

How to manage patients with resistant HBV

Clinical case 1

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Clinical Case

- Male, 35 yrs, chinese
- History of HCC in father
- ALT 166 IU/L (N=40)
- HBeAg (+)
- HBV DNA= 15 000 000 UI/mL
- Liver US: Normal
- Liver biopsy: A2 F2

Clinical case

	D0	M1	M3	M6
ALT	166	82	66	40
ADN VHB	15 000 000	2 000 000	300 000	50 000

ENTECAVIR 0.5mg/d

Question

Type of response ?

- Breakthrough
- Partial
- Primary non-response
- Other

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Anti viral treatment failure: EASL 2009 definition

○ Primary non-response

- \downarrow HBV DNA $< 1 \log_{10}$ IU/ml at week 12

○ Partial response = suboptimal

- INF α : HBV DNA > 2000 IU/ml at week 24
- NUC : \downarrow HBV DNA $> 1 \log_{10}$ IU/ml, but still detectable
 - At W24 : lamivudine and telbivudine
 - At W48 : entecavir, adefovir et tenofovir

○ Viral Breakthrough

- NUC : \uparrow HBV DNA $> 1 \log_{10}$ IU/ml / Nadir

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○ Viral Breakthrough

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Clinical Case

	J0	M1	M3	M6	M9	M12
ALT	166	82	66	40	30	30
HBV DNA	15 000 000	2 000 000	300 000	50 000	10 000	800

Entecavir 0.5mg/d

Question :

Management of patient ?

-  Check adhesion to treatment
-  Change treatment
-  Looking for resistance mutations
-  Continuing treatment

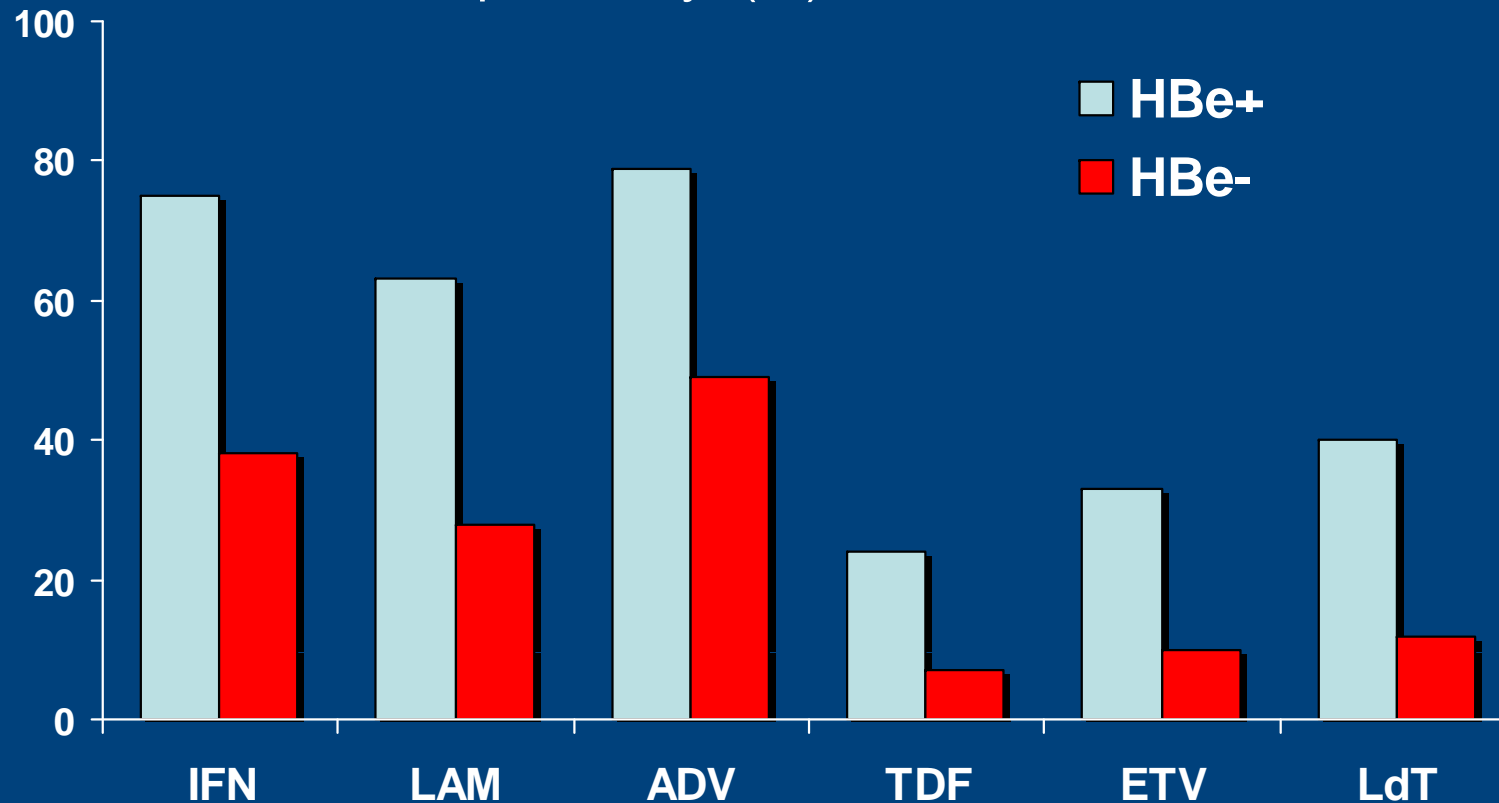
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Suboptimal response rate with HBV treatment

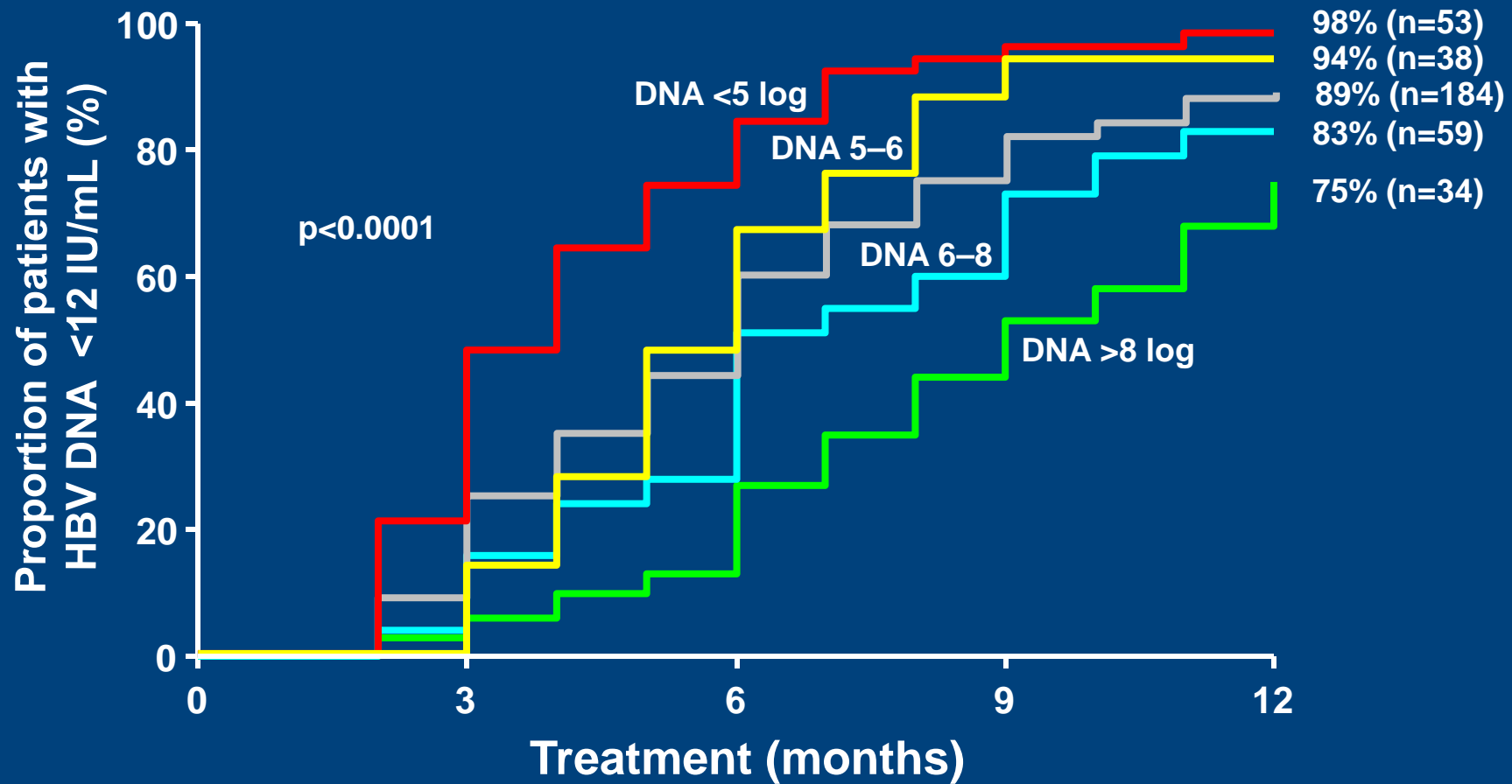
HBV DNA > 300 cop/ml à 1 yr (%)



Lau GK, et al. N Engl J Med. 2005;352(26):2682-95
Marcellin P et al. N Engl J Med. 2004; 351: 1206-17
Marcellin P et al. N Engl J Med 2008; 359 (23): 2442-55
Lai CL, et al. N Engl J Med. 2007;357:2576-88.

Marcellin P, et al. N Engl J Med. 2003;348(9):808-16
Hadziyannis S, et al. Gastroenterology. 2006;31:1743-1751
Chang TT, et al. N Engl J Med. 2006;354(10):1001-10.

12-month cumulative probability of virological response with entecavir by baseline viral load







Cohort: 82% HBeAg(-)

EASL 2009 recommendations

- Partial virological response (mutation uncommon)
 - Check adhesion
 - Lam, ADV or LdT (24 w)
 - Switch with / TDF or ETV / or add on
 - TDF or ETV (48 w)
 - Add on ETV or TDF





Question :

Treatment ?

-  TDF Add on
-  TDF Switch
-  Continuing Entecavir 0.5mg/d
-  Increase dosage of entecavir 1mg/d

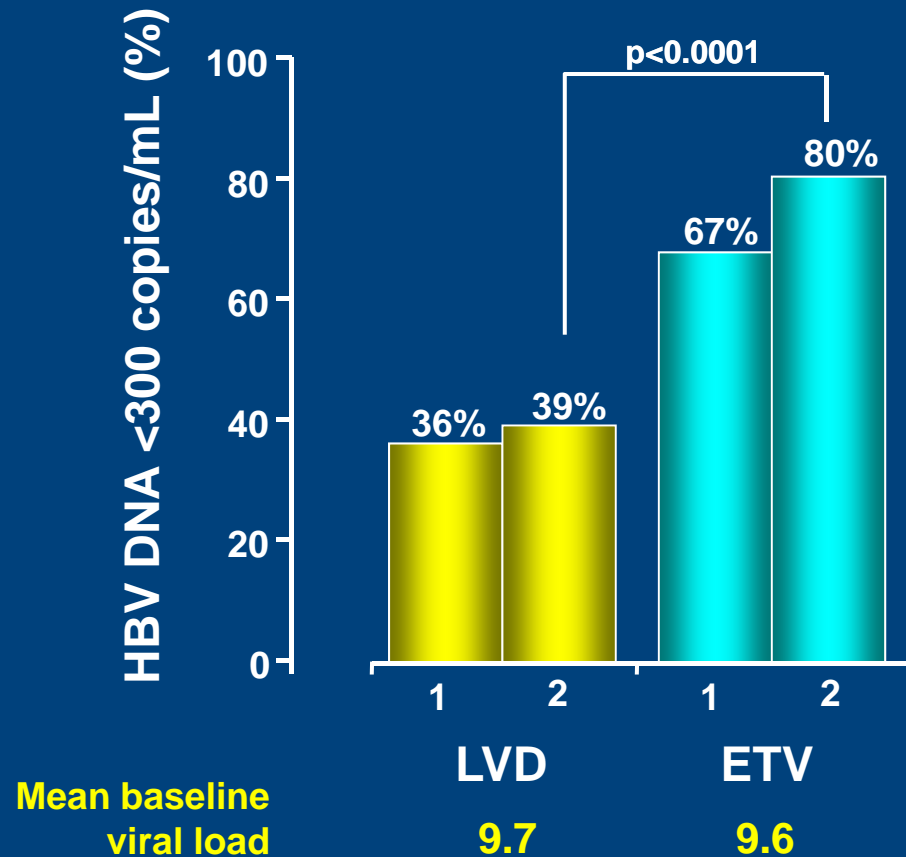
Question :

Treatment ?

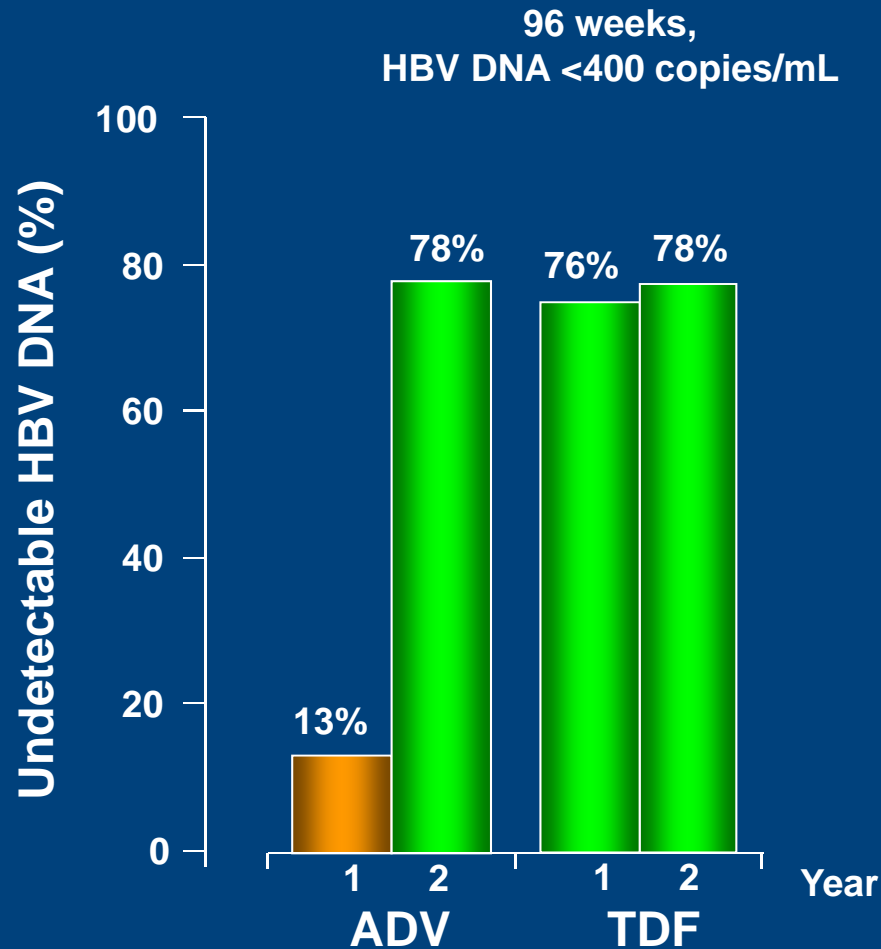
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-  TDF Switch
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HBV DNA levels in HBeAg(+) patients at 2 years cumulative confirmed analysis

Lamivudine vs entecavir^{1,2}



Tenofovir: HBV DNA levels in HBeAg(+) patients at 2 years

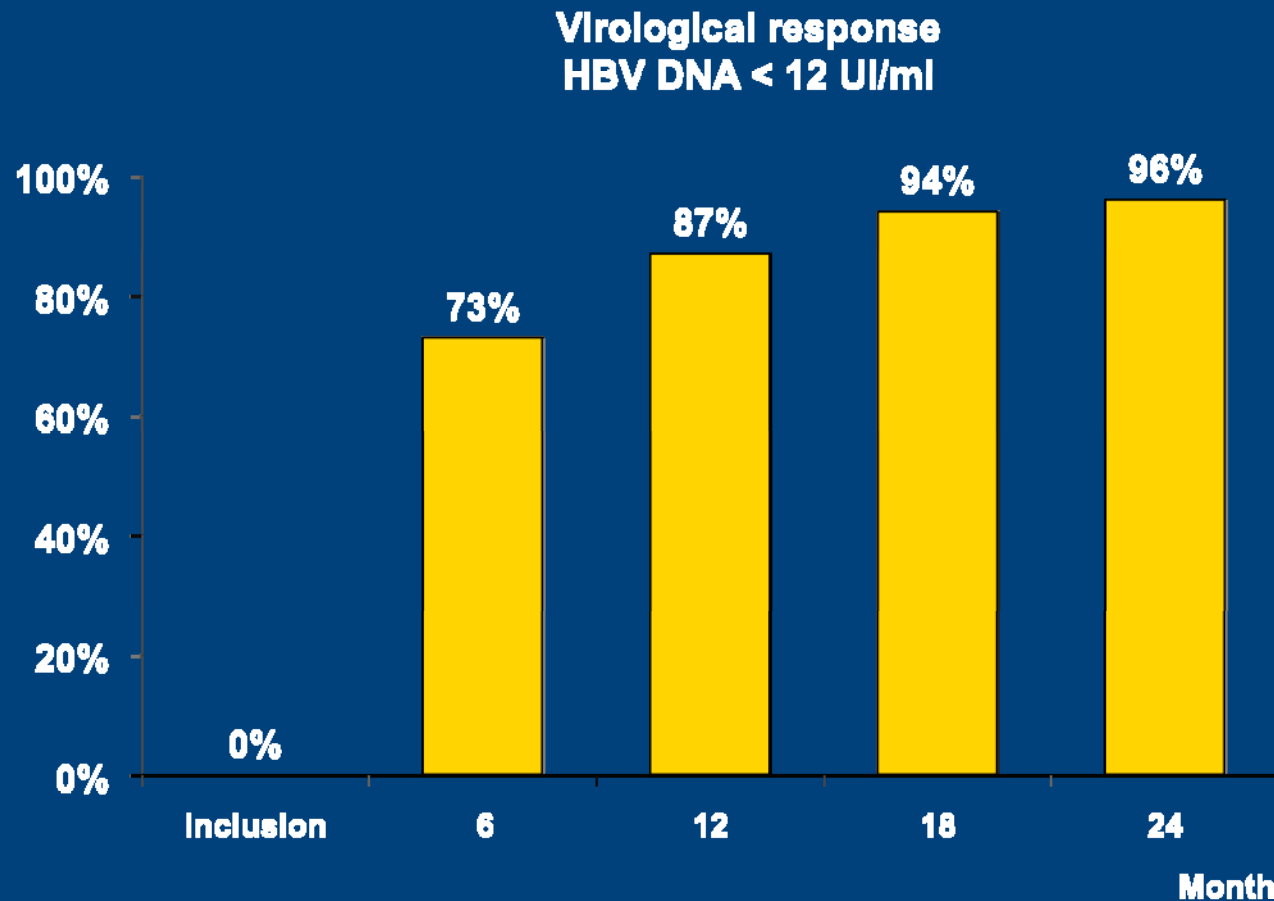


ADV-treated patients switched to TDF after 48 weeks; § HBV DNA \geq 400 copies/mL at Week 72, 28 patients added emtricitabine to TDF in a fixed-dose tablet

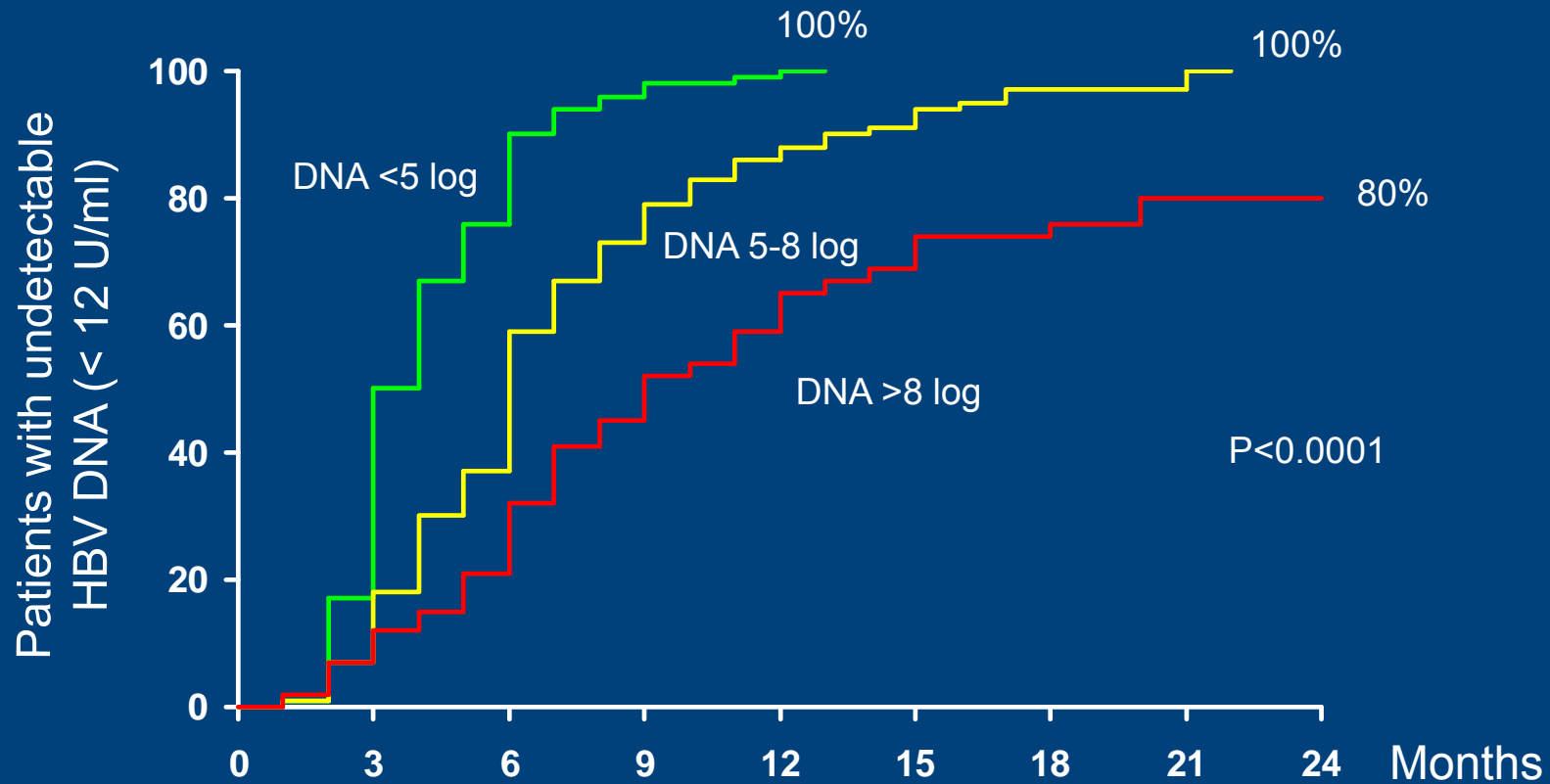
. Marcellin P, et al. *N Engl J Med.* 2008;359:2442-55.. Heathcote J, et al. 59th AASLD, Oct 31–Nov 4, 2008, San Francisco, USA. Oral 158. *Hepatology.* 2008;48(4, suppl):376A.

Entecavir in real life

- Italian retrospective multicenter study (16 centers)
- 376 patients HBV+, age 58 yrs, 75% male, 84% HBe-, 81% genotype D, 47% cirrhosis, ETV 0.5 mg/j



24-month cumulative probability of virological response with entecavir by baseline viral load



Patients still at risk	108	26	2	0	0
	199	119	23	5	0
	64	49	23	8	2

Outcome of partial responders

38/335 (11%) with partial virological response : HBV DNA 2.9 log IU/ml

		W48		W72	W84
HBV DNA (UI/ml)	Patients (n)	TDF/ETV		Undetectable HBV DNA	
13-100	7 (23%)	No		6 (86%)	7 (100%)
101-1000	8 (27%)	No		3 (37%)	4 (50%)
> 1000	15 (50%)	No : 8 Yes : 7		0 5 (60%)	1 (12%) 5 (60%)

Clinical case

	D0	M6	M12	M15	M18	M24
ALT	166	40	30	25	19	20
HBV DNA	15 000 000	20000	800	45	<12	<12

Entecavir 0.5mg/d

Conclusion

- In patients treated with second generation analogs (ETV or TDF) and with partial response at W48, don't change the treatment if HBV DNA is lower than 1000 IU/mL.