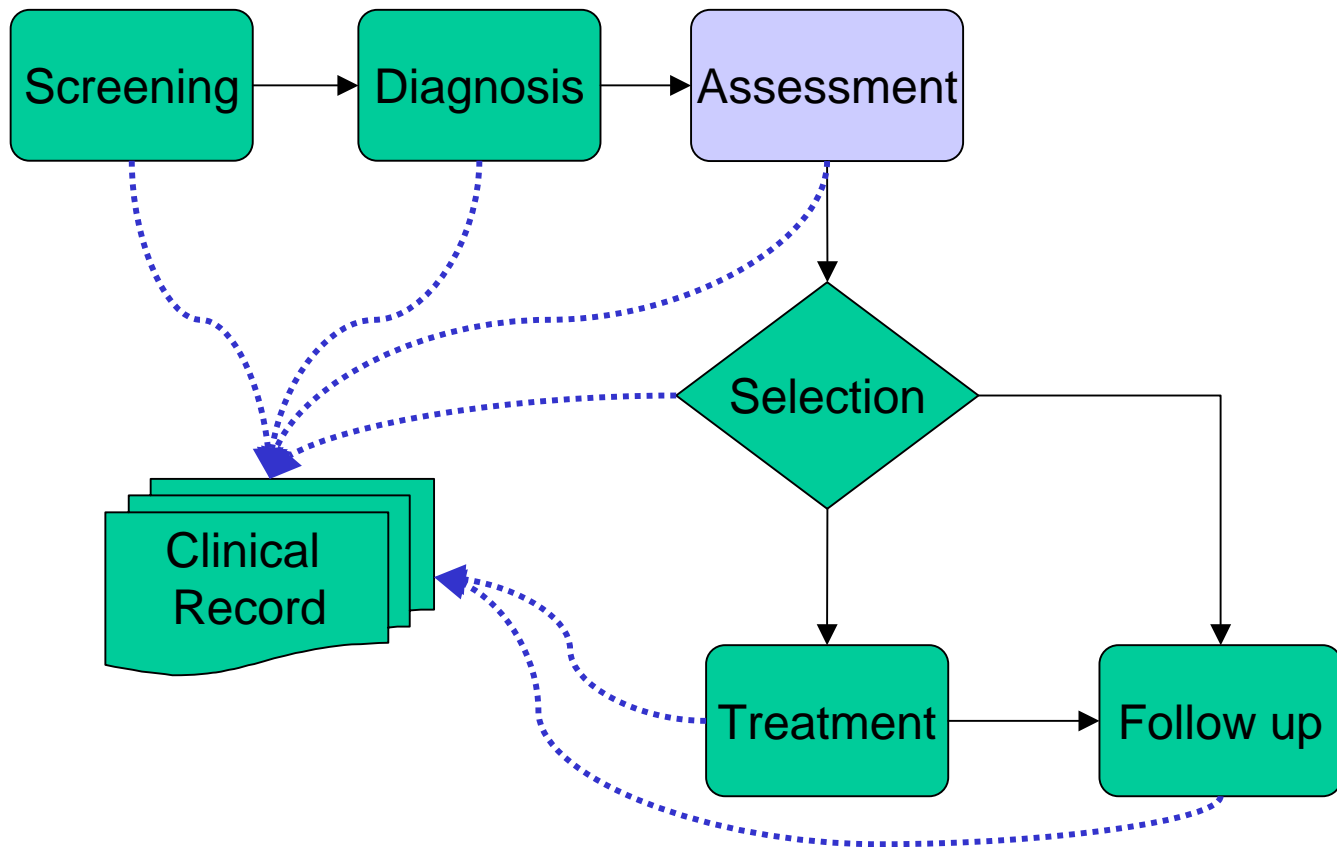


Current Management of diagnosed cases of HCV Infection

Dr Mark Thursz

Imperial College / St Mary's Hospital

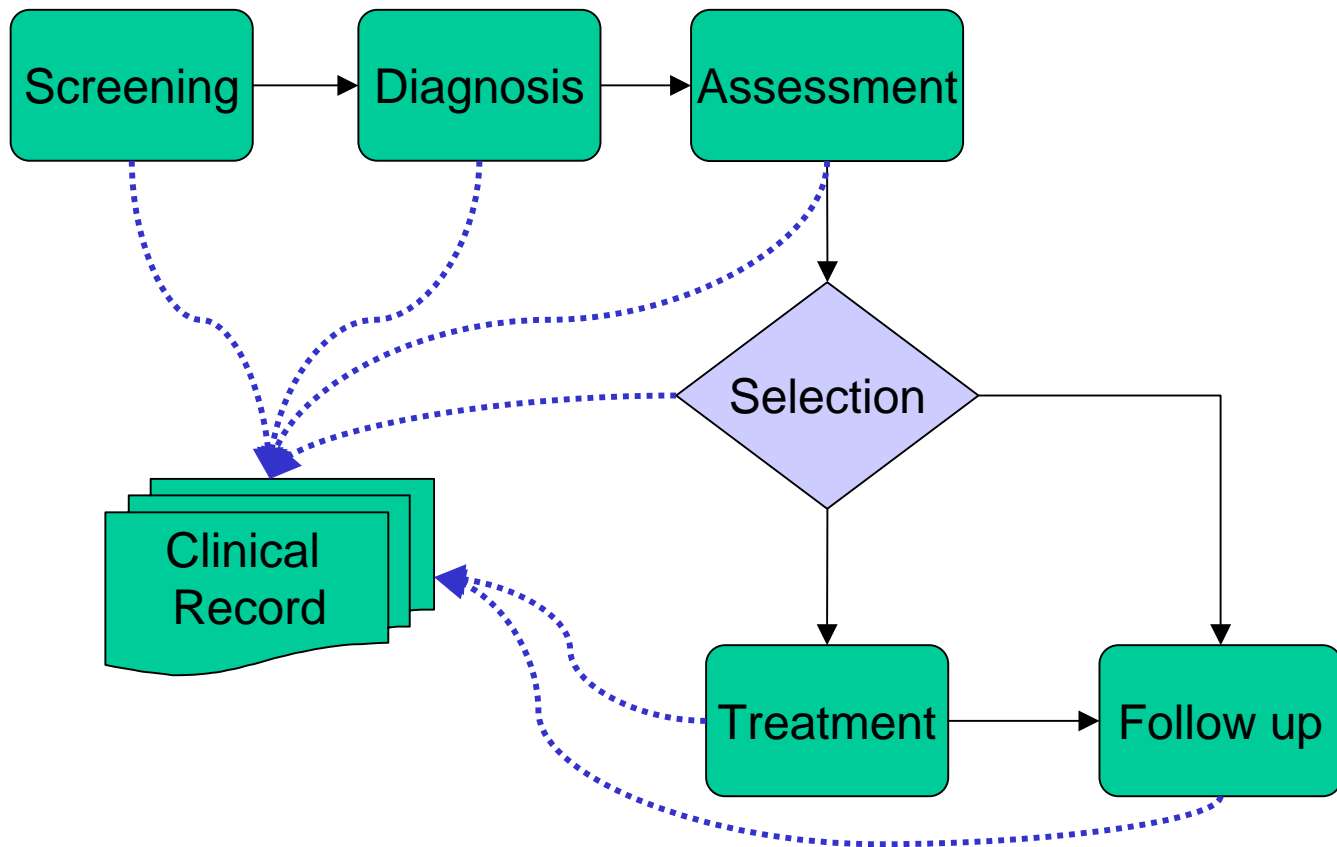
Management of HCV



Assessment

- Viral genotype
- Liver Biopsy
 - Stage
 - Additional diagnosis
- Compliance
- Psychiatric evaluation
- Co-morbid conditions
 - IHD
 - COPD
 - Alcohol
 - BMI

Management of HCV



Selection

- Who makes the decision?
 - Patient
 - Specialist nurse
 - Doctor
 - D&A worker
 - Panel
- Selection criteria
 - Need for treatment
 - Patient views
 - Severity of liver disease
 - Absence of co-morbidity
 - Non-liver symptoms
 - Compliance
 - Likely response rates
 - Ability to tolerate treatment

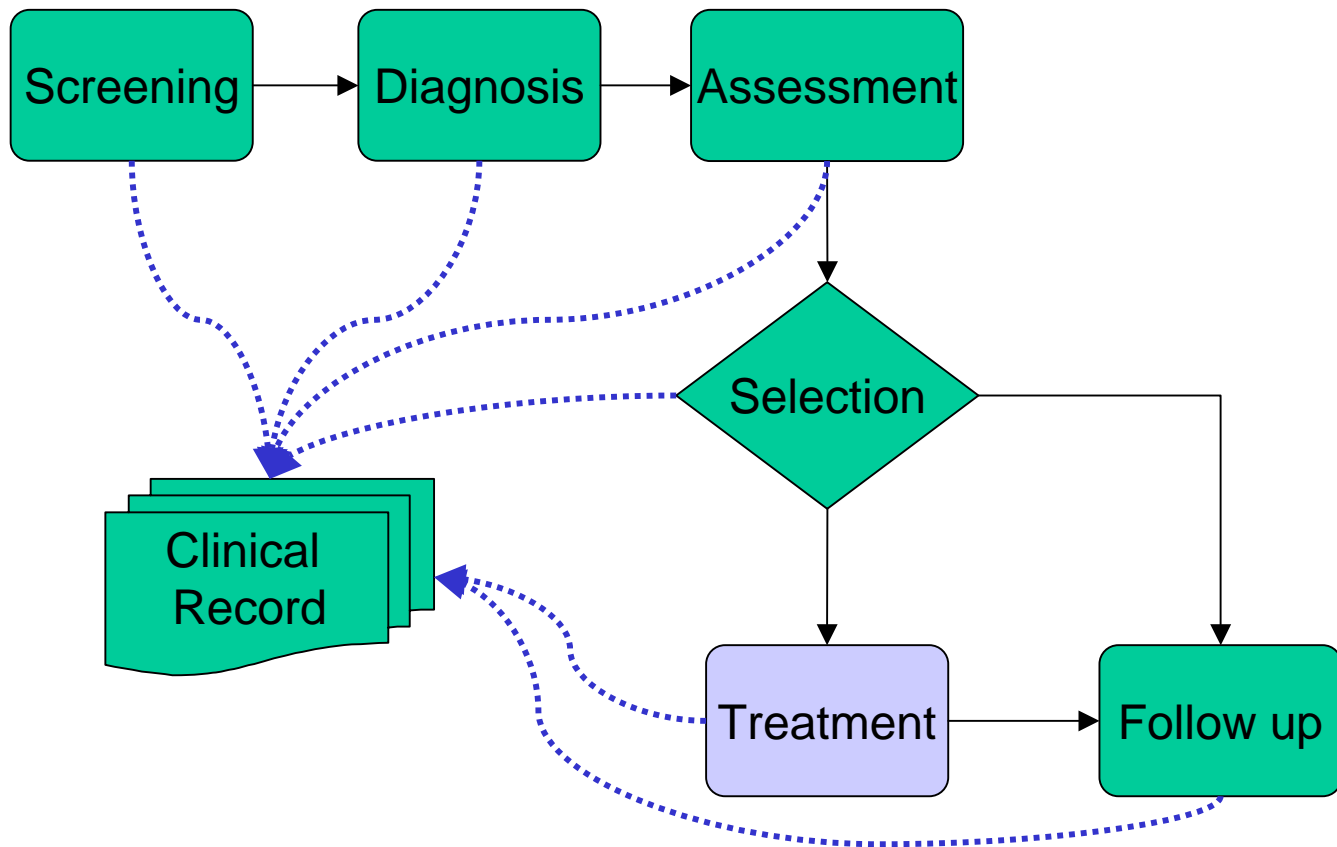
Goals of Treatment

- Prevention of long term sequelae
- Reversal of liver damage
- Elimination of virus
- Resolution of symptoms
- Abolish source of infection

Side Effects of Therapy

- Interferon
 - Myalgia / Arthralgia
 - Fatigue
 - Alopecia
 - Autoimmune thyroiditis
 - Diabetes
 - Neutropaenia
 - Thrombocytopaenia
 - Depression
- Ribavirin
 - Anaemia
 - Teratogenicity

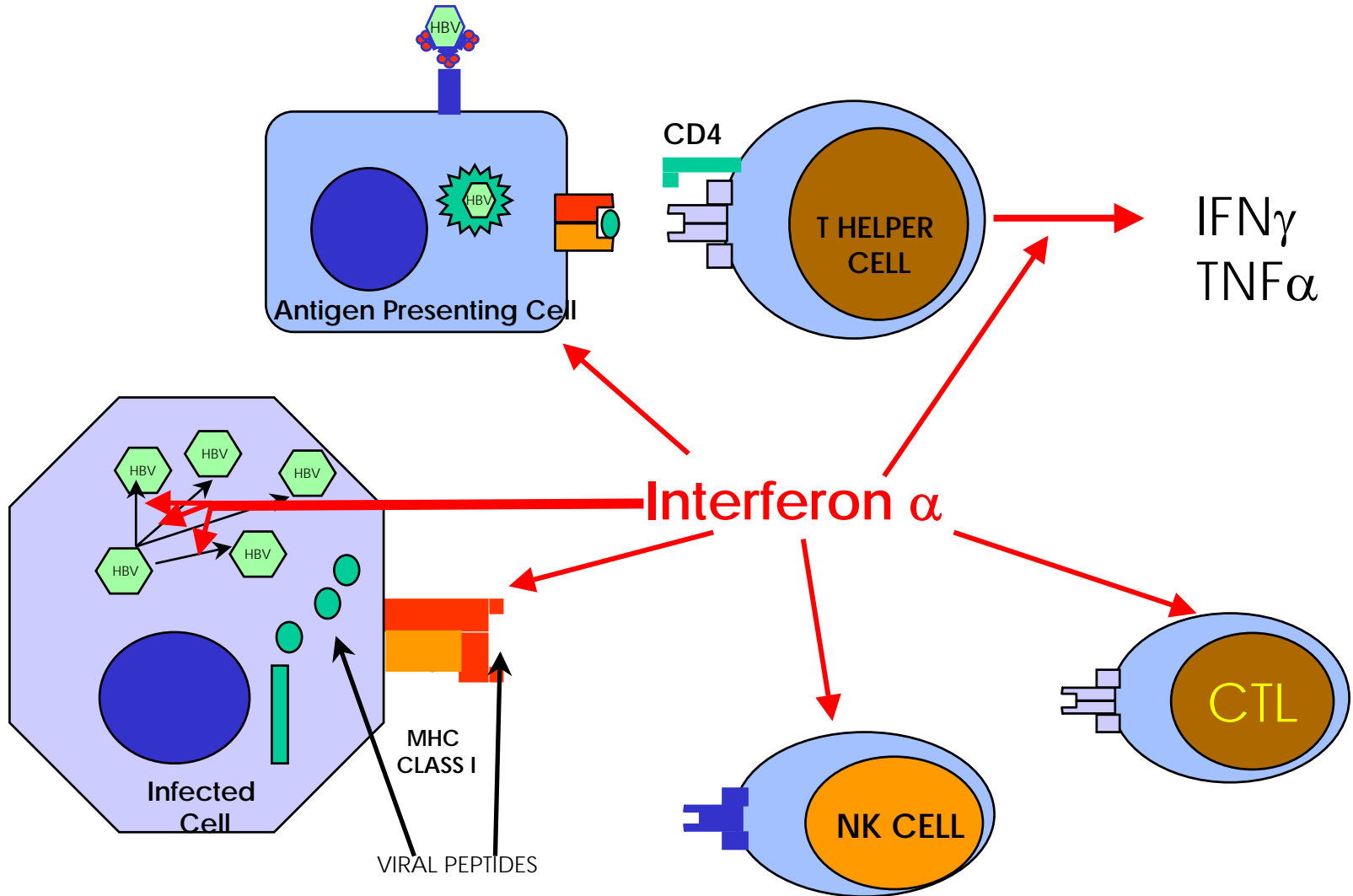
Management of HCV



Principal Drugs

- Interferon α
 - 2a , 2b, consensus,
 - Pegylated
- Ribavirin

Actions of Interferons



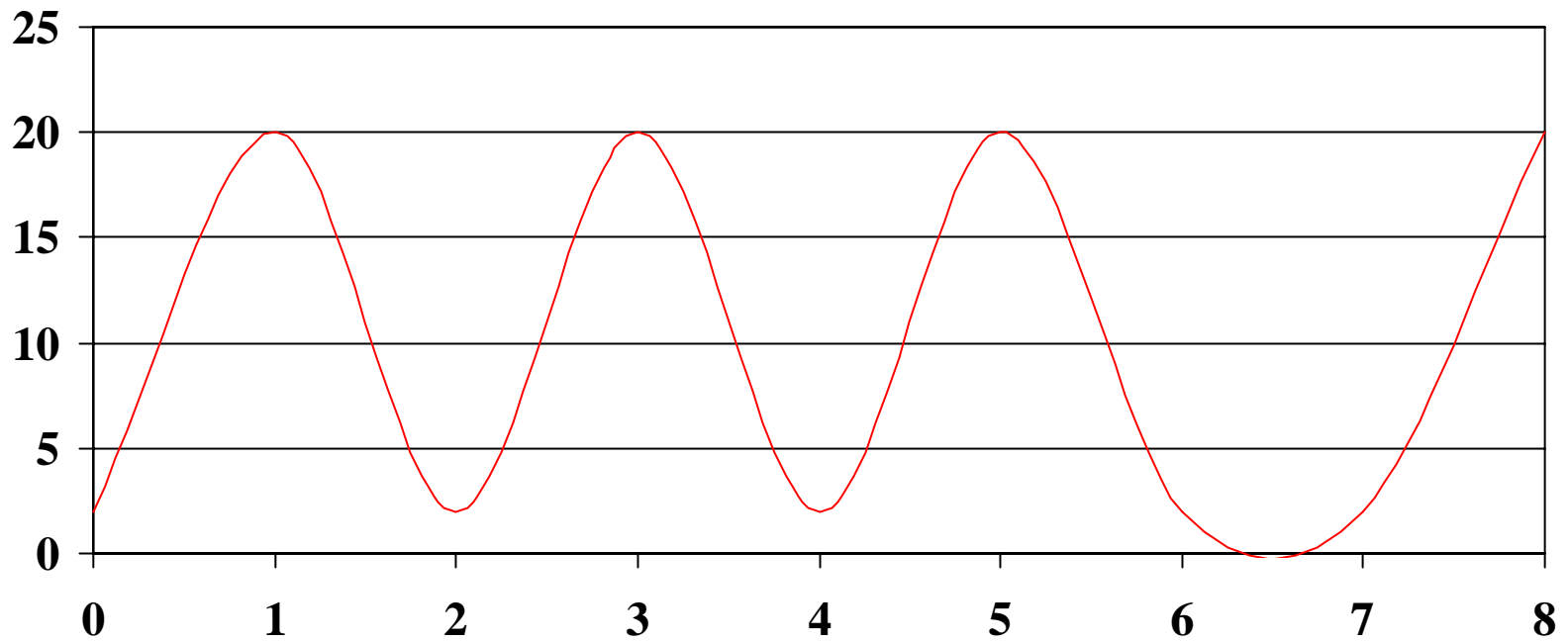
Ribavirin

- Nucleoside analogue
 - anti-viral
- Inosine monophosphate dehydrogenase inhibitor
 - reduces supply of GTP to virus
- Immunomodulator
 - induces Th1 immune responses

Pharmacokinetics of Interferon

Thrice Weekly Injection

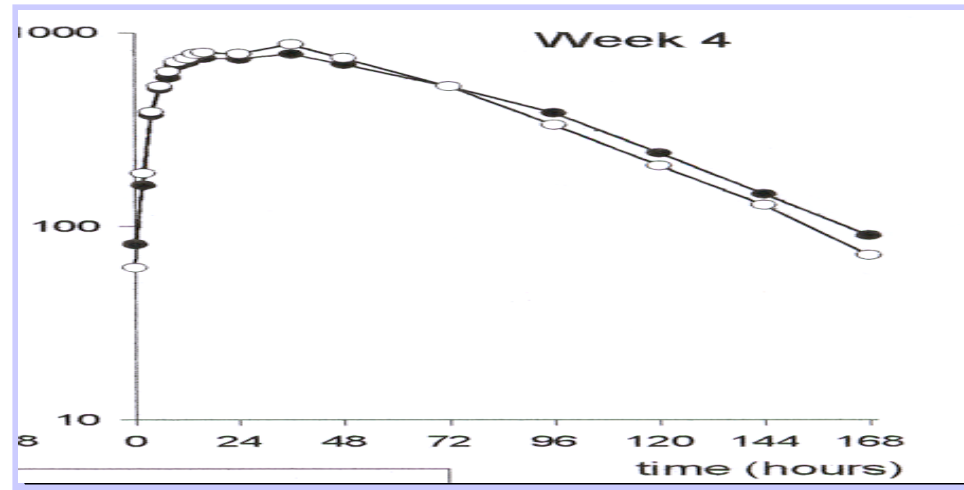
Interferon Levels



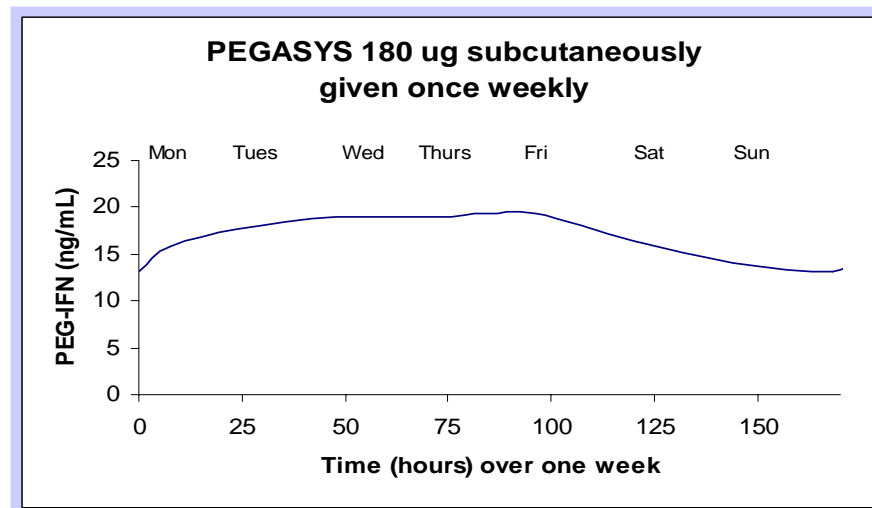
Pharmacokinetics of Interferon

Once Weekly Pegylated IFNs

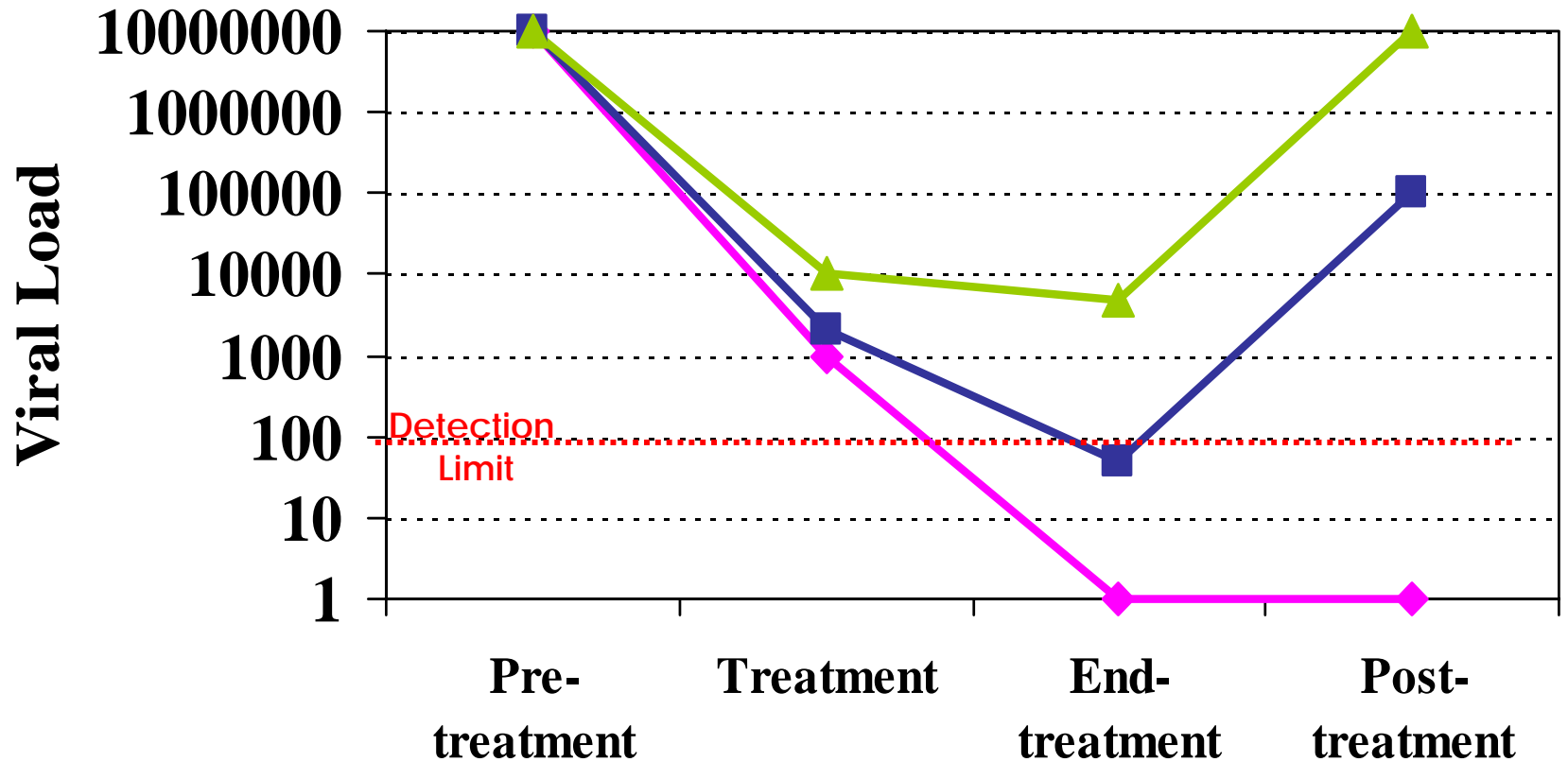
12 kD PEG
IFN α 2b



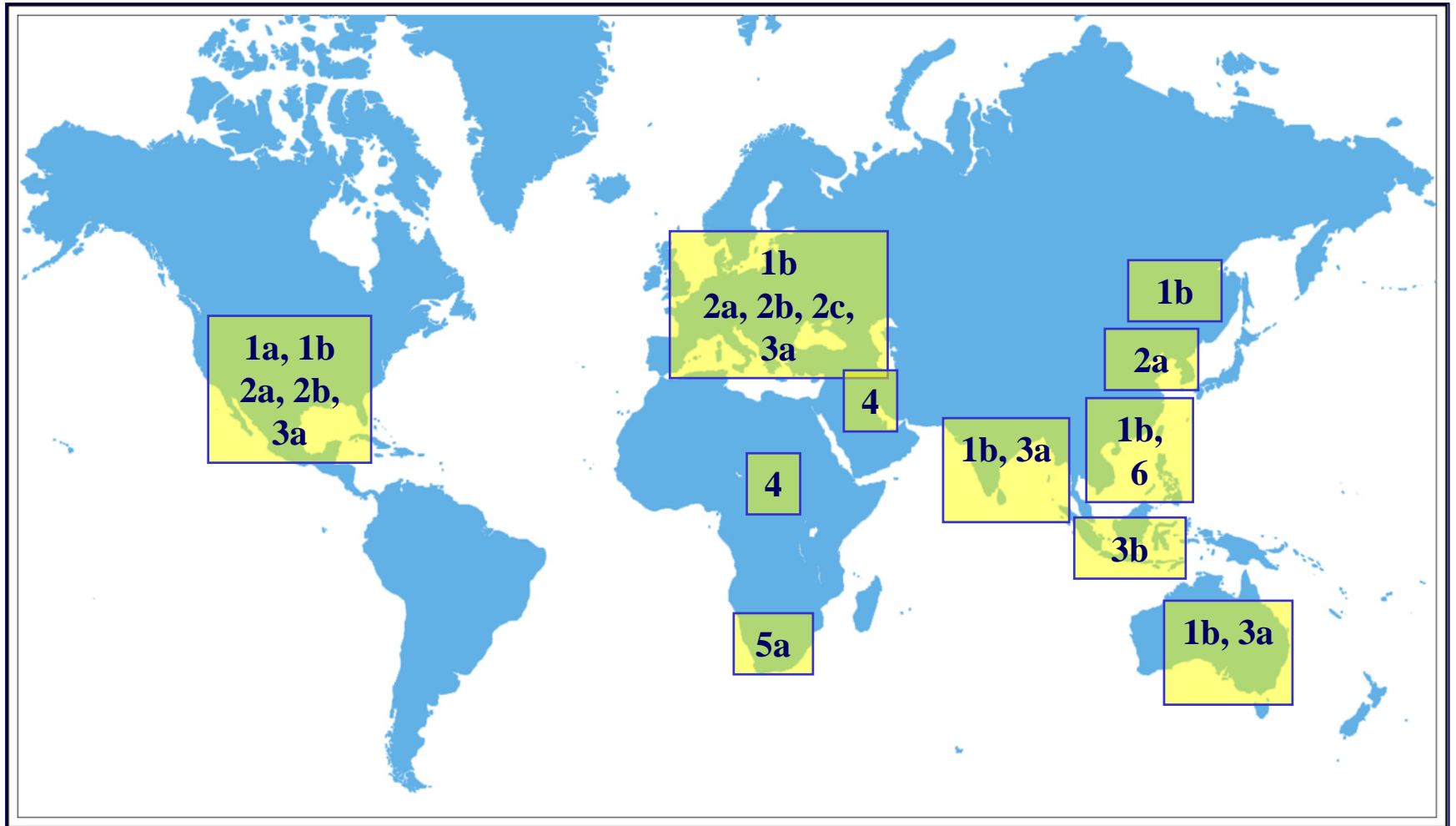
40 kD PEG
IFN α 2a



Response to treatment

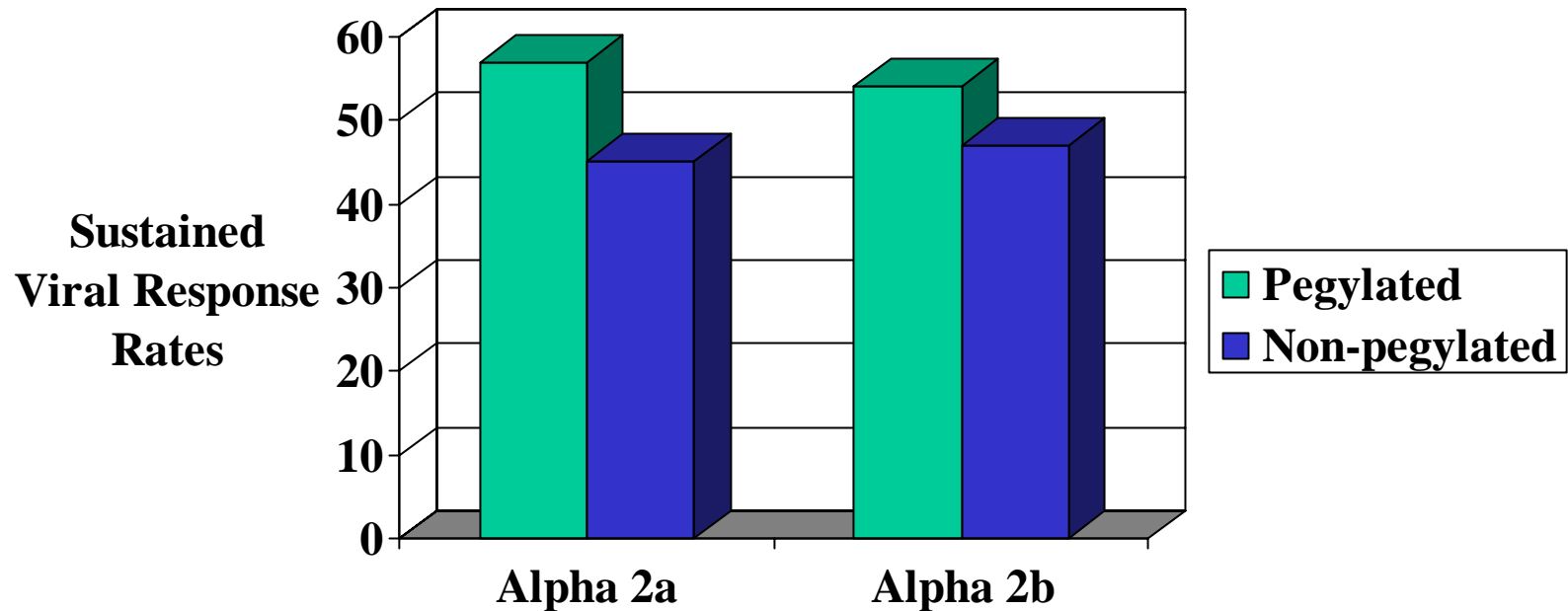


HCV Infection: Worldwide Genotype Distribution



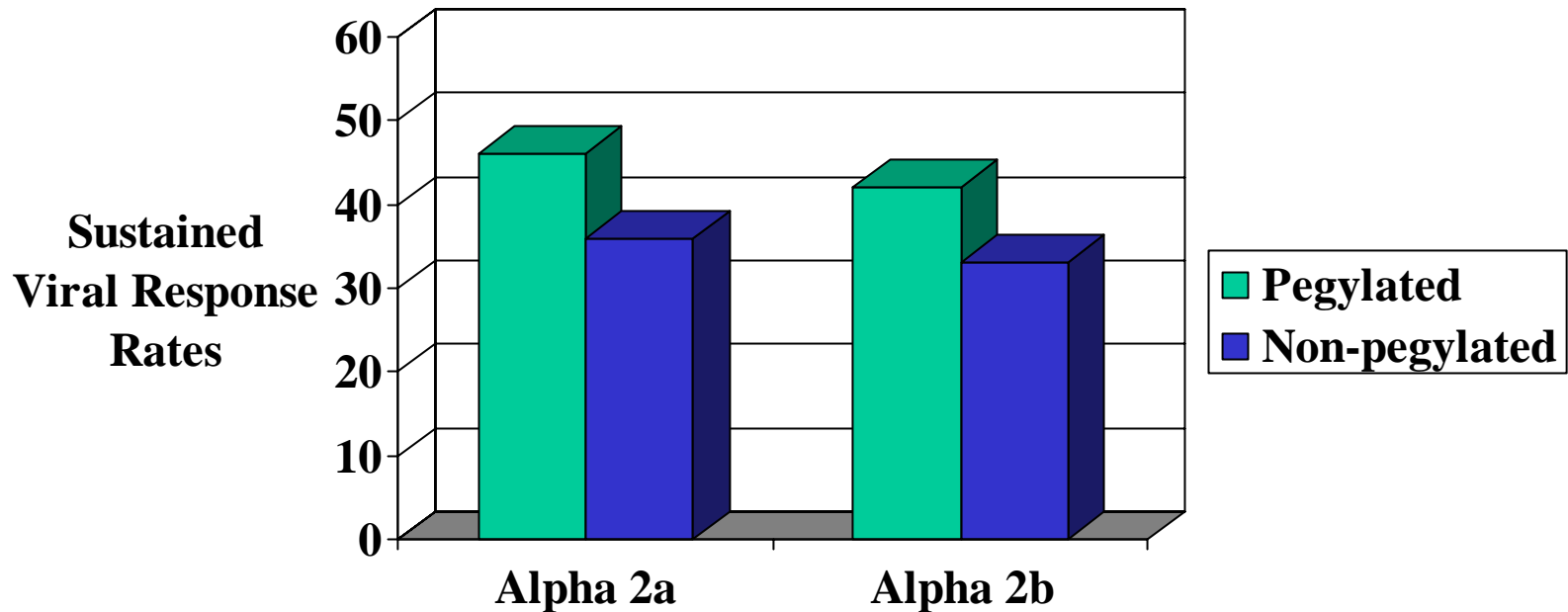
Adapted from Fang J. *Clin Liver Dis.* 1997;1:503.

Pegylated Interferons v Interferons & Ribavirin



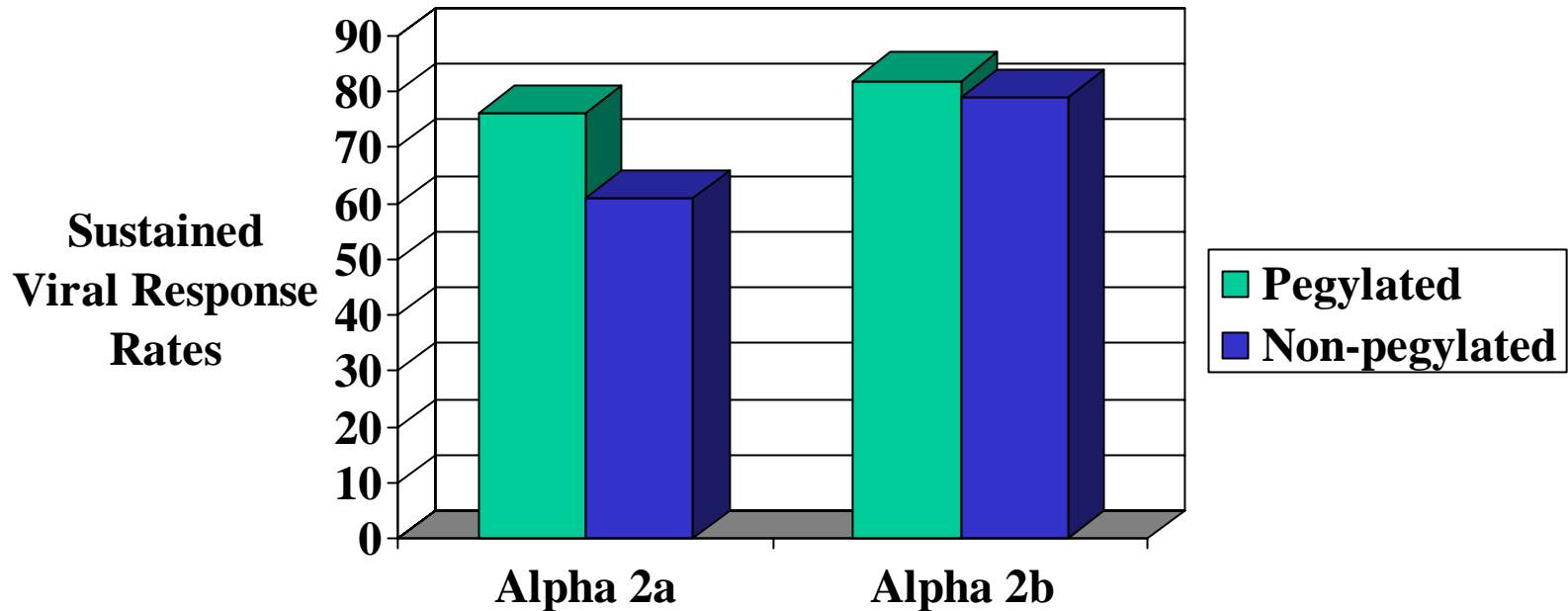
Pegylated Interferons v Interferons & Ribavirin

Genotype 1



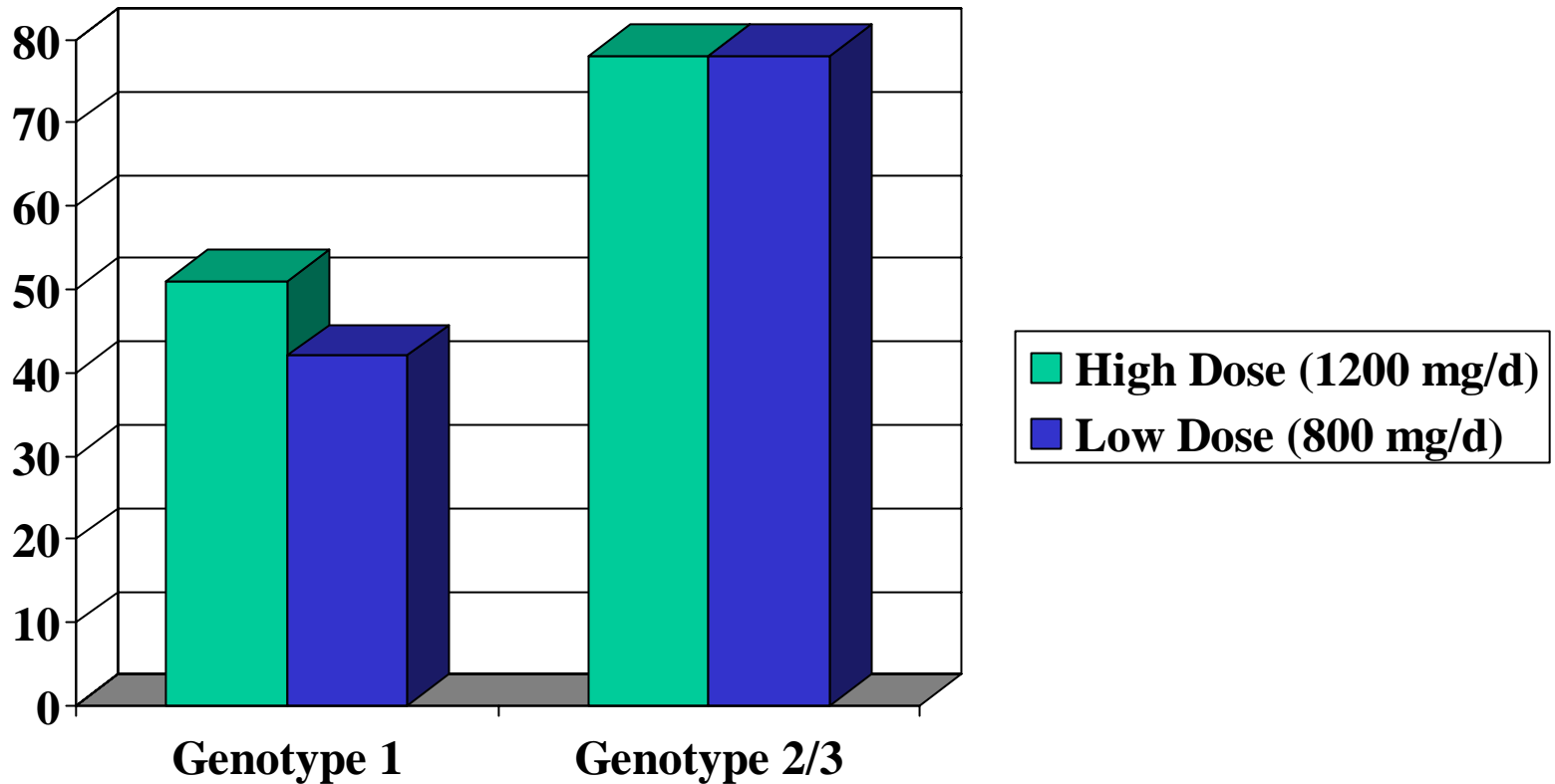
Pegylated Interferons v Interferons & Ribavirin

Genotype 2 / 3



Effect of Ribavirin Dose

Pegylated Interferon + Ribavirin



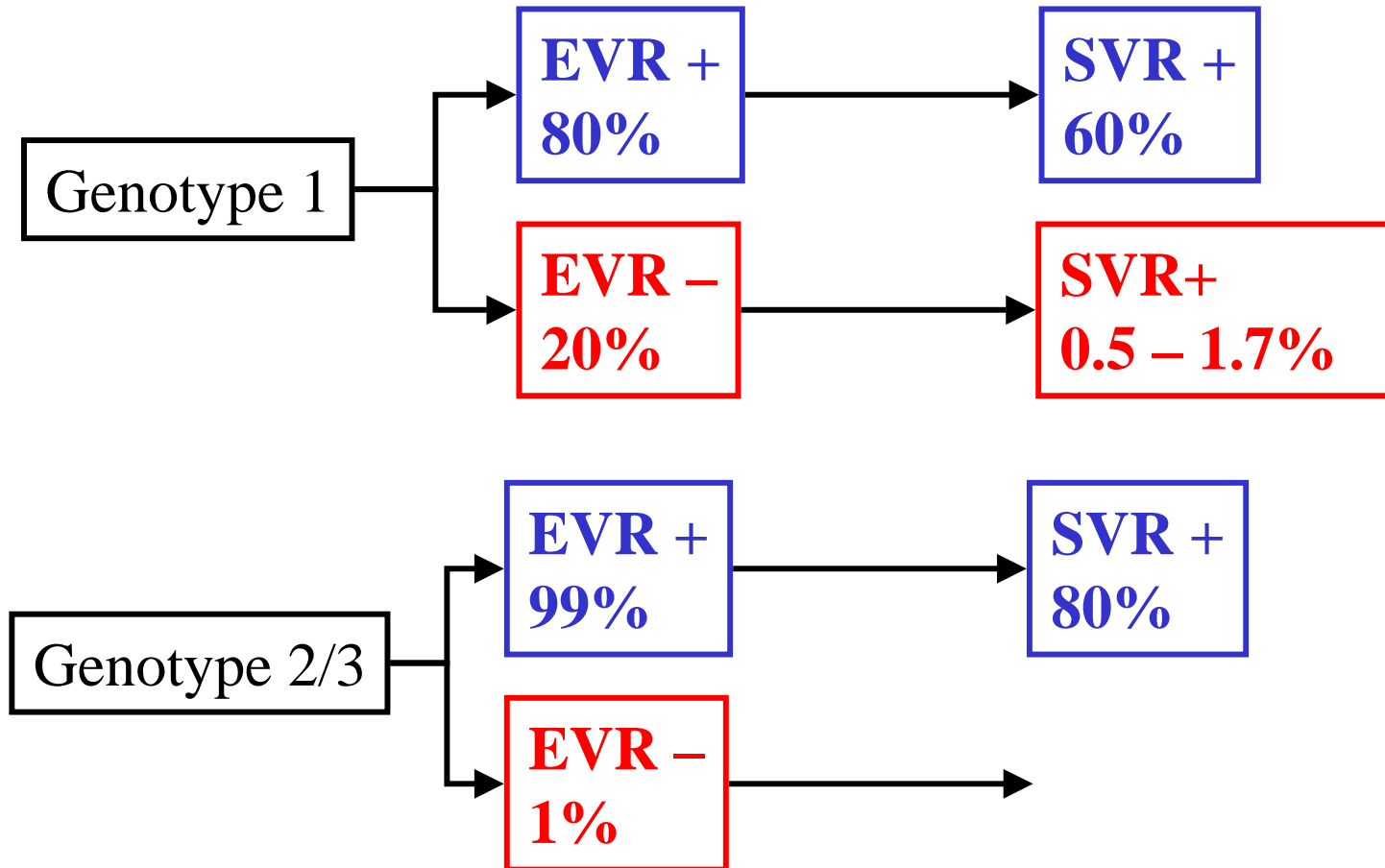
Protocol: HCV Gt 1

- Pegylated Ifn o.w. 48 weeks
 - Ifn α 2a 180 μ g
 - Ifn α 2b 1.5 μ g/kg
- Ribavirin daily 48 weeks
 - 1 – 1.2 g/d
 - >10.6 mg/kg/d

Protocol: HCV Gt 2/3

- Pegylated Ifn o.w. 24 weeks
 - Ifn α 2a 180 μ g
 - Ifn α 2b 1.5 μ g/kg
- Ribavirin daily 24 weeks
 - 1 – 1.2 g/d
 - >10.6 mg/kg/d

Predicting Treatment Failure



Early Viral Response: PCR neg or 2-log reduction

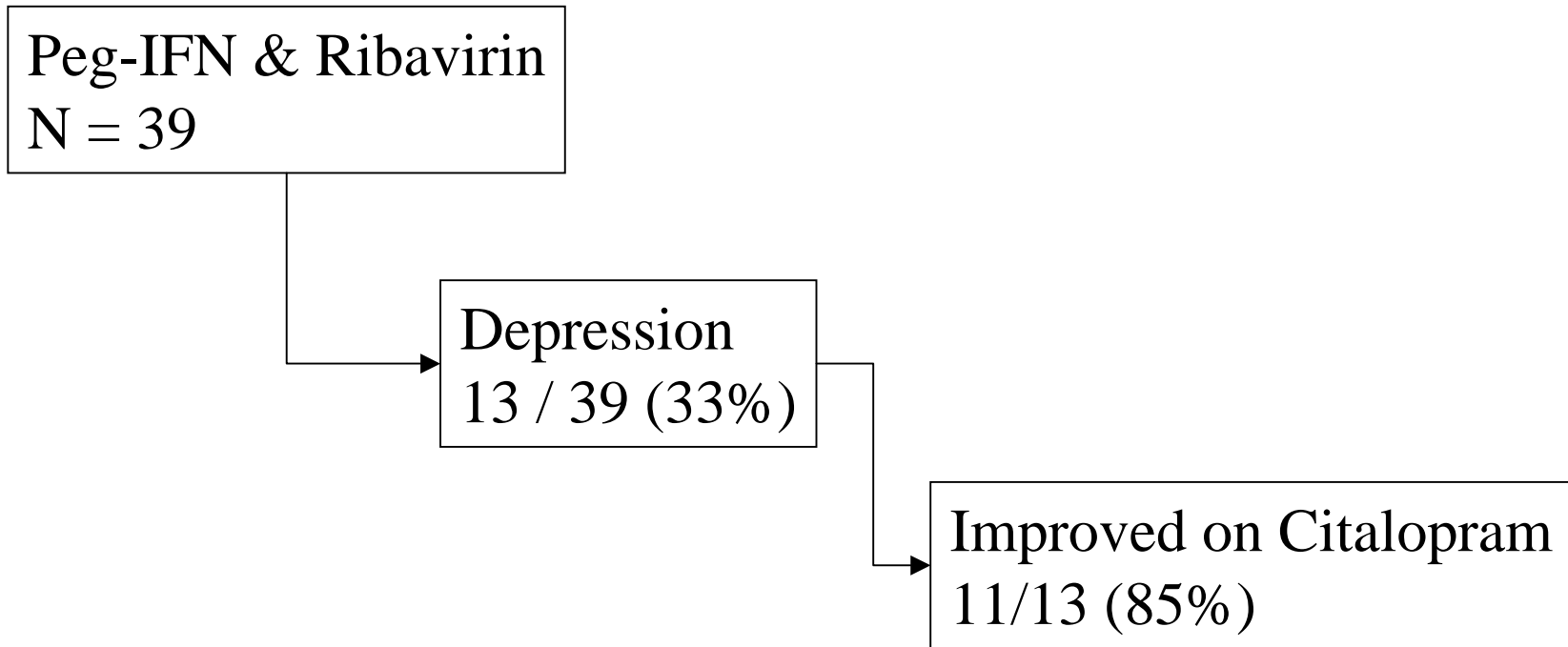
Stopping Treatment Early

- Gt 2/3 – no point
- Gt 1
 - < 2 log drop or PCR pos at 12 weeks
 - 1.6% achieve SVR
 - PCR pos at 24 weeks
 - 0% achieve SVR

Cytopaenias and Dose Reduction

Cytopaenia	Dose Reduction	Ref
Anaema	20 – 25%	Manns Fried
Neutropaenia	18 – 20%	Manns Fried
Thrombocytopaenia	3%	Sukowski

Depression



Special Cases

- Acute HCV
- Transplants
- Cirrhosis grade B & C
- Renal patients
- Haemaglobinopathies
- Paediatric patients
- **Advanced Cardiac Disease**
- IVDU
- **Treatment Failure on Interferon & Ribavirin**

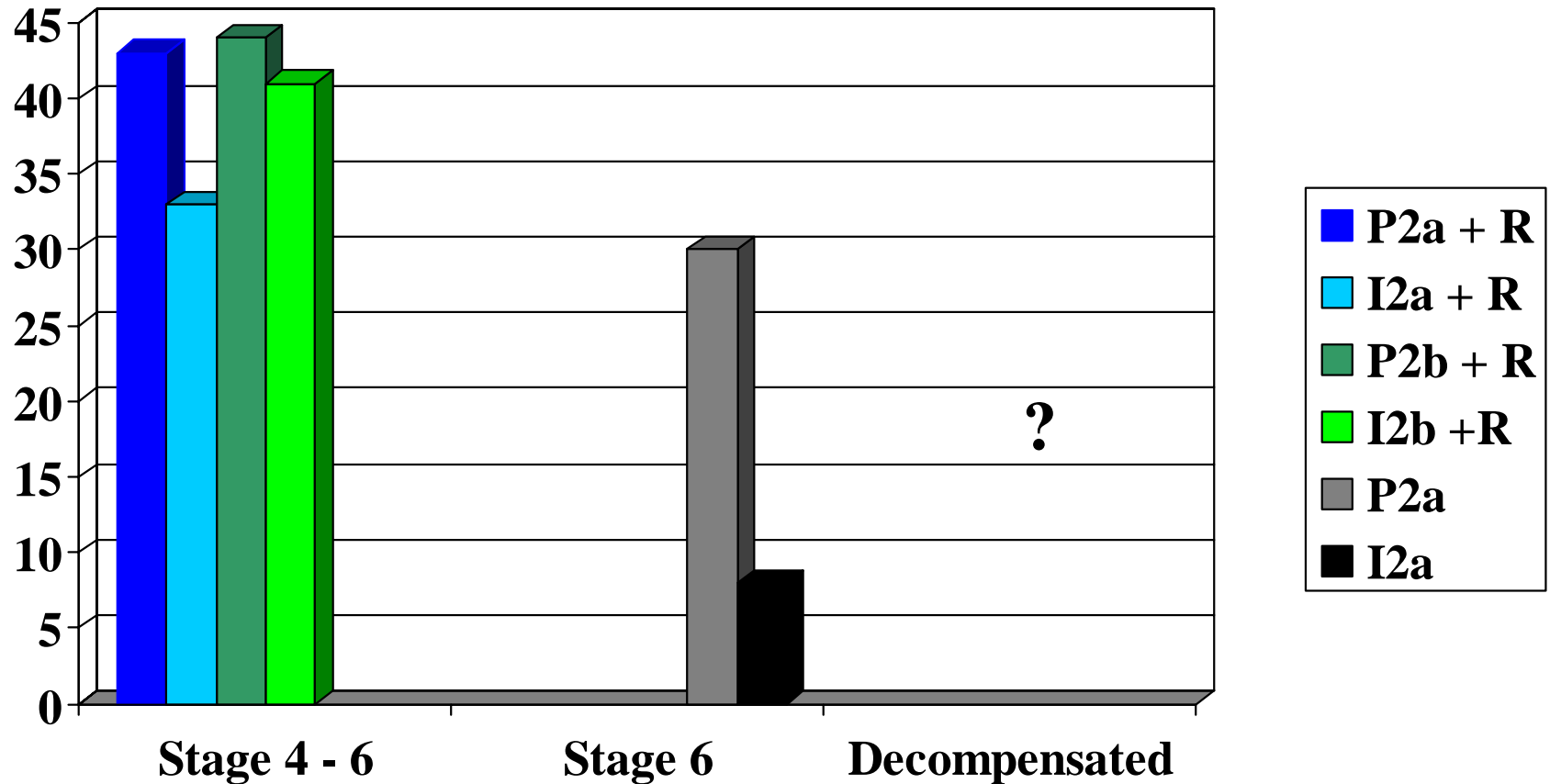
Acute HCV

- 50% will progress to chronic
- 95% respond to interferon & ribavirin

Liver Transplants

- 98% re-infected
- 10% early graft loss
- Poor response to I + R
- Trials in transplant centres

Advanced Fibrosis / Cirrhosis



Heathcote EJ. NEJM 2000;343:1673-1680

Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis..

Cirrhosis B & C

- Poor tolerance of side effects
- High rates of decompensation

- HALT-C trial in US
- Similar Trial in UK

Renal Patients

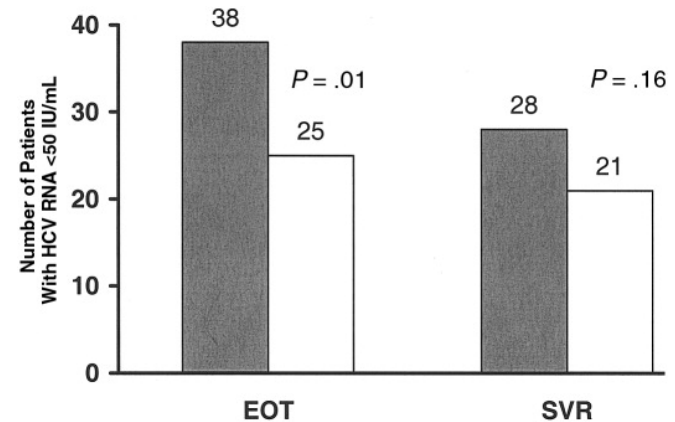
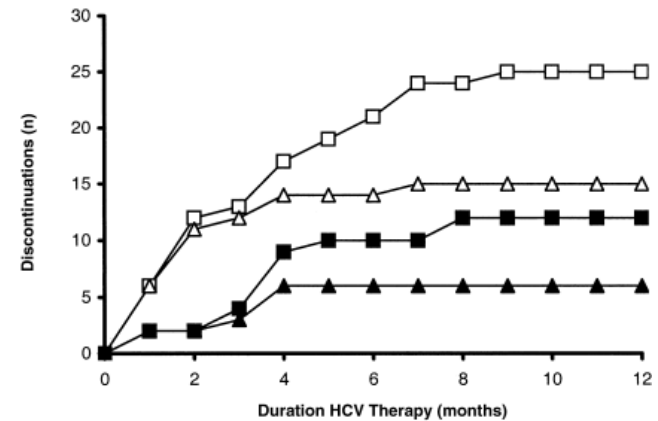
- Often mild disease
- Poor tolerance of ribavirin
 - Anaemia
 - Pharmacokinetics
- Trials required

Paediatrics

- Low fibrosis stage and rate
- No RCTs
- If mild
 - Wait until old enough for full assessment
- If severe
 - Refer to paediatric unit

Continued Drug Use

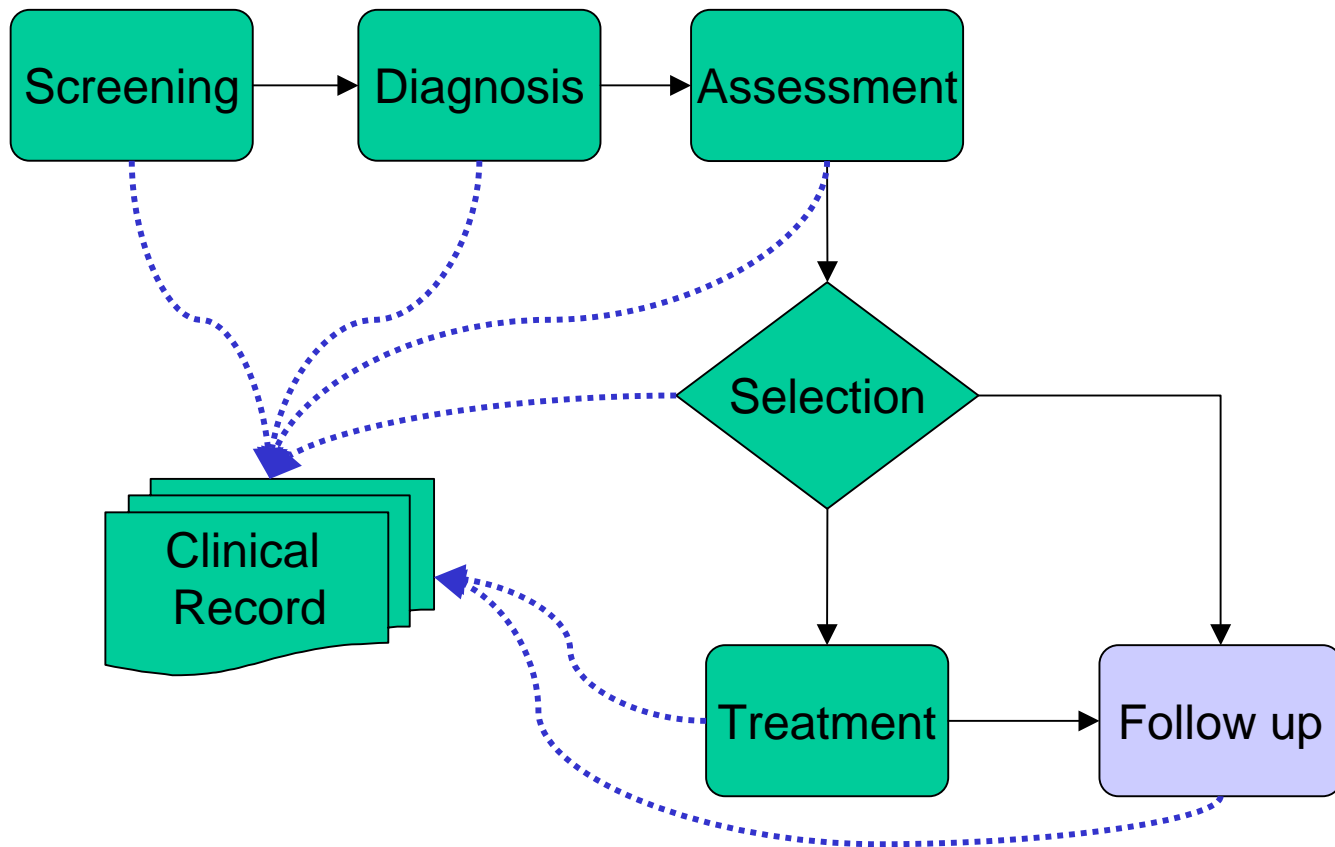
- Trials suggest re-infection is rare
- Compliance required
- Link to needle exchange programme
- Cessation of IV use should be encouraged



Novel Rx

- Short Duration Therapy
 - Rapid viral responders
 - 3/12 HCV-Gt 2/3
 - 6/12 HCV Gt 1
- Direct anti-viral
 - Protease inhibitors
 - Polymerase inhibitors
 - Helicase inhibitors
- Ribavirin replacement
 - ViraMidine
- Therapeutic Vaccination

Management of HCV



Do we achieve our goals ?

- Prevention of long term sequelae
- Reversal of liver damage
- **Elimination of virus**
- Resolution of symptoms
- **Abolish source of infection**

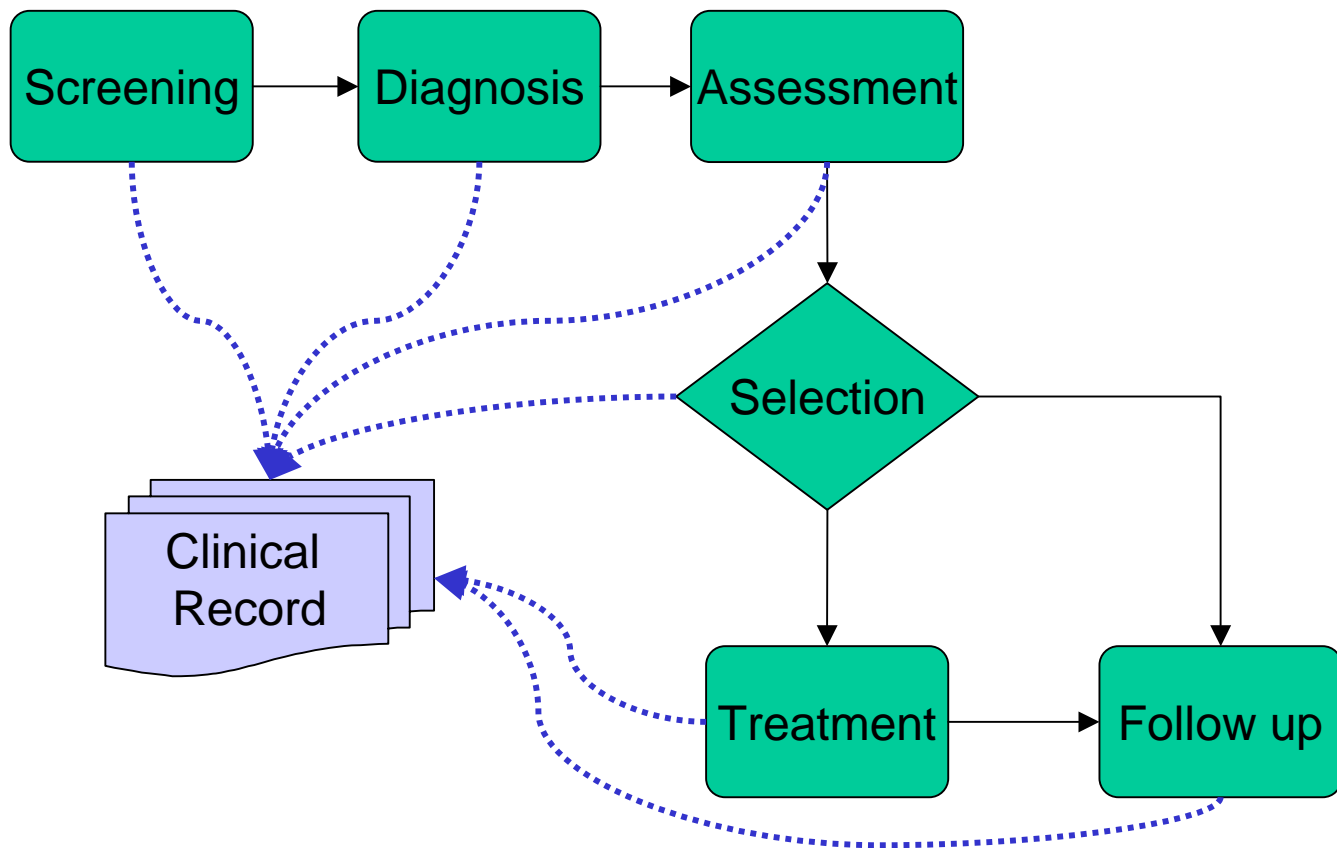
Long Term Outcome of Treatment 1

No.	Clinical Features				Initial				Final				Follow-up (yr)	Clinical Outcome
	Resp	Age (yr)	Sex	Source	Genotype	RNA	ALT	HAI	RNA	ALT	HAI	Liver RNA		
1	SR	30	M	IDU	1a	+	376	11	<100	20	3	-	11	Asymptomatic
2	SR	27	M	Tx	2a/2b	+	460	8	<100	52	3	-	10	Asymptomatic
3	SR	37	M	IDU	2a	+	306	11	<100	21	1	-	11	Asymptomatic
4	SR	40	M	Tx	3	+	272	11	<100	35	2	-	10	Asymptomatic
5	SR	29	M	Tx	2a	+	185	11	<100	23	0	-	10	Asymptomatic
6	NR	51	M	IDU	1	+	219	12	1500	23	11	NA	13	HCC/OLT
7	NR	41	M	Unknown	1b	+	419	14	$.18 \times 10^6$	181	12	NA	6	Died/Stroke
8	NR	62	F	Tx	1b	+	200	8	$.049 \times 10^6$	248	16	+	11	Symptoms
9	NR	38	M	Tx	1a	+	148	17	$>5 \times 10^6$	102	15	+	11	Symptoms
10	NR	46	M	Tx	1b	+	392	15	1.4×10^6	326	12	NA	11	Symptoms

Follow-up for Untreated and Non-Responder Patients

- Untreated
 - Minimal fibrosis
 - Repeat biopsy every 5 years
 - Non-compliant
 - Address lifestyle or psychological issues
- Non-responders
 - Monitor

Management of HCV



Summary

- Assessment and selection are essential
 - 30% of infected patients treated
- Compliance with therapy is essential
 - Full support team required
- Outcomes of therapy are poor
 - 50% of treated patients achieve SVR

Pegylated Interferon Trials

- Manns MP et al. Lancet 2001 22; 358: 958-65
 - Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial.
- Fried MW. N Engl. J Med 2002 26;347: 975-82
 - Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection.
- S.J. Hadziyannis. Ann Intern Med. 2004 Mar 2;140(5):346-55.
 - Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose.