

Patient case

Age / Gender	58-years / male
HBV diagnosed	2009
Route of transmission	Injectable drugs
ALT	108 IU/ml
Hbe Ag	Negative
HBV DNA	6.4 log IU/ml
Fibrosis	Cirrhosis (Fibroscan = 24 kPa)
Complications	Child-Pugh A5
Endoscopy	Small varices (grade I)
Treatment	TDF 245 mg/d

Patient case

TDF started in 2009

	M6	M12	M18	M24	M30	M36
ALT (IU/L)	32	24	22	25	25	21
HBV DNA (IU/ml)	132	< 12	< 12	< 12	<12	<12
GFR (ml/min)	78	73	74	71	70	67
Platelet s	152	166	167	170	171	169
LS (kPa)	-	13.4	-	9.2	-	7.2
US	Normal	Normal	Normal	Normal	Normal	Normal

How do you manage HCC screening?

1. Stop screening

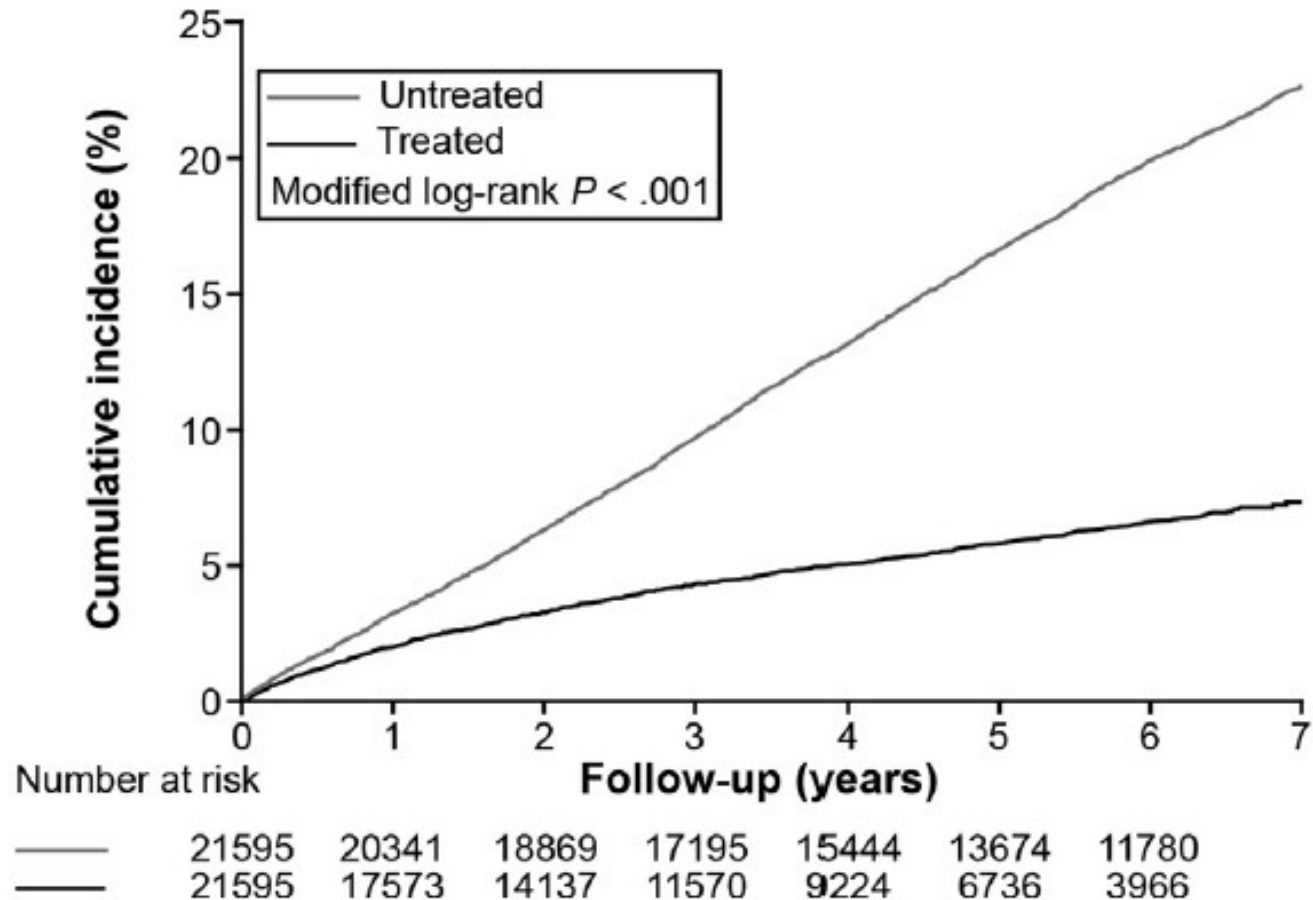
2. US every 3 months

3. US every 6 months

4. US every 12 months

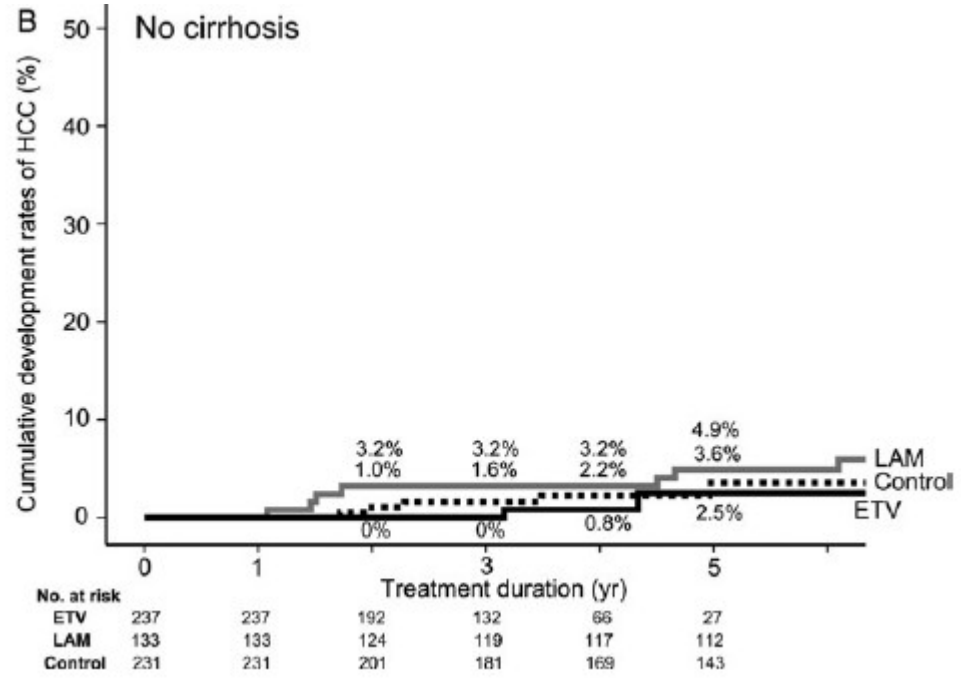
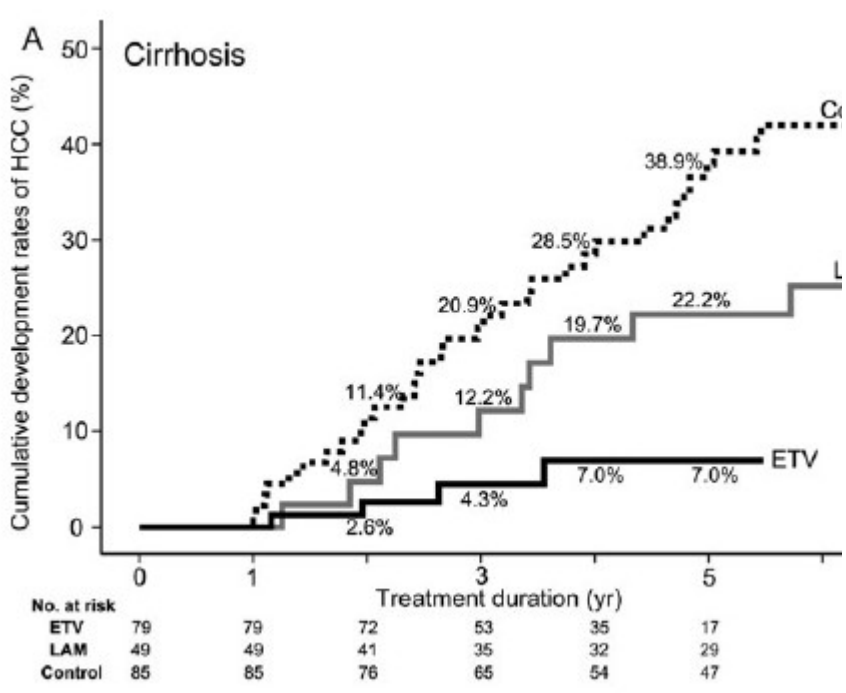
Patients treated by analogs are at lower risk of HCC

21 595 treated HBV(+) patients *versus* 21 595 matched untreated



Cirrhotic patients have the strongest benefit

472 patients on ETV compared to LAM treated and controls



FDR : age, alcool, cirrhose, AgHBe, thrombopénie, ETV

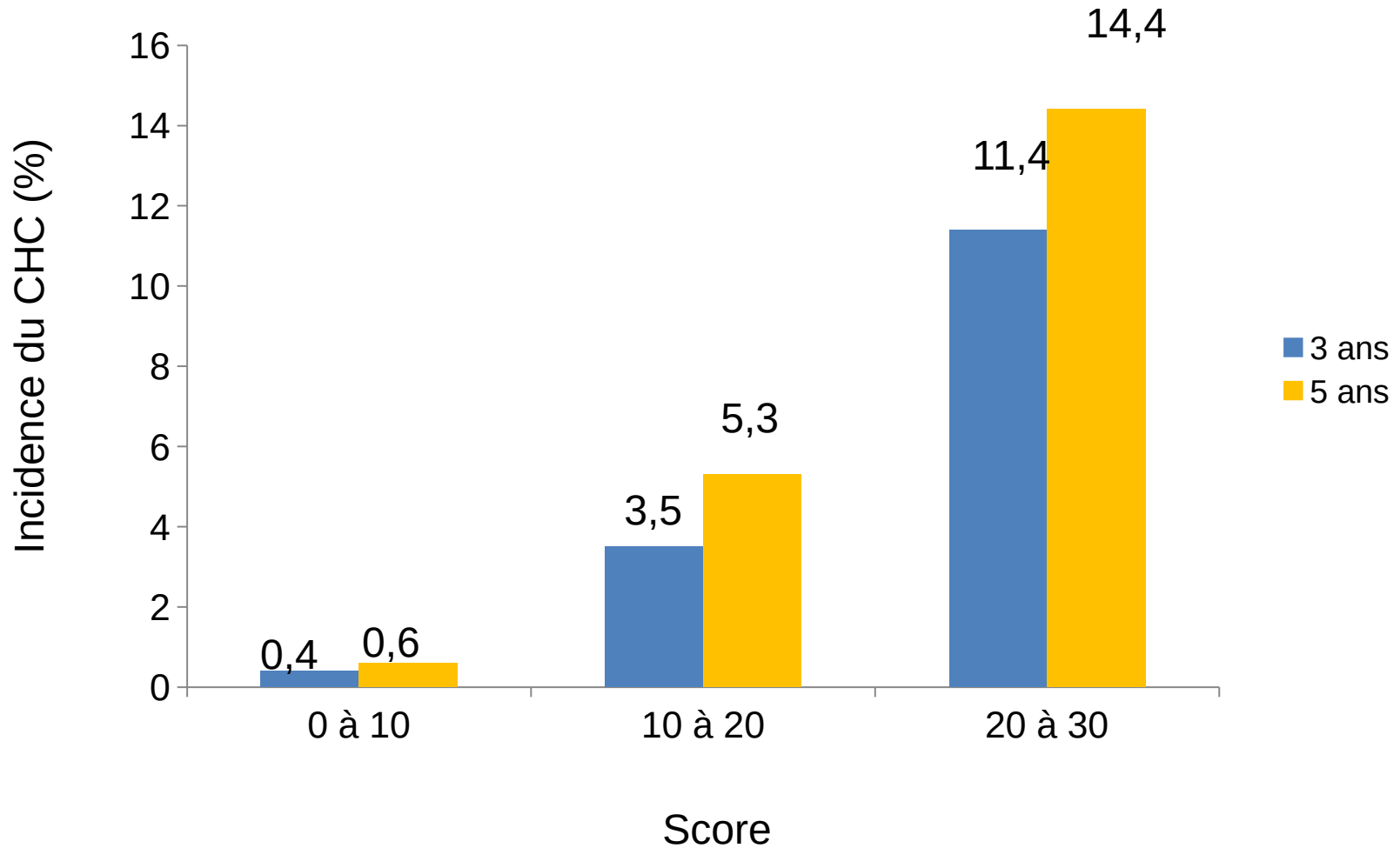
Is transient elastography useful to predict HCC risk?

- 1555 patients followed-up 69 months

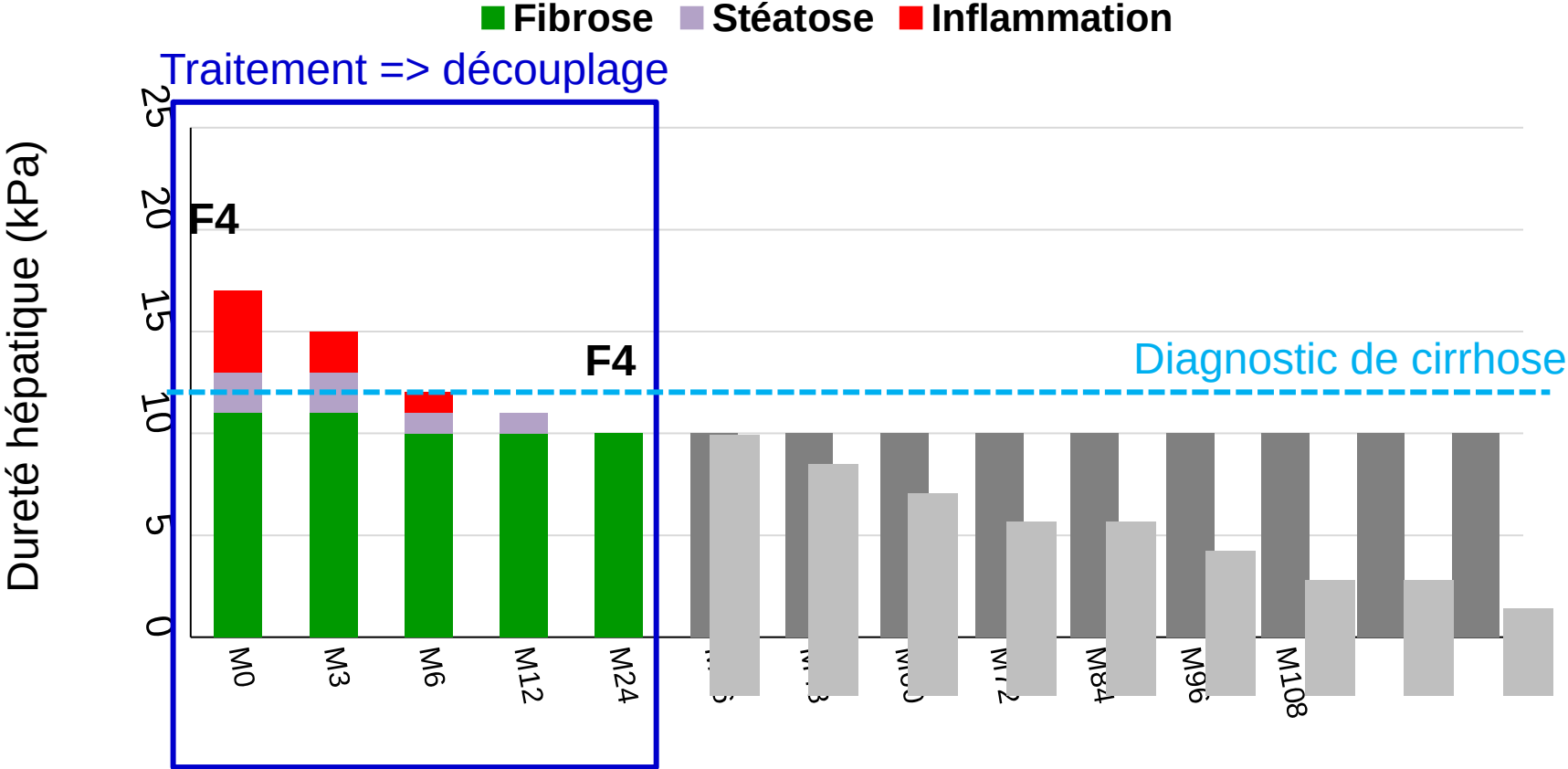
LSM-HCC Score

Age	
> 50 years	+ 10
< 50 years	0
Albumin	
< 35 g/L	+1
> 35 g/L	0
HBV DNA	
> 200 000 UI/ml	+5
< 200 000 UI/ml	0
Liver stiffness	
< 8 kPa	0
8-12 kPa	+8
> 12 kPa	+14

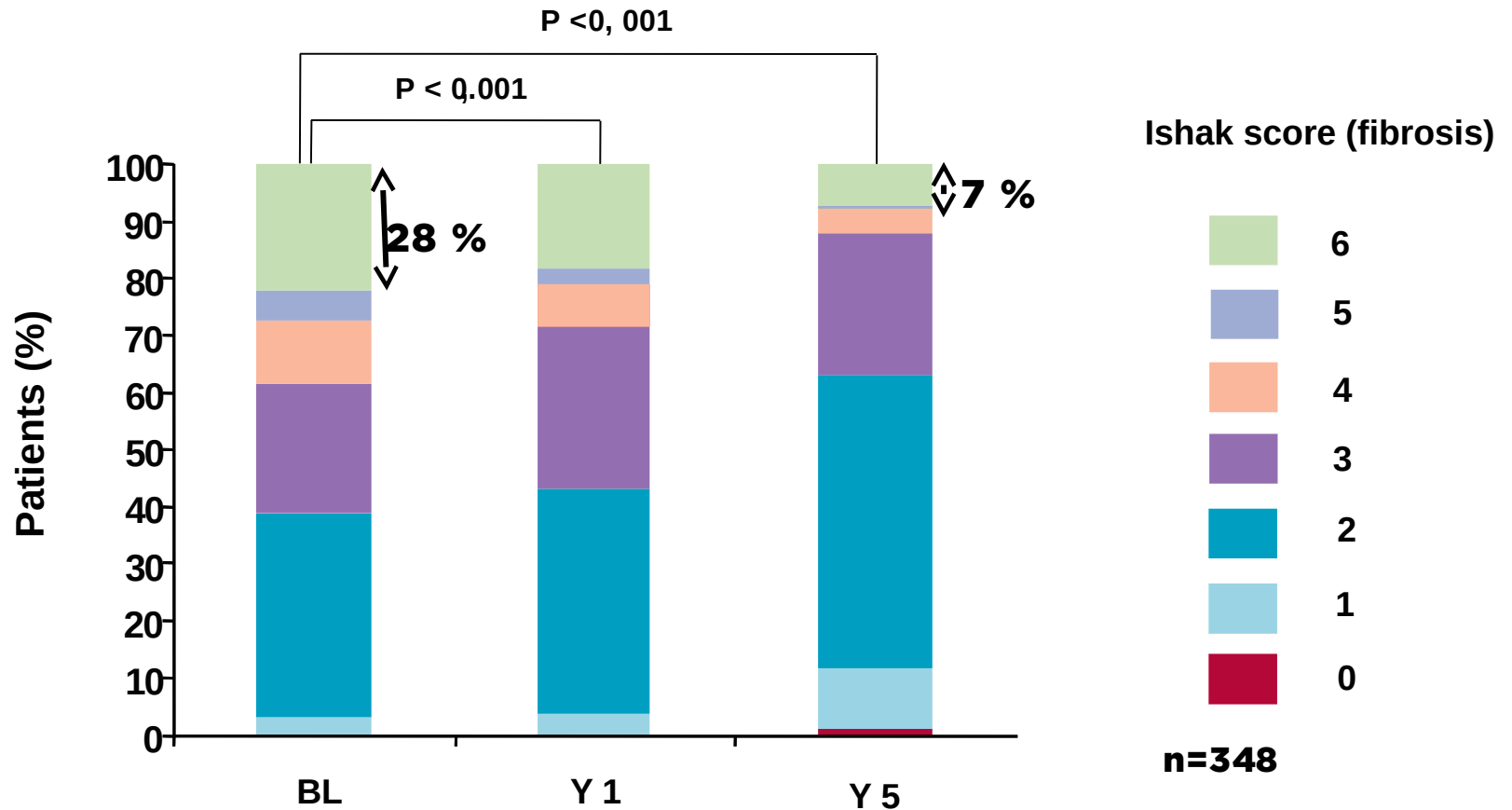
Is transient elastography useful to predict HCC risk?



What is the significance of liver stiffness decline on treatment?

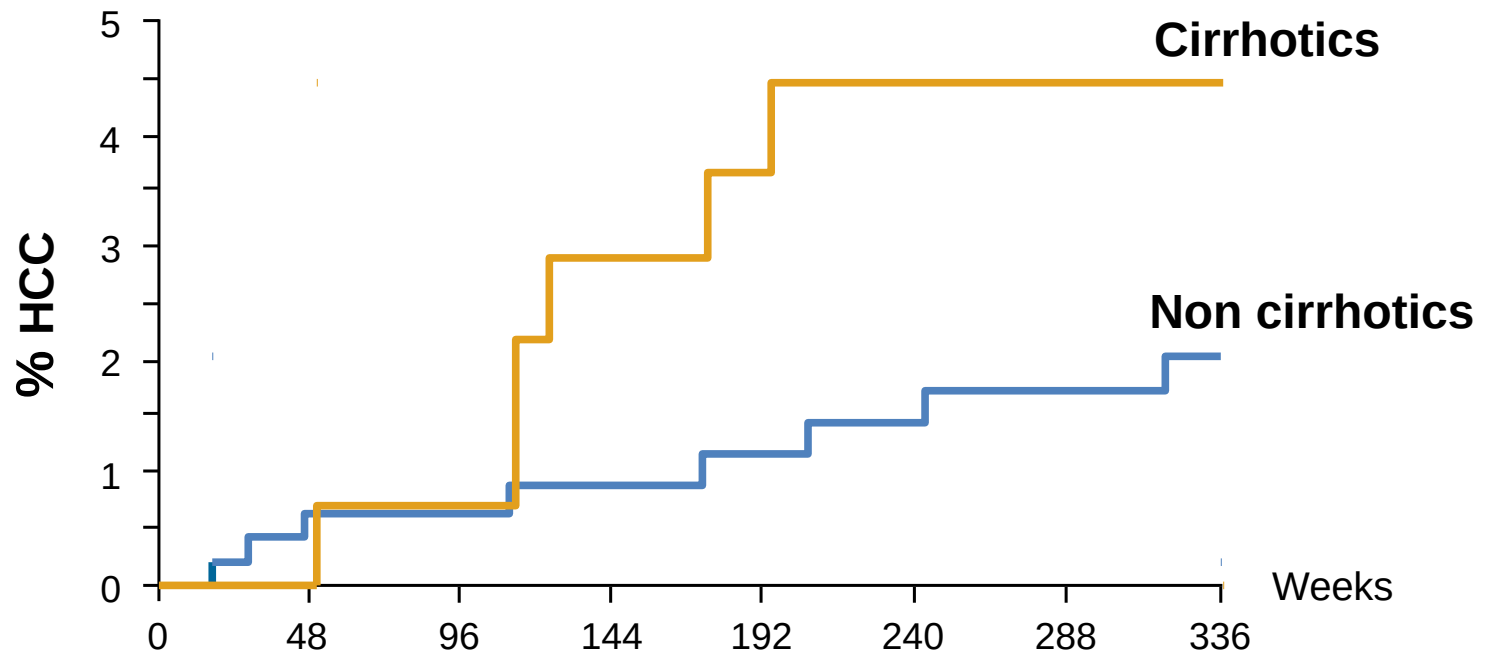


TDF and regression of fibrosis



Residual risk of HCC in patients on TDF

□ HCC incidence



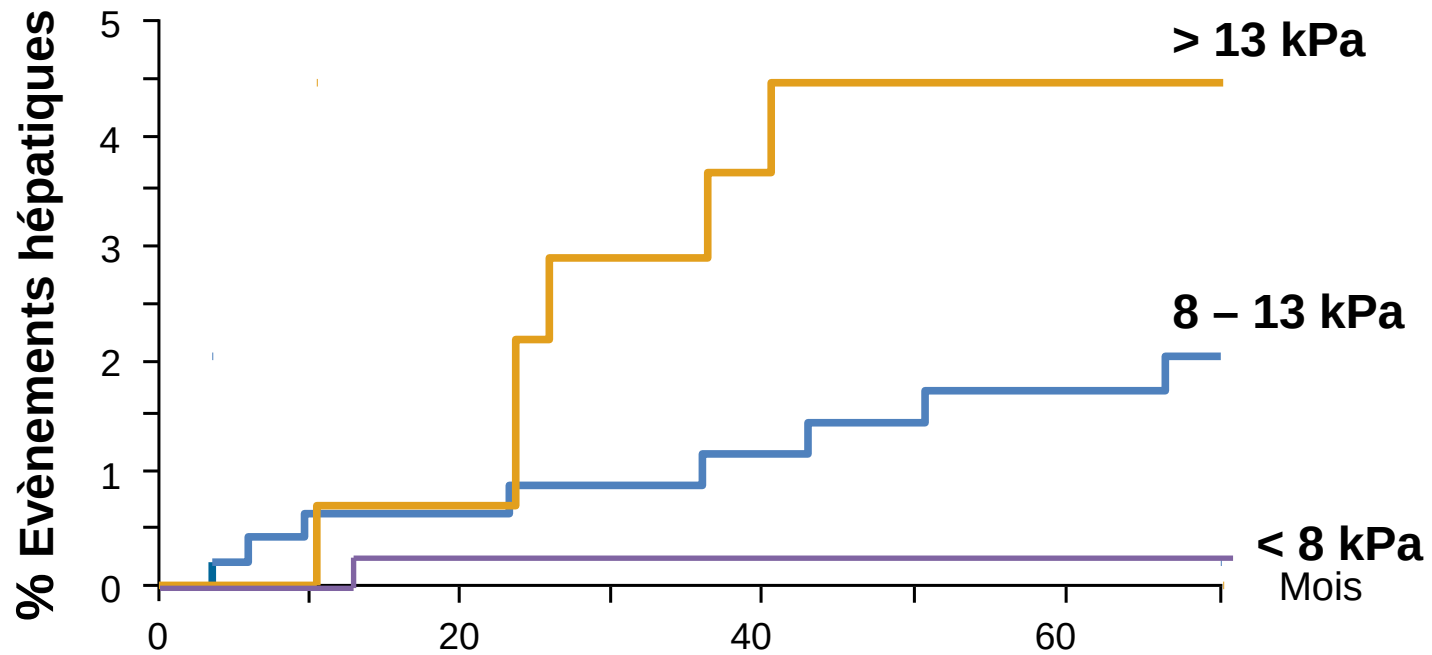
Patients at risk

Non cirrhotics	482	453	425	396	377	360	343	324*
Cirrhotics	152	146	137	132	126	120	115	109*

Long-term Tenofovir Disoproxil Fumarate (TDF) Therapy and the Risk of Hepatocellular Carcinoma;
W. Ray Kim¹ and al, EASL 2013

Liver stiffness measured on treatment is predictive of HCC incidence

Patients on ETV with HBV DNA not detectable : n=192



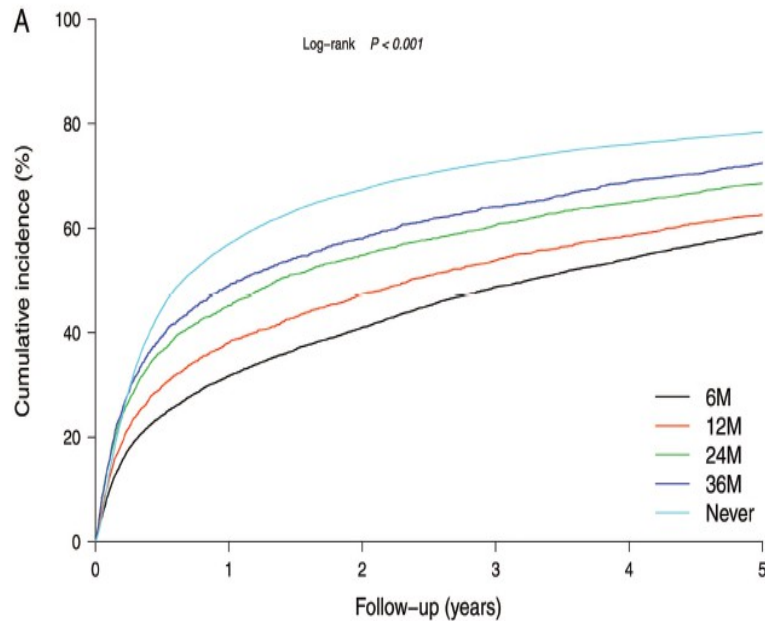
Help to select patients who need US surveillance?

What is the optimal periodicity for US screening ?

National cohort in Taiwan : 52 823 patients with HCC

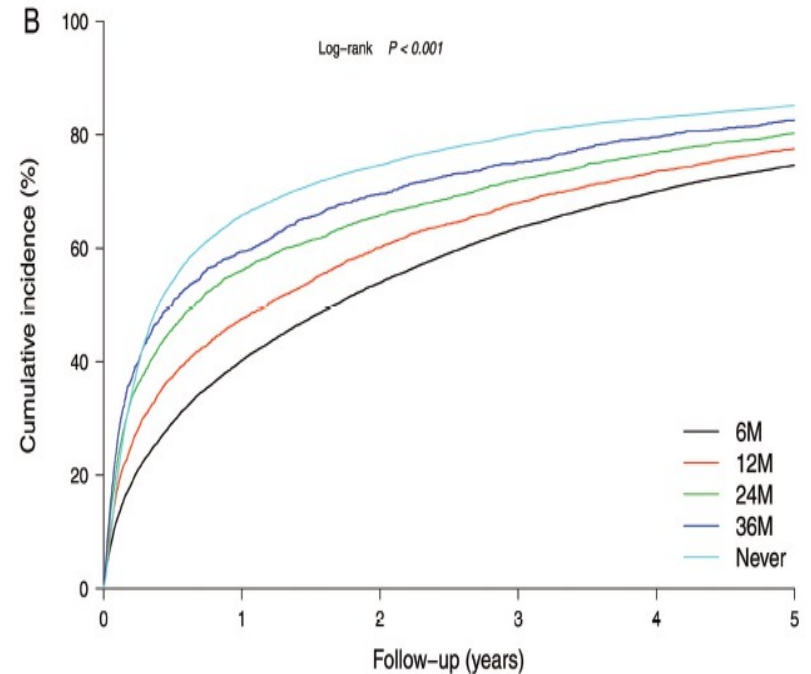
Probability of curative treatment and 5-years survival according to US periodicity

Non cirrhotics



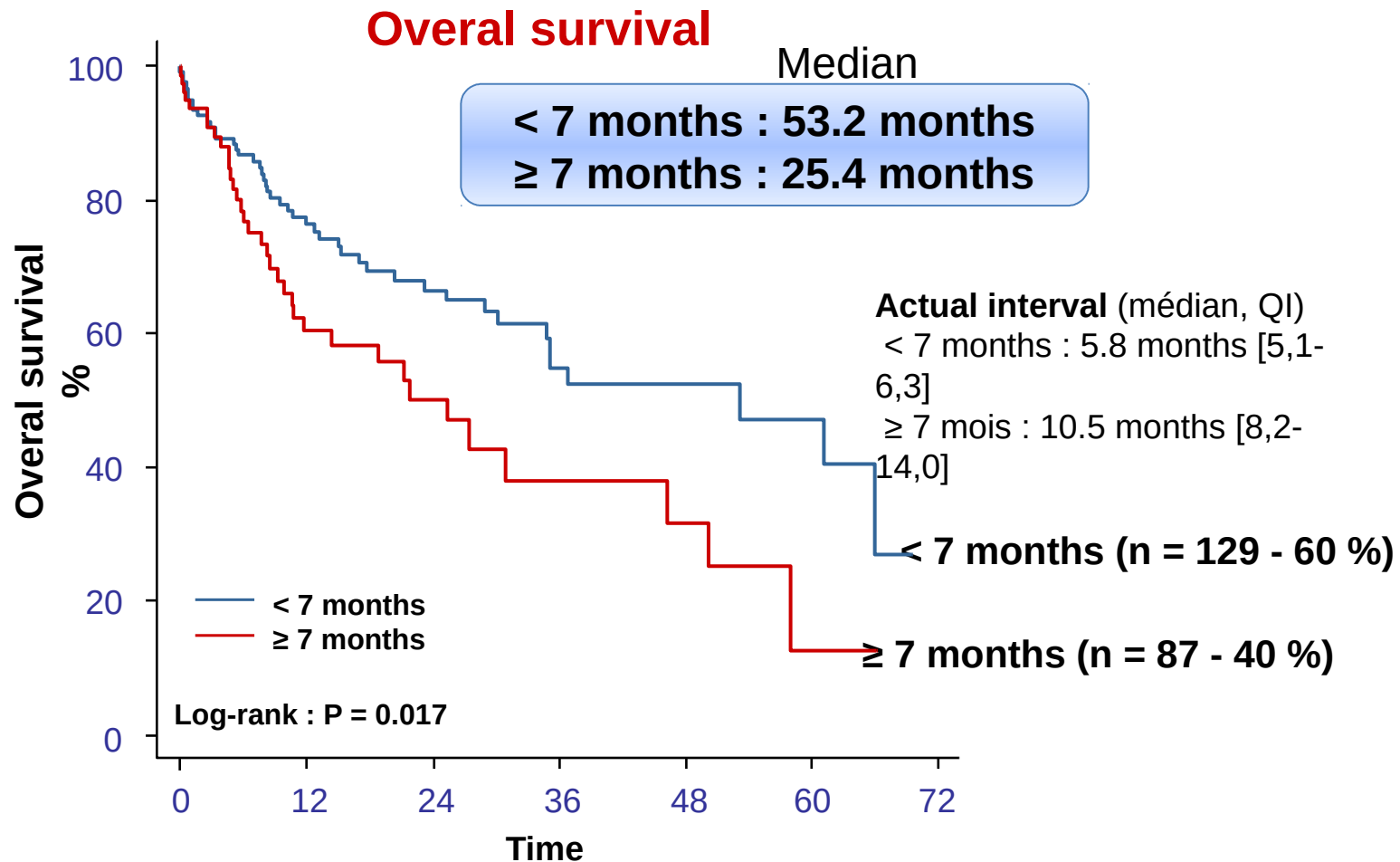
Number at risk	0	1	2	3	4	5
6M	5853	3999	3452	3003	2687	2200
12M	2093	1297	1102	966	867	715
24M	2368	1297	1070	933	831	691
36M	1572	804	660	564	488	398
Never	12967	5585	4232	3543	3110	2799

Cirrhotics



Number at risk	0	1	2	3	4	5
6M	13262	7941	6114	4830	3980	3115
12M	2744	1439	1095	880	724	569
24M	2427	1066	829	676	563	437
36M	1385	563	421	344	283	225
Never	8152	2788	2066	1633	1386	1211

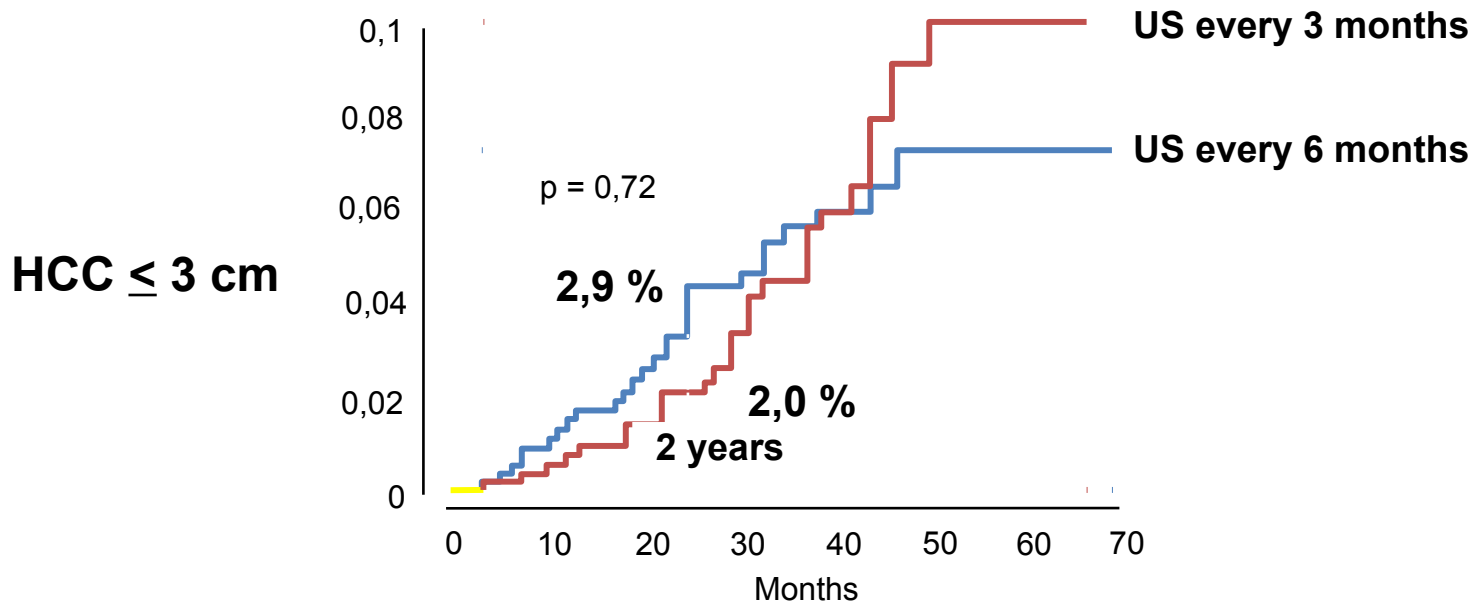
Delay > 1 month between 2 US has an impact on survival



Patients at risk

—	128 (27)	75 (8)	46 (6)	24 (1)	12 (1)	7 (2)	1
—	86 (25)	32 (4)	17 (3)	6 (1)	5 (2)	1 (0)	0

What is the optimal periodicity for US screening ?



No difference between 3 and 6 months

HCC < 3 cm : 70% of HCC diagnosed

Patient case

TDF started in 2009

	M42	M48	M54	M60	M66	M72
ALT (IU/L)	18	20	22	17	25	21
HBV DNA (IU/ml)	46	< 12	34	< 12	<12	143
GFR (ml/min)	67	66	62	57	50	51
Platelet s	152	166	167	170	171	169
LS (kPa)	-	6.3	-	7.1	-	6.5
US	Normal	Normal	Normal	Normal	Normal	Normal

Does occurrence of blips matter?

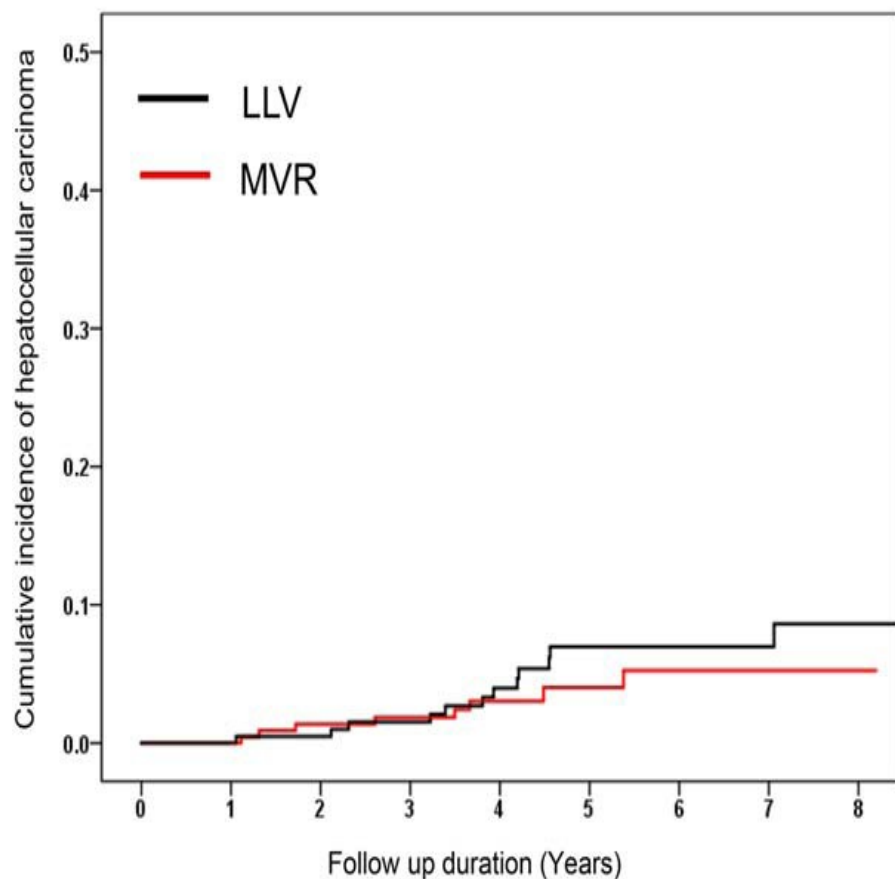
1. Yes

2. No

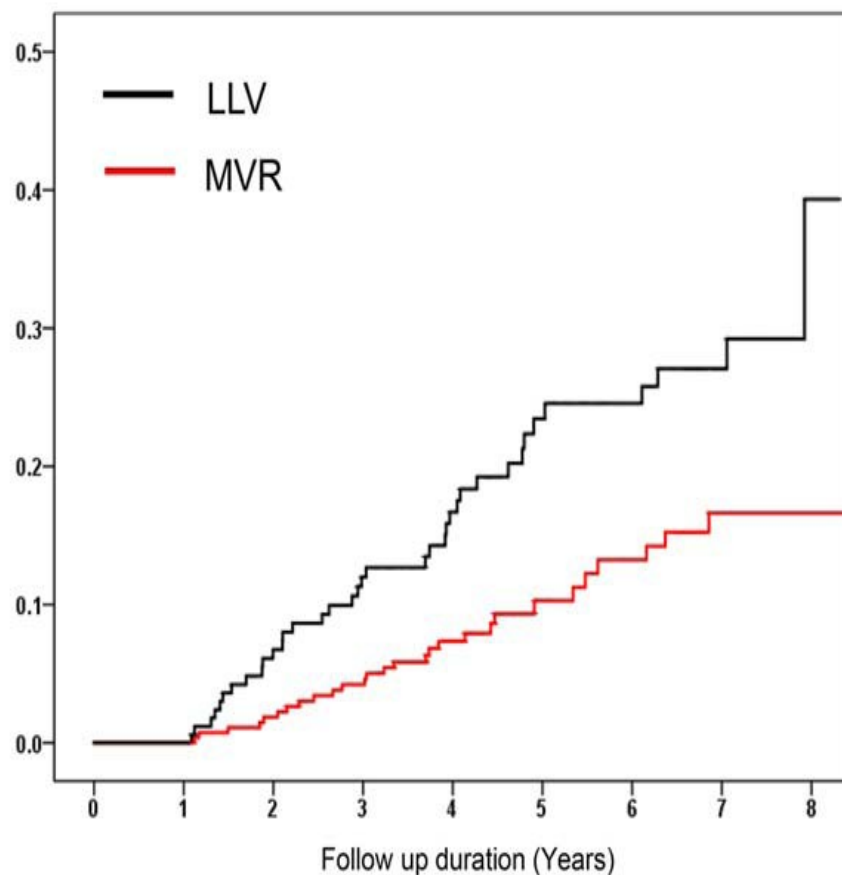
What is the impact of residual low level viremia on Nuc?

875 patients on ETV, LLV = permanent or intermittent detectable HBV DNA < 2 000 UI/ml

A Non-cirrhosis



B Cirrhosis



How do you manage the surveillance of portal hypertension ?



1. No surveillance

2. Gastroscopy every year

3. Gastroscopy every 2 years

4. Gastroscopy every 3 years

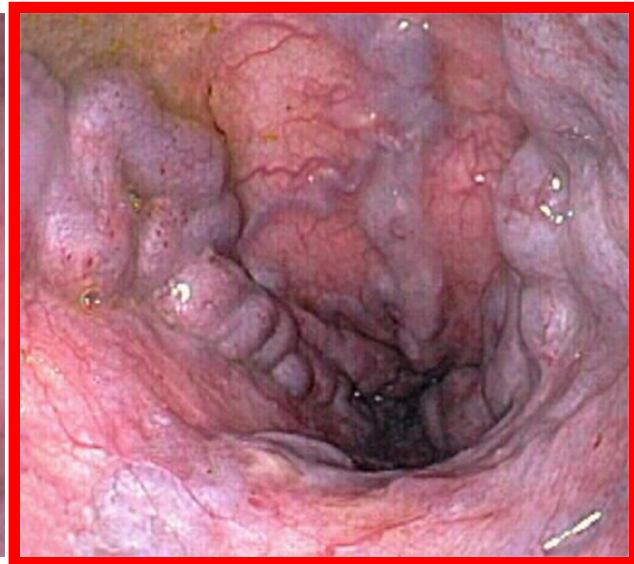
Progression of varices



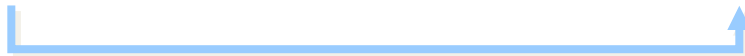
No varices



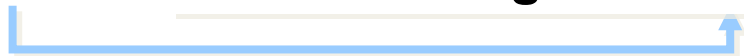
Small varices



Medium-Large Varices



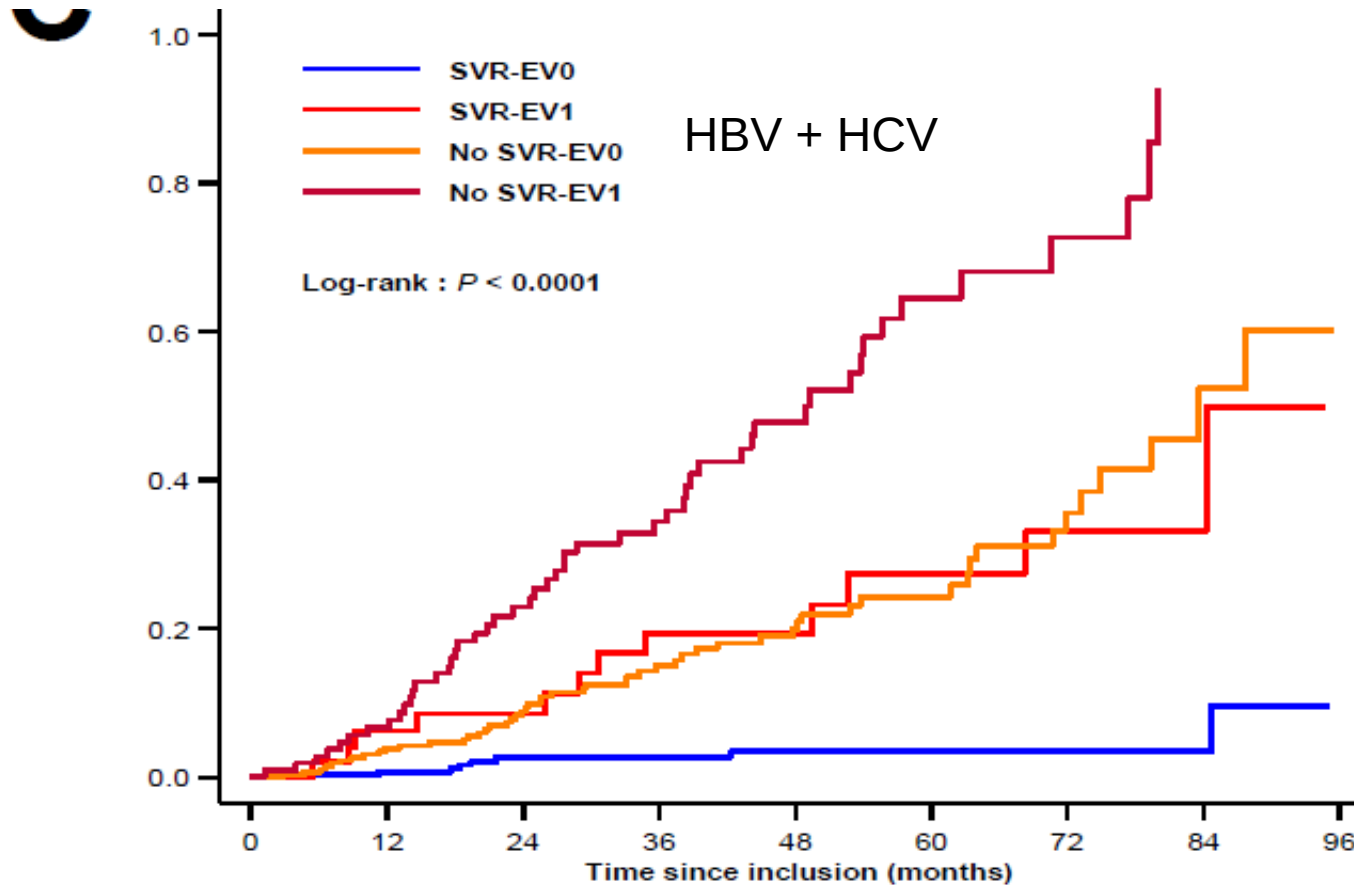
7-8%/year



7-8%/year



Impact of virosuppression on outcome



	At-risk patients																
SVR-EV0	273	(2)	231	(4)	182	(0)	139	(1)	99	(0)	69	(0)	45	(0)	17	(1)	2
SVR-EV1	55	(3)	41	(1)	35	(4)	28	(0)	22	(2)	16	(1)	12	(0)	4	(1)	0
No SVR-EV0	275	(10)	241	(11)	183	(11)	121	(6)	80	(4)	51	(6)	25	(4)	7	(1)	1
No SVR-EV1	109	(7)	92	(15)	63	(9)	44	(8)	25	(7)	12	(2)	6	(3)	1	(0)	1

Guidelines

Baveno VI	No varice	Small varices
Active disease	2 years	1 year
Controlled disease and no comorbidity	3 years	2 years

Patient case

TDF started in 2011

	W24	W48	W72	W96
ALT (IU/L)	32	24	22	25
HBV DNA (IU/ml)	132	< 12	< 12	< 12
GFR (ml/min)	78	73	72	75
Platelets	152	166	167	170
LS (kPa)	-	13	-	9
US	Normal	Normal	Normal	Normal
Endoscopy	Grade I	-	-	Normal

How do you manage the surveillance of portal hypertension ?



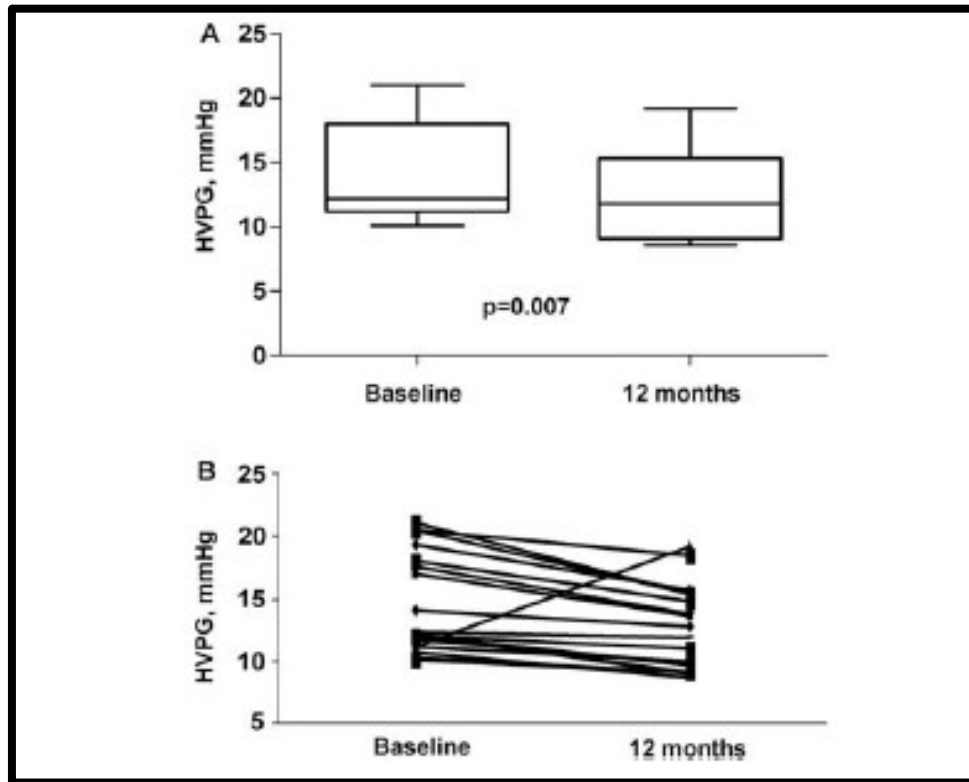
1. No surveillance

2. Gastroscopy every year

3. Gastroscopy every 2 years

4. Gastroscopy every 3 years

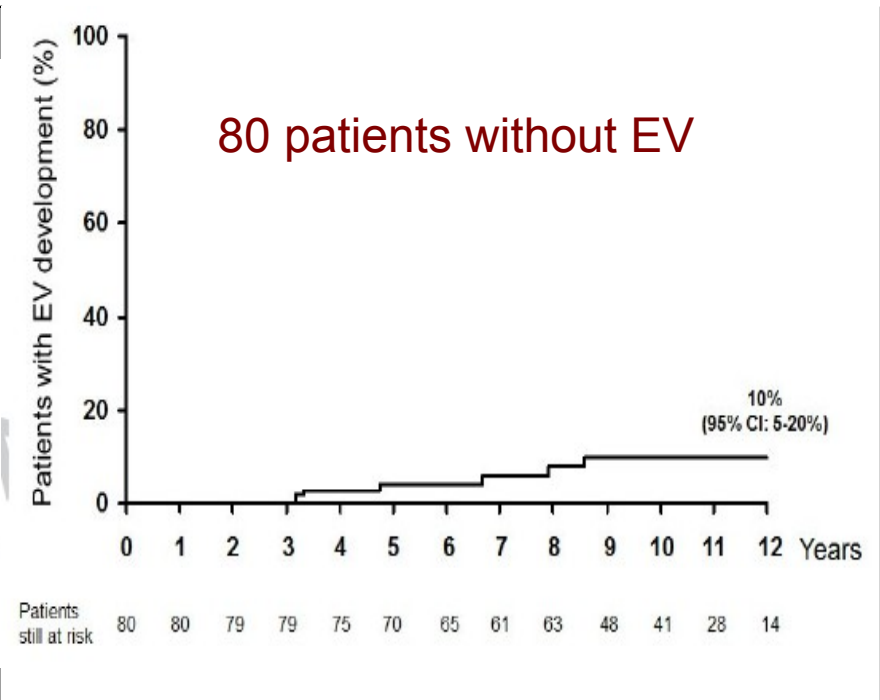
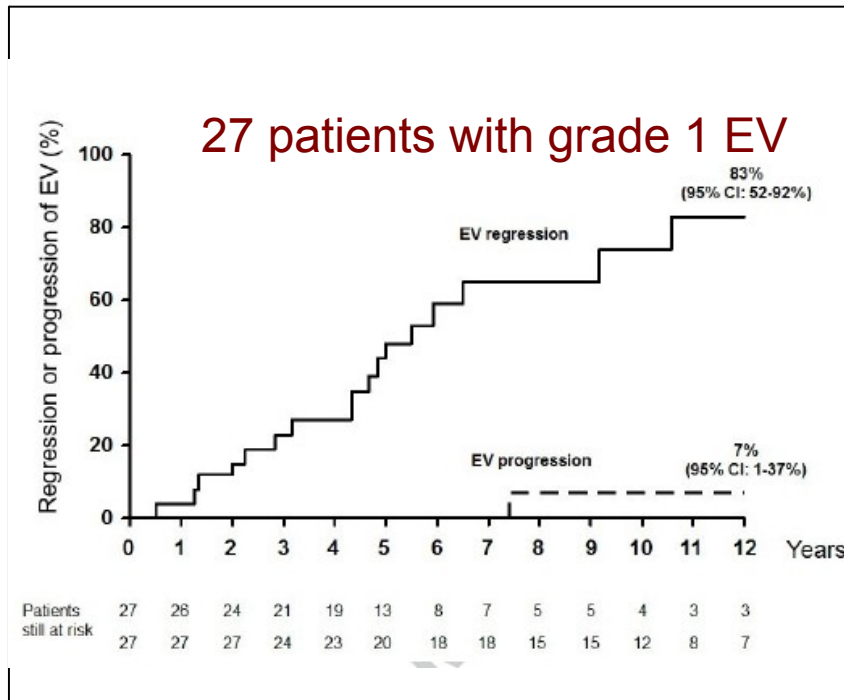
Outcome of HVPG



➤ HVPG increase in one patient with LAM resistance

Outcome small esophagus varices

Patients on treatment



➤ Progression only in patients without virosuppression

Is endoscopy always needed?

	% varices	Classification	NPV (varices)	NPV (varices at risk)	Avoided endoscopies
Augustin (n=49)	10%	LSM <25 LSM<25+Pla>150	93% 100%	100% 100%	61% 20%
Montes (n=85)	45%	LSM <20 LSM<20+Pla>120	90% 100%	- 100%	25% 15%
Ding (n=272)	-	LSM<25+Pla>100		100%	42%
Anticipate (n=379)	42%	LSM<25+Pla>100 LSM<25+Pla>150	79% 86%	95% 96.5%	45% 23%

- 20-40% of endoscopies avoided
- 5% risk of false negatives for varices at risk

Baveno VI guidelines

Baveno V

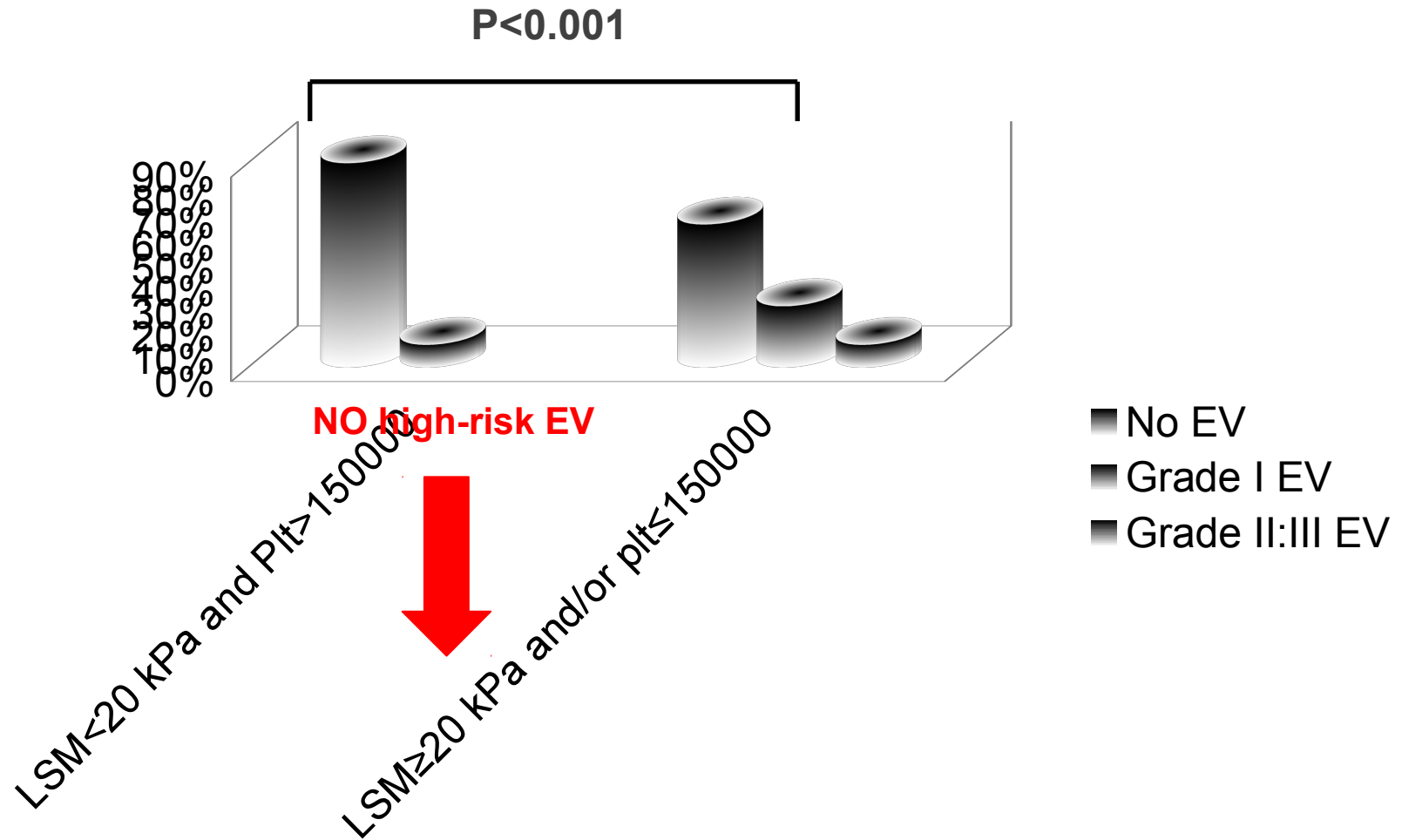
- Endoscopy at diagnosis of cirrhosis for ALL pts

Baveno VI

- Endoscopy can be avoided if $\text{Plt} > 150 \text{ G/L} + \text{LSM} < 20 \text{ kPa}^*$ (1b;A)
- Repeat $\text{Plt} + \text{LSM}$ yearly (5D)
- If Plt decrease or LSM increase, perform screening endoscopy (5D)

$\text{LSM} > 20 \text{ kPa}$: $\text{HVPG} > 10 \text{ mmHg}$

Baseline Endoscopy in the 649 Patients



➤ Endoscopy could be avoided safely in 24% of cases

Patient case

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ALT (IU/L)	18	20	22	17	25	21
HBV DNA (IU/ml)	46	< 12	34	< 12	<12	143
GFR (ml/min)	67	66	62	57	50	51
Platelet s	152	166	167	170	171	169
LS (kPa)	-	6.3	-	7.1	-	6.5
US	Normal	Normal	Normal	Normal	Normal	Normal

What do you do?

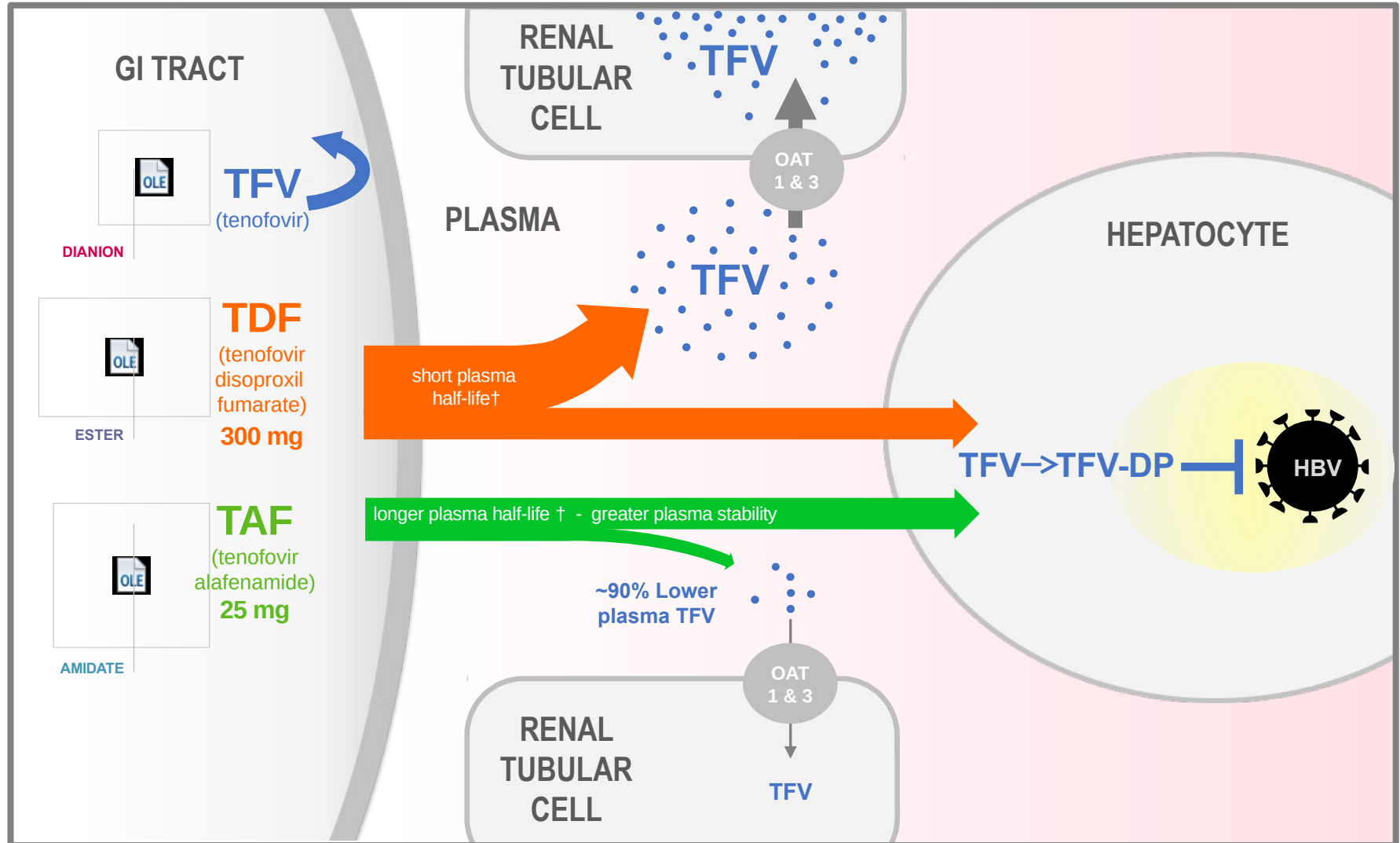


1. Continue on TDF

2. Switch to ETV

3. Switch to TAF

Tenofovir alafenamide (TAF) – A Novel Prodrug of Tenofovir



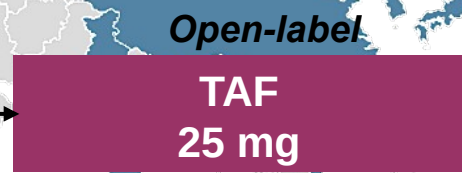
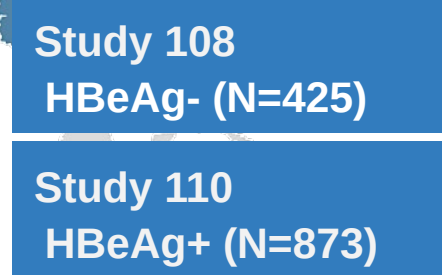
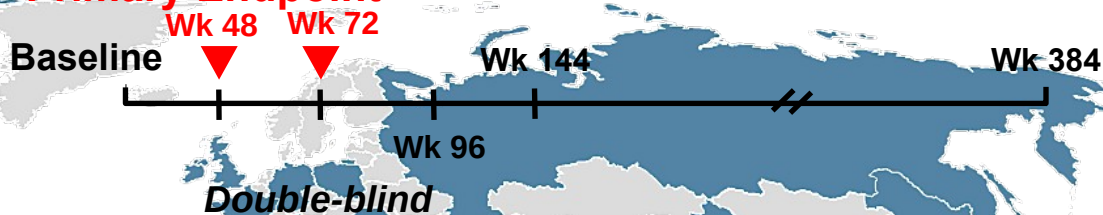
† T1/2 based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 90 minutes.

Lee W et al. *Antimicrob Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicrob Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66. Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti EASL 2016, Oral GS06; Chan, EASL 2016, Oral GS12

TAF HBV Phase 3 Program

Two phase 3, randomized, double-blind studies

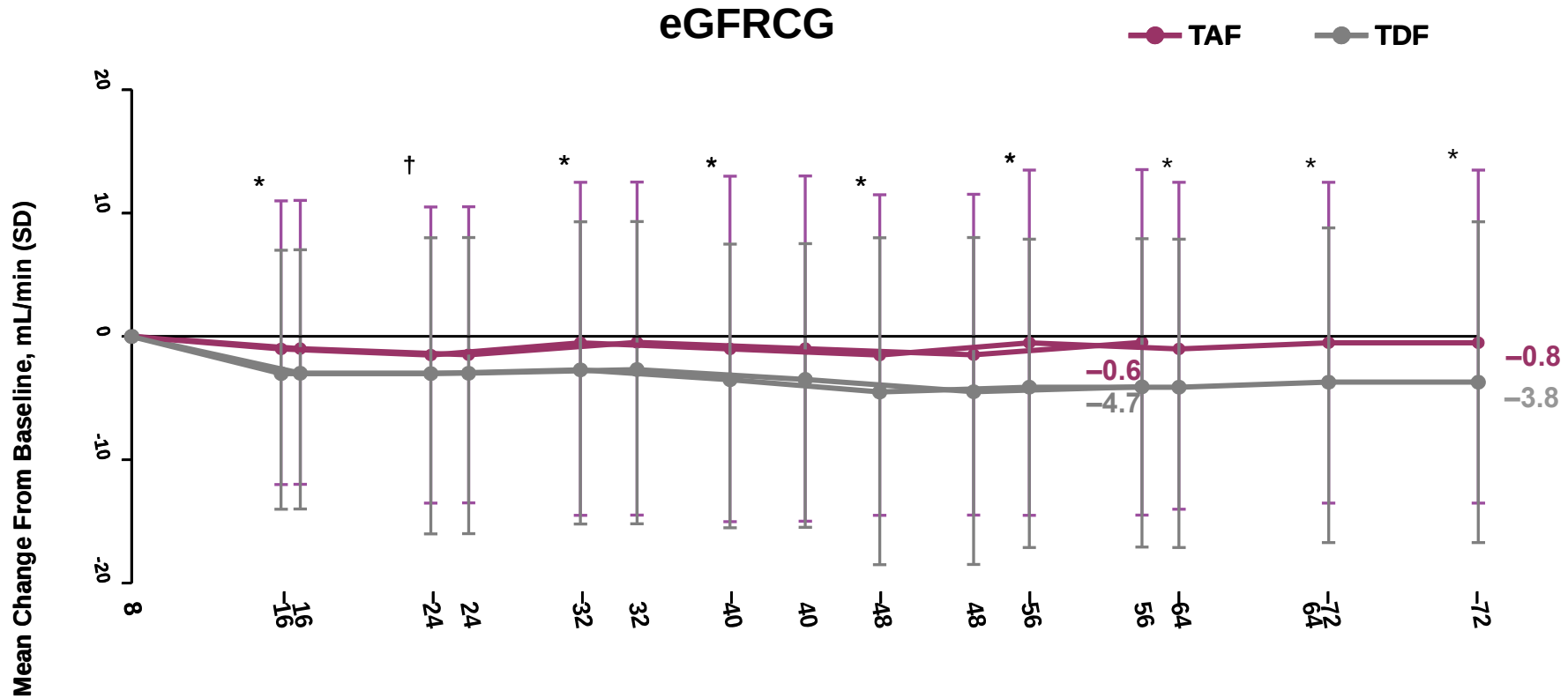
Primary Endpoint*



- **Primary endpoint** (non inferiority margin of 10%):
 - HBV DNA <29 IU/mL at Week 48
- **Key secondary endpoints**
 - ALT normalisation at Week 48
 - Renal parameters and bone mineral density at Week 48
- 95% retention rate through Week 48
- Inclusion criteria: HBV DNA $\geq 20,000$ IU/mL; ALT >60 U/L (males), >38 U/L (females), eGFR_{CG} >50 mL/min

*Non-inferiority margin of 10%

Renal Laboratory Parameters in CHB Patients Treated with TAF or TDF



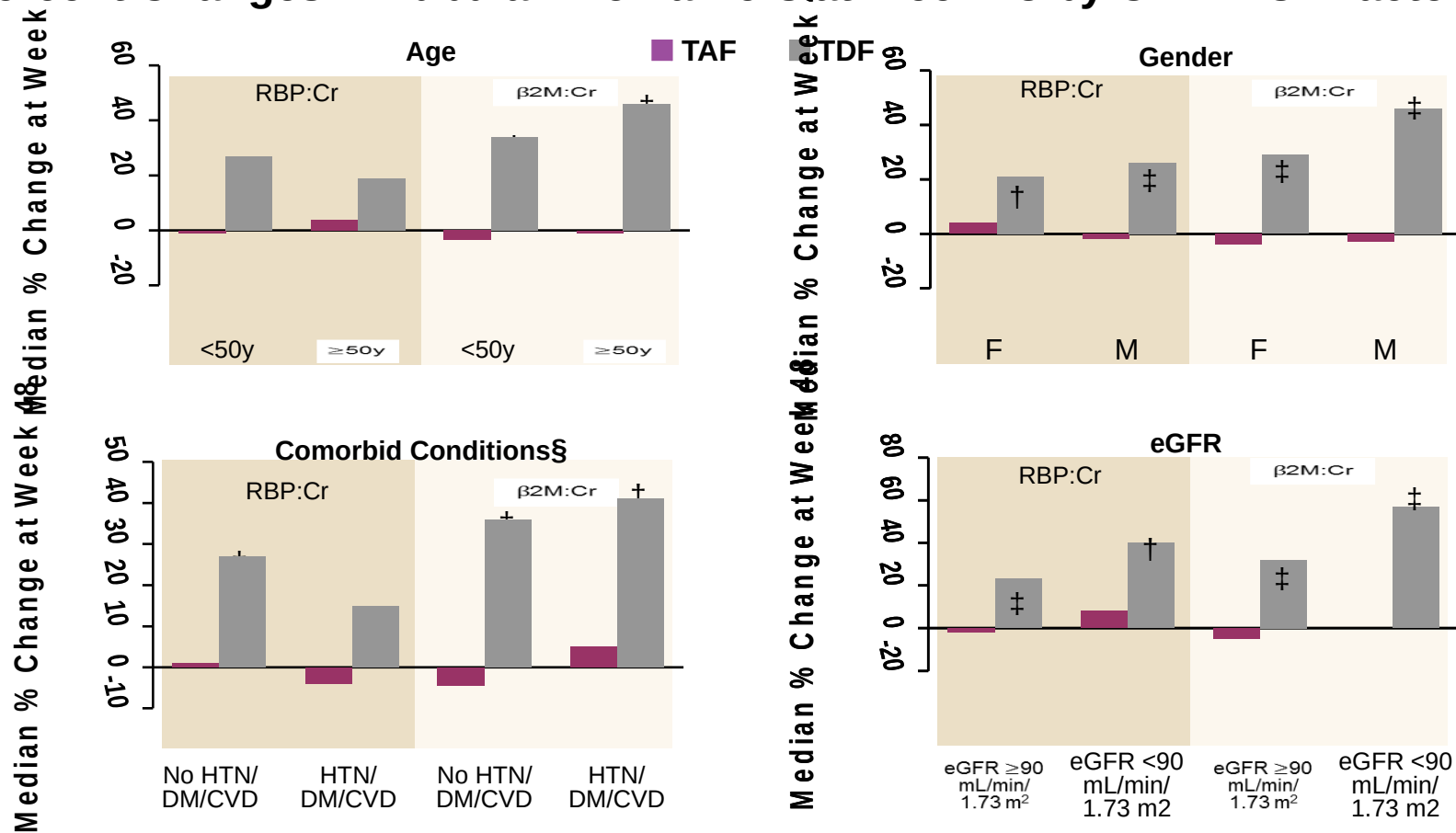
TAF treatment had statistically significant less effect on eGFR compared to TDF at 72 weeks

*p<0.001
†p<0.01



Changes in Urine Markers of Tubular Dysfunction During Treatment with TAF or TDF

Percent Changes in Tubular Biomarkers at Week 48 by CKD Risk Factor



In all patients, including those at high risk for CKD, there were significantly less changes in tubular biomarkers with TAF compared to TDF

*p<0.05; †P<0.01; ‡P<0.001

Conclusion

- **The risk of HCC persists in cirrhotic patients even in case of HBV DNA negativity and LS decline, and US surveillance should be maintained**
- **Interval > 7 months between US is associated with increased mortality**
- **Portal hypertension does not progress (and may improve) in patients on analogs. Endoscopy can be avoided in patients with LS < 20 kPa and Plt > 150 G/L.**
- **In case of tubulopathy associated with TDF a switch to ETV or TAF should be considered**