

# ‘What you need to know about liver disease’

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Consultant Gastroenterologist and Hepatologist

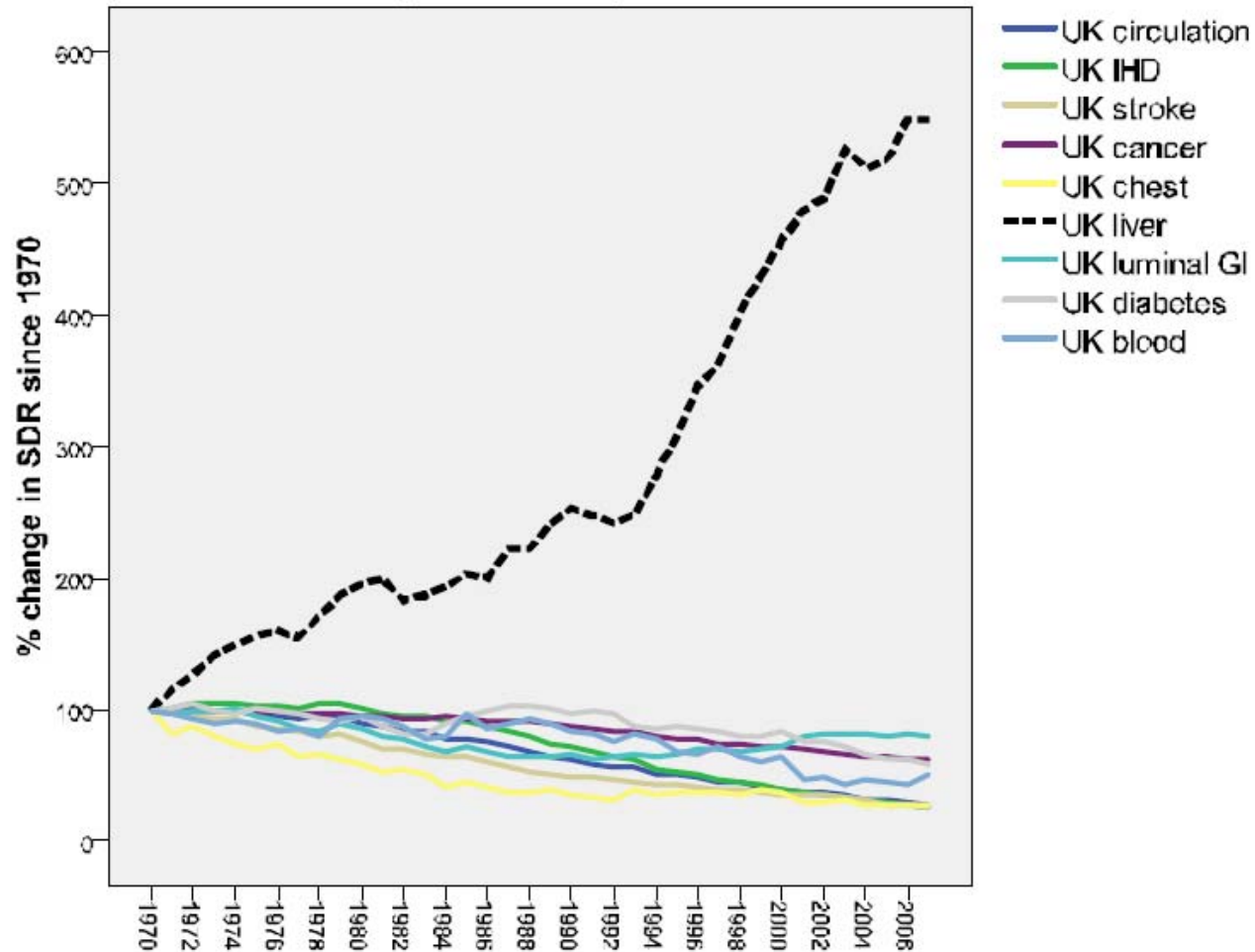
The Hillingdon Hospitals NHS Foundation Trust

# Overview

- Liver disease in the UK
- Alcohol
- Fatty liver
- Hepatitis C
- Hepatitis B

# Liver disease mortality

UK under 65 standard death rate for various diseases  
(1970 = 100%)



# Government directives

- **NHS National Outcomes Framework (2011-12)**

‘reduce mortality from liver disease’

- **National Liver Plan (2009)**

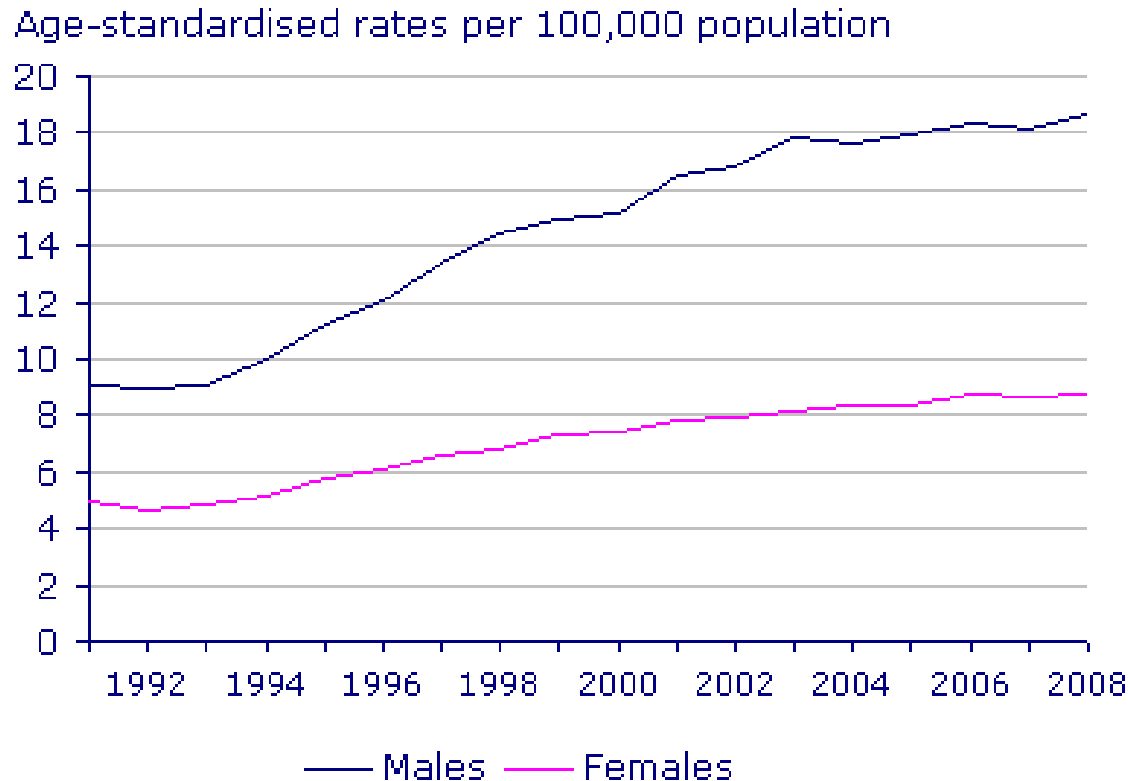
Liver ‘Tsar’- Prof. Martin Lombard

DGH provision of Liver services

Focus attention on alcohol-induced liver injury

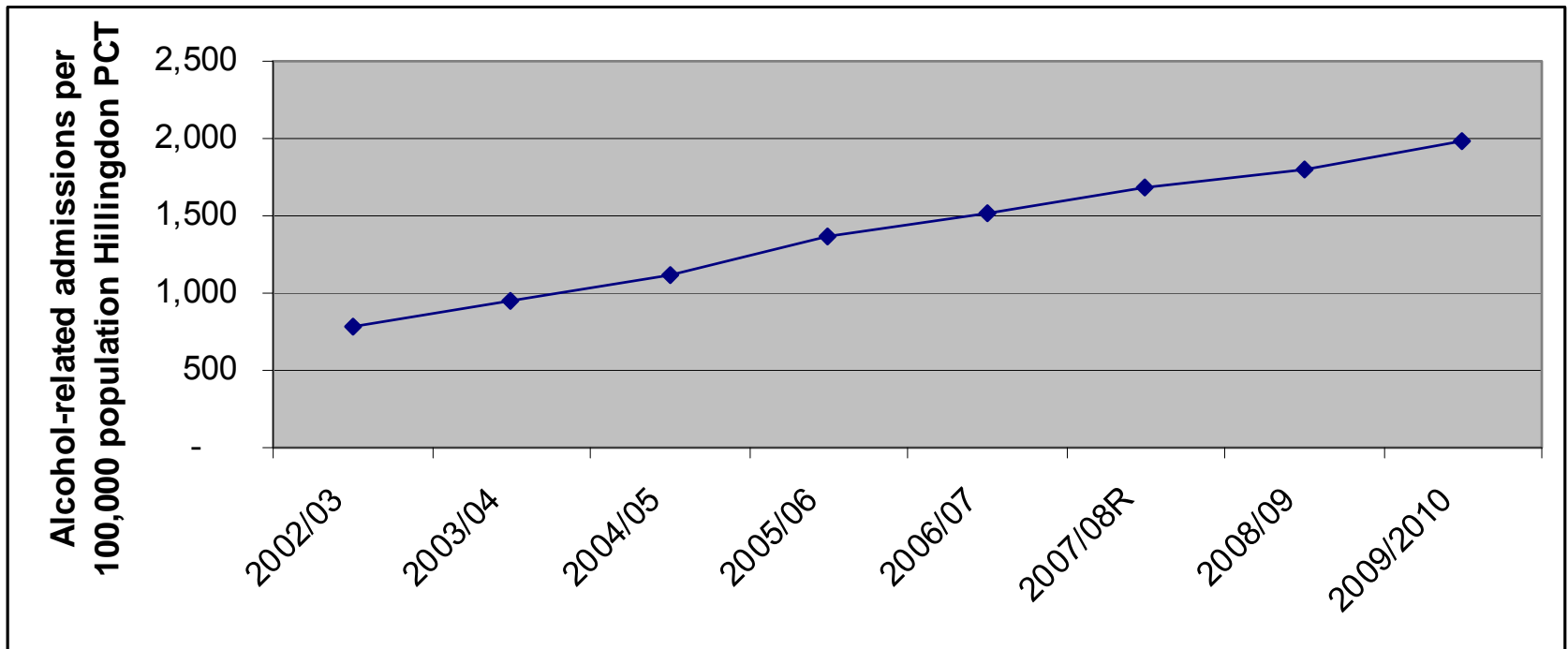
# Alcohol

# Alcohol-related death rates by sex, UK 1991-2008



- Alcohol-related deaths doubled between 1991 and 2007

# Local alcohol-related admissions



- 1342 alcohol-attributable admissions - 3473 bed days (Nov '09-Oct '10)

# United Kingdom Alcohol Treatment Trial (UKATT)

**Table 2** Mean (95% confidence intervals) adjusted scores for primary and secondary outcomes across social behaviour group and motivational group combined at baseline and three and 12 months

Outcome measures	Baseline (n=742)	3 months (n=689)	12 months (n=617)
Days abstinent (%)	29.5 (26.1 to 32.9)	42.7 (38.2 to 47.2)	46.0 (40.8 to 51.2)
No of drinks* per drinking day	26.8 (24.9 to 28.7)	17.9 (16.3 to 19.5)	19.2 (17.2 to 21.2)

- Pragmatic randomised trial
- Psychological therapy
- >25% no alcohol-related problems at FU
- 40% at least 'much improved' with a reduction in alcohol-related problems of 2/3 or more
- 48% at least somewhat improved with a reduction in alcohol-related problems of 1/3 or more

# Alcohol-induced cirrhosis: abstinence

(Verrill C. *et al. Addiction* 2009)

- 100 consecutive liver biopsies (Southampton)  
Survival data
- Abstinence at 1 month post diagnosis most important for determining survival
- 7 year survival 72% vs 44% for those continuing to drink

# Alcohol

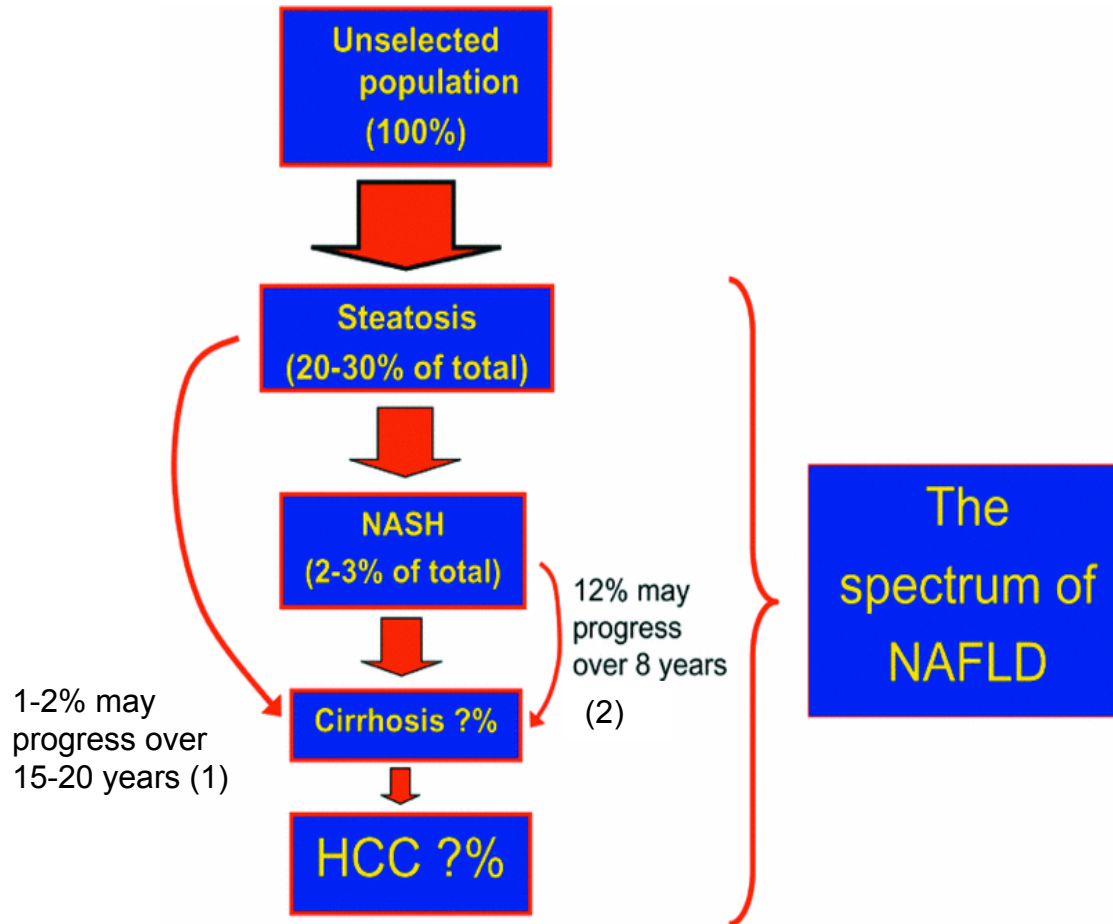
- Please always consider referral to community alcohol services  
HDAS (HAGAM)
- Nothing to lose

# Fatty liver disease

# Fatty liver disease

- NAFLD- Non-Alcoholic Fatty Liver Disease
- NASH- Non-Alcoholic Steatohepatitis

# NAFLD- Natural history



- (1) Day CP (2005) Gastroenterology
- (2) Fassio E *et al* (2004) Hepatology

# NAFLD- Epidemiology 1

- NAFLD

'normal'	10-20%	Ruhl CE (2004) Clin. Liver Dis.
BMI >30	65-75%	Angulo P (2002) NEJM
BMI >35	85-90%	Andersen T (1984) Int. J. Obesity

# NAFLD- Epidemiology 2

## NASH

2-3% of the population

Neuschwander-Tetri BA (2003) Hepatology

15-20% obese population

Wanless IR (1990) Hepatology

Of those with NASH

40-95% obese

>50% T2DM

Cortez-Pinto H (2004) Best Prac. Res. Clin. Gastro.

<80% dyslipidaemia

# NAFLD- clinical diagnosis

- Most clinically asymptomatic
- Incidental finding: blood tests or imaging
- Fatigue, RUQ pain, hepatomegaly Sanyal (2002) Gastro.
- Complications of cirrhosis  
10% of cases of cryptogenic cirrhosis at OLT Clark (2003) JAMA

# NAFLD- clinical diagnosis

- Exclude Alcohol

No consensus threshold

70 g/week women 140 g/week men

# NAFLD- secondary causes of hepatic steatosis

- **Viral hepatitis:**  
HBV/ HCV
- **other liver/biliary disease**
- **Cytotoxic drugs:** MTX
- **Antibiotics:** tetracycline
- **Drugs:** Amiodarone, tamoxifen, oestrogens, antiretrovirals
- **Inborn errors of metabolism:** Wilson's, Homocystinuria
- **Metabolic disorders:** small bowel bypass, TPN, starvation/ cachexia

# NAFLD- imaging

- USS

Sensitivity 60-94%, specificity 88-95%

Morbidly obese 49% and 75% Mottin *et al* (2004) *Obes. Surg.*

- CT (Unenhanced) for >33% steatosis

Sensitivity 93% and PPV 76% Charatcharoenwiththaya (2007) *Clin. Liv. Dis.*

- CT (Enhanced)

Sensitivity 54% and specificity 95% saddeh *et al* (2002) *Gastroenterology*

# Who to biopsy

Angulo *et al*  
(1999) Hepatology

- Age >45
  - Obesity and/or
  - Diabetes
  - AST/ALT >1
- 
- Significant predictors of severe fibrosis

Ratziu *et al*  
(2000) Gastroenterology

- Age  $\geq 50$  (OR 15.1)
  - BMI >28 (OR 5.7)
  - TG >1.7mmol/L (OR 5)
  - ALT >2ULN (OR 4.6)
- 
- Independently associated with septal fibrosis

# Treatment options

- Lifestyle modifications
- Long-term weight management
- Increased activity
- Dietary intervention (reducing CHO and sat fat)
- Address CVS risk
  - Treatment of dyslipidaemia and hypertension

# NAFLD- bottom line

## Higher risk

- Age >45
- Obesity and/or
- Diabetes
- AST/ALT >1
  
- Significant predictors of severe fibrosis

## Treatment

- Lifestyle modifications
- Long-term weight management
- Increased activity
- Dietary intervention (reducing CHO and sat fat)
  
- Treatment of dyslipidaemia, hypertension and hyperglycaemia

# Hepatitis C



Blood donation  
screened 1991



Drug use



migration



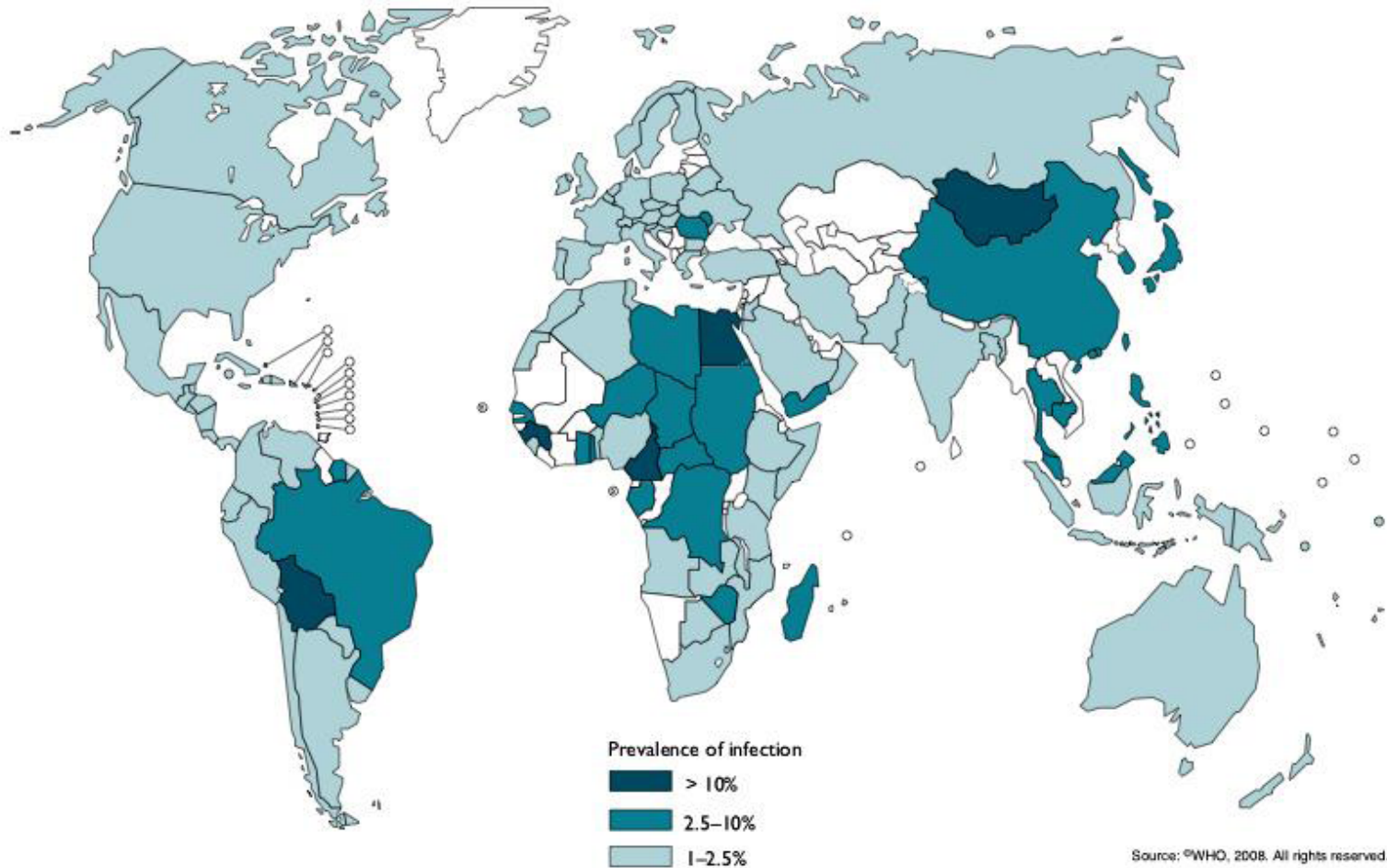
# Hepatitis C



- Worldwide- chronic hepatitis C infects 175 million people
- UK- up to 500,000 have hepatitis C
- Hillingdon- over 1300 have hepatitis C
- Only 20-30% have been diagnosed

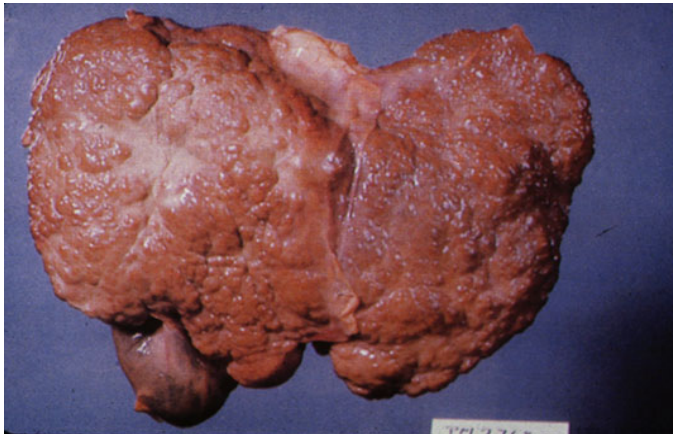
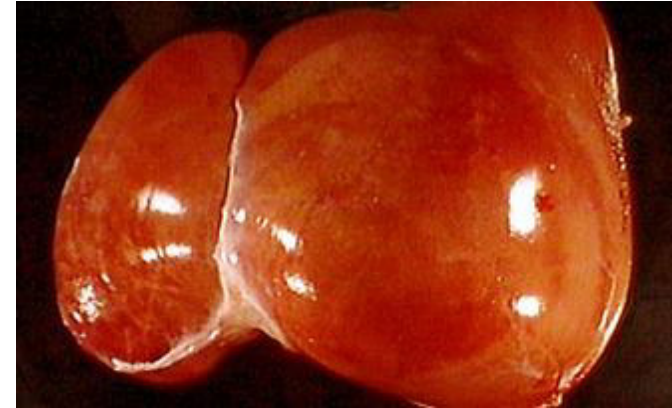
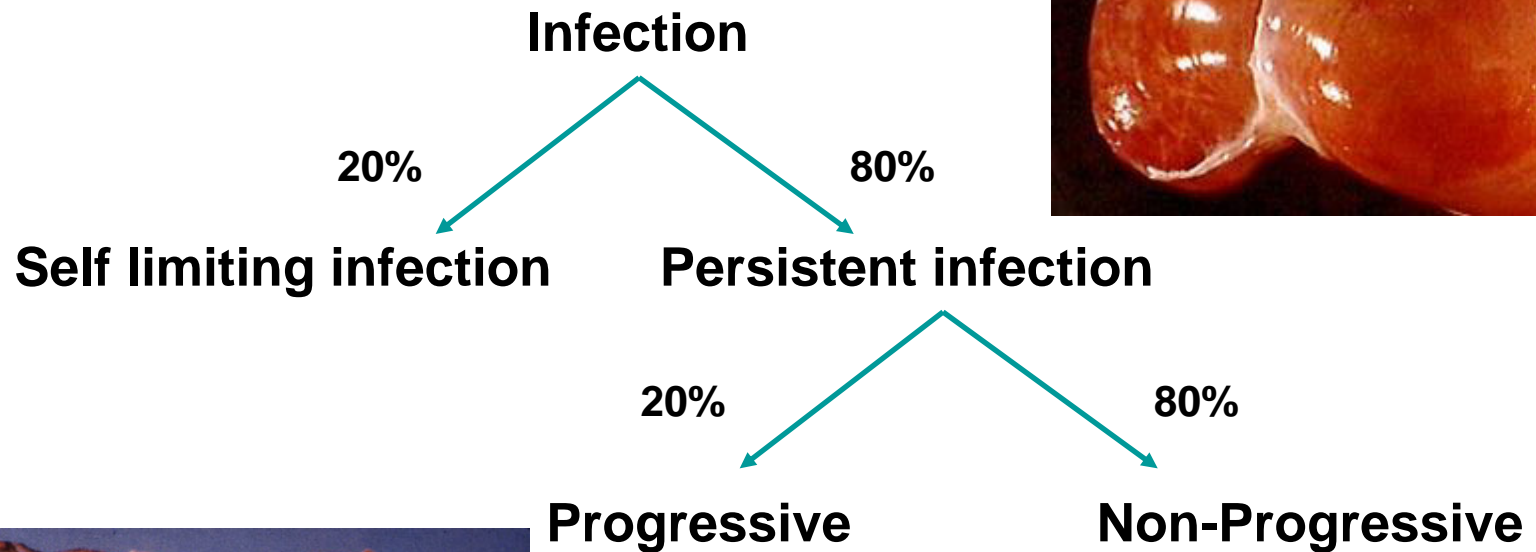
# Hepatitis C

Hepatitis C, 2007



Source: ©WHO, 2008. All rights reserved.

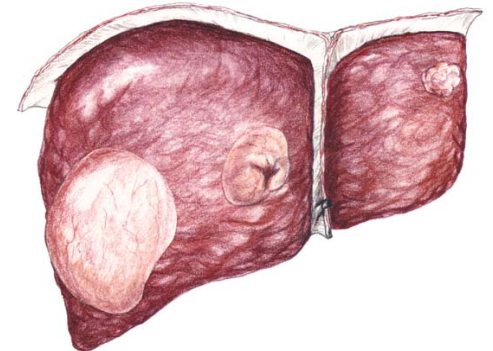
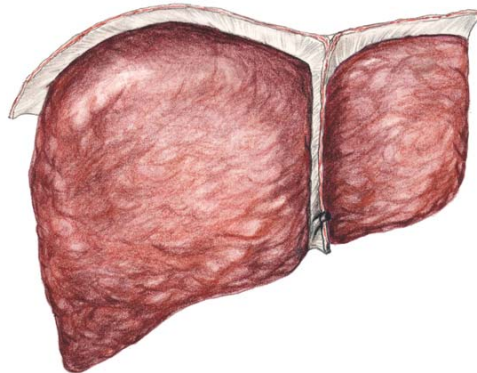
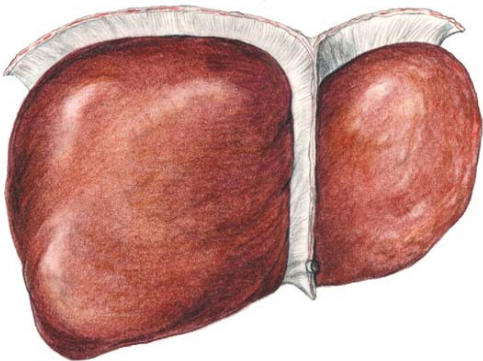
# Outcome of hepatitis C infection



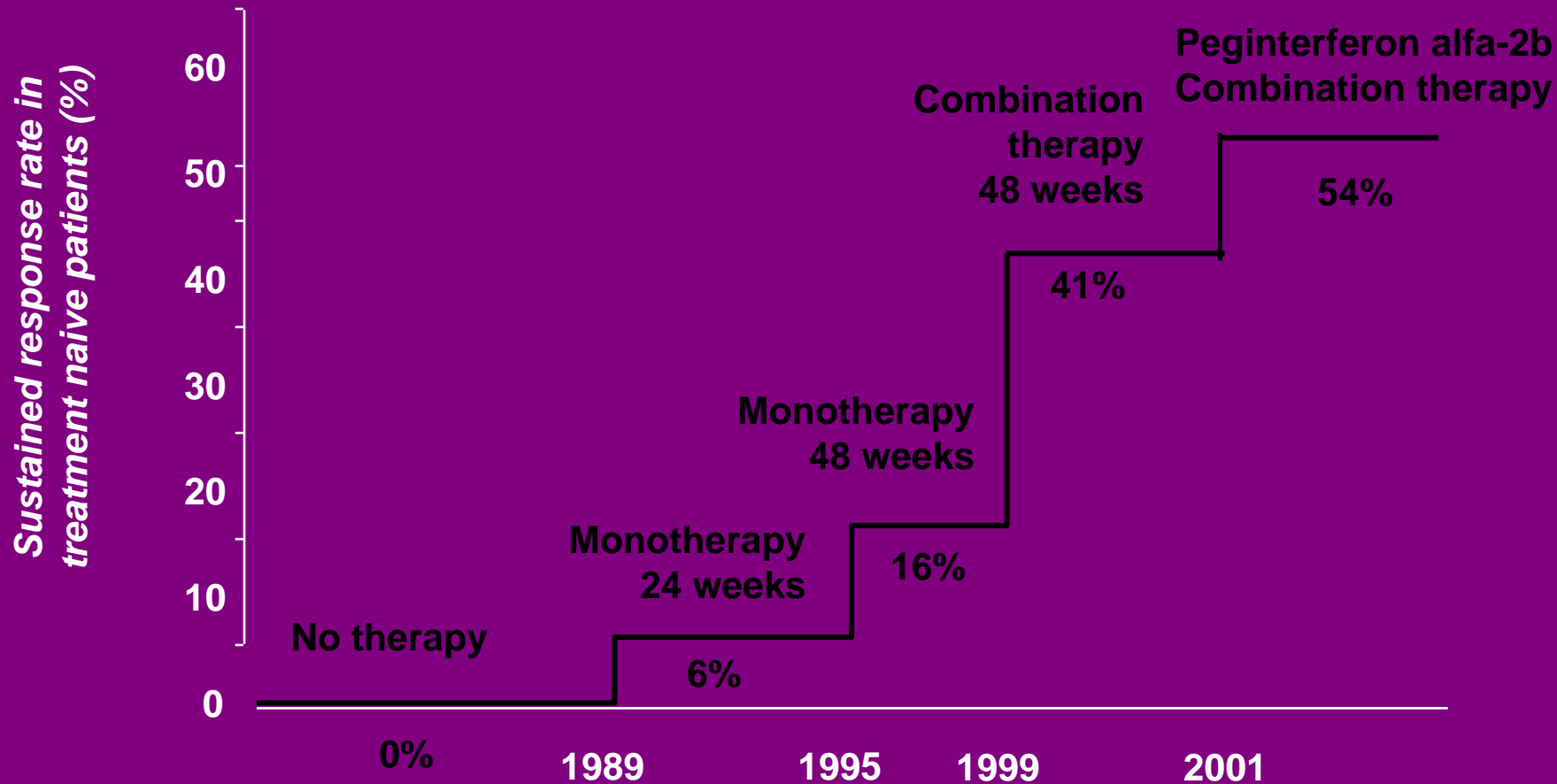
# Hepatitis C treatment

- Finite duration 6-12 months
- Aim viral eradication

**Hepatic fibrosis** → **Cirrhosis** → **Liver cancer**

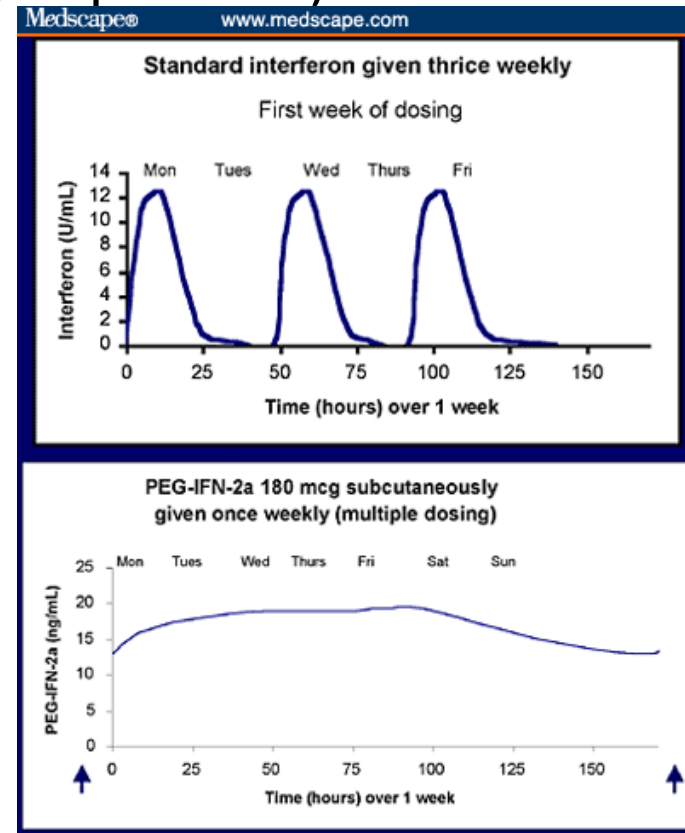
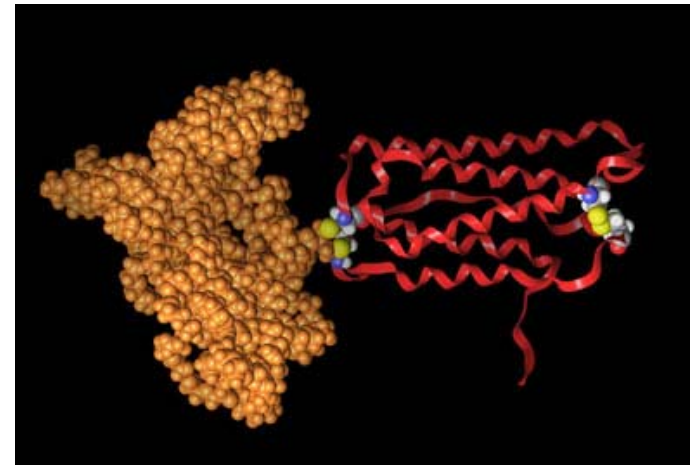


# Improvements in sustained virologic response rates with progressions in therapy

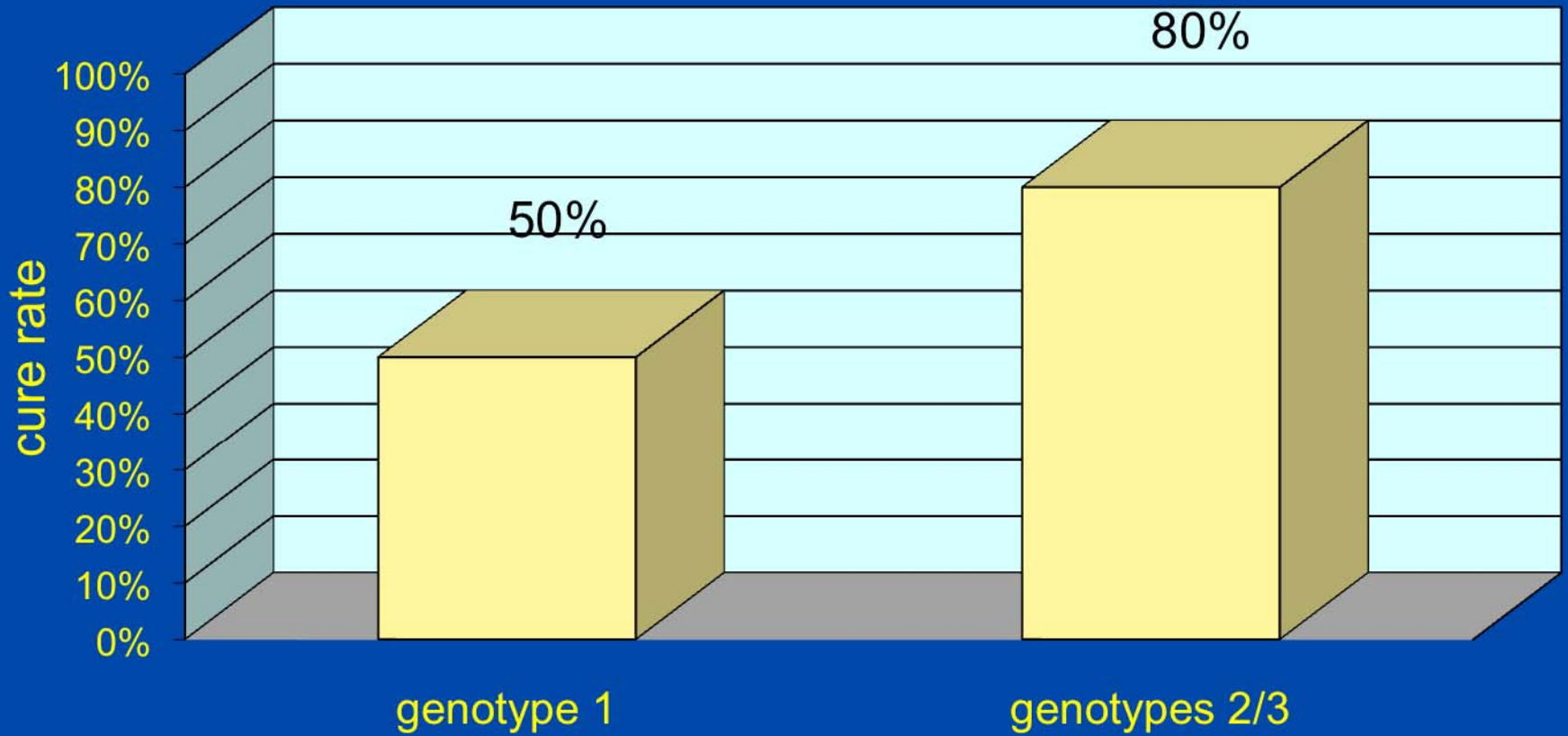


# Pegylated Interferon

- Flu-like symptoms
- Lethargy
- Neuropsychiatric (aggression, anxiety, depression)
- Neutropenia
- Rashes
- Anorexia and weight loss
- Alopecia
- Thyroid dysfunction
- Nephrotoxic
- Cardiac disturbance  
(high/low BP or arrhythmia)



# Peg-IFN & Ribavirin



# Hep C- secret of successful treatment



Mary Haight

Viral Hepatitis  
Nurse Specialist

Advertising world  
hepatitis day

28<sup>th</sup> July 2011

# Hepatitis C- bottom line

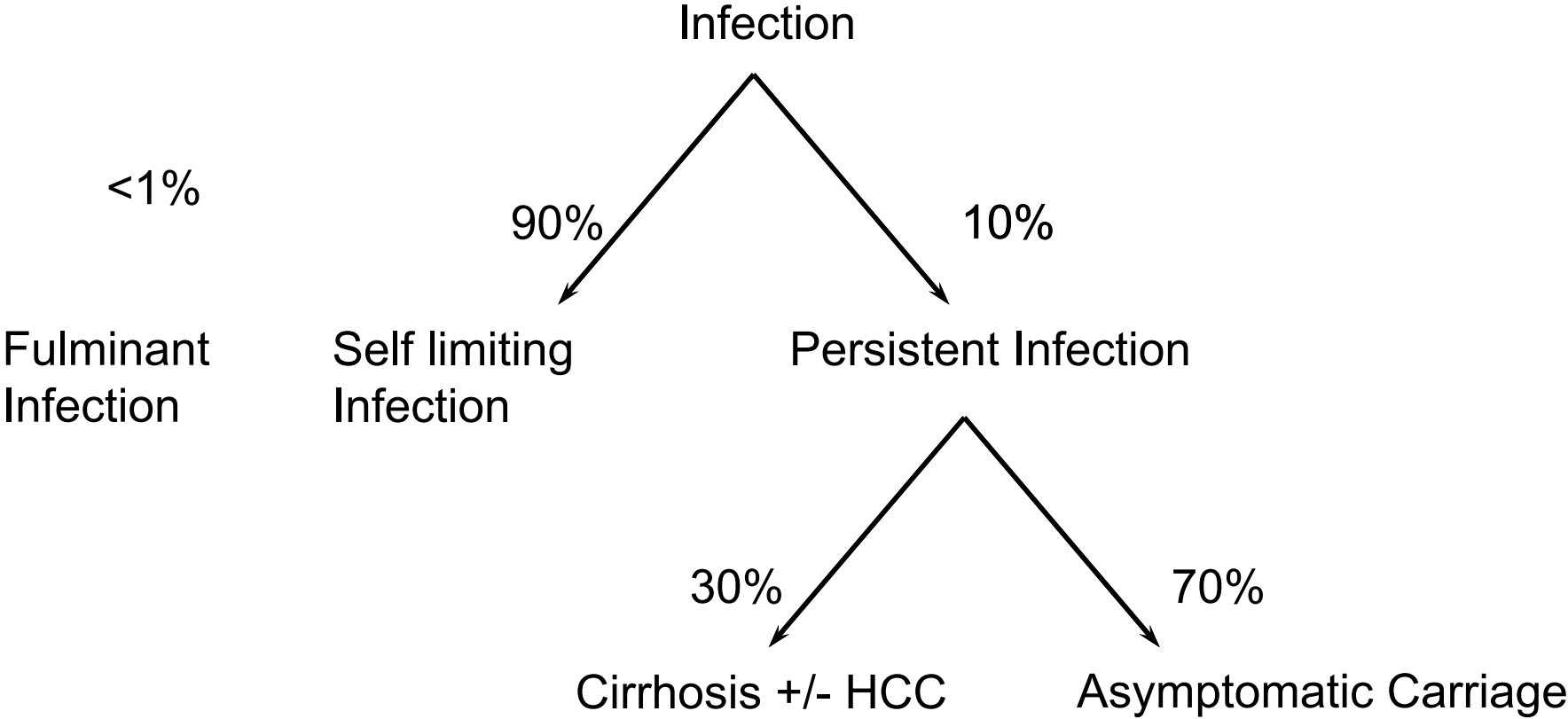
- Chronic disease
- Can be successfully treated
- 50-80% success rate dependent upon genotype and host factors
- Cirrhosis and liver cancer may be prevented
- Reduces 'pool of infection'

# Hepatitis B

# Hepatitis B

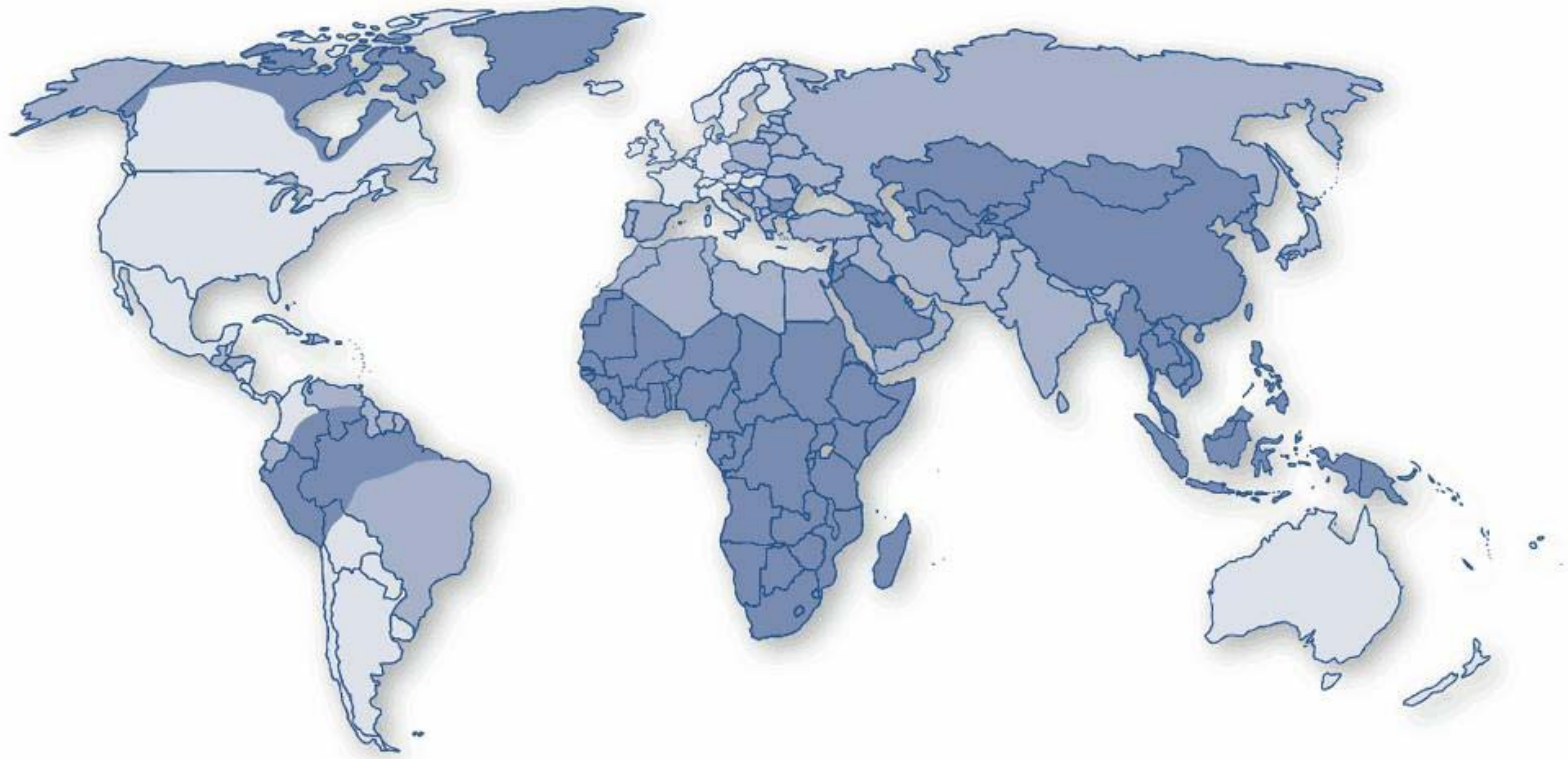
- Worldwide- 1 in 3 people have had hepatitis B
- UK- up to 180,000 have hepatitis B
- Hillingdon- up to 2000 have hepatitis B
- Worldwide- 25% of hepatitis B carriers die due to complications of liver disease

# Outcome of Hepatitis B infection



# Hepatitis B prevalence

Prevalence of Hepatitis B Virus Chronic Infection, 2006



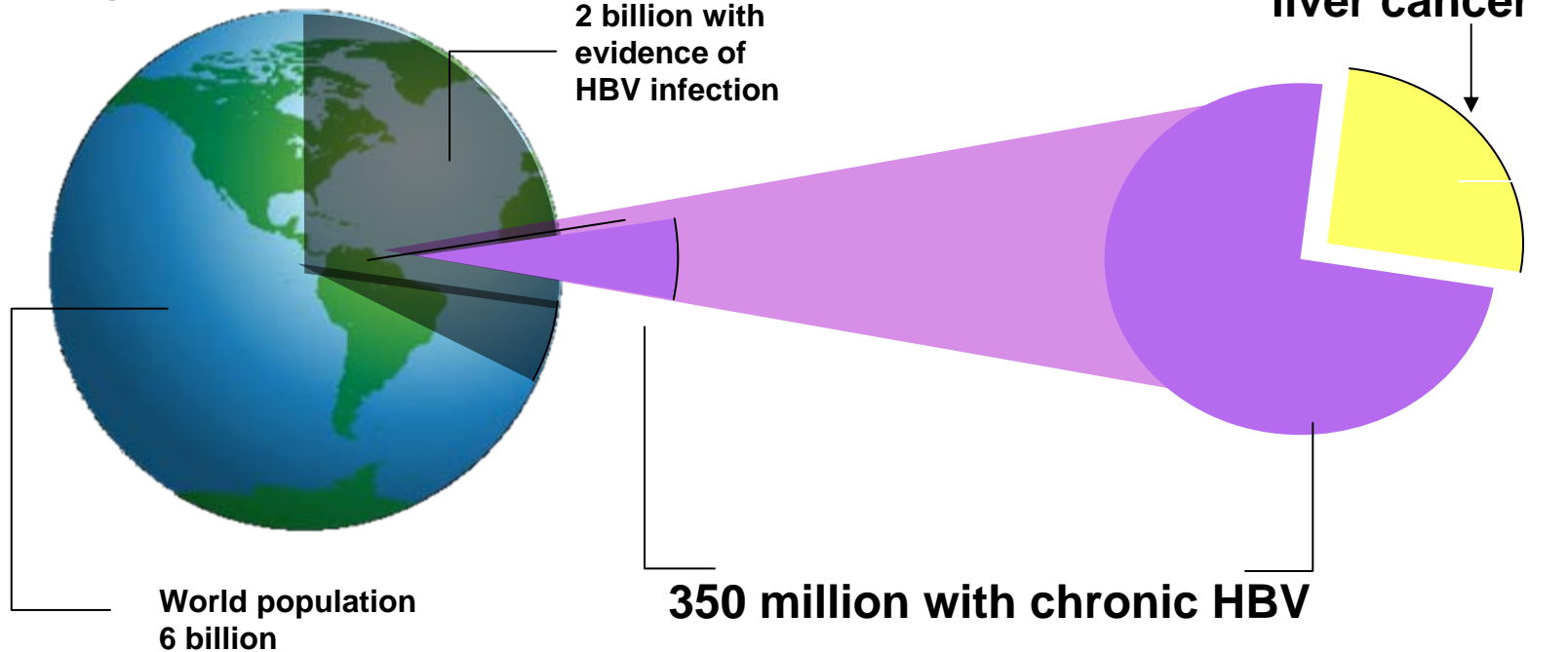
Prevalence of hepatitis B surface antigen



Acknowledgment: Adapted from Centers for Disease Control and Prevention

# 2 Billion Infected with HBV Worldwide

- Almost half of the world's population lives in an area with high HBV prevalence

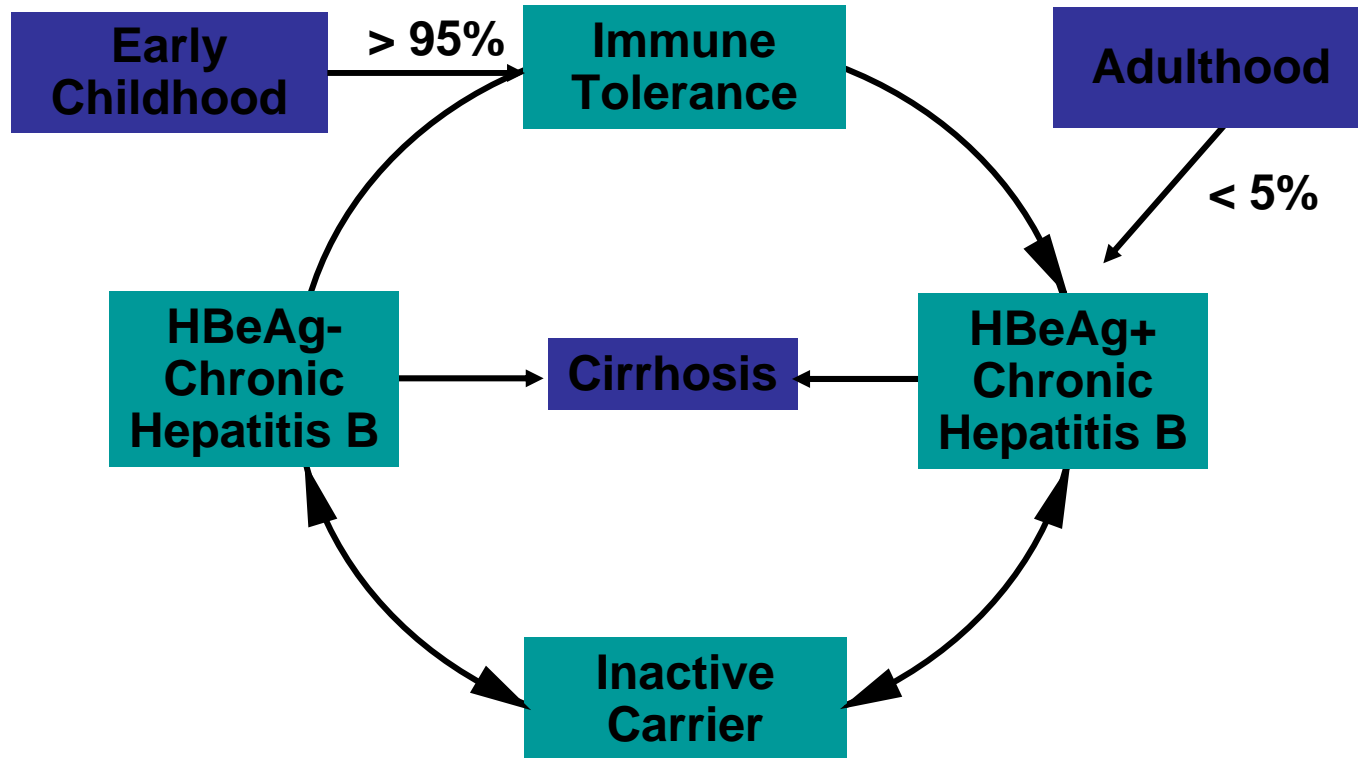


- 500,000 -1,200,000 deaths yearly due to HBV complications

# What Is a “Normal” ALT Level?

- 9221 first-time potential blood donors
- 74% suitable donors after exclusion of anaemia, serologic reactivity on screening assay, seizure, sexual, and other risk
  - 57% determined to be at “low risk” for liver disease
    - BMI < 25
    - Normal serum cholesterol, triglycerides, and glucose levels
    - Absence of concurrent medication use
- Updated healthy ALT upper limits determined from the group of low-risk individuals
  - **Males: 30 IU/L**
  - **Females: 19 IU/L**

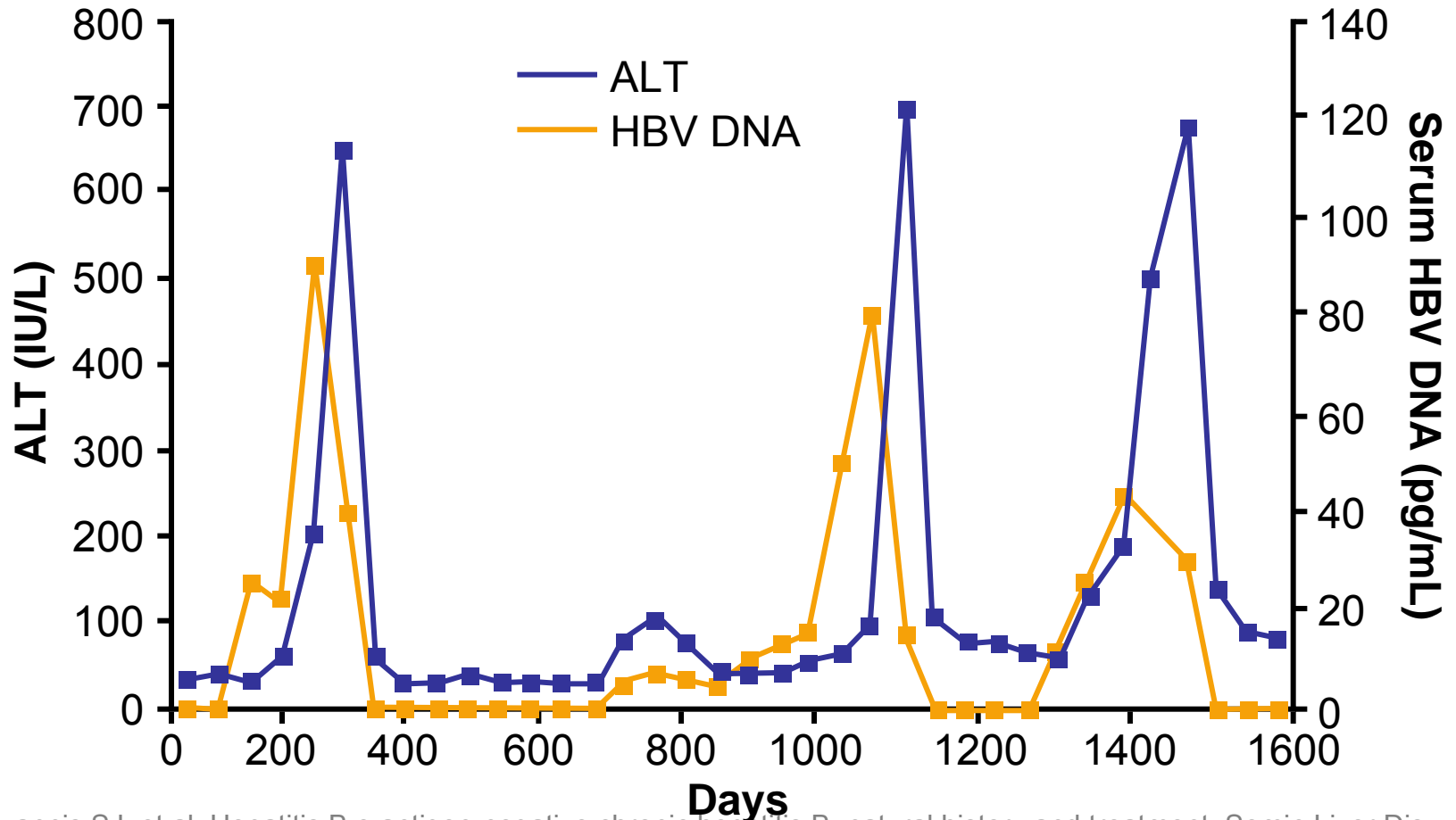
# Natural History of HBV Infection



# Phases of Chronic HBV Infection

	<b>Immune Tolerance</b>	<b>Immune Active/ HBeAg-Positive CHB</b>	<b>Nonreplicative (Inactive Carrier)</b>	<b>HBeAg-Negative CHB</b>
Typical HBV DNA, IU/mL	> 200,000 and often > $10^{7-8}$	200,000 - $2 \times 10^9$	< 2000	2000 - $2 \times 10^7$
HBeAg	Positive	Positive	Negative	Negative
ALT	Normal	Elevated or fluctuating	Normal	Elevated or fluctuating
Other observations	Liver biopsy typically normal or minimal findings	Active inflammation on liver biopsy	HBsAg may become undetectable	Active inflammation on liver biopsy
Treatment candidate?	No	Yes	No	Yes

# HBeAg-negative patients require frequent monitoring



Hadziyannis SJ, et al. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. *Semin Liver Dis.* 2006;26(2):130-141. Reprinted by permission. Slide from Clinical Care Options/ Hepatitis

# Hepatitis B- case 1

- 21 yo YM originally from China
- HBsAg +ve, DNA  $1 \times 10^6$  iu/ml, ALT 13
- Management  
Monitor LFT and HBV DNA 4-6 months

# Phases of Chronic HBV Infection

	<b>Immune Tolerance</b>			
Typical HBV DNA, IU/mL	> 200,000 and often > $10^{7-8}$			
HBeAg	Positive			
ALT	Normal			
Other observations	Liver biopsy typically normal or minimal findings			
Treatment candidate?	No			

# Hepatitis B- case 2

- Mr SM 49 yo originally from Hong Kong
- HBeAg –ve, DNA 200-1000 iu/ml, ALT 20
- Management  
Monitor bloods 6 monthly

# Phases of Chronic HBV Infection

			<b>Nonreplicative (Inactive Carrier)</b>	
Typical HBV DNA, IU/mL			< 2000	
HBeAg			Negative	
ALT			Normal	
Other observations			HBsAg may become undetectable	
Treatment candidate?			No	

# Hepatitis B- case 3

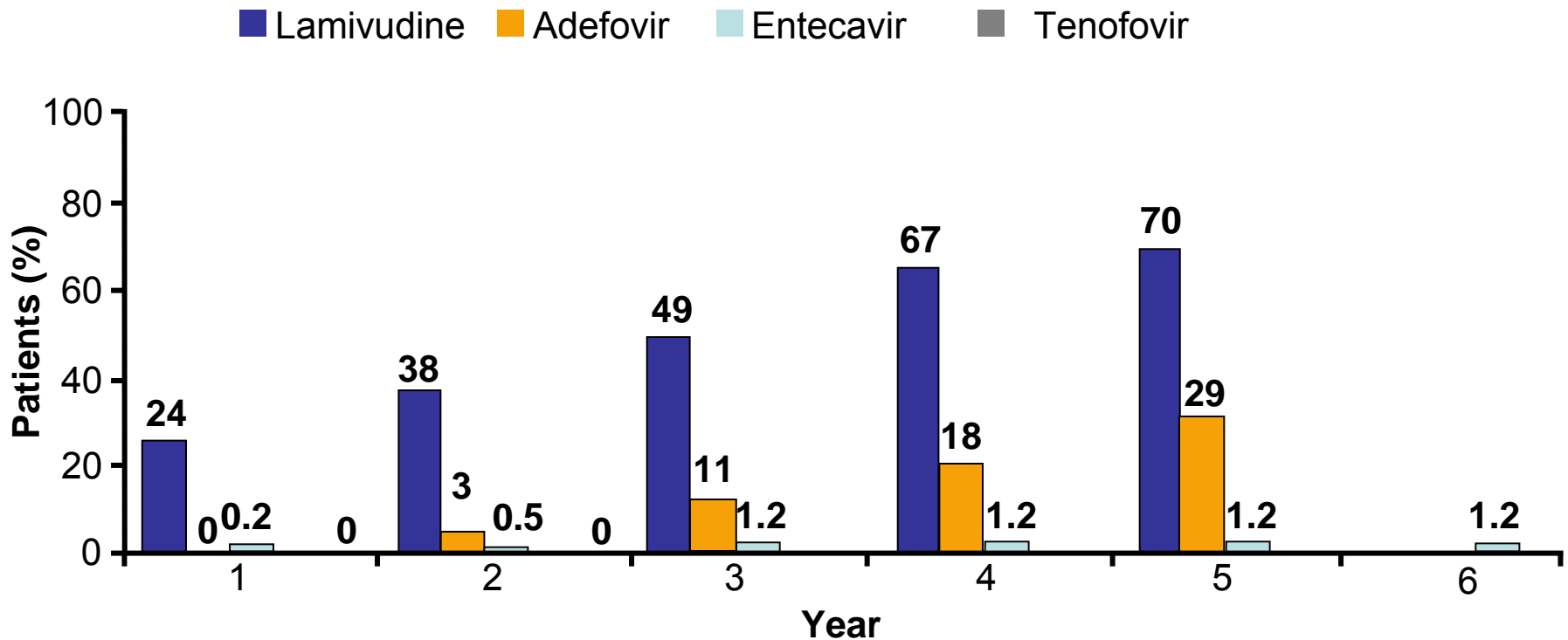
- Mr KM 52 yo, originally from Hong Kong
- Brother died of liver cancer age 44
- HBeAg -ve, DNA  $1 \times 10^5$  iu/ml, ALT 40-65
- → Liver biopsy moderate fibrosis
- Started on antiviral treatment

# Phases of Chronic HBV Infection

				<b>HBeAg-Negative CHB</b>
Typical HBV DNA, IU/mL				2000 - $2 \times 10^7$
HBeAg				Negative
ALT				Elevated or fluctuating
Other observations				Active inflammation on liver biopsy
Treatment candidate?				Yes

# HBV treatment: cumulative rates of resistance

*Not head-to-head trials; different patient populations and trial designs*



EASL clinical practice guidelines. J Hepatol. 2009;50:227-242. Tenney DJ, et al. EASL; 2009; Copenhagen, Denmark. Abstract 20.

Slide adapted from Clinical Care Options/ Hepatitis

# Hepatitis B- bottom line

- Long term follow up (bloods +/- imaging)
- Evolving management paradigms
- Treatment is indefinite
- Treatment is directed at viral suppression
  
- High viral loads with elevated ALT= risk of liver cancer +/- cirrhosis

# Summary

- Liver disease in the UK      **Future innovation.....**
- Alcohol
- Fatty liver
- Hepatitis C
- Hepatitis B

# The Future

- ↑ Burden of GI/ Liver disease
- ↑ Patient expectations
- ↓↓ ££ Resources
- Challenges and opportunities to deliver high quality patient care

Future innovations....

- Liver (viral hep) clinic ✓
- Collaborative working
- ?Shared-care pathways (eg. Hepatitis B)
- ?Community Liver nurse  
Cirrhosis and Hep B FU



# Treatment options

- Lifestyle modifications
- Long-term weight management
- Increased activity
- Dietary intervention (reducing CHO and sat fat)
- Address CVS risk
  - Treatment of dyslipidaemia and hypertension

# Treatment: lifestyle

- Lifestyle
- 10% wt loss- improvement in LFT
- 6/12 ↓CHO diet (ketogenic) biweekly meetings Tendler (2007) Dig Dis Sci (n=5) Improvement in steatosis (P=0.2), inflammation (P=0.02), fibrosis (P=0.07)
- 12/12 intense nutritional counselling. Huang (2005) Am J Gastro  
16/23 completed study. 9/15 histological improvement (p=0.06)
- 3/12 study (n=25) Ueno *et al* (1997) J. Hepatol.  
improvement in histological parameters (p=0.05)

# Treatment: weight loss drugs

- Orlistat  
(lipase inhibitor, reduces fat absorption)

Improved LFT/ USS/ histology (n=10) Harrison (2004) APT

Improved LFT/ USS (n=21) Hatzitolios (2004) Ind J Gastro

# Treatment: weight loss surgery

- Improvement in diabetes, LFT and liver histology following gastroplasty

Schaffer et al (2006) J Clin Gastro.

Stratopoulos et al (2005) Obes. Surg.

# Treatment: lipid-lowering agents

- Clofibrate n=16, 1 yr.  
No change to ALT/ histology
- Atorvastatin 3 studies n=56, 6-12/12.  
Improvement of ALT, lipids, inflammation, ballooning, Mallory bodies.
- Pravastatin n=5, 6/12  
Improvement- lipids, LFT.  
Fibrosis score- no change

# Treatment: metformin

- 15pts 12/12 metformin 500mg tds. No effect on ALT or histology
- 36pts RCT 6/12. metformin 850mg bd. Improved ALT, no significant change in histology
- 110 pts open-label RT 12/12 metformin 1g bd. Improved ALT and histology.

# Treatment: glitazones

- Insulin sensitising drugs
- ? Anti-inflammatory and anti-fibrotic properties

Pioglitazone 18 pts 48/52. Improved ALT, histology, ↓liver volume (MRI)

Rosiglitazone 25pts 12/12. Improved ALT and fibrosis

- **Meta-analysis 42 trials with rosiglitazone, increased risk of MI**

# Treatment: others

- Antioxidants (vit E, vit C)
- UDCA no benefit
- UDCA + vit E 48pts RCT 24/12. 15 on UDCA/ vit E. Improvement in ALT and regression of steatosis.