

14th Australia and New Zealand Haemophilia Conference
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Hepatitis C treatment and care

Relevance to haemophilia

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Risk factors for HCV infection

- **Blood contamination**
 - Transfusion of blood products before 1990 [~70% haemophilia]
 - Injection drug use (now >90% of new infections)
 - Nosocomial spread (universal precautions)
 - Body piercing, tattooing
 - Medical spread (vaccinations, shistosomiasis eradication etc)
- Sexual spread
- Birth in hyper-endemic country
 - Egypt (genotype 4)
 - Vietnam/south China (genotype 6)
 - Italy –genotypes 1B and 2

HCV testing in people with haemophilia

- **Meaning of positive anti-HCV test (with risk factor)**
- **PCR for HCV RNA to determine continuing infection:**
 - 73% positive [Zhang M et al. Blood 2006;107:892-7]
 - Lower – age <2 yrs, infected after 1983, +HBV
- **Genotype (1,2,3,4), viral load: relevance to therapy**
- **Exclude co-infections (HBV, HIV) and co-morbidity (FBG, lipids)**
- **Assess likely severity of liver disease**

Outcomes of acute hepatitis C

- Most infections asymptomatic
- Outcome: 45-85% chronicity (15-55% resolution)
- Better: younger age, women, genotype 3 (vs 1), HBV co-infection, jaundice
- Resolution most likely in first 3 mo
- Altered by antiviral treatment

Antiviral therapy for acute hepatitis C

- Reduces chronicity [to 5-20%]
- Safe to wait 12 weeks
- Daily IFN (5 mU) has produced best results
- PEG-IFN seems equivalent [*not on Section 100*]
- 16 wk treatment for genotypes 2 and 3
- 24 wk treatment for genotype 1
- Ribavirin not needed

Co-morbidity in hepatitis C

relevance to natural history and patient care

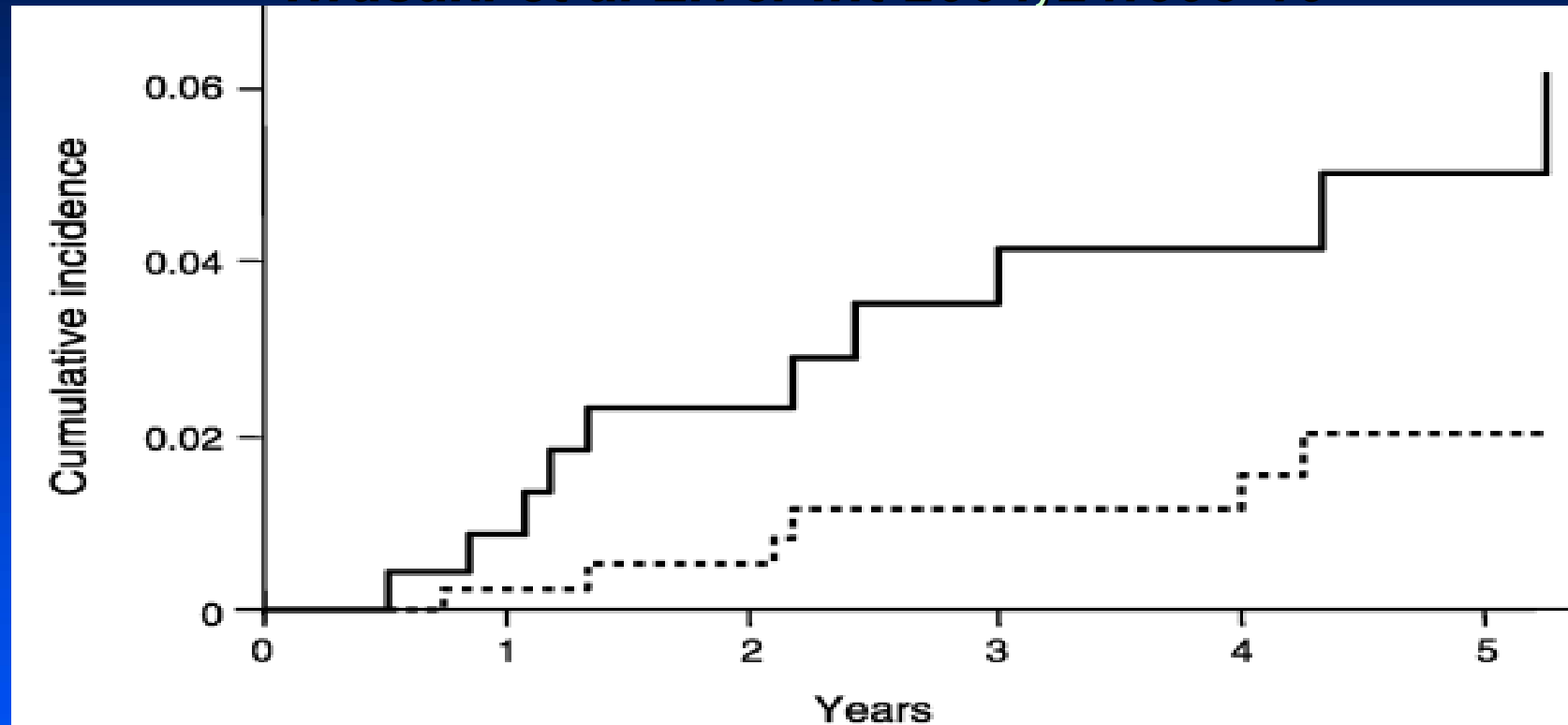
- **Alcohol**
- **Other toxins; iron**
- **Metabolic – central obesity, insulin resistance, obesity, diabetes, steatosis (fatty liver disease)**
- **Immune deficiency – HIV; transplantation**
- **Co-infections - other hepatitis viruses (HBV, HDV)**

Alcohol worsens severity of chronic hepatitis C

- **Threshold for fibrotic progression unclear**
 - >80 g/day, at least 5 yr *Khan M et al J G H 1998;13:419-26*
 - >50 g/d *Monto A et al Hepatology 2004;39:826-34*
 - >20 g/d *Colletta C et al Hepatology 2005;42:759-61*
 - Not “light” or “moderate”; not “binge”
 - **Lifetime alcohol** increases rate of cirrhosis [*Meta-analysis 20 studies. Hutchinson Clin Gastroenterol Hepatol 2005;3:1150-9*]

Alcohol increases risk of HCC in hepatitis C (even after SVR)

Iwasaki et al Liver Int 2004;24:603-10



Alcohol abuser with HCC	2	5	7	8	9
Patients at risk	228	193	161	133	101
Non-alcohol abuser with HCC	1	2	4	4	6
Patients at risk	409	360	305	258	210

Effects of alcohol on treatment outcome

- Management guidelines: *curb alcohol dependence before antiviral therapy, support during therapy*
- Exclusion of those with alcohol history recently challenged [*Anand B et al Gastroenterol 2006;130:1606*]
- Threshold unclear; compliance is the issue

Effects of other toxins on hepatitis C

- **Iron – debated (*in vitro*, Fe suppresses HCV replication)**
 - 2 studies favour associations between HFE, increased hepatic Fe and worse fibrosis
 - 2 studies find no such effect
 - 1 study found phlebotomy beneficial; several others did not
- **Cigarette smoking – worsens fibrosis**
- **Opiates –?suboptimal treatment response**

Drug deaths are more frequent than liver deaths in young people with HCV

Amin J et al. Lancet 2006;368:938-45.

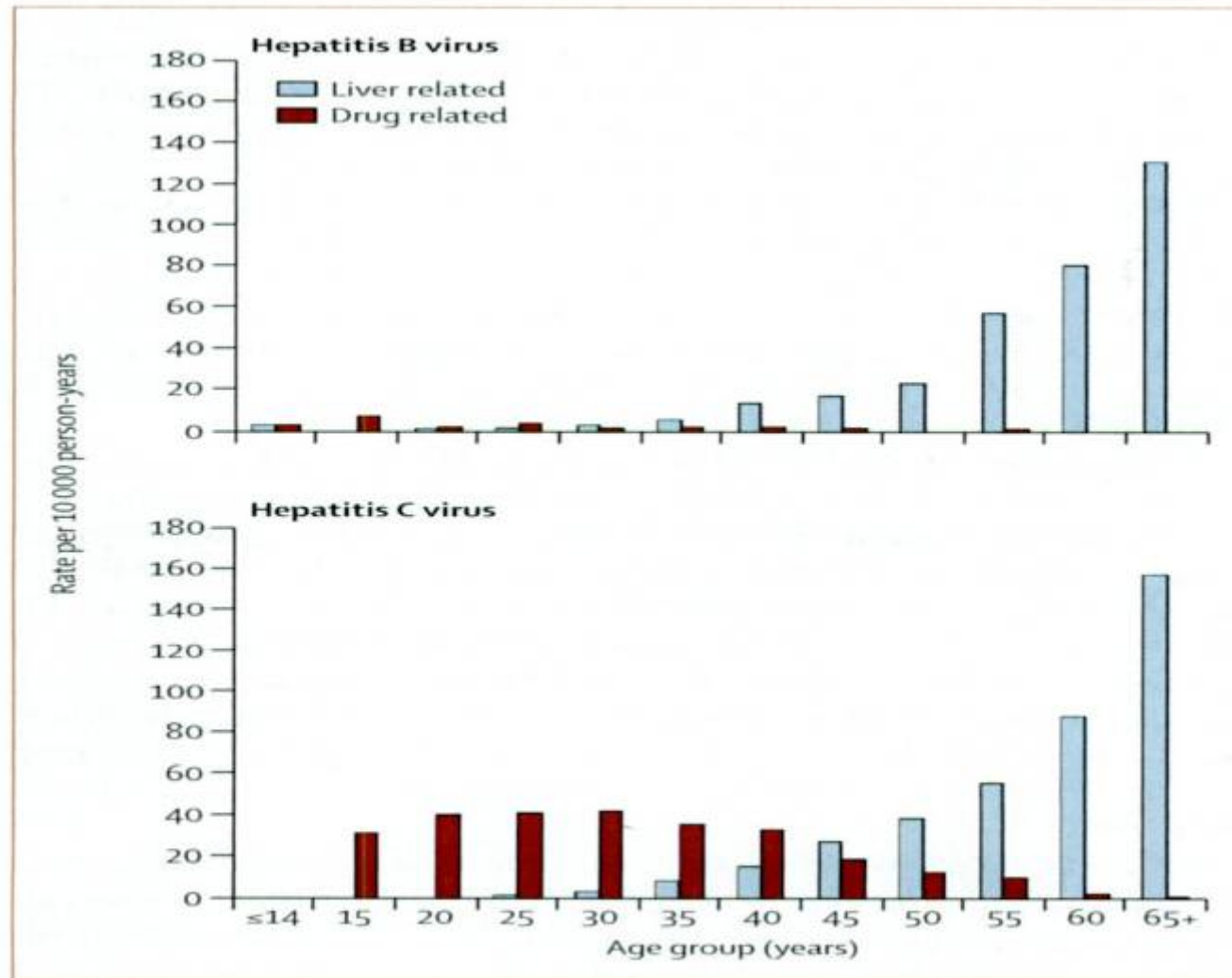


Figure 1: Incidence of liver related and drug related deaths by age group and type of viral hepatitis

Metabolic factors and hepatitis C

- **Obesity**
- **Central obesity**
- **Insulin resistance**
- **Type 2 diabetes**
- **Steatosis** [*E Powell, A Clouston Hepatology 2005;42:5-13*]

What's fat got to do with it?



Steatosis in hepatitis C

- **Common**
- **Genotype-specific mechanisms**
 - **Genotype 2,3: direct viral effect**
 - **Genotype 1,4: principally host determinants (insulin resistance)**
- **Alcohol, central obesity, raised BMI**
- **Associated with more activity, more severe fibrosis**
- **Obesity reduces response to IFN-based treatment**

Insulin resistance and hepatitis C

- Higher prevalence type 2 diabetes
- “Adjusted” incidence increased 11-fold
- Associated with portal activity
- *More severe fibrosis*
- **Reduced response to IFN-based antivirals**

Management of hepatitis C and metabolic syndrome

- Correct central obesity; monitor waist
- *Gradual* [0.5 - 1.0 kg/wk], *sustained* wt reduction
- Correct IR (exercise, low fat, low GI/high fibre diet)
- Treat obesity (appetite suppression, bariatric surgery)
- Control hyperglycaemia (anti-diabetics)
- Correct lipids (diet, statins, gemfibrozil)

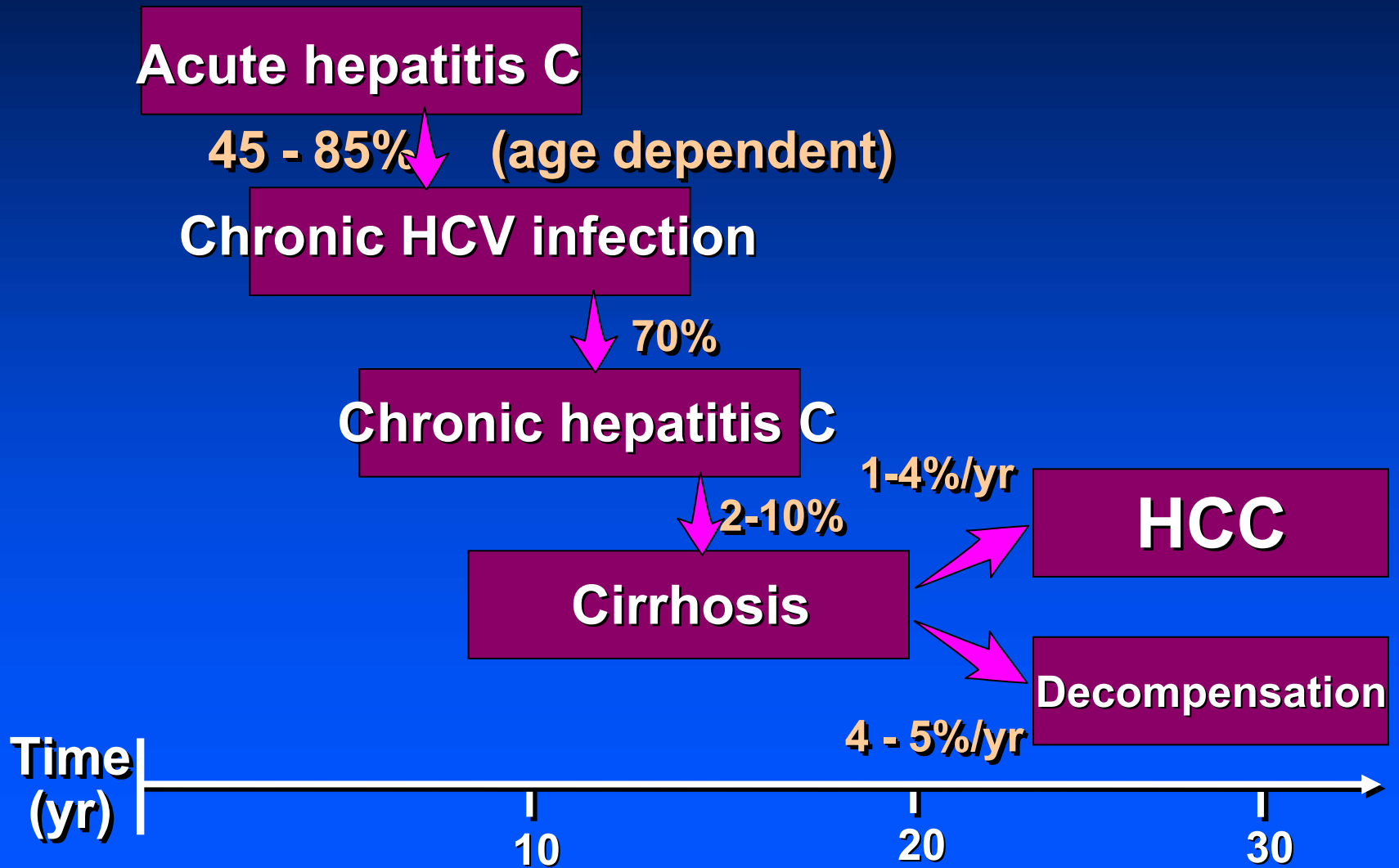
Does this increase chance of SVR to antiviral therapy?

HBV co-infection and chronic hepatitis C

Gaeta GB et al J Hepatol 2006;44:S1-8-S13

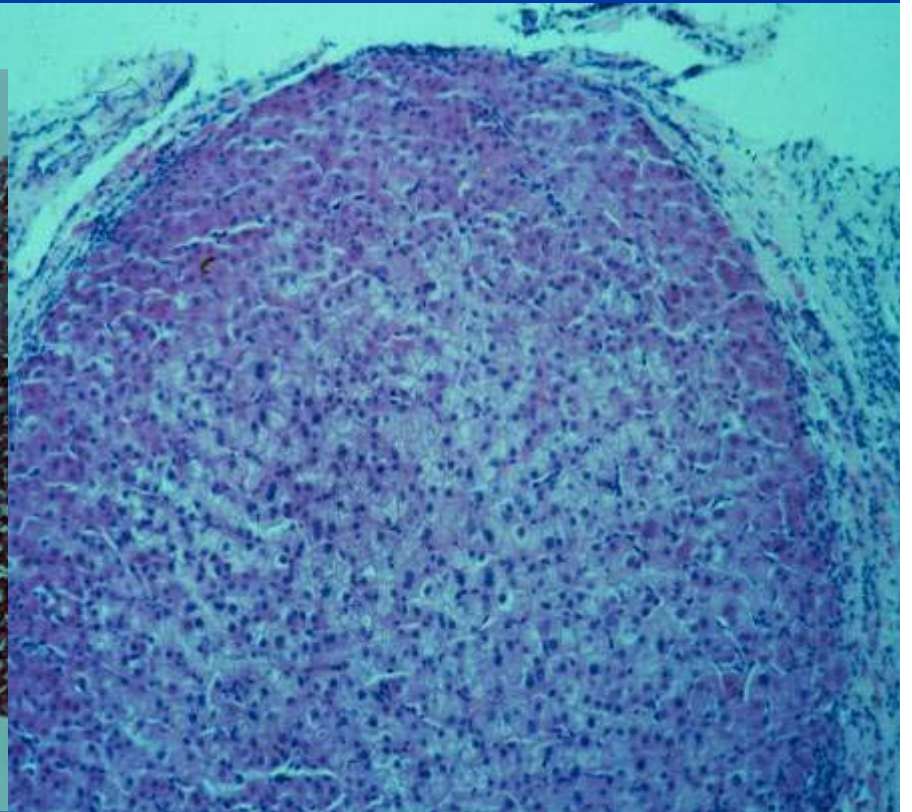
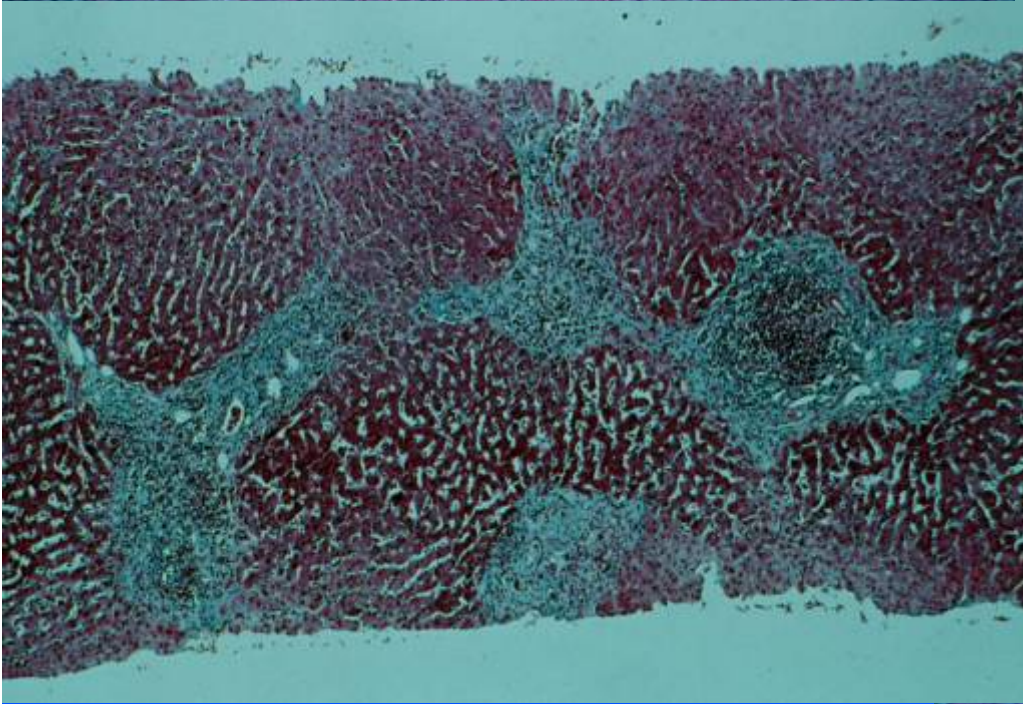
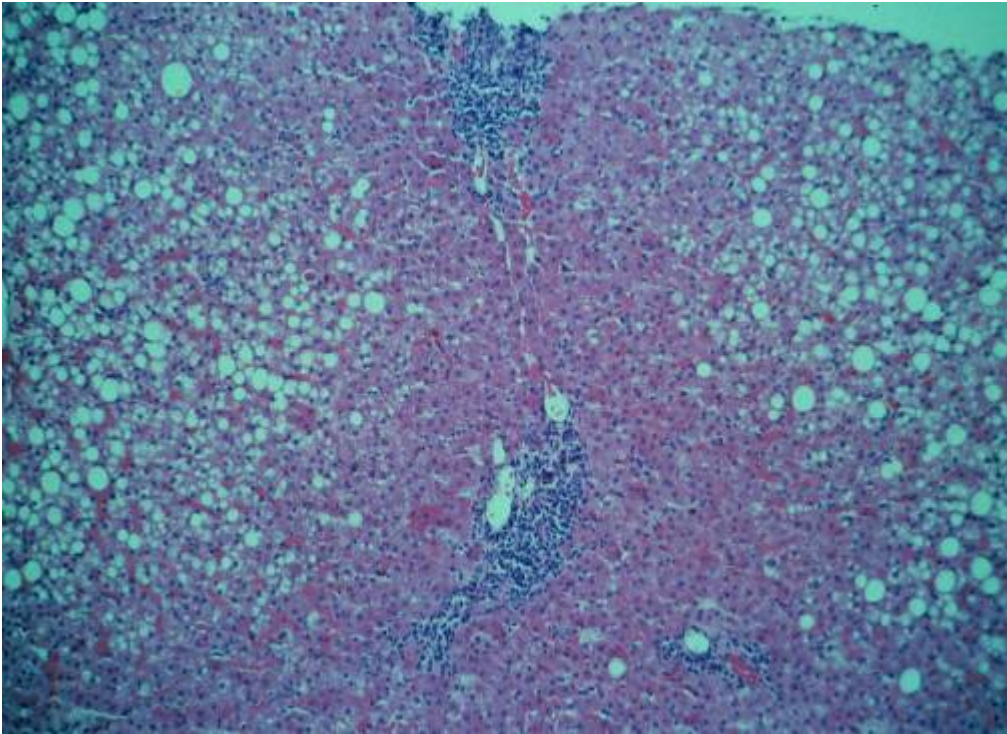
- 5-10% HCV+ also HBsAg positive (higher with HIV)
- Usually HBeAg negative, HBV DNA $<10^4$ IU/mL
- Mechanisms of “viral interference” unclear
- Much higher rate of cirrhosis and HCC
- Treat “dominant” infection
 - Promising results with pegylated-interferon/
ribavirin for HCV RNA positive cases

Outcomes of HCV infection



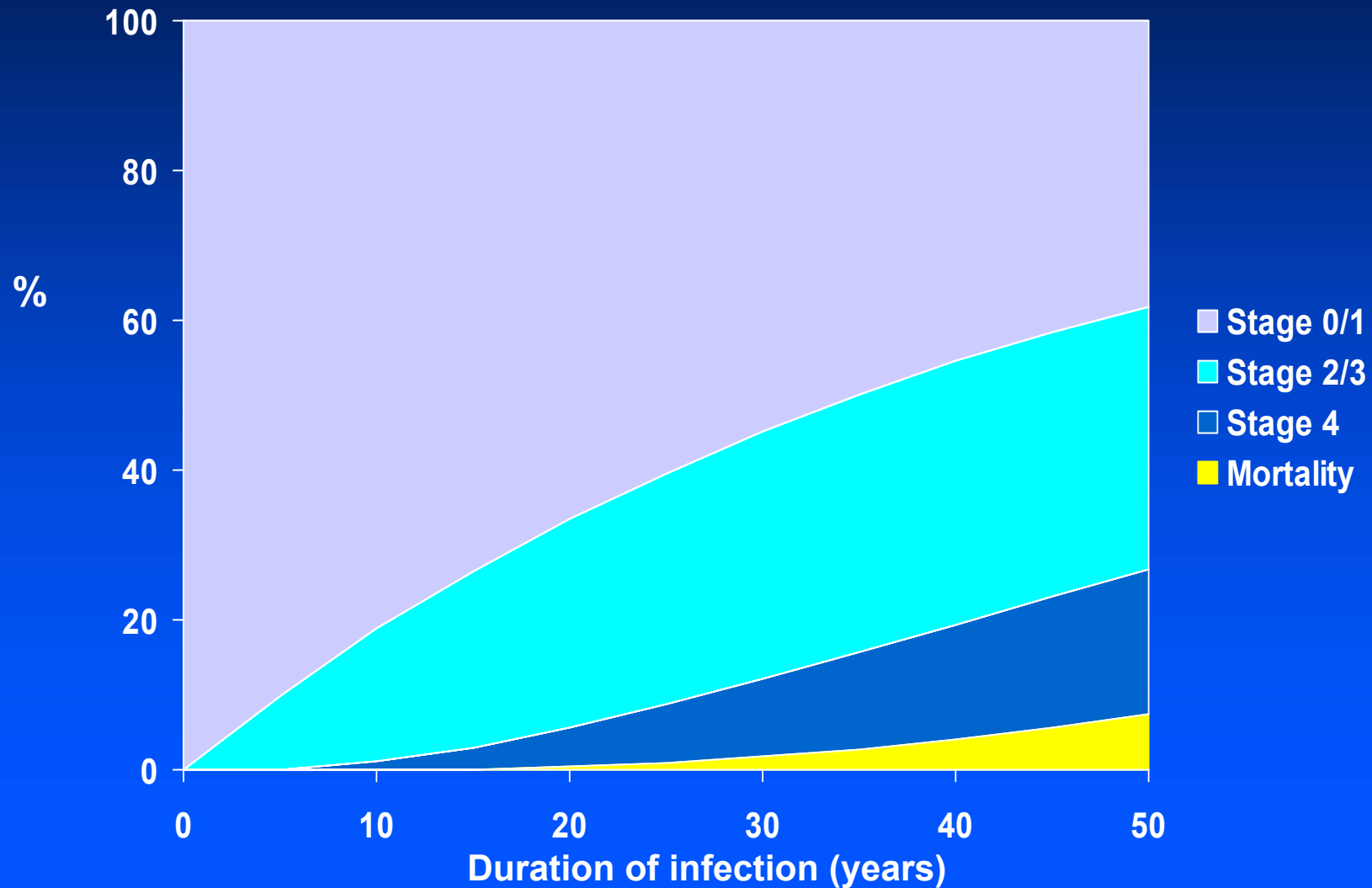
Staging chronic hepatitis C

Fibrosis stages 1, 3, 4



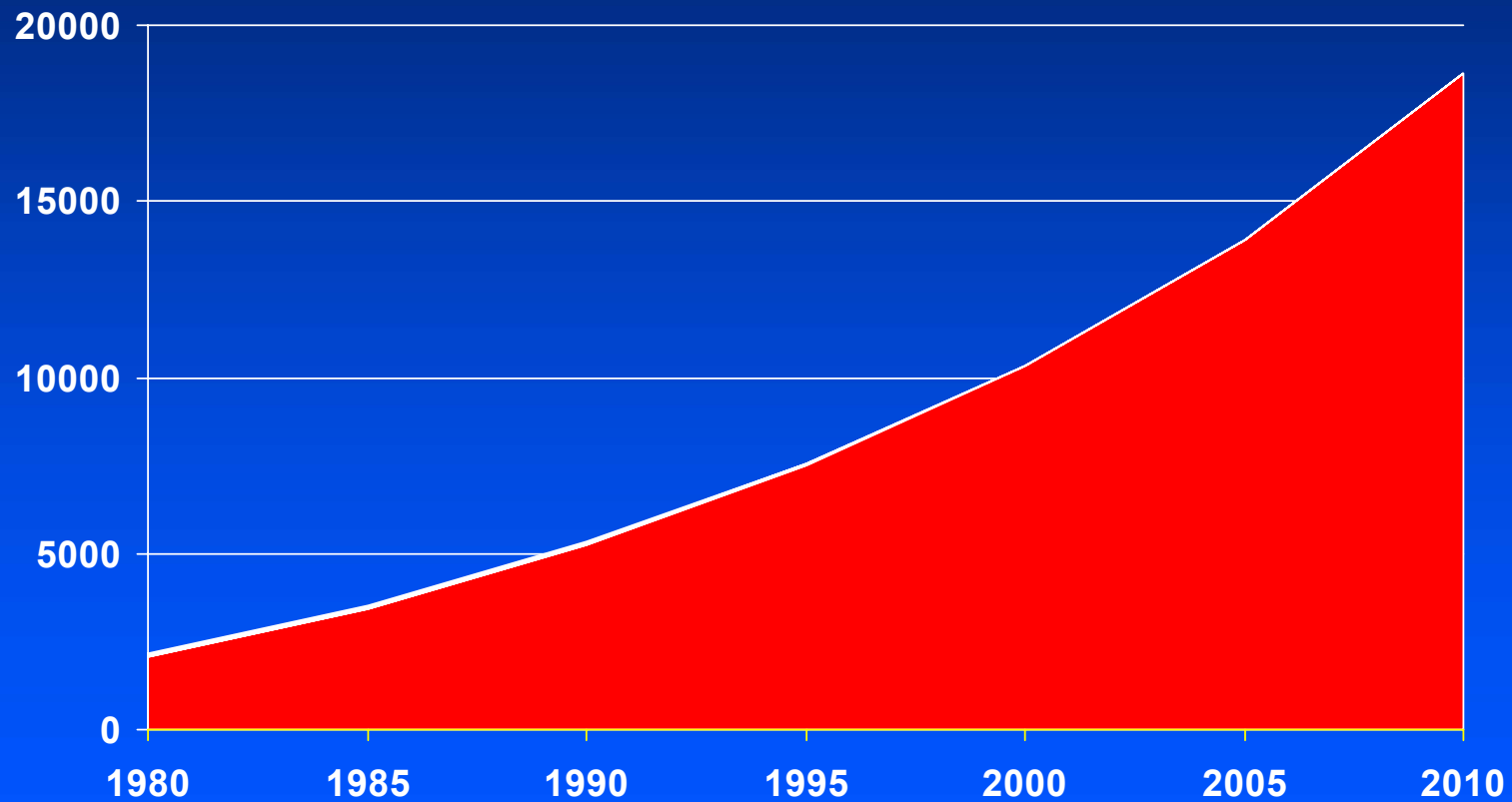
Progression of liver disease in chronic hepatitis C

(Markov Modelling - *Dore et al 2004*)

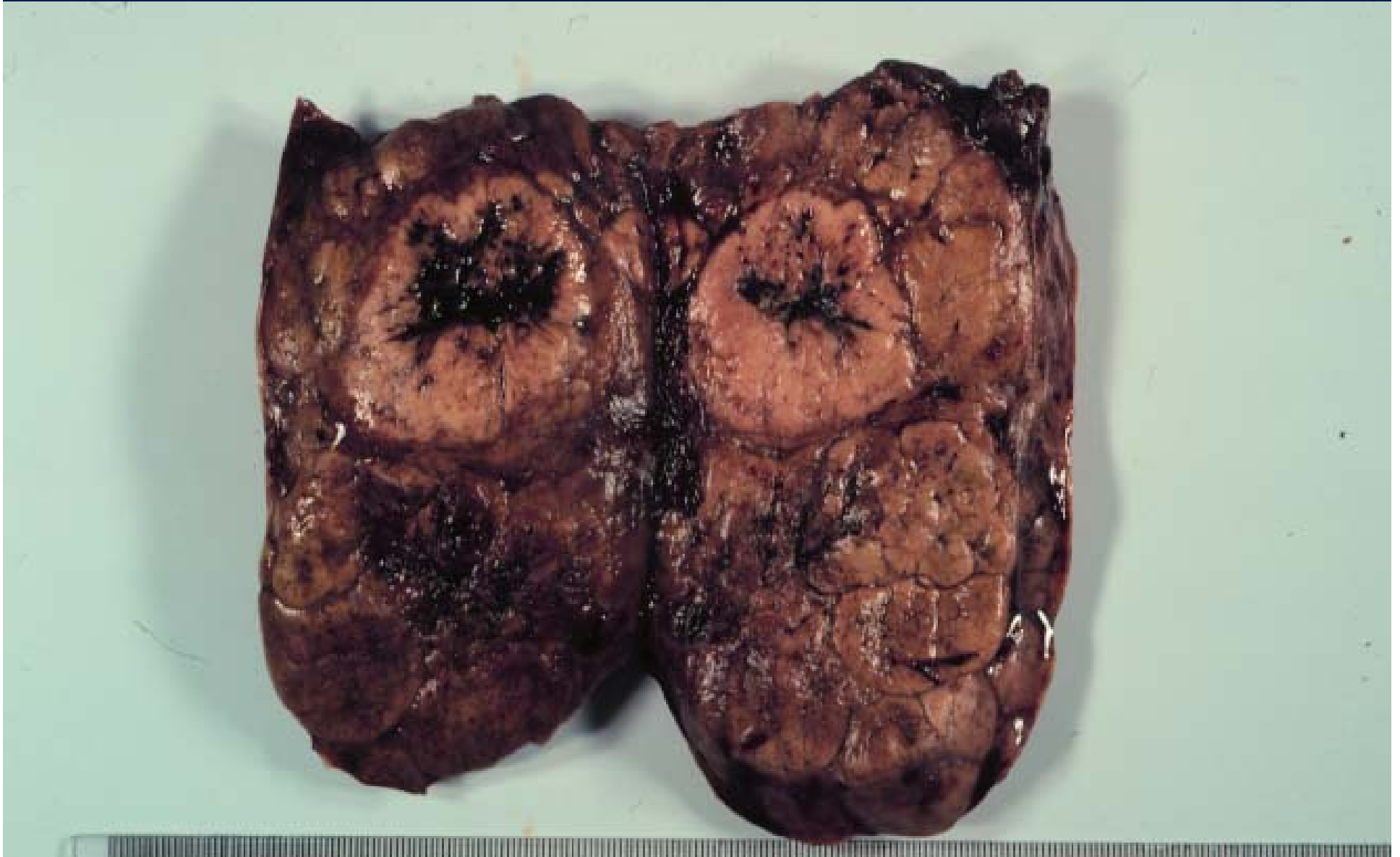


Estimates and projections of Australians with HCV-related cirrhosis

(Law et al 2004)



Hepatocellular carcinoma complicates cirrhosis



Fibrotic progression rates for chronic hepatitis C

Overall: 0.12 fibrotic grades/yr

- *one stage worse every 8-10 yr*

Age >50 yrs: 0.33 /yr

- *one stage worse every 3-4 yr*

Normal ALT: 0.08 /yr

- *one stage worse every 12-15 yr*

Factors that influence fibrotic progression rate

- Age at infection
- ALT
- Lifetime alcohol history
- Central obesity/ insulin resistance
- Immunodeficiency
- Co-infections

Can we avoid liver biopsy?

Fibrotic predictive indices (at least 8 published;
**Maor Y et al. Haemophilia 2007;13:1-8*)

- **Age, AST, platelet count, alcohol history, total cholesterol, insulin resistance**, alpha-2 macroglobulin, apolipoprotein A1 and hyaluronan most useful variables
- **FPI of above 5 variables:** area under ROCs 0.84, 0.77 for test and validation cohorts (*Sud and Hui et al. Hepatol 2004;39:1239*)
- **At score of ≥ 0.2 , sensitivity 96% and NPV 93%**
 - **avoid liver biopsy 48% of cohort** [67% **Maor et al 2007*]
- **At ≥ 0.8 , FPI was 94% specific and PPV of 87%**
 - **Identify most patients with severe fibrosis**

Can we avoid liver biopsy?

- Pay attention to age* and duration of infection, hard liver edge/presence of spider naevi (not symptoms)
- Continued activity (ALT and AST)
- Lifetime alcohol history
- Central obesity
- Subtle (serial) changes in serum albumin, platelets
- Hepatic imaging (portal hypertension)
- Fibroscan (promising but not available in Australia)

*** Recommended before children submitted to treatment**

Liver biopsy with haemophilia

- Not contraindicated
- Pre-test, intra-test (6 hr after), post-test clotting factors
- Manage by haemophilia clinic (aim for 1 U/mL - 100% cover)
- Trans-jugular biopsy - experienced centres

Haemophilia 2007;13:164-71; J Gastroenterol Hepatol 2007;22:614-33

Do we still need liver biopsy?

- **Use liver biopsy when patient MAY have severe fibrosis, but not very keen on therapy (all children)**
 - need evidence liver disease severe enough to warrant therapy
 - Or mild enough to allow no therapy (“therapeutic relief”)
- **Do NOT use liver biopsy if informed patient keen to have therapy, irrespective of result! (PBS Section 100)**
- **...or clinical, imaging and/or laboratory evidence suggests cirrhosis, and patient prepared to be treated**

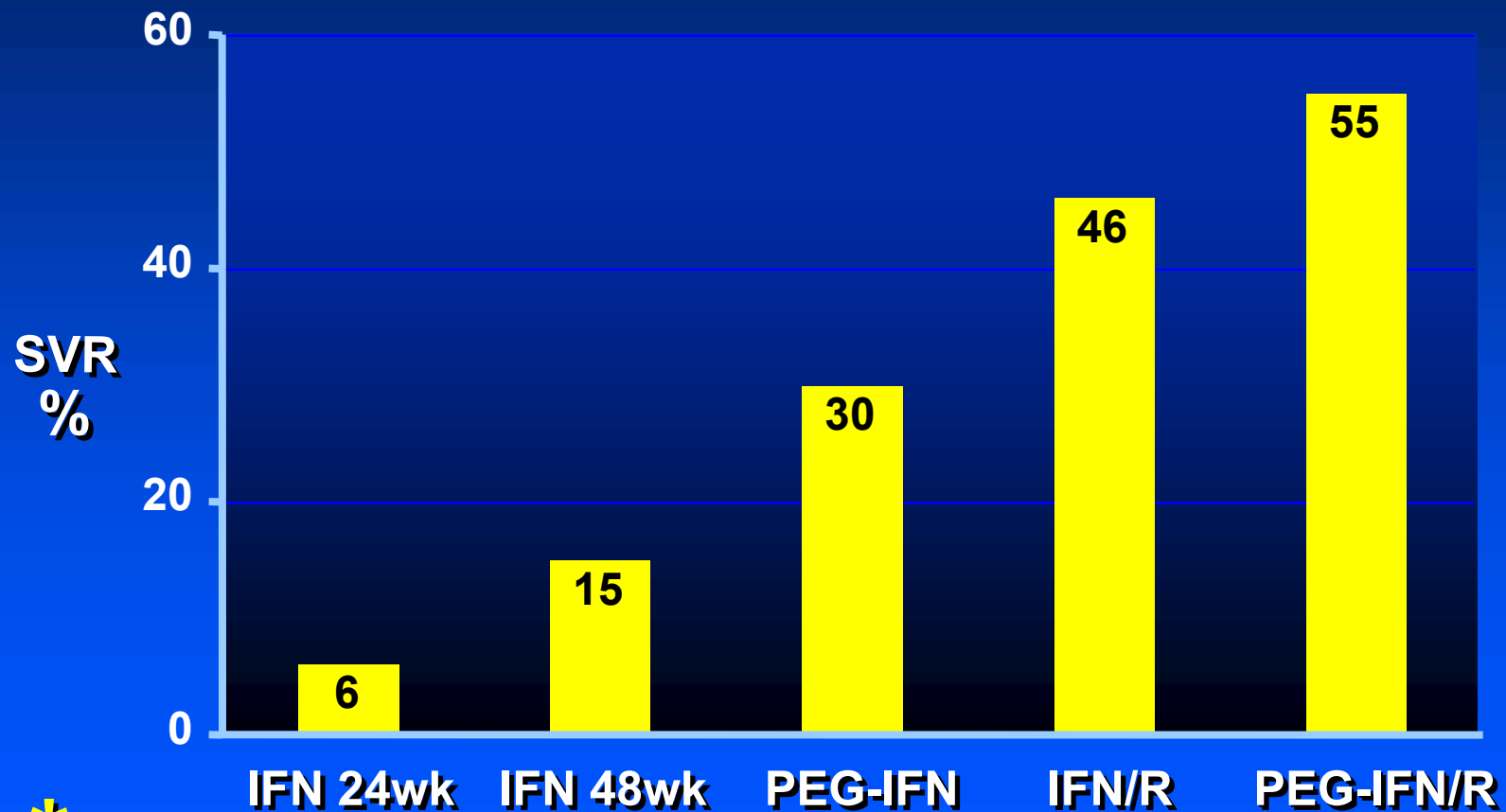
Treatment outcomes

- Sustained viral response (SVR) [PCR negative 6 mo post-treatment]
- End of treatment viral response with relapse
- Nonresponse
- Intra-treatment responses
 - 4 wk PCR negative = rapid virus response (RVR)
 - 12 wk viral response = >2 log reduction viral titre (“12 wk stopping rule”)

Benefits of SVR

- **Fibrotic regression**
- **Reduces HCC by 90%**
- **Decreases liver-related complications, need for liver transplantation, death**
- **Improves quality of life**

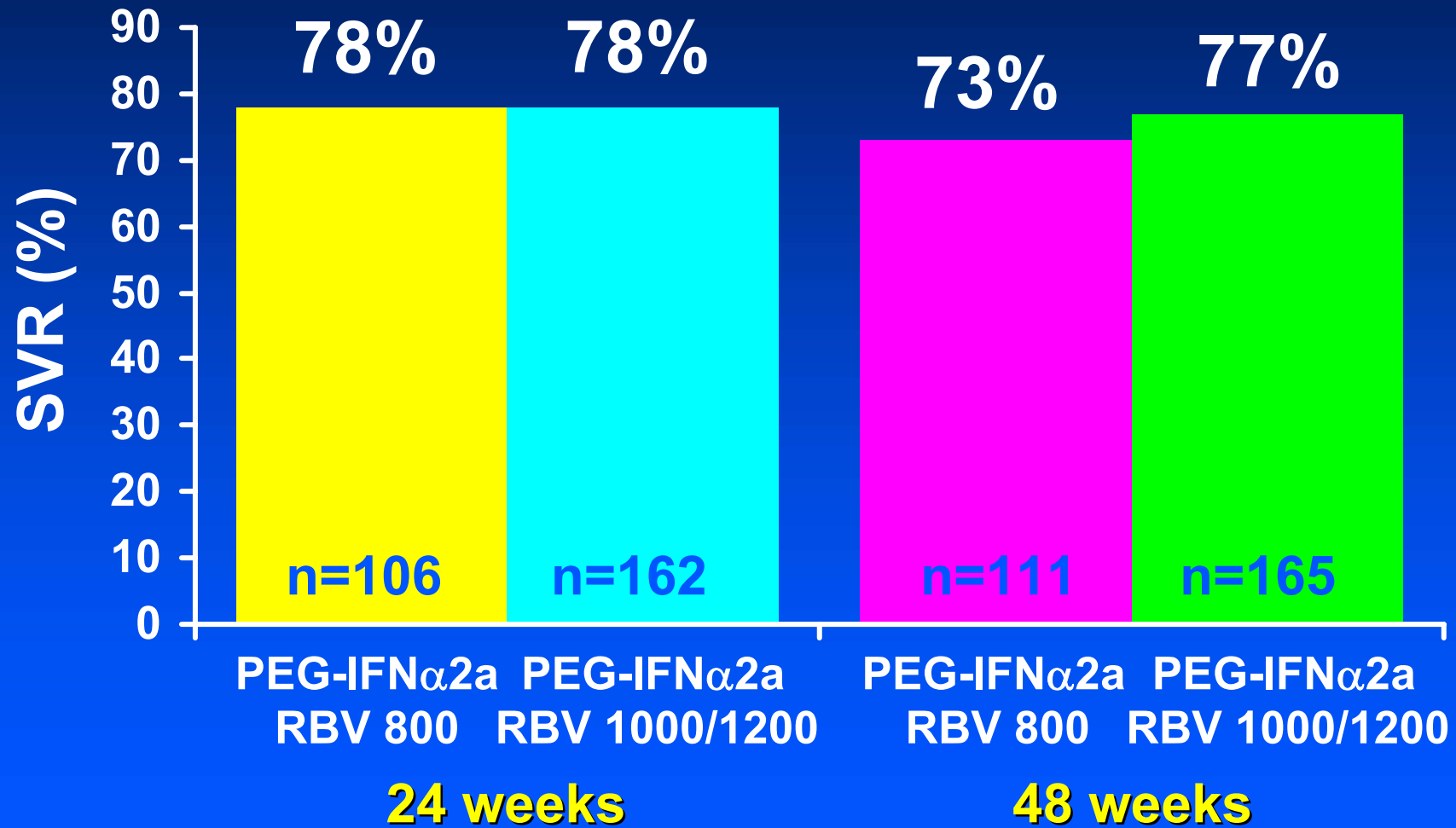
Evolution of treatment for chronic hepatitis C*



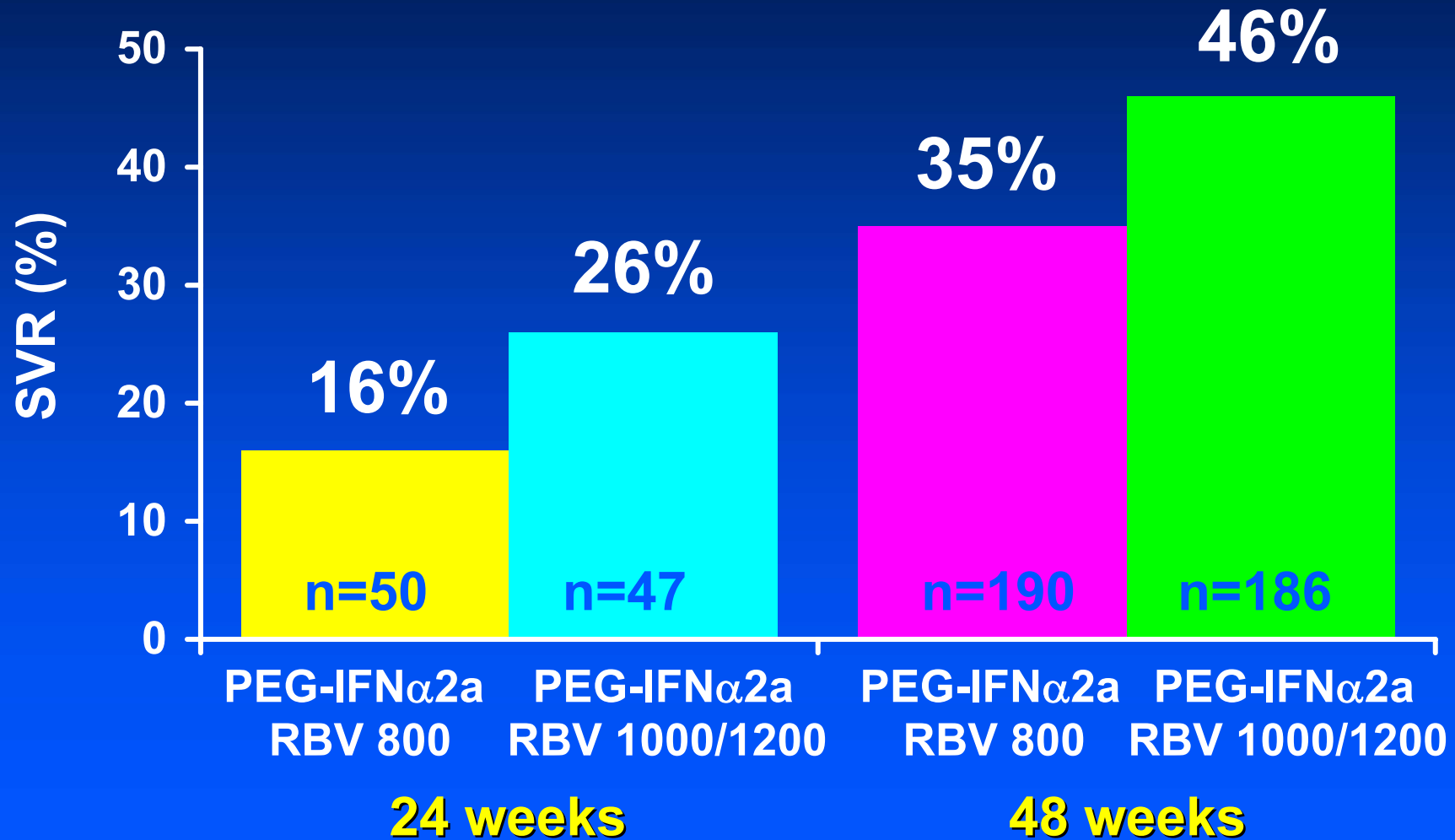
*Similar results reported for haemophilia
Posthouwer D et al Haemophilia 2006;12:473-8*

SVR genotypes 2,3

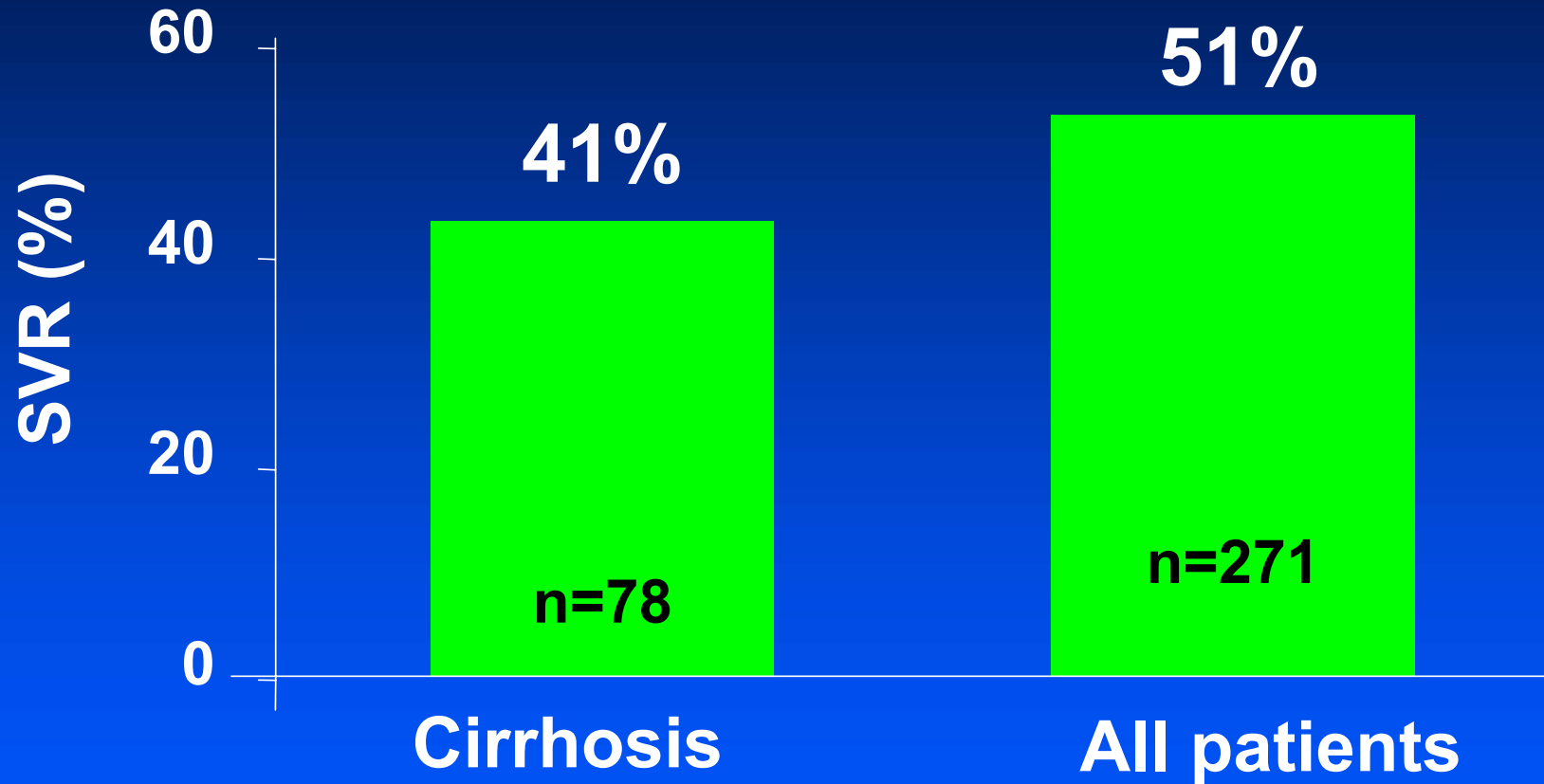
[Hadziyannis et al Ann Intern Med 2004]



SVR genotype 1 *high viral titre*



SVR genotype 1 *cirrhosis*



Treatment: PEG-IFN α 2A + RBV 1000-1200 mg for 48 weeks

Treatment course for chronic hepatitis C

- GENOTYPES 1 and 4: 48 wk full dose Peg-IFN and ribavirin (1000-1200 mg/day)
 - 12 wk “stopping rule”
 - Rapid viral response (RVR) – PCR neg at 4 wk, 24 wk treat
- GENOTYPES 2 and 3: RVR at 4 wk –consider 16 wk Peg-IFN/ R (1000 mg/day) [but relapse may be higher]
- If no RVR, continue for 24 weeks (at least) –
individualisation of therapy is now the state of the art!

**Who should be advised
to have treatment?**

Treatment decisions should be informed by

- *Natural history* - fibrotic stage, activity (ALT, biopsy), duration of infection
- Evidence of cirrhosis
- Age – 50 yrs a watershed!
- Chance of SVR (HCV genotype, viral load, obesity)
- Motivation and insights of affected person
- Symptoms vs co-morbidity, risks adverse effects

NOT altered by concomitant haemophilia

Adverse effects of Peg-IFN/ribavirin

- Pregnancy monitoring: double contraception
- Cough pharyngitis, GIT symptoms from ribavirin
- Pruritus, serious rash, worsening psoriasis
- Insomnia, *depression (liberal use of SSRIs)
- Thyroid (relatively common)
- Neuropathy, retinopathy, deafness

**22% one series [Posthouwer Haemophilia 2007;13:98-103]*

Haematologic effects Peg-IFN/ribavirin

- Hb drops ~30 g/L; from wk 1, nadir wk 4-6, then stable
- Concomitant rise in bilirubin, uric acid
- Effects on neutrophils, platelets more than for IFN
- Use of EPO and CSFs fashionable (~30% cases) in USA and Europe – evidence of efficacy equivocal
- Lower doses ribavirin; may lose therapeutic efficacy
- 80:80 dose: duration principle – *some drug for longer is better!*

Monitoring during antiviral treatment

- Before treatment, identify special risk of AE's (depression, cardiac, haematological, autoimmune, thyroid)
- During therapy, monitor to prevent serious AE's (FBC 4 wks, TSH 12 wks)
- Monitor ALT encourages compliance; don't use alone
- *PCR wks 4, 12, 24, 48; discontinue genotype 1, if fail to obtain drop of pretreatment viral titre ≥ 2 logs at 12 wks*

With careful case selection, patient preparation and support/monitoring during treatment, dropout rates should be <10% for 6 mo and <15% for 12 mo treatment

Combination treatment: *issues*

- Case selection, contraindications
- Pre-treatment counselling
- Routine support and monitoring
- Special contexts: methadone, prisons
- Post-treatment monitoring
- **Retreatment**
 - Only when previous treatment suboptimal (IFN monotherapy)
 - Good results, especially genotypes 2/3
- **Other approaches to treatment**
 - No treatment (or herbal medicines)
- **Liver transplantation**

How long will PEG-IFN/ribavirin be standard of care?

- Protease inhibitors [telaprevir {VX-950}; valopicitabine {NM283}] - mutations 156V/T, 36/155 within 4 weeks
- Mutated variants sensitive to interferon *in vitro*
- Peg-interferon in combination therapy likely to remain
- Ribavirin substitutes generally disappointing
- However, combinations of PEG-IFN and protease inhibitors appear very promising

Immunosuppression and chronic HCV + HIV

- **Hi proportion of HIV-infected also anti-HCV+ (29% France; 54% USA)**
- **Liver disease = AIDS as cause of death [HCV + HBV higher]**
- **Importance of CD4+ count [<200 /mL], high viral load**
 - **More rapid fibrotic progression: 25% cirrhosis in 15 yrs**
 - **Lower age of HCC**
 - **Lower SVR with IFN-based therapy (improved with PEG-IFN/ribavirin)**
 - **Increased rate of hepatic ADRs to HAART**

Treatment of HCV co-infection in someone with HIV

- Treat HCV before HAART if CD4+ count >300 (particularly genotype 3)
- Avoid didanosine and AZT
- Apply 2 log stopping rules
- Improved responses with PEG-IFN/ribavirin
- Consider loading dose PEG-IFN and longer therapy

Self-care is best care

- **Avoid excessive alcohol**
- **Avoid central obesity, diabetes – exercise!**
- **Stop smoking**
- **Vaccinate/avoid risk factors for other hepatitis viruses and HIV**
- **Understand course of hepatitis C, and what can be done to improve this if required**
- **Positive approach to health and life-style**