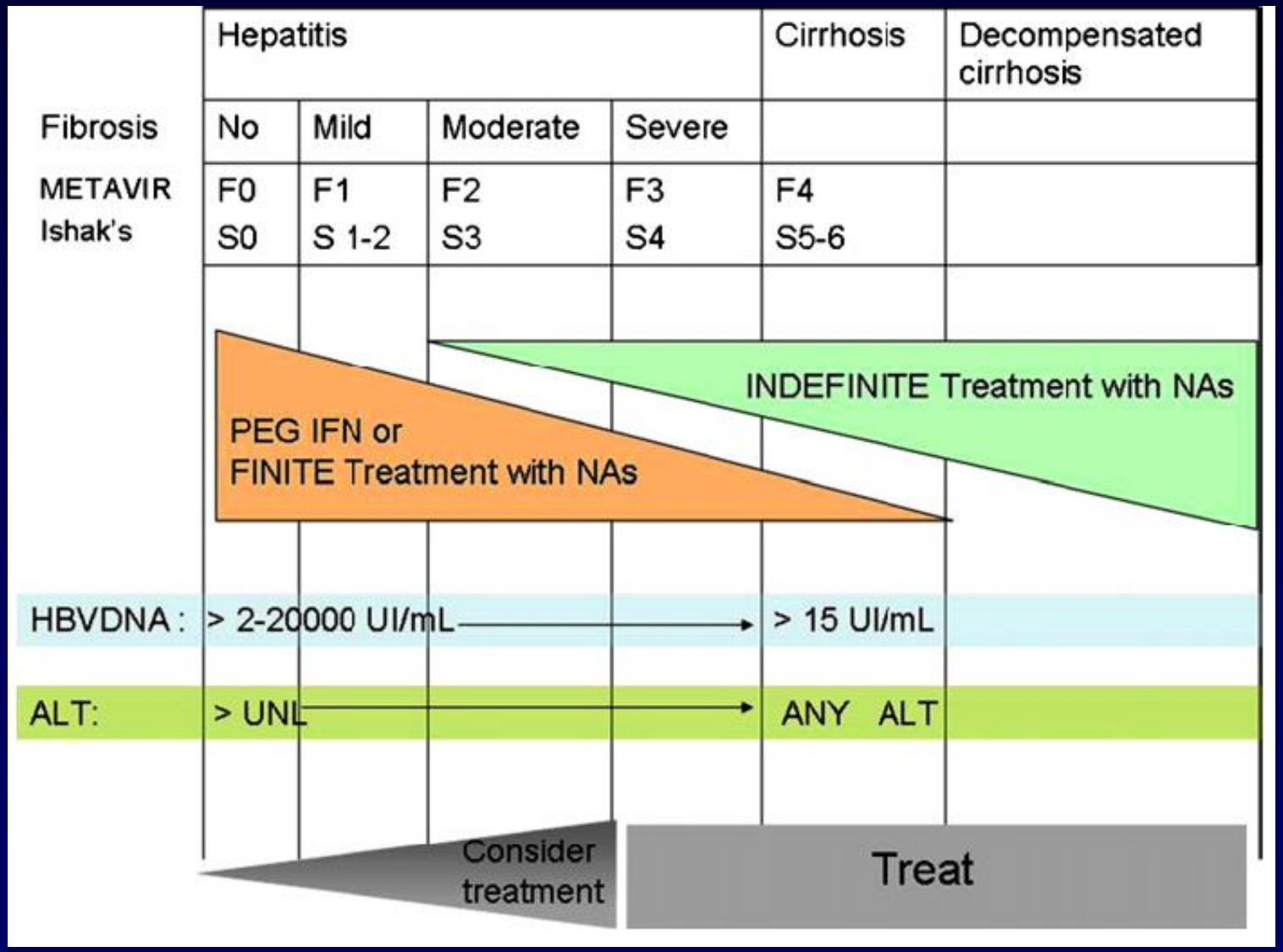


HBV genotype in 97 HBsAg immigrants 2012-2014

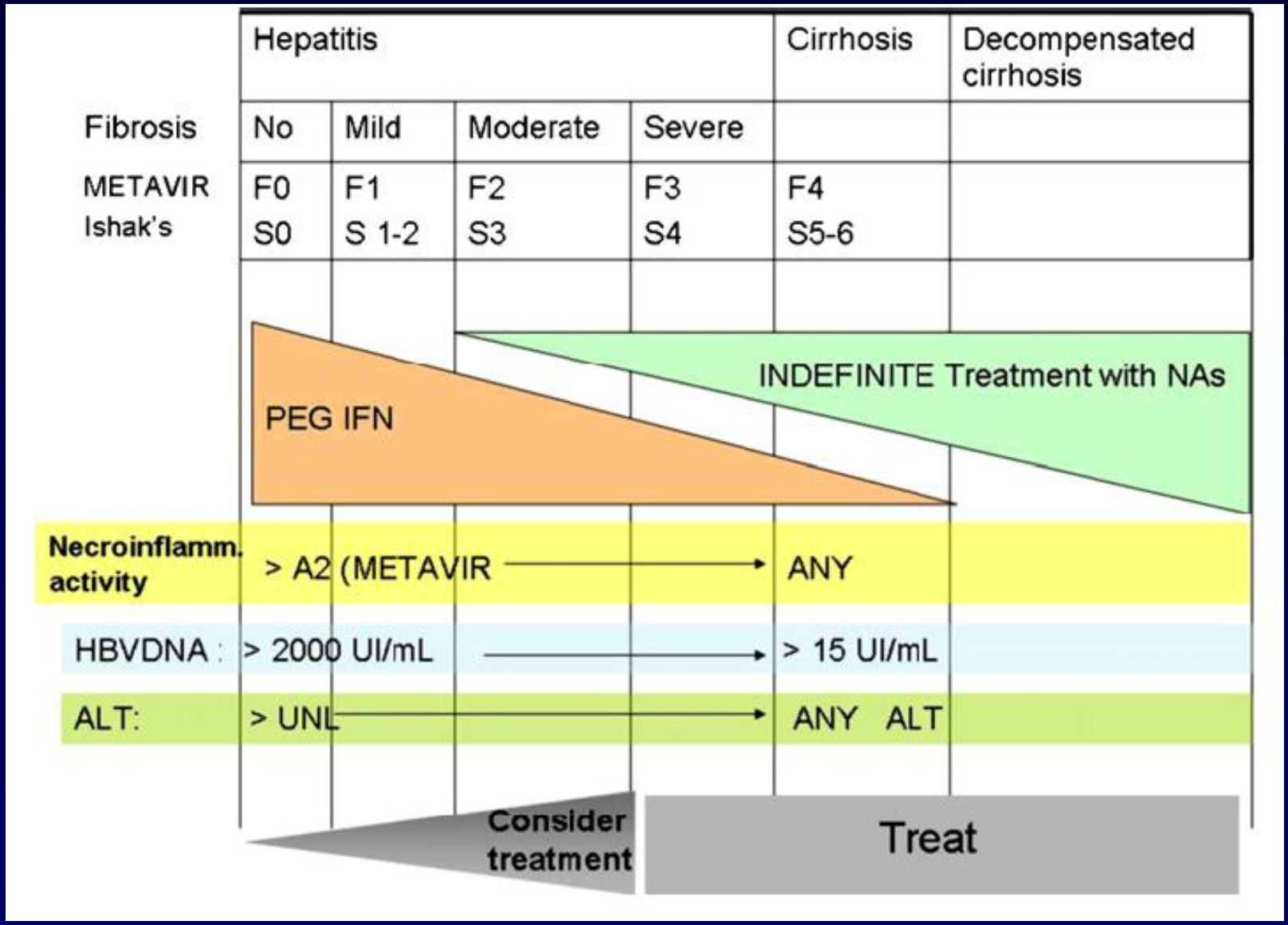


Coppola N, submitted

"Paradigma di Stresa" pazienti con epatite cronica HBeAg positiva con o senza cirrosi



“Paradigma di Stresa” pazienti con epatite cronica HBeAg negativa con o senza cirrosi



Terapia Epatite Cronica B

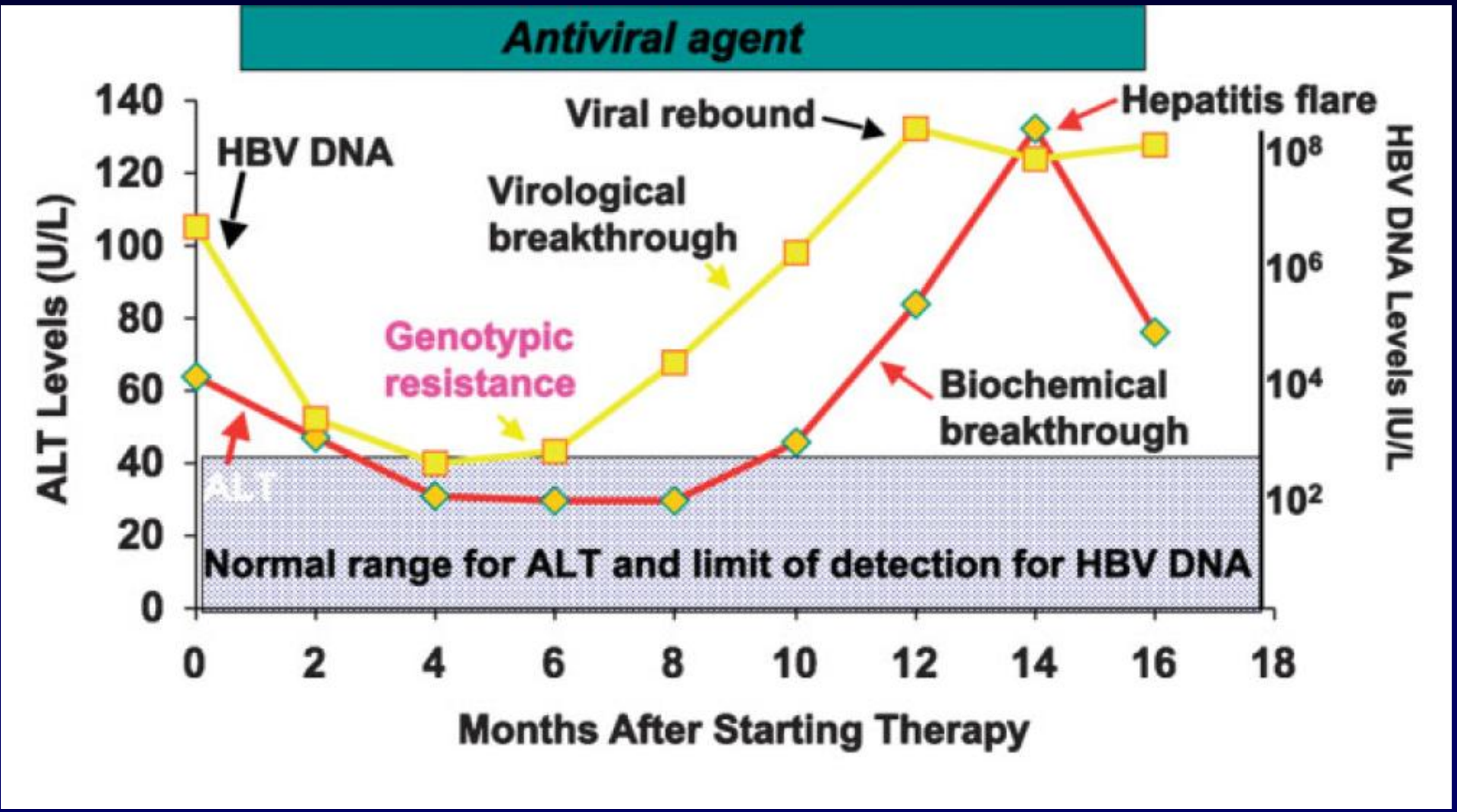
- Indicazione
- Opzioni terapeutiche
- Scelta della migliore opzione terapeutica
- **Monitoraggio della risposta terapeutica**
- Possibili scenari futuri

Monitoring of Patients Receiving Nucleos(t)ide Analogue Therapy

Time Point	Monitoring
q12 wks	▪ Liver panel ▪ Serum creatinine (if receiving TDF or ADV)
q12-24 wks	▪ HBV DNA levels
q24 wks	▪ HBeAg/anti-HBe (if initially HBeAg positive)
q6-12 mos	▪ HBsAg in HBeAg-negative patients with persistently undetectable HBV DNA

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

Virological and clinical dynamic of genotypic resistence



How to Use Entecavir or Tenofovir

Duration, based on clinical endpoints

- HBeAg positive: continue treatment until HBV DNA undetectable and HBeAg seroconversion achieved; continue for ≥ 6 mos after anti-HBe appearance
  - Close monitoring for relapse required after treatment discontinuation
- HBeAg negative: continue treatment until HBsAg clearance

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

Terapia Epatite Cronica B

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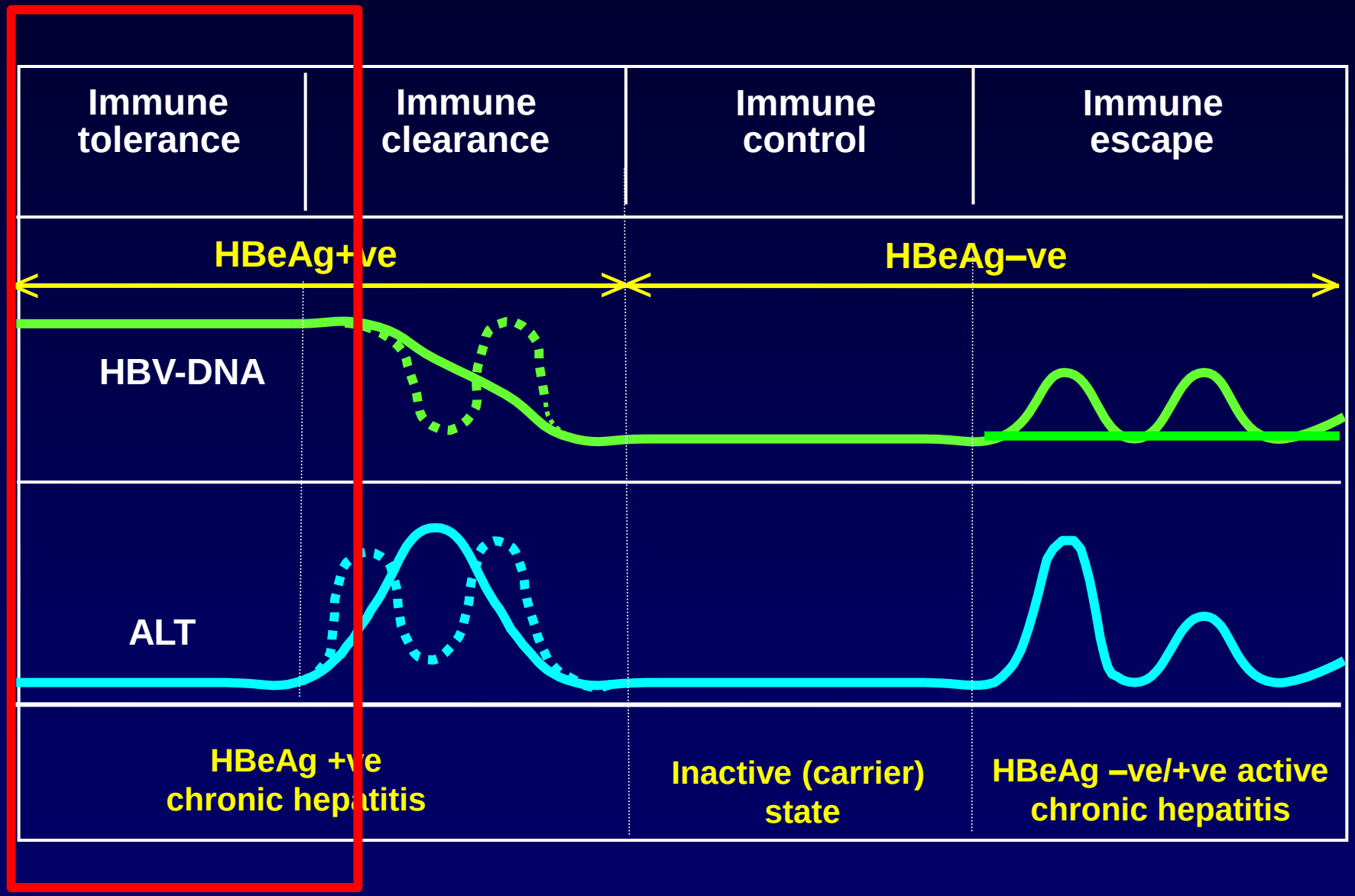
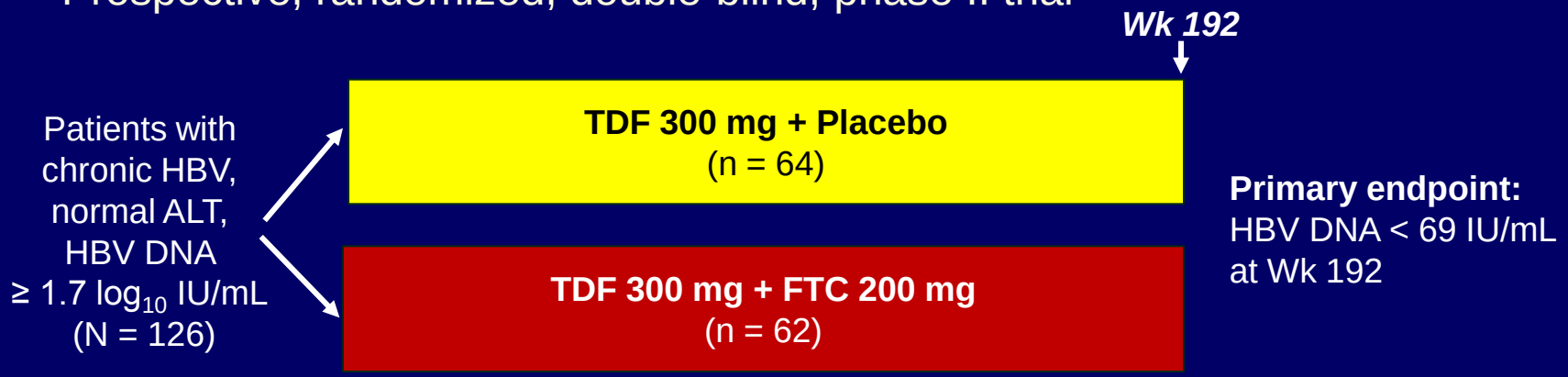

Immune tolerance
Immune clearance
Immune control
Immune escape
HBeAg+ve
HBeAg–ve
HBV-DNA
ALT
HBeAg +ve chronic hepatitis
Inactive (carrier) state
HBeAg –ve/+ve active chronic hepatitis

Effects of Tenofovir Disoproxil Fumarate in Hepatitis B e Antigen-Positive Patients With Normal Levels of Alanine Aminotransferase and High Levels of Hepatitis B Virus DNA

Henry L. Y. Chan,[1] Chi Kuen Chan,[2] Aric Josun Hui,[3] Sing Chan,[4] Fred Poordad,[5] Ting-Tsung Chang,[6] Philippe Mathurin,[7] John F. Flaherty,[8] Lanjia Lin,[8] Amy Corsa,[8] Anuj Gaggar,[8] G. Mani Subramanian,[8] John G. McHutchison,[8] Sam Lee,[9] and Edward J. Gane[10]

- Prospective, randomized, double-blind, phase II trial



Baseline Characteristic	TDF	TDF/FTC
Mean age, yrs (SD)	33 (9.5)	33 (11.2)
Asian race, %	87.5	90.3
Mean HBV DNA, $\log_{10}$ IU/mL (SD)	9.2 (0.4)	9.2 (0.4)
HBV genotype, %		
▪ B	51.6	51.6
▪ C	37.5	45.2
▪ Other	10.9	3.2

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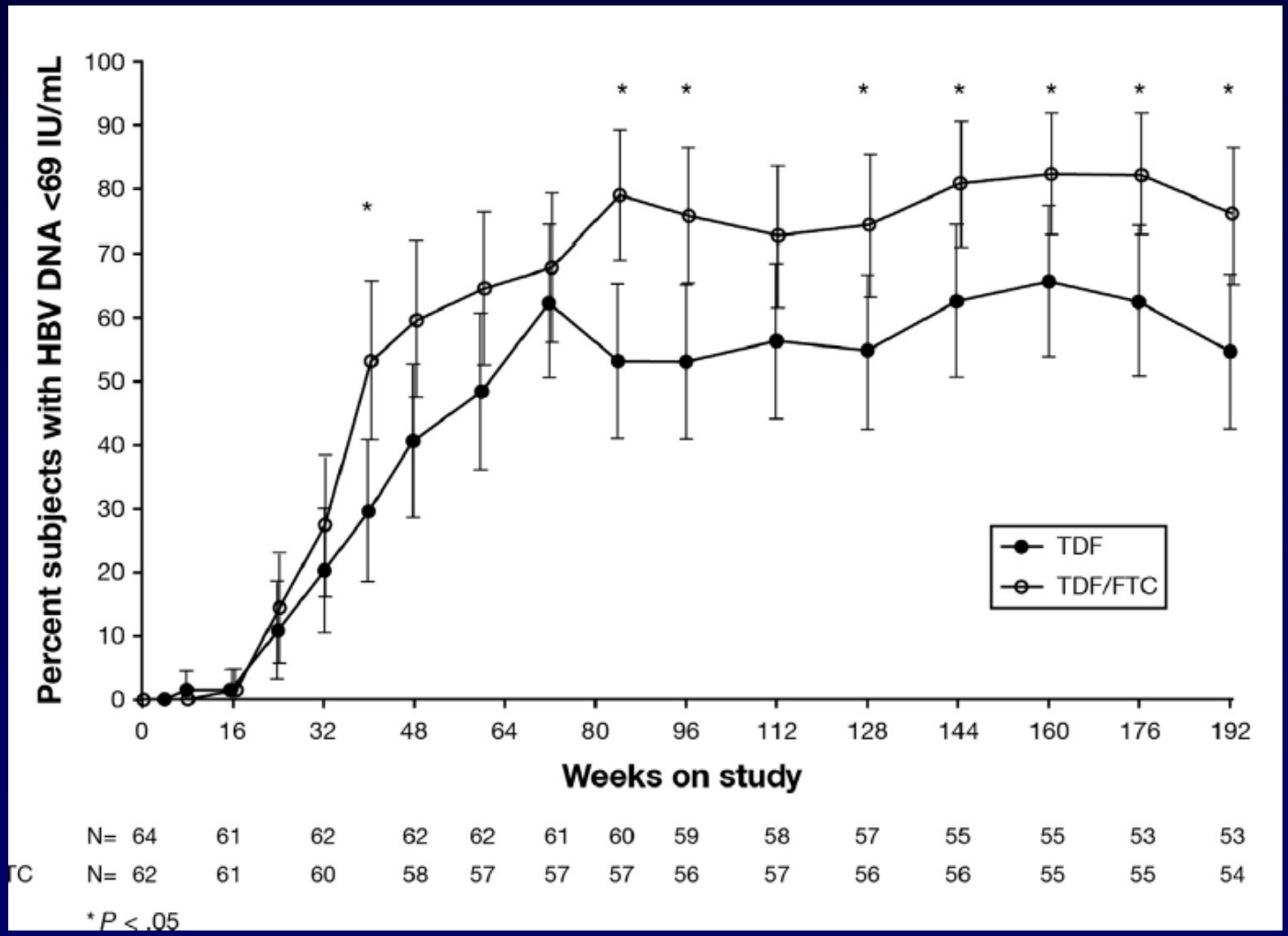

Gastroenterology 2014

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Table 2. Virologic, Biochemical, and Serologic Responses at Week 192

Virologic, biochemical, and serologic responses	TDF 300 mg+placebo (n = 64)	TDF 300 mg+FTC 200 mg (n = 62)	*P* value
Intention to treat analysis			
HBV DNA change from baseline, *log 10 IU/mL*, mean (SD)	−6.32 (1.463)	−6.70 (0.913)	.070
HBV DNA <69 IU/mL , n/N (%)	35/64 (54.7)	47/62 (75.8)	.016
HBV DNA <29 IU/mL , n/N (%)	29/64 (45.3)	43/62 (69.4)	.007
Normal ALT, n/N (%)	41/64 (64.1)	44/62 (71.0)	.451
HBeAg loss, n/N (%)	4/63 (6.3)	1/62 (1.6)	.365
HBeAg seroconversion , n/N (%)	3/63 (4.8)	0/62 (0)	.244
Per-protocol analysis			
HBV DNA change from baseline, *log 10 IU/mL*, mean(SD)	−6.32 (1.463)	−6.70 (0.913)	.070
HBV DNA <69 IU/mL , n/N (%)	35/53 (66.0)	47/54 (87.0)	.012
HBV DNA <29 IU/mL , n/N (%)	29/53 (54.7)	43/54 (79.6)	.008
Normal ALT, n/N (%)	41/53 (77.4)	44/54 (81.5)	.639
ALT U/L, median (range)	29 (7-104)	24.5 (10-100)	.515
ALT U/L, week 192 change from baseline, median (range)	4 (−98 to 58)	2.5 (−30 to 66)	.354
HBeAg loss, n/N (%)	4/52 (7.7)	1/54 (1.9)	.201
HBeAg seroconversion, n/N (%)	3/52 (5.8)	0/54 (0)	.115
HBsAg <2000 IUl/mL, n/N (%)	5/49 (10.2)	5/52 (9.6)	.921

Off-Therapy Durability of Response to Entecavir Therapy in Hepatitis B e Antigen-Negative Chronic Hepatitis B Patients

Wen-Juei Jeng,[1,2] I-Shyan Sheen,[1,2] Yi-Cheng Chen,[1,2] Chao-Wei Hsu,[1,2] Rong-Nan Chien,[2,3] Chia-Ming Chu,[1,2] and Yun-Fan Liaw[1,2]

95 patients (39 cirrhosis) were treated with ETV for a median of 721 (395-1,762) days before stopping therapy and were then monitored with serum HBV DNA and ALT at least every 3 months

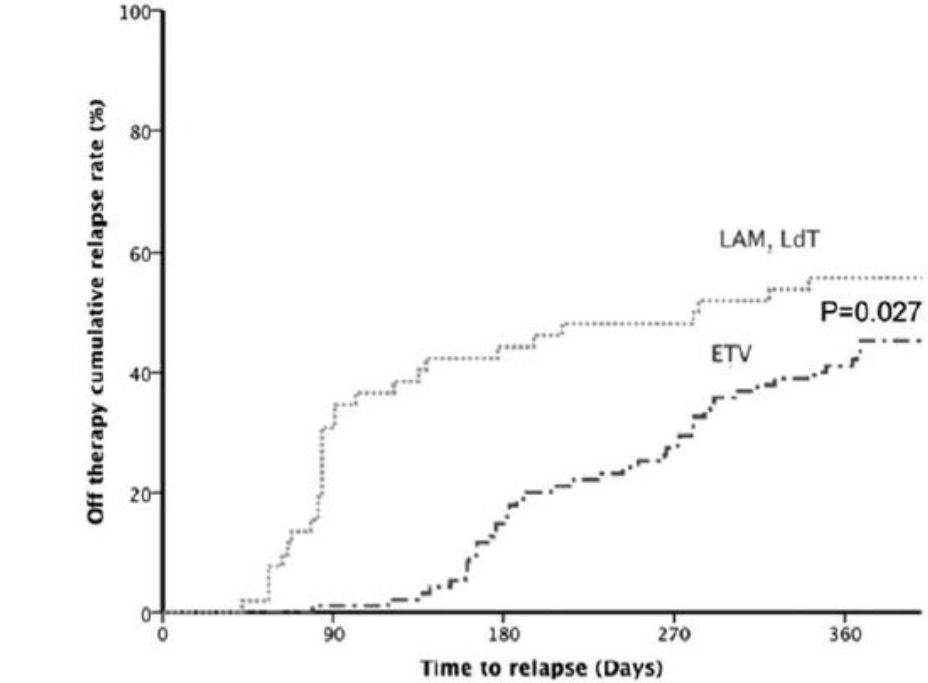

Fig. 1. One-year cumulative relapse rate after cessation of ETV therapy was 45.3%, significantly lower and relapses occurred later than those after cessation of LAM or LdT.

Heaptology 2014

Off-Therapy Durability of Response to Entecavir Therapy in Hepatitis B e Antigen-Negative Chronic Hepatitis B Patients

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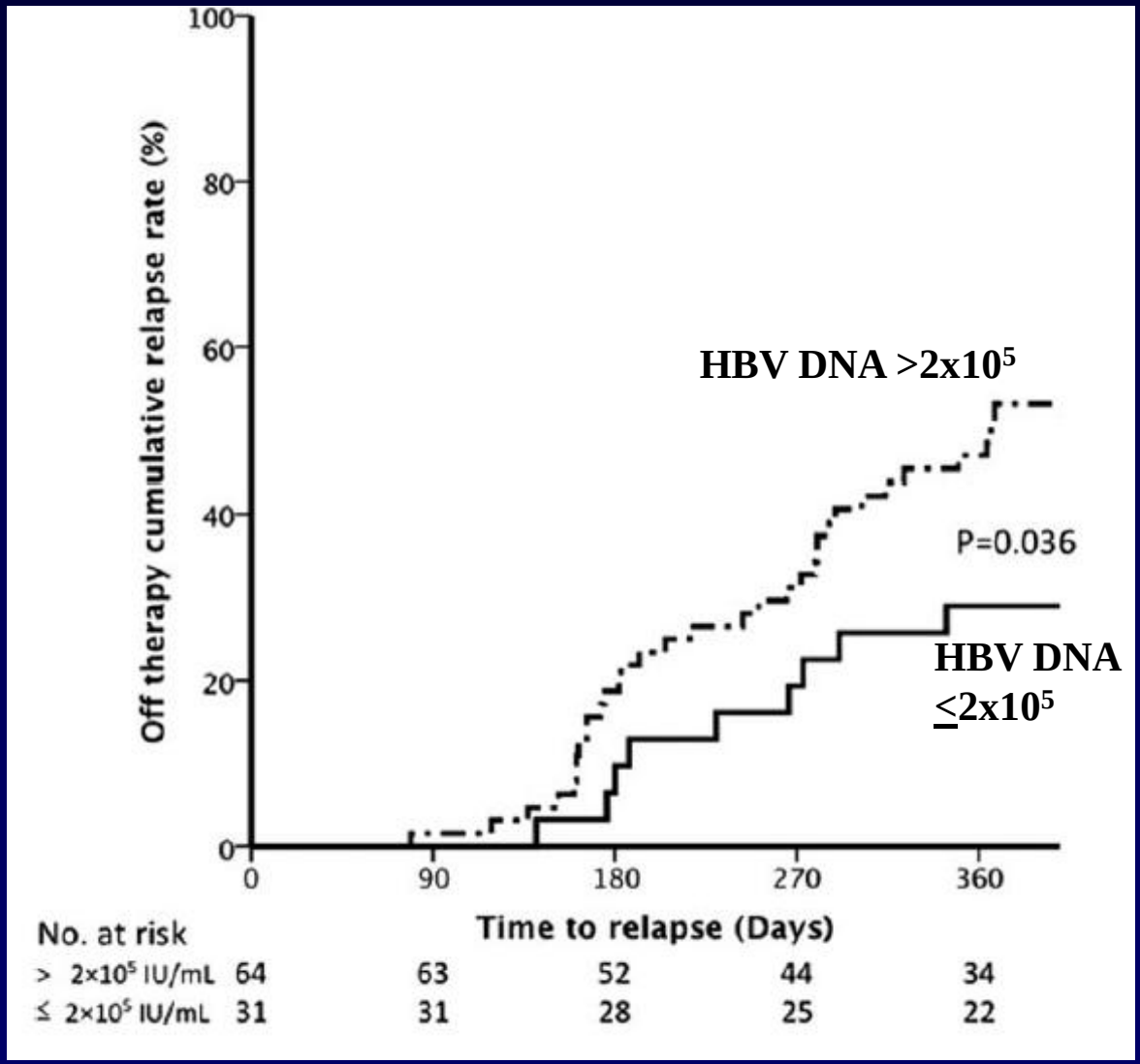

Heaptology 2014

SEQUENTIAL COMBINATION THERAPY WITH NUCS AND PEG-IFN IN HBeAg POSITIVE pts WITH PRIOR LONG-TERM EXPOSURE TO NUCS

192 pts receiving at least 2-year t of NUCs without achieving HBeAg loss or seroconversion

Peg-IFN to on-going NUCs (83 pts)

NUCs monotherapy (109)

48-wk

Follow-up 24 wks

	NUCs monotherapy	combination therapy
achieved complete response		
HBeAg loss composited with HBVDNA *<2000 IU/ml*	***13.8%***	***60.24%***
HBsAg loss	**0**	**27.7%**

HBsAg level at BL, wk 12 and wk 24 were strong predictors of treatment responses in combination group:

-BL HBsAg *<1000 IU/ml: 100% pts* achieved complete response and 91% pts achieved HBsAg loss.

-BL HBsAg ≥1000 IU/mL: response rate was significantly lower in those who experience no decline in HBsAg level at wk 12

Sequential combination therapy of NUCs + PEG-IFN effectively resulted in high rates of complete response and HBsAg loss in pts with prior long-term exposure to NUCs.

EASL 2014 ABST O117

Conclusioni

- Trattamento per l'epatite cronica B ben codificata
- Posibili scenari futuri:
  - Trattamento anche in stati siero/virologici, oggi non indicati
  - Ottimizzazione della sospensione del trattamento con NUC
  - Possibili schemi terapeutici sequenziali