Hepatitis C: outcome of acute infection

◆ recovery	21%
◆ chronic infection	79%
◆ cirrhosis	8%
◆ death in end-stage liver disease	1.6%

Liver 1993;13: 274

Hepatitis C: outcome of acute infection

- Persistent HCV viremia without hepatitis
- Persistent viremia after resolved acute hepatitis
- Persistent viremia with chronic hepatitis
- Resolved acute viremia with clearance of HCV

Cuypers et al. 1991

Hepatitis C: clinical features

Incubation period:	Average 6-7 wks Range 2-26 wks
Clinical illness (jaundice):	30-40% (20-30%)
Chronic hepatitis:	70%
Persistent infection:	85-100%
Immunity:	No protective antibody response identified

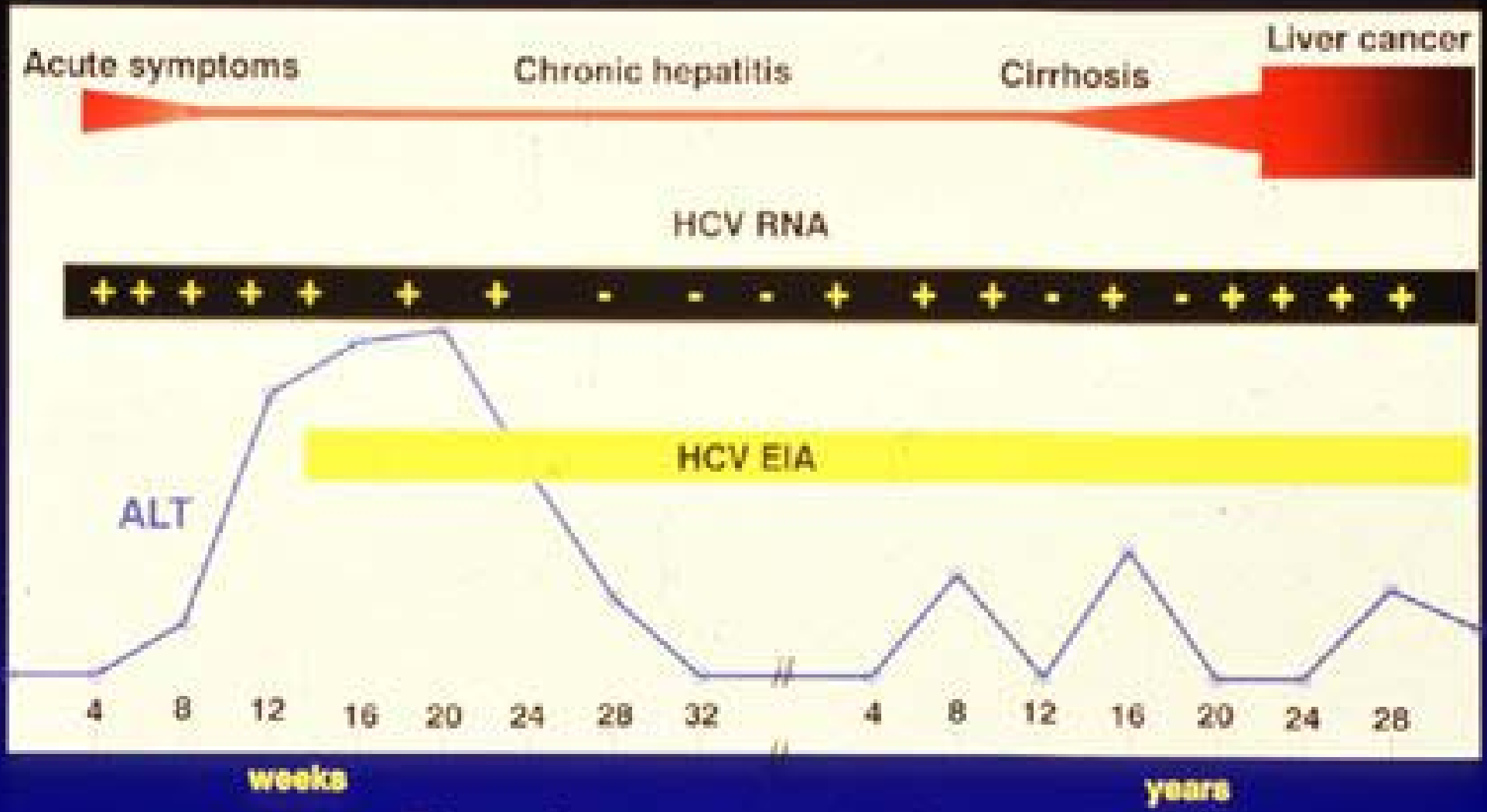
Hepatitis C disease

- Symptoms occur frequently, but are difficult to assess and quantify
- ALTs can be helpful as indirect measure in the context of histological activity
- Symptoms disappear after successful treatment
- only a minority will go to endstage liver disease?
- Inevitable progress to endstage if you do nothing?

Hepatitis C: disease outcome

- incubation period is 50-150 days
- 33% become symptomatic
  - 90% elevated ALTs
  - 50-70% initially anti-HCV positive, 95% RNA positive
- chronicity rate exceeds 80%?
- 10-20% each decade get cirrhosis
- vast majority symptom free for at least 20 years
- “healthy carrier” does not exist?
- fulminant outcome rare but severe

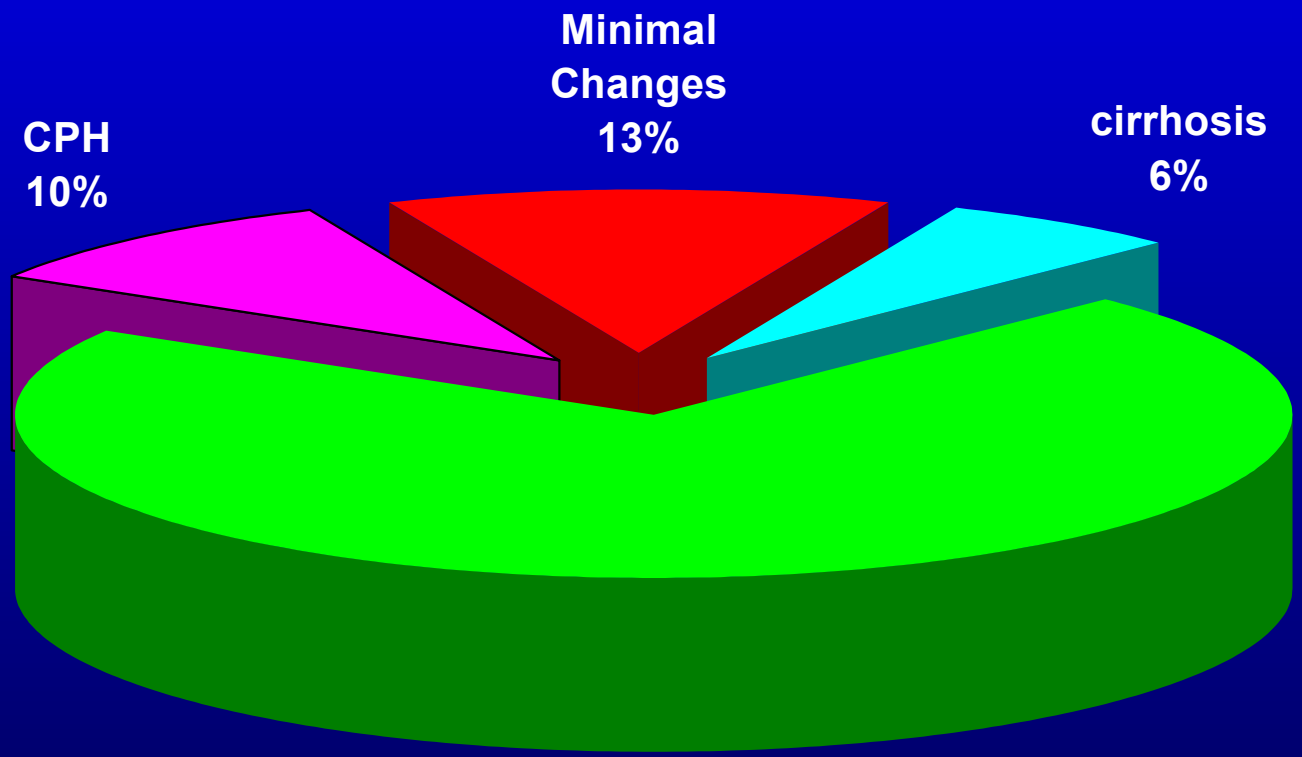
Natural History of Acute HCV Infection



Viral Hepatitis Prevalence & Mortality

	hepatitis C	hepatitis B	HIV/AIDS
global prevalence	3% 170 million	35% 1.2 billion	0.50% 36.1 m
chronic infection	2.30% 129 million	6% 350 million	0.50% 36.1 m
deaths per year	476 000	1.2 million	2.8 million
annual death rate	0.40%	0.49%	7.80%
lethality	7-10 %		~100 %

Liver histology in HCV+ blood donors



Esteban, 1994

Hepatitis C: follow-up

15 years	20%	CPH
18 years	23%	CAH
20 years	51%	cirrhosis
28 years	5%	HCC

- treat active disease, others control every 3 years

Tong et. al 1996

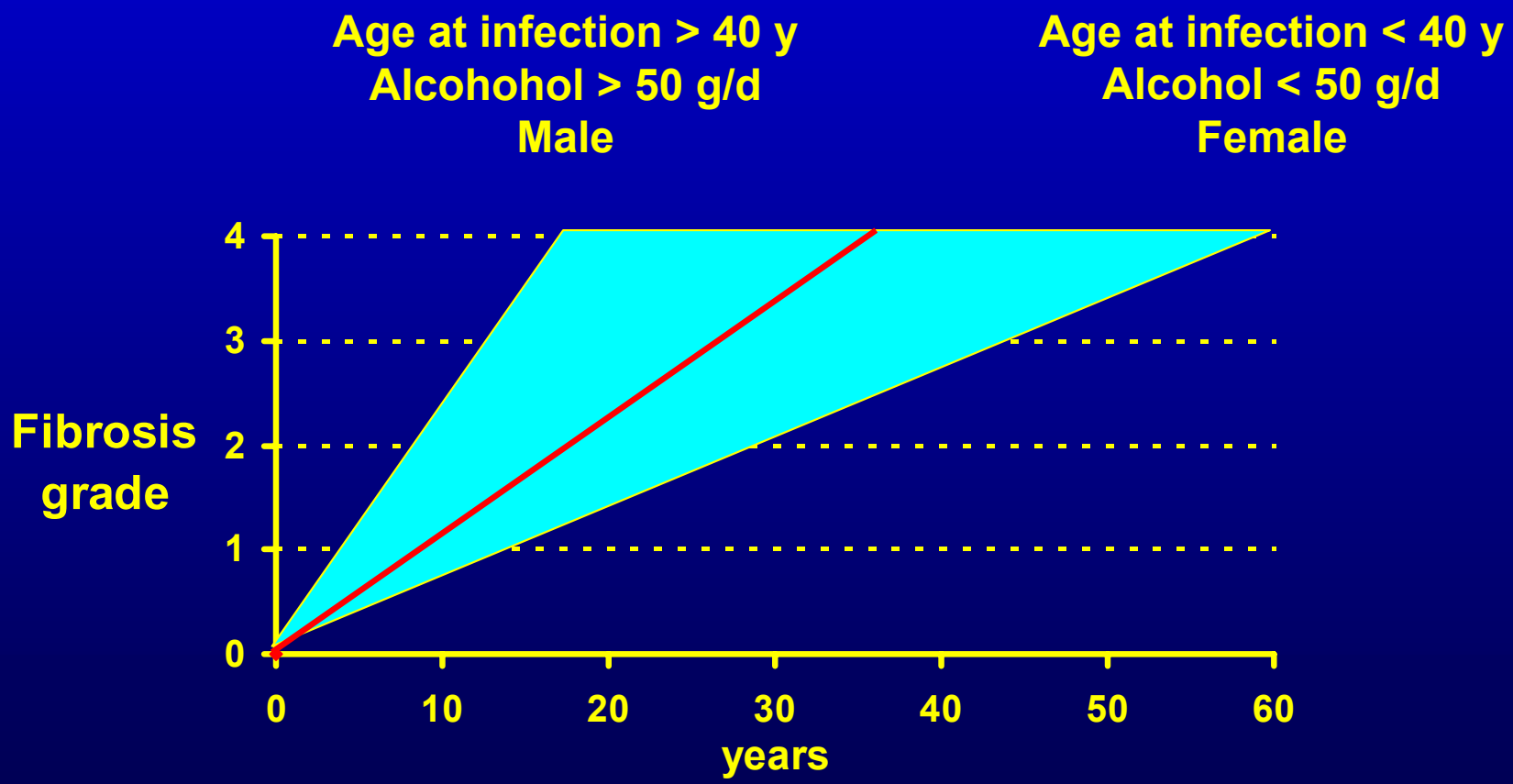
Hepatitis C outcome

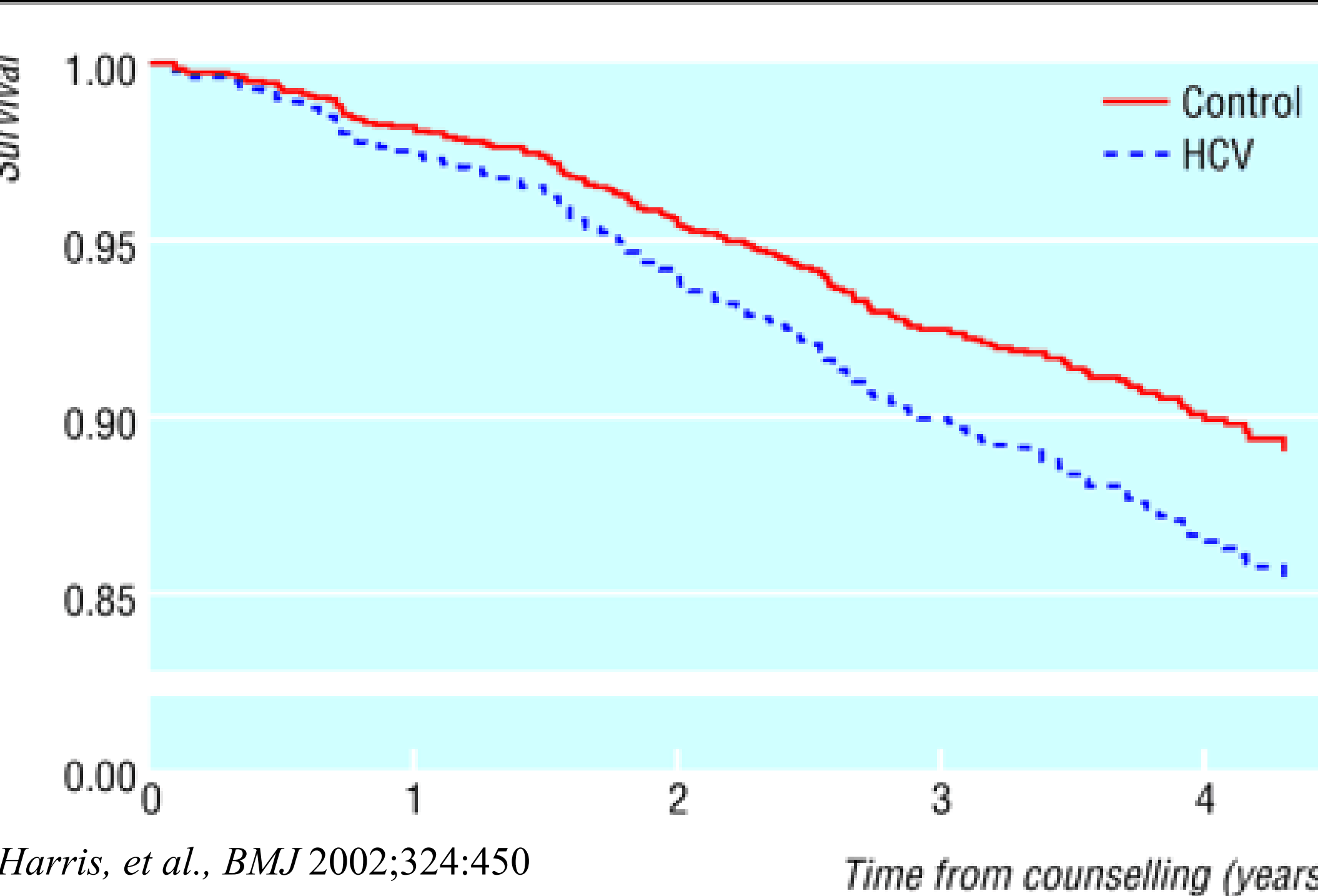
Survival	5 years	10 years
◆compensated liver	91%	79%
◆decompensated liver	18%	9%

- Schalm, 1999

PROGRESSION OF FIBROSIS IN CHRONIC HEPATITIS C

Poynard *et al.* (1997). Lancet 349: 825-832





Harris, et al., BMJ 2002;324:450

Table 3. Adjusted Relative Incidence of End-Stage Liver Disease (ESLD) Among 1667 Persons With Hepatitis C Virus Infection

Variable	No. (Person-Years)	No. With ESLD	Incidence Rate per 1000 Person-Years	Adjusted Relative Incidence (95% CI)
Age at enrollment, y				
<38	1426 (9333)	17	1.82	1.00
≥38	498 (3388)	23	6.79	3.67 (1.96-6.88)
Average alcohol use, g/wk				
<90	924 (6256)	11	1.76	1.00
90-260	504 (3352)	9	2.68	1.57 (0.65-3.79)
≥260	496 (3112)	20	6.43	3.60 (1.73-7.52)

*Relative incidence calculated by multivariate Poisson regression. Approximately the same estimates were derived by replacing age in the model with time from first injection drug use (categorized at the median), which itself remained associated with ESLD. CI indicates confidence interval.

Thomas et al, JAMA 2000

Clinical outcome after anti-D infection

mean time of infection 17 years		
estimated exposed neg.	1176-5312	
total anti-HCV pos	704	13-60%
total HCV-RNA pos	390	55.4%
symptoms		81.0%
fatigue		66.0%

grade		stage	
0	2%	no fibrosis	49%
1-3	41%	perip./portal fibr.	34%
4-8	52%	por.-portal bridg.	10%
9-18	4%	port-central bridg.	5%
		cirrhosis	2%

Kenny- Walsh et al, NEJM 1999

Clinical outcome after anti-D infection

mean time of infection 20 years	
exposed 2867	cohort 1018
acute hepatitis	90%
symptomatic	49%
icteric	20%
anti-HCV pos after 20 years	85%

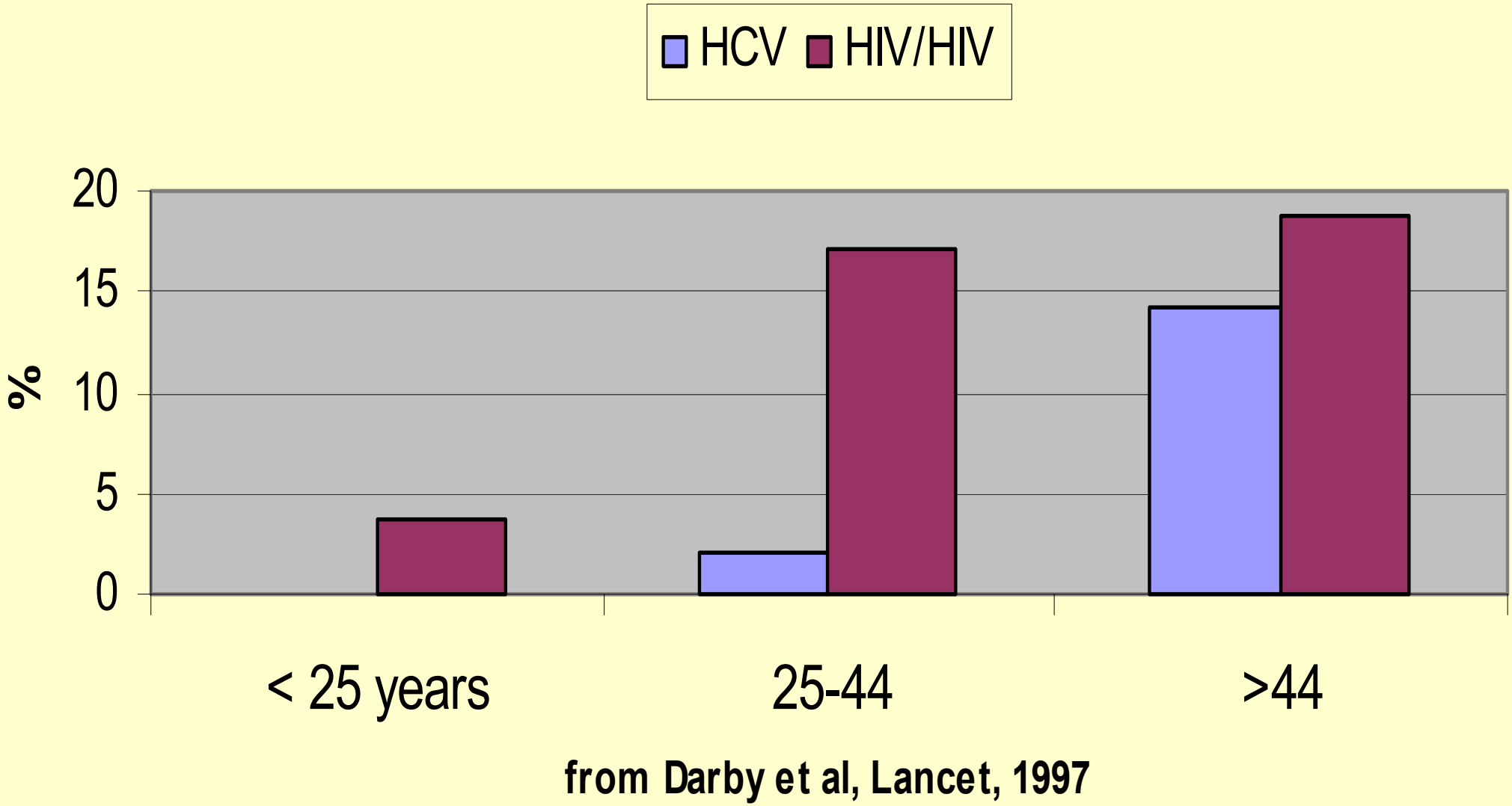
histology in 44 % of RNA pos	
minimal or no hepatitis	96%
portal fibrosis	47%
septal fibrosis	3%

Wiese et al, Hepatology 2000

Haemophilia severity and HIV status

from Darby et al, Lancet, 1997		
	25 year cumulative risk	
	of death from liver disease	
Severe haemophilia, HIV negative	underlying cause	contributory cause
all ages	1.4	3.4
<25	0.1	0.3
25-44	2.2	5.5
>44	14.3	28
Moderate haemoph., HIV negative	underlying cause	contributory cause
all ages	1.2	2.1
<25	0.1	0.1
25-44	1.9	3.8
>44	4.1	6.6
Mod/severe haemoph., HIV positive	underlying cause	contributory cause
all ages	6.5	10.9
<25	3.8	7.2
25-44	17.1	24.2
>44	18.7	28.9

Risk of death from liver disease



from Darby et al, Lancet, 1997

HIV/Hepatitis C co-infection

- HIV infection modifies the natural history of hepatitis C with unusual rapid progression to cirrhosis
- HIV related immuno-deficiency may determine higher viremia levels and more severe liver damage

Hepatitis C: prognostic factors

- Consumption of alcohol
- Age, Duration of infection?
- Sex
- HCV genotype/serotype (worse for 1 and 4)?
- Co-infection with other hepatitis viruses?
- Route of infection (worse for blood product recipients than for drug-abusers)?
- Ethnic origin?
- Dialysis?

Hepatitis C: immune response

IL2 production by T cells in response to 15-mer synthetic E1 (1a) peptides from HCV

controls	IFN clear HCV	no resp. IFN	unttt pat.
0%	88%	22%	55%

Sarobe et al., 1996

Hepatitis C: immune response

- In 50% of patients with CAH there is a deficiency of the antibody response to the E2/NS1 HVR
- In these patients the variation of is E2/NS1 lower than in patients with frequent or persistent antibody response
- This defect may be the cause of persistent HCV infection

Yoshioka et al, 1996

Hepatitis C: immunogenetic factors

- HLA-B14 was more frequent in patients with chronic HCV infection in Italy
- HLA-DR5 seems to be a protective factor in Italy
- Immunogenetic factors may have a role in determining susceptibility to HCV

Zavaglia et al, 1996

- DR antigens are not associated with disease severity

Czaja et al, 1996

Hepatitis C: immune-escape

- accumulation of mutations
- extra-hepatic replication sites provide reservoir for re-infection
- in situ suppression of CD8+ mediated cytotoxicity?
- impaired presentation of antigen via MHC class 1?

Hepatitis C: outcome and treatment

Patient Selection Guidelines

Two approaches have been proposed:

- *1) The virological approach*

  seeks to identify (viral load and genotype) patients with a high probability of response without concern for severity of liver disease

  this approach is expensive and requires specialised virological expertise, and is therefore not favoured

Hepatitis C: outcome and treatment

Patient Selection Guidelines

Two approaches have been proposed:

- *2) The disease approach*

  involves focussing treatment on acute disease or on moderate to severe chronic hepatitis with a higher risk of progressing to cirrhosis over a relatively short time-frame

  This is the currently preferred approach. In general, early treatment produces better results, and patients should be treated before their disease reaches an irreversible stage, e.g. cirrhosis, especially if resources are limited

Hepatitis C: outcome and treatment

Patient Selection Guidelines

- Patients with acute hepatitis and those with recent infections have the highest success rates with current antivirals and should be treated
- Minimal requirements are anti-HCV or HCV RNA positivity or the detection of abnormal ALTs over at least 6 months, and histological finding of moderate or severe hepatitis with fibrosis
- biopsy is desirable unless clinically contraindicated

Hepatitis C: outcome and treatment

Patient Selection Guidelines

- Patients with *minimal hepatitis* often are not treated, depending upon age and available resources. This approach will be modified, as more effective and cost-effective antiviral agents become available
- Patients with *compensated cirrhosis* exhibit reduced responsiveness and significant side effects. Depending of age and available resources, these patients should receive the lowest priority for treatment

Hepatitis C: outcome and treatment

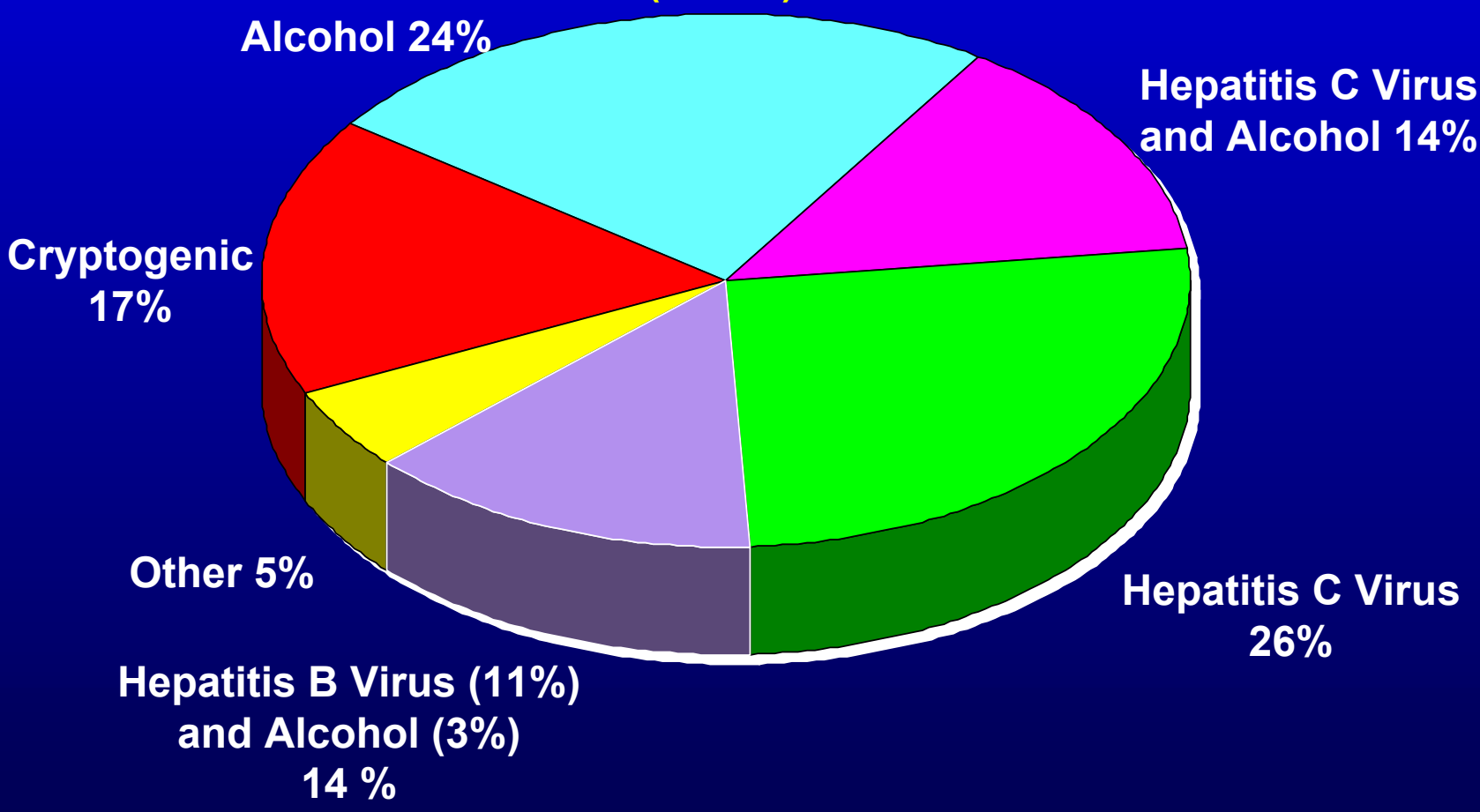
Patient Selection Guidelines

- Patients *excluded* include those with decompensated cirrhosis and carriers with persistently normal ALTs

Primary Etiology of Chronic Liver Disease
Mutually Exclusive Groups

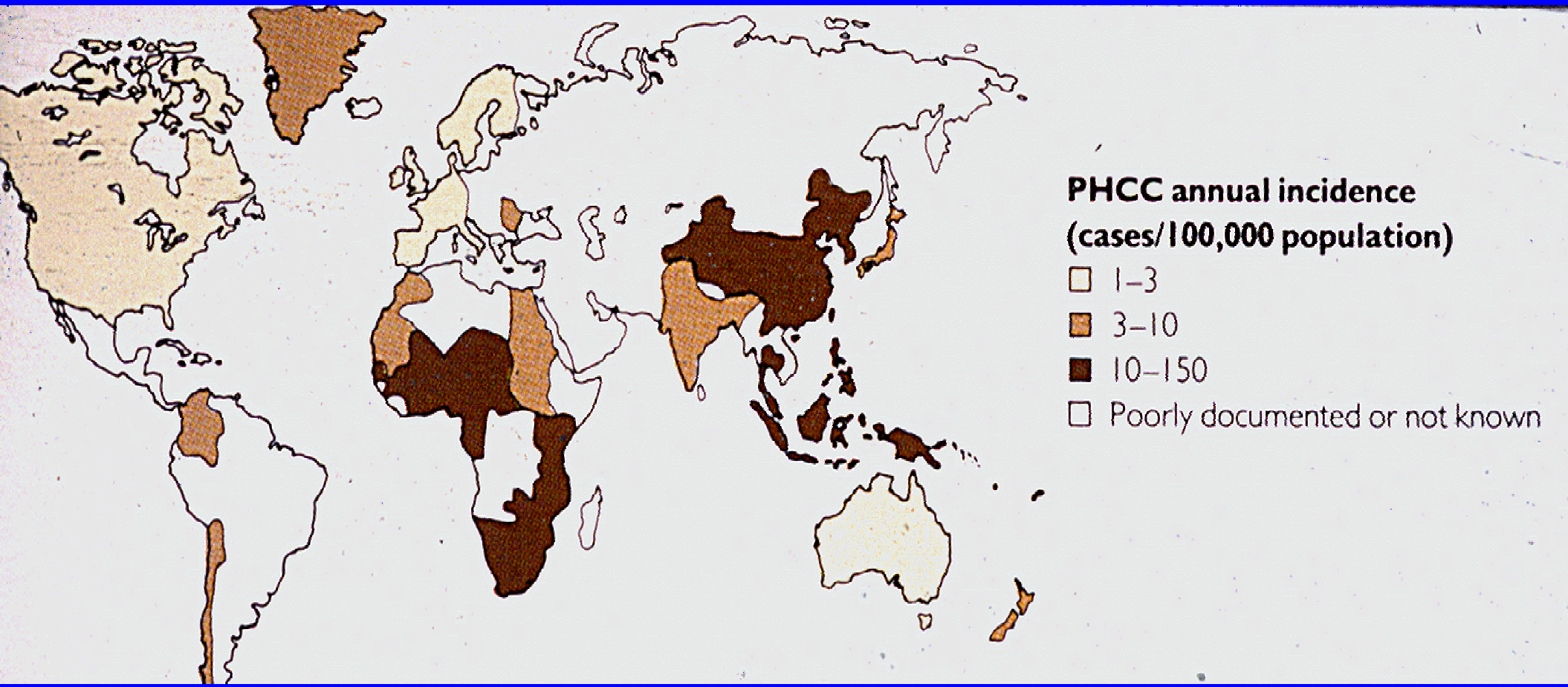
Jefferson County, Alabama, 1989

(n=140)

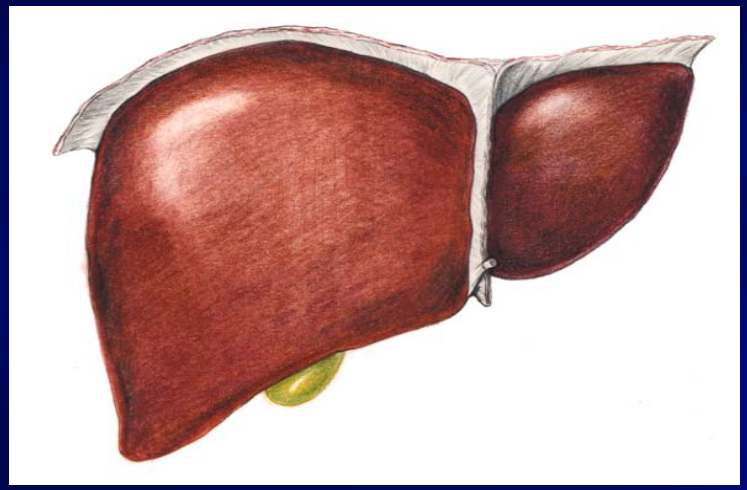


Source: CDC unpublished data

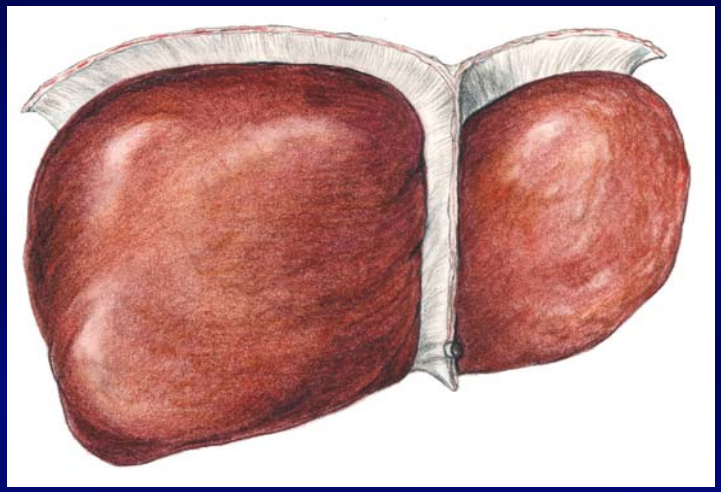
Geographic distribution of liver cancer



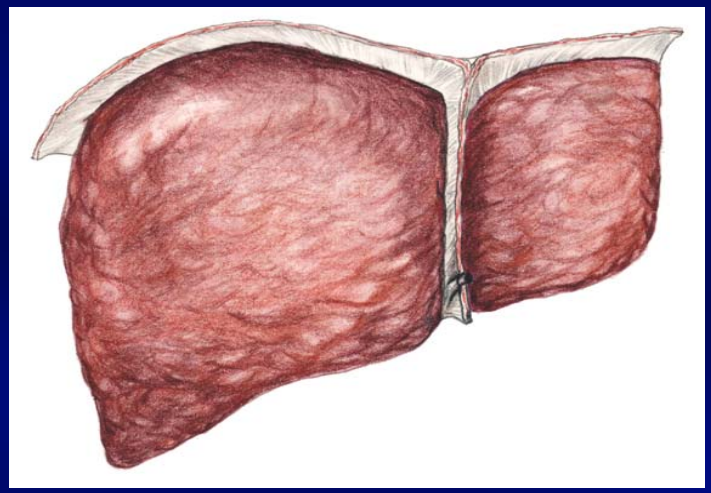
Healthy Liver



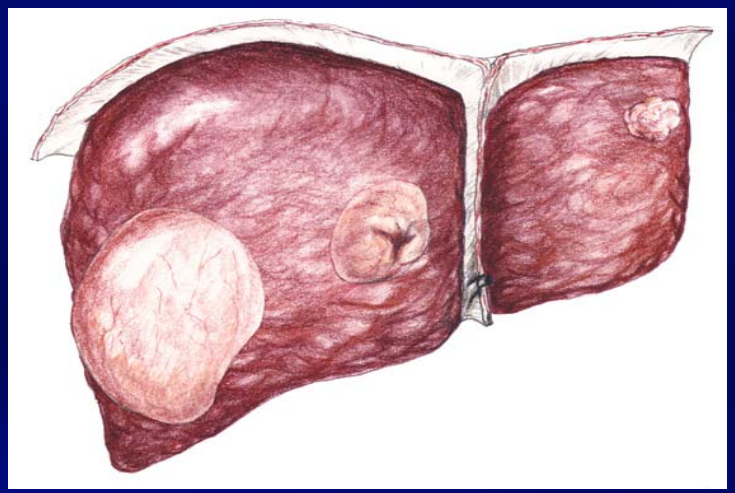
Hepatic Fibrosis



Cirrhosis



Liver Cancer



Hepatitis C: treatment goals

to reduce morbidity and mortality through

- cure - complete elimination of HCV and normalization of ALTs
- stop disease progression
- better quality of life
- reduce the pool of chronic carrier and diminish thereby transmission

Hepatitis C outcome: conclusions

- short term complications are rare
- after 10-30 years wide spectrum of symptoms
  - > none - fatal end sage liver disease (ESLD)
- viral load correlates with outcome but not with occurrence of disease
- little consensus on disease co-factors
  - heavy alcohol, ?moderate?, older age
- little consensus on laboratory markers of ESLD

outcome and natural history poorly understood

WHO's mission

- Norms and standards
- Technical support
- Transfer of knowledge
- Advocacy tools to assist countries to access bilateral support
- Coordinate intercountry activities
- Assistance with development of operational research
- (direct support) e.g. vaccines