“Milestones in the treatment of liver diseases, a journey through four decades (1968 to 2013)”

by Jenny Heathcote, MD

University of Toronto


The
Pakenham Arms
Ale
& Cider
House
PAKENHAM ARM
Priority over
oncoming
vehicles
0207 837 6933

Patients uco Sheila Sherlock 1968

In Patients

Fulminant Hepatic Failure

Acute Budd Chiari “OCP”

Decompensated cirrhosis:-

- GI bleed, Ascites, HRS
- Encephalopathy

Out Patients

Jaundice with pruritus

Hepatosplenomegaly NYD

Hepatic encephalopathy (post porto-caval shunt)

Wilson Disease

1968 → 2013: What changed the field of Hepatology?

INVESTIGATIONS	THERAPIES
Ascitic taps - Diagnostic + Therapeutic	Corticosteroids / Azathioprine / diuretics
GI endoscopy – by luminal	(Potent) Broad spectrum antibiotics
Virology	β blockers (non selective)
Ultrasound	Antiviral therapies
CT scan	UDCA
ERCP (Diagnostic / Therapeutic)	Midrodrine / Terlipressin
MRI / MRC	Variceal sclerotherapy/banding
Transient elastography	TIPS
	Radiofrequency/alcohol oblation (HCC)

Liver Transplant (DD and LD)

Recognition of the Specialty

Medical Journals : only Hepatology

All after 1980

Hepatology	J. Viral Hepatitis
J. Hepatology	Hepatology International
Liver ⟶	Liver International

A 40 year story: PBC

1950 Presentation: Symptoms of Cholestasis

1960 Diagnosis AMA and liver biopsy

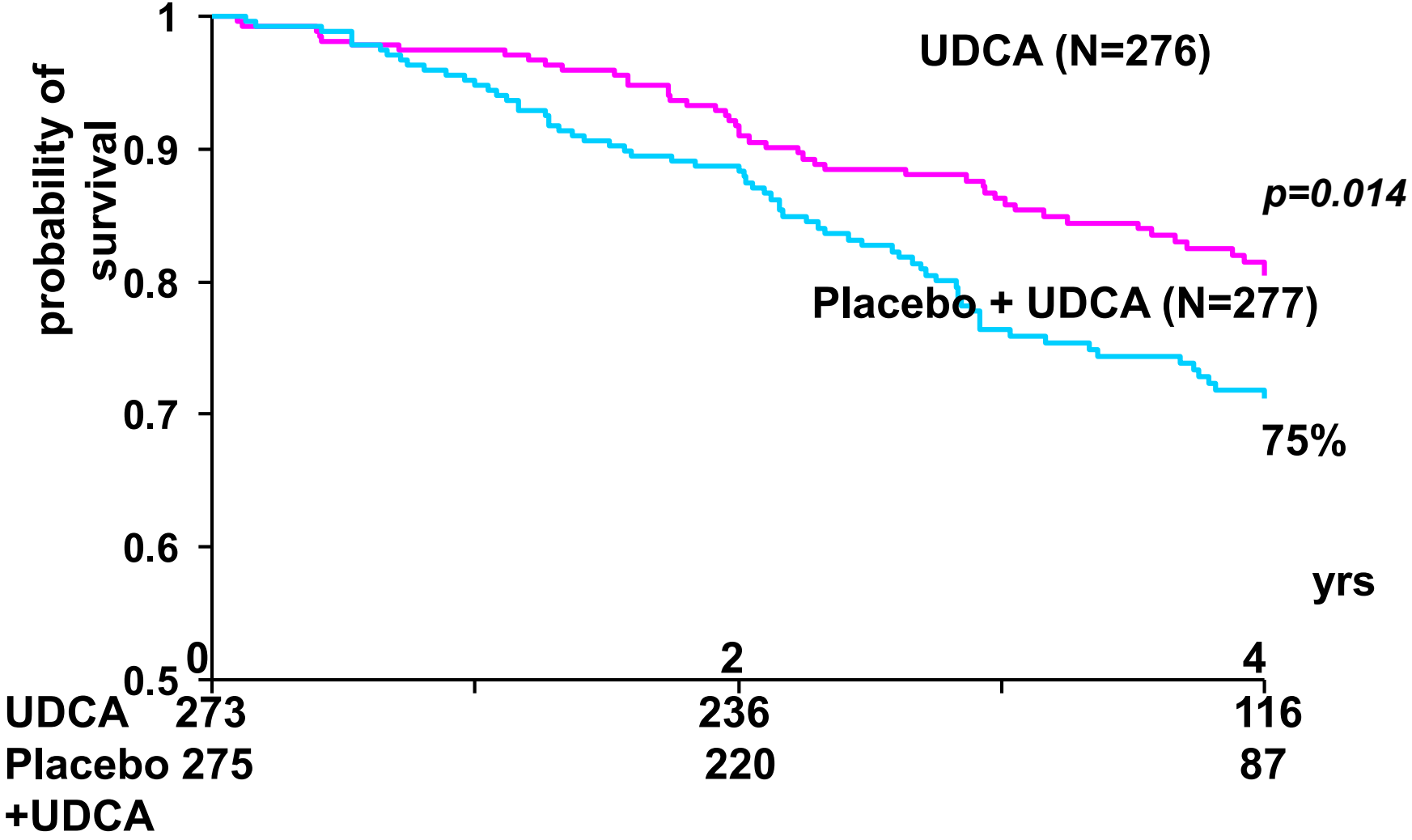
Treatments evaluated

No sample size calculations
No stratification
Short duration

PBC : Therapies Evaluated (all investigator initiated)

Drug (9)		Outcome
Azathiprine	(2)	Negative
D-Pencillamine	(6)	Negative
Cyclosporine	(3)	Toxic
Clorambucil	(1)	Toxic
Colchicine	(2)	Toxic
Prednisolone	(1)	Toxic
Budesonide	(3)	Histology better
Methotrexate	(1)	Negative
UDCA	(15)	Delays death + need for Tx
Total	**34**	

Combined (3 centers) analysis of RCT of UDCA (13-15mg/kg/d) in PBC probability of survival free of Transplantation



Poupon et al., Gastroenterology 1997;113(3):886

PBC : status in 2013:

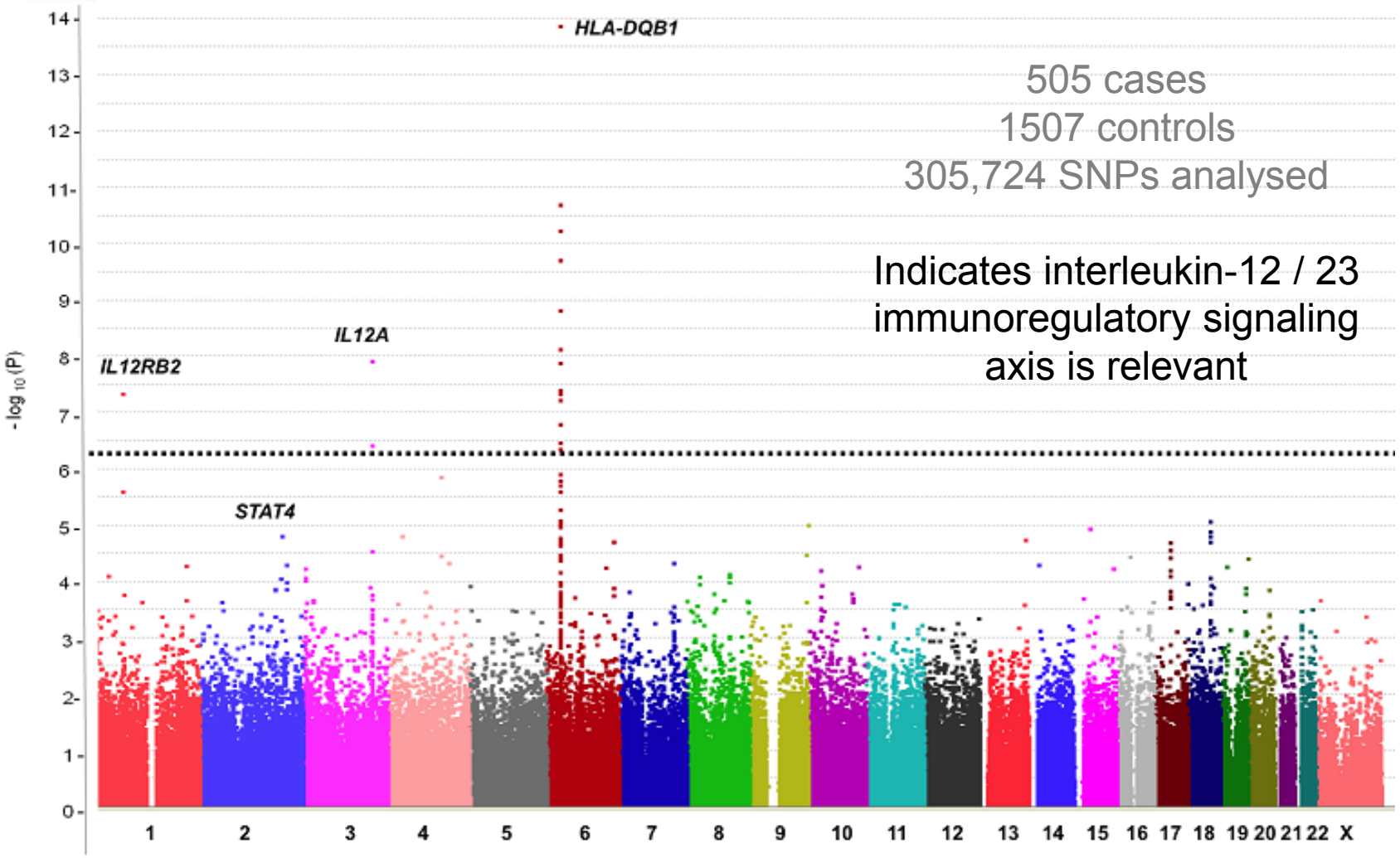
1. ↑ Predominantly asymptomatic at diagnosis

2. ↓ Need for liver transplant
   Confounded in part by earlier diagnosis

3. Overlap with other AILD

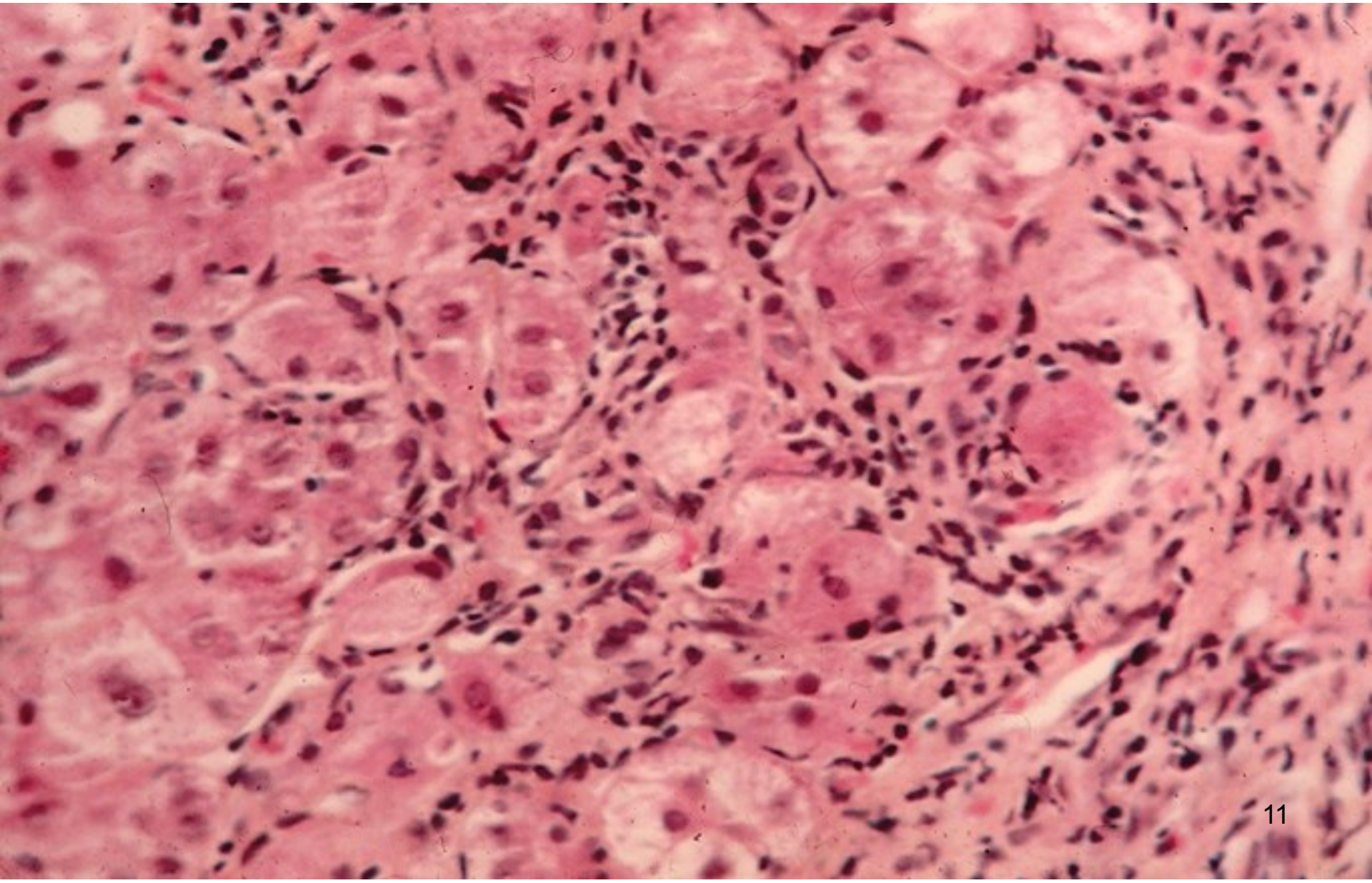
4. Family members often affected : First genetic profile reported (GWA) : 2009

Genome Wide Analysis : PBC



NEJM 2009 – Hirschfield et al.

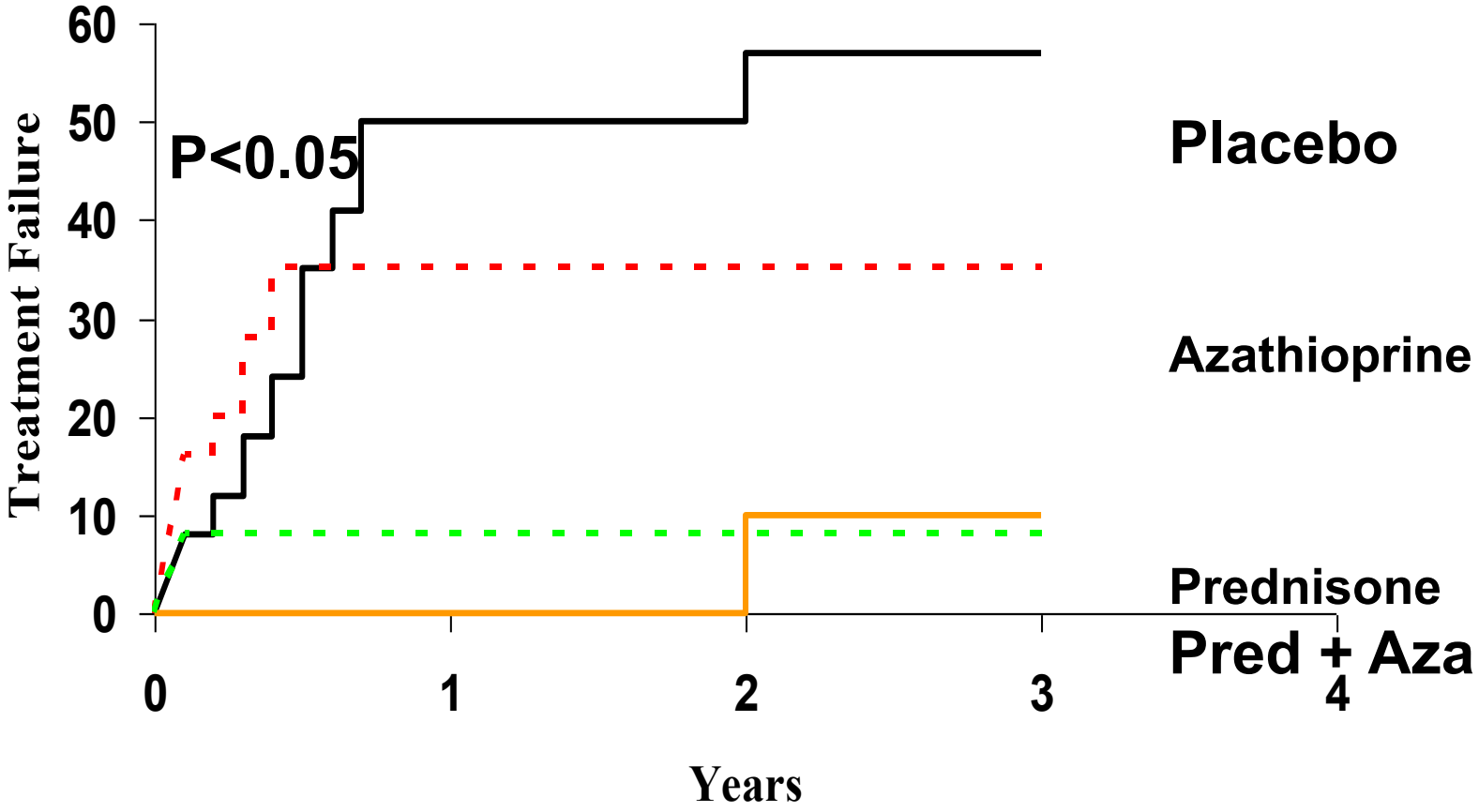
Pathology of AIH (1960's)



Spectrum of AIH

- **Classical presentation symptomatic chronic hepatitis ± cirrhosis**
- Acute hepatitis
- Fulminant hepatitis
- “Burned out” decompensated cirrhosis
- Asymptomatic chronic hepatitis ± cirrhosis
- Overlapping PBC/ PSC
- De Novo or recurrent AIH following liver tx

AIH: Response to Immunosuppressive Therapy

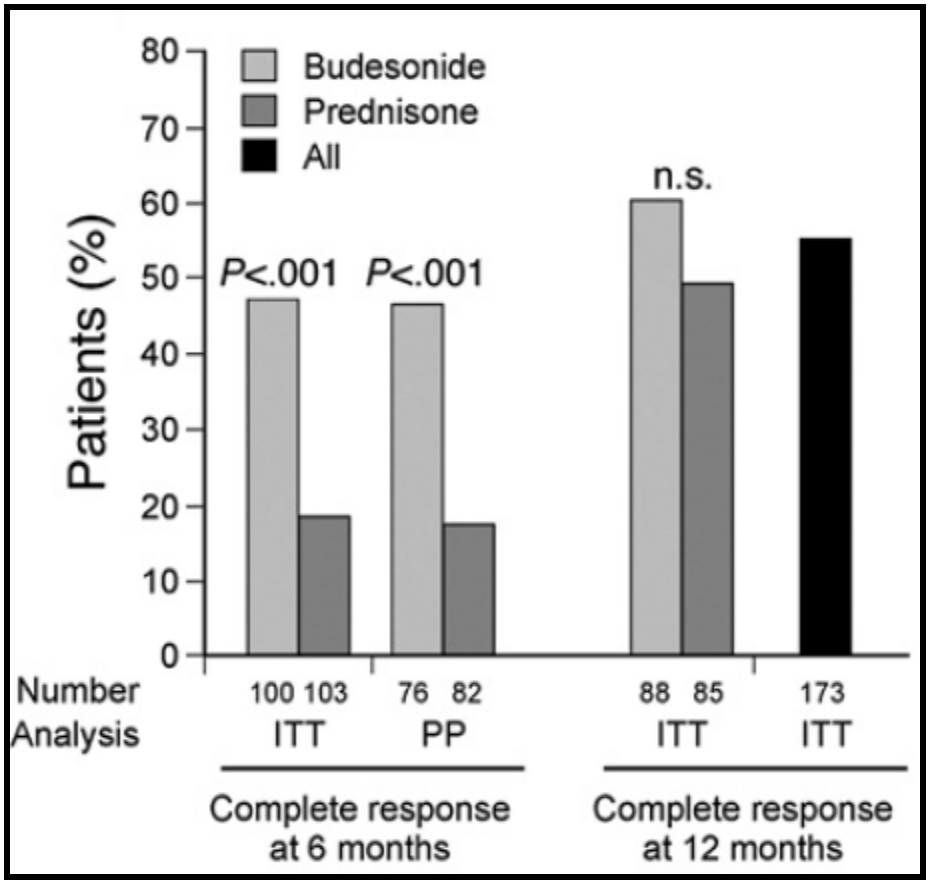


NB: Both drugs seem safe in pregnancy

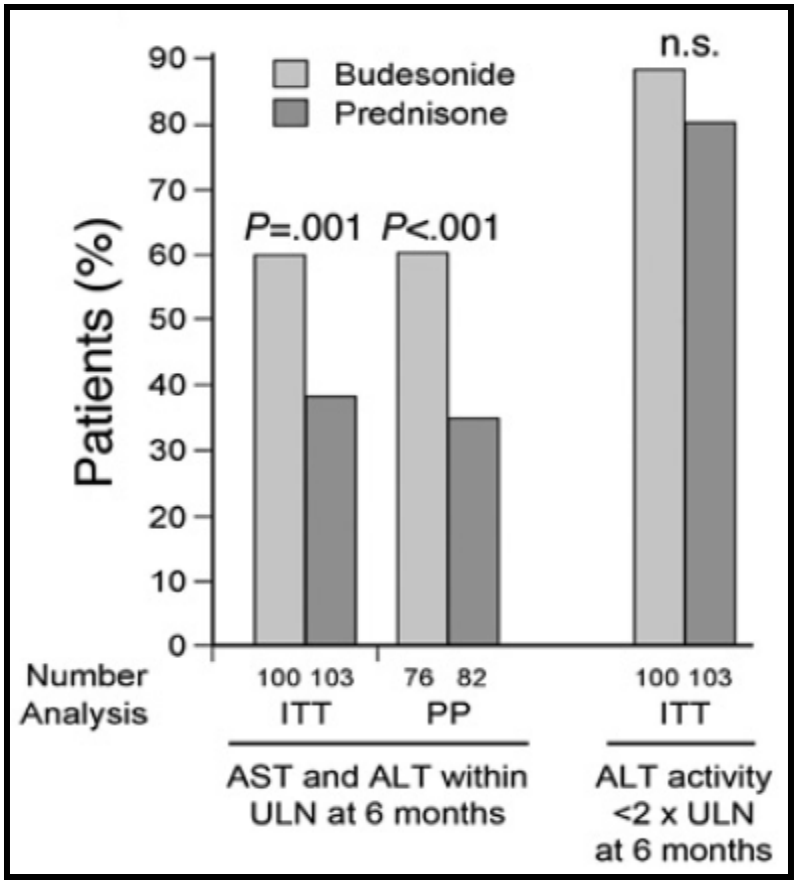
Soloway et al., Gastroenterology 1972; 63: 820-33

Budesonide vs Prednisone
Non-cirrhotic AIH

ALT + symptoms



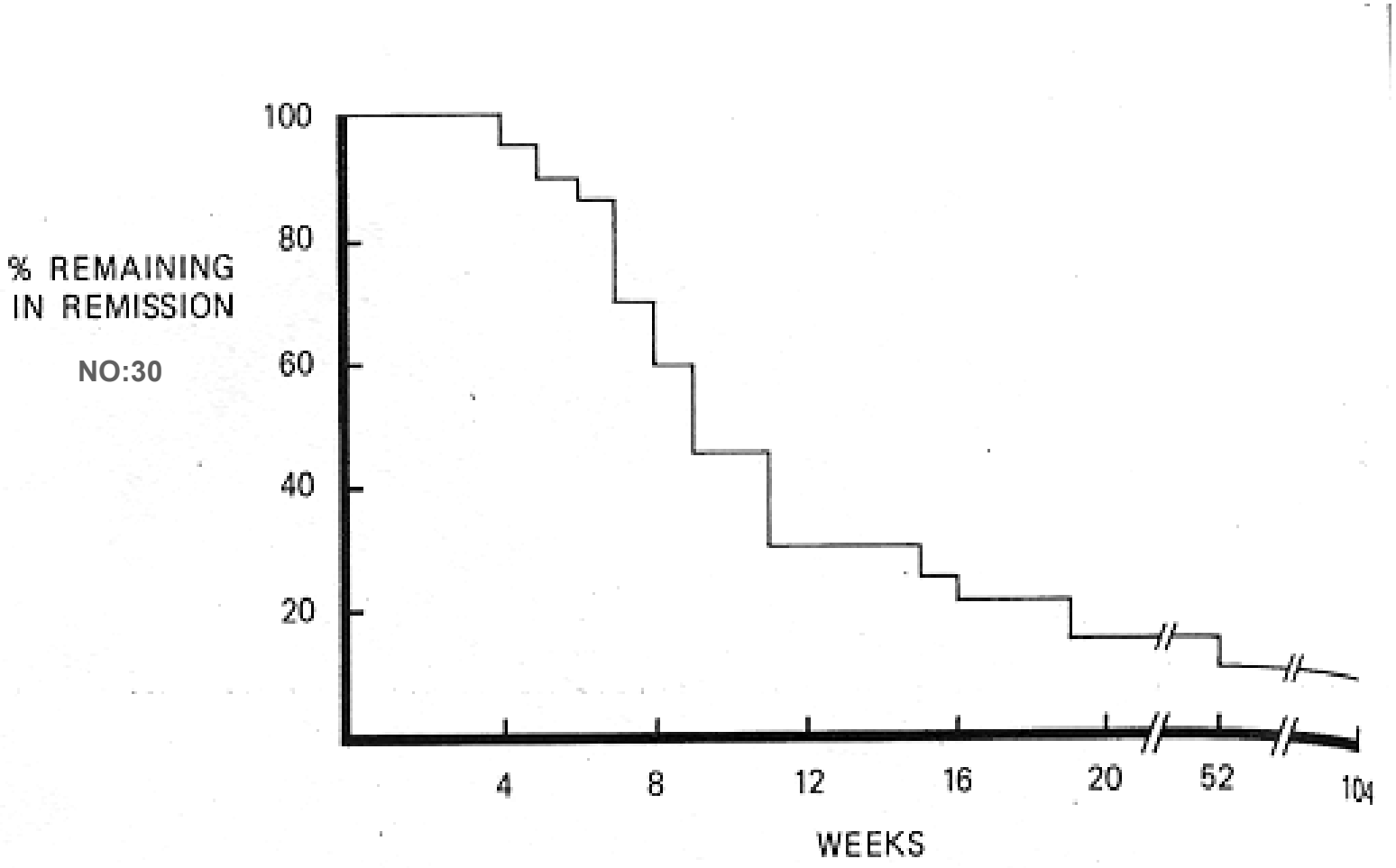
ALT alone



(combined with symptoms)

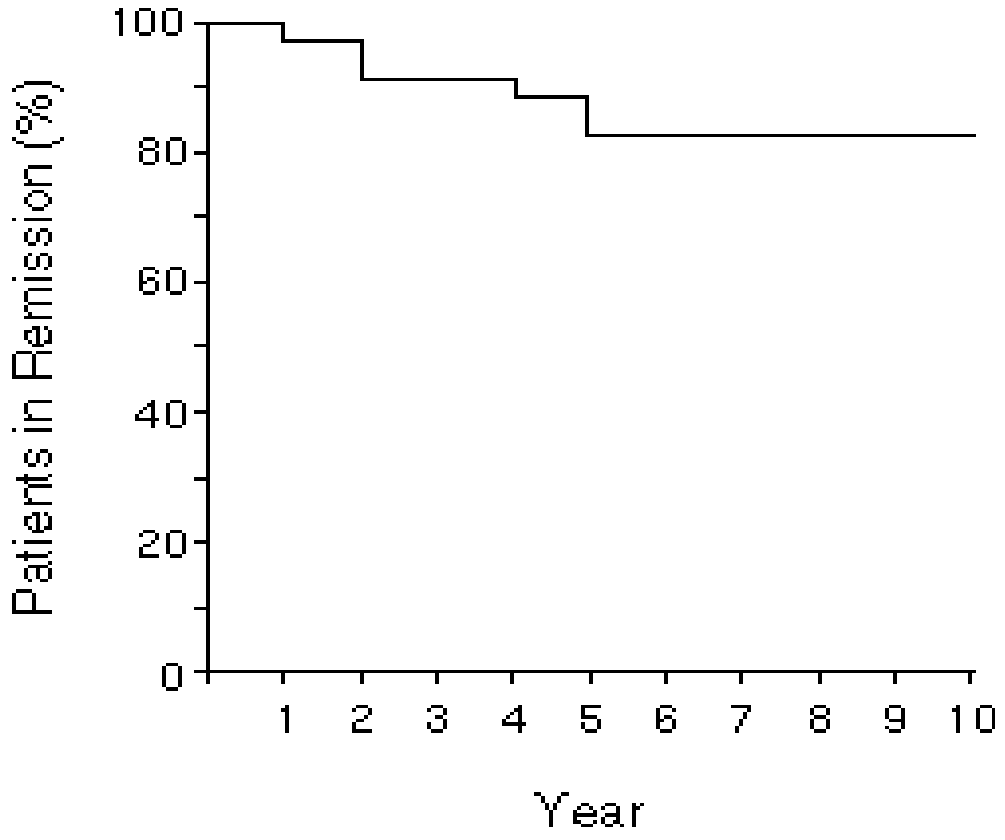
M. Manns – Gastroenterology 2010;139:1198

AIH: Patients remaining in remission following withdrawal of Prednisone ± Azathioprine



Hegarty et al., Hepatology 1983;3(5):686

Sustained remission during treatment with 2mg Azathioprine/kg/day in AIH



No. of Patients										
Total eligible for analysis	70	66	59	49	42	38	36	34	31	30
Cumulative total with relapses	2	5	5	6	7	7	7	7	7	7
Cumulative total excluded	2	6	13	23	30	34	36	38	41	42

Johnson et al., N Engl J Med. **1995**;333:959

Drugs Inducing an AIH-like Syndrome

Prescription

Methyldopa

Minocycline

Nitrofurantoin

Orlistat

?INH ± rifampin

Trazidone

Infliximab

Statins (unmask AIH)

Indomethecin

IFN α

Halothane

OTC

Black cohosh

Chaparral leaf

Kava Kava

Valerian

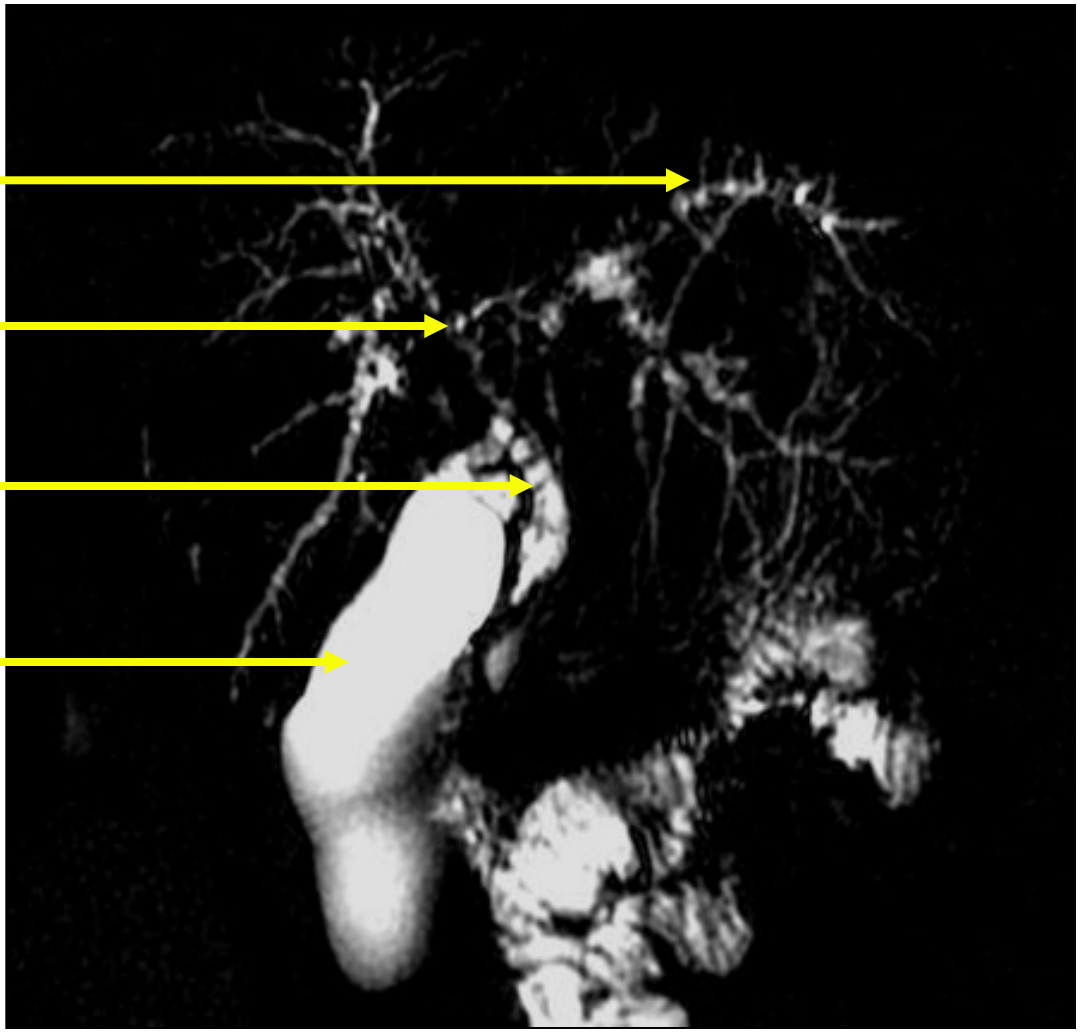
St. John's Wort

Echinacea

Management issues : AIH

1. Asymptomatic ? require treatment
2. Drug therapy during pregnancy:
   Prednisone, Azathioprine, – few problems
3. Pediatric cases - overlap with PSC
4. Drug induced
5. AMA+ve ?overlap with PBC
6. Recurrence post transplant

Primary Sclerosing Cholangitis (PSC)



MRCP: "revolutionized" ability to diagnose

Primary Sclerosing Cholangitis

1960's: Diagnosis rarely made

1980's: Affects all ages – babies → elderly

to ERCP / **MRCP** findings diagnostic

2000's In children 50% have overlapping AIH

Associated with IBD / colon cancer / cholangiocarcinoma

Therapy: Antibiotics with fever (blood culture optimal)

Therapeutic ERCP - stricture/stones

UDCA – any benefit ?

Liver transplant

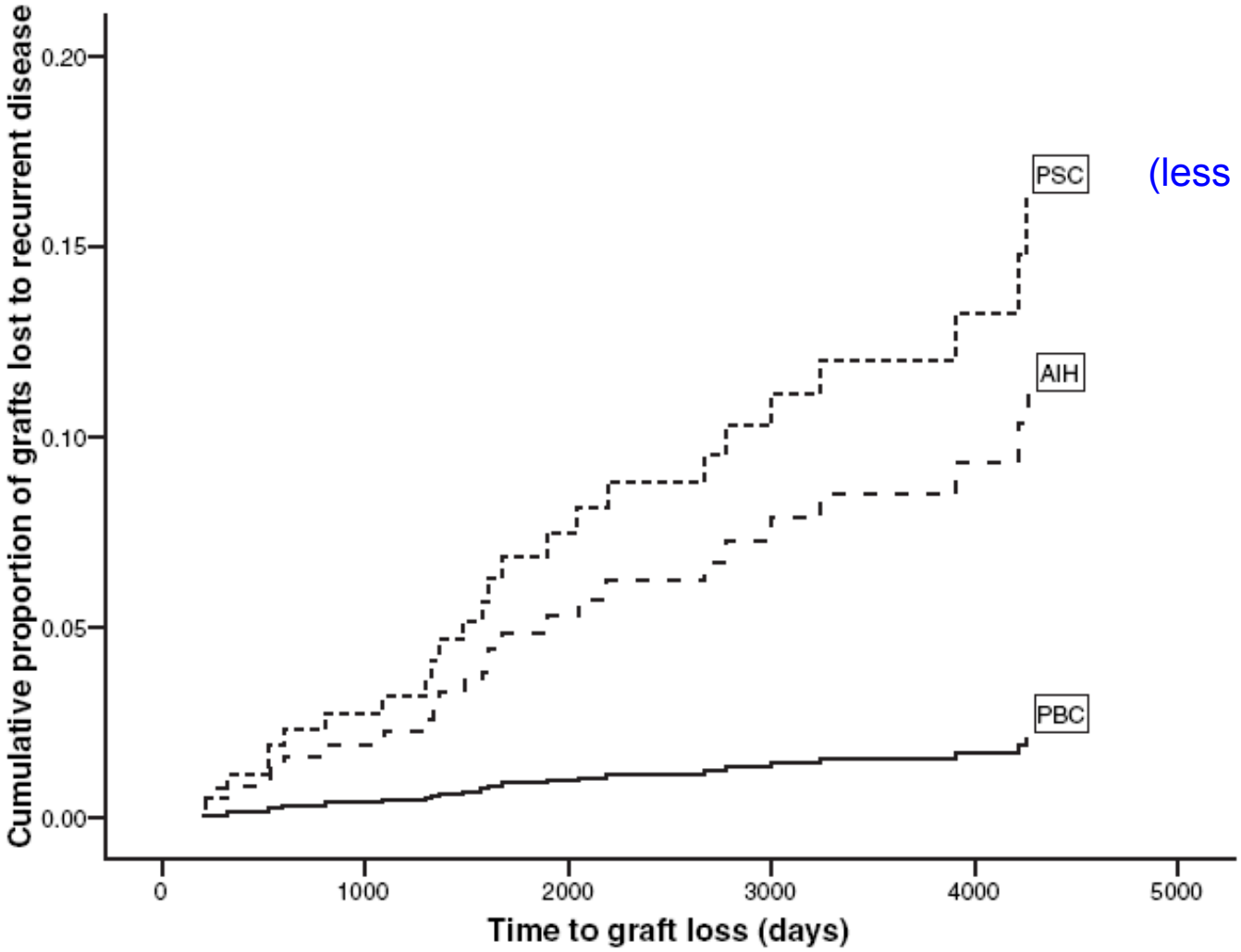
Unlikely any effective therapy – structural problem

Management : PSC

- Cholangitis – risk factors:
  - intrahepatic stones, strictures, instrumentation, long term stenting (give antibiotics if patient far from a hospital)
- Annual Surveillance for colon cancer if IBD present
- OGD for varices
- Dilate symptomatic strictures (short term stents)
- Avoid ‘ostomy’ (stomal varices)
- Assess for osteoporosis and vitamin deficiency in icteric disease
- Always consider potential ‘secondary’ SC – 20%

Transplant (recurrence upto 15%)

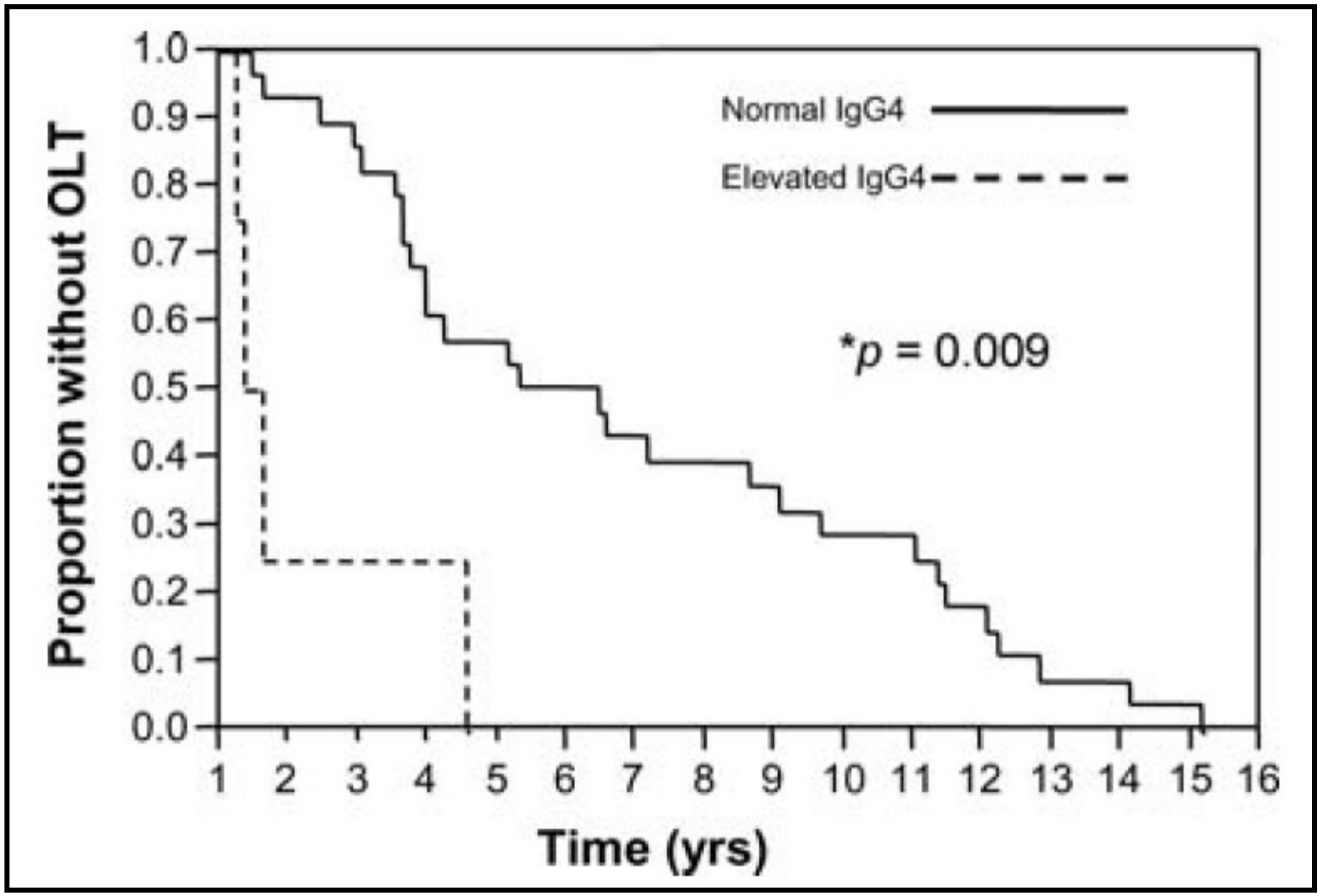
Recurrent AILD after OLT



(less if colon missing)

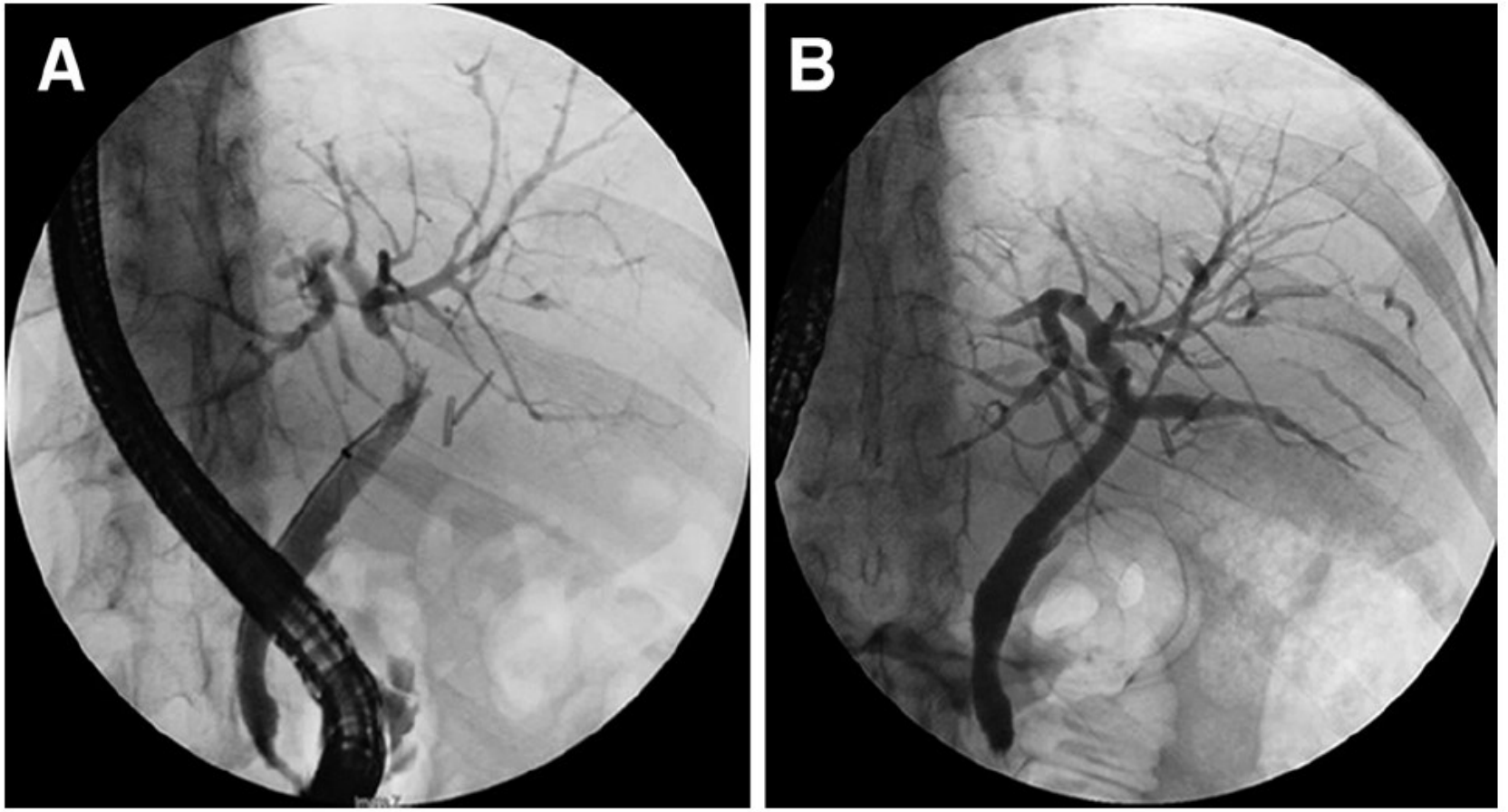
Schreuder et al. Transplant Int. 2009; 22:144

PSC: Outcome ± ↑ IgG4



Mendes et al., Am J Gastroenterol 2006;101:2070

IgG4-associated sclerosing cholangitis with intrahepatic strictures mimicking PSC (A) before treatment, and (B) after 12 weeks of steroid therapy



Ghazale et al. Gastroenterol 2008; 134:706

Hepatitis B

Identified 1968 – Nobel Prize (B.Blumberg)

1970's – 1990's:

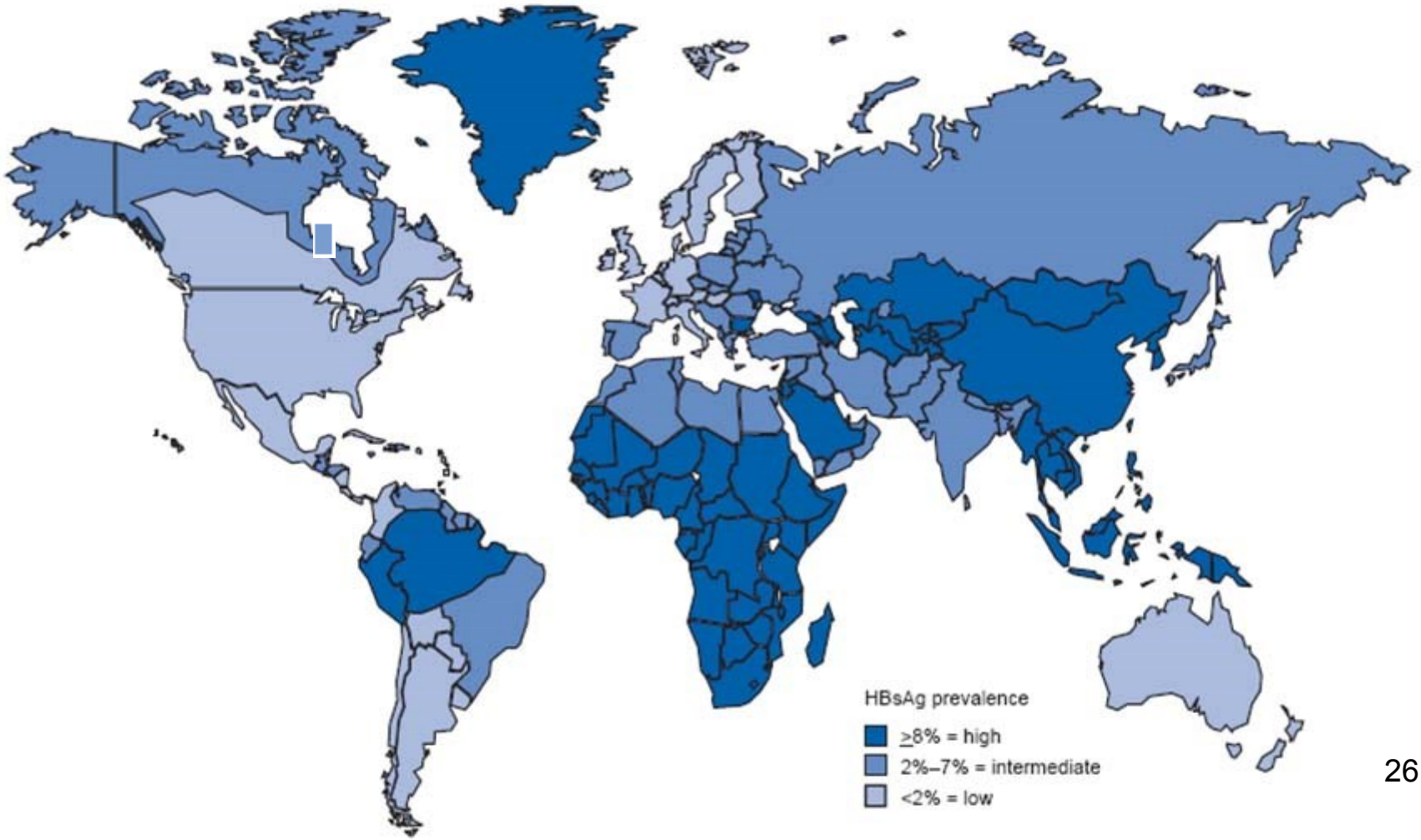
* Transmission (vertical, perinatal, parenteral, sexual)

*** Major risk factor for HCC**

Chronic infection follows vertical or early childhood infection

High rate of chronically silent disease (region specific)

Global Distribution of HBV



Risk Factors for HCC

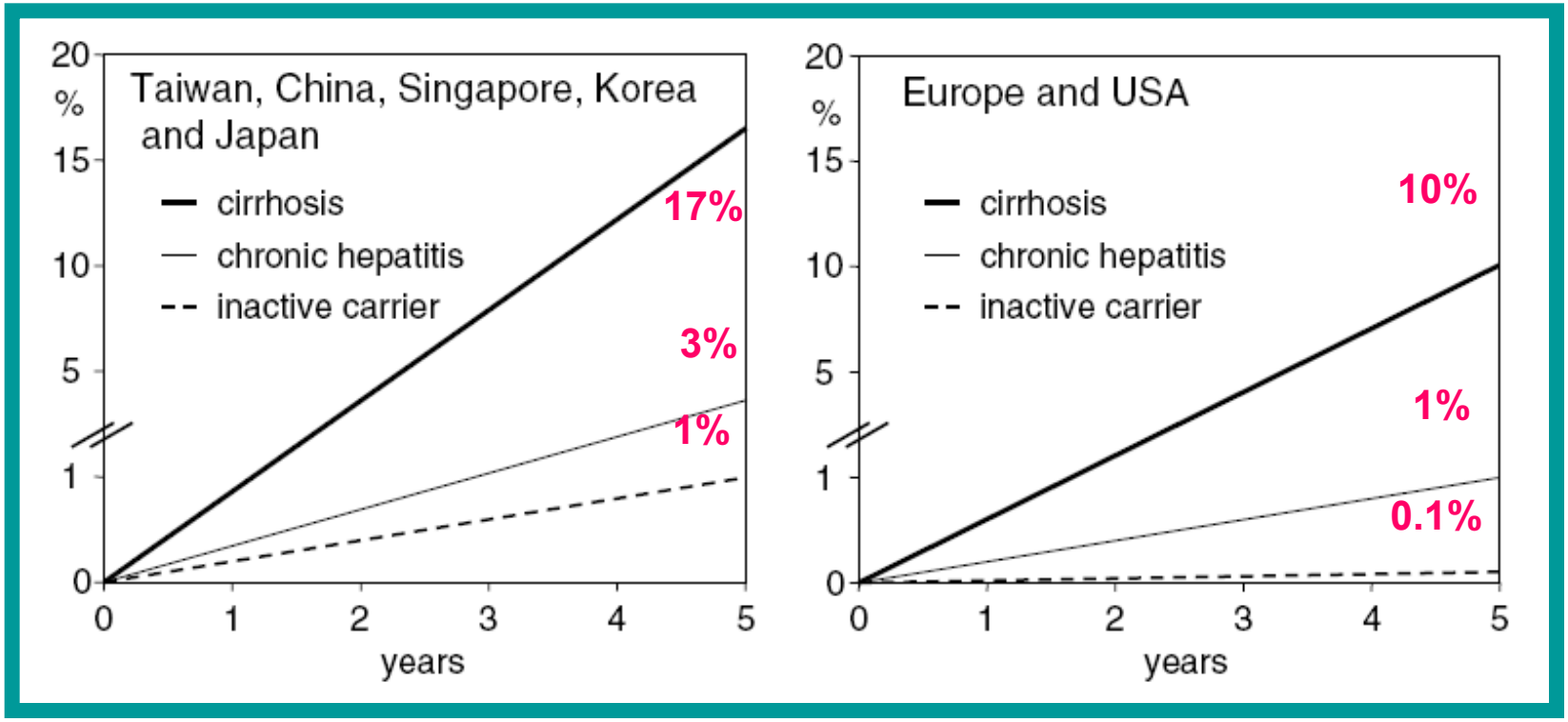
- Several independent HCC risk factors identified in multivariate analysis
  - Cigarette smoking had no significant effect

Risk Factor	Adjusted RR (95% CI)	P Value
Elevated baseline HBV DNA • ≥ 10^5 copies/mL • 10^4 to < 10^5 copies/mL	 6.4 (4.1-10.1) 2.5 (1.5-4.3)	 < .001 < .01
HBeAg-positive status	2.3 (1.6-3.3)	< .001
Male gender	2.1 (1.4-3.2)	< .01
ALT ≥ 1 x ULN	1.7 (1.2-2.6)	< .01
Alcohol use	1.6 (1.1-2.3)	< .05
Older age	1.10 (1.08-1.12)	< .01

ALT, alanine aminotransferase; RR, risk ratio; ULN, upper limit of normal

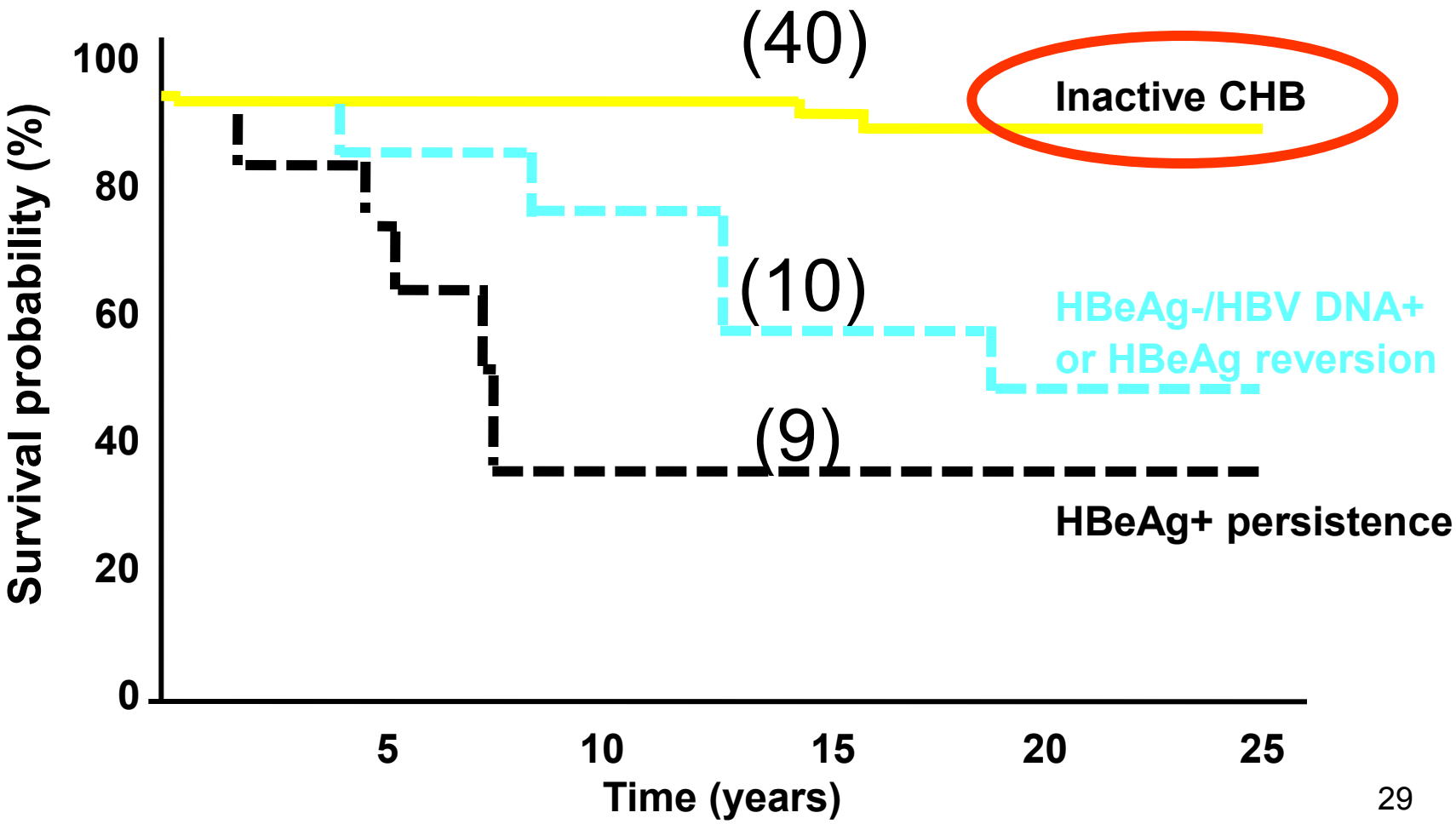
Chen, et al. JAMA 2006;295:65

Progression of HCC in CHB variable Far East v Mediterranean



Fattovich et al - J Hepatol 2008

25-Year Survival Rates in Untreated adults with CHB

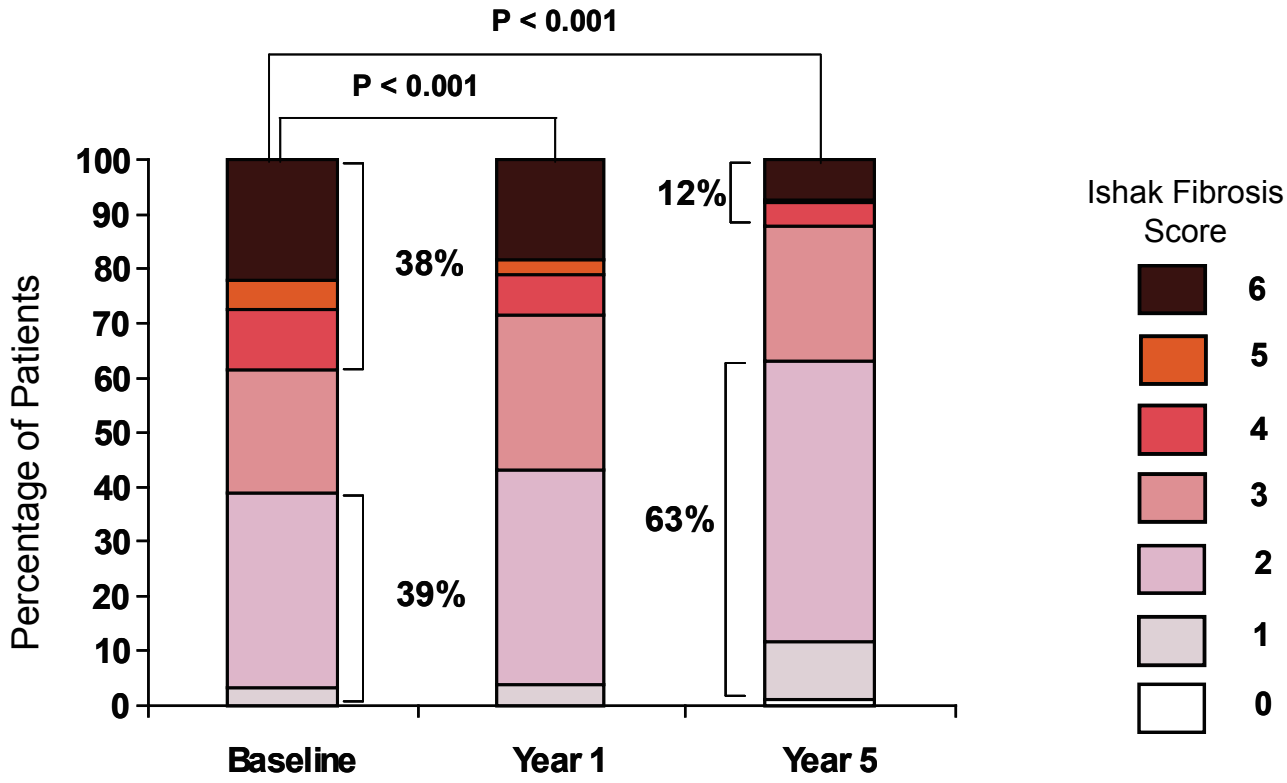


Fattovich et al. Gut 2008

Liver Fibrosis : Regression over 5 Years of Treatment with TDF* (no drug resistance)

Patients with cirrhosis (Ishak score ≥5): 28% at Baseline, 8% at Year 5

Patients with Ishak score ≤2: 39% at Baseline, 63% at Year 5



*Sign test

Marcellin P et al. LANCET 2012

Oral Antiviral Therapy improves the Natural History of Chronic Hepatitis B

1. Resolves acute on chronic liver failure
2. Prevents reactivation (post Tx or with IST)
3. May reduce rate HCC (both IFN + oral Rx)
4. Induces regression of chronic liver disease

NB: May increase viral clearance (IFN+, ?oral Rx)

Unanswered question should we treat?

1. Immune tolerant (high HBV DNA)

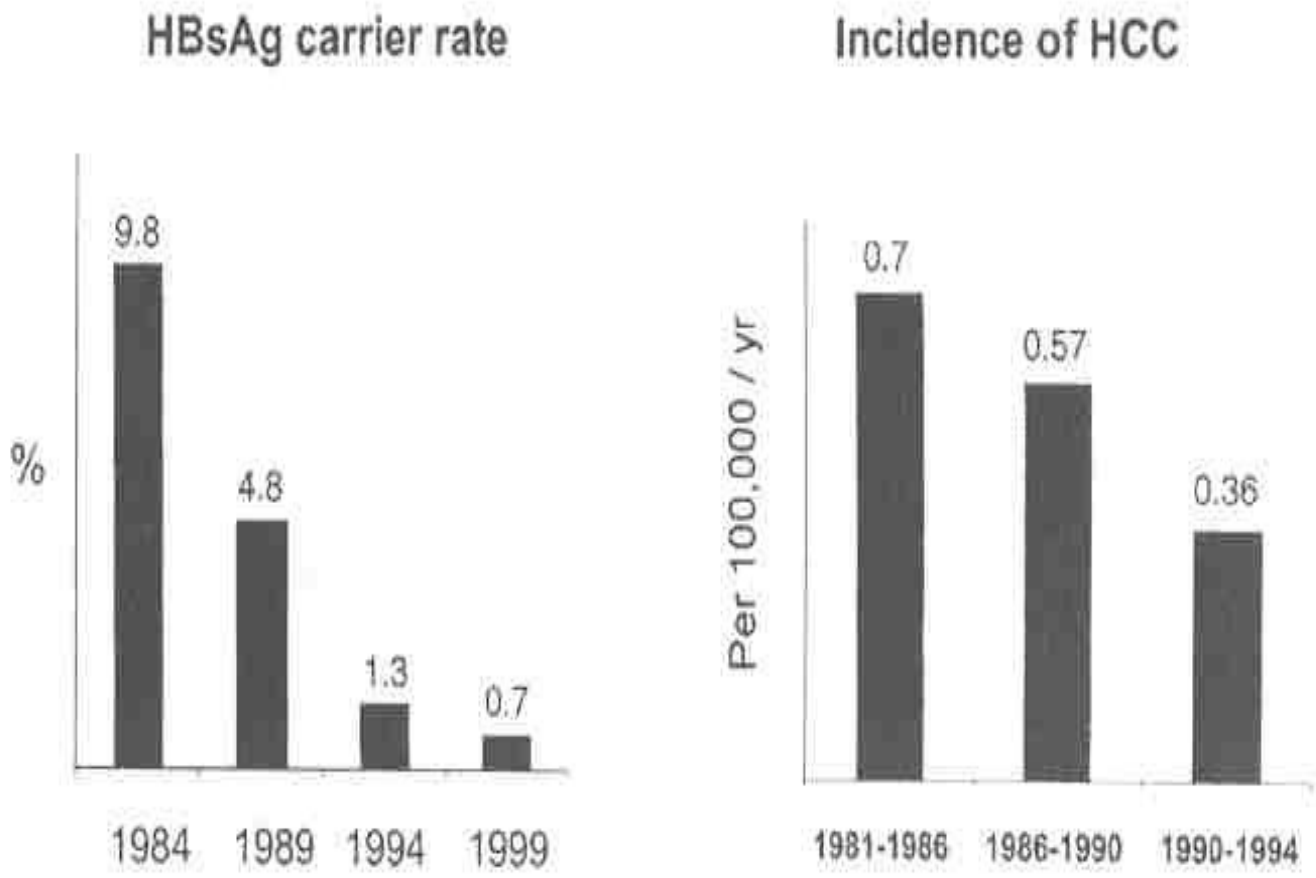
2. Pregnant women high HBV DNA (currently only vaccinate their babies)

3. HBeAg-ve CHB with minimal liver damage but with ongoing viral replication

4. Healthcare workers with CHB to prevent transmission

5. **Can we cure CHB ?**

Impact of Universal HBV Vaccination on HBV Infection and HCC in Taiwanese Children

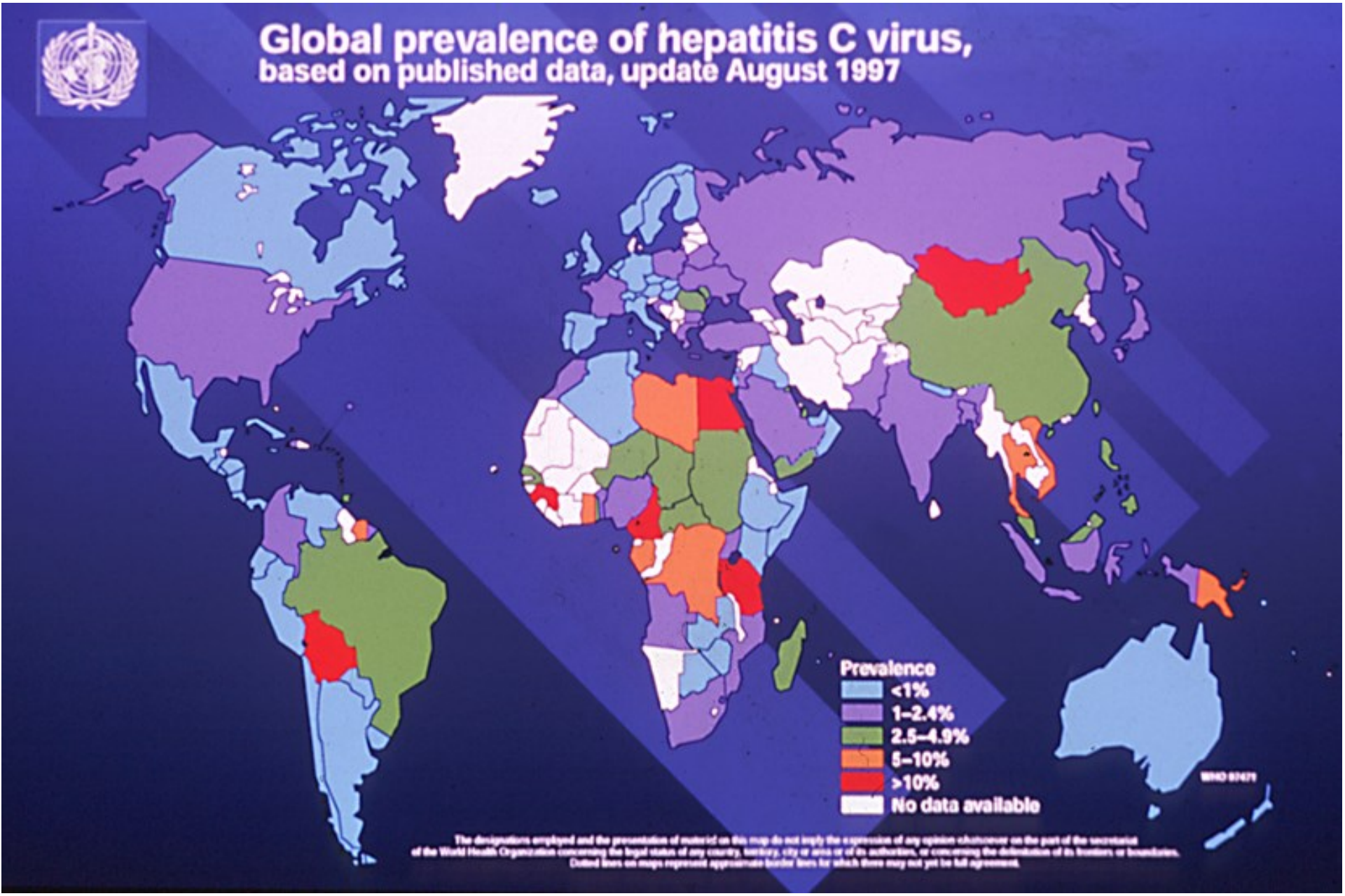


M-H Chang, NEJM 1997

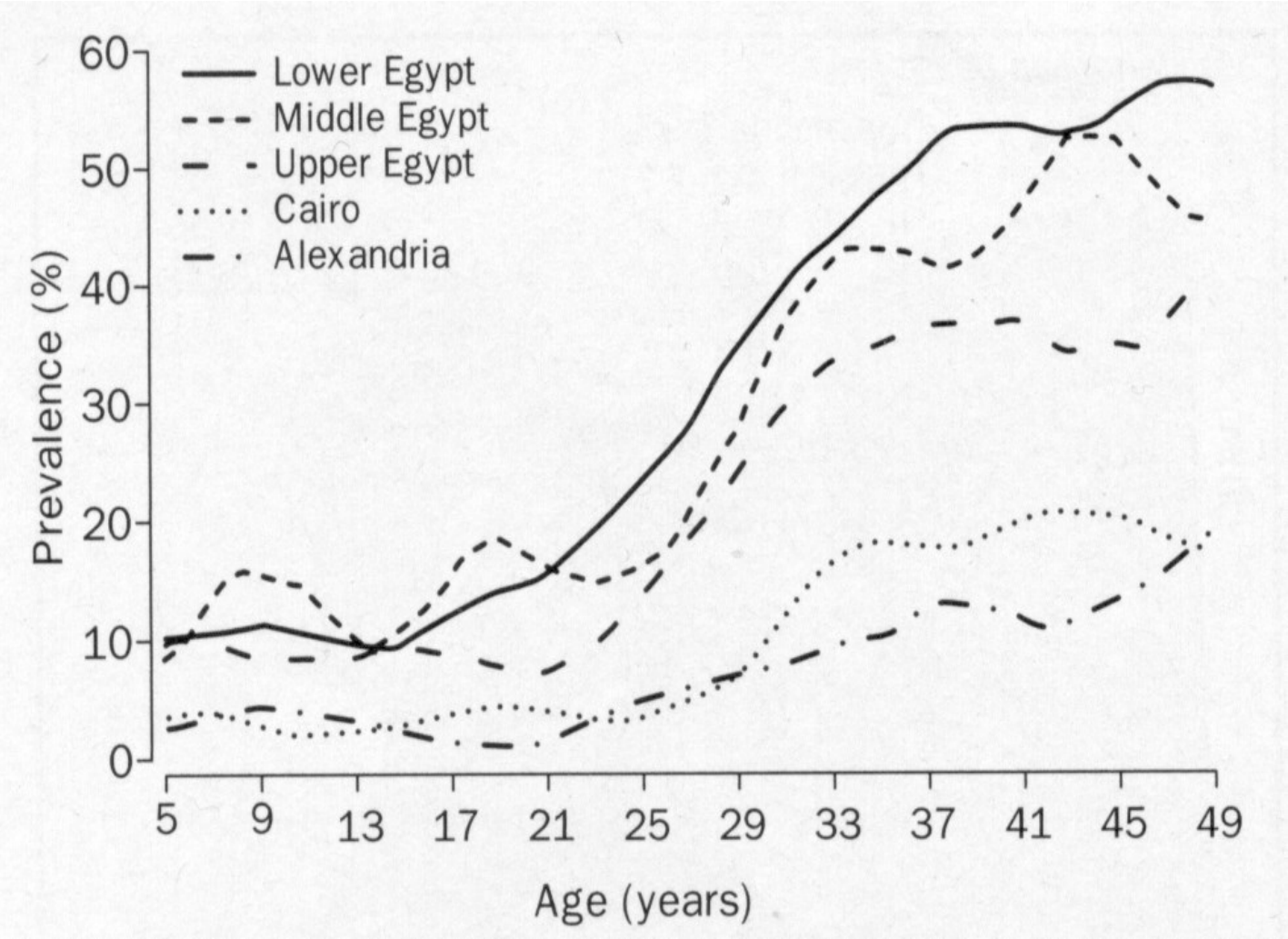
Hepatitis C

Identified 1989 – Lasker Award (Houghton/Alter)

Clinically silent chronic disease follows acute infection in the majority


Global prevalence of hepatitis C virus,
based on published data, update August 1997
Prevalence
<1%
1–2.4%
2.5–4.9%
5–10%
>10%
No data available
WHO 97471

Prevalence of Antibodies to HCV by Age and Region in Egypt



Frank et al., Lancet 2000;355:890

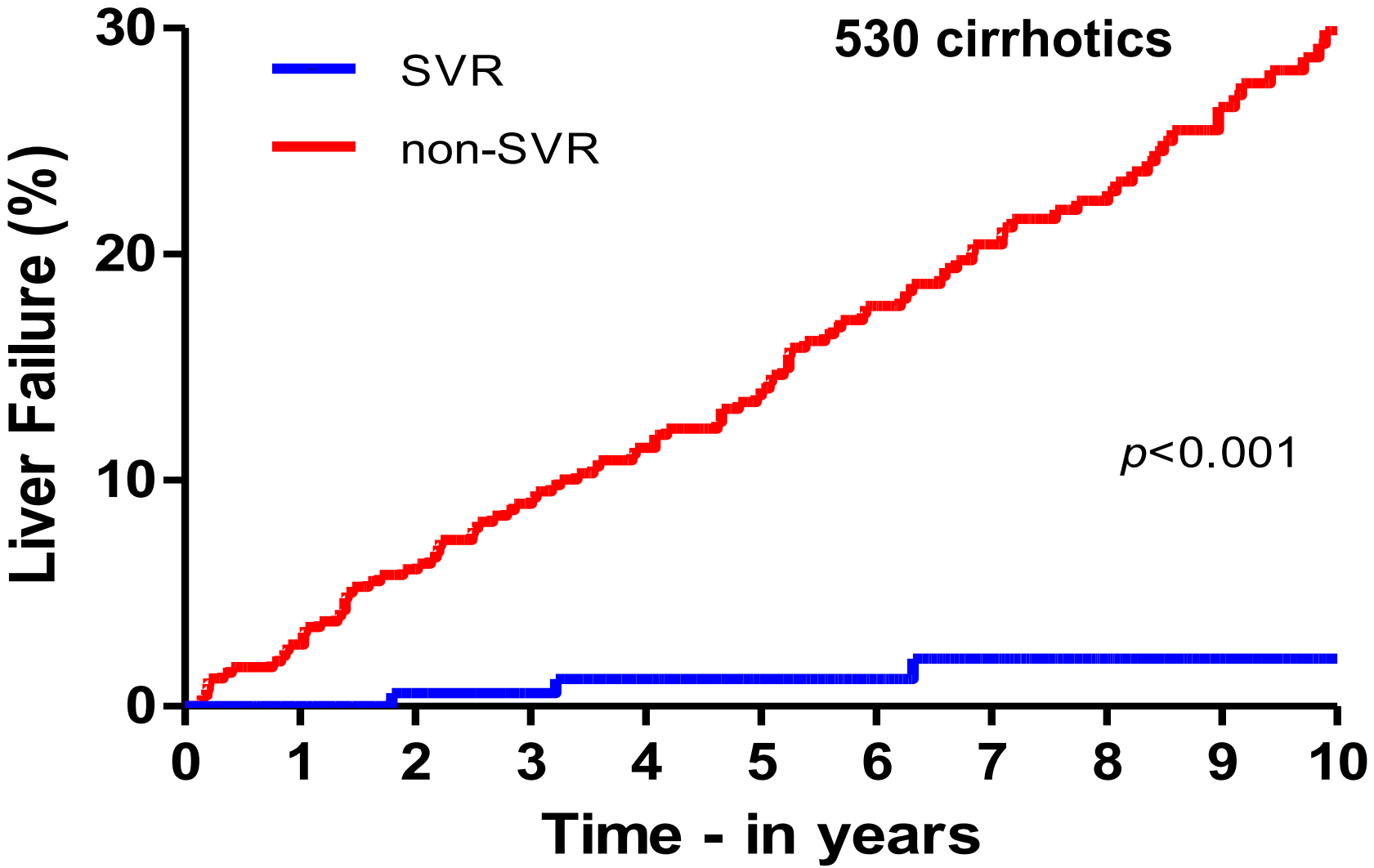
Chronic Hepatitis C

Blood to blood transmission : need to be imaginative !
Several non hepatic manifestations
e.g. cryoglobulinemia + renal failure
Major risk factor HCC
Antiviral therapy Peg IFNά + rbv↑ Survival and ↓ HCC
↑ rates sustained viral clearance to new Rx
Liver Transplant – recurrence universal

(MOST INFECTED UNDIAGNOSED - ? NEED ROUTINE SCREEN)

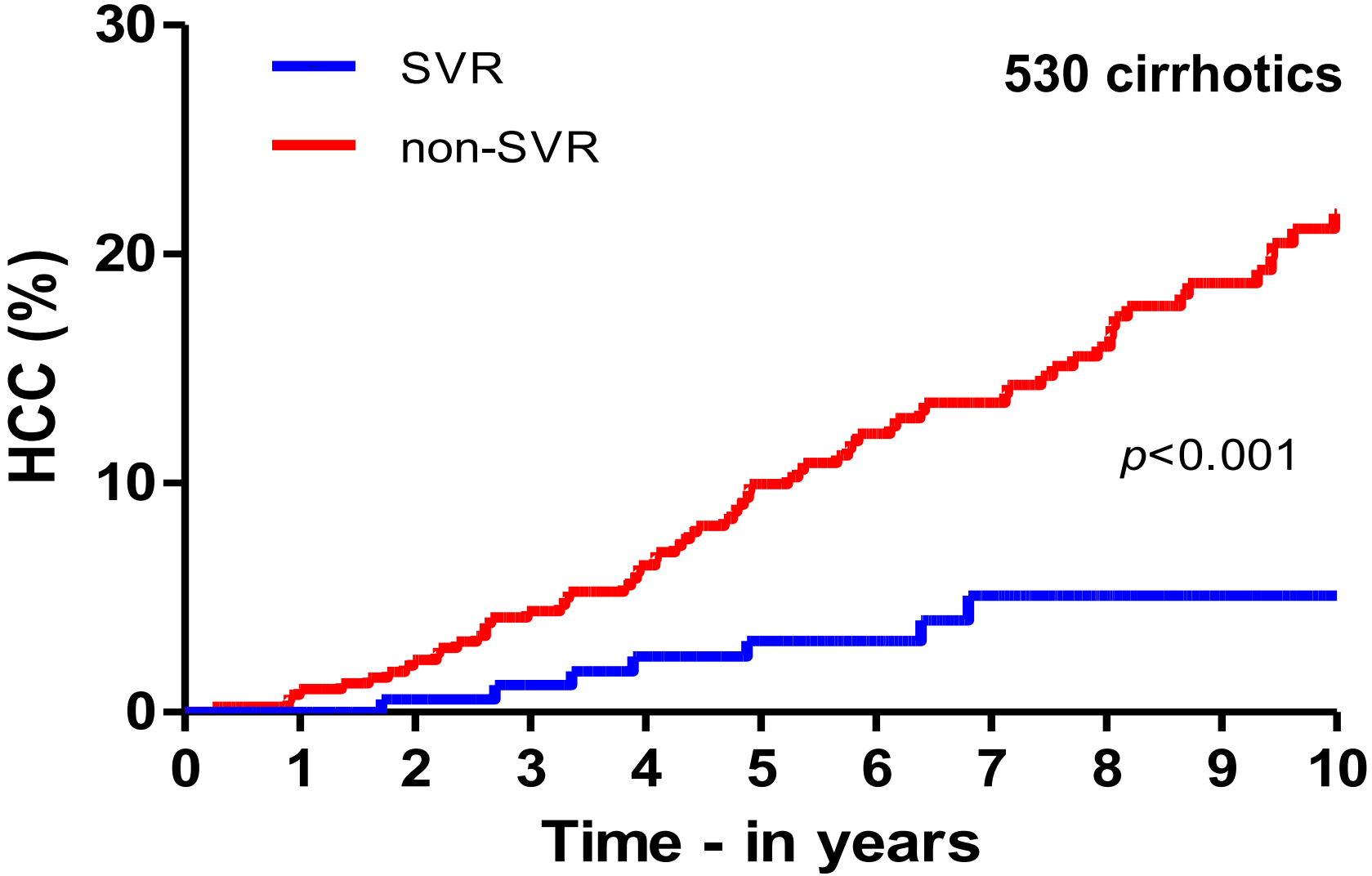
No sustained long term immunity (no vaccine)

Association SVR and Liver Failure



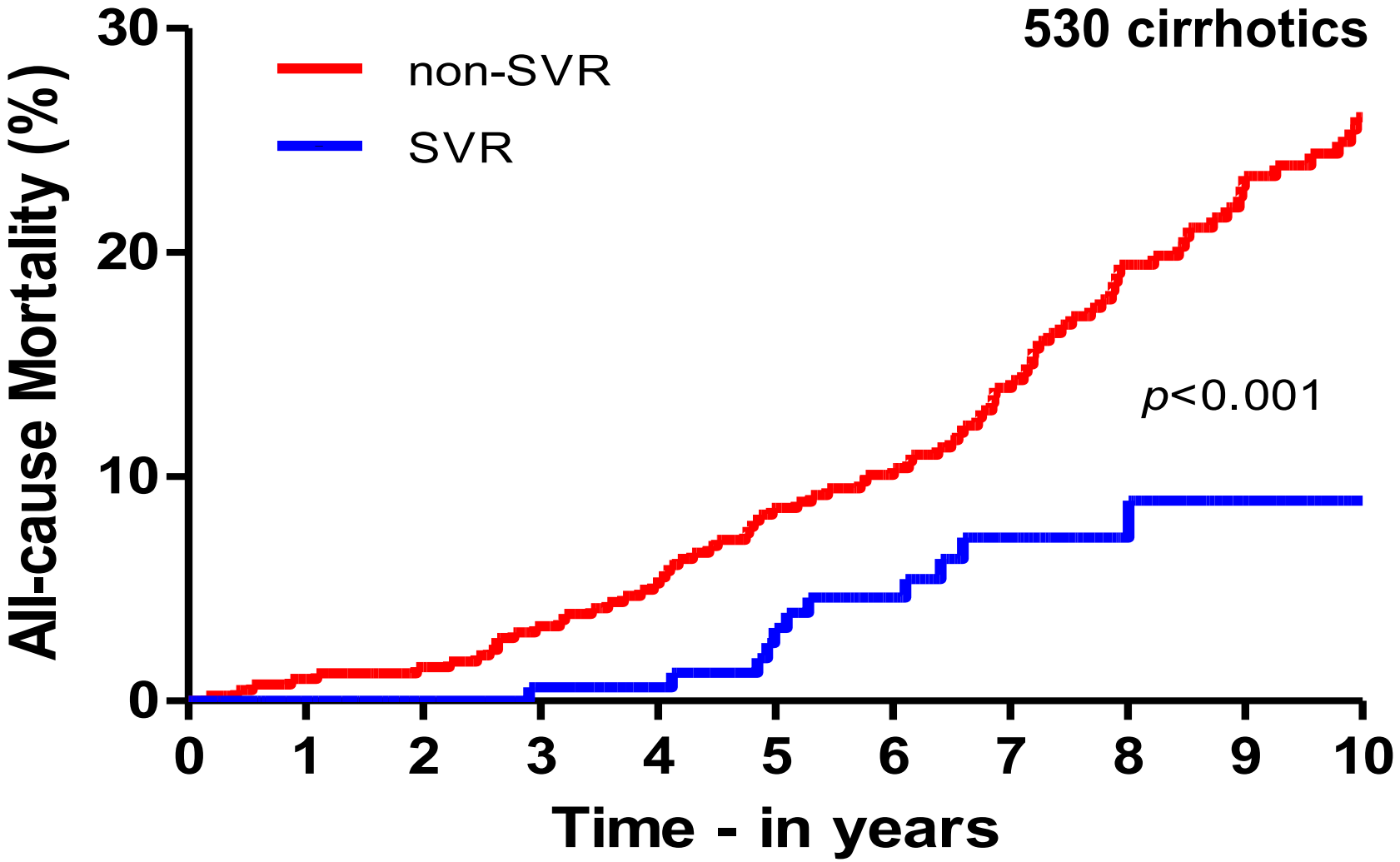
A. Van der Meer - JAMA 2012;308:2584

Association SVR and HCC



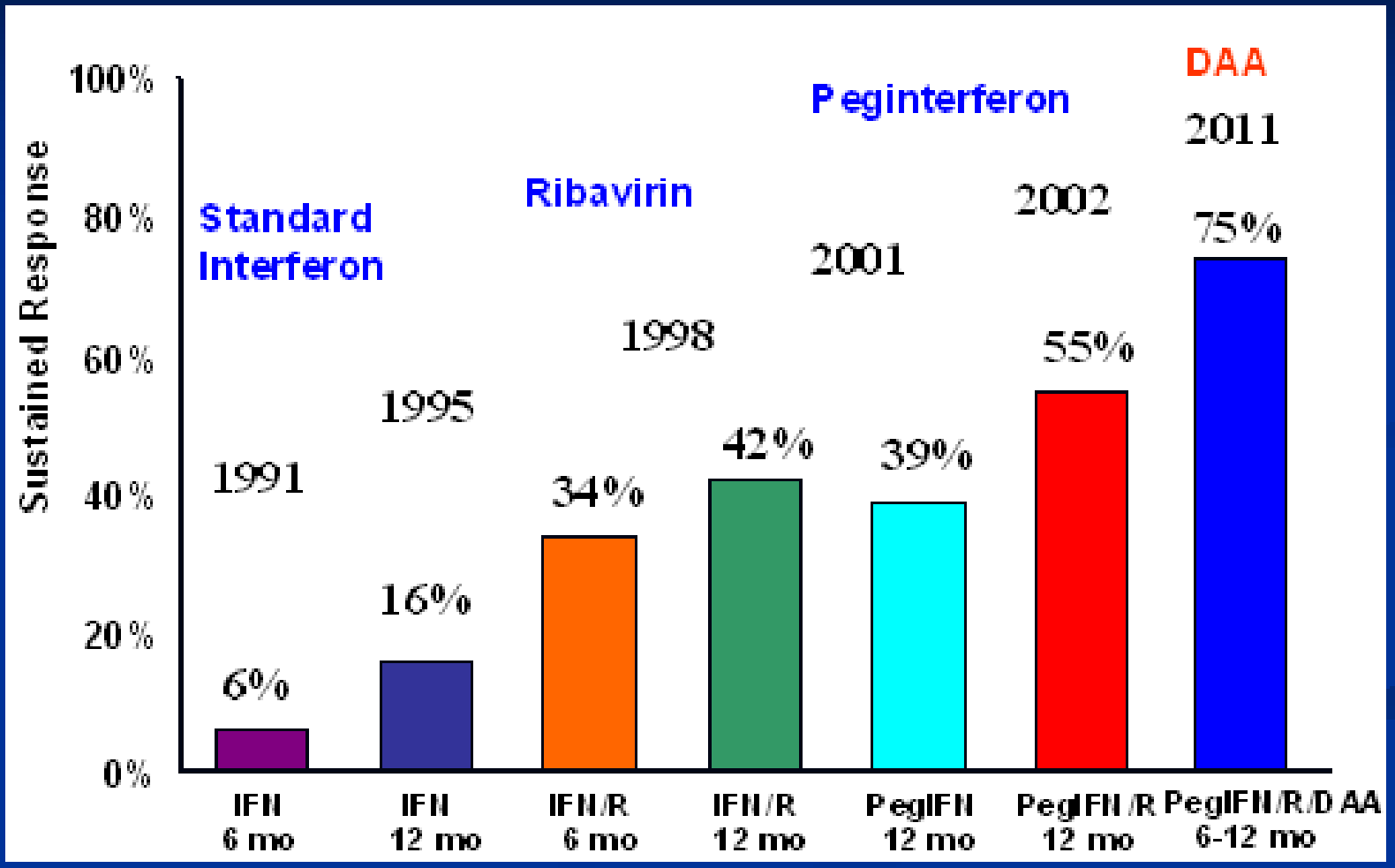
A. Van der Meer - JAMA 2012;308:2584

Association SVR and all-cause mortality CHC with advanced Hepatic Fibrosis



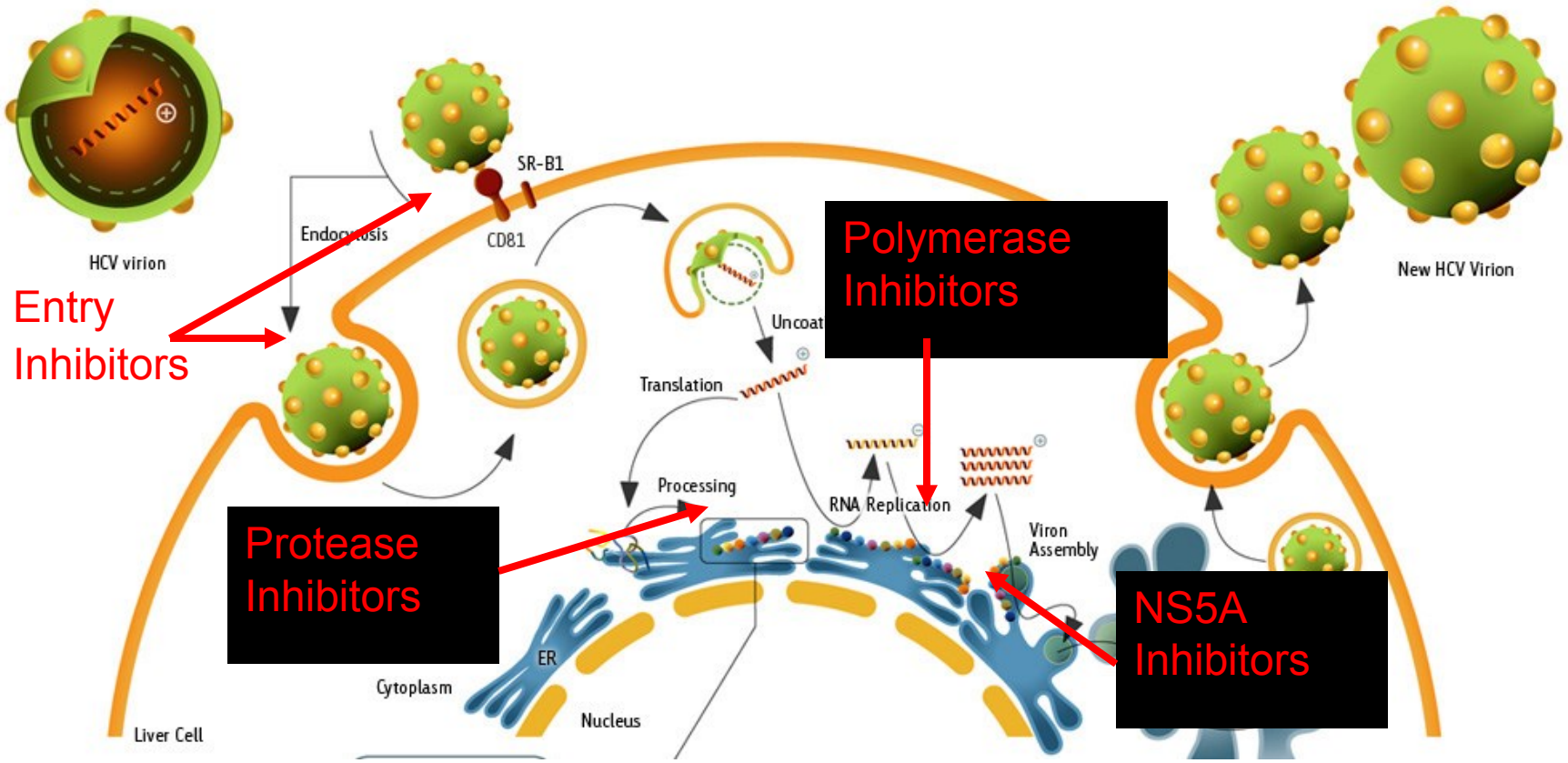
A. Van der Meer - JAMA 2012;308:2584

The Good News



Kindly lent by Dr. J. Feld

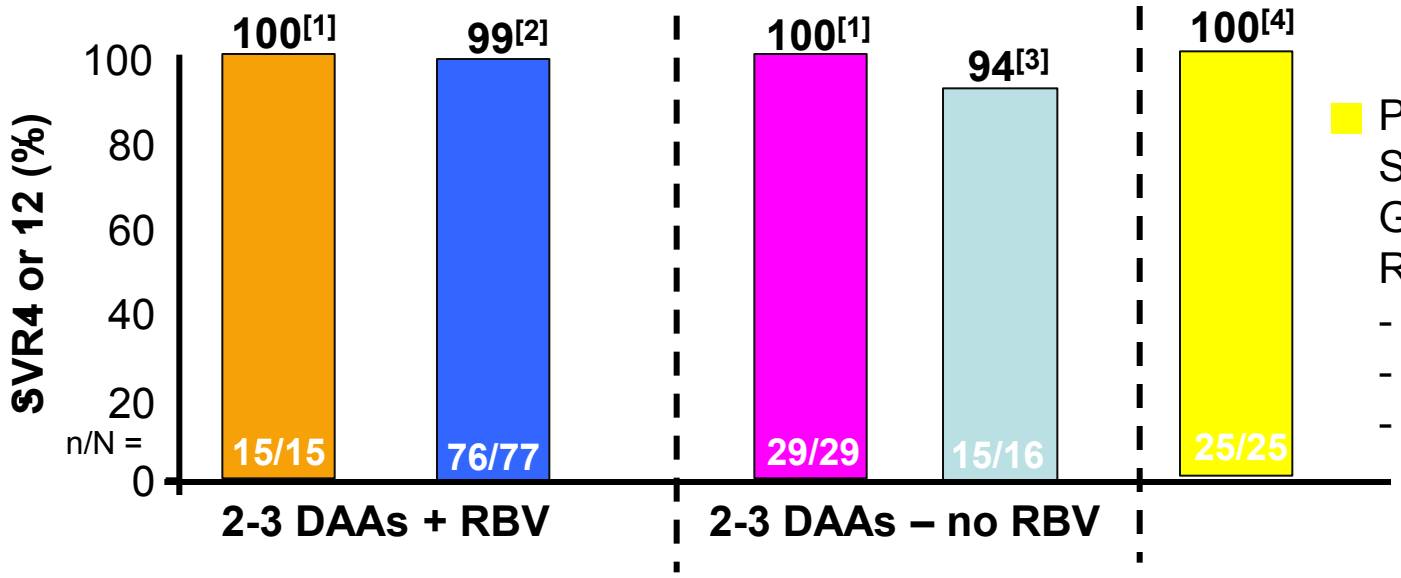
The Lifecycle - Lots of Targets



Manns Nat Rev 2007

New DAA + RBV (IFN free)

- Sofosbuvir (Nuc) + Daclatasvir (NS5A) + RBV x 24 wks
- ABT-450/r (PI) + ABT-333 (NNI) + ABT-267 (NS5A) + RBV x 12 wks
- Sofosbuvir (Nuc) + Daclatasvir (NS5A) x 24 wks
- Daclatasvir (NS5A) + Asunaprevir (PI) + BMS 791325 (NNI) x 12 wks

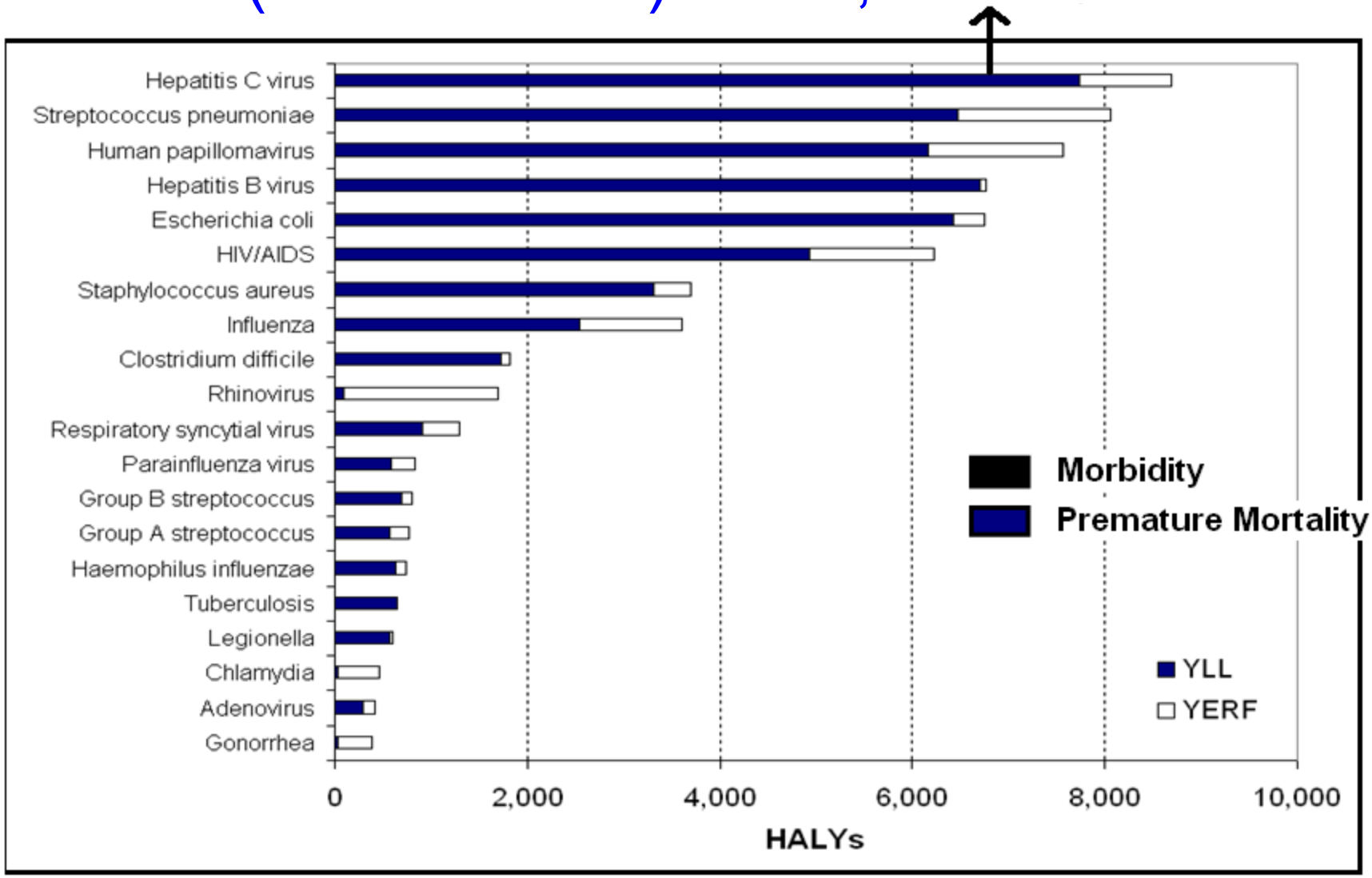


- Perfectovir? Sofosbuvir (Nuc) + GS-5885 (NS5A) + RBV X 12 wks
  - 1 pill OD
  - No AEs
  - No DDIs

- Major caveats: small n, no patients with cirrhosis

1. Sulkowski M, et al. AASLD 2012. Abstract LB-2. 2. Kowdley KV, et al. AASLD 2012. Abstract LB-1 3. Everson G et al. AASLD 2012. Abstract LB-3. 4. Gilead Press Release

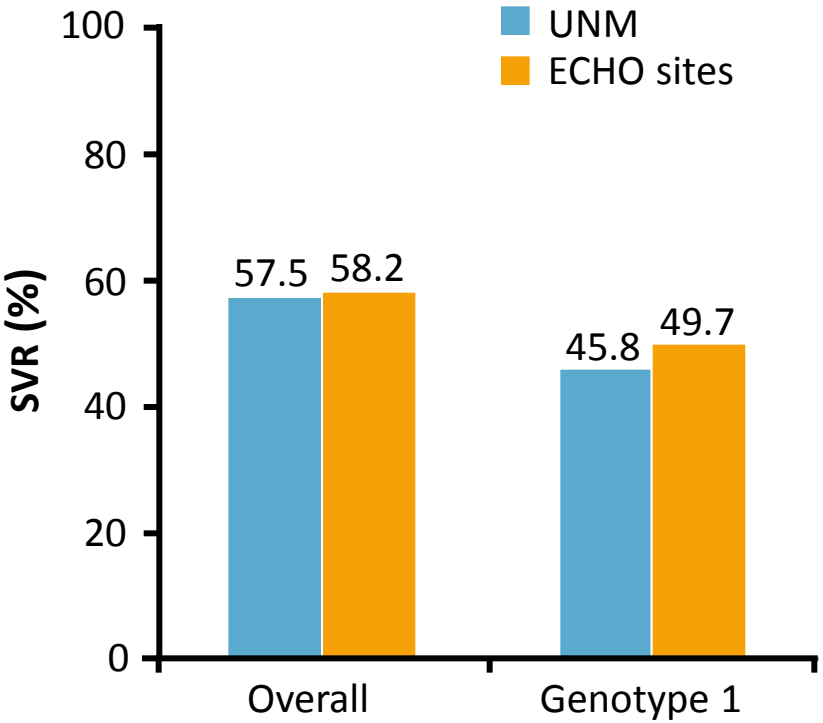
Burden of Top 20 Infectious Diseases (2003 – 2005) – Ont, Canada



J.Kwong et al - PLoS One 2012;7(9):e44103

Project ECHO – Patient Outcomes Rx CHC

- Prospective cohort study compared HCV outcomes at UNM HCV clinic vs patients treated by PCPs at 21 ECHO sites
  - N = 407 treatment-naive patients; primary endpoint: SVR



- SAEs at UNM vs ECHO sites: 13.7% vs 6.9%

Arora S, et al. N Engl J Med. 2011;364:2199-2207.

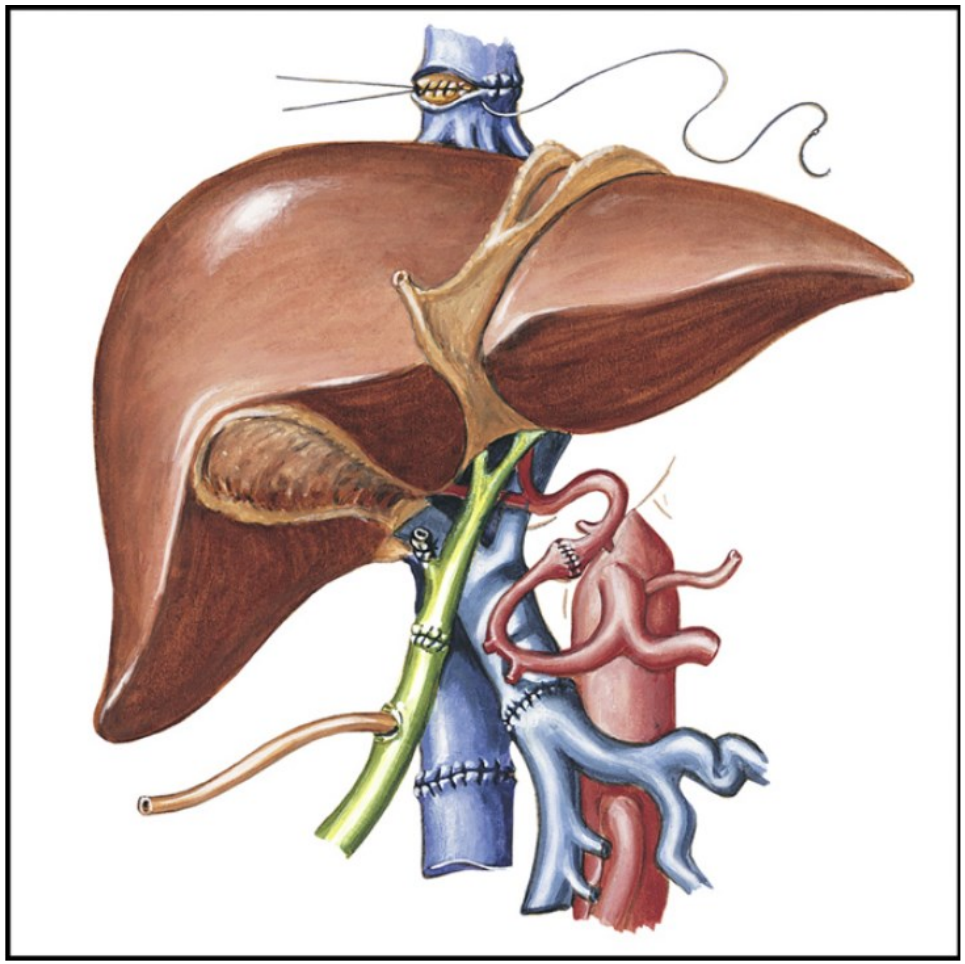
Improved outcomes in all cirrhotics

Since 1968

- Making the diagnosis – and establishing etiology
- Specific therapies eg : Antiviral therapy – regression of fibrosis +/- viral clearance
- U/S screening –HCC
- Ascites – screen SBP/ effective antibiotics ↓mortality HRS
- Variceal screening / prophylactic therapy
- Suspect sepsis if any deterioration

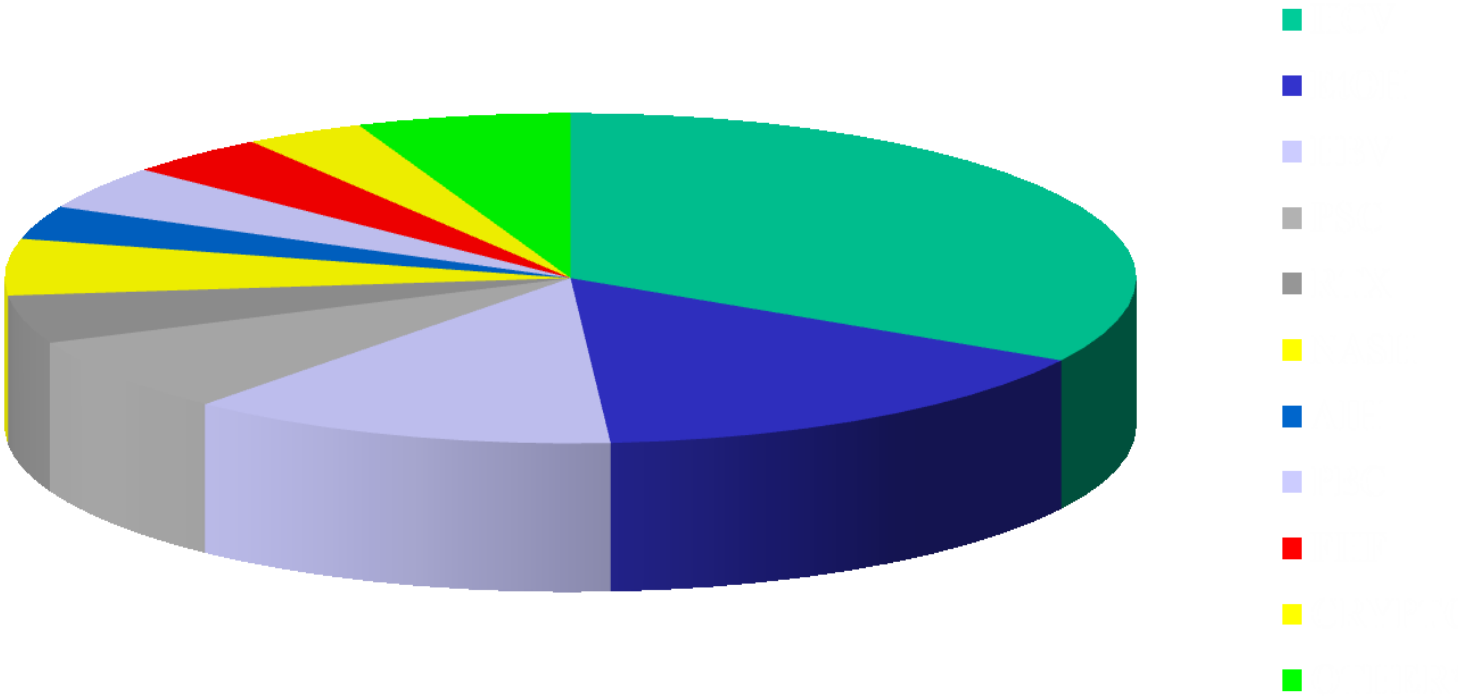
Liver Transplantation

2012 Lasker-DeBakey Award (T. Starzl)



Vilharinho S et al – Cell 2012;150;6:1096

Indications for Liver Transplant
UHN – 2000 - 2011

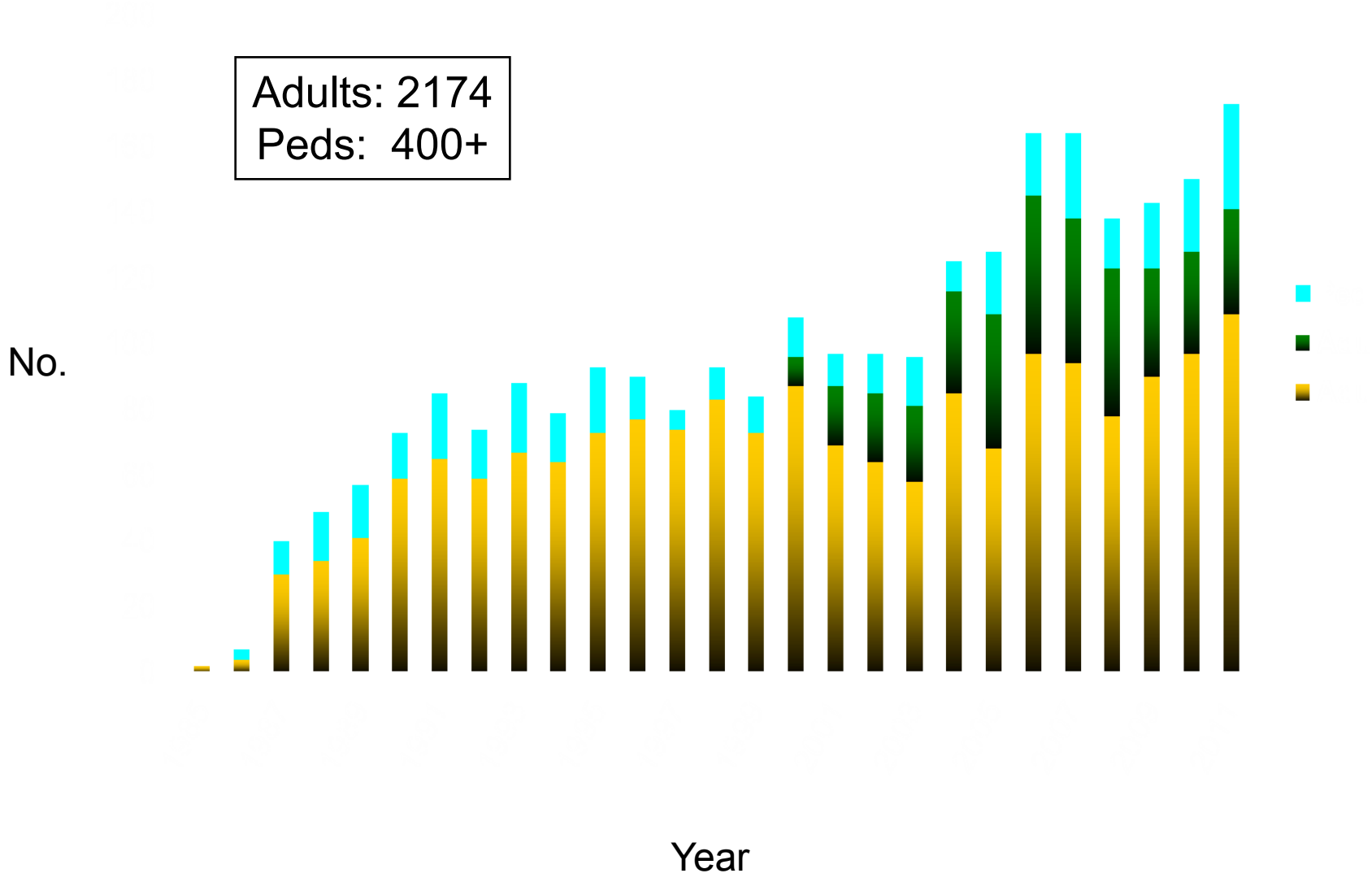


N = 1372

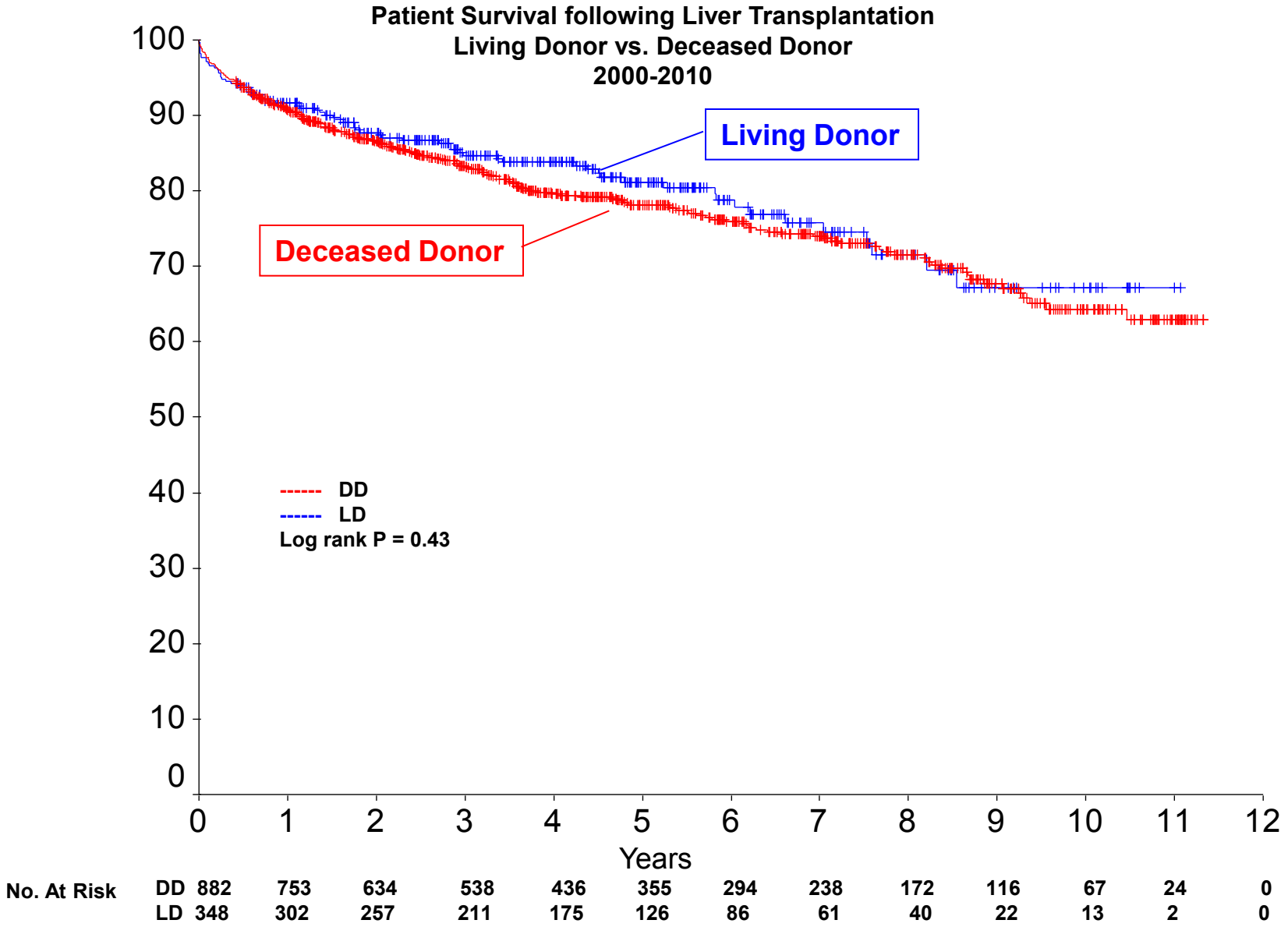
HCC (n=463) listed according to underlying liver diagnosis

* Other: TPN, AATD, BCS, Wilsons, PCLD, CF, Alagille, GranHep, FAP, et al.

Liver Transplant in Toronto
1985 – 2011



Survival: DD vs LD Liver Transplant



Room for Improvement

Knowledge Transfer

Preventive Health Strategies:	Effectively translate knowledge adapted to the particular communities (MD and patients)
Healthcare Promotion:	Public health and education policy e.g. screening and use of treatment guidelines
Clinical Science:	Well designed clinical trials Cost / Benefit Analyses
Translational science:	Collaboration with basic scientists e.g. genetics, virology, pharmacology

1979 - 2013

THANK YOU FOR YOUR SUPPORT

University of Toronto

Toronto Western Hospital

My mentors and mentees

Collaborators

CIHR, NIH, “Industry”, Donors

The “TEAM” at TWH

The End