Current Management of diagnosed cases of HCV Infection

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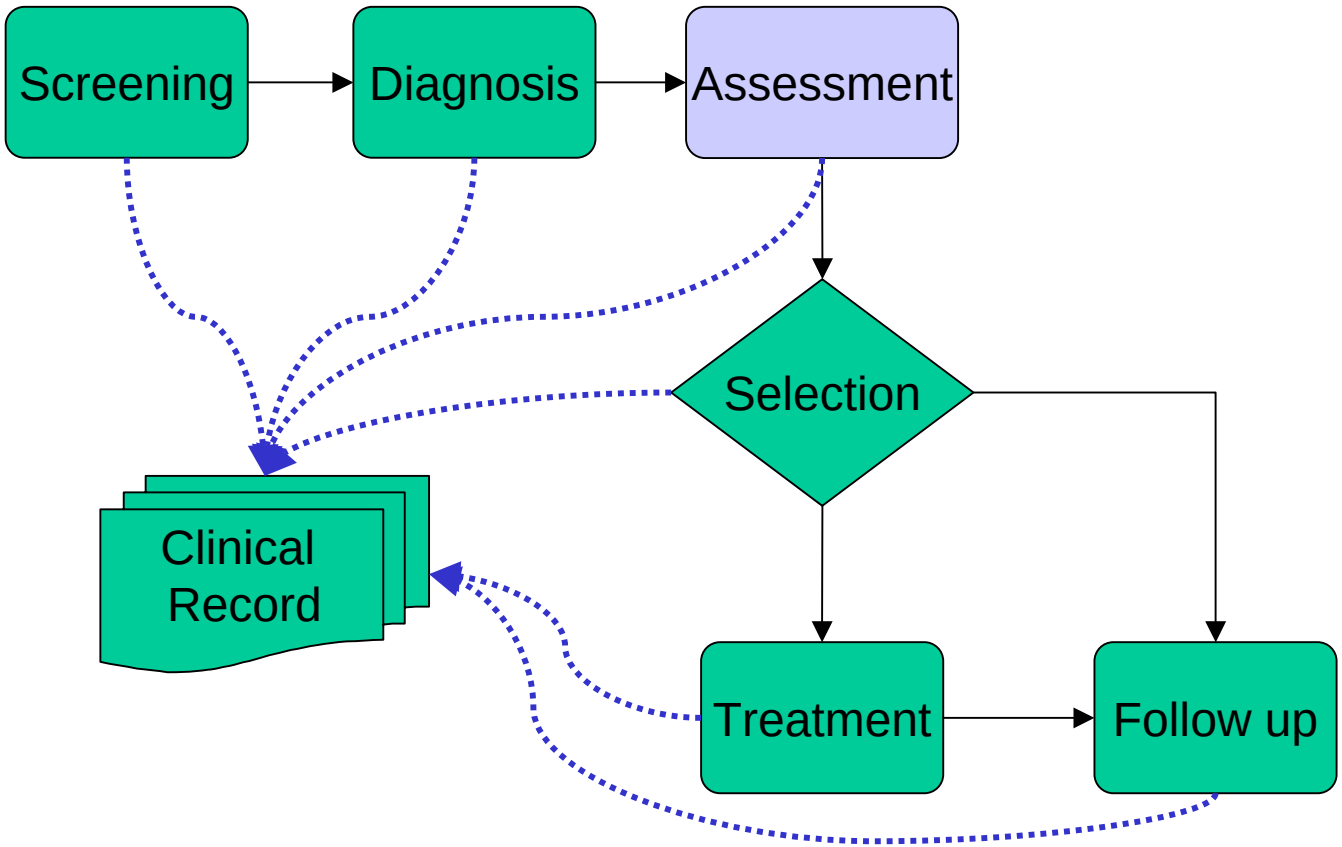
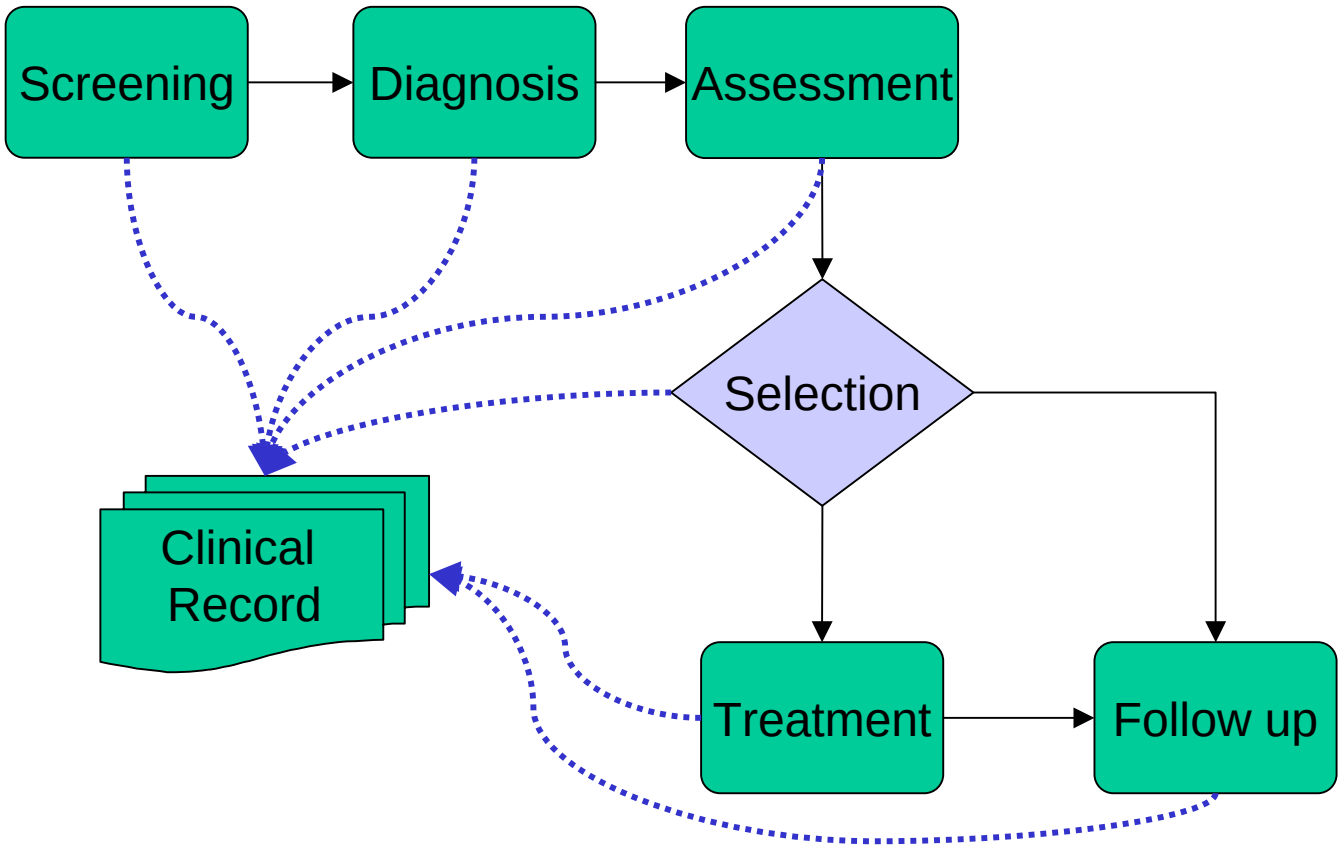
Management of HCV



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

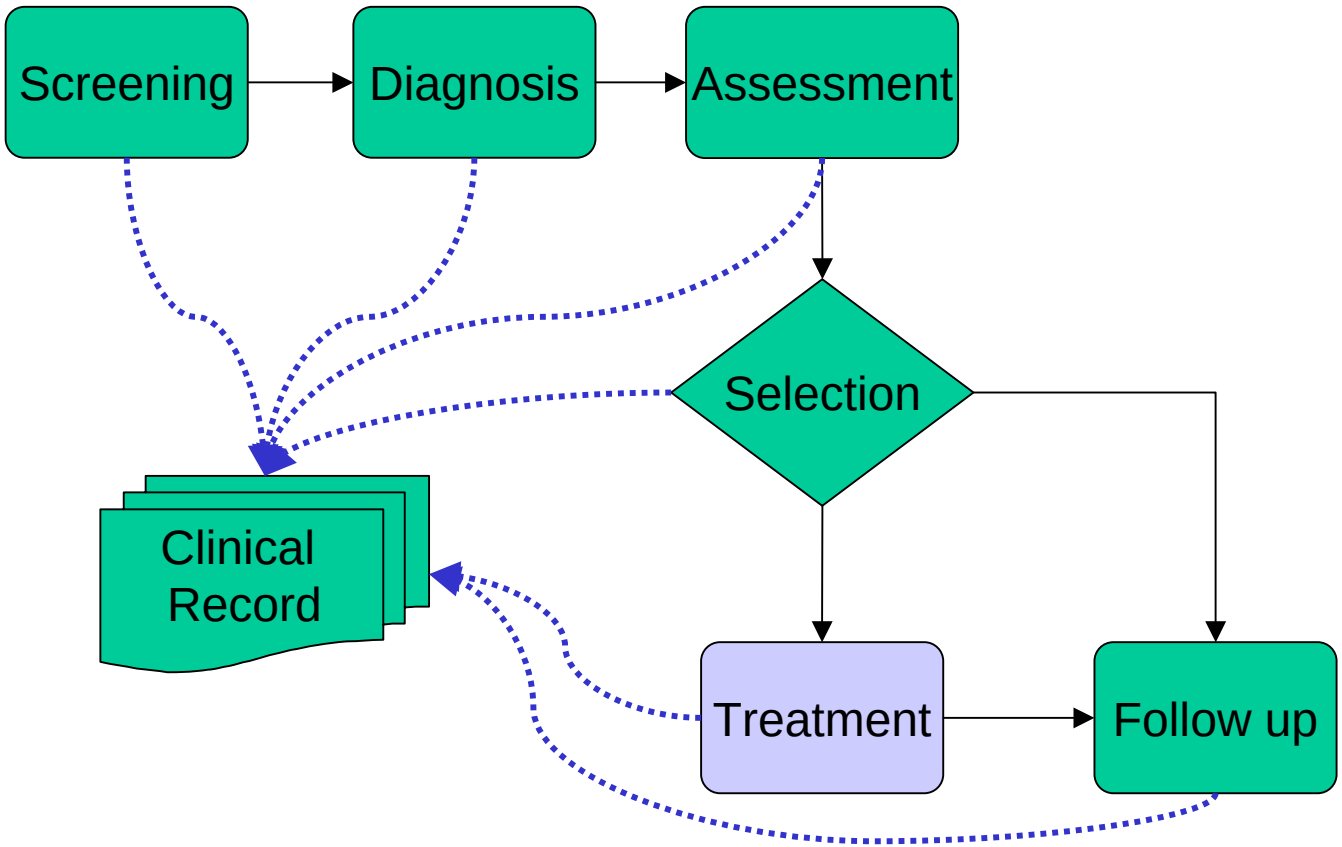
Goals of Treatment

- 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

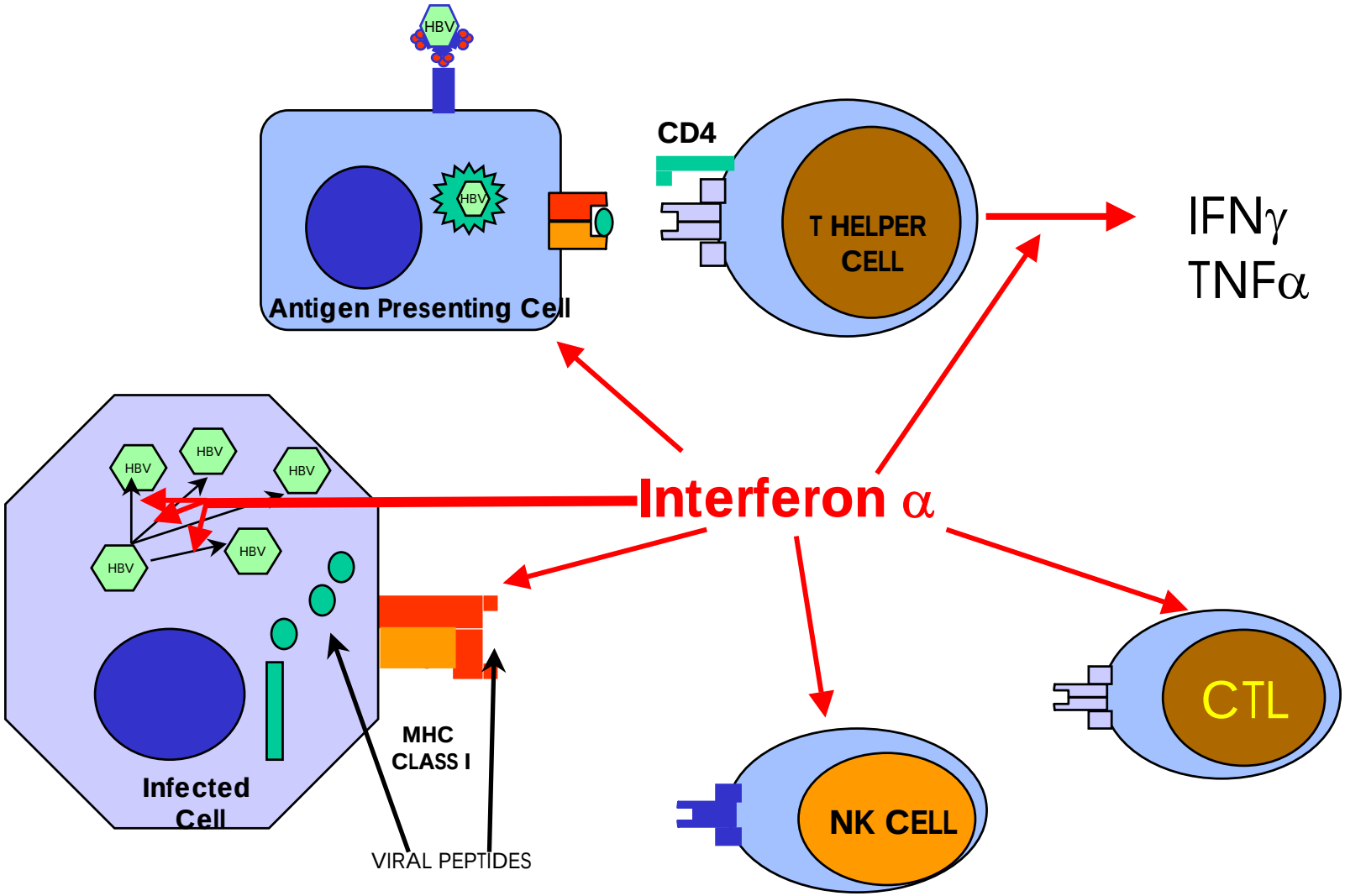
Management of HCV



Principal Drugs

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

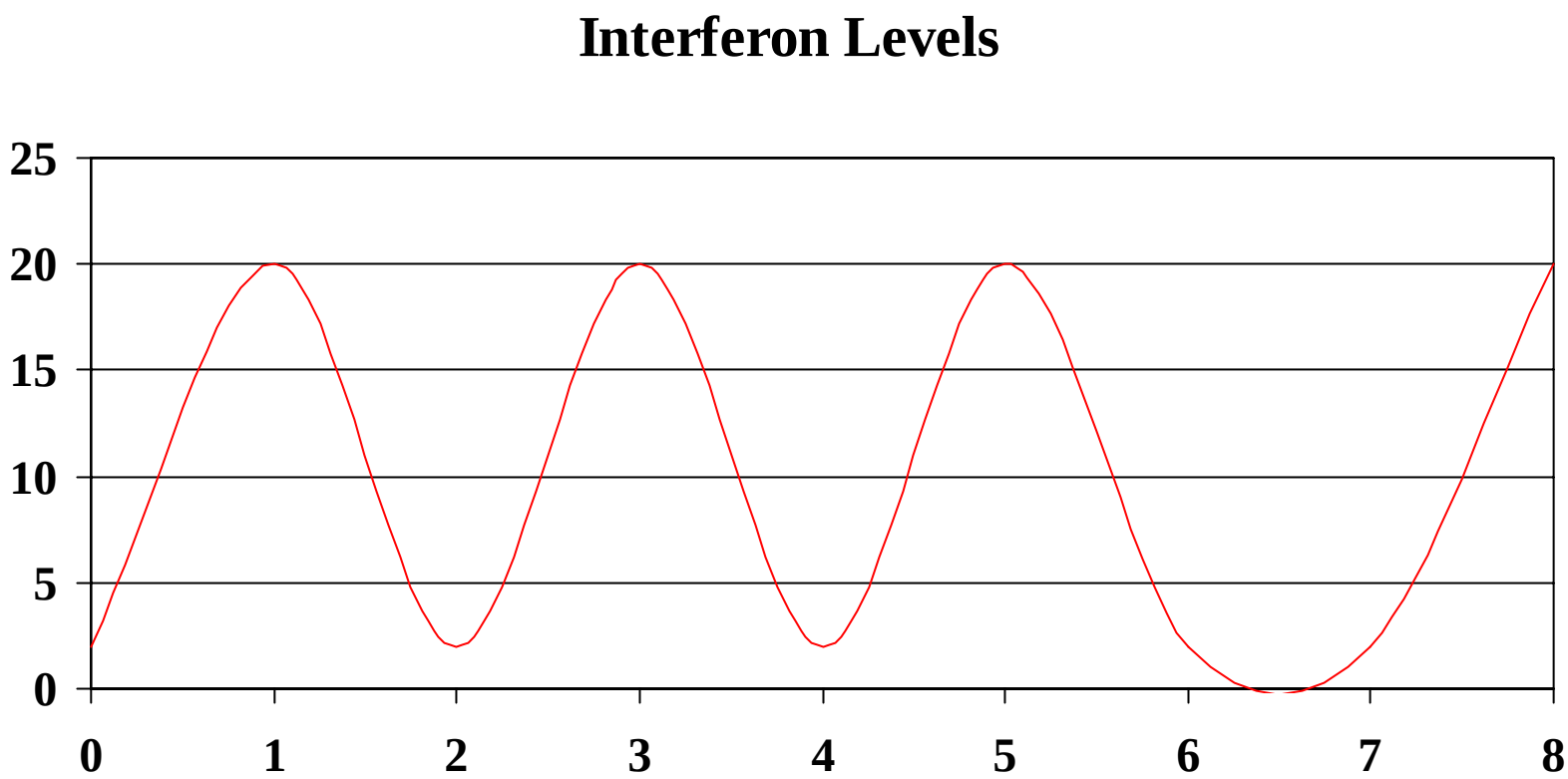
Actions of Interferons



Ribavirin

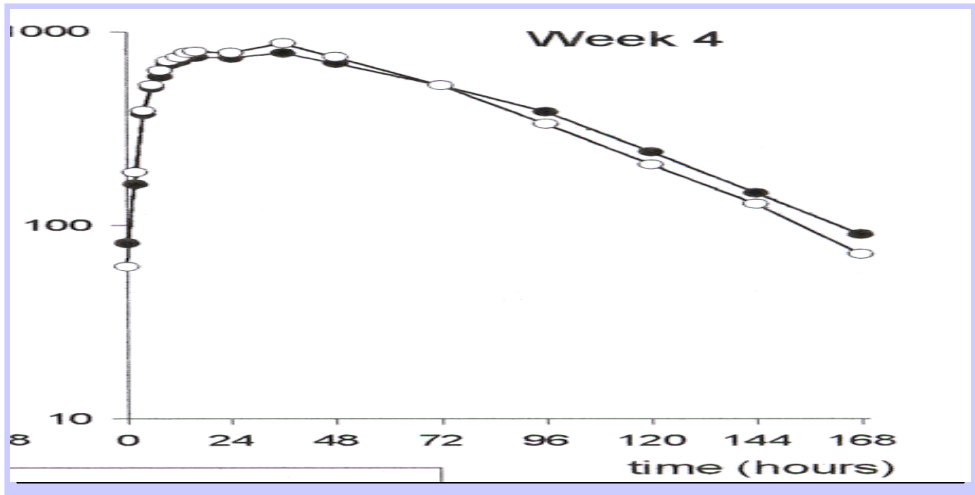
- Nucleoside analogue
  - anti-viral
- Innosine monophosphate dehydrogenase inhibitor
  - reduces supply of GTP to virus
- Immunomodulator
  - induces Th1 immune responses

Pharmacokinetics of Interferon Thrice Weekly Injection

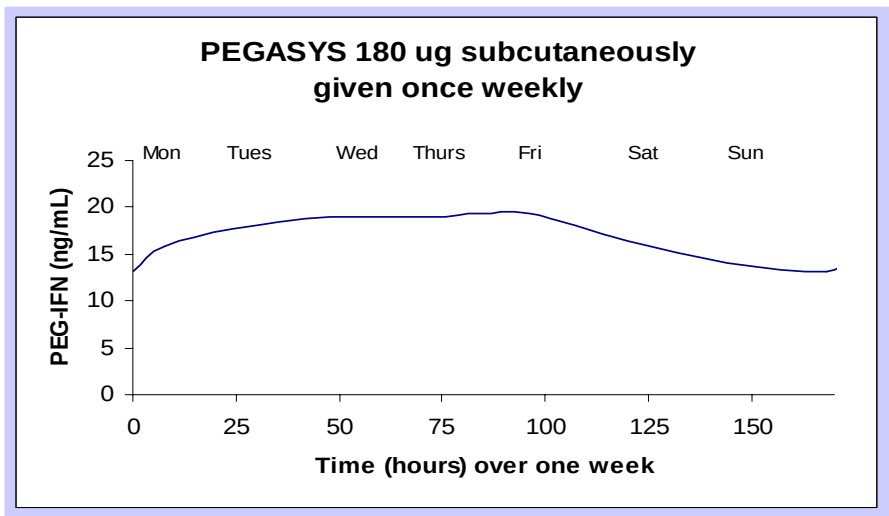


Pharmacokinetics of Interferon Once Weekly Pegylated IFNs

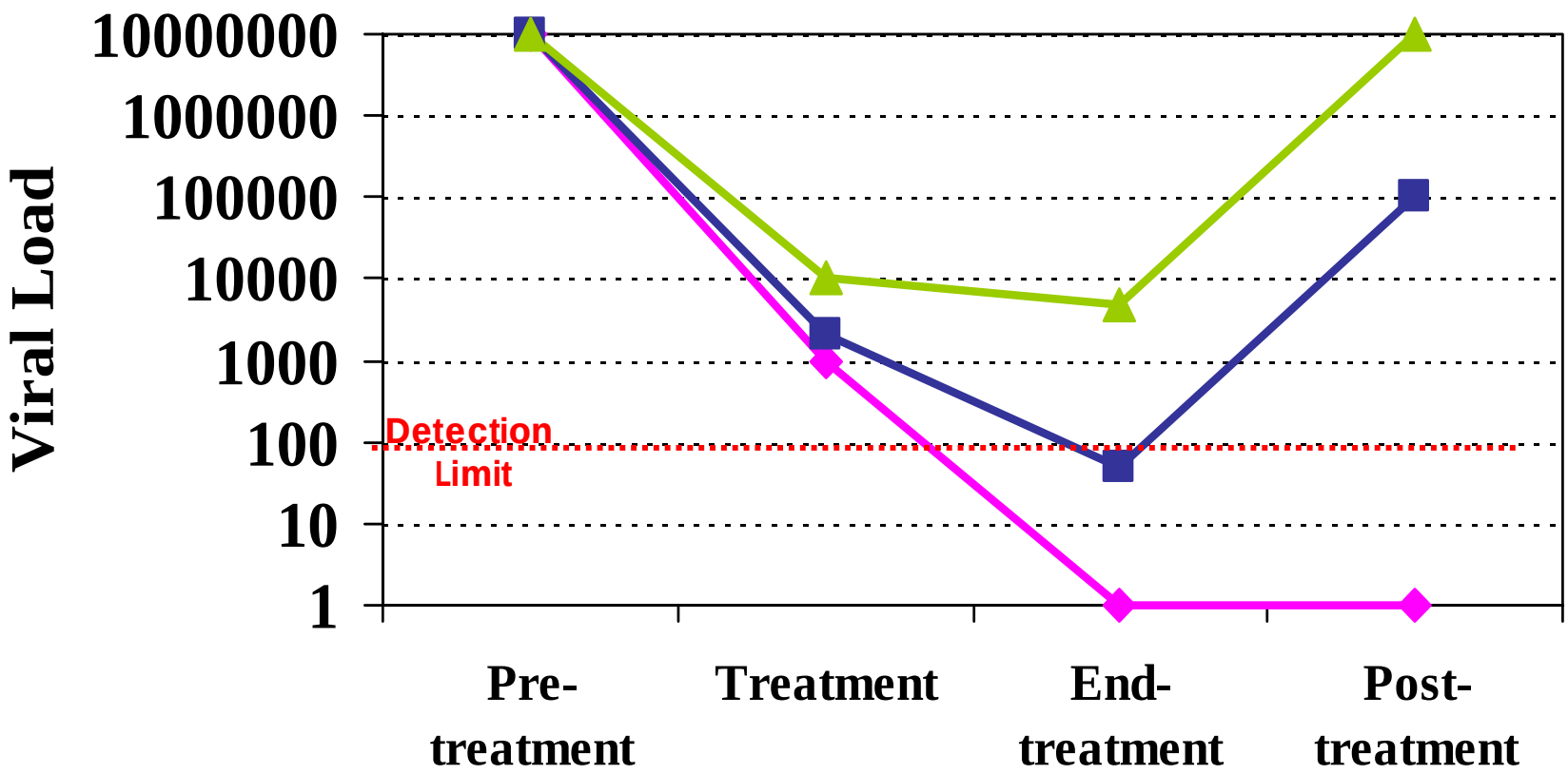
12 kD PEG IFNα2b



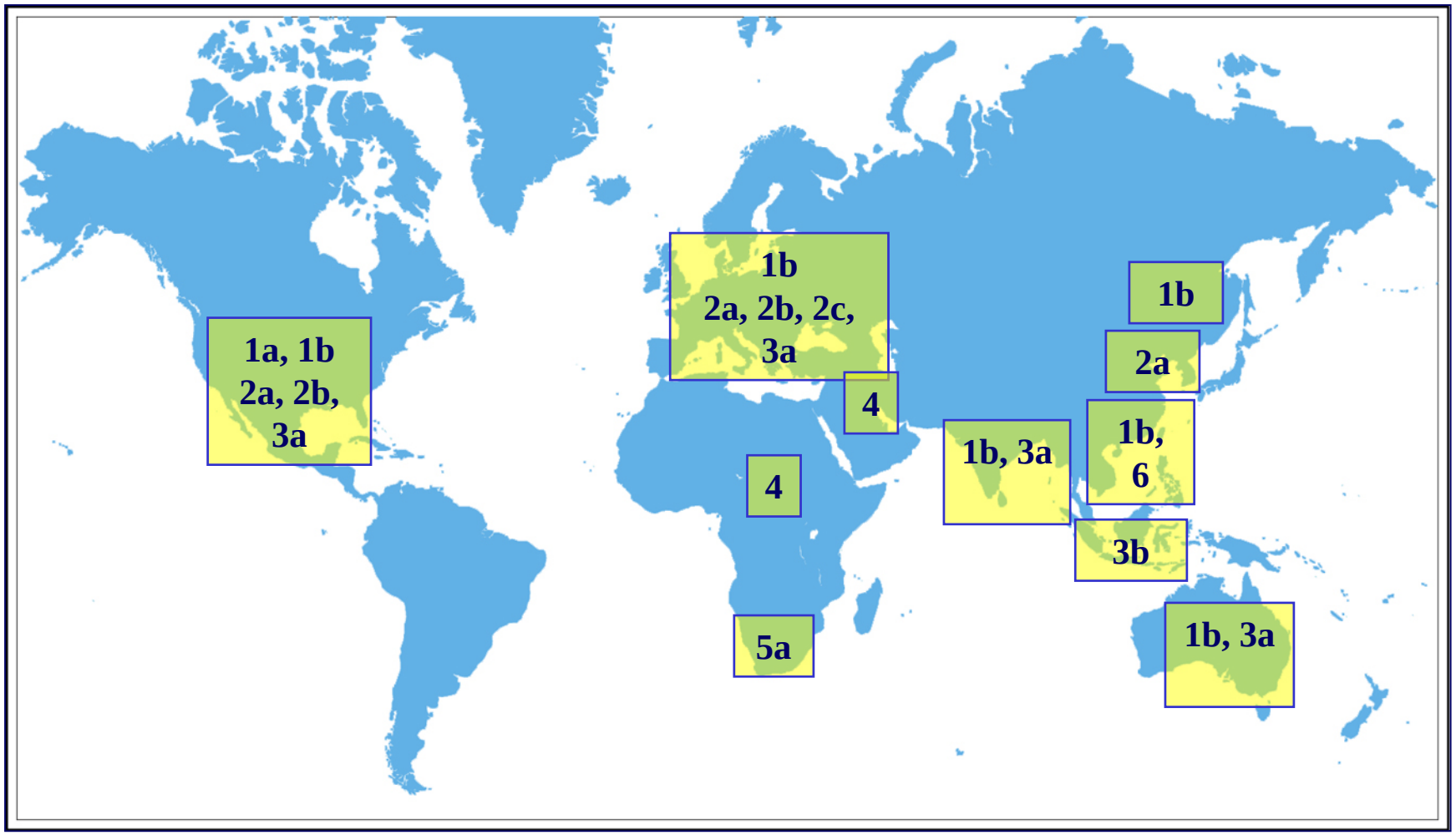
40 kD PEG IFNα2a



Response to treatment

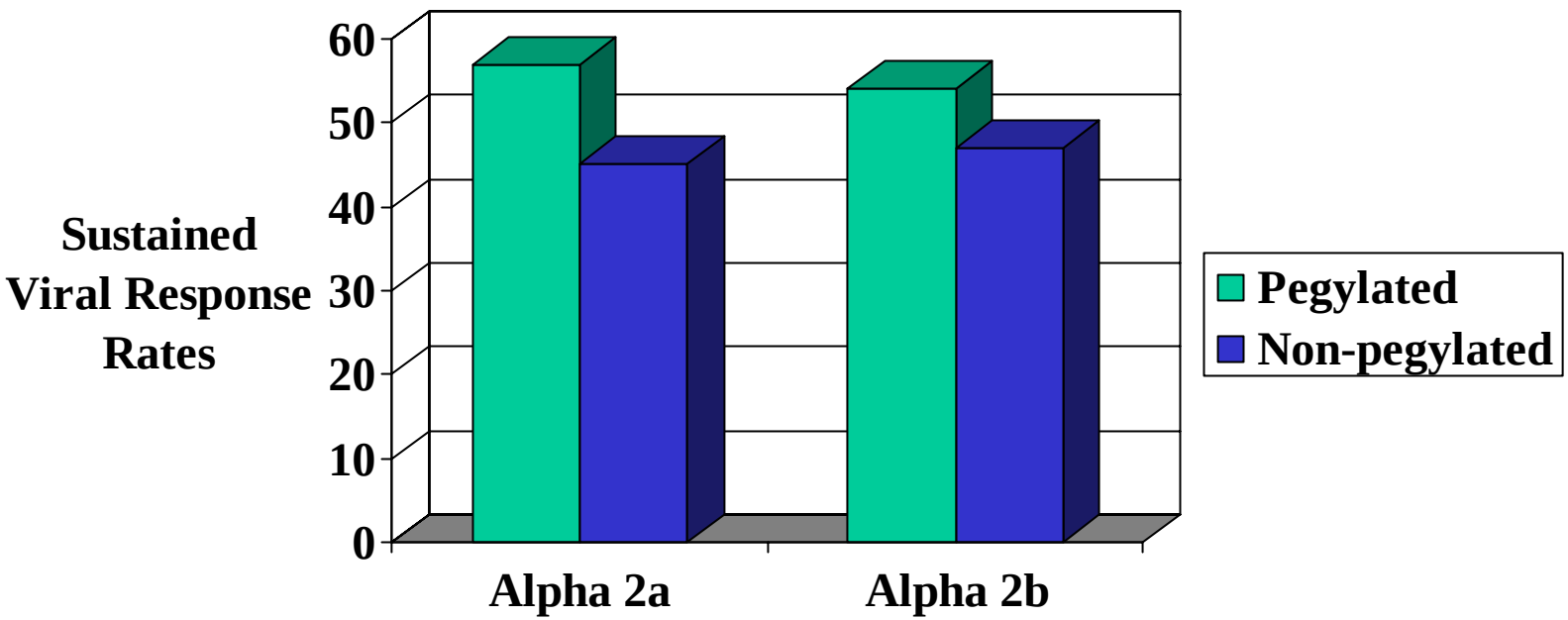


HCV Infection:
Worldwide Genotype Distribution



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

Pegylated Interferons v Interferons & Ribavirin



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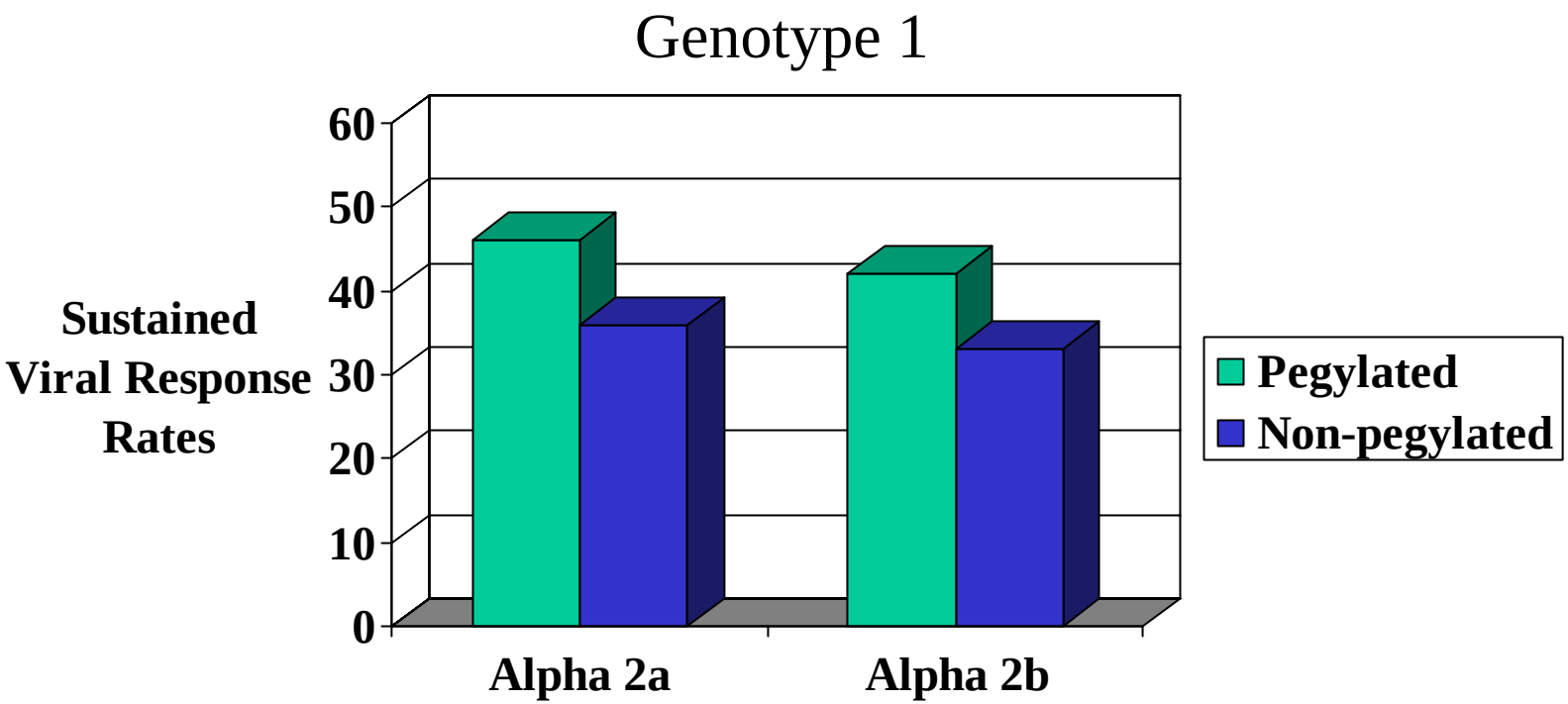
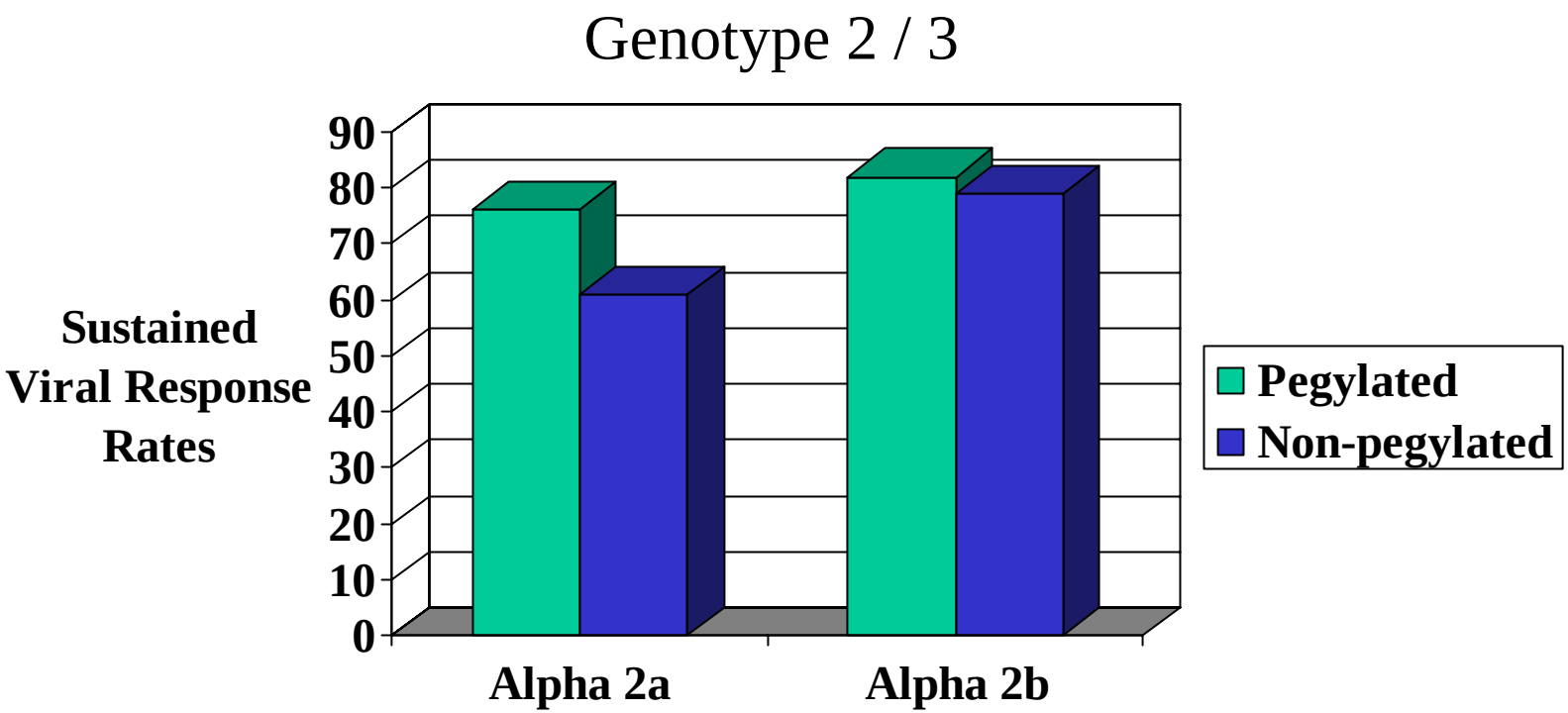
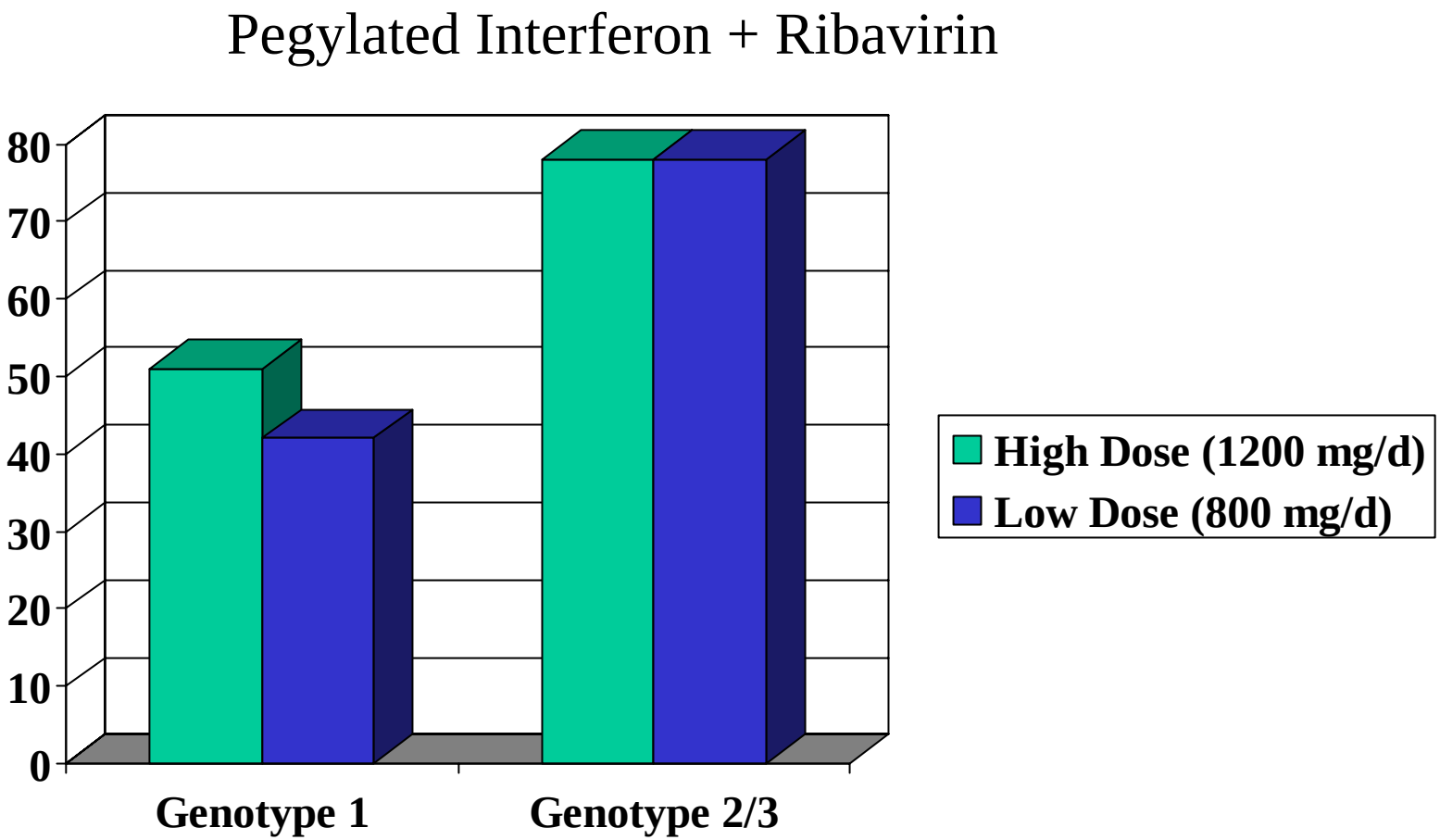


Pegylated Interferons v Interferons & Ribavirin



Effect of Ribavirin Dose



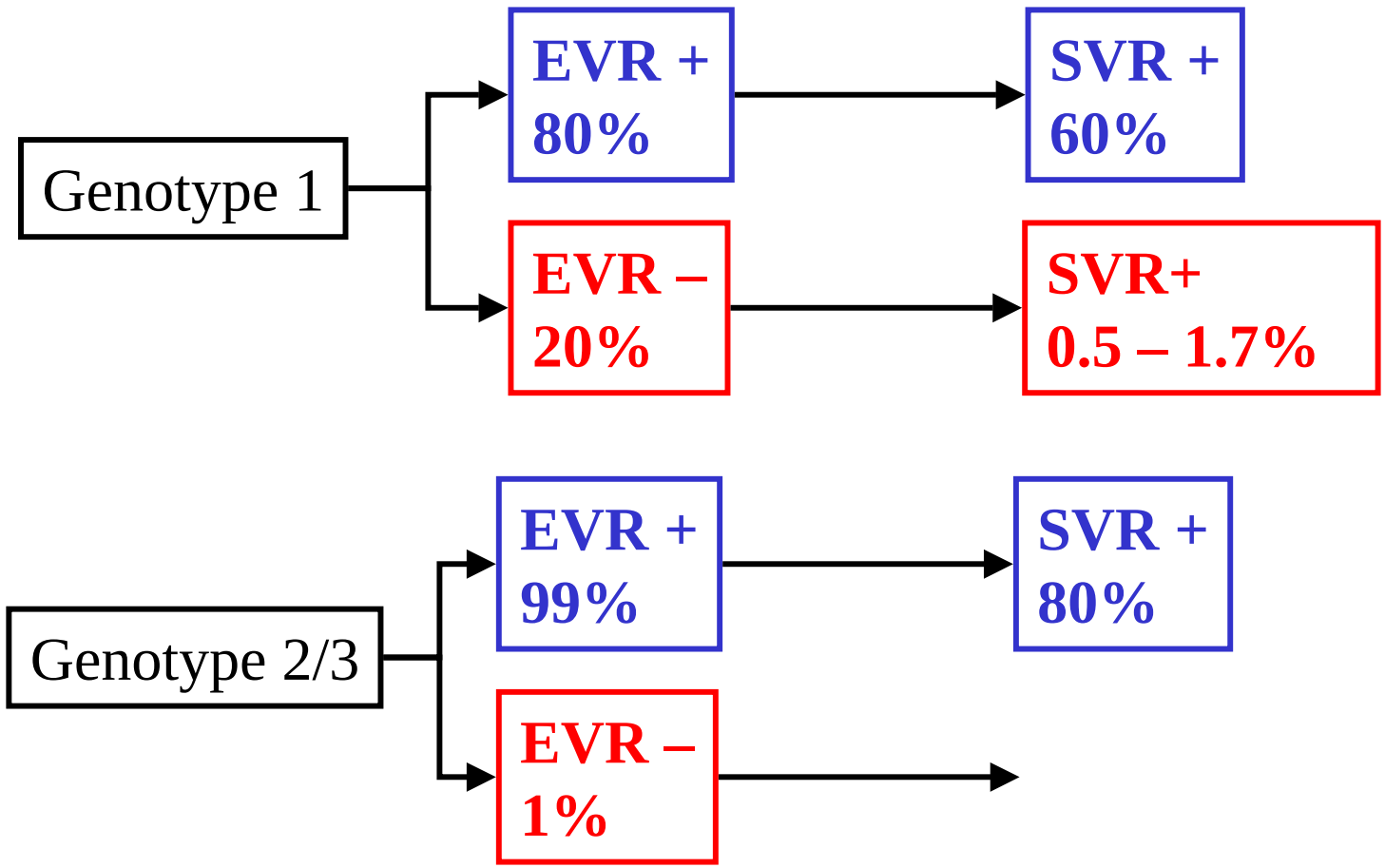
Protocol: HCV Gt 1

- Pegylated Ifn o.w. 48 weeks
  - Ifnα2a 180 μg
  - Ifnα2b 1.5 μg/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
  - Ifnα2a 180 μg
  - Ifnα2b 1.5 μg/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

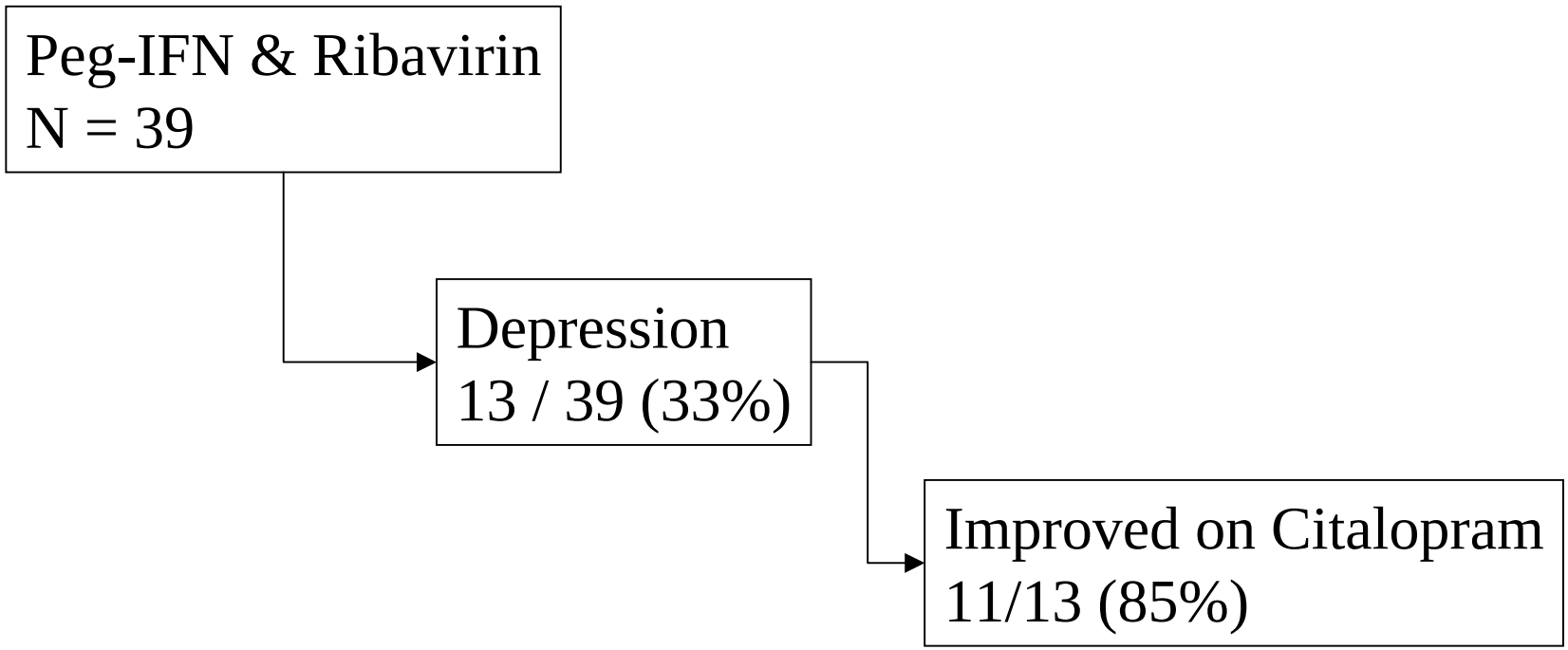
Stopping Treatment Early

- 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



Hauser Mol Psychiatry 2002

Special Cases

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

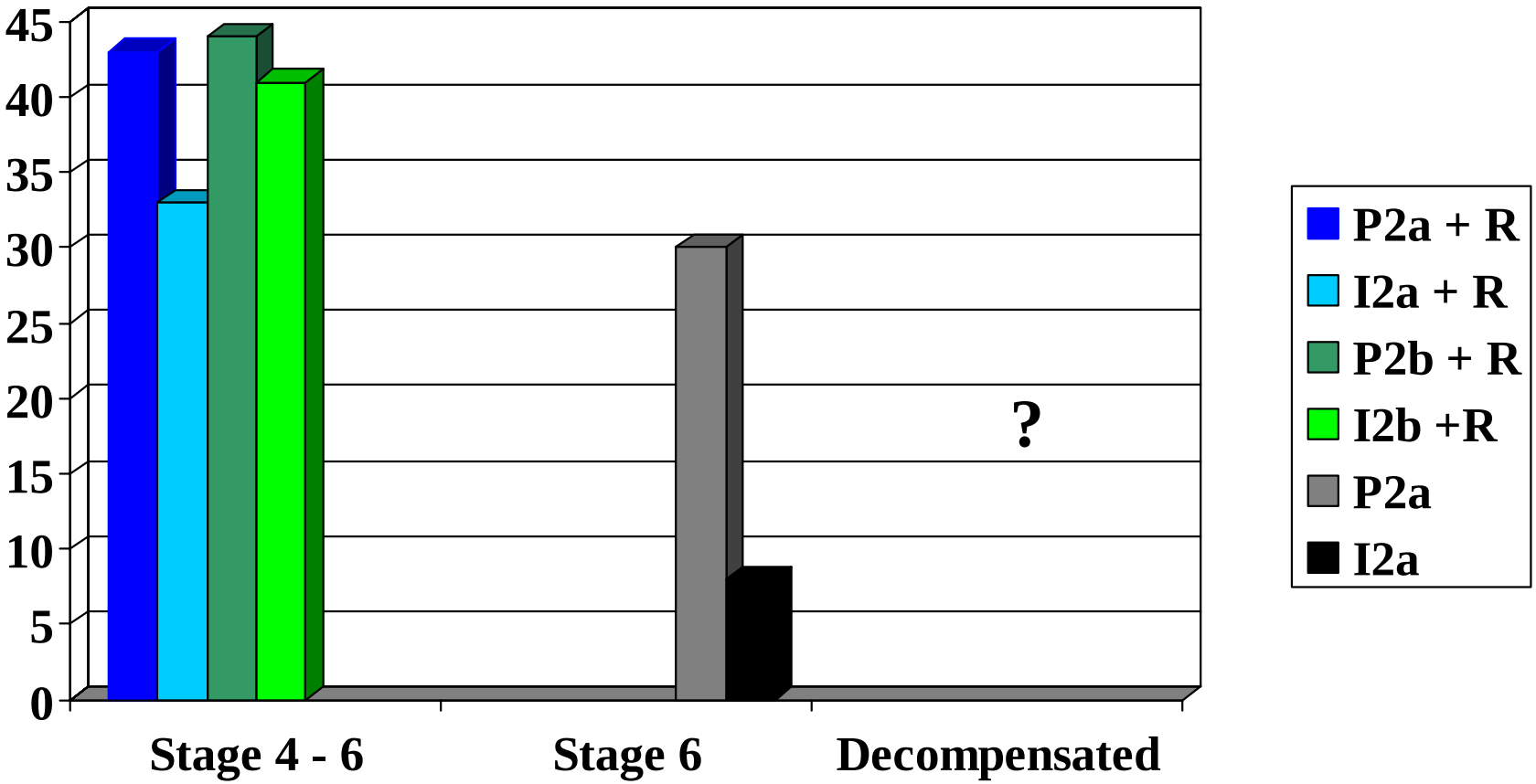
Acute HCV

- 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

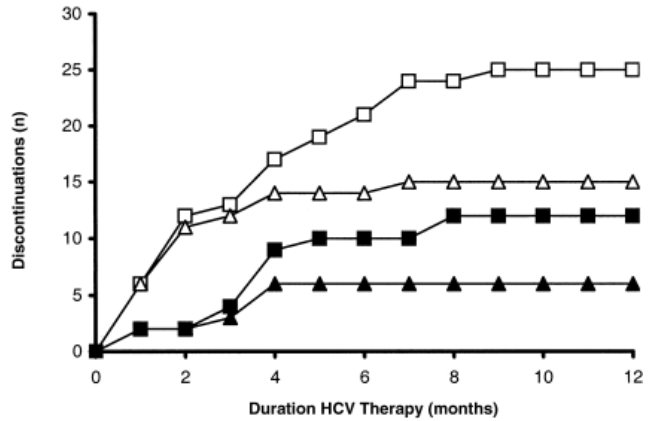
- Often mild disease
- Poor tolerance of ribavirin
  - Anaemia
  - Pharmacokinetics
- Trials required

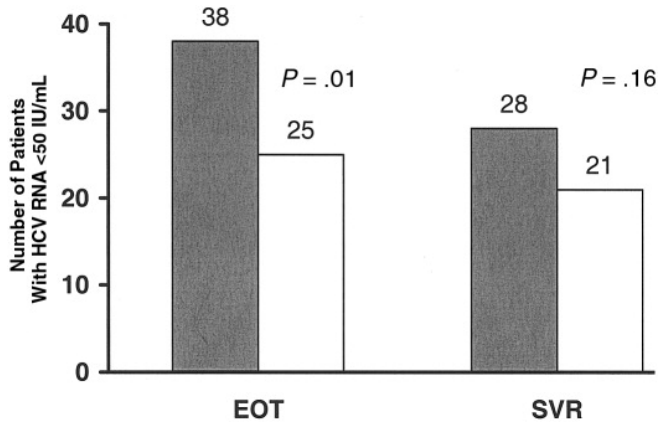
Paediatrics

- 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

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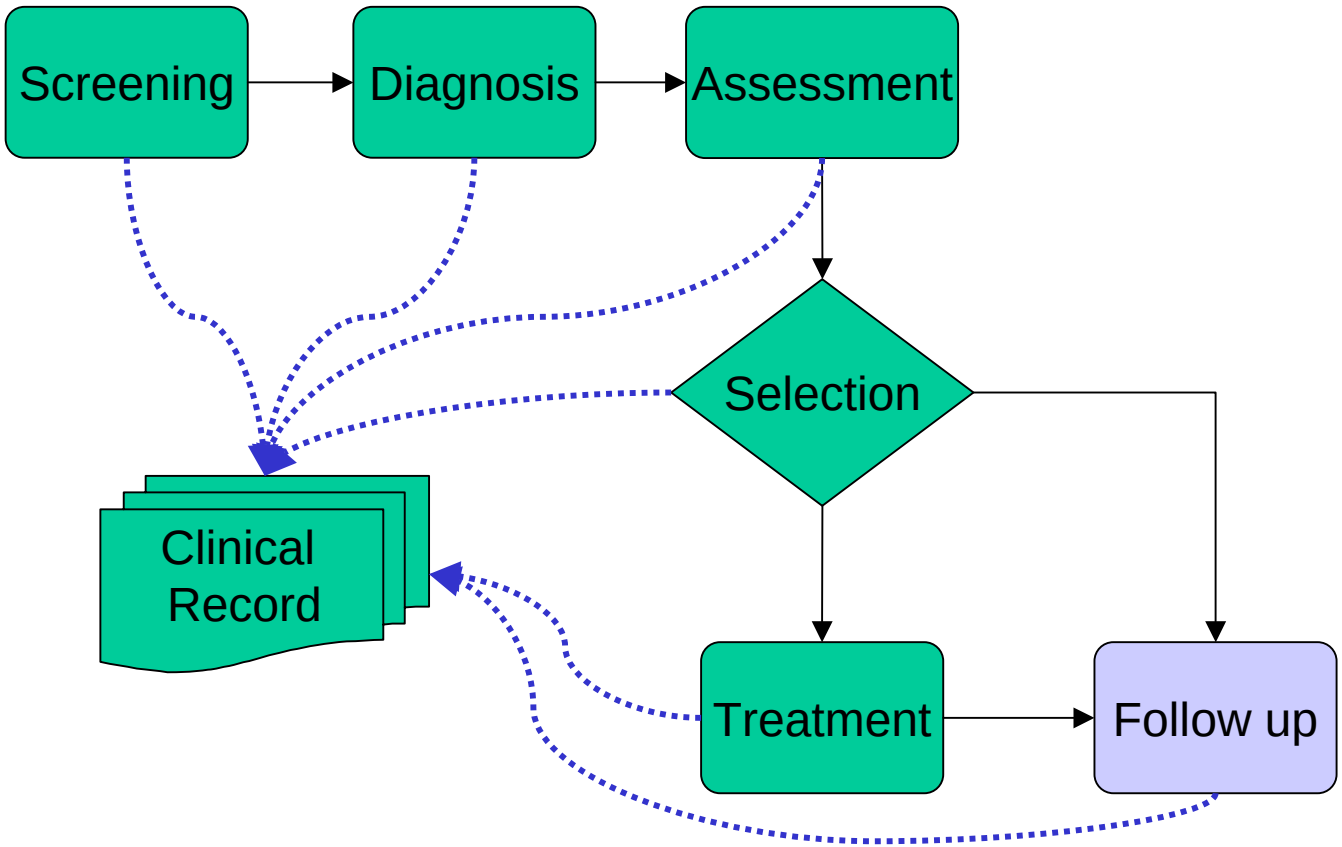

Do we achieve our goals ?

- 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

	Clinical Features					Initial			Final				
No.	Resp	Age (yr)	Sex	Source	Genotype	RNA	ALT	HAI	RNA	ALT	HAI	Liver RNA	Follow-up (yr)	Clinical Outcome
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

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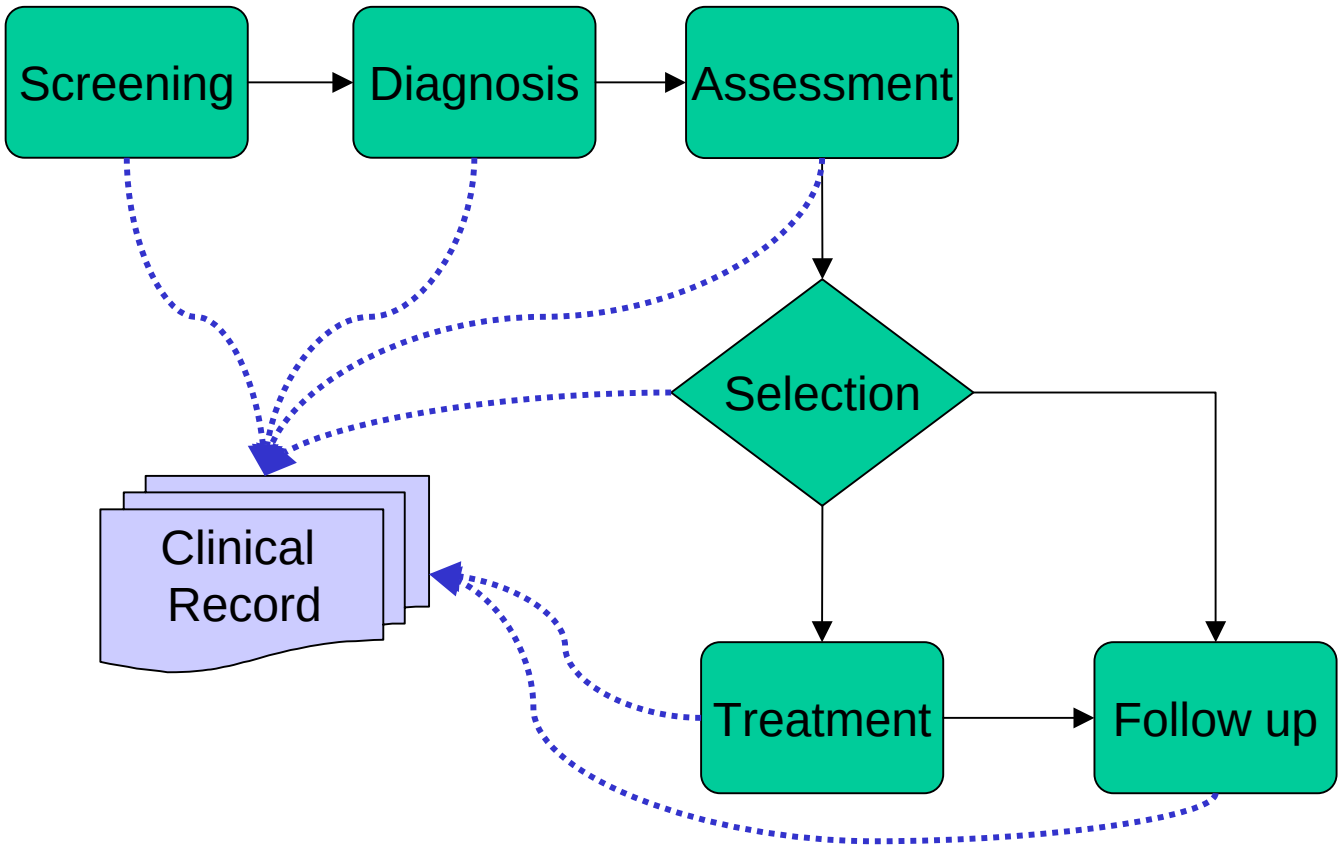

Summary

- 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.