ISMETT Istituto di Ricovero e Cura a Carattere Scientifico

UPMC LIFE CHANGING MEDICINE

6th INTERNATIONAL CONGRESS

INFECTIONS & TRANSPLANTATION

Varese, 18-20 Maggio 2017
ATA Hotel

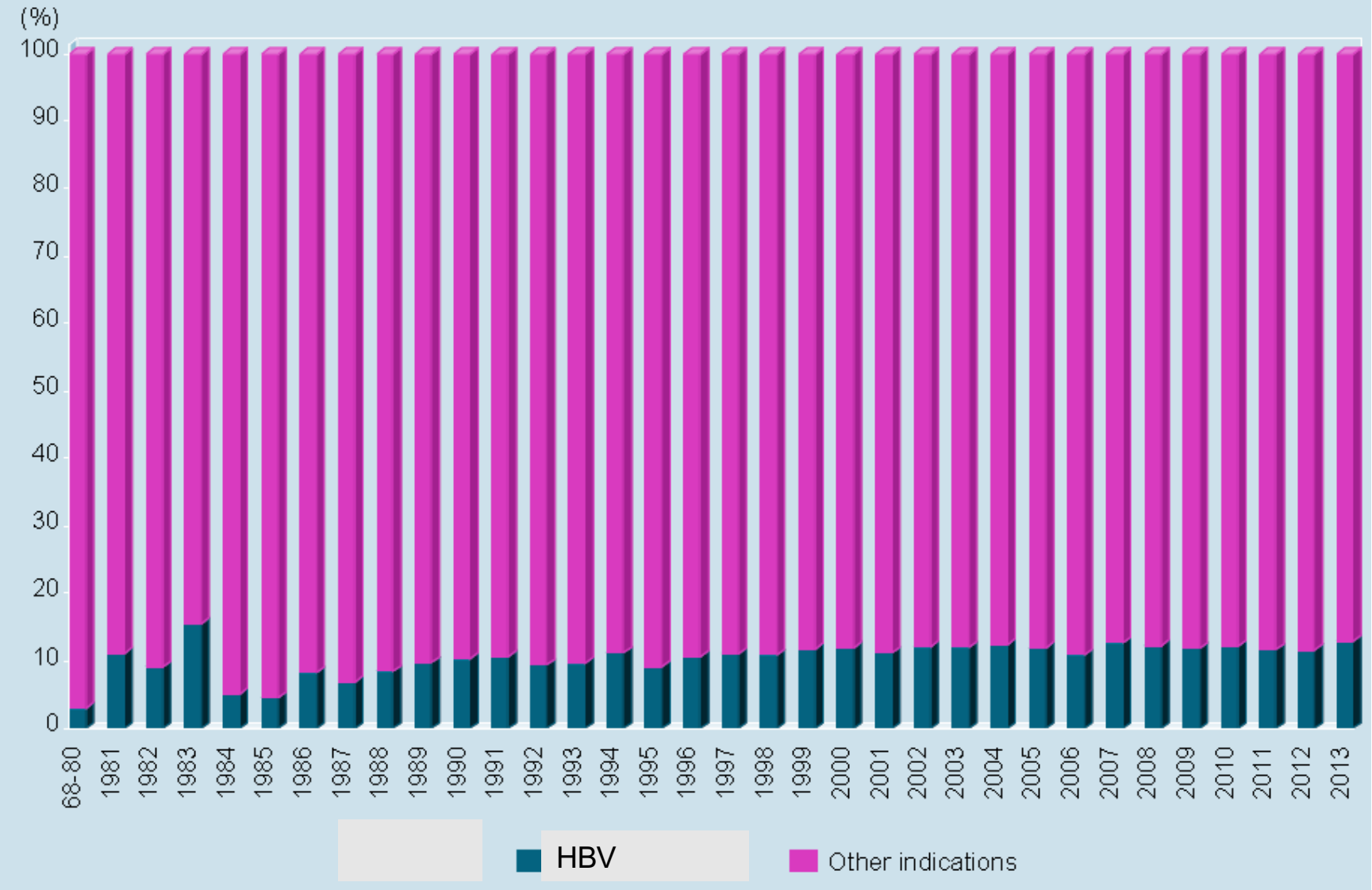
Prevenzione della recidiva di HBV dopo trapianto di fegato

Riccardo Volpes

ISMETT-IRCCS, Palermo

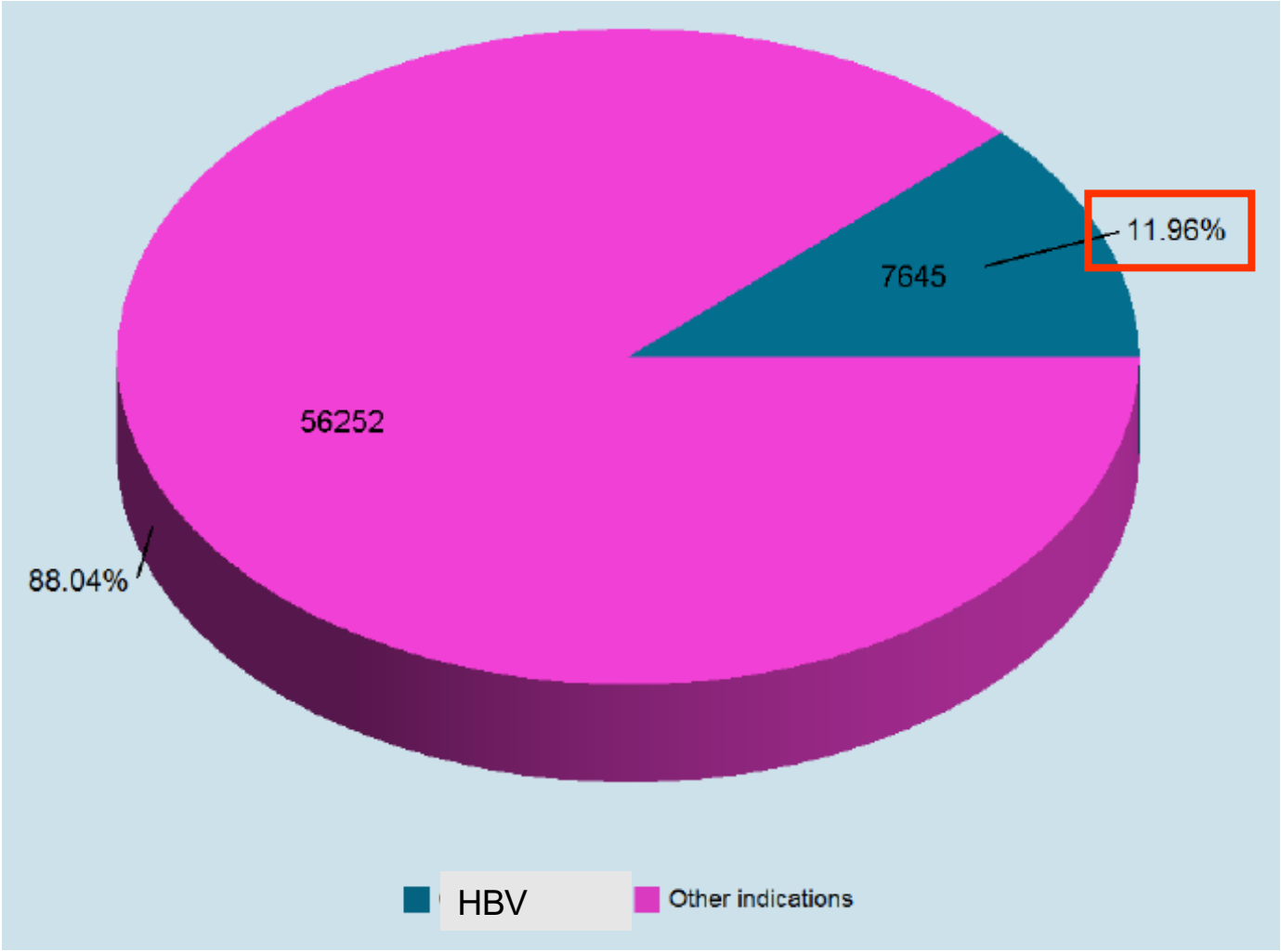
Evolution of LT for HBV in Europe

93,534 Adult Recipients May 1968 – December 2013



Proportion of LT for HBV Among Overall indications

63,897 Adult Recipients January 2000 – December 2013



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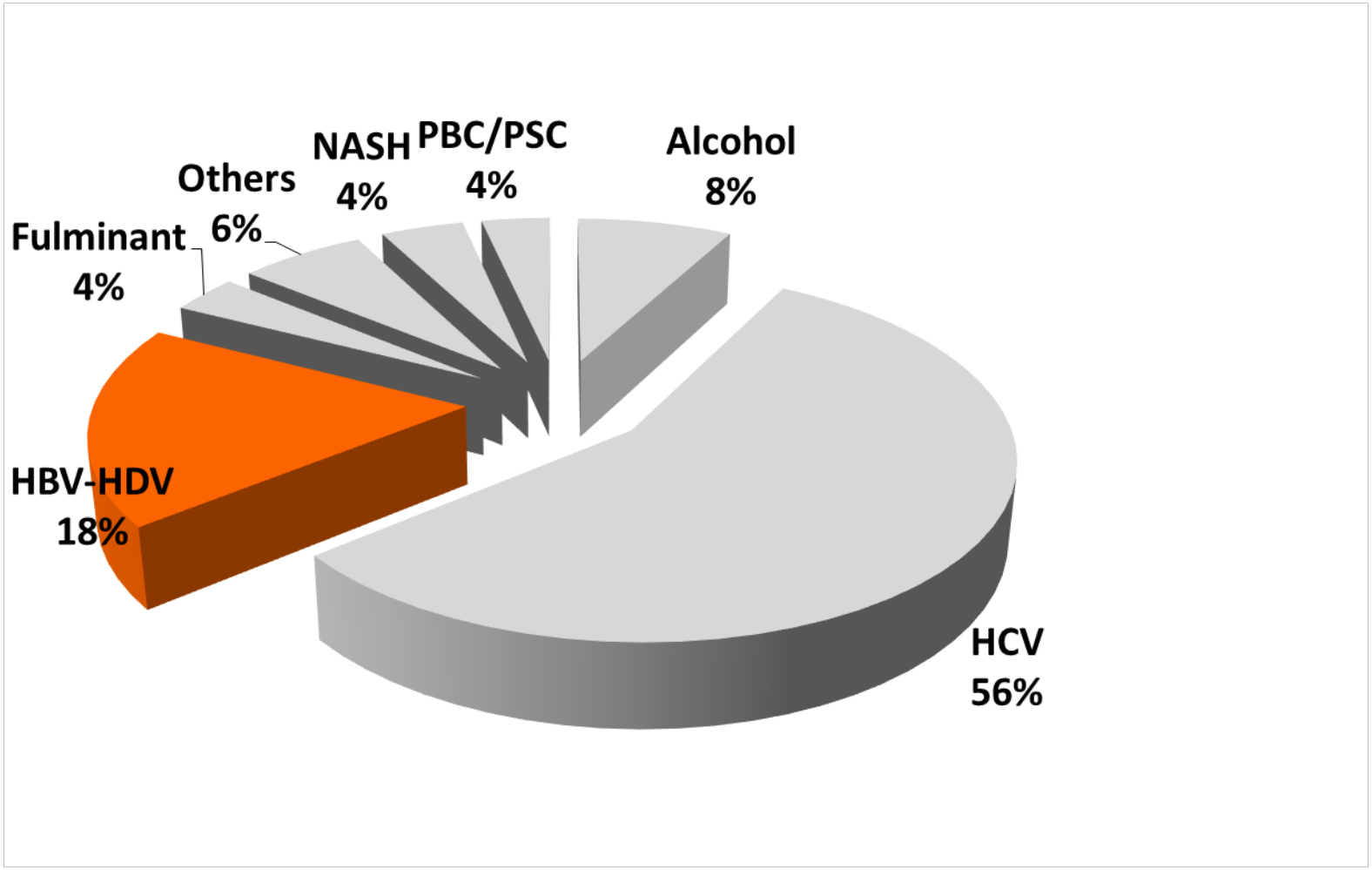
Etiology of liver diseases leading to liver transplantation
ISMETT experience – 1000 pts



HBV

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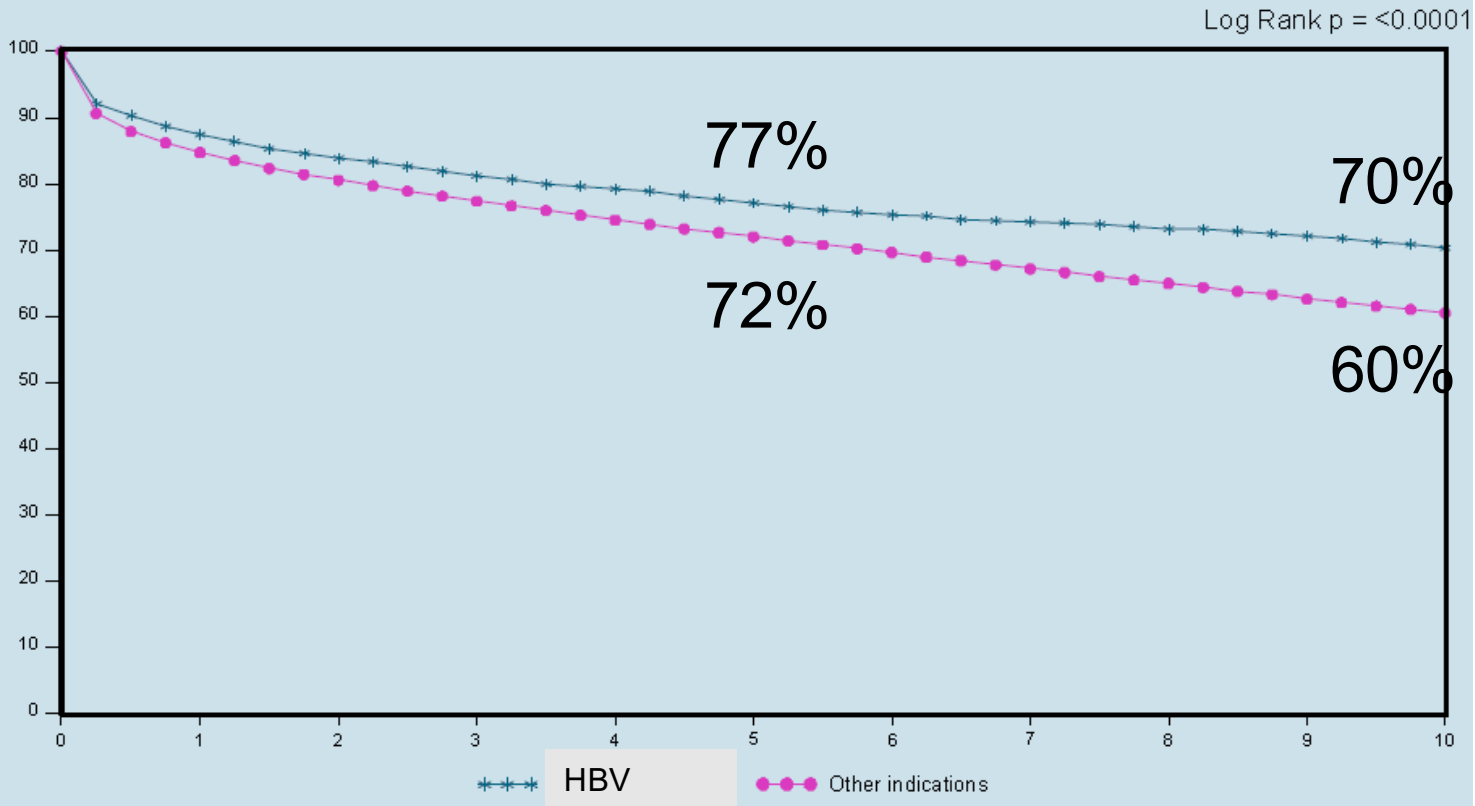
Patient Survival after LT for HBV Compared to the Others

63,737 Adult Recipients January 2000 – December 2013



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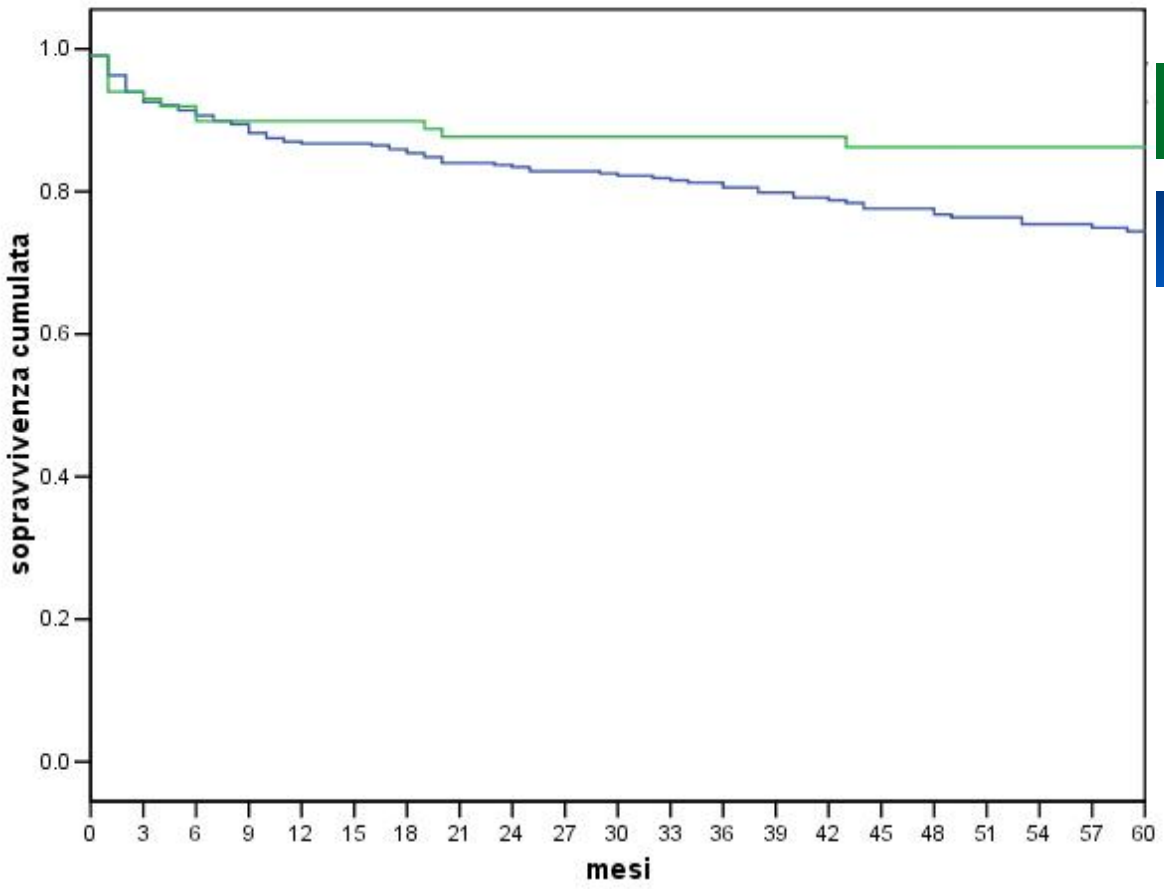
5 yrs patient survival after LT in ISMETT

HBV+ vs other etiologies



HBV +

Others

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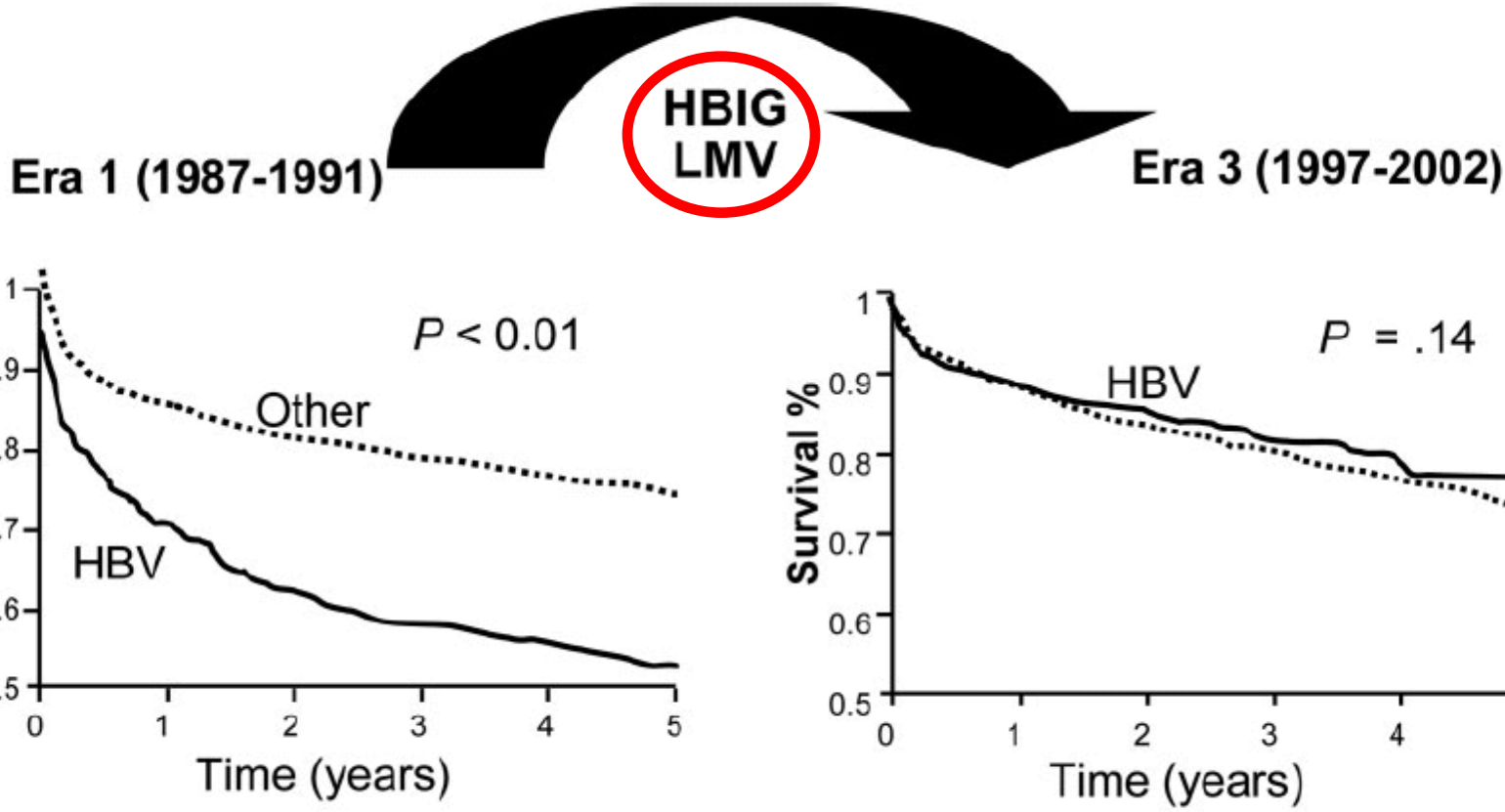
5 yrs survival for HBV+ pts after LT
Change outcome over a decade



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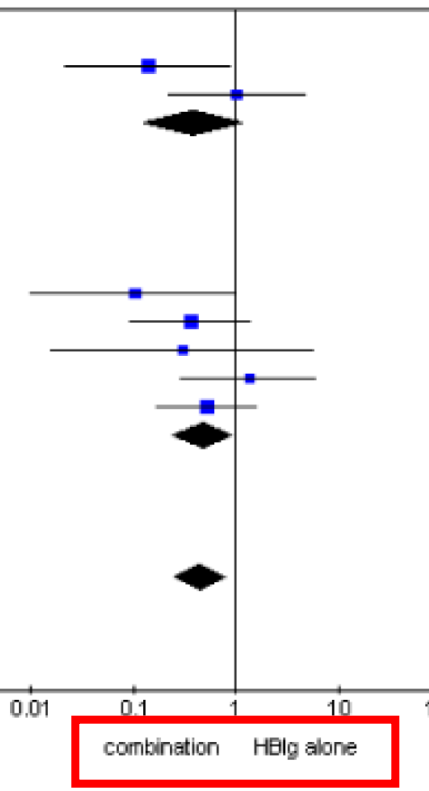
Overall mortality
Combination treatment vs HBIG alone

Review: lamivudine and adefovir for prevention of recurrence of HBV after liver transplantation (7.09)
Comparison: 04 lamivudine or adefovir and HBIG versus HBIG alone
Outcome: 01 overall mortality

Study or sub-category	lamivudine + HBIG n/N	HBIG n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 Prospective NRCT					
McCaughan [39]	1/9	8/10		23.18	0.14 [0.02, 0.90]
Dumortier [38]	2/17	5/43		8.67	1.01 [0.22, 4.72]
Subtotal (95% CI)	26	53		31.84	0.38 [0.13, 1.10]
Total events: 3 (lamivudine + HBIG), 13 (HBIG)					
Test for heterogeneity: Chi² = 2.67, df = 1 (P = 0.10), I² = 62.5%					
Test for overall effect: Z = 1.78 (P = 0.08)					
02 retrospective					
Han [41]	1/59	2/12		10.17	0.10 [0.01, 1.03]
Seehofer [42]	2/17	13/40		23.72	0.36 [0.09, 1.43]
Honaker [46]	0/9	2/14		6.12	0.30 [0.02, 5.61]
Ben-Ari [44]	2/9	4/24		6.67	1.33 [0.29, 6.06]
Yilmaz [43]	3/16	9/25		21.48	0.52 [0.17, 1.64]
Subtotal (95% CI)	110	115		68.16	0.46 [0.23, 0.91]
Total events: 8 (lamivudine + HBIG), 30 (HBIG)					
Test for heterogeneity: Chi² = 3.76, df = 4 (P = 0.44), I² = 0%					
Test for overall effect: Z = 2.22 (P = 0.03)					
Total (95% CI)	136	168		100.00	0.44 [0.25, 0.77]
Total events: 11 (lamivudine + HBIG), 43 (HBIG)					
Test for heterogeneity: Chi² = 6.41, df = 6 (P = 0.38), I² = 6.4%					
Test for overall effect: Z = 2.84 (P = 0.004)					



Katz et al. Transpl Infect Dis 2009

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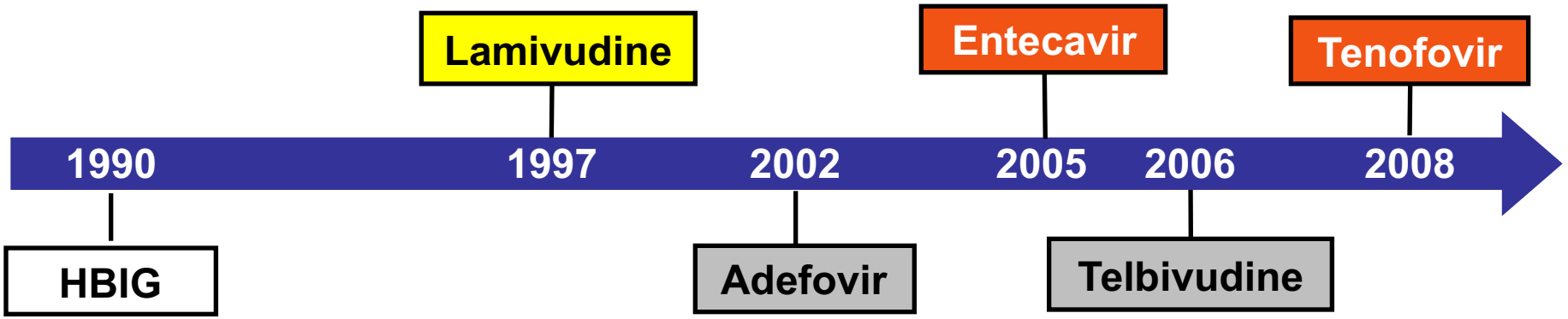
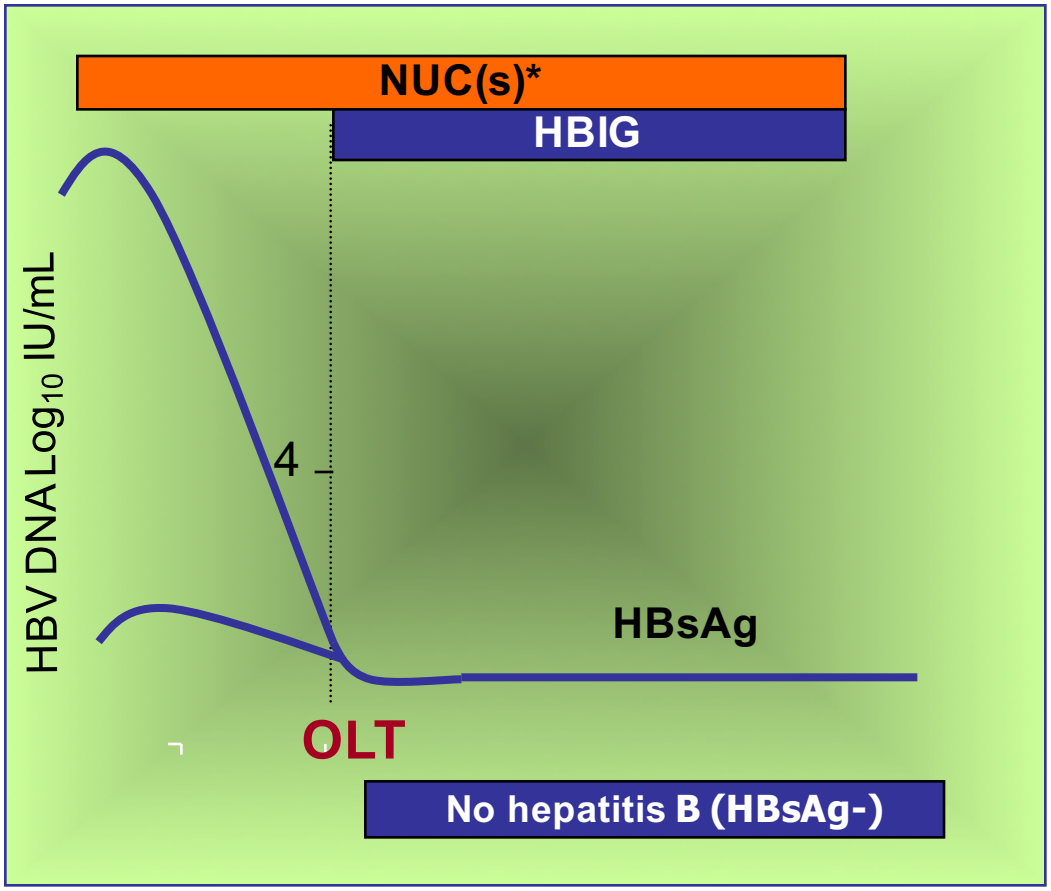
LAMIVUDINE + HBIG

Authors	N°	LAM pre-LT (months)	HBV DNA - at LT (%)	HBIG route of administration	HBV recurrence (%)
Markowitz (1998)	14	3	93	IV	0
Yao (1999)	10	8.6	80	IV then IM	10
Yoshida (1999)	7	NR	100	IM	0
Angus (2000)	37	3.2	NR	IM	3
Marzano (2001)	33	4.6	100	IV	4
McCaughan (1999)	9	0	NR	IM	0
Rosenau (2001)	21	4.6	77	IV	10
Roche (2003)	15	4.6	73	IV	7
Han (2000)	59	NR	NR	IV	0
Seehofer (2001)	17	106	71	IV	18

Prevention of HBV recurrence after LT
The landscape



Liver transplantation in HBV+ patients
Combined prophylaxis (NUCs+HBIG)



Long-term prophylaxis for HBV recurrence post-LT
ISMETT protocol

HBsAg+ recipient

OLT

HBV-DNA neg.

Anhepatic phase	HBIG 10.000 U. i.v.
Daily from 2 to 7 day	HBIG 5.000 U. i.v.

Since day 1	oral NA
Since day 90	HBIG 1.000 U. i.m./s.c. monthly

AntiHBs titer ≥100 UI

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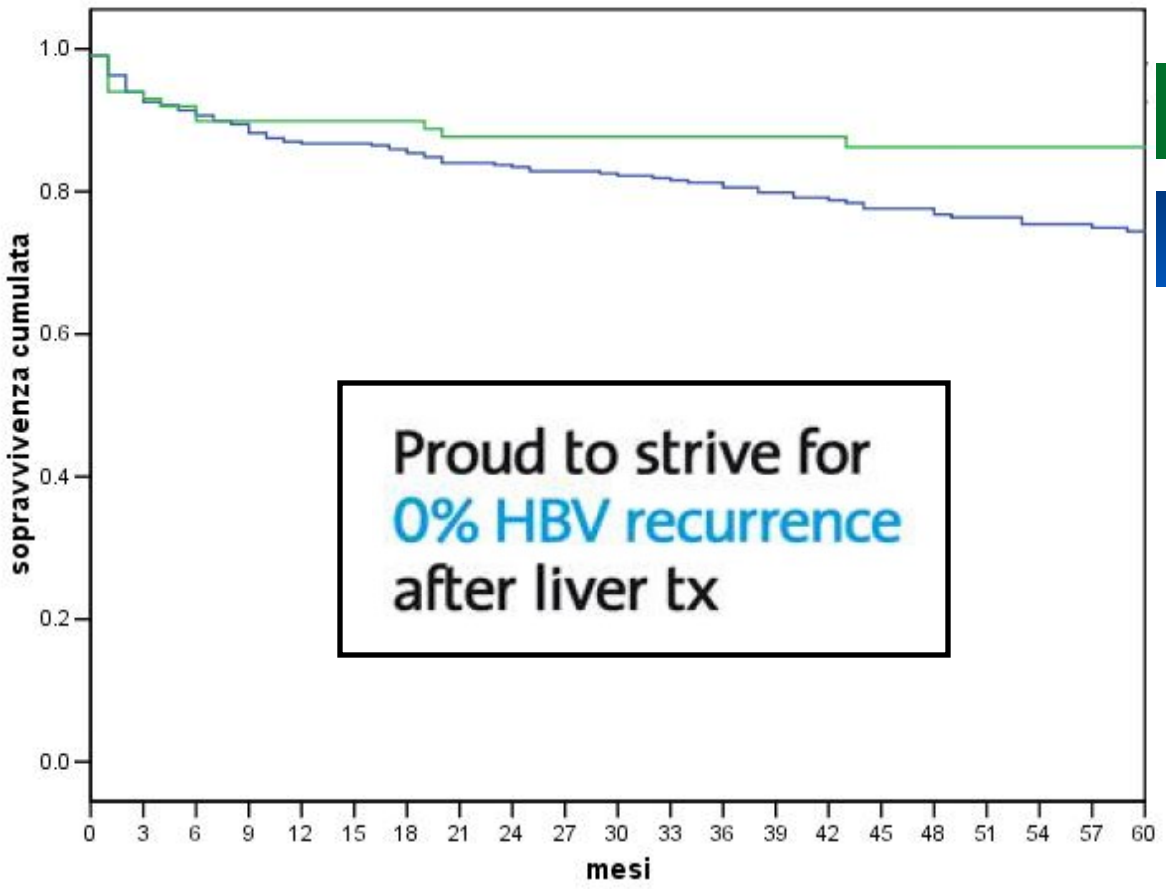
5 yrs patient survival after LT in ISMETT

HBV+ vs other etiologies



HBV +

Others

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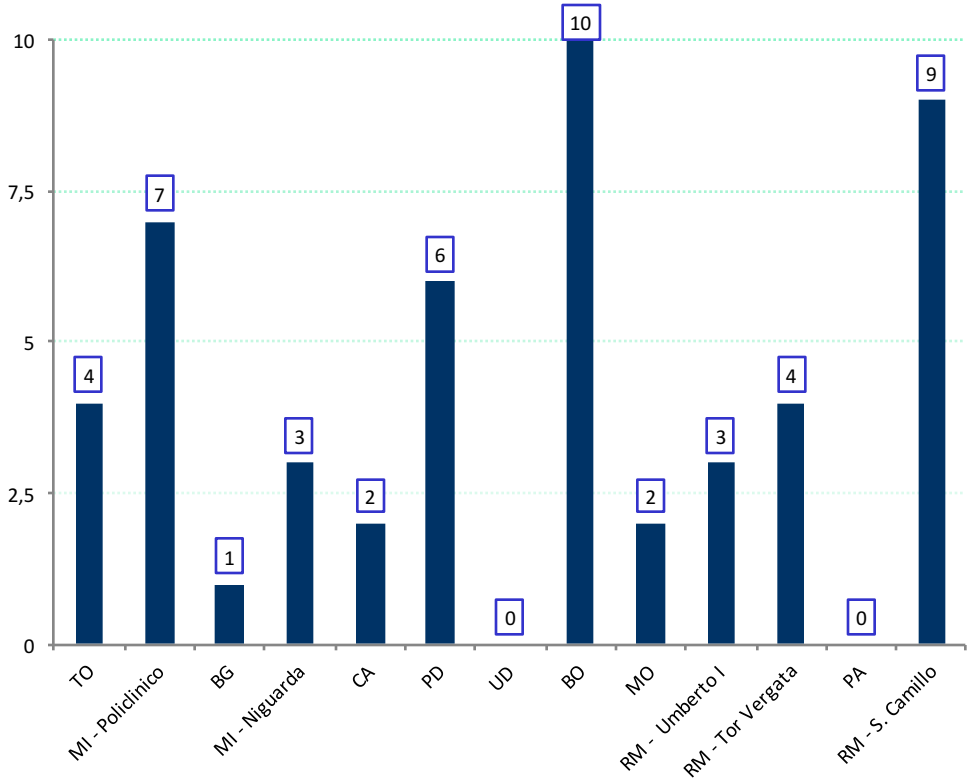
HBV recurrence after LT in Italy

	1983-2011	2011
	2,260	128
HBV recurrence after LT	98 (4%)	0



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UPMC LIFE CHANGING MEDICINE

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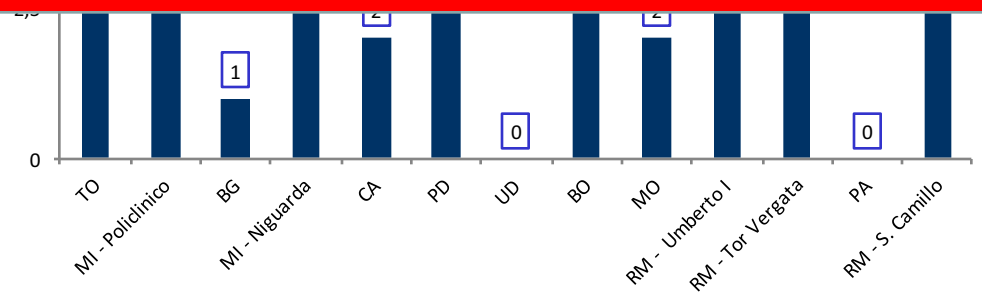
ADHERENCE



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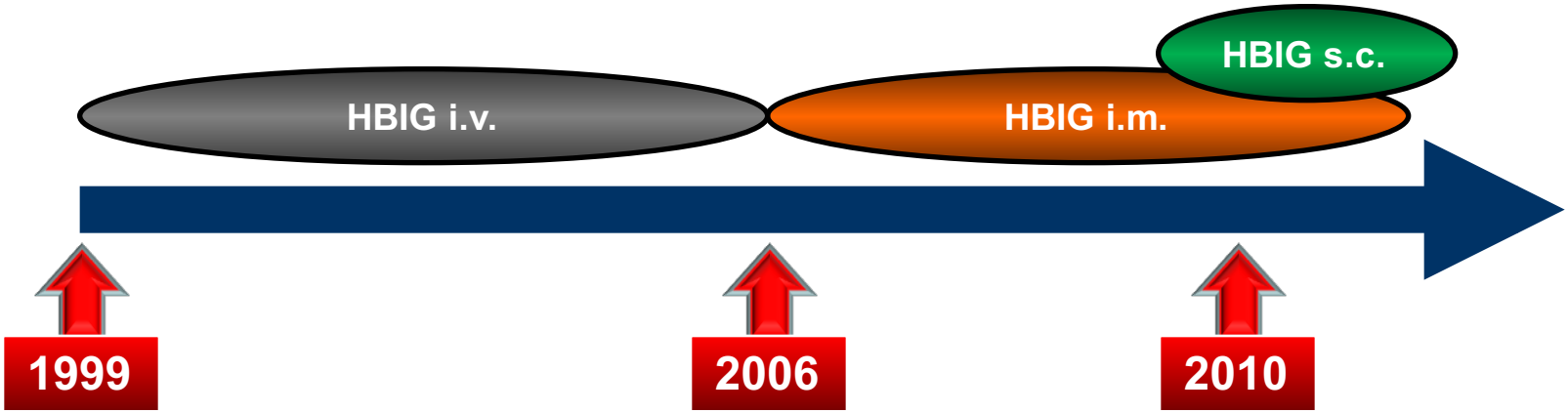
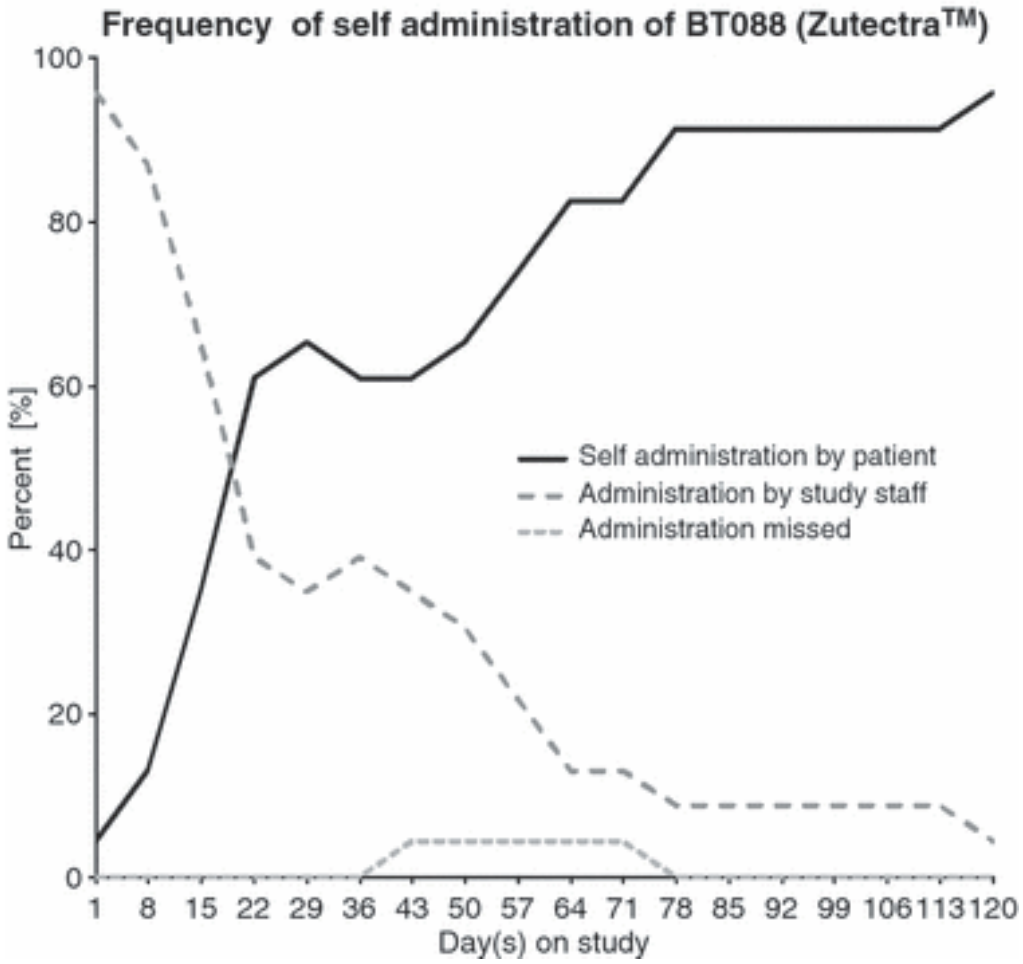
Long-term prophylaxis for HBV recurrence post-LT
ISMETT protocol

From day 1	oral NA
From day 90	long-term HBIG



Self administration of subcutaneous HBIG



Yahyazadeh et al Transplant Intern 2011

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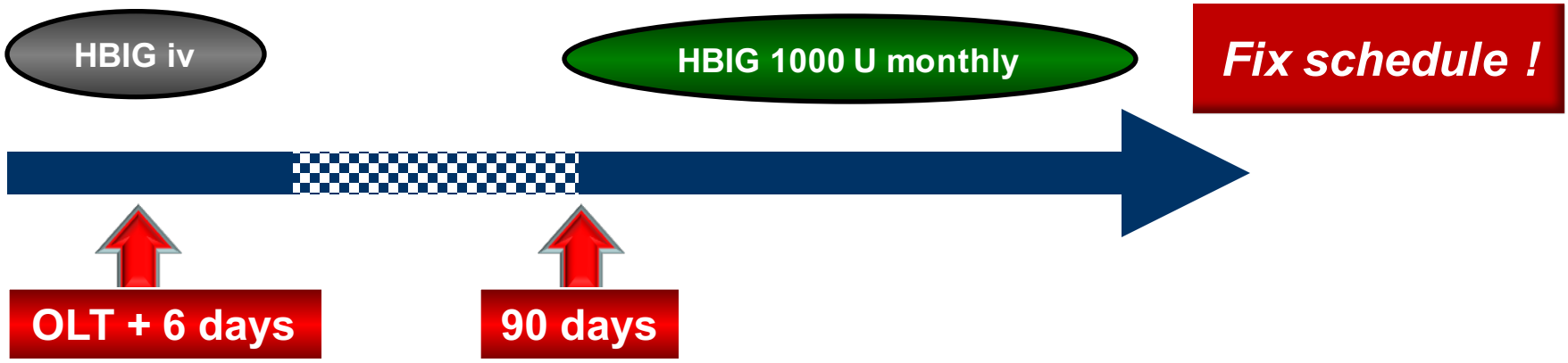
"Early" conversion to HBIG

95 pts post-LT



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Long-term prophylaxis for HBV recurrence post-OLT

- NA + low-dose HBIG

EFFICACY → 0% RECURRENCE

Prophylaxis for HBV recurrence after liver transplantation

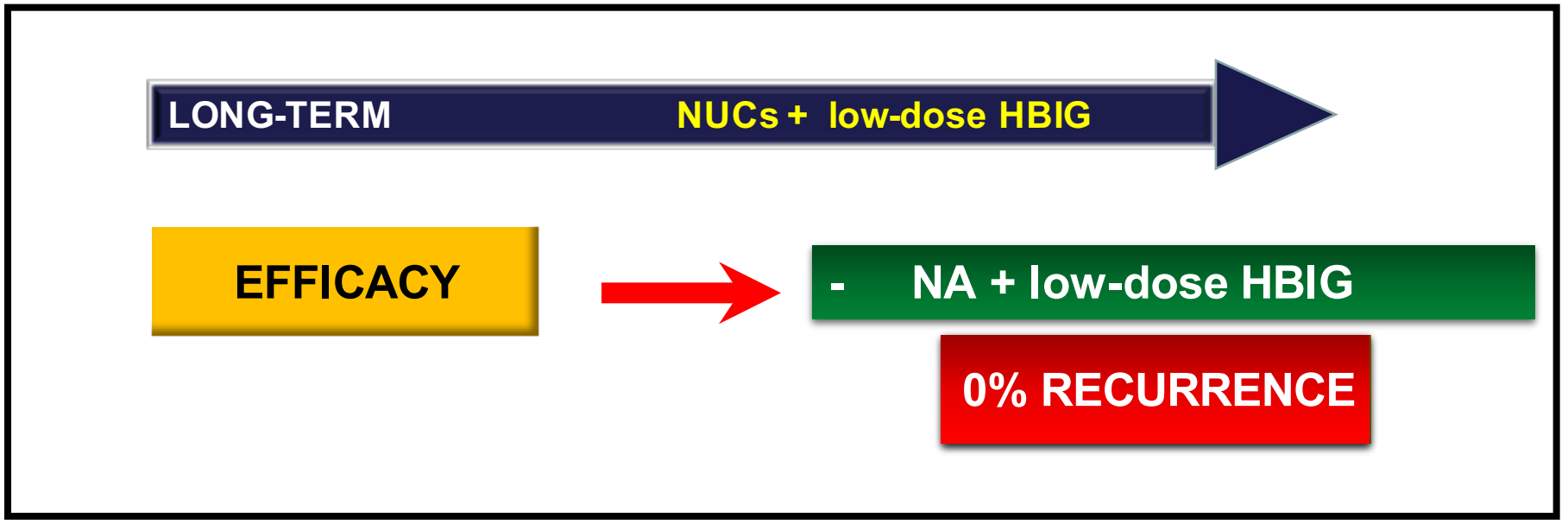
Is HBIG still needed?

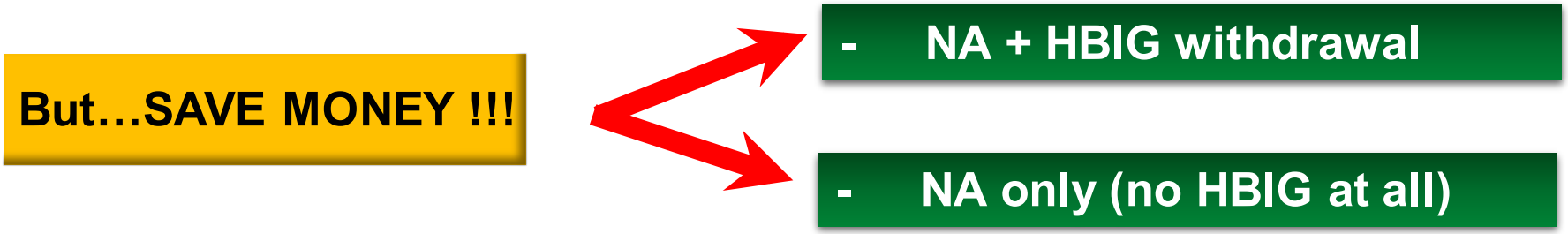
Costs of HBIg

Lamivudine	$111/mo
Intramuscular HBIG*	$750/injection
Intravenous HBIG†	$10,000/infusion
Retransplantation‡	$499,000
Death	$10,000
Liver biopsy	$325
Laboratory tests§	$150/mo

Huy- Han, Liver Transplantation 2003

Long-term prophylaxis for HBV recurrence post-OLT
The future





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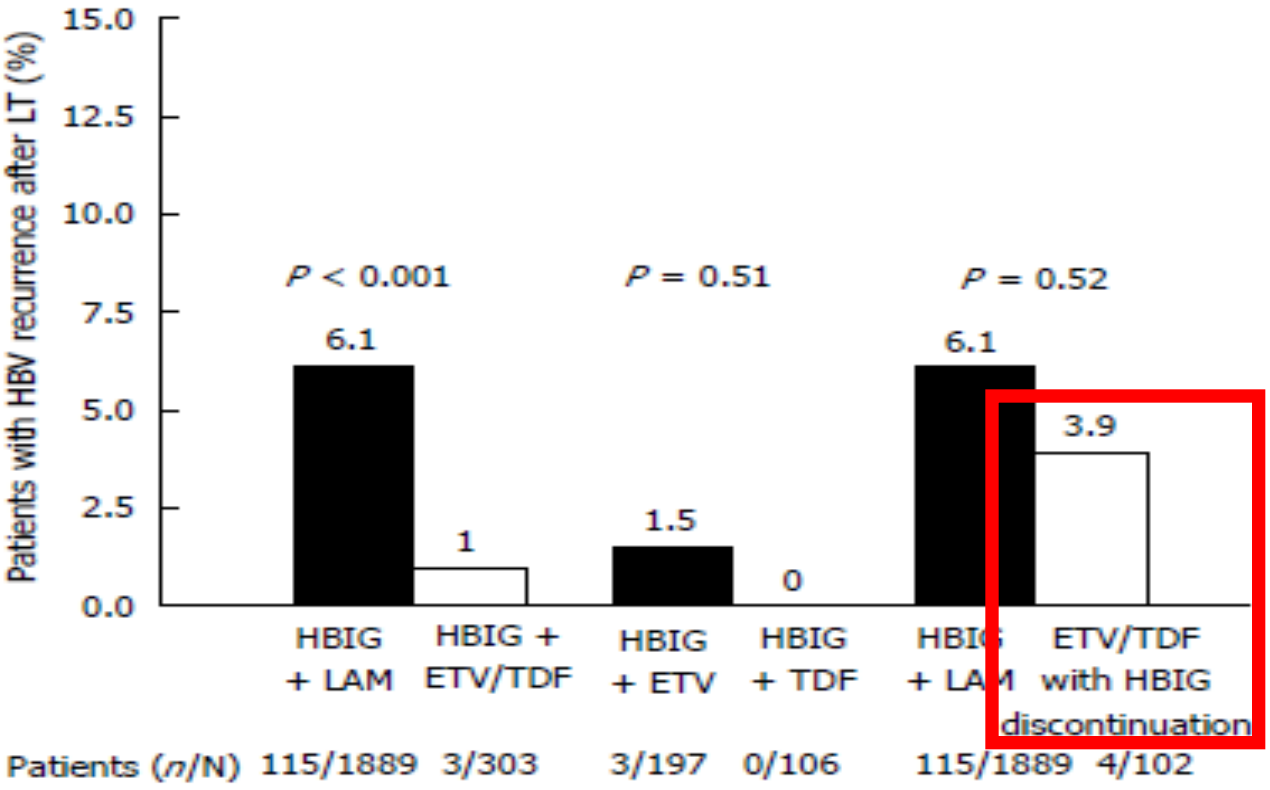
NA + HBIG at LT and then *HBIG withdrawal*



Cholongitas E, World Journal of Gastroenterology 2013

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NA only (*NO HBIG at all*)

Oral Nucleoside/Nucleotide Analogs Without Hepatitis B Immune Globulin After Liver Transplantation for Hepatitis B

James Fung, MD[1–3], See-Ching Chan, MS, PhD[2,3], Cindy Cheung, MPhil[2], Man-Fung Yuen, MD, PhD[1,3], Kenneth Siu-Ho Chok, MBBS[2], William Sharr, MBBS[2], Albert Chi-Yan Chan, MBBS[2], Tan-To Cheung, MBBS[2], Wai-Kay Seto, MD[1], Sheung-Tat Fan, MS, MD, PhD, DSc[2,3], Ching-Lung Lai, MD[1,3] and Chung-Mau Lo, MS[2,3]

Am J Gastroenterol 2013; 108:942–948

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Of the 362 patients, 176 (49%), 142 (39%), and 44 (12%) were on lamivudine (LAM), entecavir (ETV), and combination therapy (predominantly LAM+adefovir), respectively, at the time of transplant. The median follow-up length was 53 months. The rate of hepatitis B surface antigen seronegativity and hepatitis B virus (HBV) DNA suppression to undetectable levels at 8 years was 88 and 98%, respectively. The virological relapse rates (>1 log increase IU/ml) at 1, 3, 5, and 8 years was 5, 10, 13 and 16%, respectively. The virological relapse rate at 3 years for LAM, ETV, and combination group was 17, 0, and 7%, respectively ($P<0.001$). Forty-two patients had virological relapse, of which 36 had YMDD mutation (31 in the LAM group and 5 in the combination group). The overall 8-year survival was 83%, with no difference between the three treatment groups ($P=0.94$). No mortality from HBV recurrence occurred in the 362 patients.

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UPMC LIFE CHANGING MEDICINE

NA only (*NO HBIG at all*)

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Table 3. Relative risk of virological rebound after liver transplantation

Parameters at the time of transplant	Relative risk	*P* value
Lamivudine therapy	15.21 (95% CI, 2.04–113.29)	0.010
Hepatocellular carcinoma	7.48 (95% CI, 1.84–30.37)	0.023
HBV DNA > 3log IU/ml	4.17 (95% CI, 1.81–9.62)	<0.001

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(*Transplantation* 2015;99: 1321–1334)

Review

OPEN

Rational Basis for Optimizing Short and Long-term Hepatitis B Virus Prophylaxis Post Liver Transplantation: Role of Hepatitis B Immune Globulin

Bruno Roche,[1,2,3] Anne Marie Roque-Afonso,[2,3,4] Frederik Nevens,[5] and Didier Samuel[1,2,3]

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Time of LT	Low risk patients - Undetectable HBV DNA levels - HBeAg negative - Fulminant hepatitis B - HDV coinfection [a]	High risk patients - Detectable HBV DNA levels - HBeAg positive - Presence of drug-resistant HBV - HIV coinfection - High risk of HCC recurrence - Poor compliance to antiviral therapy
Anhepatic phase and first post operative week	HBIg IV [b]	
Post-LT	Combination prophylaxis with low-dose IV or IM [c] HBIG and antiviral(s) to maintain anti-HBs levels >100 IU/l Discontinuation of HBIG is possible and maintain only long term antiviral(s)	Combination prophylaxis with low-dose IV or IM [c] HBIG and antiviral(s) to maintain anti-HBs levels >100 IU/l. Cessation of HBIG is not recommended

Review Article

Prevention and Treatment of Recurrent Hepatitis B after Liver Transplantation

Rakhi Maiwall and Manoj Kumar*

Journal of Clinical and Translational Hepatology **2016** vol. 4 | 54–65

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- Start patient on NA when listed for LT
- Monitor HBV-DNA while listed

Assess risk status

Low-risk patient
- Undetectable HBV-DNA at LT

- NO HBIG
- High potency NA (ETV or TFV)

High-risk patient
- Detectable HBV-DNA at LT
- Presence of drug-resistant HBV
- HIV/HDV coinfection
- HCC at LT

- HBIG
- High potency NA (ETV or TFV)

Maiwall J Clin Transl Hepatol 2016; 4:54-65

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UPMC LIFE CHANGING MEDICINE

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Assess risk status

Low-risk patient
- Undetectable HBV-DNA at LT

- NO HBIG
- High potency NA (ETV or TFV)

High-risk patient
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- Presence of drug-resistant HBV
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- HCC at LT

- HBIG
- High potency NA (ETV or TFV)

Maiwall J Clin Transl Hepatol 2016; 4:54-65

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Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

Prevention of HBV recurrence after liver transplantation

Recommendations

- All patients on the transplant waiting list with HBV related liver disease should be treated with NA (Evidence level II, grade of recommendation 1).
- Combination of hepatitis B immunoglobulin (HBIG) and a potent NA is recommended after liver transplantation for the prevention of HBV recurrence (Evidence level II-1, grade of recommendation 1).
- Patients with a low risk of recurrence can discontinue HBIG but need continued monoprophylaxis with a potent NA (Evidence level II-1, grade of recommendation 2).

Prevention of HBV reinfection after liver transplantation

ELITA
European
Liver and Intestine
Transplant Association

ELITA clinical practical guidelines 2017

PRAGUE
May 24 – 27, 2017
THE 2017 JOINT INTERNATIONAL
CONGRESS OF ILTS, ELITA & LICAGE

ILTS
INTERNATIONAL LIVER TRANSPLANTATION SOCIETY

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Grazie

Riccardo Volpes

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ISMETT, Palermo

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