Hepatitis virus and liver transplantation

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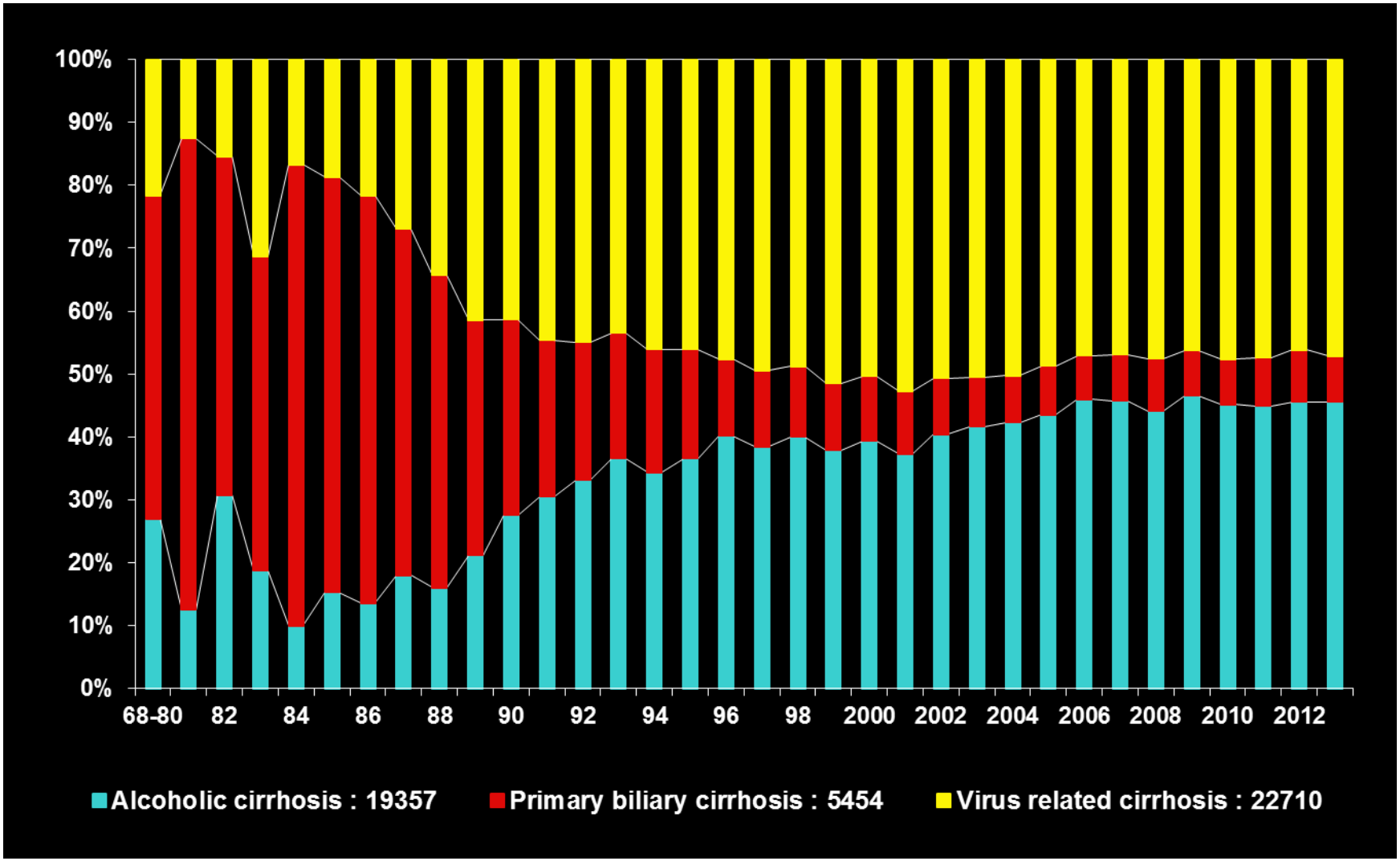
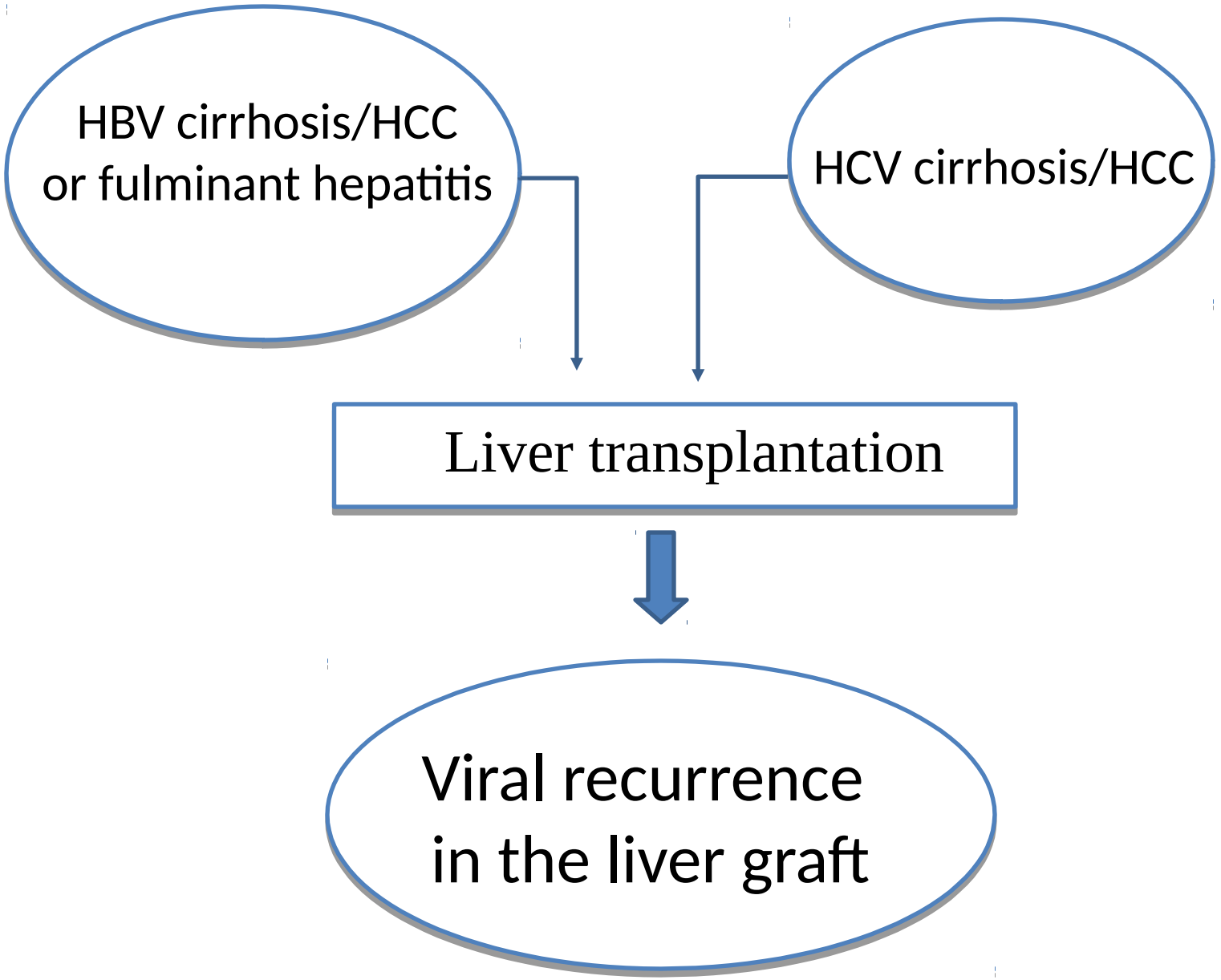
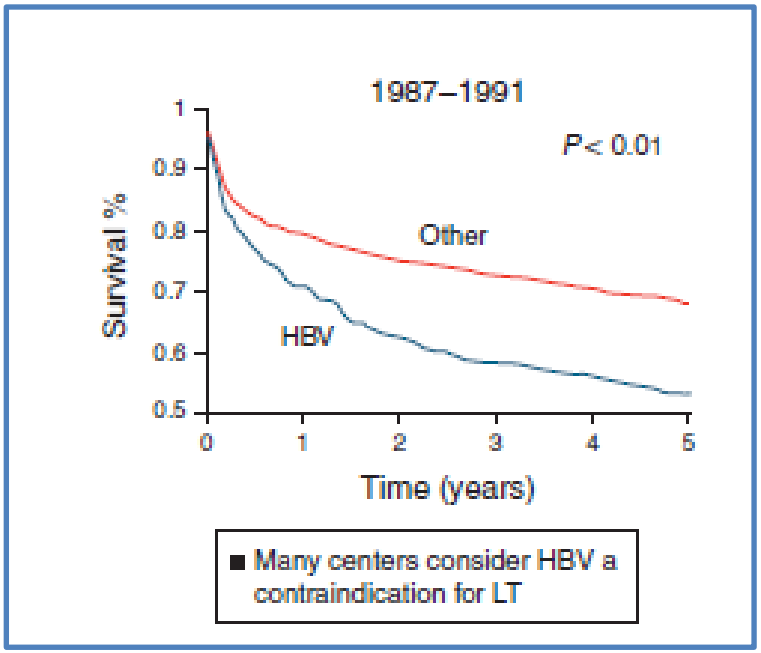
Evolution of Indications for Cirrhosis in Europe




HBV cirrhosis/HCC
or fulminant hepatitis
HCV cirrhosis/HCC
Liver transplantation
Viral recurrence
in the liver graft

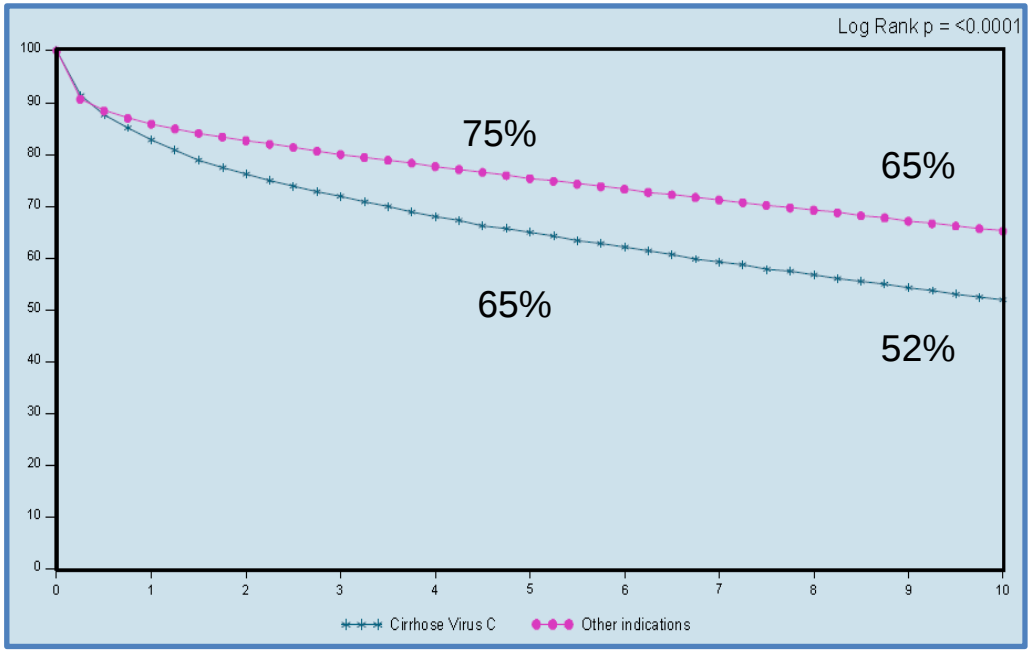
Impact of virus recurrence on patient survival
Historical cohorts

LT for HBV



Terrault et alt. Am J Gastro 2013

LT for HCV



ELTR 2013

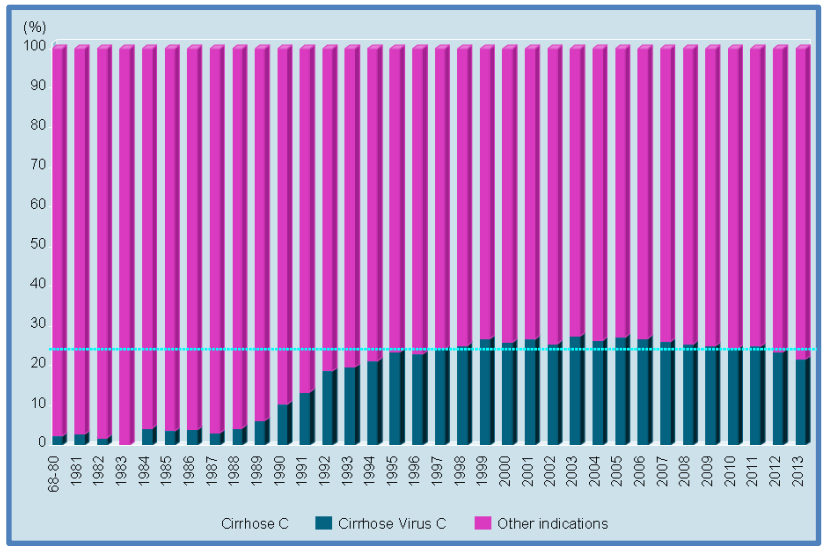
Outline

- Epidemiology of liver transplantation for HCV and HBV liver diseases
- Indication for liver transplantation in cirrhotics
- Liver transplantation for HCV
  - Natural history of HCV recurrence
  - Should HCV be treated before transplantation?
  - How to treat HCV recurrence after LT
- Liver transplantation for HBV
  - How to prevent HBV recurrence
- The issue of HEV after liver transplantation

Proportion of cirrhotic patients transplanted for viral diseases. ELTR data

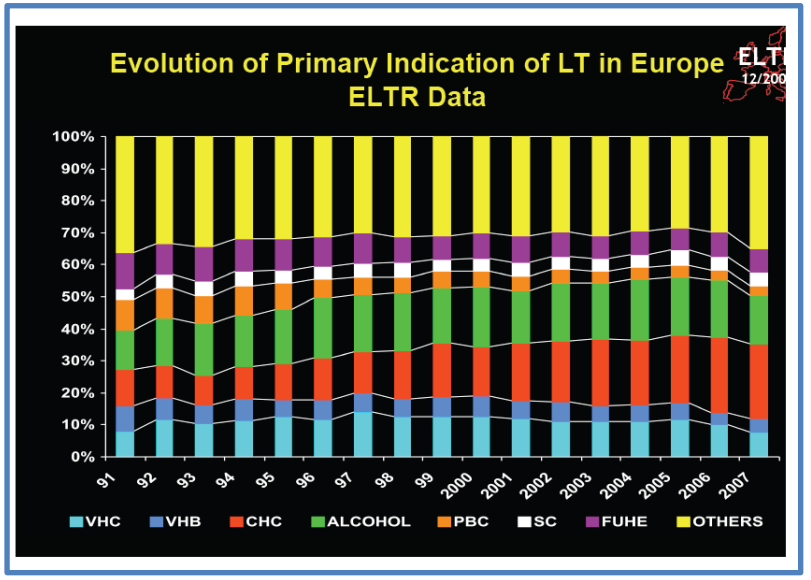
LT in HCV patients

15%



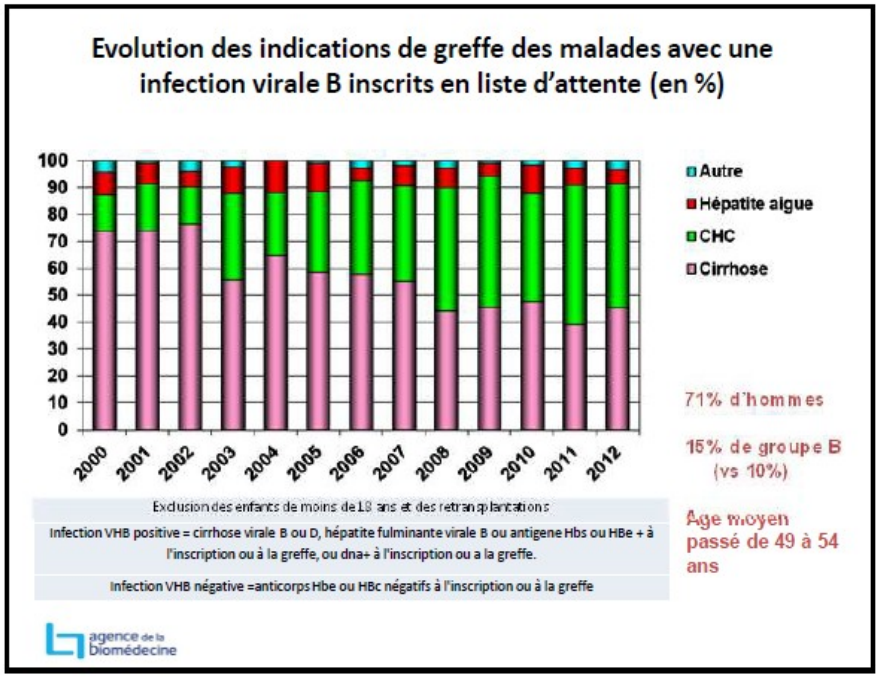
45%

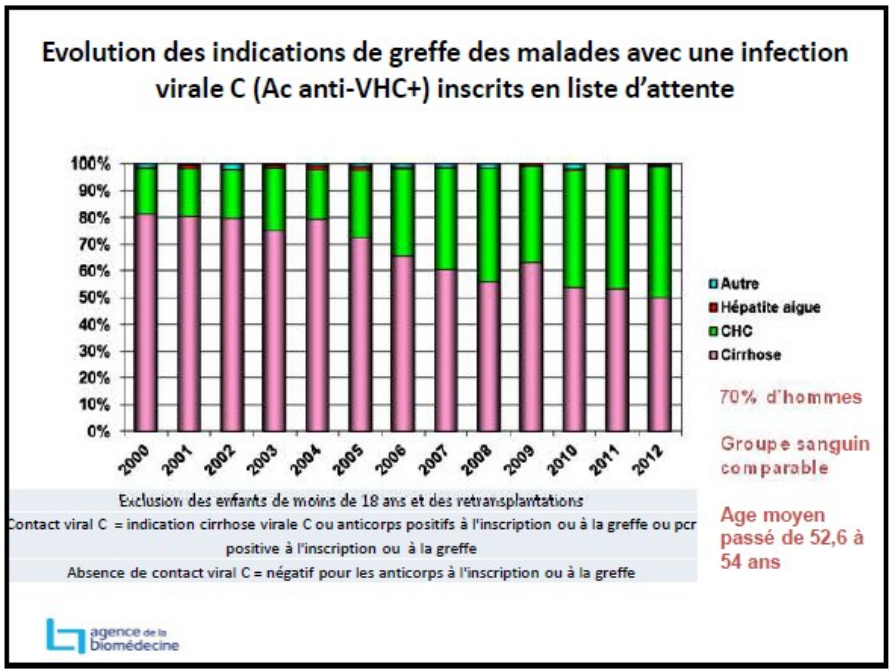
HBV



ELTR 2013
93,534 adult patients

Proportion of HBV and HCV candidates listed for ESLD vs HCC in France over time





Outline

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Indication of liver transplantation for viral cirrhosis is not specific

MELD score

[9.57 loge creatinine mg/dL + 3.78 logebilirubin mg/dL + 11.20 loge INR + 6.43 (constant for liver disease etiology)]

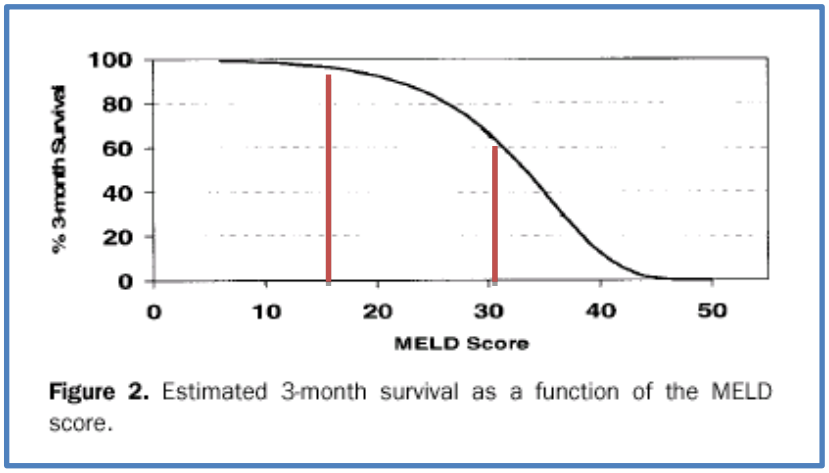
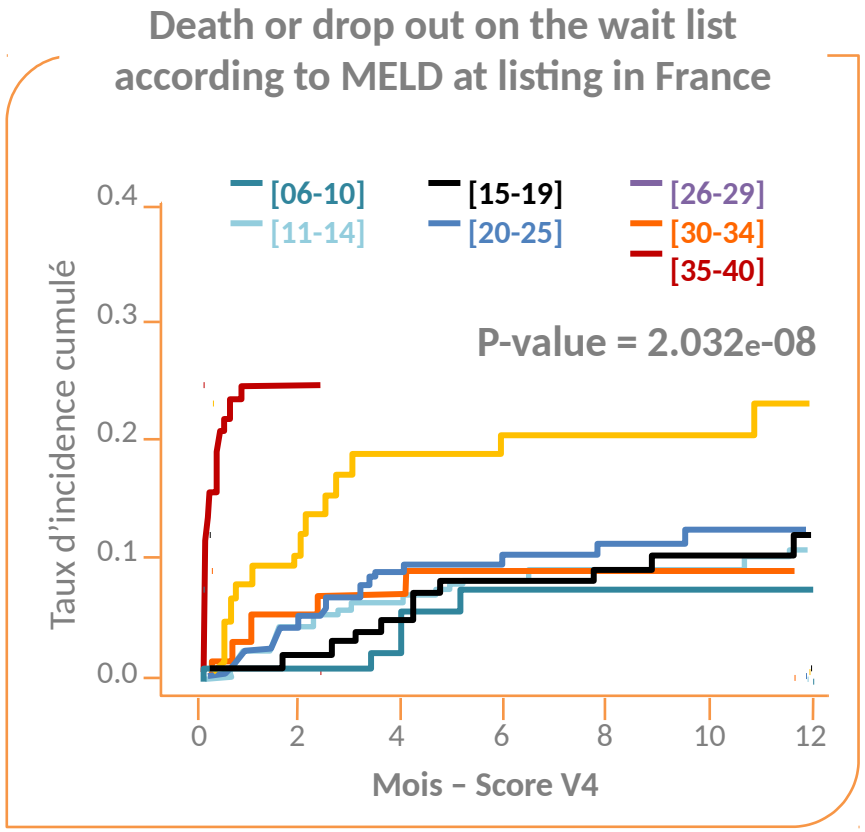


Figure 2. Estimated 3-month survival as a function of the MELD score.

Wiesner Gastroenterology 2003



Source Agence de la Biomédecine

Outline

- Epidemiology of liver transplantation for HCV and HBV liver diseases
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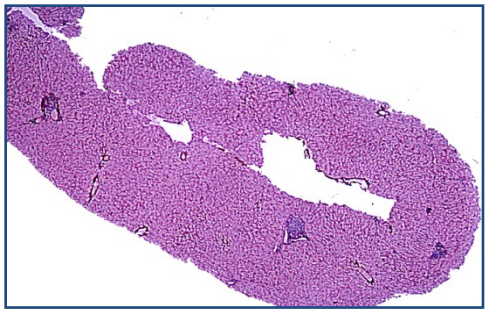
Recurrence of HCV in the liver graft
Natural history

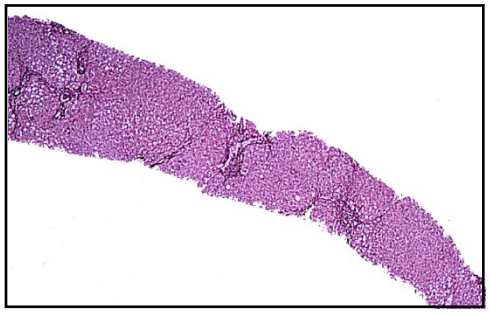
Recurrence/HCV replication: 95%

Fibrosing cholestatic hepatitis: 2-10%

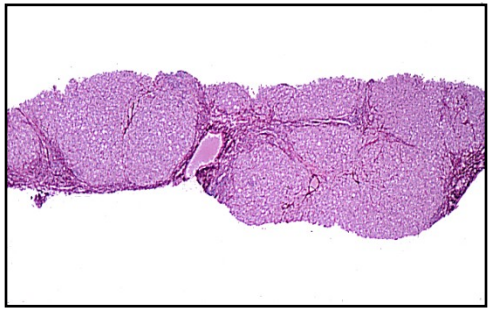
Acute (lobular) hepatitis
2 to 4 months post LT



Minimal injury
20-30%



Chronic active hepatitis: 60-80%



Cirrhosis:
10-30% at 5 yrs
Graft lost:
3-10% at 5 yr

Two different strategies to face HCV recurrence

To Prevent HCV recurrence
To Avoid LT ?

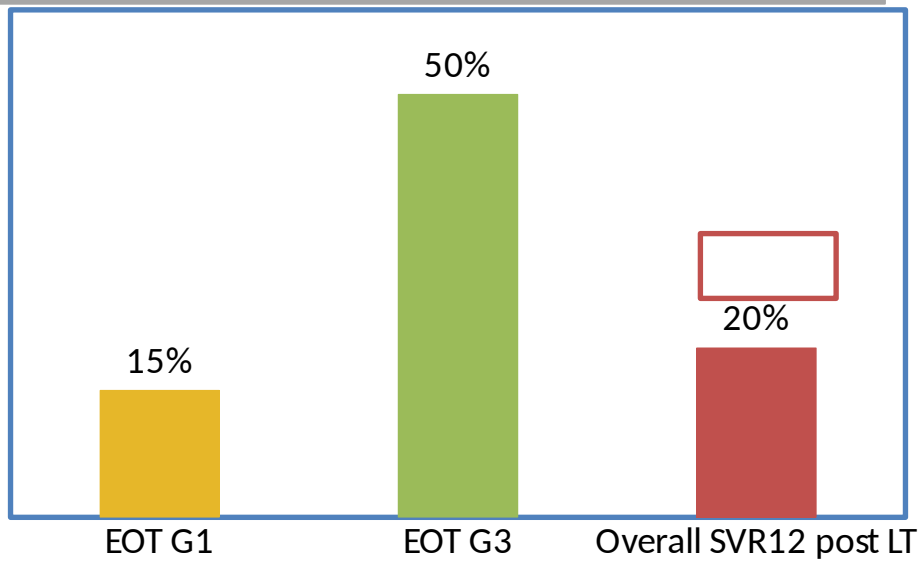
Treatment of HCV recurrence

To prevent de novo fibrosis/cirrhosis
To improve survival
To prevent
- Renal function impairment ?
- Post LT diabetes ?

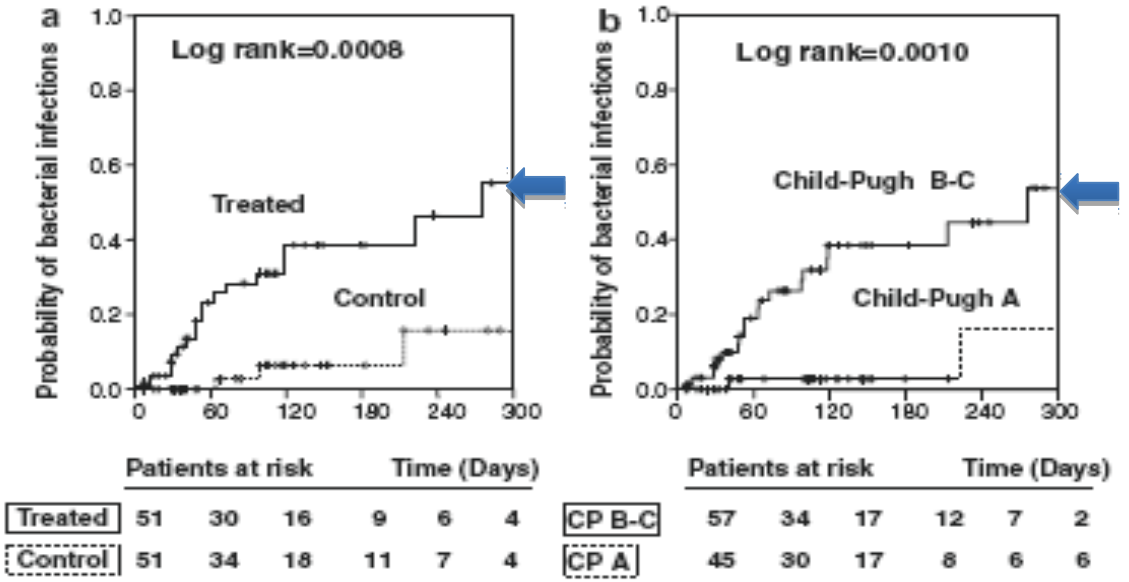
The « historical » dual therapy pre LT: Peg-IFN and Ribavirin

- Limited efficacy

Carrión JA et al. J Hepatol. 2009.



- High rate of side effects, risk of infection and death



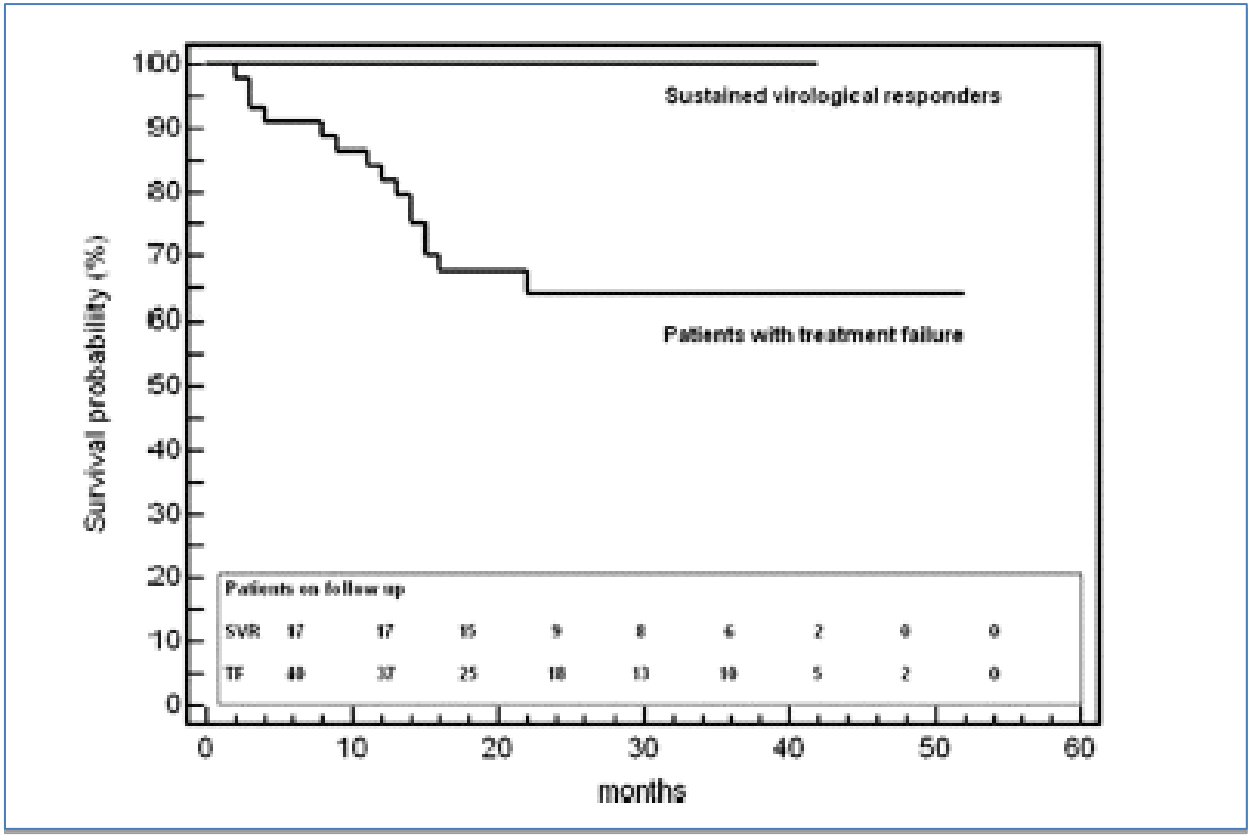
The « historical » dual therapy: Peg-IFN and Ribavirin post LT

Review author	Studies	Patients	Years	ETVR	SVR	Tolerability	Rejection
Wang	21 (1 CT)	587	1980–2005	42% (38–46%)	27% (23–31%)	Dose reduction 66% (61–70%) D/C 26% (20–32%)	5% (3–7%)
Berenguer	19 (2 CT)	611	2004–2007	42.2% (17–68%)	30.2% (0–50%)	Dose reduction 68% D/C 27.6%	6.4% (0–25%)
Xirouchakis	6 CT	264	2005–2007	NA	41% (29.6–77.7%)	NA	5%

CT: controlled trial; D/C: discontinuation; ETVR: end of treatment virological response; NA: not applicable

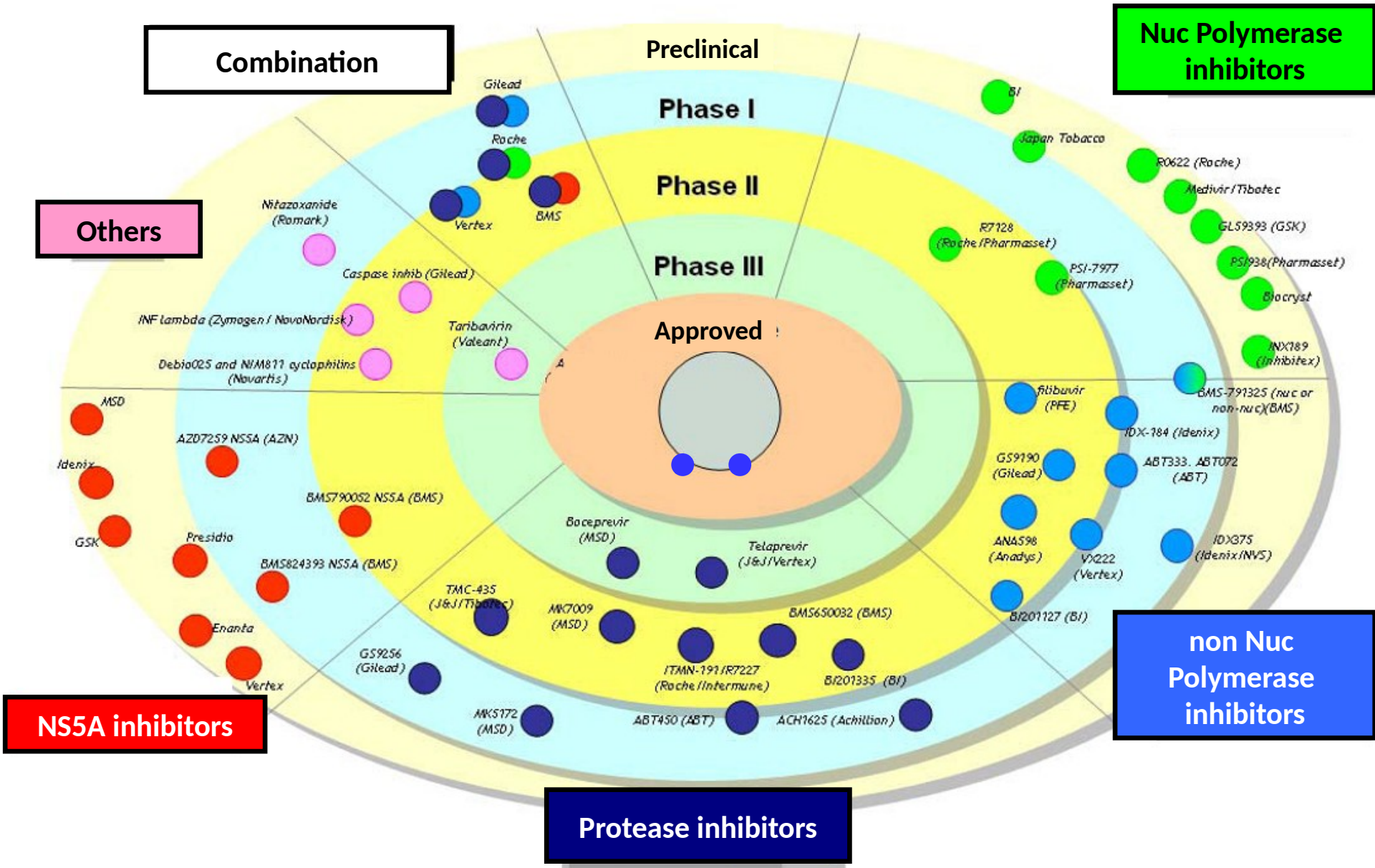
Roche B, et al. Liver Int. 2012

Beneficial impact of anti viral therapy on survival



Pisciotto et al. J Hepatol 2007

HCV Drugs in Development : direct antiviral agents



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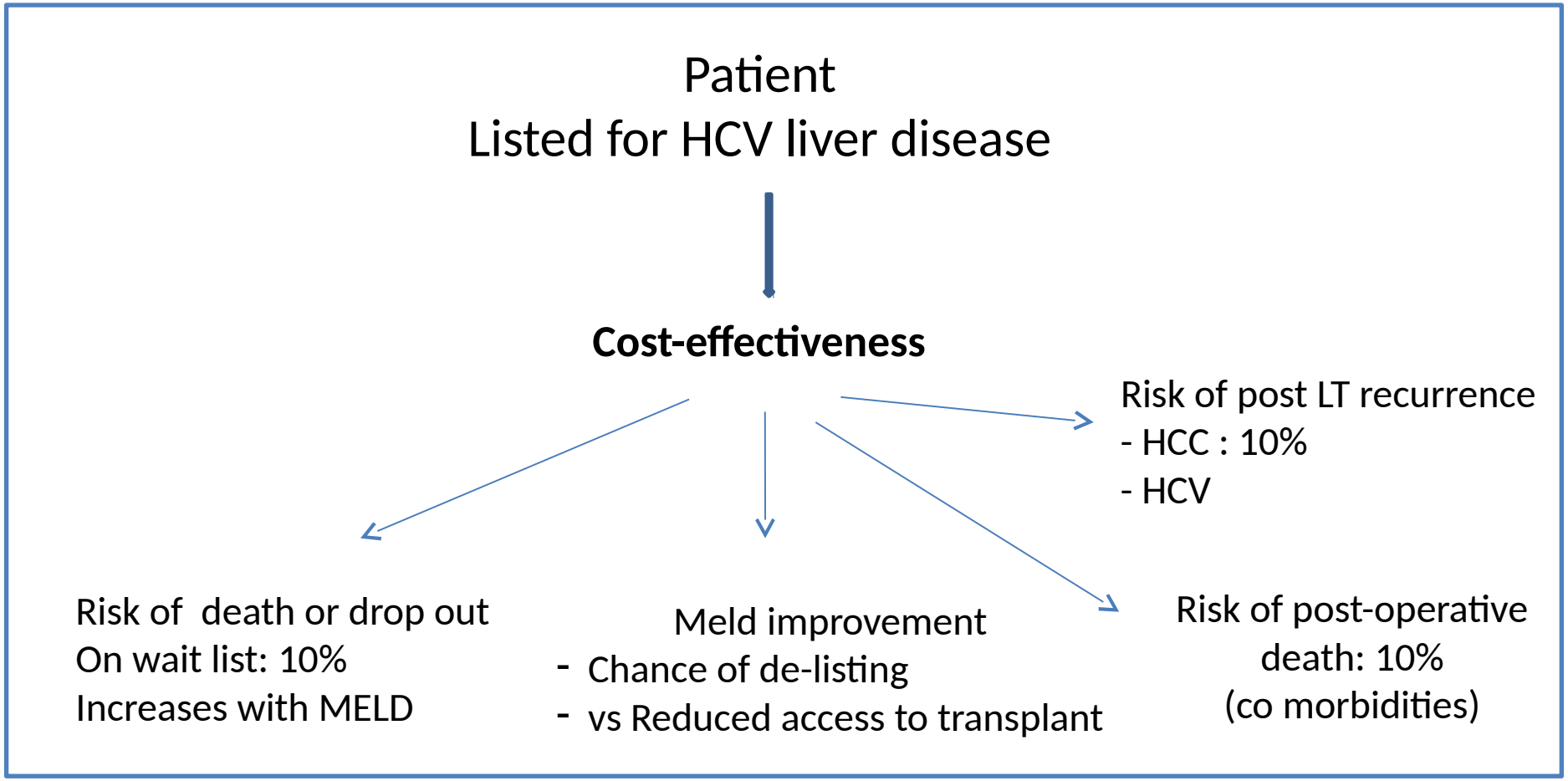
Principles to take into account in the decision -making process before treating LT candidates with DAA



✉ Avoid futile DAA treatment

Main issues

1- Which compounds can be used safely in decompensated cirrhotics?

2- What is the impact of DAAs on SVR, liver function and de-listing pre transplant ?

2-What is the impact of pre LT DAA on HCV recurrence post-LT ?

3- Who should be treated or not treated before LT among decompensated cirrhotics/among pts listed for HCC

4- What is the impact of post LT DAA treatment on HCV recurrence : SVR ? Survival ? best timing for treatment ?

5- Can we expect a beneficial impact of HCV tt on extra hepatic manifestations of HCV, irrespective of liver injury ?

6 -How to take into account drug to drug interactions and frequent renal impairment in LT candidates and recipients ?

DAA PK in Cirrhotics

Table 3. Pharmacokinetics (change in AUC) of DAAs in hepatic impairment (graded according to CTP score) and recommendation.

Drug	CTP A (5-6 points)	CTP B (7-9 points)	CTP C (≥10 points)
Sofosbuvir [38,108]	NR	NPD	NPD
Simeprevir [109]†	NR	NR	AUC x 3
Daclatasvir [110, 111]¥	NR	NR	NR
Asunaprevir [112]	NR	AUC x 9.8	AUC x 32
Ledipasvir [113]	NR	NR	NR
ABT-450/r [114]§	NR	NR	AUC x 11
Dasabuvir [114]	NR	NR	NR
Ombitasvir [114]	NR	NR	NR
MK-8742 [103]	NR	NR	NPD
MK-5172 [103]	NR	NR	NPD

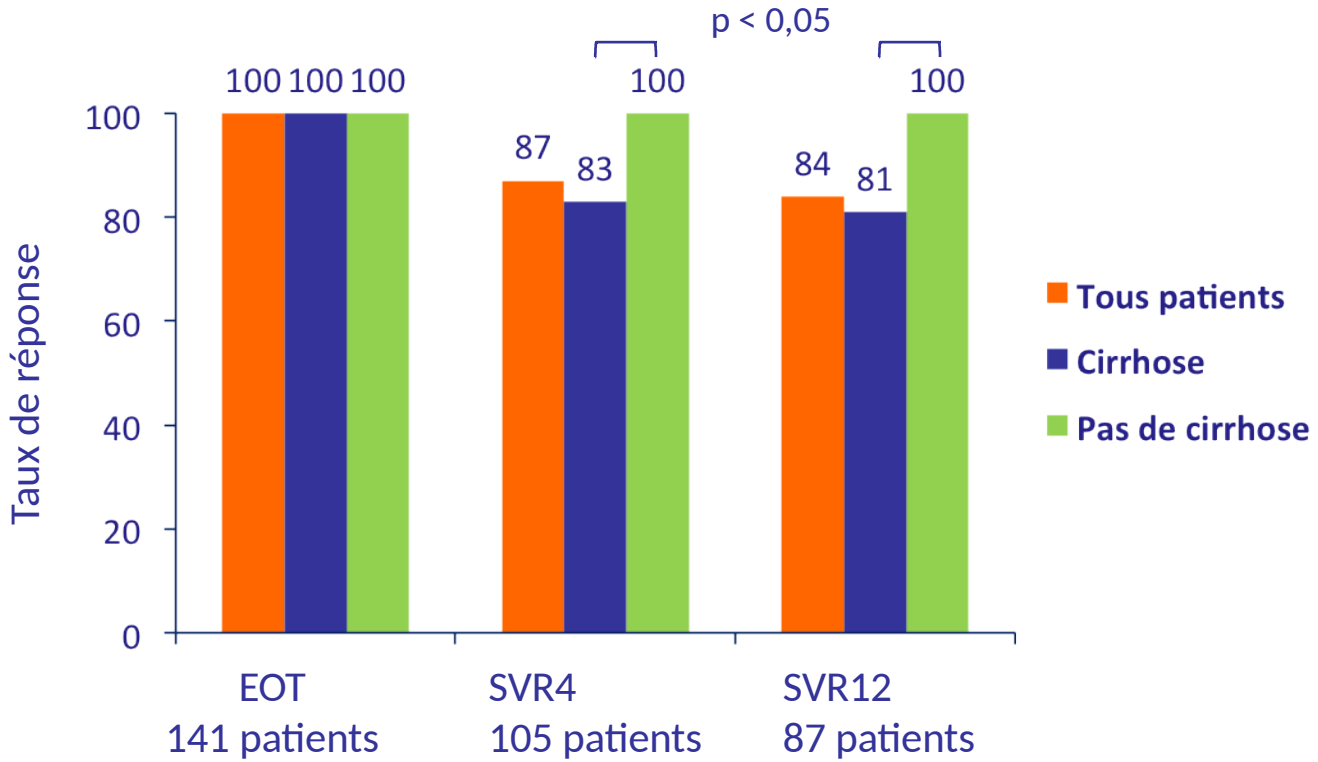
NR, dose adjustment not required; NPD, no pharmacokinetic data or studies

Gamballi J Hepatol 2014

Sofosbuvir/Simeprevir ± RBV in patients G1 on the Waiting List

- US study, 147 patients G1
  - SOF + SMV x 12 weeks = 127 patients
  - SOF + SMV + RBV x 12 weeks = 20 patients
- Genotype 1a (70 %), Cirrhosis (78 %), IL-28 non CC (79 %)
- Median MELD : 12 (7-17)

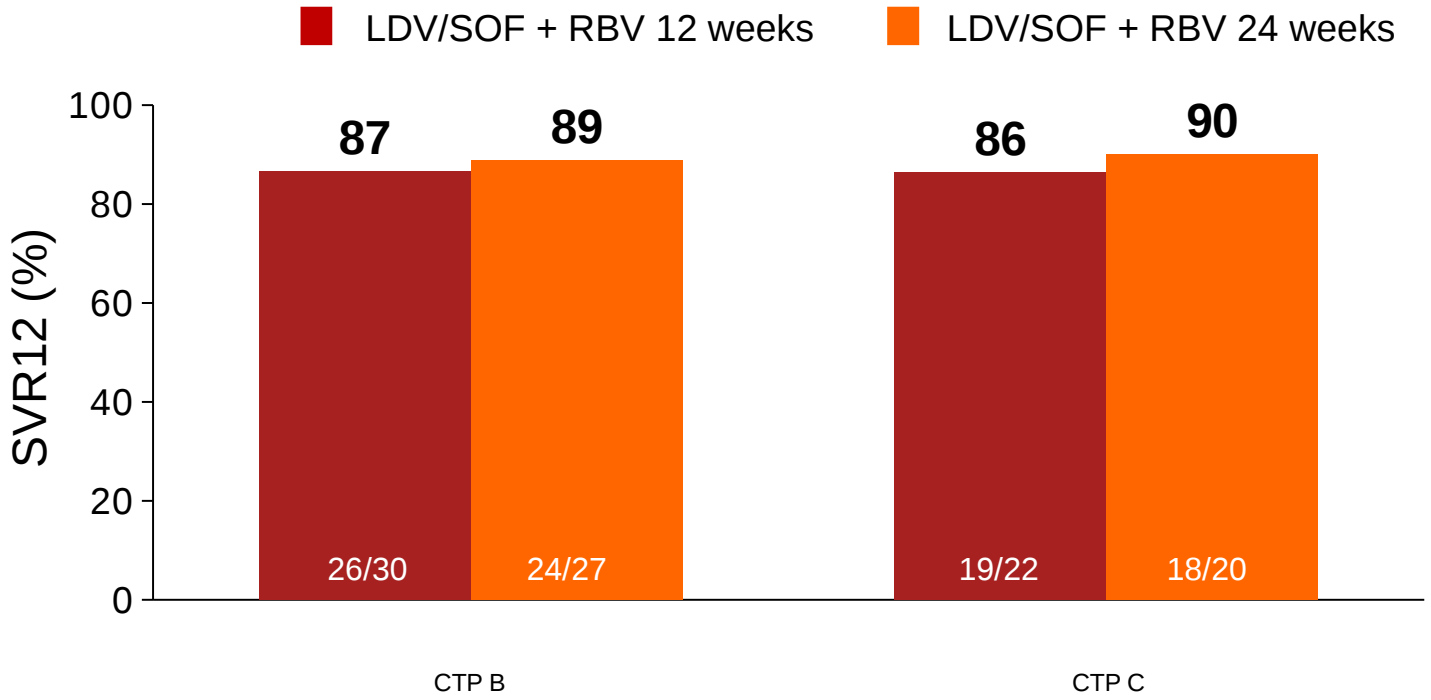
Virologic Response ITT



Aqel B, Etats-Unis, AASLD 2014, Abs. 19 actualisé

SOLAR-1: LDV/SOF + RBV in Decompensated Cirrhosis

Prospective, multicentre study of 12 or 24 weeks of LDV/SOF + RBV in TN and TE HCV GT 1 and 4 patients with CTP B (N=59) or CTP C (N=49) clinically decompensated cirrhosis



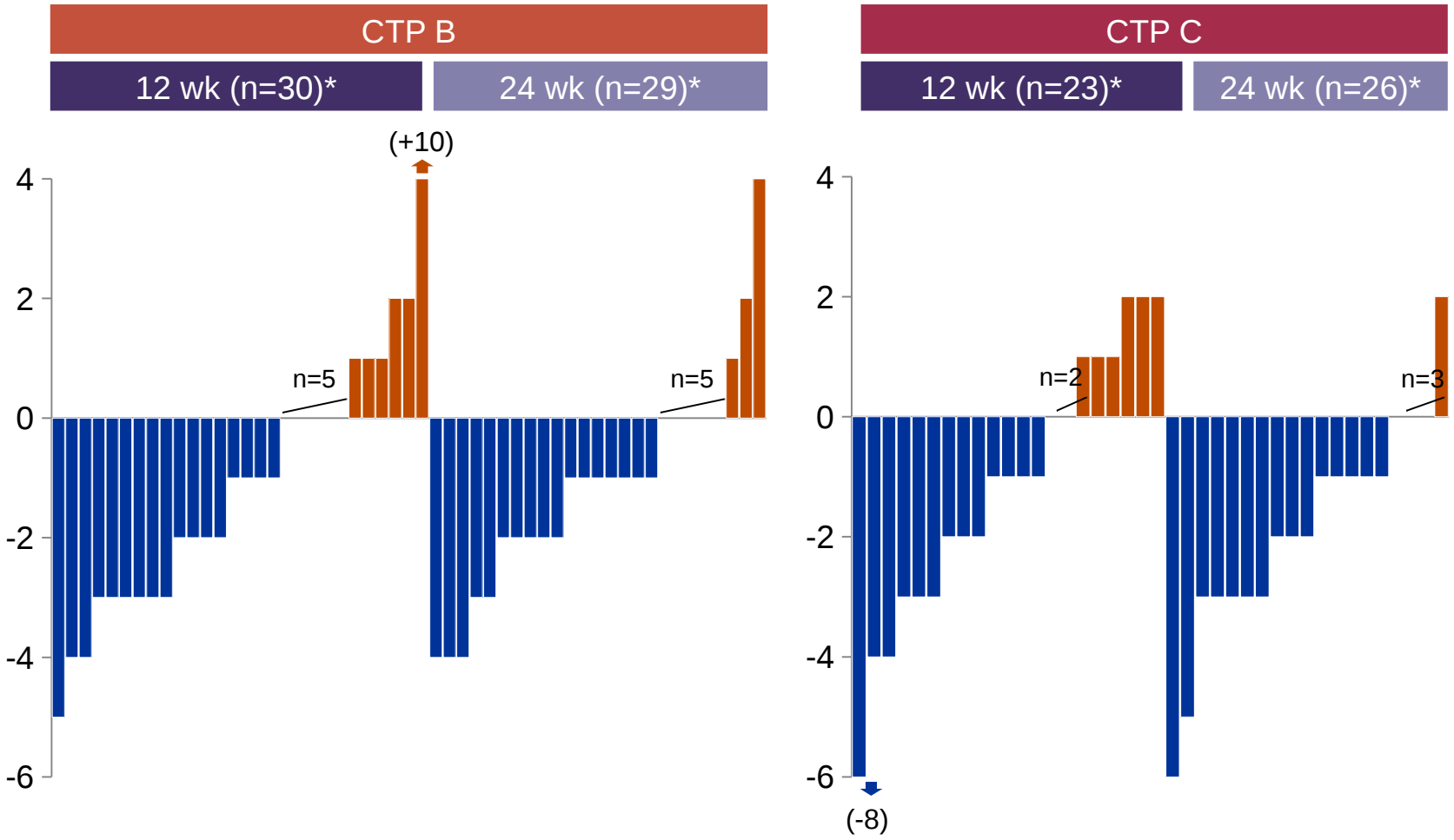
SVR rates were similar with 12 or 24 weeks of LDV/SOF + RBV

Virological response was associated with improvements in bilirubin, albumin, MELD and CTP scores in both CTP class B and C patients

LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen;
Error bars represent 90% confidence intervals;
TE: treatment-experienced; TN: treatment-naïve

Flamm S, et al. AASLD 2014; Oral #239.

SOLAR-1: LDV/SOF + RBV in decompensated cirrhosis: Change in MELD from Baseline



LDV/SOF + RBV for 12 weeks is not an EMA-recommended treatment regimen

*Missing FU-4: n=2 CTP B 12 wk; n=4 CTP B 24 wk; n=2 CTP C 12 wk; n=7 CTP C 24 wk; BL: baseline; FU: follow-up

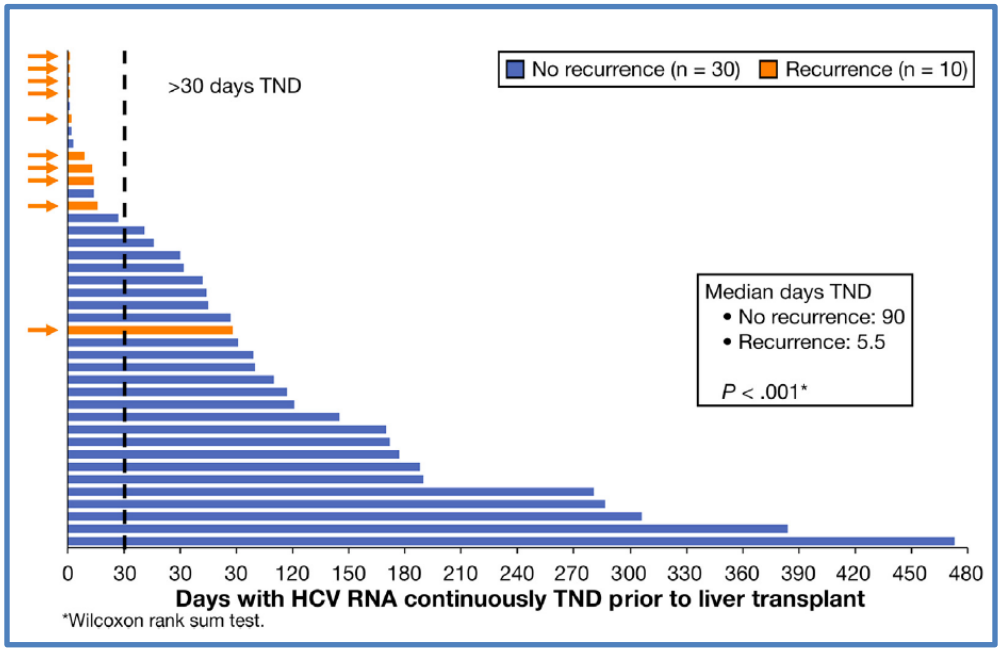
Flamm S, et al. AASLD 2014; Oral #239.

1- What is the impact of pre LT DAA on prevention of HCV recurrence post-LT ?

61 HCC-HCV LT candidates receiving SOF+RBV before LT
43 pts (70%) with HCV RNA negative at LT

Table 2. Post-Transplant Virologic Response by Visit for Patients With HCV-RNA Level Less Than the LLOQ at the Last Measurement Before Liver Transplantation

	Sofosbuvir-ribavirin for ≥12 weeks (N = 32)	Sofosbuvir-ribavirin for any duration (N = 43)
Post-transplant week 1		
<LLOQ, n/N (%)	28 (88%)	37 (86%)
90% CI	74%–96%	74%–94%
Post-transplant week 2		
<LLOQ, n/N (%)	26 (81%)	35 (81%)
90% CI	66%–92%	69%–90%
Post-transplant week 4		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 8		
<LLOQ, n/N (%)	24 (75%)	31 (72%)
90% CI	59%–87%	59%–83%
Post-transplant week 12		
<LLOQ, n/N (%)	24 (75%)	30 (70%)
90% CI	59%–87%	56%–81%



Curry et al. Gastroenterology 2015

Forthcoming ELITA recommendations for DAA treatment Pre LT

1- Simeprevir, Asunaprevir and ABT 450 are discouraged in decompensated Child C cirrhotics

2- Dual treatment with SOF + LEDI, SOF + DACLA or SOF + SIME +/- RBV can be considered, depending on liver function impairment , duration of treatment & GT

3- A significant improvement of MELD score resulting in de-listing is unlikely in Child C patients and MELD scores > 23-25 and the expected increased waiting time associated with a slight improvement in MELD makes post LT DAA treatment reasonable in these patients

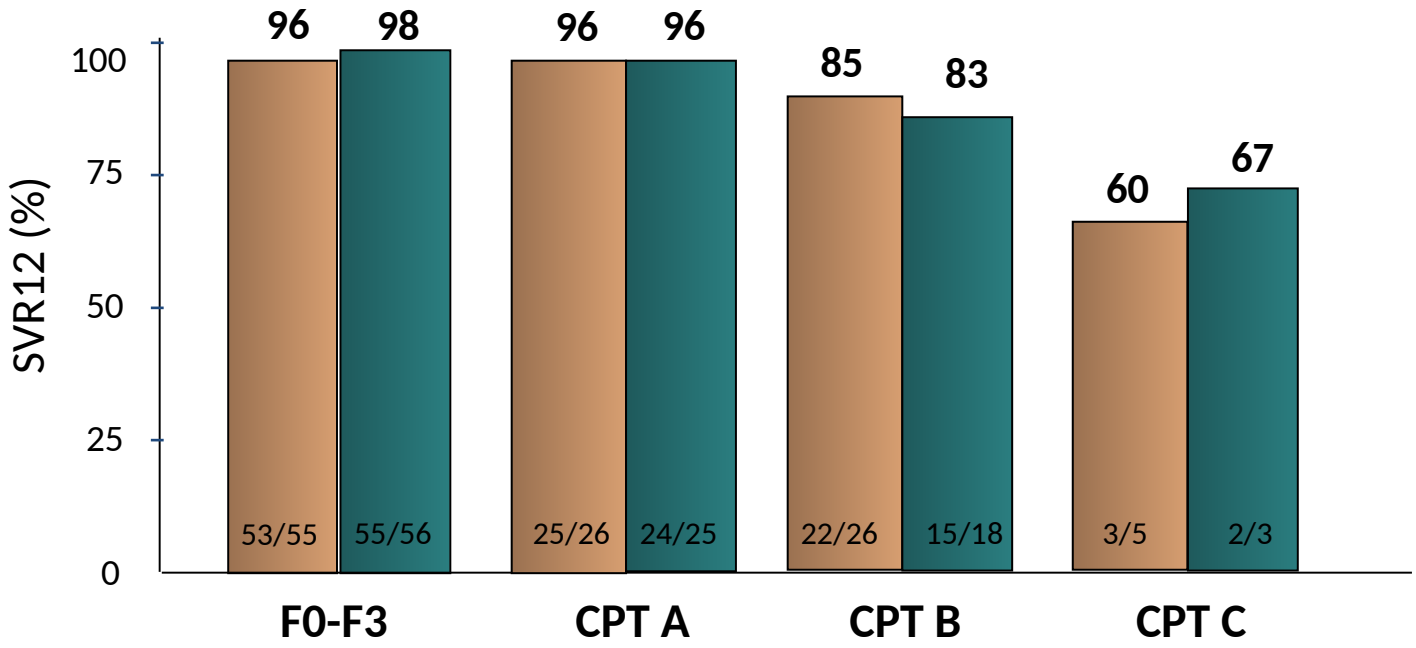
4-A significant liver function improvement can be achieved in Child B patients on treatment

- further studies are required to determine predictors of improvement and de-listing and the optimal MELD cut-off under which DAA can be considered

5- In HCV LT candidates, a minimal 30-day period of viro-suppression on DAA is recommended before placing the patient in active position on the wait list to effectively prevent HCV recurrence

Treatment of post LT recurrence
SOLAR1 : Sofosbuvir/ledipasvir+ RBV post LT: 12 vs 24 w

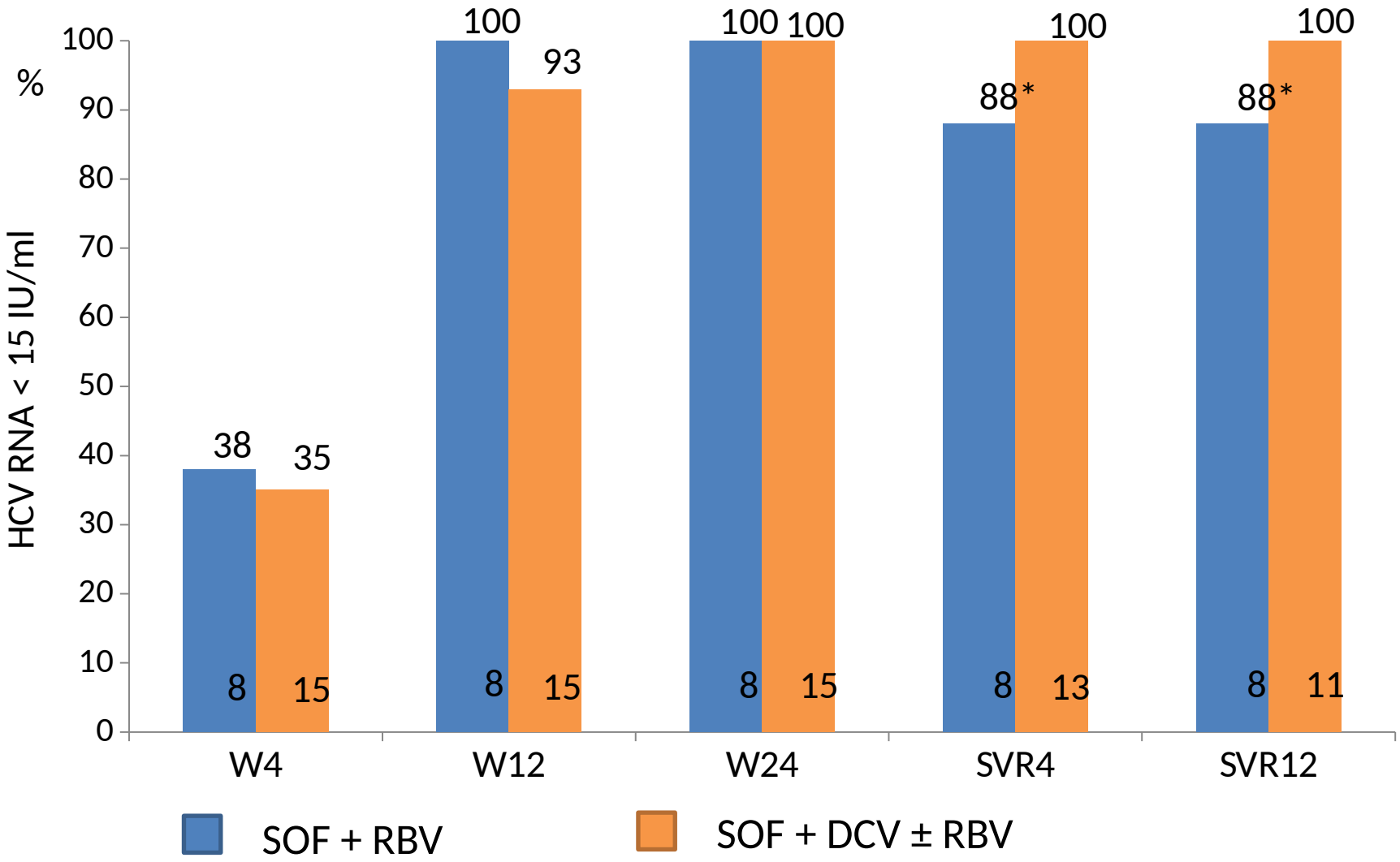
214 HCV-infected LT recipients: F0-F3 or cirrhotics CPT A, B and C



Safety:
7deaths (2 CPT A, 5 CPT B), most progression of liver disease

Reddy et al AASLD 2014

French Cupilt Cohort
Fibrosing Cholestatic Hepatitis: Virological response



* : 1 relapse in HIV co-infected patients, G1b, F4

Leroy et al. AASLD 2014

Preliminary ELITA recommendations. DAA in the Post-LT setting

- In patients with early significant liver injury (early fibrosis > F2, FCH), DAA treatment is strongly recommended to prevent further deterioration and reduced efficacy
- In patients with advanced recurrence, including decompensated cirrhosis, DAA treatment is recommended to achieve liver function improvement or consider reLT in SV Responders.
- Optimal timing of treatment in patients with no significant liver injury (fibrosis ≤F1, no FCH) is not defined so far. Further studies are required
  - to define best timing and duration of preemptive therapy
  - To determine the impact of early treatment on extra-hepatic manifestations of HCV : renal function/diabetes
- Long-term follow-up is necessary to demonstrate the expected beneficial impact on survival.

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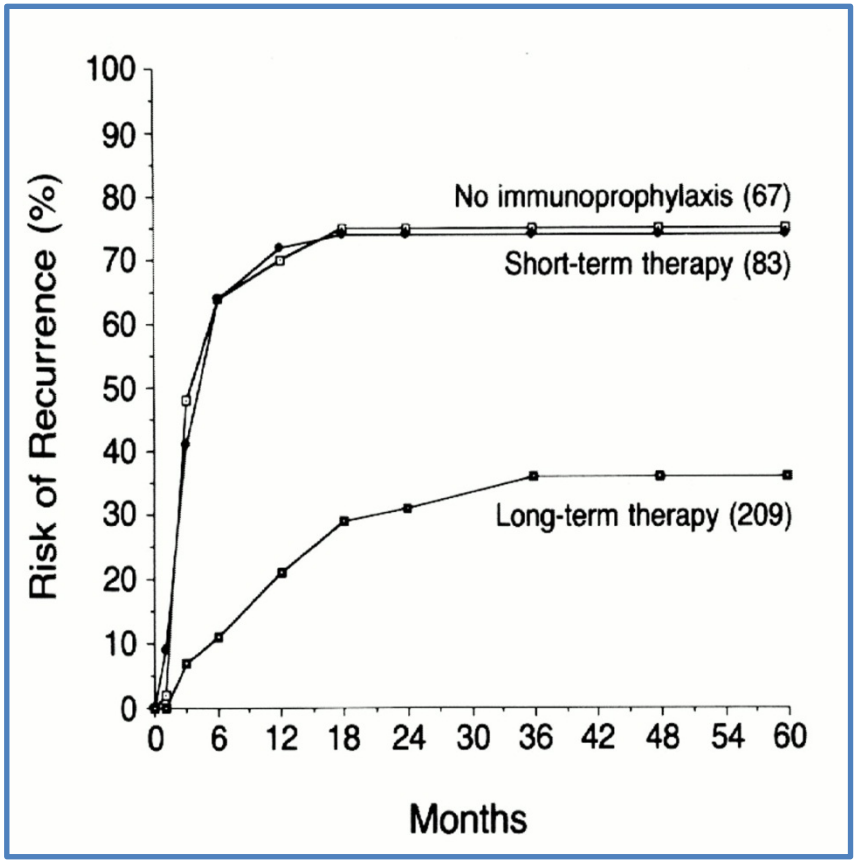
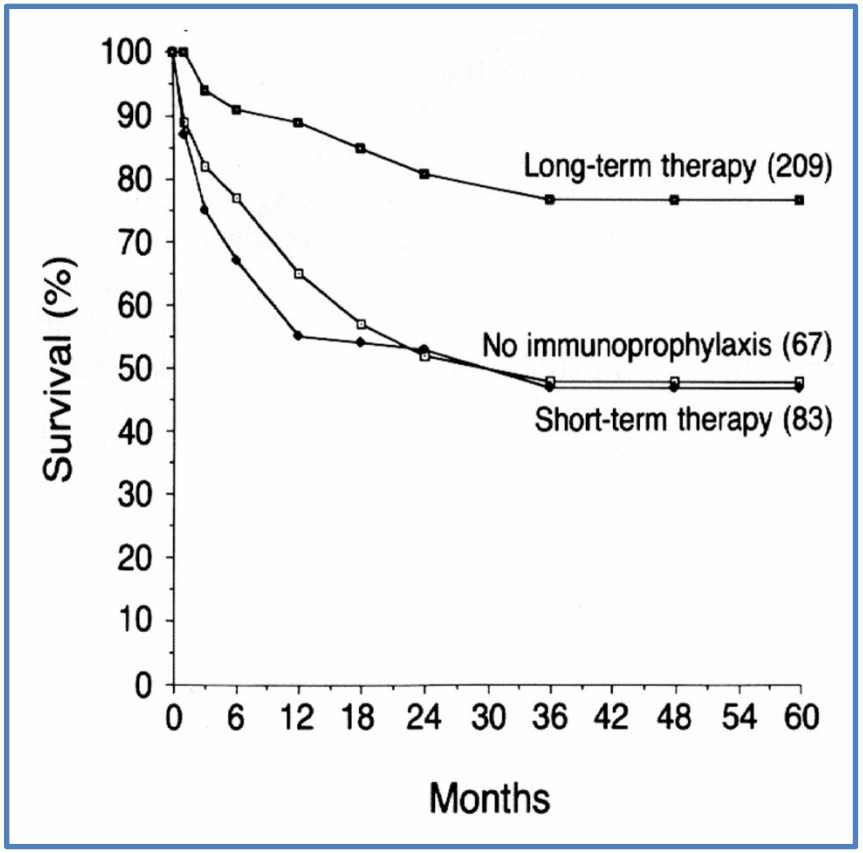
Natural History of HBV recurrence after liver transplantation without prophylaxis

KEY ISSUE

How to prevent HBV recurrence ?

HBV Recurrence and Survival
According to high doses/long term HBIG Prophylaxis





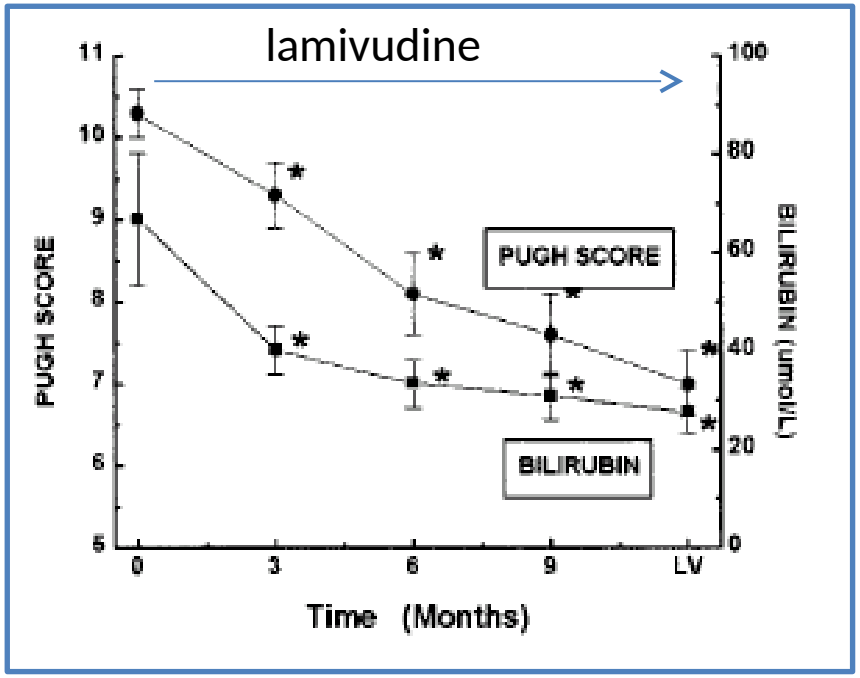
D. Samuel et al. NEJM 1993;329:1842-7

Dramatic Changes in Prophylaxis of HBV Infection Post-transplantation

- Before transplantation
  - Lamivudine (2000) or adefovir
  - Nucleos(t)ide analogues
- After transplantation
  - Anti-hepatitis B immunoglobulins (HBIG)-1990
  - Nucs first generation monoprophylaxis (2000)
  - Combination HBIG + Nucs
  - Combination HBIG + Nuc, then HBIG discontinuation
  - Nucs Second generation alone

Aims of pre LT treatment in HBV candidates

Improvement in liver function and delisting



Villeneuve et al. Hepatology 2000; 31 : 207

Impact on the risk of recurrence Post transplant

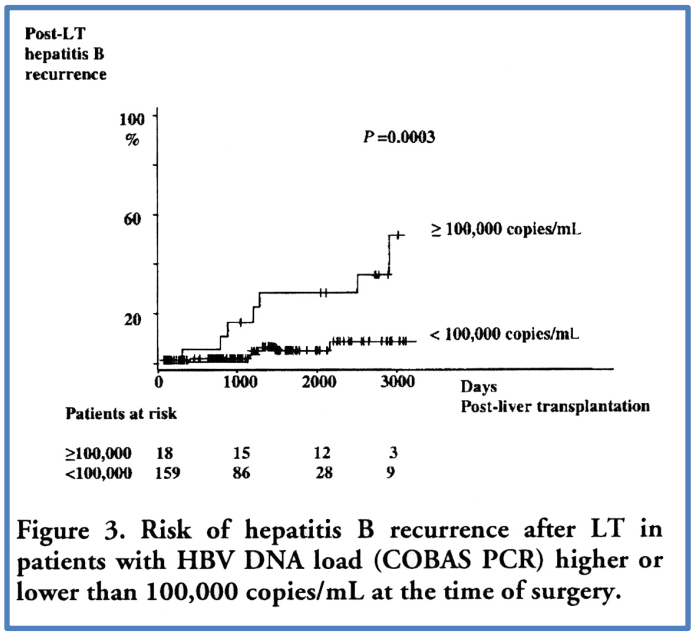


Figure 3. Risk of hepatitis B recurrence after LT in patients with HBV DNA load (COBAS PCR) higher or lower than 100,000 copies/mL at the time of surgery.

Marzano Liver Transplant 2004

Predictors of survival in HBV Cirrhotics Patients on Lamivudine

Pre transplant

- High-risk patients :

  ✉ start with Nucs and proceed with transplantation once HBV DNA < 5 log

- Low risk patients :

  → Close follow-up and MELD/CP monitoring

  - Inactive status if reasonable improvement , based on clinical judgment and staff meeting decision.

    ✉ consider de-listing when MELD <15

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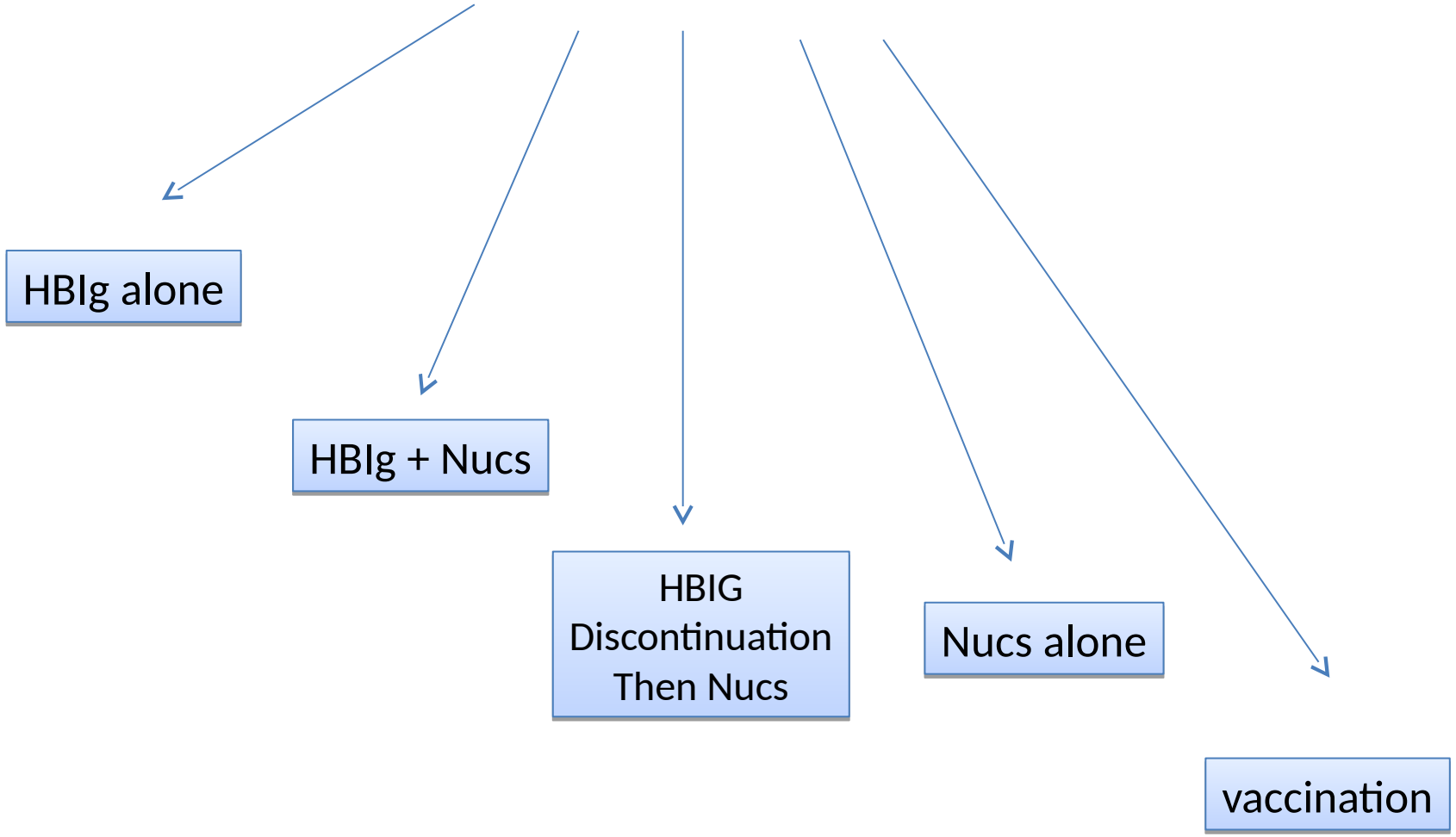
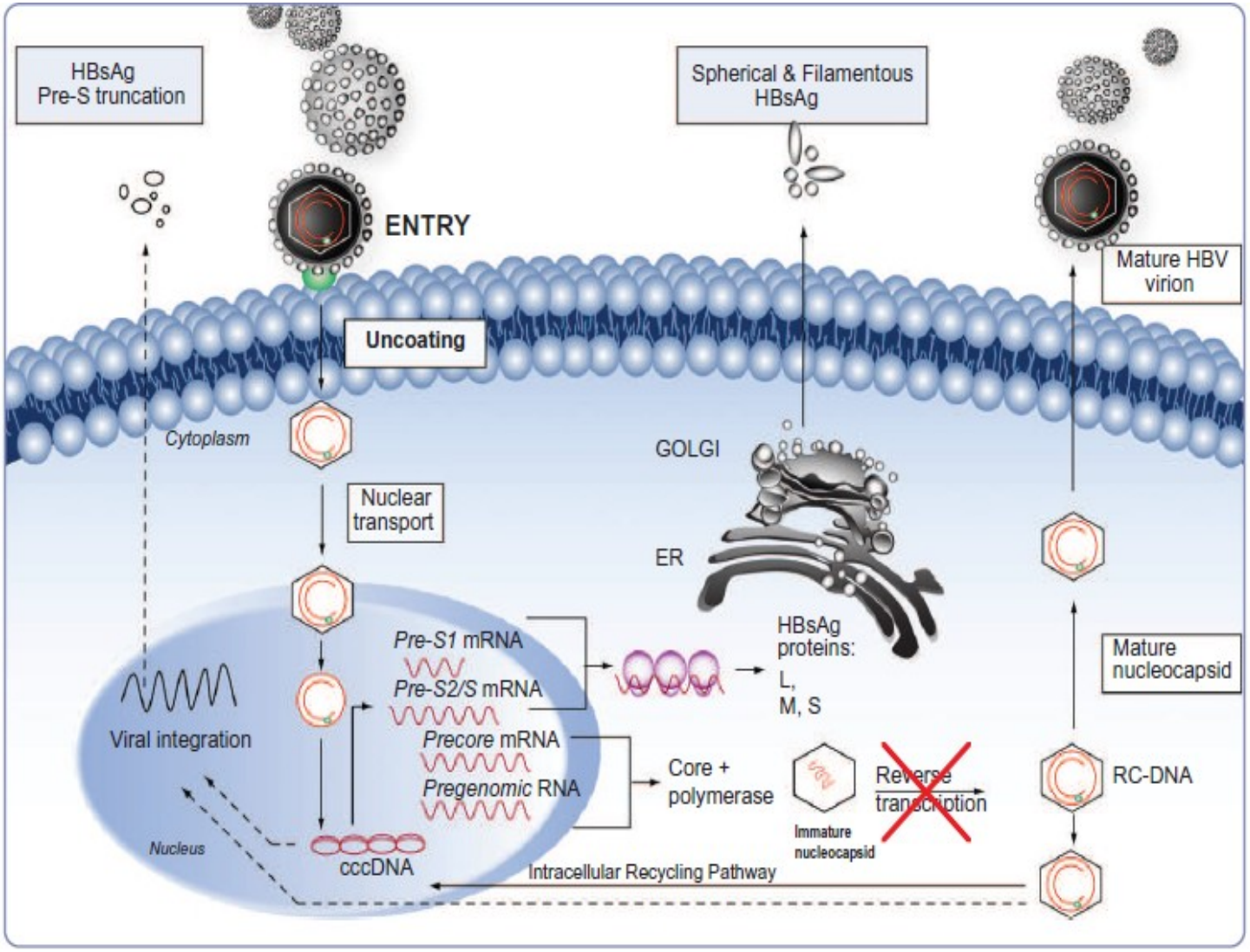
Further strategies to prevent HBV recurrence post transplant



Place of HBIG in Combination Protocol?

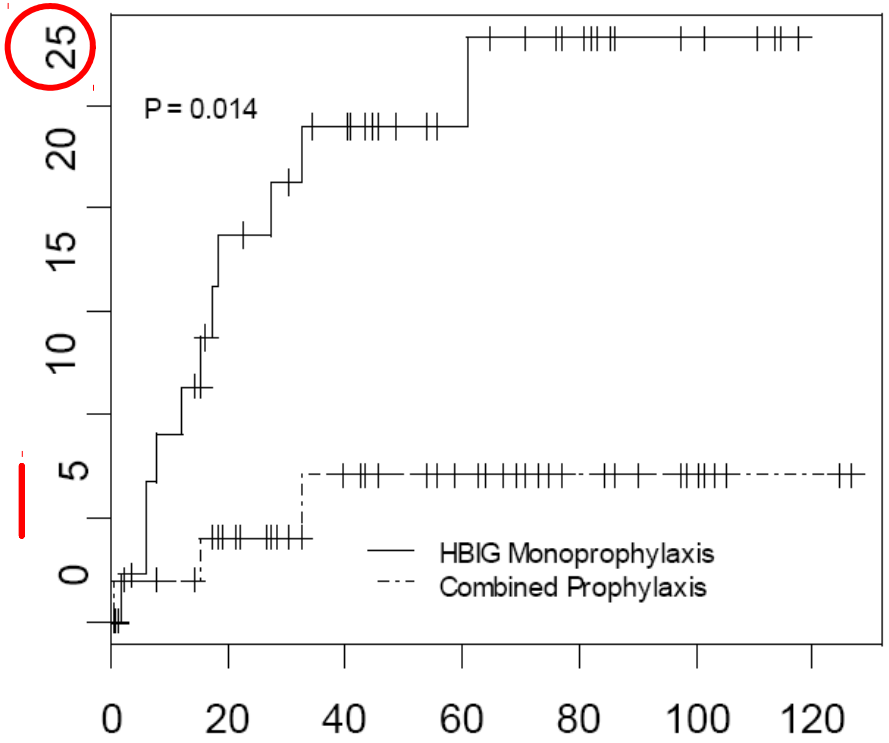
- **High doses HBIG at start is essential**
  - **Immediately makes HBsAg negative**
  - **Protects graft from immediate reinfection**
  - **Dose related to HBV DNA level at liver transplant**
- **On medium term**
  - **Lower doses can be used**
  - **Anti-HBsAb Level between 50-100 IU protective**
  - **IM monthly or SC/week HBIG as effective**
  - **Possibility of discontinuation in favourable cases**

HBV DNA and HBsAg Used 2 Distinct Pathways
Nucs Alone not Able to Block HBsAg



Chan J Hepatol 2011

Prevention of HBV Recurrence after transplantation
HBIG Monoprophylaxis vs Combined HBIG + Nucleos(t)ide

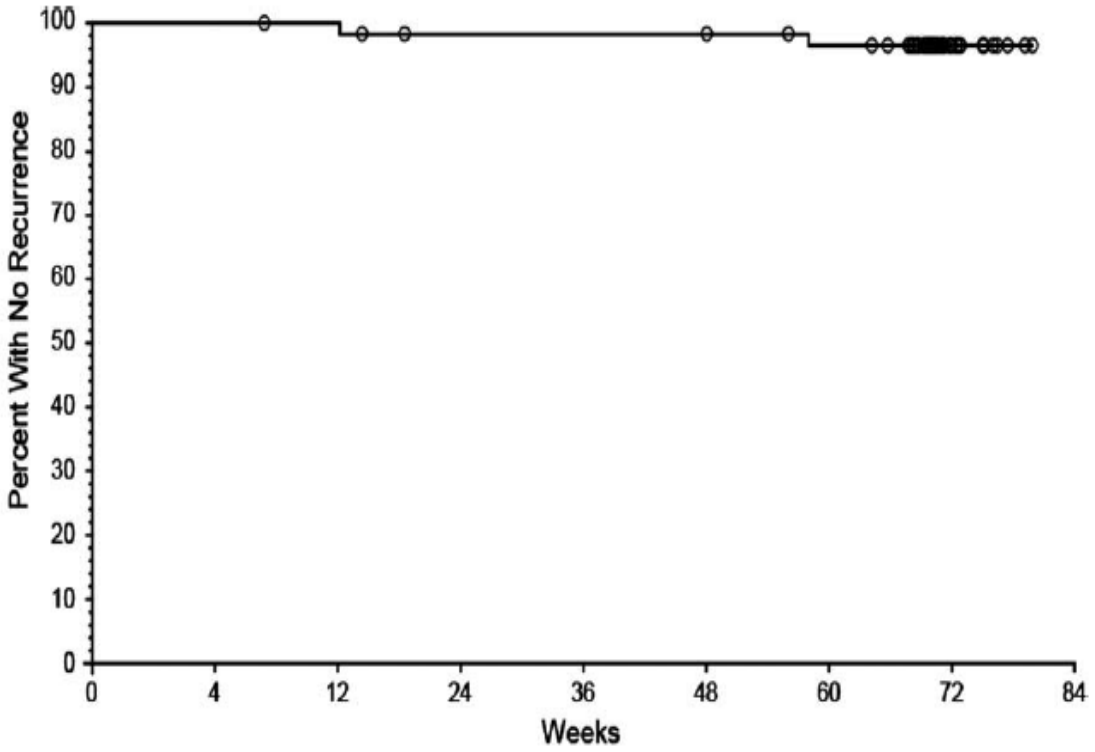


Factors independently associated with HBV recurrence:

- HBV DNA at LT> 10^5 copies/ml
- HCC at LT
- HBIG monoprophylaxis

Faria Gastroenterology 2008

HBIG + Entecavir Prophylaxis



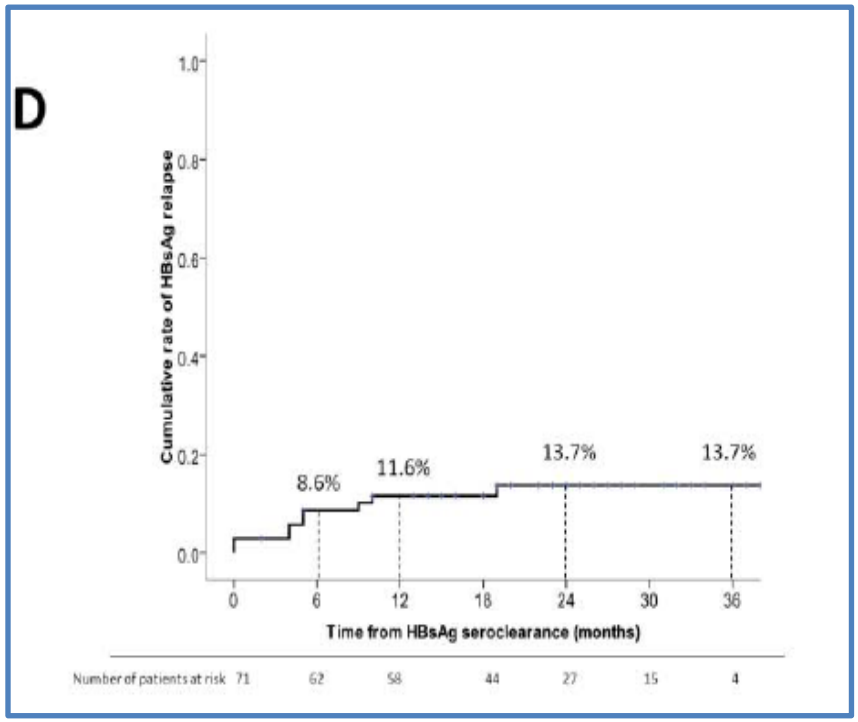
Weeks	BL	0–4	>4–12	>12–24	>24–36	>36–48	>48–60	>60–72	>72–84
Number at risk	61	61	60	57	57	57	54	13	0
Proportion without HBsAg recurrence	1	1	1	0.9833	0.9833	0.9833	0.9655	0.9655	0.9655

Figure 2. Kaplan-Meier plot of the proportion of evaluable patients without HBsAg recurrence. BL, baseline.

Perrillo R et al. Liver Transpl 2013;19:887-895

What can be achieved with Nucs Monoprophylaxis ? Entecavir

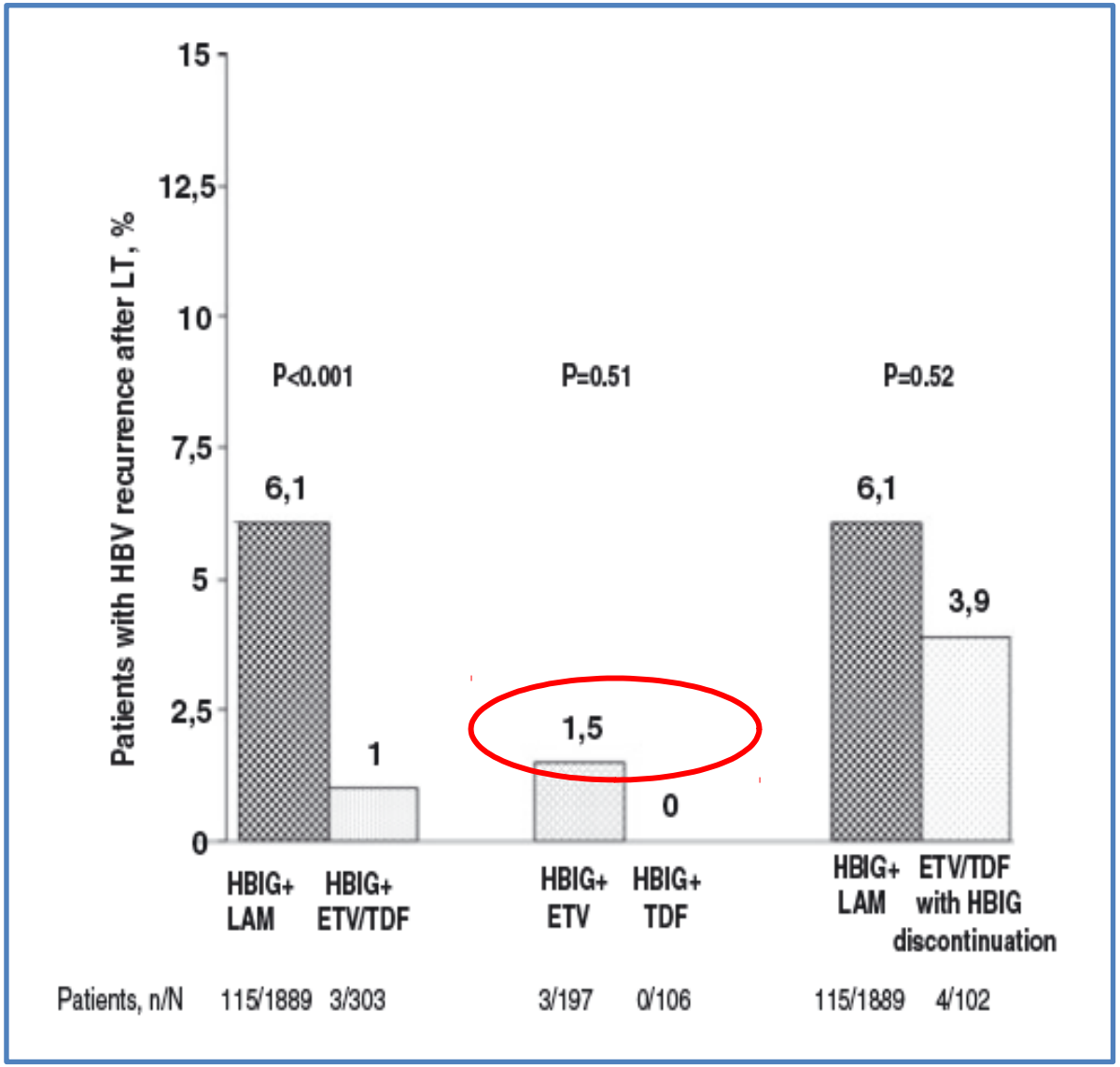
- 80 Patients, mean follow up 3 years
- 91% HBsAg loss at 2 years
- HBsAg reappearance: in 10 pts
- At end of FU :
  - 18 Pts (22%) HBsAg positive,
  - One Pt HBV DNA positive



HBs Ag Relapse

Fung Gastro 2011

HBV Reinfection According to Prophylaxis



Cholongitas E AJT 2013

Recommendations for HBV prophylaxis after transplantation

No up-dated Consensus meeting

Expert position paper

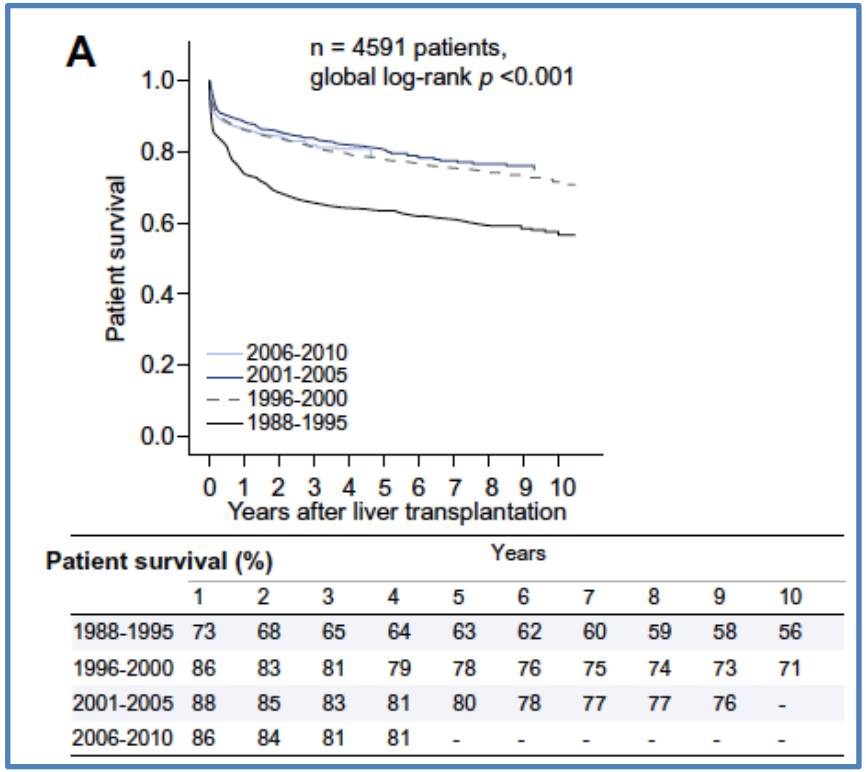
Table 1. Individualized approach to HBV prophylaxis

Risk profile for recurrence	
Lower risk	**Higher risk**
HBV DNA undetectable pre-LT	HBV DNA ≥103 IU/ml at time of LT
HDV negative	HDV coinfection (if become HBsAg positive, HDV recurs)
Wild-type HBV	Drug-resistant HBV (e.g., HIV coinfected, other heavily NA-exposed patients)
Adherent	Risk of nonadherence
HBV prophylaxis strategies	
NA monotherapy	NA plus low-dose HBIG
NA with short-term HBIG	
Prophylaxis withdrawal	

HBV, hepatits B virus; HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen; HDV, hepatitis D virus; LT, liver transplant; NA, nucleos(t)ide analogues.

Terrault et al. Am J Gastro 2013

Improvement of post LT survival in HBV patients over time



Patient survival (%)	Years									
	1	2	3	4	5	6	7	8	9	10
1988-1995	73	68	65	64	63	62	60	59	58	56
1996-2000	86	83	81	79	78	76	75	74	73	71
2001-2005	88	85	83	81	80	78	77	77	76	-
2006-2010	86	84	81	81	-	-	-	-	-	-

HBV according to transplantation period

Burra J Hepatol 2013

Take home messages

- Viral liver diseases are leading indications of LT
- A switch from transplantation for decompensated cirrhosis to LT for HCC has happened over the last decade.
- HCV and HBV recurrences hamper medium term survival rates post LT and should be prevented
- Considerable improvement in HBV prophylaxis has been achieved with excellent long term survival with a combination of mid term HBig + Nucs.
  - Individualized regimens with Hbig withdrawal can be proposed in favourable cases.
- Similar results are expected in HCV pts based on pre- and post LT DAA treatments which can achieve $\geq$ 90% SVR
- Further studies are required to determine evidence-based best strategies and impact on survival in HCV pts.