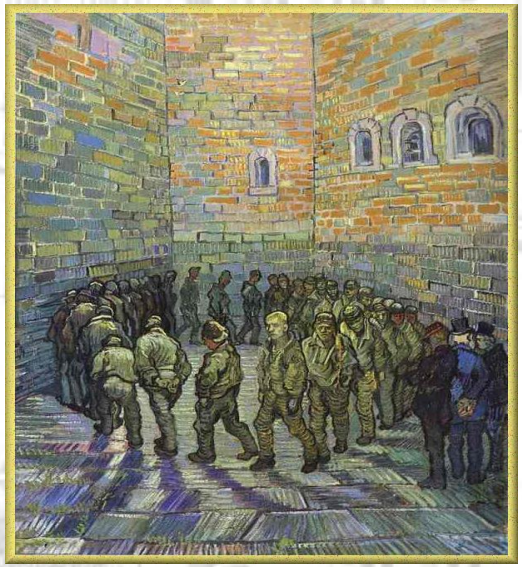
Epatite cronica B tra presente e futuro

L'AGORA' PENITENZIARIA 2017
XVIII Congresso Nazionale SIMSPe-ONLUS
Salute in Carcere e Lea 2017: Punto di svolta?
Roma
5-6 ottobre 2017

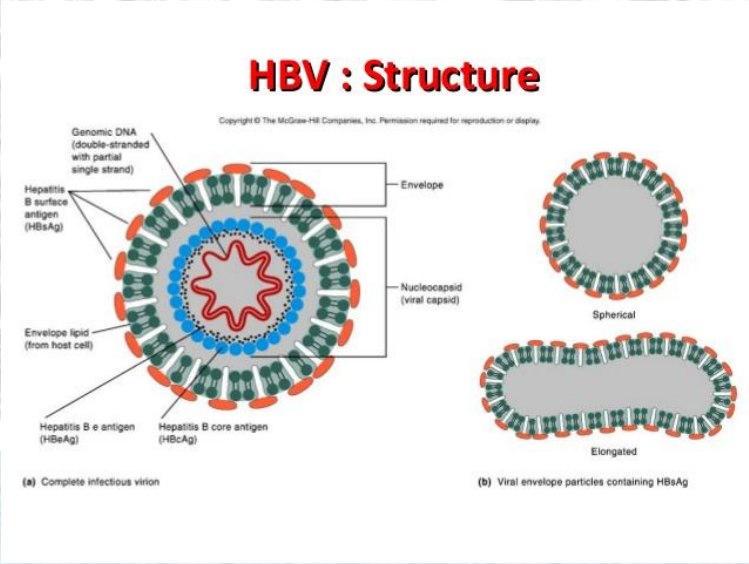


E. Pontali

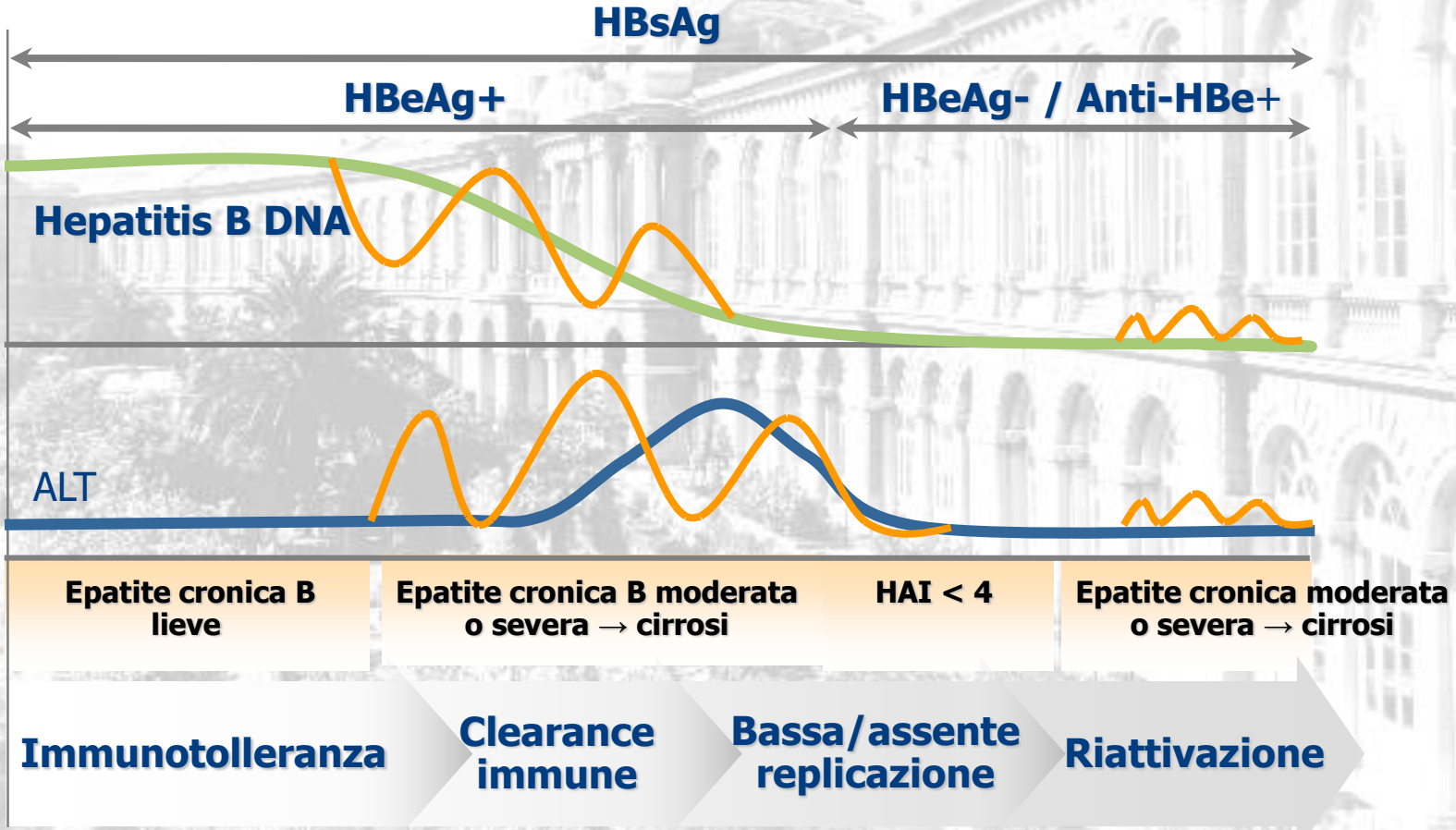
S.C. Malattie Infettive - E.O. Galliera
& ASL3 Genovese – Genova

Concetti base

- Rara cronicizzazione di forme acute
- In carcere più facilmente casi connatali/perinatali negli stranieri e casi misconosciuti negli italiani
- Virus integrato
- Prevenire la fibrosi



La Storia naturale dell'infezione



5 fasi non sempre sequenziali ed obbligatorie ma comunque in equilibrio dinamico

Perché trattare?

2 principali approcci

- **Trattamento curativo di durata definita**

  che cura l'epatite cronica per ottenere una SVR

- **Trattamento soppressivo di durata indefinita**

  che inibisce la replicazione virale e l'attività di malattia

Quando trattare? - ieri

Sono candidati alla terapia farmacologica i pazienti con epatite cronica B **HBeAg positivi** da almeno 6 mesi con:

1) HBV DNA $\geq$ 20.000 IU/ml e ALT persistentemente $\geq$ 2 ULN per 3 - 6 mesi;

2) HBV DNA $\geq$ 20.000 IU/ml e

- ALT fluttuanti

oppure

- ALT oltre i limiti superiori della norma specialmente se età >40 anni e biopsia indicativa per trattamento (Ishak *staging* $\geq$2 per i pazienti candidati a terapia con Peg-IFN, $\geq$ 3 per i pazienti candidati a terapia con NUC)

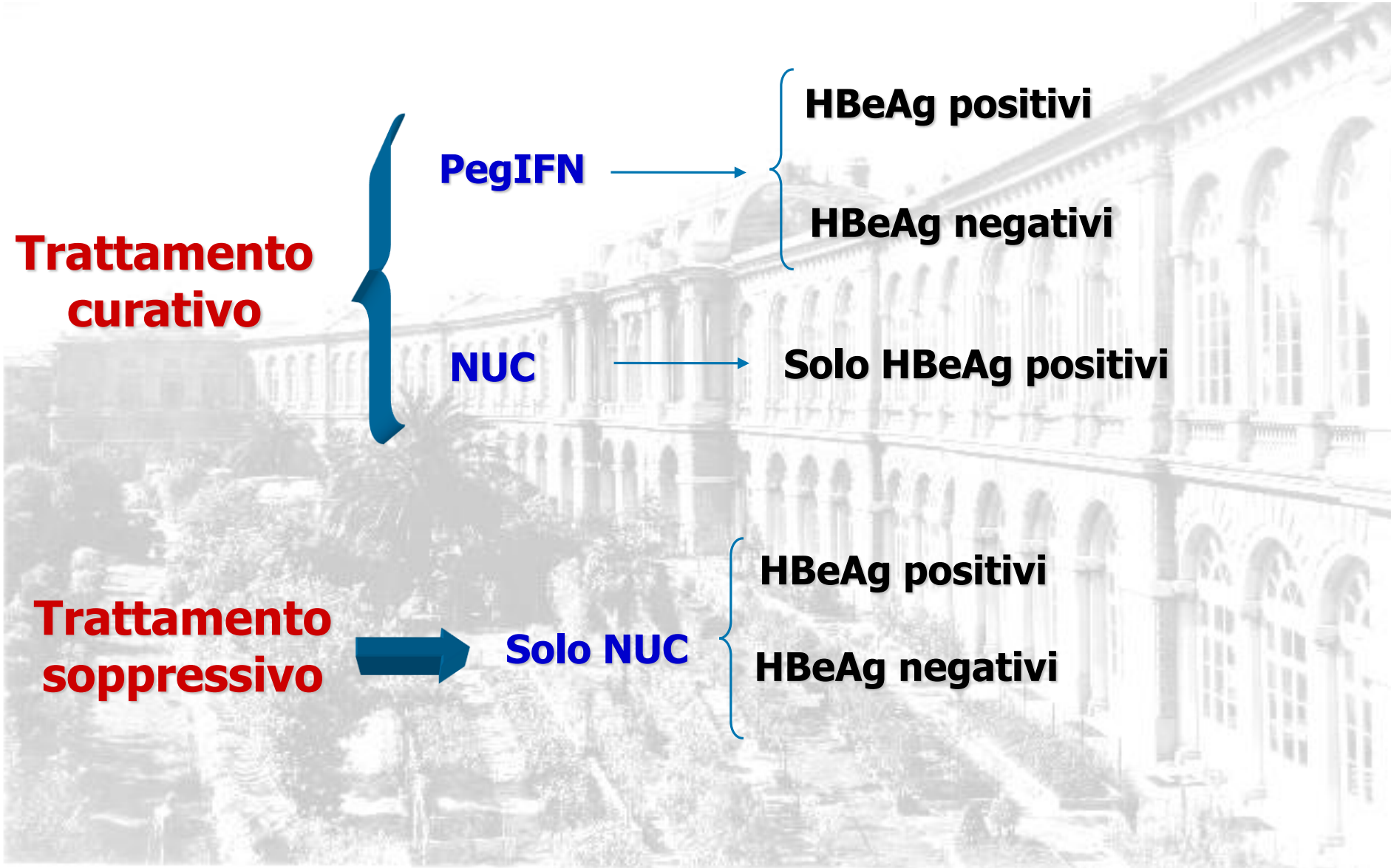
oppure

- ALT persistentemente normali in presenza di fattori di rischio associati (età >35 anni, familiarità positiva per HCC, etnia asiatica) e biopsia indicativa per trattamento (Ishak *staging* $\geq$ 2 per i pazienti candidati a terapia con Peg-IFN, $\geq$ 3 per i pazienti candidati a terapia con NUC).

Quando trattare? - oggi

Guidelines	HBeAg Positive			HBeAg Negative		
	HBV DNA, IU/mL	ALT	Liver Biopsy Results	HBV DNA, IU/mL	ALT	Liver Biopsy Results
AASLD 2016[3]	> 20,000	≥ 2 x ULN	N/A	> 2000	≥ 2 x ULN	N/A
APASL 2016[10]	> 20,000	> 2 x ULN	N/A	> 2000	> 2 x ULN	N/A
EASL 2017[4]*	> 2000	> ULN*	At least moderate necroinflammation and/or fibrosis*	> 2000	> ULN*	At least moderate necroinflammation and/or fibrosis*
	> 20,000	> 2 x ULN	N/A	> 20,000	> 2 x ULN	N/A

N/A, not applicable.
*In patients with HBV DNA > 2000 IU/mL, treatment indicated if ALT > ULN and/or at least moderate fibrosis.


Trattamento curativo
PegIFN
HBeAg positivi
HBeAg negativi
NUC
Solo HBeAg positivi
Trattamento soppressivo
Solo NUC
HBeAg positivi
HBeAg negativi

Quali farmaci a disposizione

- PEG-IFN
- Entecavir
- Tenofovir DF
- Tenofovir AF

TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB: Wk 96 Serology and ALT

- HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 in both arms[1]
  - Minimal decline in HBsAg in both arms for HBeAg-negative pts (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)[2]

Serology in HBeAg-Positive Study, n/N (%)[1]	TAF (n = 581)	TDF (n = 292)	*P* Value
HBeAg by Wk 96			
▪Loss	123/565 (22)	51/285 (18)	.20
▪Seroconversion	99/565 (18)	35/285 (12)	.05
HBsAg by Wk 96			
▪Loss	7/576 (1)	4/288 (1)	.88
▪Seroconversion	6/576 (1)	0/288 (0)	.08

- In both studies, significantly higher rates at Wk 96 of ALT normalization with TAF

Wk 96 ALT Normalization, %	HBeAg Negative[2]			HBeAg Positive[1]		
	TAF	TDF	*P* Value	TAF	TDF	*P* Value
By central laboratory criteria*	81	71	.038	75	68	.017
By AASLD criteria†	50	40	.035	52	42	.003

*ULN for age < 69 yrs (≥ 69 yrs): men, ≤ 43 U/L (35 U/L); women, ≤ 34 U/L (32 U/L). †ULN: men, ≤ 30 U/L; women, ≤ 19 U/L.

1. Agarwal K, et al. EASL 2017. Abstract FRI-153. 2. Brunetto M, et al. EASL 2017. Abstract PS-042.

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TAF vs TDF in HBeAg-Negative and HBeAg-Positive CHB: Wk 96 Safety

- Rates of treatment-emergent AEs and grade 3/4 laboratory abnormalities similar between arms, except for higher rates of LDL abnormalities for all pts on TAF (not adjusted for BL)
  - Improved renal and bone safety profiles for TAF vs TDF maintained through Wk 96

Safety Outcome	HBeAg Negative[1]			HBeAg Positive[2]		
	TAF (n = 285)	TDF (n = 140)	*P* Value	TAF (n = 581)	TDF (n = 292)	*P* Value
Any AE, n (%)	229 (80)	108 (77)	--	441 (76)	219 (75)	--
▪Grade 3/4	18 (6)	8 (6)	--	40 (7)	14 (5)	--
▪Serious AE	24 (8)	16 (11)	--	36 (6)	13 (4)	--
Death, n (%)	0	2*	--	2 (< 1)*	1 (< 1)*	--
Laboratory abnormalities in ≥ 2% pts						
▪Grade 3/4, n/N (%)	95/282 (34)	39/140 (28)	--	214/577 (37)	106/288 (37)	--
▪Fasting LDL, %	7	< 1	--	6	1	--
Change from BL to Wk 96						
▪Mean spine BMD, %	-0.86	-3.06	< .001	-0.69	-2.34	< .001
▪Mean hip BMD, %	-0.31	-2.96	< .001	-0.33	-2.30	< .001
▪Median $eGFR_{CG}$, mL/min	-0.6	-3.6	.011	-1.8	-5.0	< .001

*Due to HCC in cirrhotic pt, multiorgan failure in pt with bilateral bronchopneumonia, H1N1 influenza, HCC unrelated to treatment, and cardiopulmonary arrest unrelated to treatment.

1. Brunetto M, et al. EASL 2017. Abstract PS-042. 2. Agarwal K, et al. EASL 2017. Abstract FRI-153.

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Studies 108 and 110 Open-Label Extension: Switch to TAF vs TDF in CHB

- Analysis of open-label extension data from 2 phase III trials (Studies 108 and 110) in HBV-infected pts switching from TDF to TAF at Wk 96
  - 88% of pts achieved virologic suppression at Wk 96 (preswitch) and Wk 120 (post switch)
  - Significantly higher proportion of pts achieved ALT normalization after switch to TAF

Normalized ALT, n/N (%)	Pts Switching From TDF to TAF		*P* Value
	Wk 96: Preswitch	Wk 120: Post Switch	
By central laboratory criteria*	125/161 (78)	136/153 (89)	< .001
By AASLD criteria†	83/176 (47)	106/167 (63)	< .001

*ULN for age < 69 yrs (≥ 69 yrs): men, ≤ 43 U/L (35 U/L); women, ≤ 34 U/L (32 U/L). †ULN: men, ≤ 30 U/L; women, ≤ 19 U/L.

- Significant improvements in CrCl and change in hip and spine BMD at Wk 120

Chan HLY, et al. EASL 2017. Abstract PS-041.

Slide credit: clinicaloptions.com

La Fibrosi:

Cirrosi & HCC

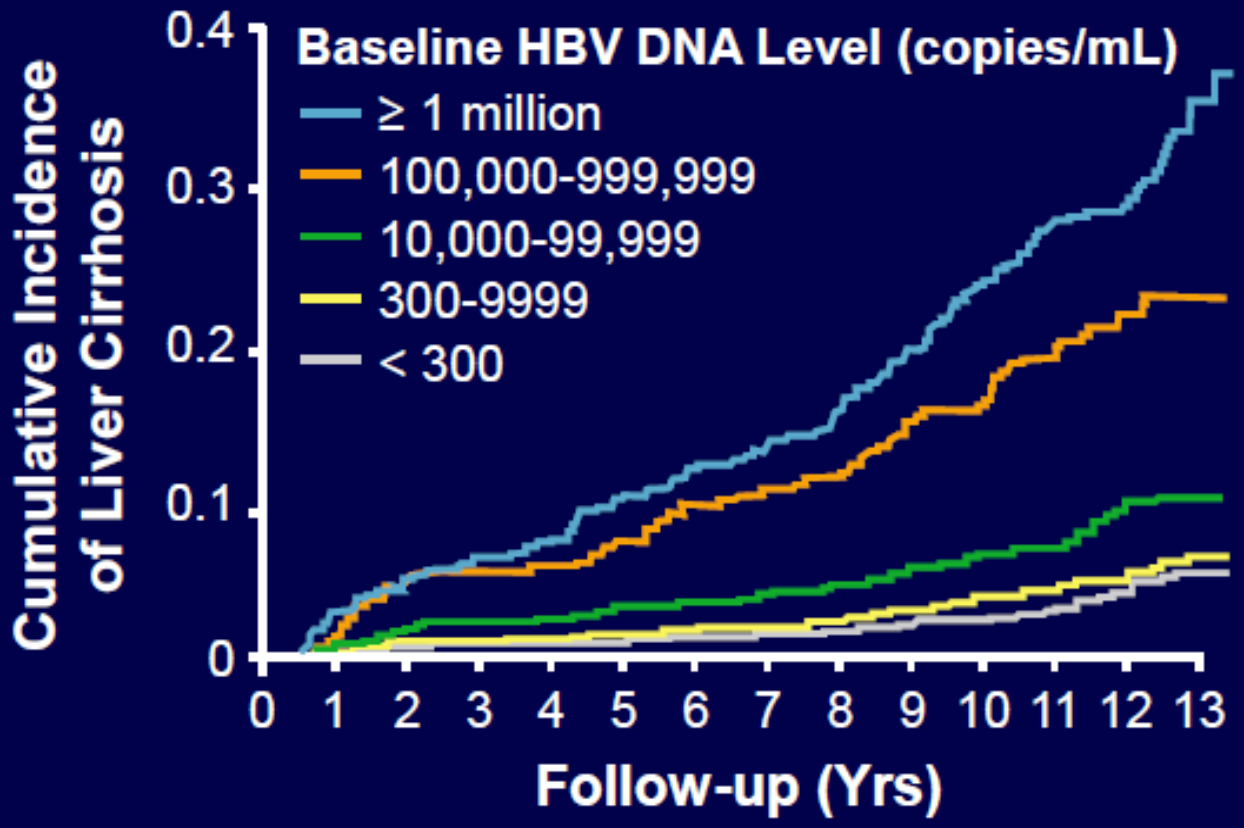
Agorà Penitenziaria 2017 – Roma 5-6 Ottobre

Risk Factors for Progressive Fibrosis

- Host:
  - Male sex
  - Increasing age
  - Metabolic syndrome
  - Alcohol consumption
  - Coinfections
    - HCV, HDV, HIV
- Virus:
  - HBV DNA levels (except for immune tolerant)
  - HBeAg positive
  - HBV genotype (?)
    - C > B > A/D

REVEAL: HBV DNA Level and Risk of Cirrhosis

- Long-term (mean follow-up: 11.4 yrs) cohort study to determine risk of cirrhosis and HCC in untreated, HBsAg-positive individuals in Taiwan (N = 3582)

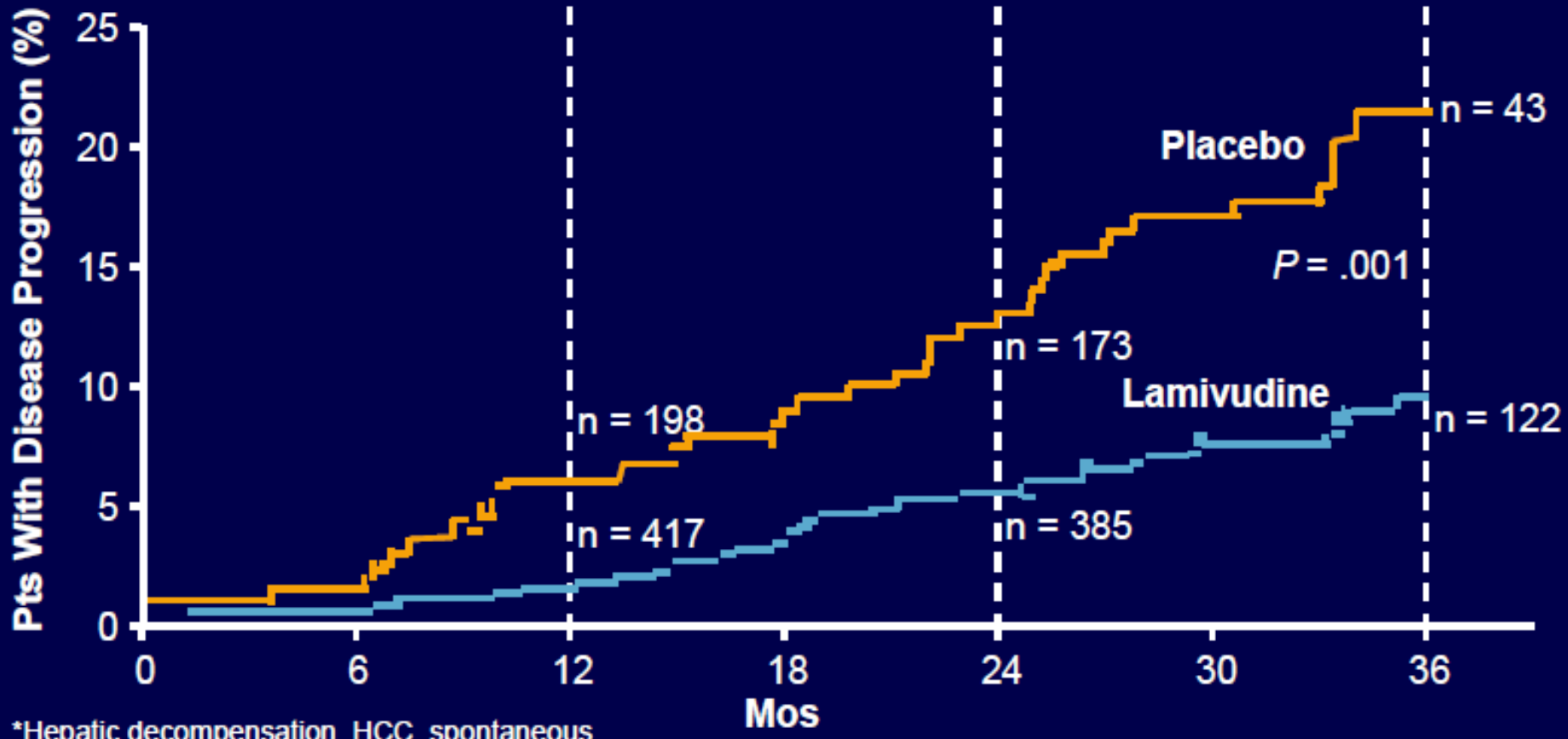


Iloeje UH, et al. Gastroenterology. 2006;130:678-686.

Slide credit: clinicaloptions.com

HBV Treatment Reduces Risk of Disease Progression Including Decompensation

- Placebo-controlled, double-blind, parallel group study of pts with chronic HBV infection and cirrhosis (F4) (N = 651) followed until HBeAg seroconversion or disease progression*

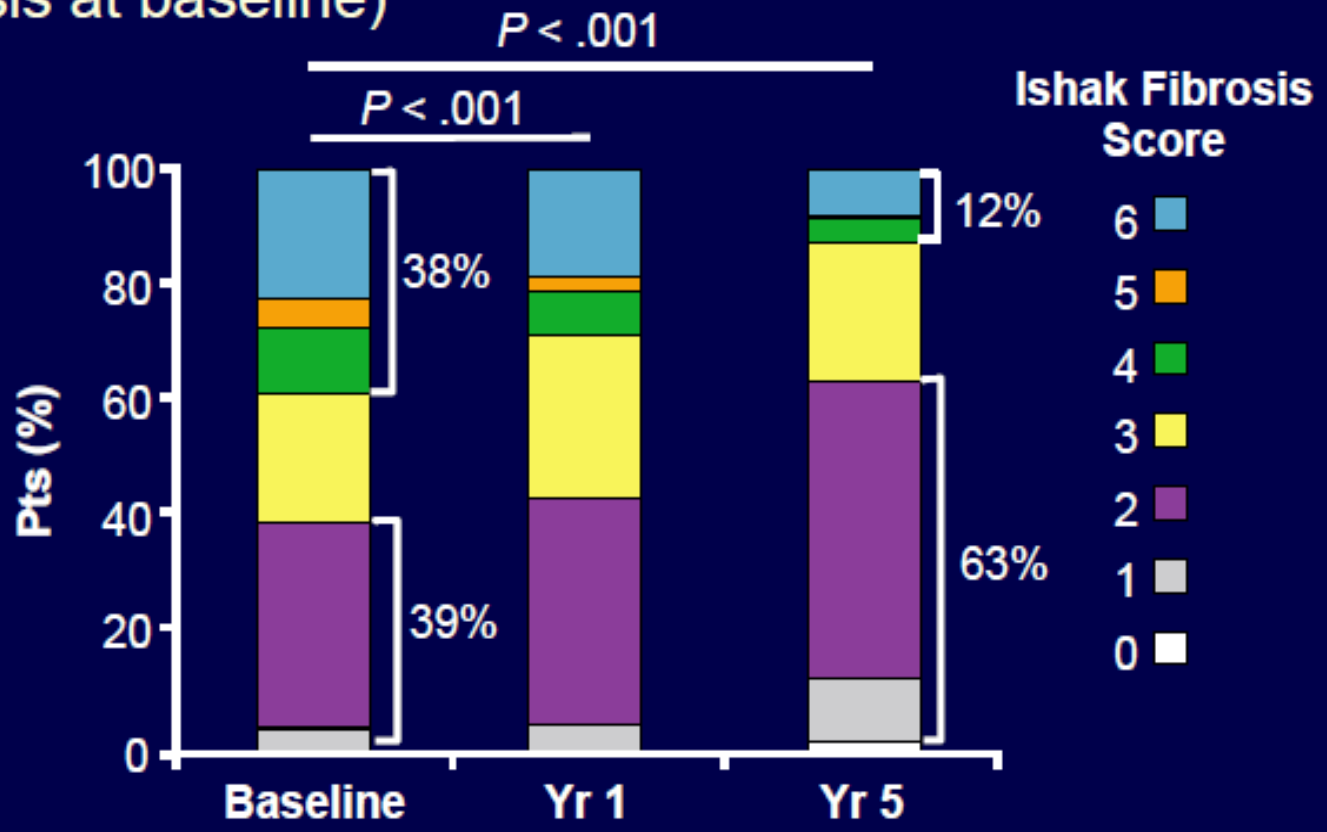


*Hepatic decompensation, HCC, spontaneous bacterial peritonitis, bleeding gastroesophageal varices, or death related to liver disease.

Liaw YF, et al. N Engl J Med. 2004;351:1521-1531.

Long-term TDF in Pts With HBV: Regression of Fibrosis, Cirrhosis

- Overall regression of fibrosis in 51% of pts through 5 yrs (176/348 pts with matched biopsies)
- Reversal of cirrhosis in 74% of pts through 5 yrs (71/96 pts with cirrhosis at baseline)

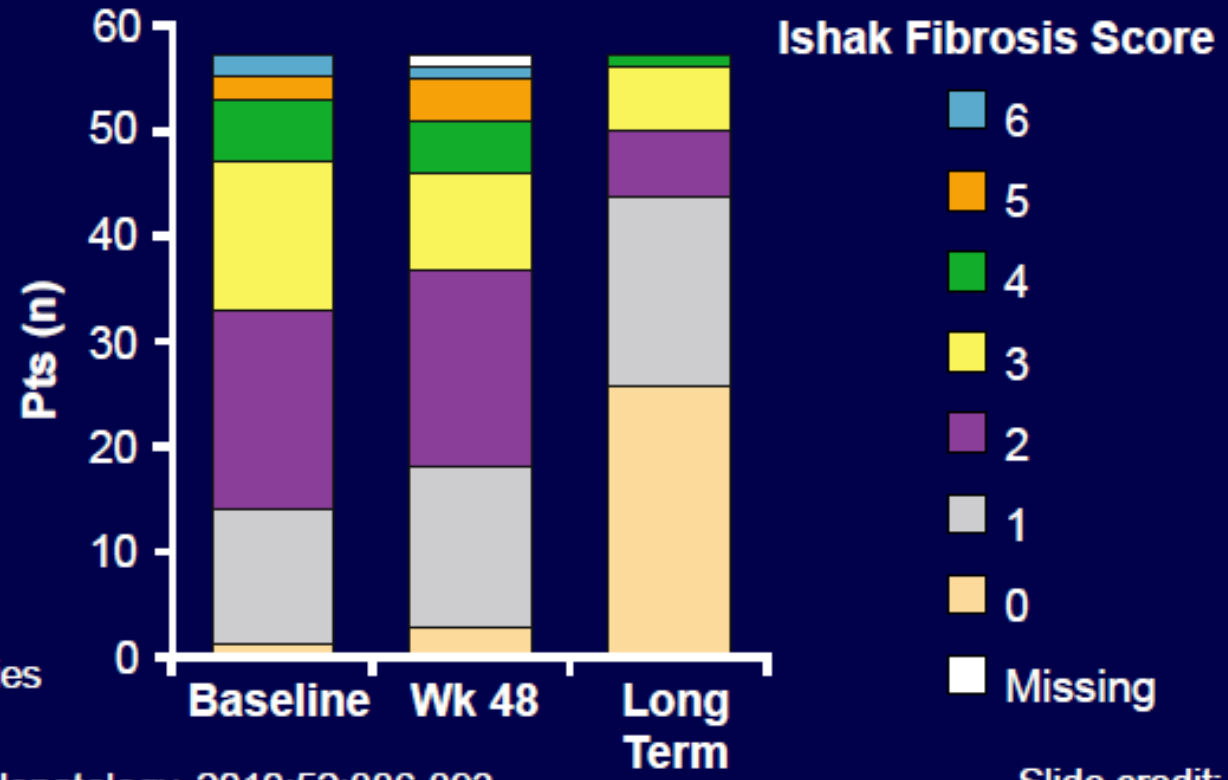


Marcellin P, et al. Lancet. 2013;381:468-475.

Slide credit: clinicaloptions.com

Long-term Entecavir in Pts With HBV: Regression of Fibrosis, Cirrhosis

- Regression of fibrosis (≥ 1-point decrease in Ishak score) in 88% of pts (50/57 pts with matched biopsies and baseline Knodell scores ≥ 2)
- Reversal of cirrhosis in 4/10 pts with cirrhosis at baseline (median decrease in Ishak score: 3 points)



n = 57
matched biopsies

Chang TT, et al. Hepatology. 2010;52:886-893.

Slide credit: clinicaloptions.com

Summary

- HBV is a very dynamic disease
- Fibrosis may progress quickly both in HBeAg-positive and HBeAg-negative disease
- Antiviral therapy can:
  - Suppress HBV DNA
  - Reduce inflammation—ALT and HAI
  - Reverse fibrosis
  - Reduce the risk of HCC and liver-related events
- New agents have similar efficacy on surrogate endpoints and a better safety profile

Le sfide e le Incognite

- Prima sfida: ottenere soppressione replicazione virale: facile
- Seconda sfida: Ottenere negativizzazione HBsAg e comparsa persistente di titolo elefato HBsAb: lento e raro con le terapie attuali – area di studio per le terapie future

Cosa fare in carcere

- Diagnosi: sierologie, ematochimici
- Stadiazione: ETG, Fibroscan, biopsia
- Trattamento: eligibilità, prescrizione, continutià terapeutica
- Riattivazione???
- Ma anche prevenzione
  Vaccinazione

Grazie per l'attenzione