

First line therapy of hepatitis B : interferon or analogues

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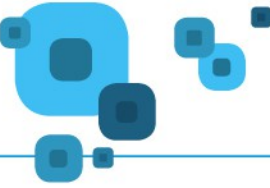


Clinical case

- ❑ A 58-year old man is referred for therapeutic evaluation of Hepatitis B
- ❑ Employee in a bank
- ❑ Screening of Ag HBs was performed in 1989 during his military service. No specific treatment was proposed due to the lack of molecules with antiviral efficacy at that time
- ❑ He was lost of follow-up until 2013
- ❑ He does not drink alcohol and there is no other comorbidities
- ❑ He disclose overweight (BMI 28)

Biological features

- ❑ White cell count 9,200/mm³, Hemoglobin 14.5 g/dL, MCV 88 fl, Platelet count 295,000/mm³
- ❑ INR 1
- ❑ Serum creatinine 0.8 mg/dL, glycemia 0.9g/dl, Bilirubin 3 mg/dL, Albumin 3. g/dL
- ❑ AST 100 IU/L (ULN: 40 IU/L), ALT 120 (ULN: 40 IU/L), GGT 70 IU/L (ULN:55 IU/L), ALP 157 IU/L (ULN: 240 IU/L)
- ❑ Alpha-fetoprotein, ferritin and serum iron within the normal ranges
- ❑ Screening negative for HIV, HCV and HDV
- ❑ HBsAg +, HbeAg +, anti-Hbe –
- ❑ HBV DNA at 750 000 IU/ml
- ❑ Abdominal ultrasonography was normal
- ❑ Liver Stiffness : 9 kPa
- ❑ Fibrotest 0.56
- ❑ Liver biopsy was performed. Result= A2F2



What treatment do you recommend ?

✱ PegIFN for 48 weeks

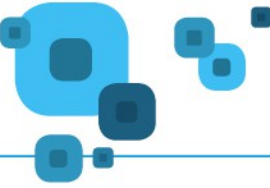
✱ Entecavir or Tenofovir

✱ Or Combined therapy PegIFN + Entecavir or PegIFN + Tenofovir

✱ Lamivudine

✱ No treatment





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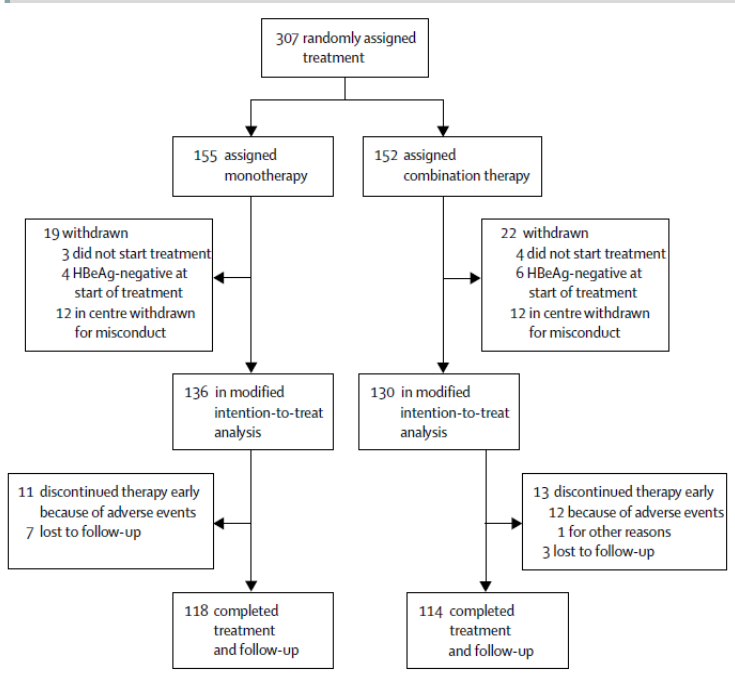
✱ No treatment



Combined therapy PEGIFN + Analogues is not Inefficient

12 | Treatment Survival AaHbe seroconversion

100 g/week pegylated interferon alfa-2b + placebo vs 100 g/week pegylated interferon alfa-2b and 100 mg/day lamivudine



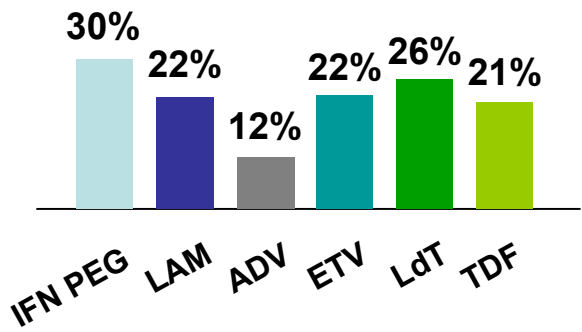
	End of therapy			End of follow-up		
	Combined therapy (n=130)	Monotherapy (n=136)	p	Combined therapy (n=130)	Monotherapy (n=136)	p
Virological response in serum						
HBeAg loss	57 (44%)	40 (29%)	0.01	46 (35%)	49 (36%)	0.91
HBeAg seroconversion	33 (25%)	30 (22%)	0.52	38 (29%)	39 (29%)	0.92
HBV DNA <200 000 copies/mL	96 (74%)	40 (29%)	<0.0001	41 (32%)	37 (27%)	0.44
HBV DNA <400 copies/mL	43 (33%)	13 (10%)	<0.0001	12 (9%)	9 (7%)	0.43
HBsAg loss	9 (7%)	7 (5%)	0.54	9 (7%)	9 (7%)	0.92
HBsAg seroconversion	8 (6%)	6 (4%)	0.53	9 (7%)	7 (5%)	0.54
Biochemical response in serum						
ALT returned to normal	66 (51%)	46 (34%)	0.005	46 (35%)	44 (32%)	0.60

Table 2: Response at the end of treatment and the end of follow-up

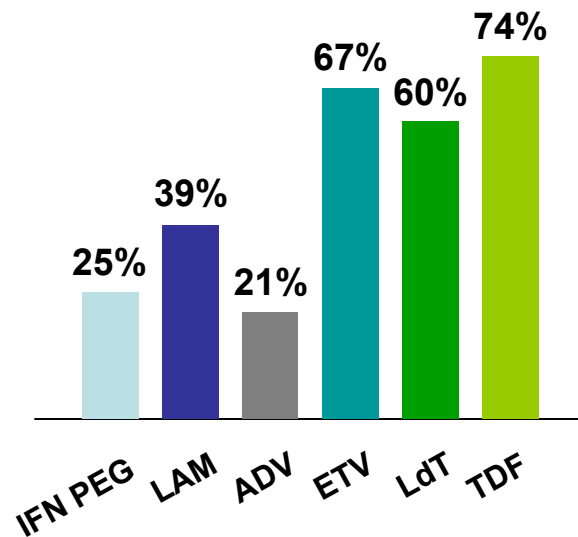
*diminution in log10de la CV from baseline values

1-Year results of antiviral therapy in AgHBe patients

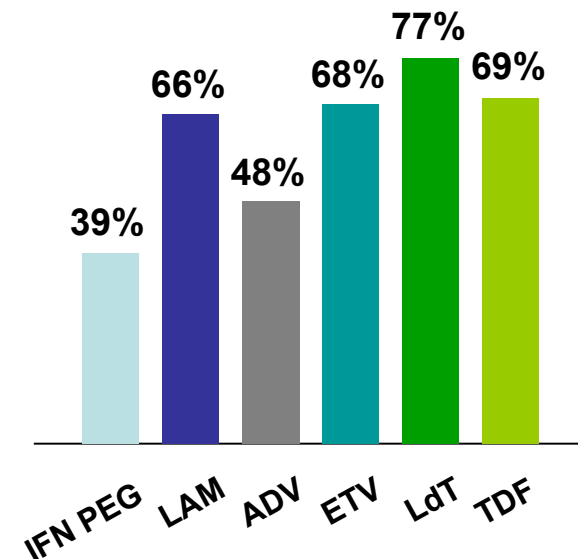
AgHbe Seroconversion



Undetectable DNA

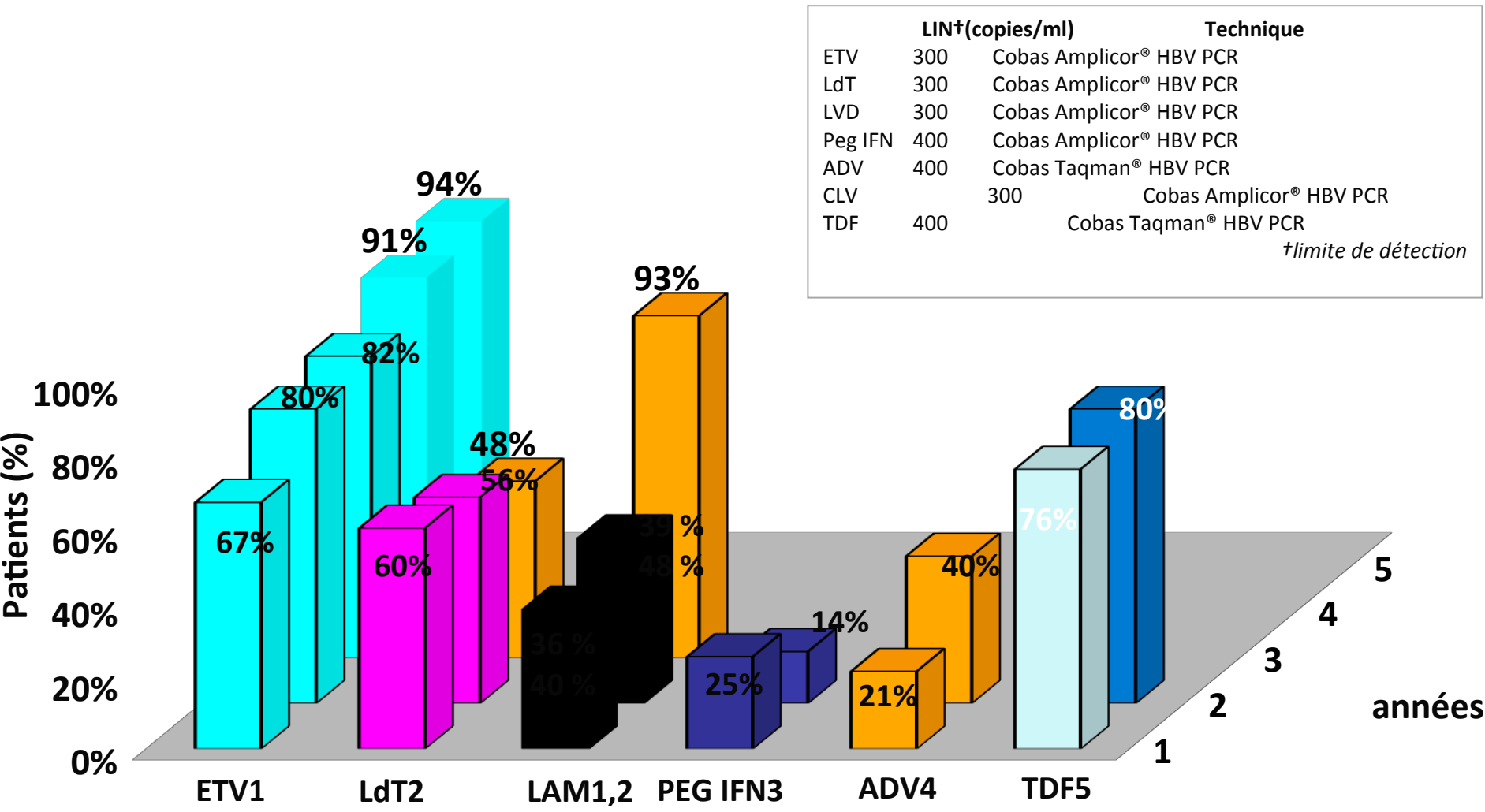


Normal ALT



5-Year results of antiviral therapy in AgHBe patients

Undetectable DNA



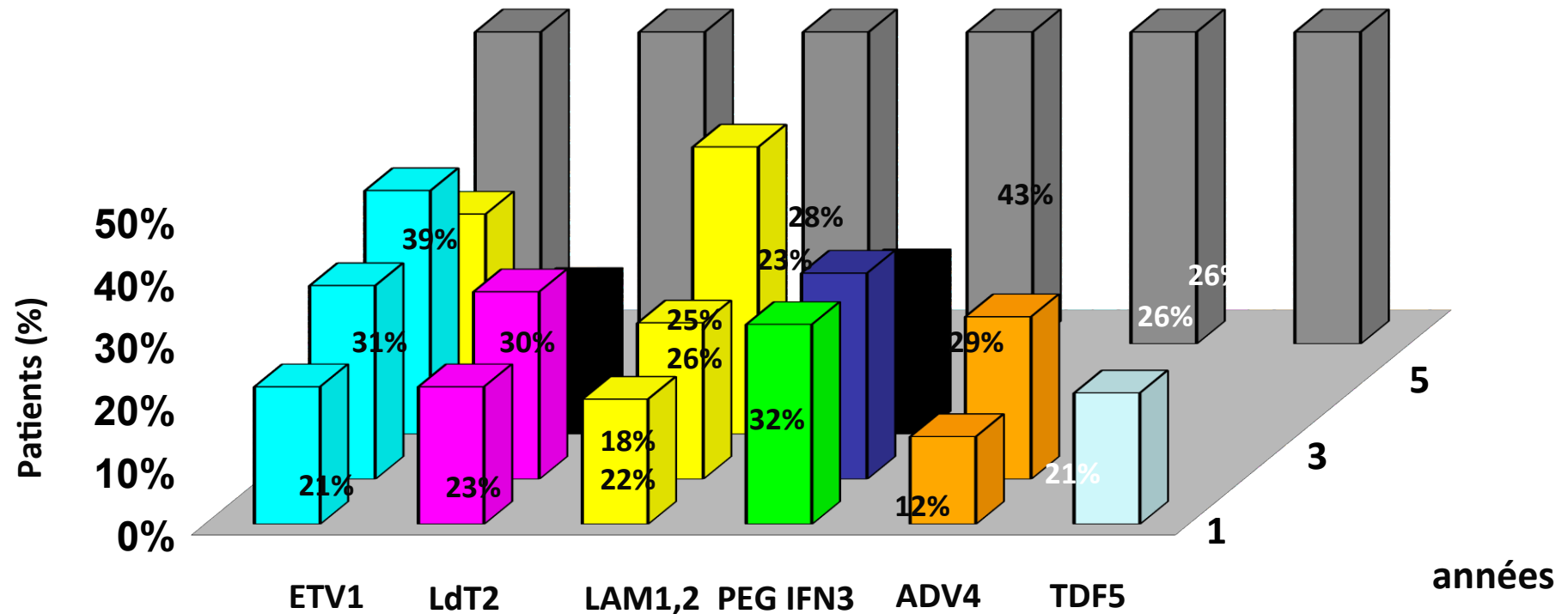
	LIN†(copies/ml)		Technique
ETV	300		Cobas Amplicor® HBV PCR
LdT	300		Cobas Amplicor® HBV PCR
LVD	300		Cobas Amplicor® HBV PCR
Peg IFN	400		Cobas Amplicor® HBV PCR
ADV	400		Cobas Taqman® HBV PCR
CLV	300		Cobas Amplicor® HBV PCR
TDF	400		Cobas Taqman® HBV PCR

†limite de détection

1. Chang et al. N Engl J Med 2006. Han et al. Hepatology 2008. 2. Lai et al. N Engl J Med 2007. Liaw et al. Gastroenterology 2009. 3. Lau et al. N Engl J Med 2005. 4. Marcellin et al. N Engl J Med 2003. 5. Heathcote et al. Hepatology 2007. Heathcote et al. J Hepatol 2008. Heathcote et al. Hepatology 2009.

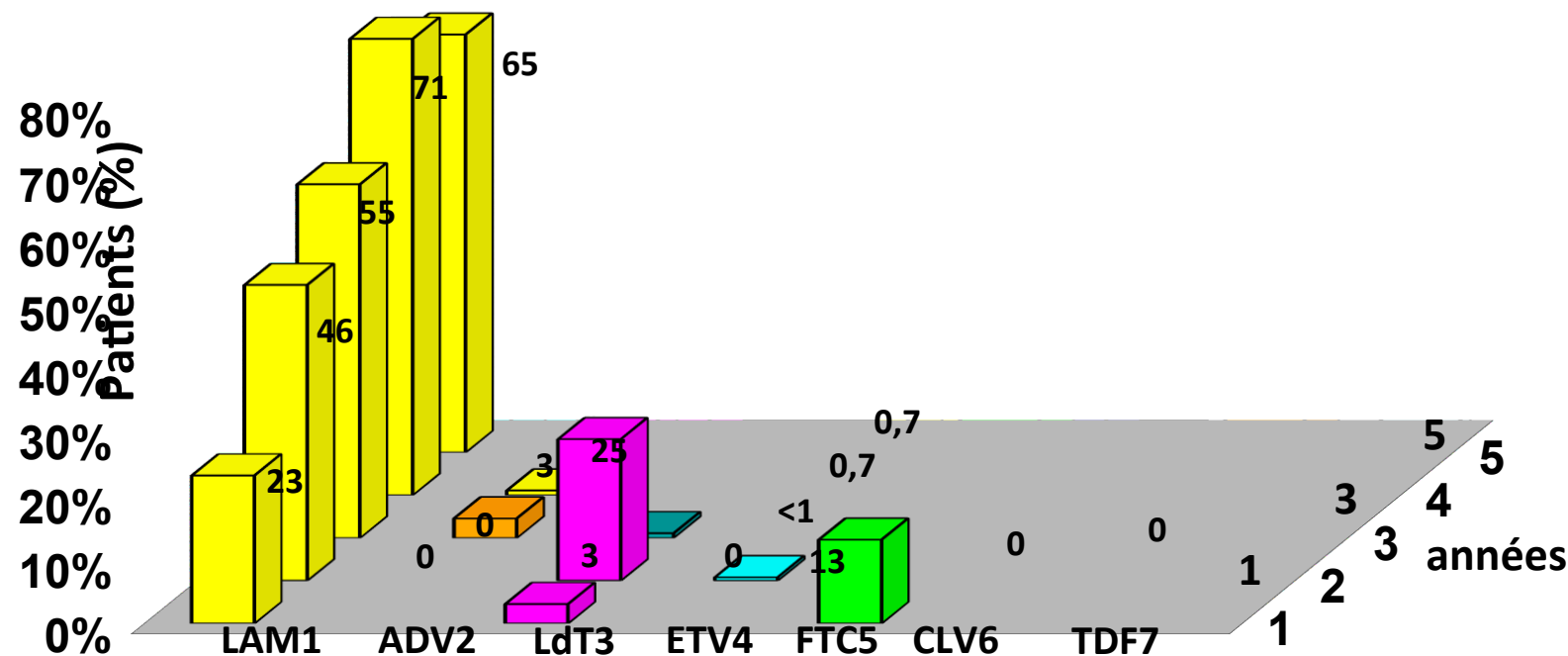
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1. Chang *et al.* *N Engl J Med* 2006. 2. Lai *et al.* *N Engl J Med* 2007. Liaw *et al.* *Gastroenterology* 2009. 3. Lau *et al.* *N Engl J Med* 2005. 4. Marcellin *et al.* *N Engl J Med* 2003. 5. Heathcote *et al.* *Hepatology* 2007. Heathcote *et al.* *Hepatology* 2009.

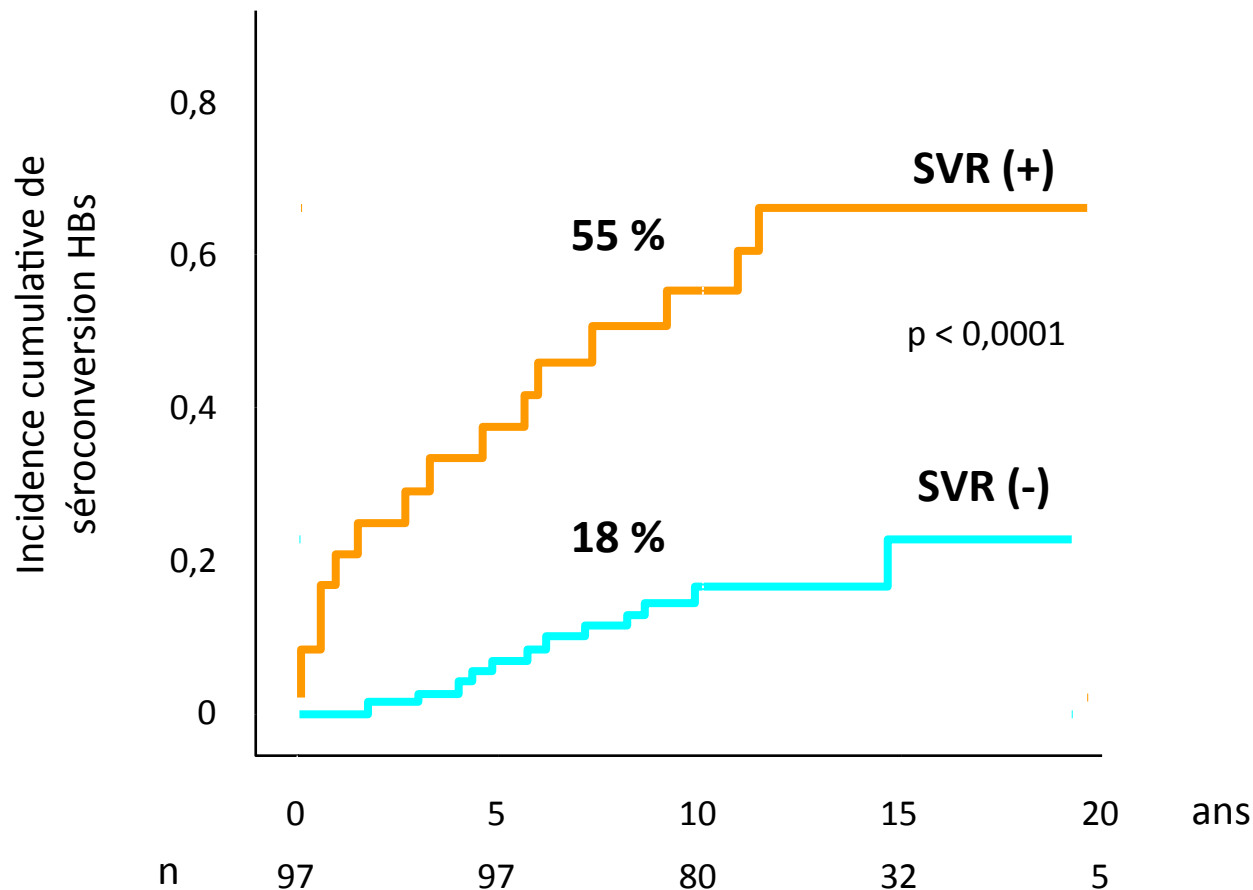
HBV resistance development to analogues



1. Lok et al. Gastroenterology 2003. 2. Marcellin et al. J Hepatol 2005. 3. Lai et al. Hepatology 2006. Liaw et al. Gastroenterology 2009. 4. Colonna et al. Hepatology 2006. 5. Shiffman et al. Hepatology 2004. 6. Chung. Hepatology 2006. 7. Heathcote et al Hepatology 2007.

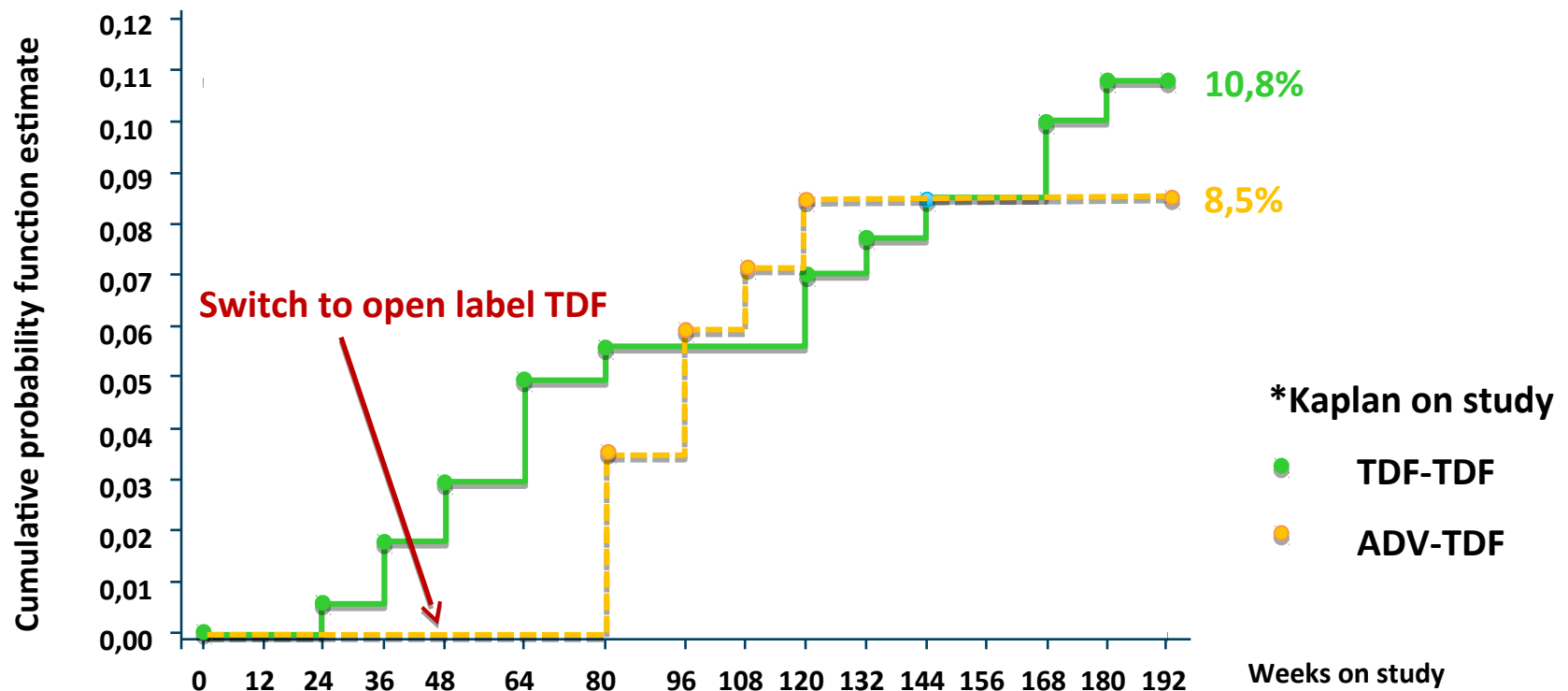
AgHBs seroconversion after AgHBe seroconversion

SVR = Hbe seroconversion HBe + undetectable DNA



AgHBs loss with TDF

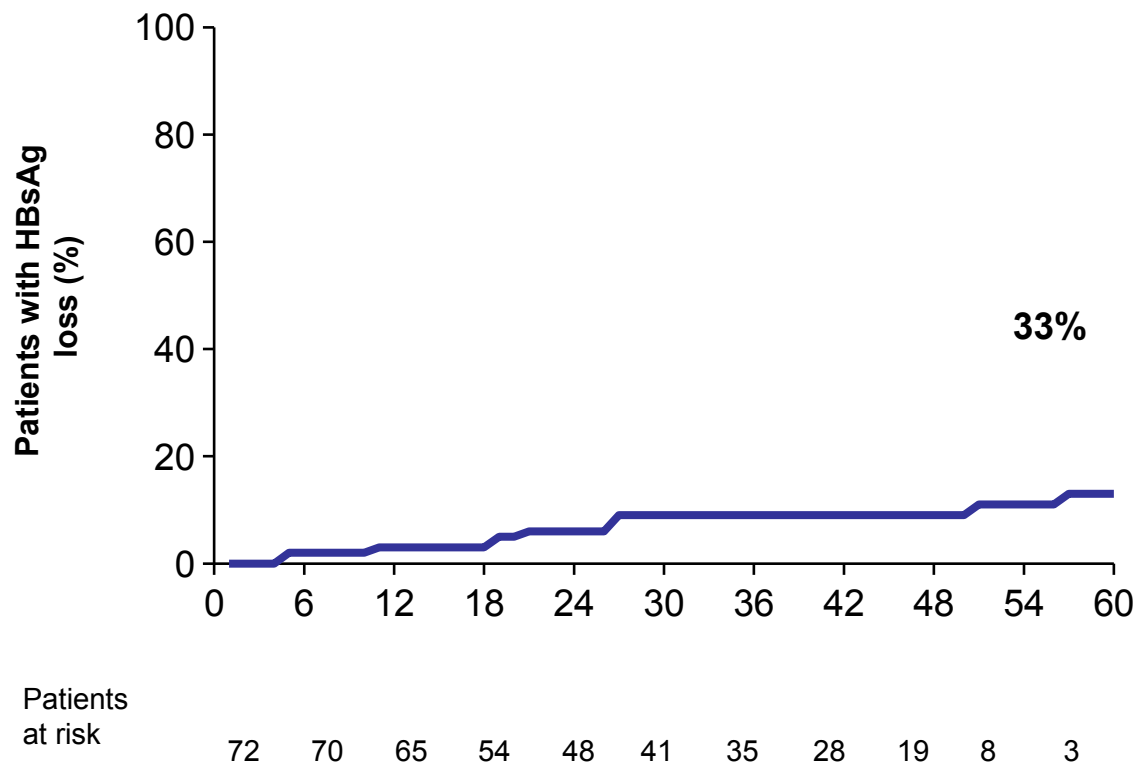
❑ Étude 103 suivi après 4 ans de traitement par **ténofovir disoproxil** :



- Cumulative probability of seroconversion to anti-HBs: 7.7% TDF-TDF and 7.3% ADV-TDF
- 18/23 patients discontinued treatment for HBsAg loss; 3 patients regained HBsAg off treatment (1 patient was lost to follow up, 1 patient restarted therapy and subsequently lost HBsAg, and 1 patient remained off treatment based on HBsAg negative local laboratory results)

AgHBs loss with ETV

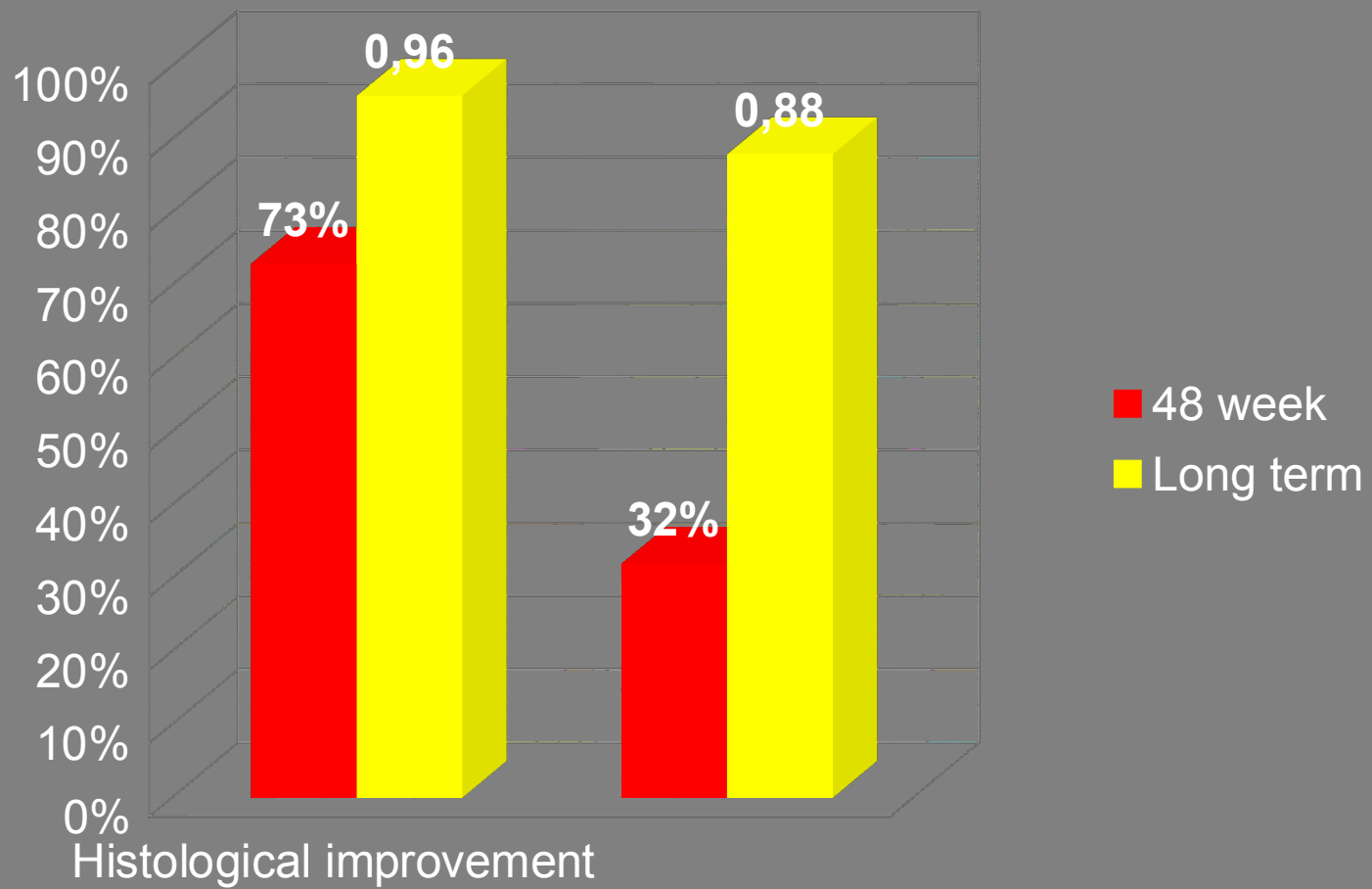
HBsAg loss in HBeAg-positive patients*:
13 patients



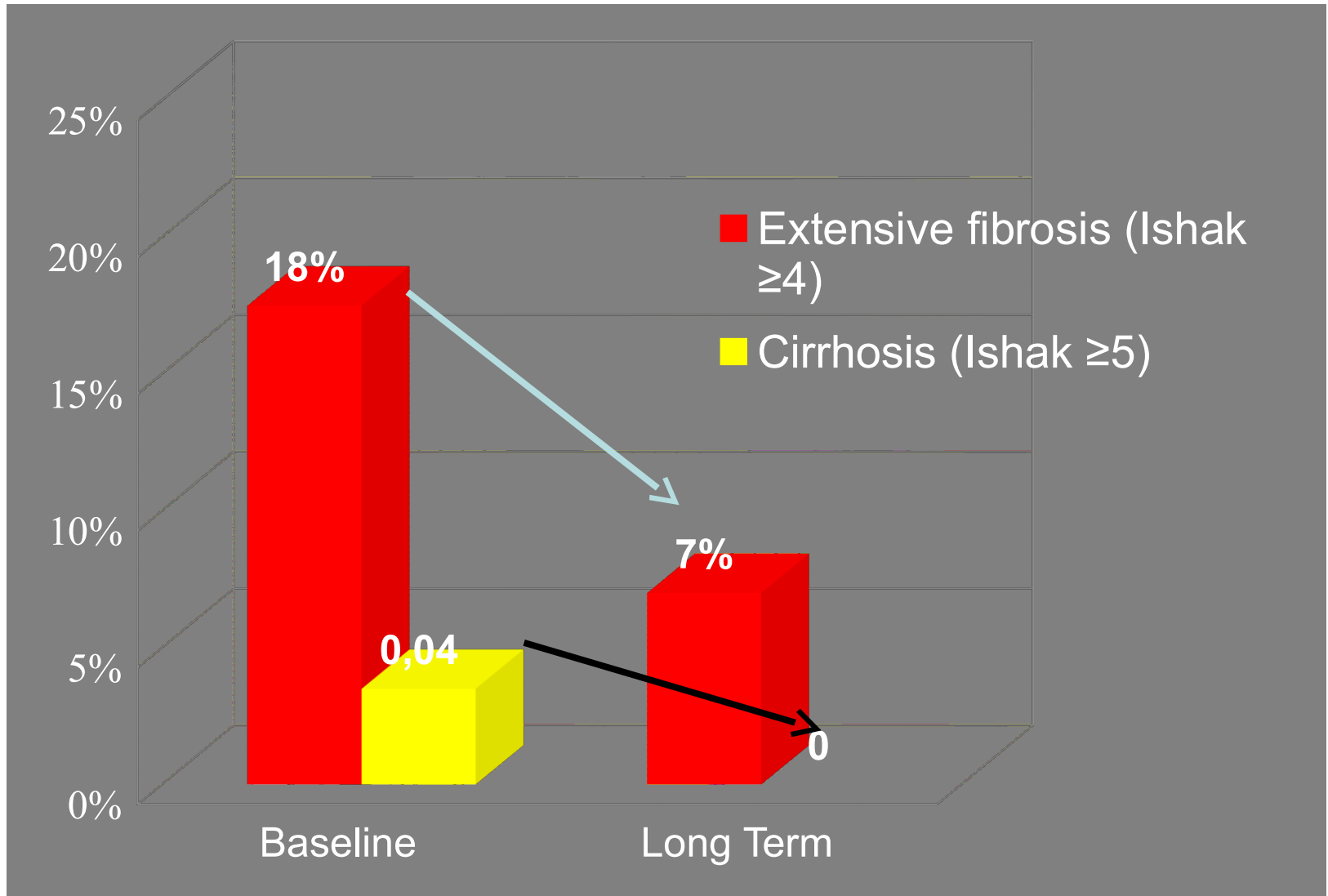
*Kaplan-Meier estimates

Adapté de Lampertico *et al.* AASLD 2010.

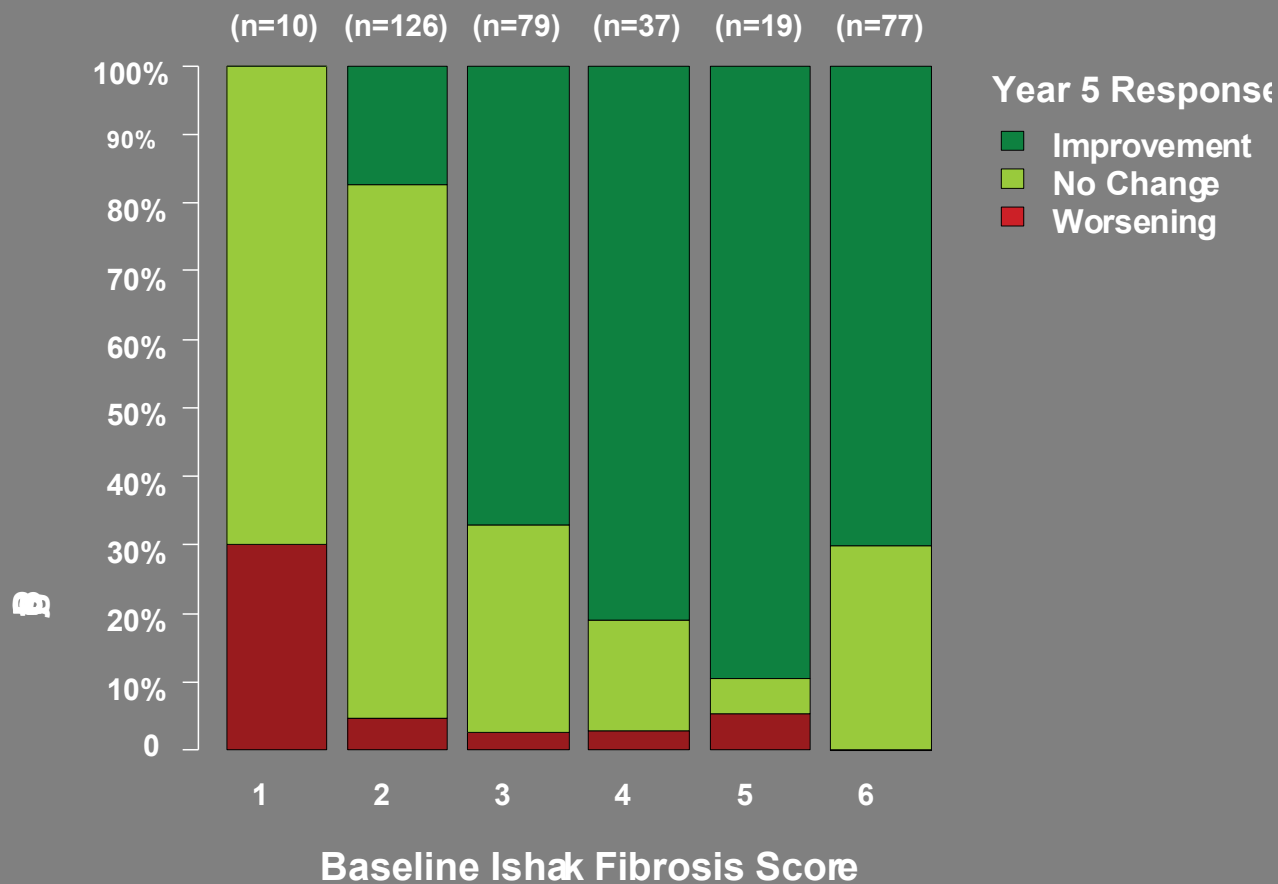
Long-term ETV therapy and fibrosis regression



Long-term ETV therapy and fibrosis regression

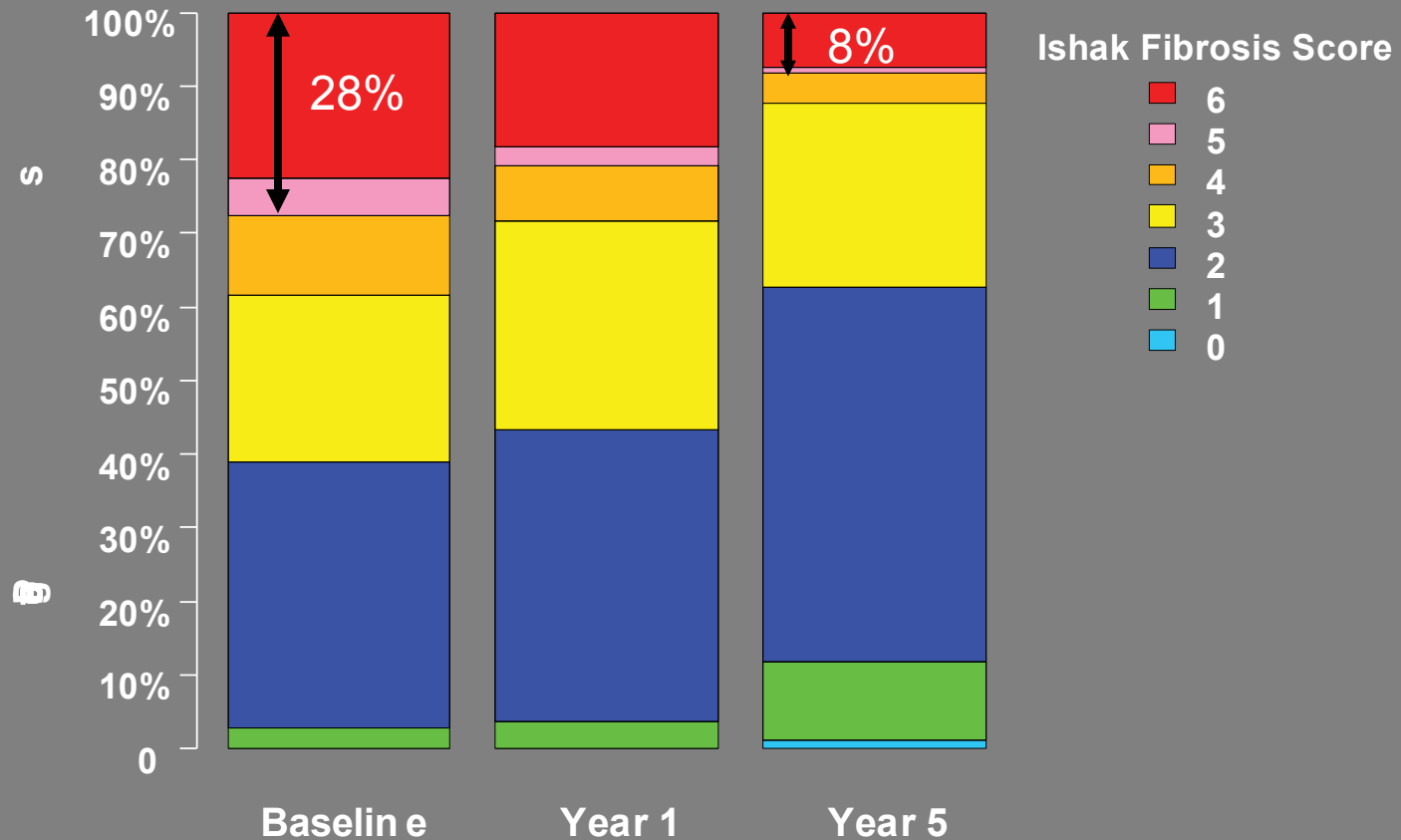


Long-term TDF therapy and fibrosis regression



96% of patients (335/348) disclosed improvement (≥ 1 unit of fibrosis score) or no change in Fibrosis stage at 5 years

Long-term TDF therapy and fibrosis regression



- 344/ 348 patients had histological analysis at baseline, 1 and 5 years

Marcellin P, Lancet 2012

Question 2

Among the following sentences, which they are correct?

- A/ At baseline, there is no predictive variables of response to Peg IFN
- B/ Age, High ALT and elevated DNA level are predictive factors of response to IFN
- C/ Definition of response to therapy is similar for PegIFN therapy or analogues
- D/ PegIFN induces AgHBe serconversion in 40 % of cases in Patients with ALT > 2
- E/ Efficacy of analogues is reduced in patients with high viral load ($\geq 10^8$ UI/ml)
- F/ Combined treatment with ETV plus TDF results in a higher proportion than ETV or TDF alone in patients with high viral load ($\geq 10^8$ UI/ml)

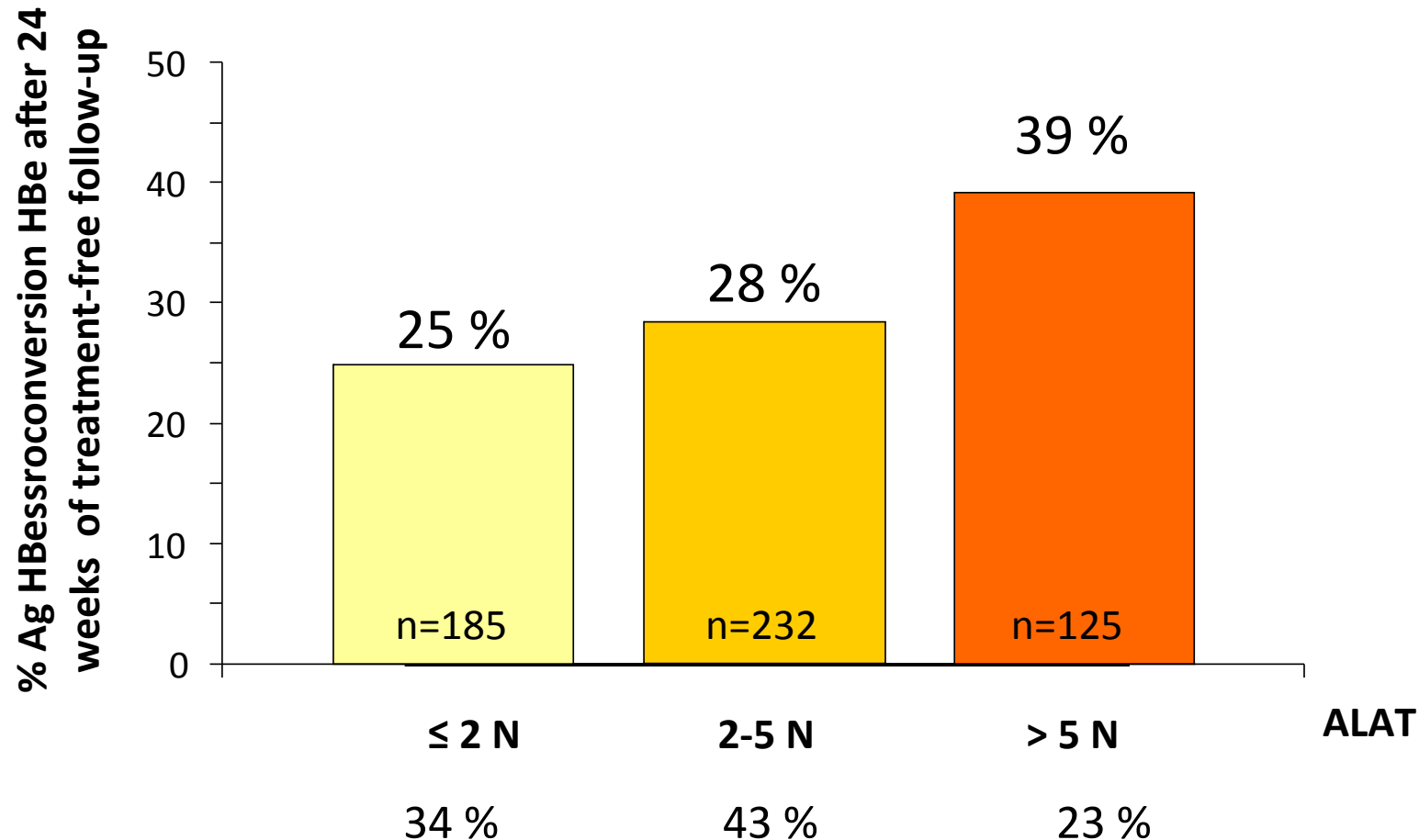
Responses to Question 2

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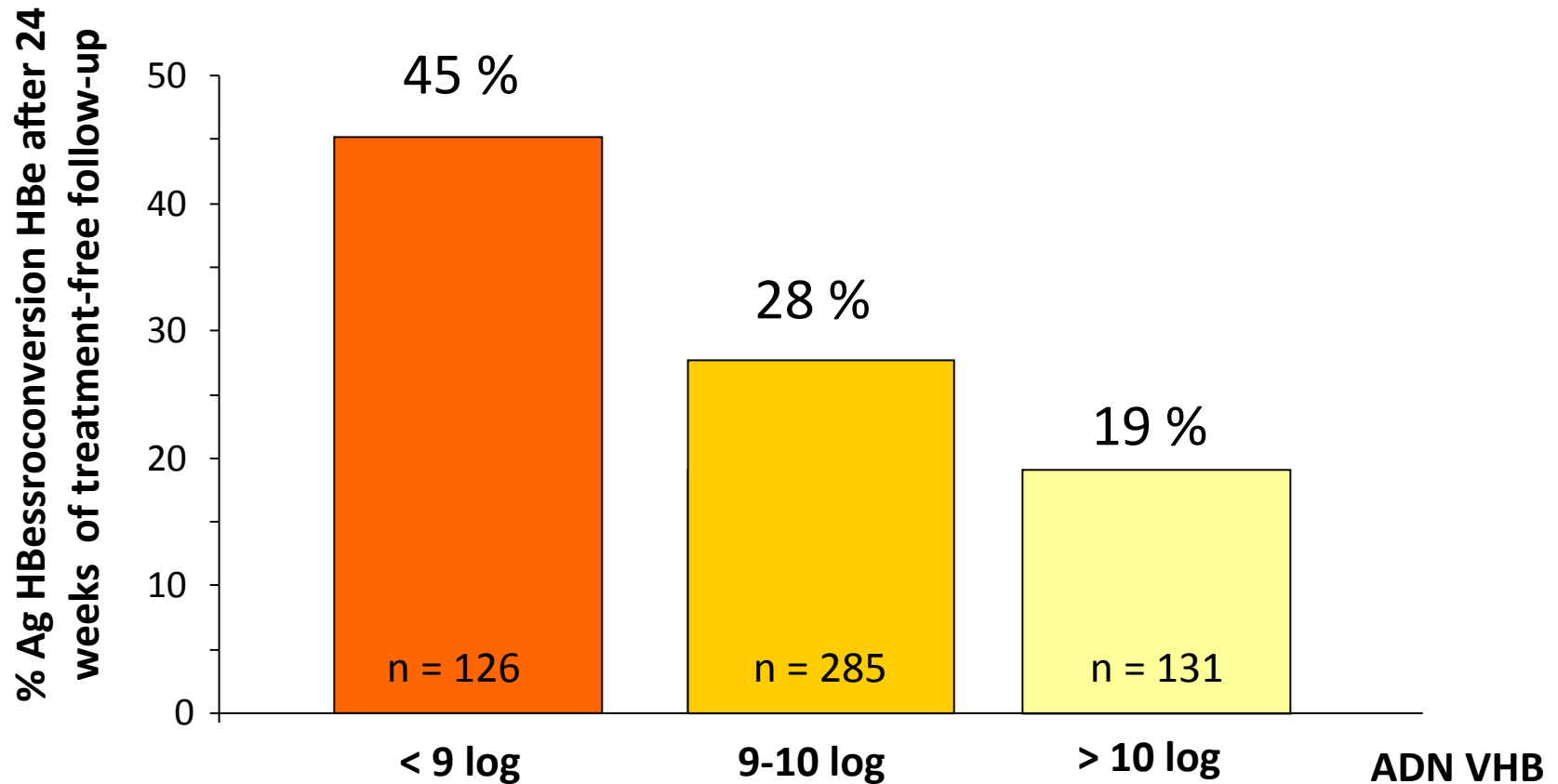
HBeAg Seroconversion in patients treated with PegIFN

□ 542 AgHBe + treated with Peg-IFN α 2a $\pm$ LAM during 48 weeks

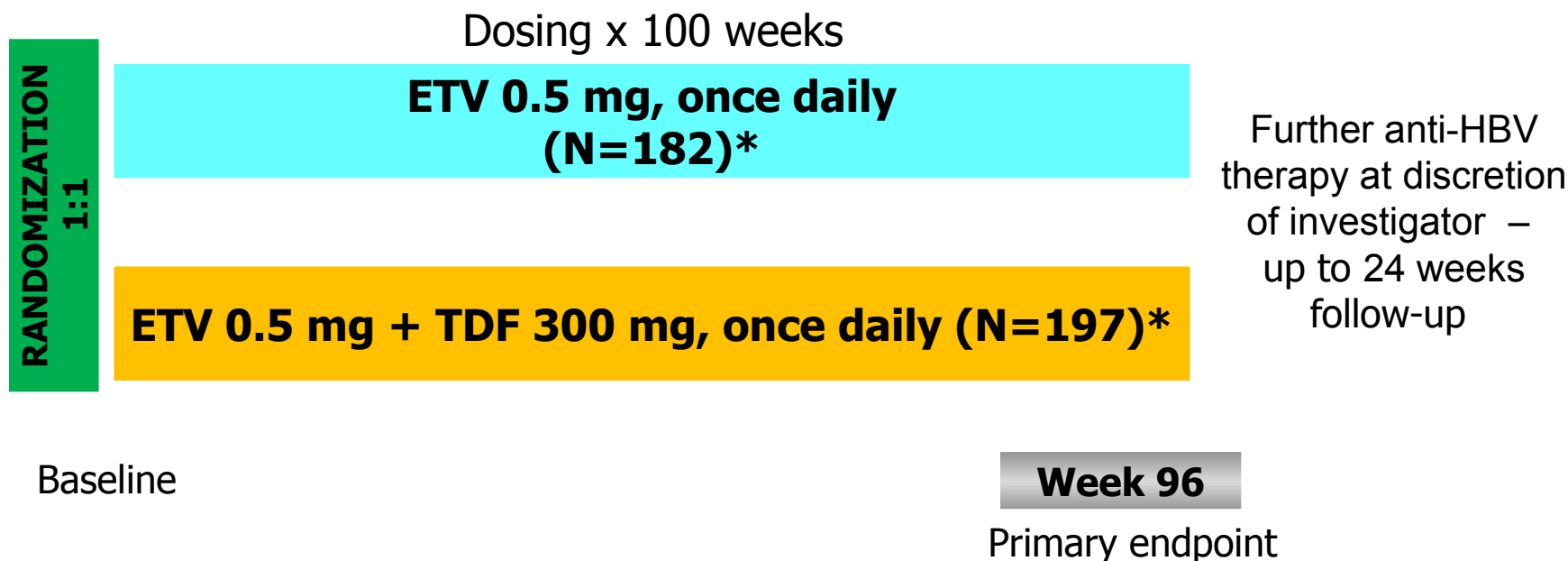


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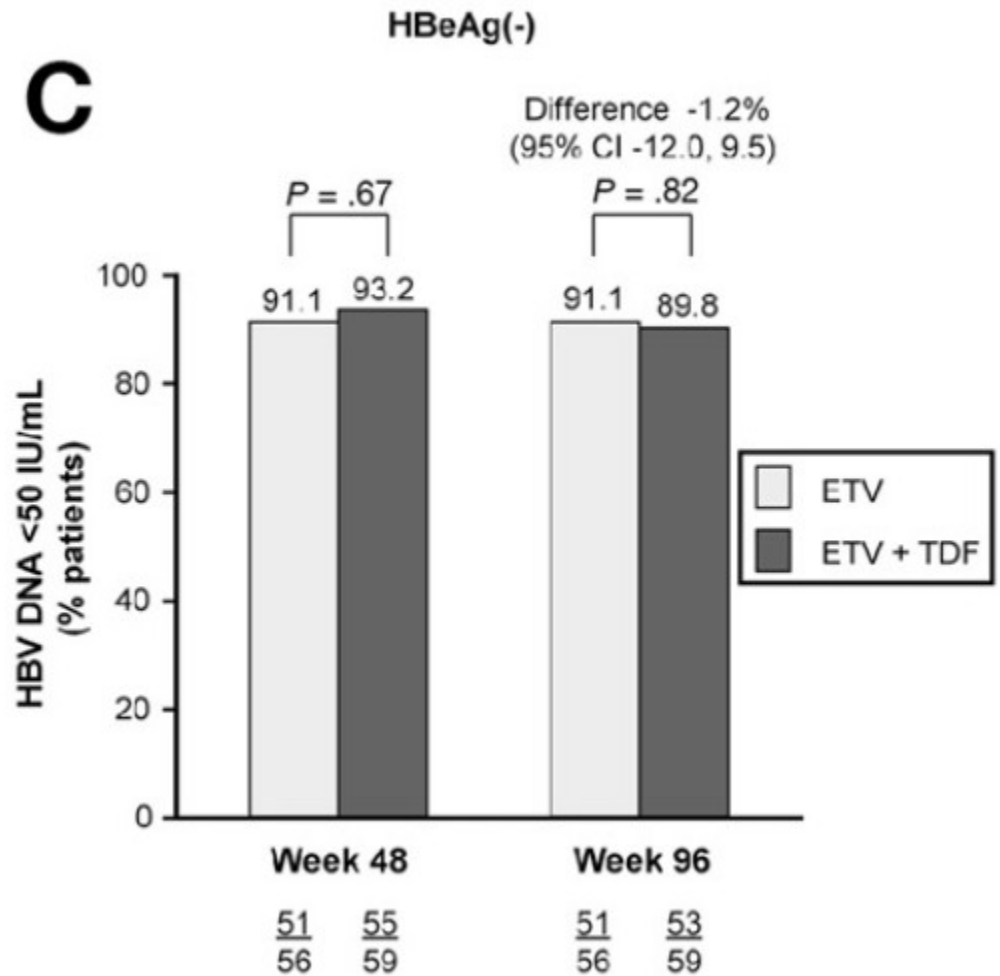
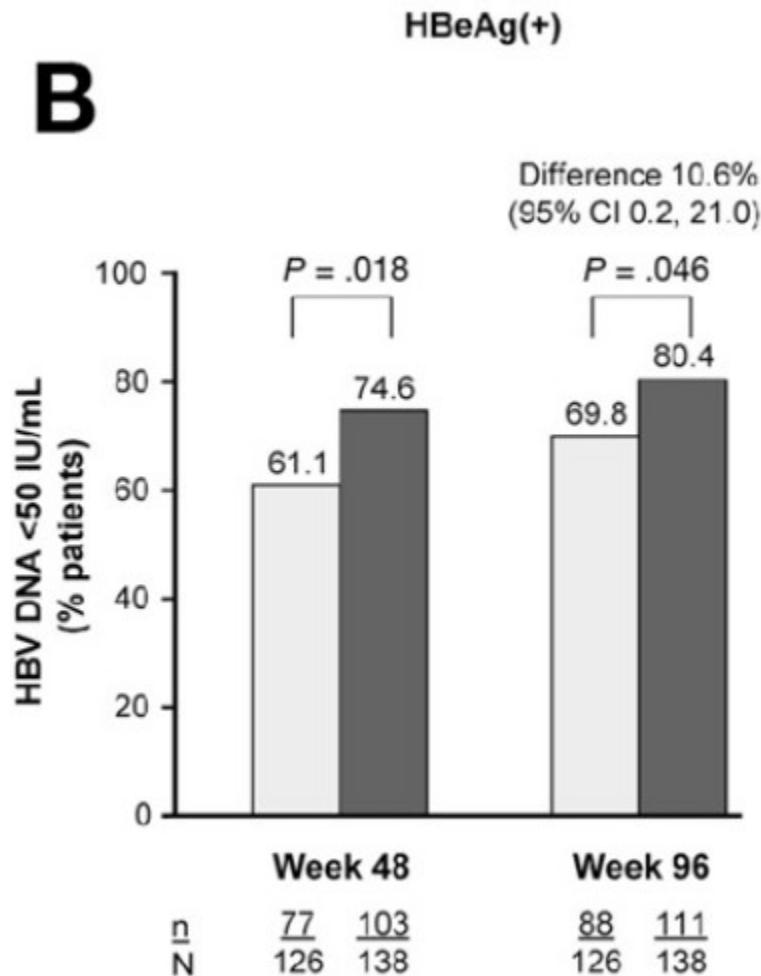


Combined Ananalog: incremental benefit in AgHBe+ ETV vs ETV + TDF (BE-LOW study)



Randomized, open-label, Phase IIIb trial
NA-naïve CHB, HBeAg(-) patients capped at 30%

Combined Ananalog: incremental benefit in AgHBe+ ETV vs ETV + TDF (BE-LOW study)



Question 3

Among the following sentences, which are correct?

- A/ Efficacy of PegIFN varies according to HVB genotype
- B/ IL-28 genotype predicts response to Peg IFN
- C/ Genotype A is associated with the highest rate of response to therapy and Genotype D with the lowest
- D/ Kinetic of AgHBe quantification is not useful to predict AgHBe serconversion in AgHBe + patients
- E/ Kinetic of DNA is not useful to predict AgHBe serconversion in AgHBe + patients

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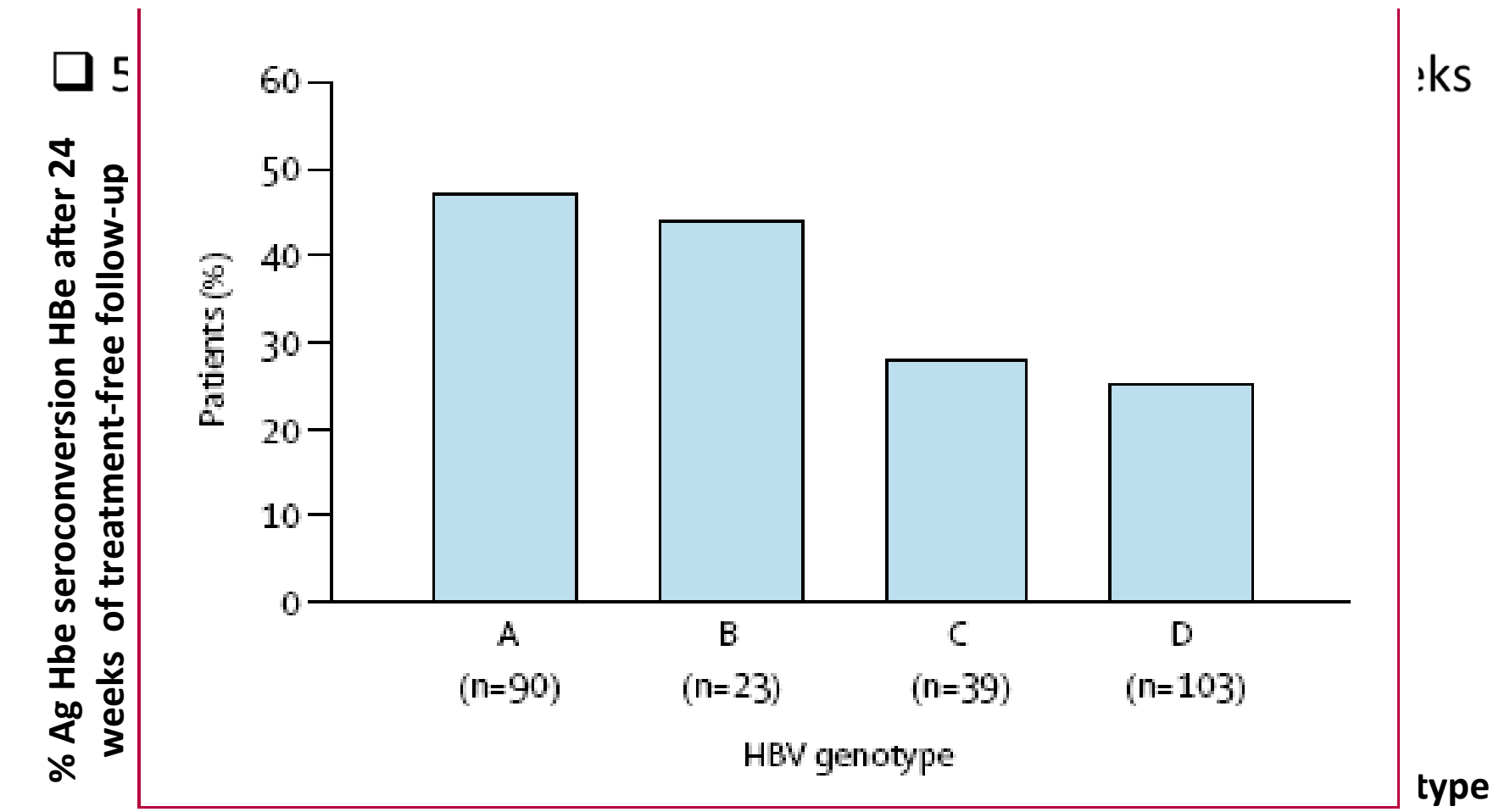


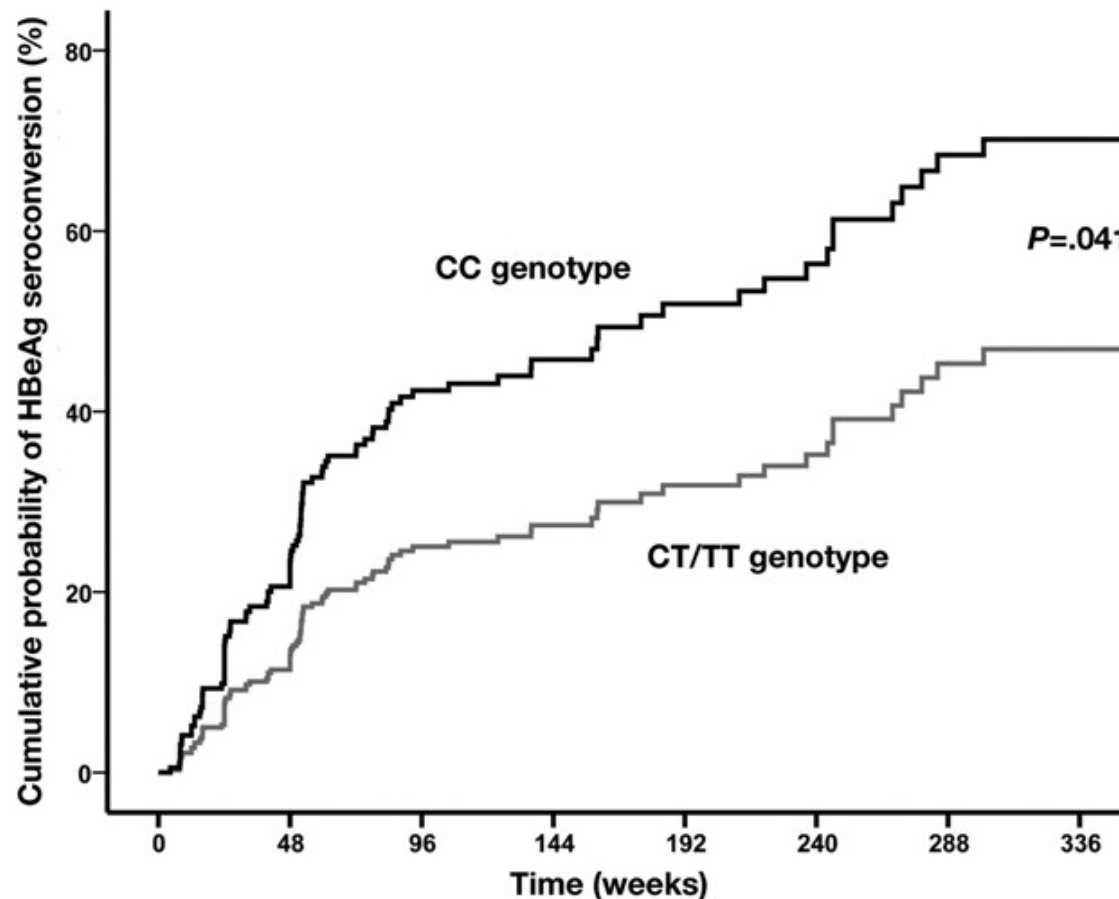
Figure 3: Proportion of patients responding to treatment (serum HBeAg loss) by HBV genotype

Janssen HL et al Lancet 2005

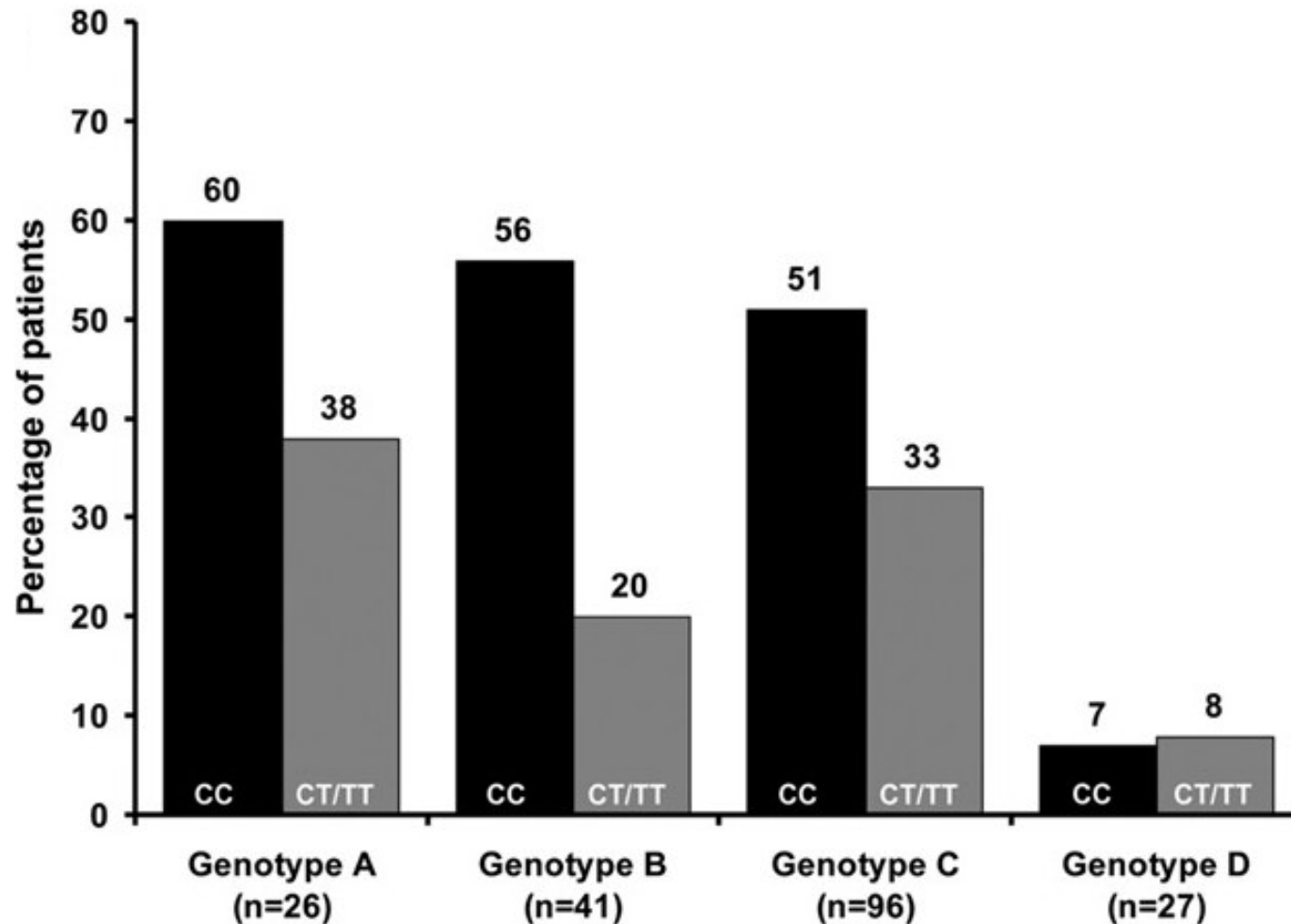
IL28B and AgHBe seroconversion after PegIFN

□ 205 patients AgHBe + traités par Peg-IFN ± LAM

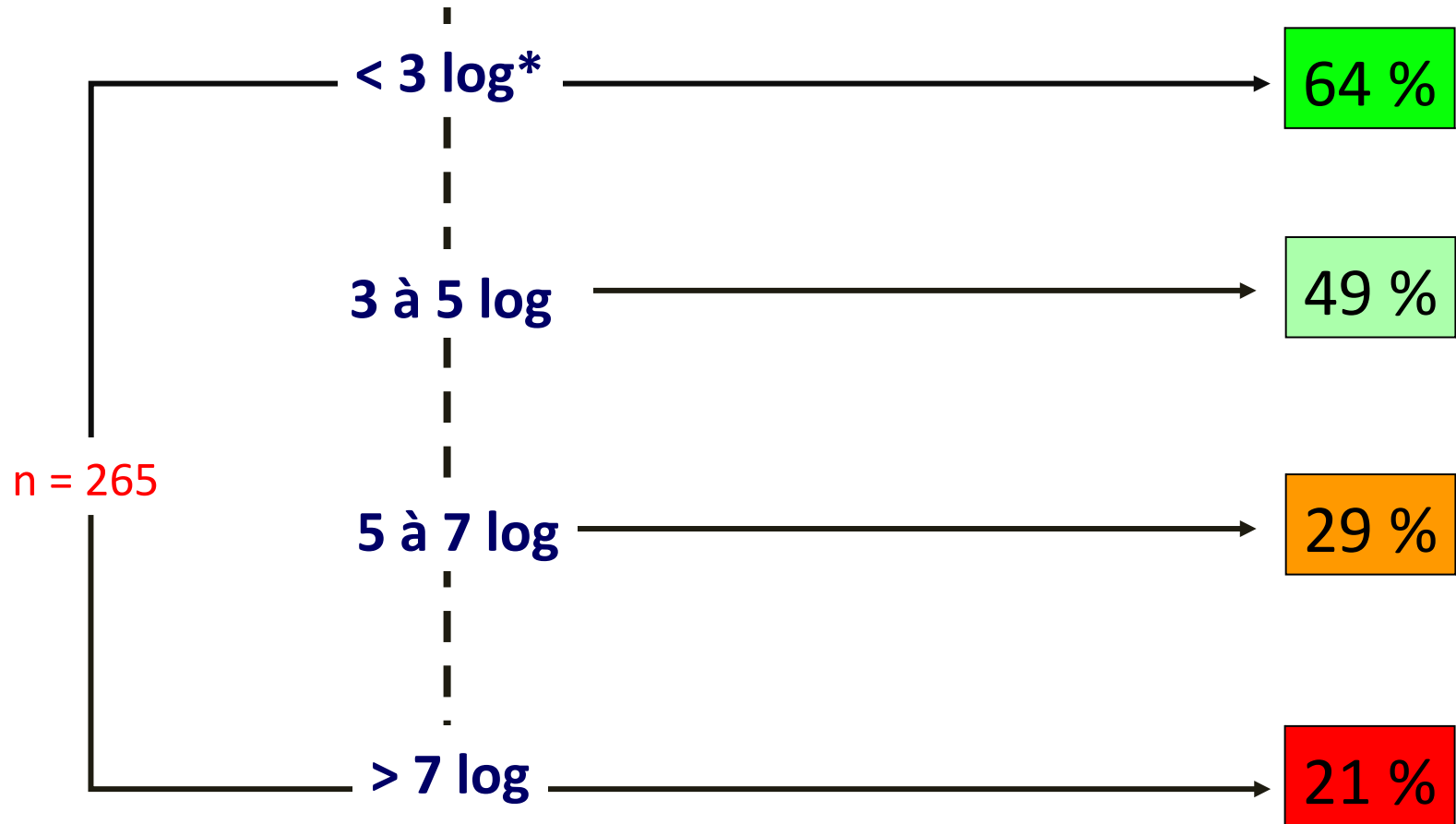
→ IL28B facteur prédictif indépendant



IL28B , HBV genotype predict response to PegIFN

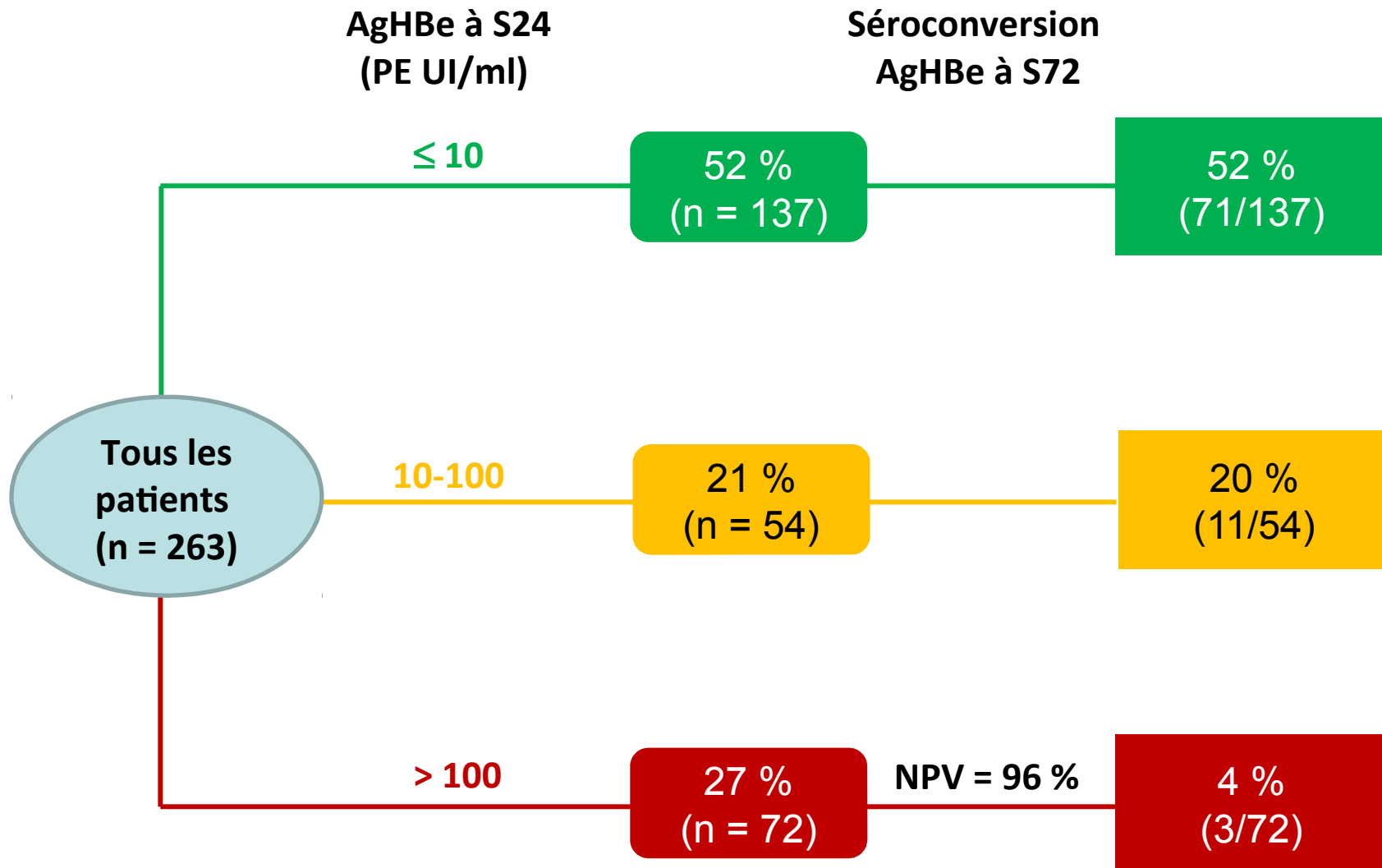


DNA at week 12 predicts AgHbe seroconversion



* copie/ml

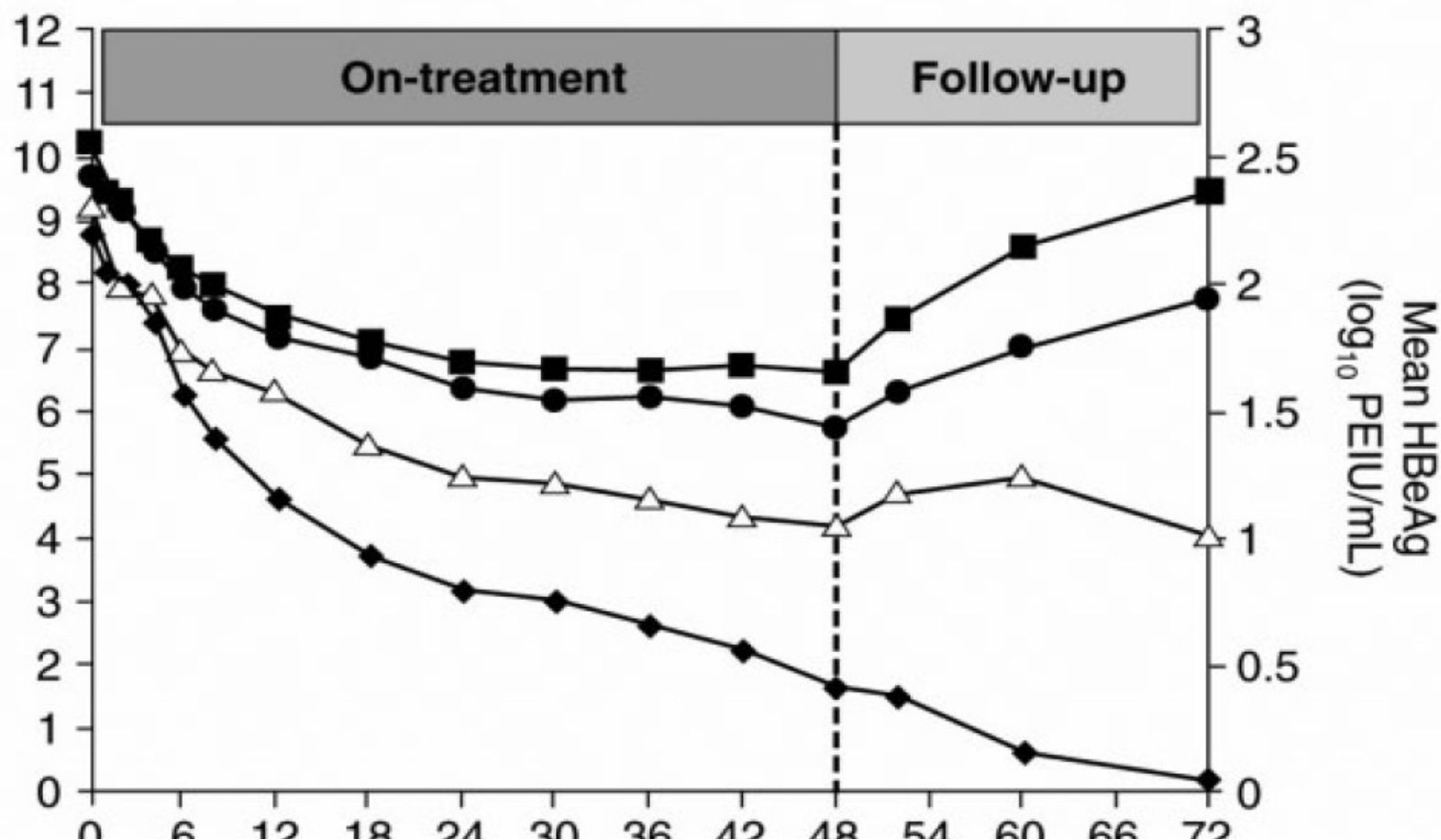
AgHBe at week 12 predicts AgHbe seroconversion



AgHBe/DNA at week 12 predict AgHBe seroconversion

eAg seroconversion at wk 48 & 72 (non-responders) n=171

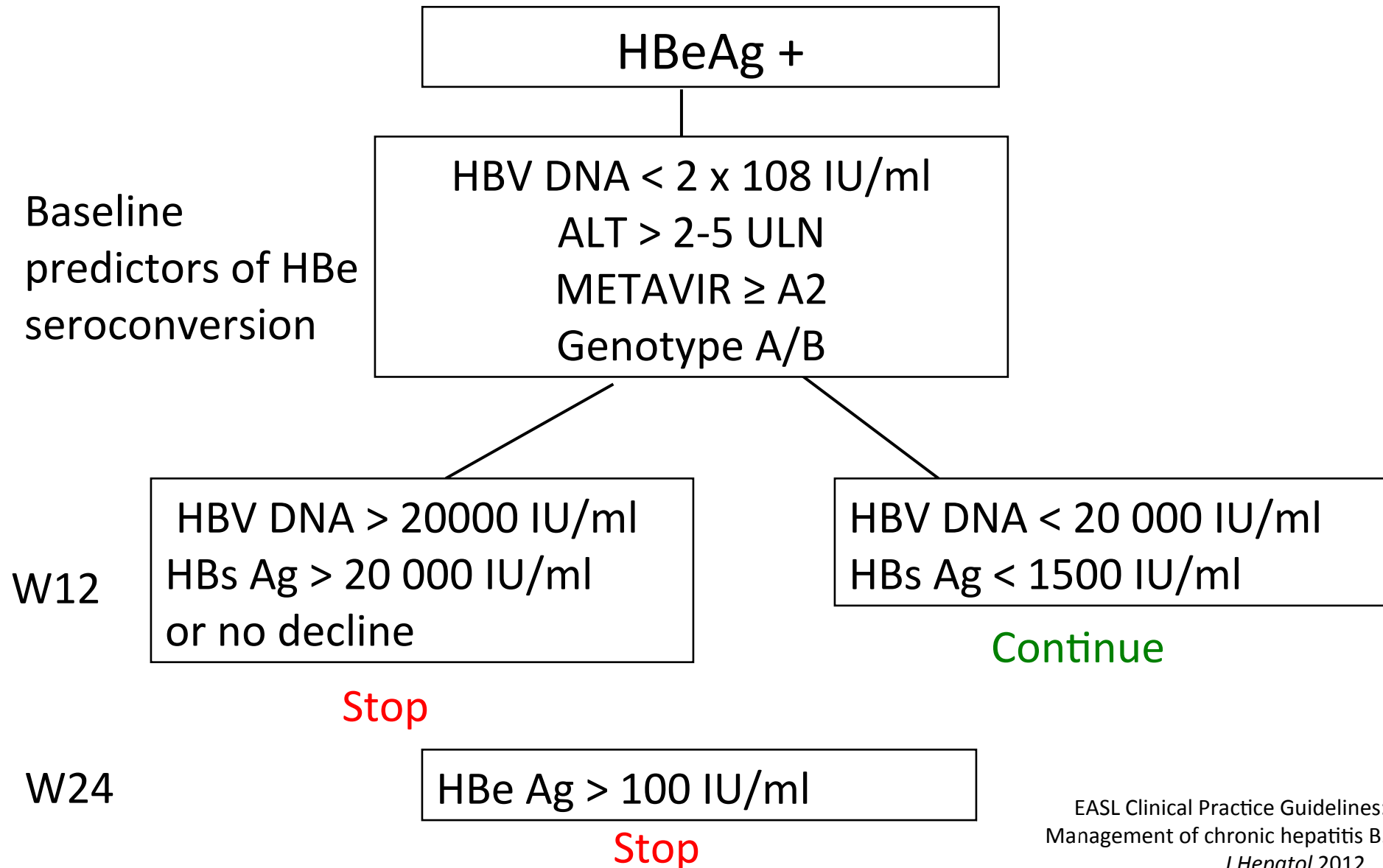
eAg seroconversion at wk 48 but with it at 72 (late responders) n=28



Finally what I will choose

EASL Guidelines :

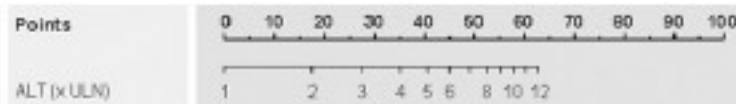
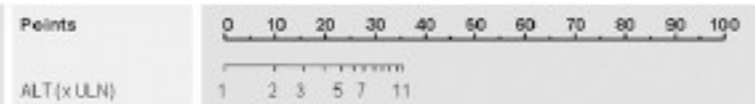
Antiviral therapy in HBV patients



PegIFN HBV Treatment index

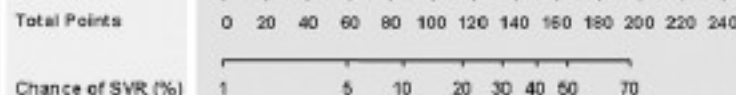
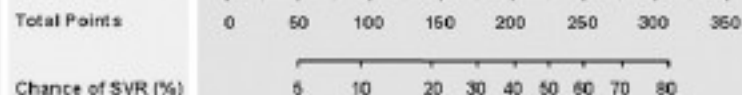
Sustained Response

clearance of AgHBe and HBV DNA < 2 000 UI/ml after 24 weeks of treatment-free follow-up traitement



Points per variable:

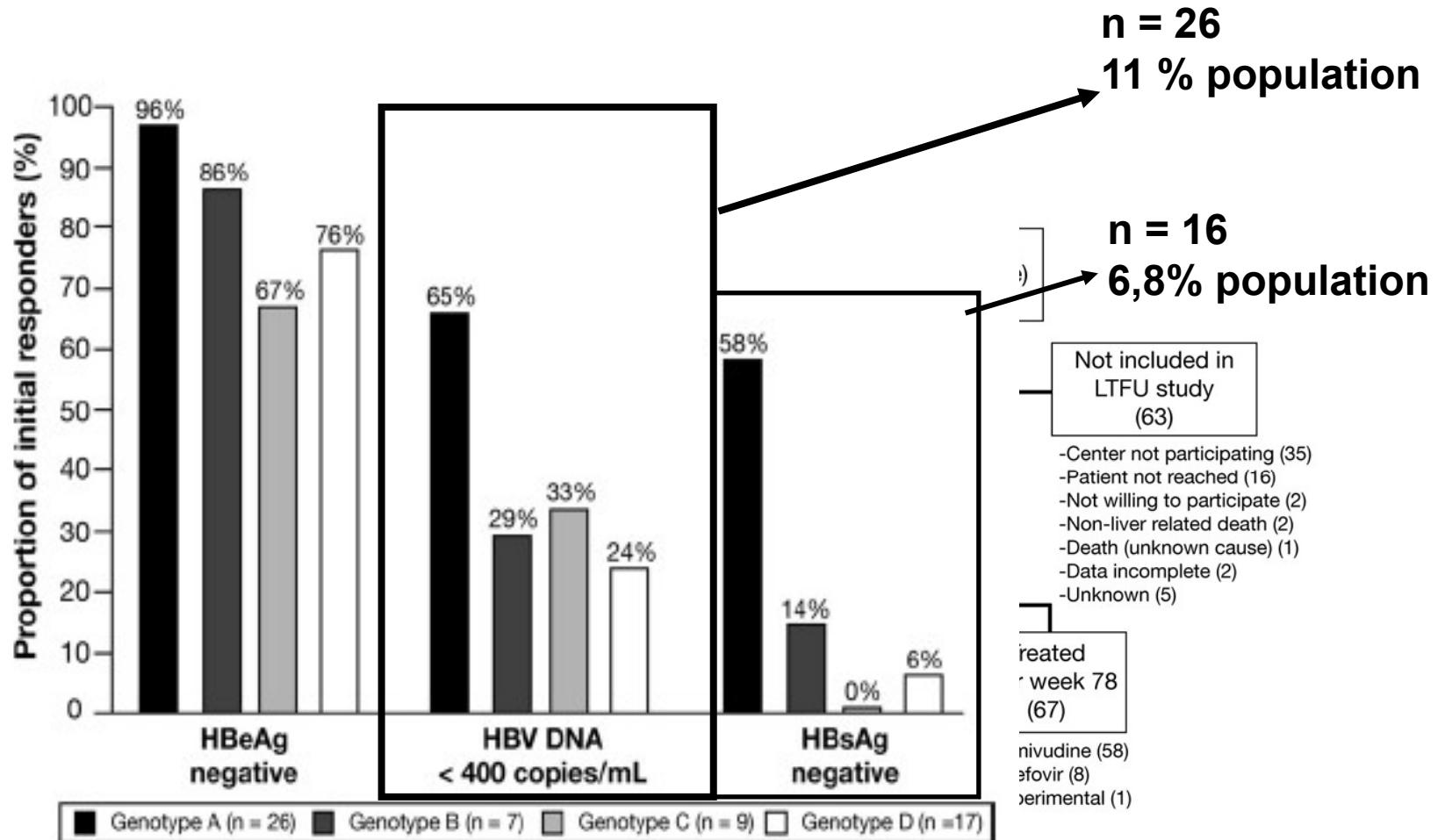
For example,
a genotype C–infected woman (62 points), age 25 (67 points),
with serum ALT level of 2.7 ULN (25 points), and serum HBV-
DNA level of 9.2 log₁₀ copies/mL (40 points) has a total score of
194 points, which converts to a probability of sustained
response of 37%.



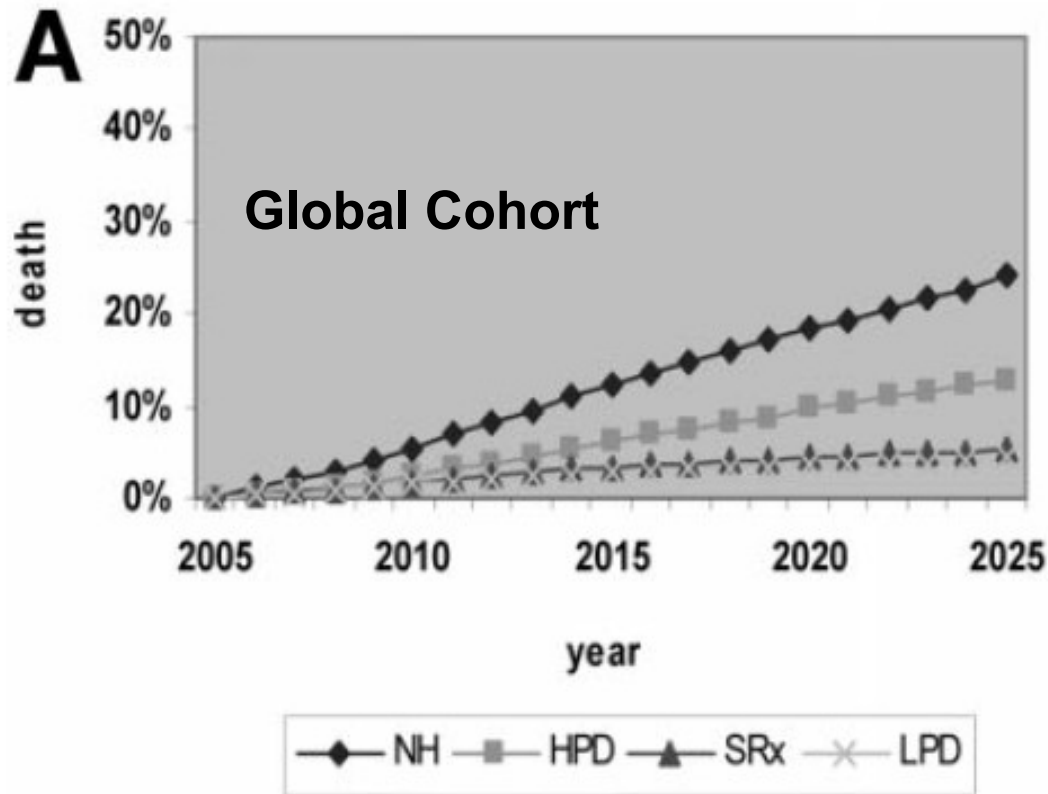
%

PegIFN

Analysis in Intention to treat using the same criterion of efficacy than Analogues



Potential Impact of Long-Term Nucleoside Therapy on the Mortality and Morbidity in Hepatitis B: a modeling approach

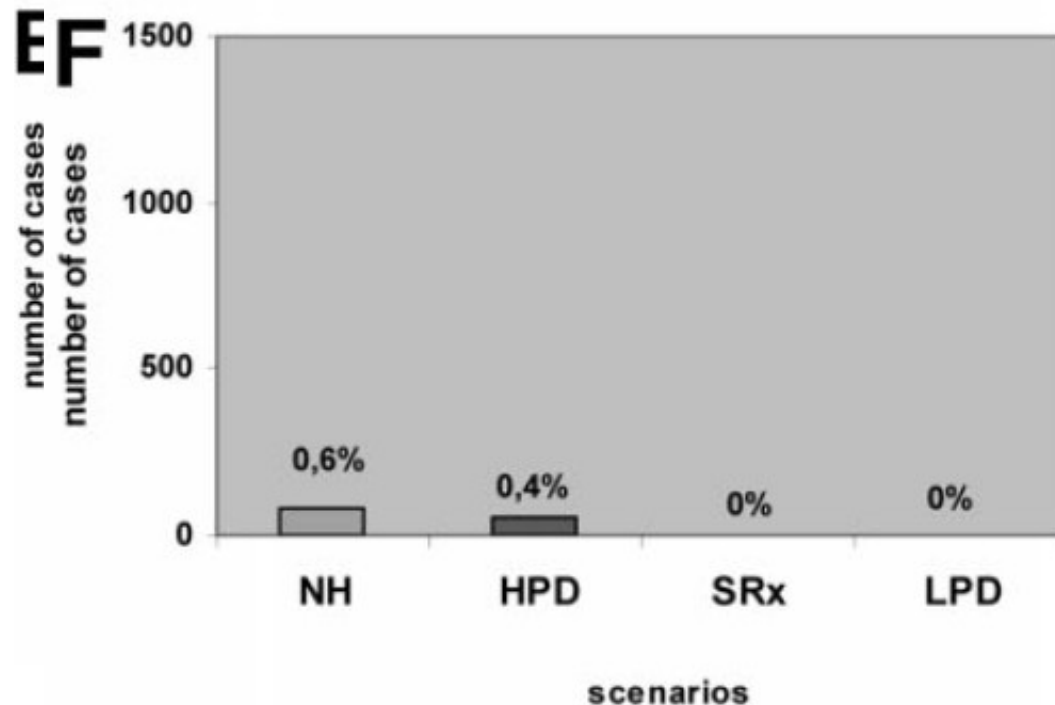


NH=Natural History HPD=High Resistance Profile drug

SRX= Salvage Therapy LPD=High Resistance Profile drug

Potential Impact of Long-Term Nucleoside Therapy on the Mortality and Morbidity in Hepatitis B: a modeling approach

Cumul Cumulative number of liver transplants 2005-2025



NH=Natural History HPD=High Resistance Profile drug

SRX= Salvage Therapy LPD=Low Resistance Profile drug

Estimated proportions of 1st line therapy in european CHB patients

Estimated proportions of 1st line therapy in CHB patients in European countries

70-90% vs 10-30%



I will choose ETV or TDF