

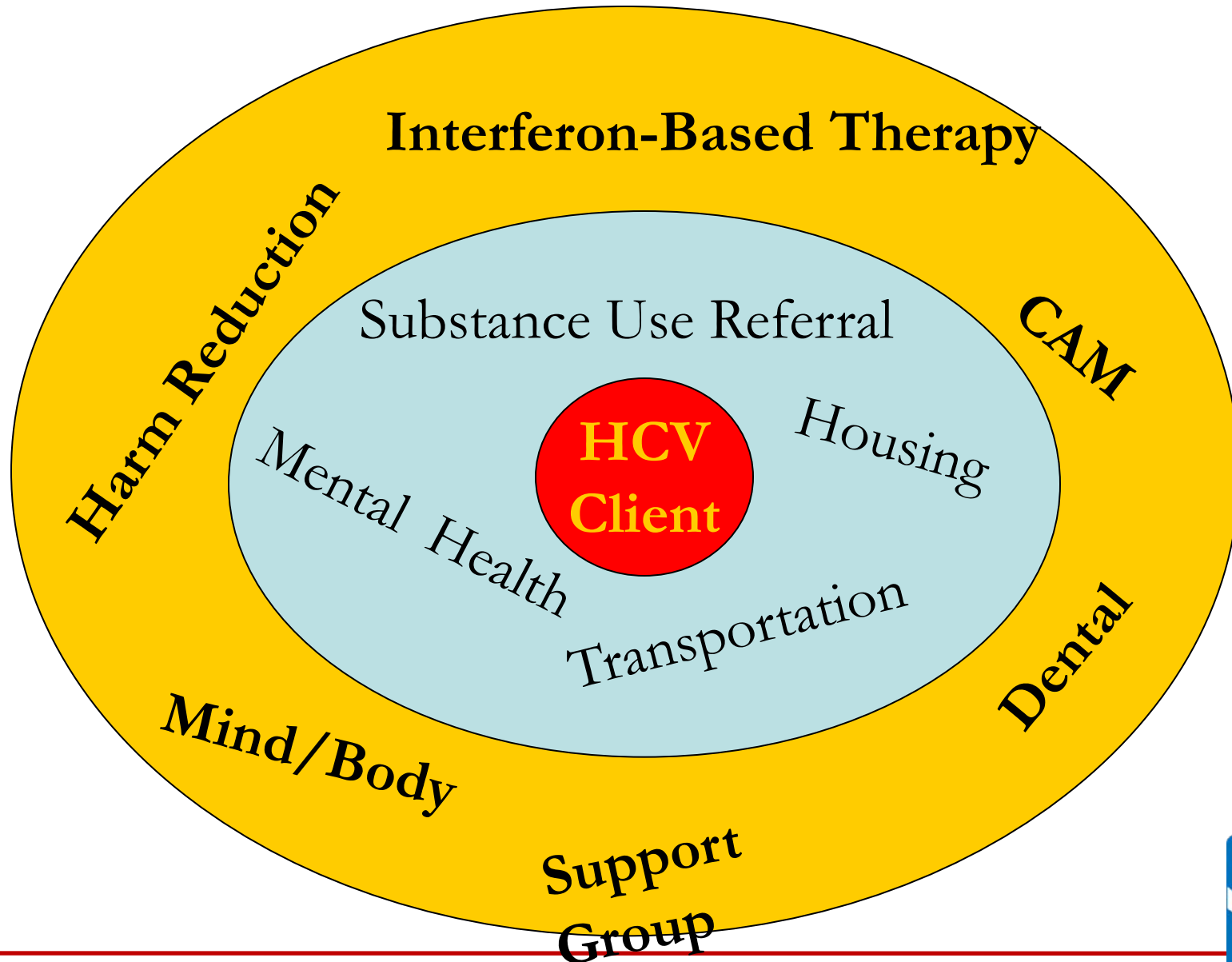


Choices, health and wellness for people with
long-term disease.

HCV
Clinical Management
Allopathic (Western) Medicine



Define Treatment



HCV Treatment Choices

- western (allopathic) medicine
- traditional Chinese medicine
- naturopathic medicine
- integrative medicine
- other client chosen options
 - **Ayurveda, homeopathy, mind-body therapies, etc.**

Treatment Choices

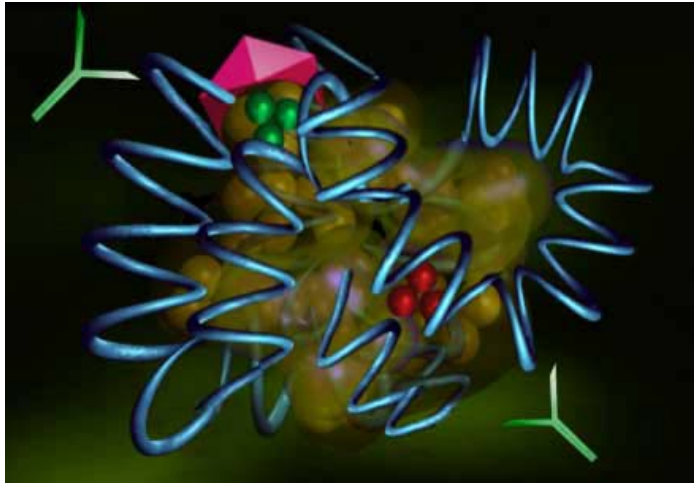
Western (Allopathic) Medicine

- standard therapy is interferon-based
- current standard of care is pegylated interferon + ribavirin
- only method of treatment proven in clinical trials to reduce HCV to undetectable levels
 - overall sustained response rate is ~50%

Interferons

- glycoproteins produced by cells in response to infection
- biological properties of interferons:
 - **anti-viral**
 - **immunostimulatory**
 - **anti-proliferative**
 - **anti-angiogenic**

Pegylated Interferons

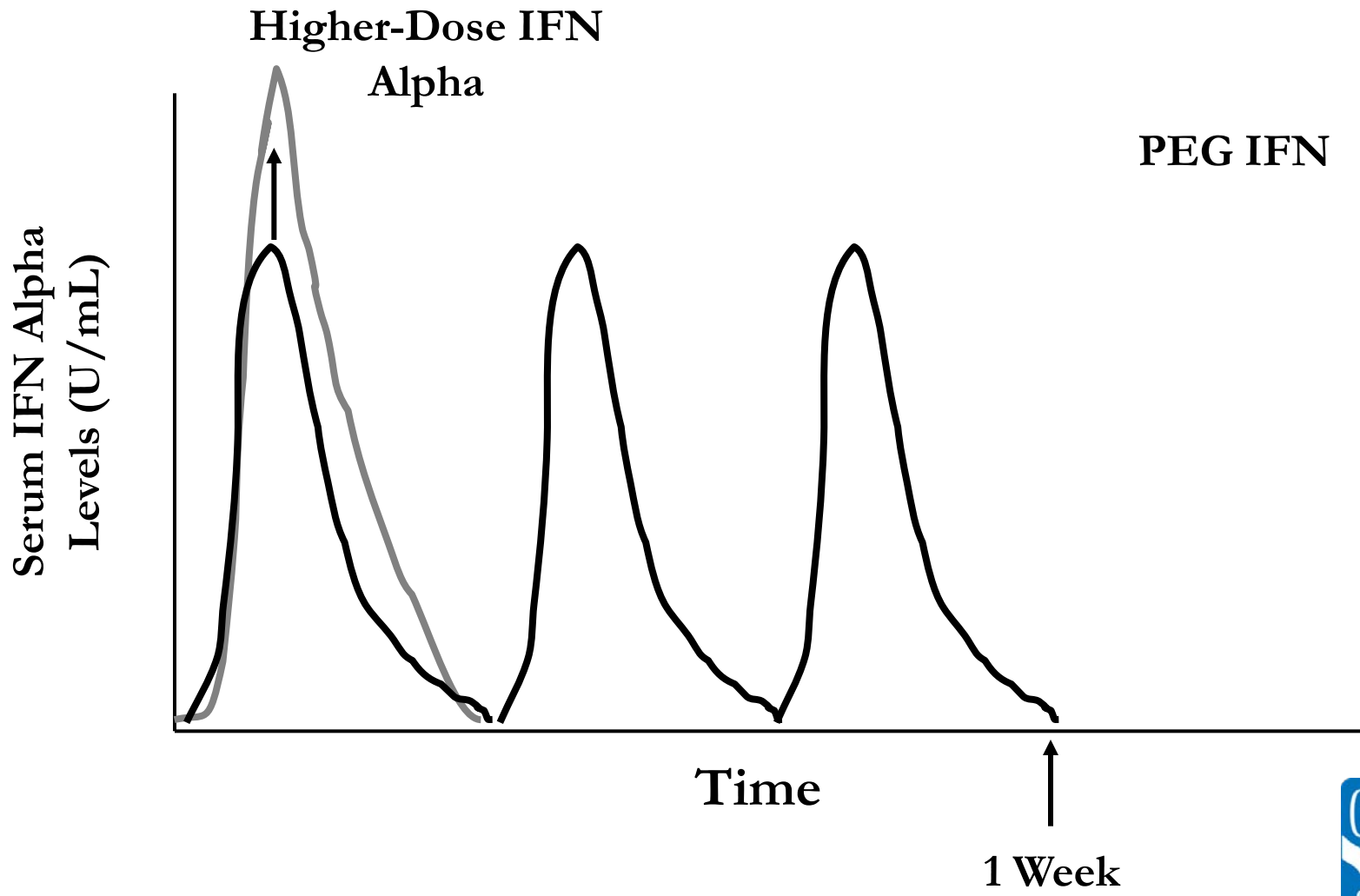


- covalent attachment of variably configured **polyethylene glycol (PEG)** chains to sites on the interferon molecule
 - delays absorption
 - decreases clearance rate
 - allows once per week dosing
 - alters properties and activity of parent compound
 - prolongs immune activation and cytokine-derived antiviral effects

Pegylated Interferons

- two pegylated interferons are now FDA-approved
 - peginterferon alfa-2a (Pegasys® - Roche/Genetech)
 - peginterferon alfa-2b (PEG-Intron® - Schering/Merck)

Optimizing Interferon-Alpha Kinetics with Pegylation



Ribavirin

- guanosine analogue
- active against many viruses *in vitro* and *in vivo*
- mechanism of action against HCV unclear
 - depletion of intracellular triphosphate pools
 - inhibition of viral-dependent polymerase
 - immunomodulatory
 - mutational deletions
- 3 manufacturers:
 - Copegus® (Roche/Genentech)
 - Rebetol® (Schering/Merck)
 - Ribasphere® (generic, Three Rivers Pharma.)
 - generic ribavirin (Novartis)

Goals of Allopathic Treatment for HCV

- primary goal
 - eradicate HCV infection
- secondary goals
 - slow disease progression
 - improve hepatic histology (function)
 - prevent hepatocellular carcinoma

Indications for Interferon-Based Therapy

- stage 2-3 fibrosis and/or grade 3-4 necrosis/
inflammation on liver biopsy
- stage 4 fibrosis (cirrhosis) with compensated liver
function
- genotype 2 or 3, viral load < 2 million IU/mL
- severe symptoms related to cirrhosis or extrahepatic
symptoms (e.g., cryoglobulinemia)
- desire to be pregnant without risk of vertical
transmission

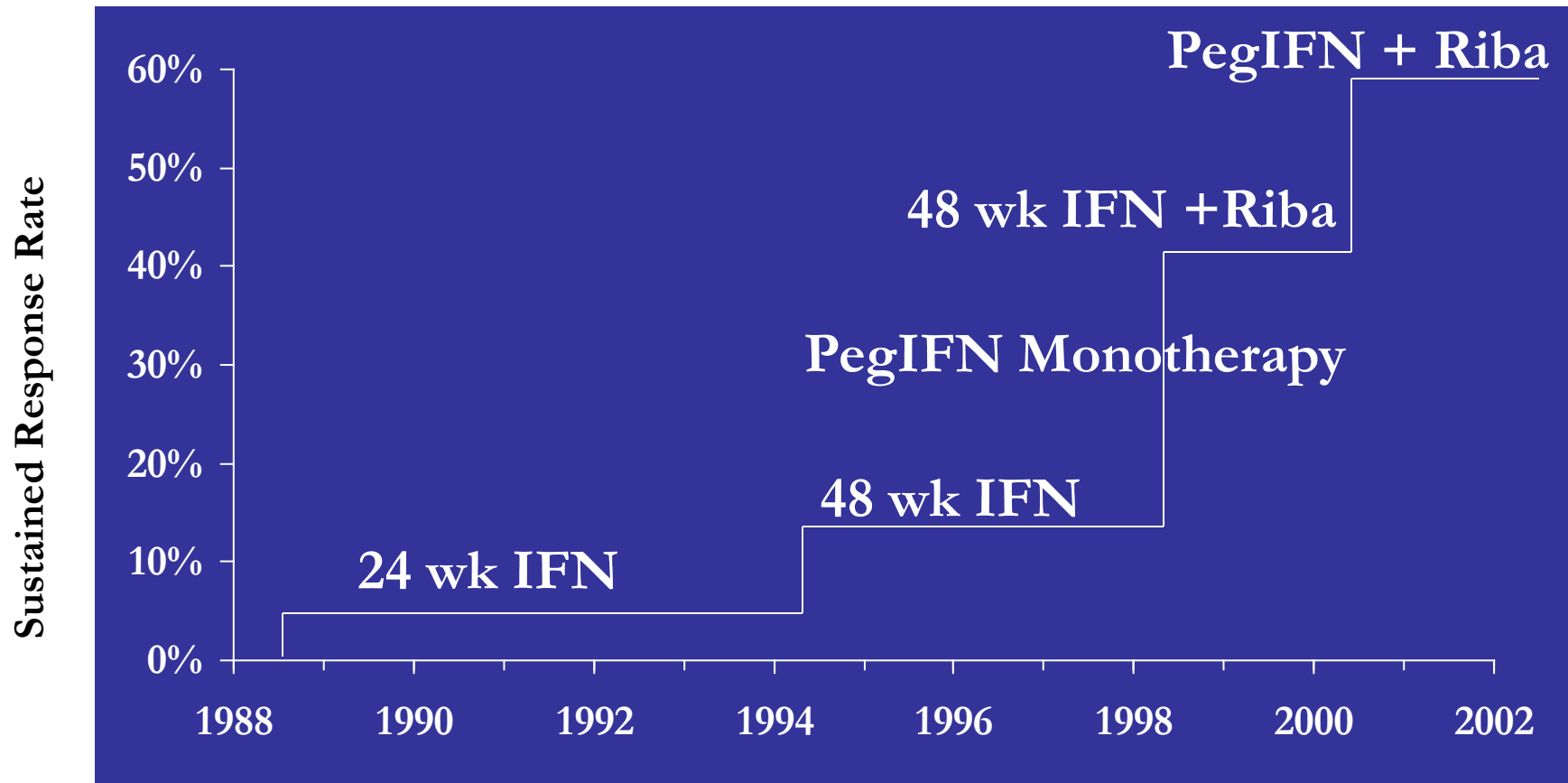


Contraindications to PegInterferon/Ribavirin Therapy

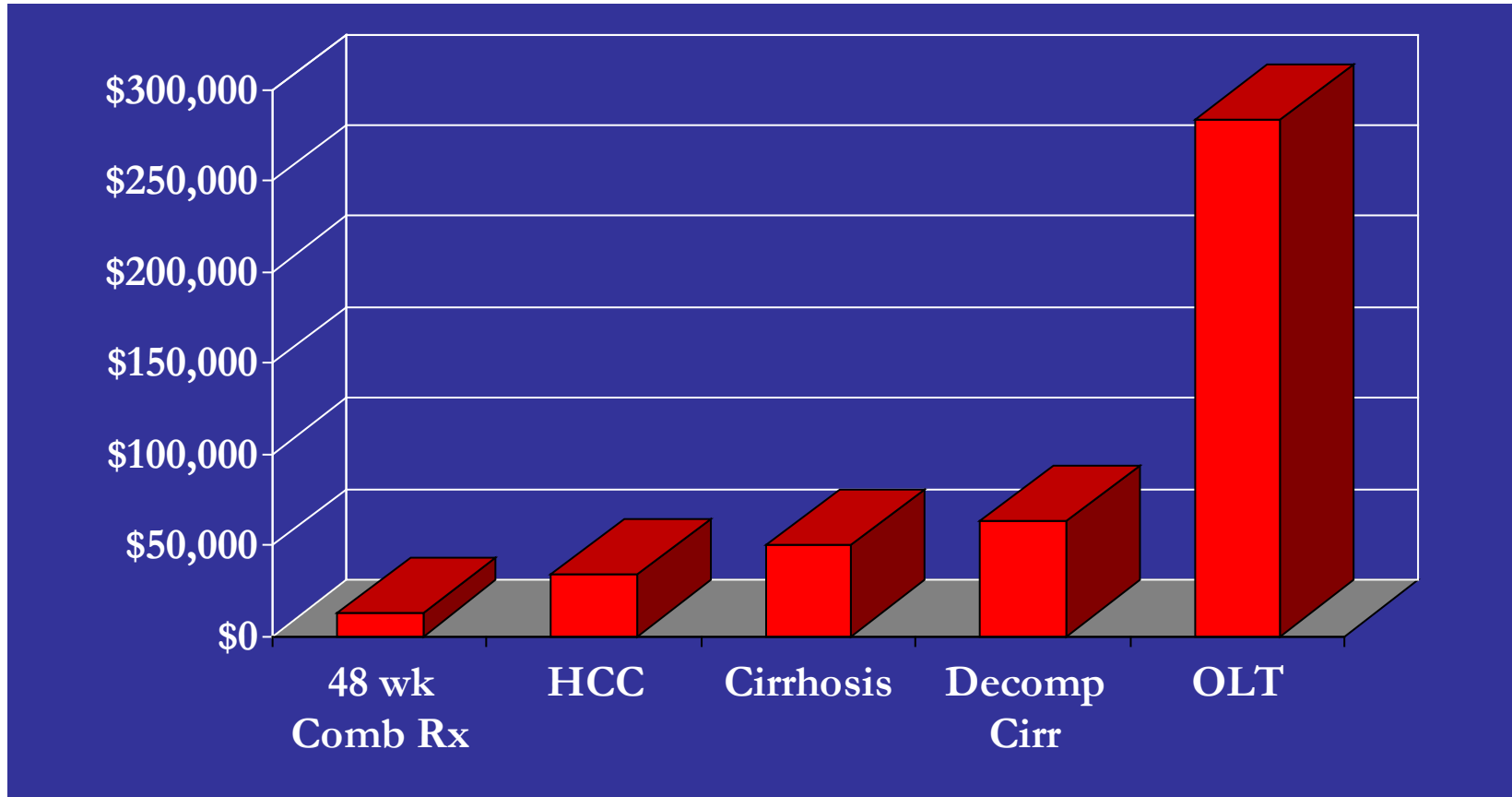
- pregnancy or breast feeding
- unwilling to practice reliable birth control
- anemia (hemoglobin <11 g/dL)
- uncontrolled cardiac or cerebrovascular disease
- renal failure
- unstable neuropsychiatric disease
- active alcohol or drug use (physician may treat active drug user if stable)
- allergy or hypersensitivity to IFN or ribavirin



Therapeutic Advances in HCV Viral Eradication



HCV Treatment vs. Complication Costs



Benefits of Sustained Viral Response

- improved liver function
- improved liver histology
- decreased infectivity
- loss of HCV RNA virus from the liver
- improved quality of life
 - increased productivity, fewer missed days of work, and less likely to work shorter hours

Sustained Viral Response (SVR)

means HCV is cured!



Other Benefits of Sustained Viral Response

- markedly decreased risk for hepatocellular carcinoma
- eliminate risk for hepatic decompensation
- improved overall survival

Standard Interferon-Based Therapy

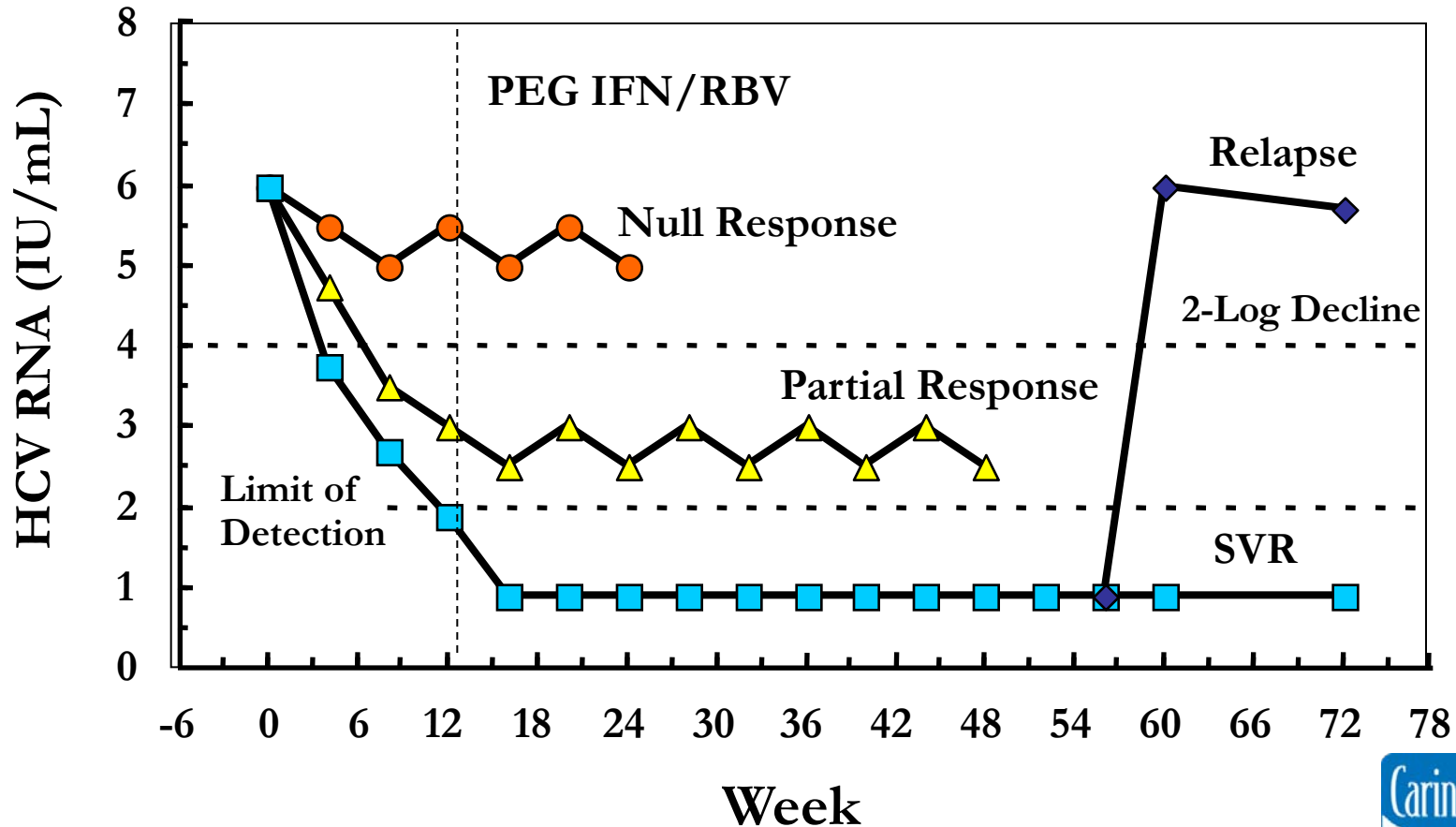
- genotype 1a/b
 - pegylated interferon alfa-2a or 2b (see below) plus ribavirin (1000-1200 mg/d) for 48 weeks
- genotypes 2, 3
 - pegylated interferon alfa-2a plus ribavirin (800 mg/d) for 24 weeks
- emerging data
 - genotype 1 - treat for up to 72 weeks
 - genotype 2, 3 - treat for 14-16 weeks
 - treatment duration is based on early (4 week) virologic response

Pegylated Interferon Dosing

- peginterferon alfa-2b – 1.0-1.5 μ g/kg once weekly
- peginterferon alfa-2a – 180 μ g once weekly



Definitions of Response to Anti-HCV Therapy



Definitions of Response to Anti-HCV Therapy

- **Relapse**

HCV RNA became and remained undetectable during treatment but reappeared after treatment stopped.

- **Non-response**

HCV RNA drops by two logs but does not become undetectable

- **Null response**

HCV RNA drops less than one log after four weeks and less than two logs after 12 weeks of treatment

- **Viral breakthrough**

HCV RNA reemerged after becoming undetectable during treatment.

Definitions of Response to Anti-HCV Therapy

- **Very rapid virological response (vRVR)**

HCV RNA has become undetectable after 14 days of treatment

- **Rapid virological response (RVR)**

HCV RNA undetectable after 4 weeks of treatment

- **Extended rapid virological response (eRVR)**

HCV RNA is undetectable after 4 weeks of treatment and remains undetectable at week 12

- **Partial early virological response (pEVR)**

HCV RNA has dropped by at least 2 logs

Definitions of Response to Anti-HCV Therapy

- **Complete early virological response (cEVR)**

HCV RNA is undetectable after 12 weeks of treatment

- **End-of-treatment response (EOT)**

HCV RNA is undetectable at the end of treatment

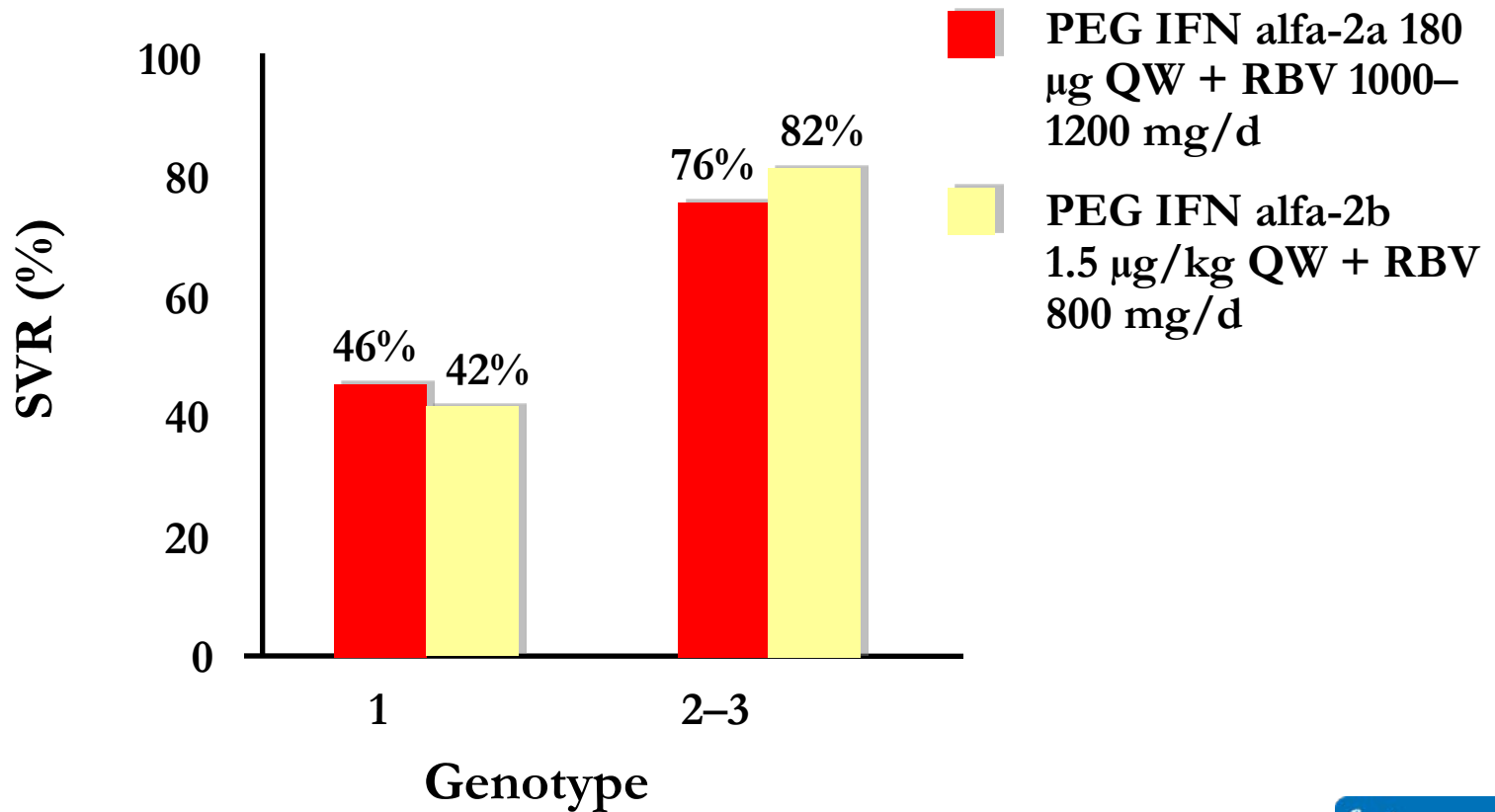
- **SVR-12**

HCV RNA remains undetectable 12 weeks after therapy is completed

- **Sustained virological response (SVR)**

No HCV RNA detectable after completion of treatment - **Cure**

HCV Response Rates with PegInterferon + Ribavirin*



*Data summary—not a direct comparative study

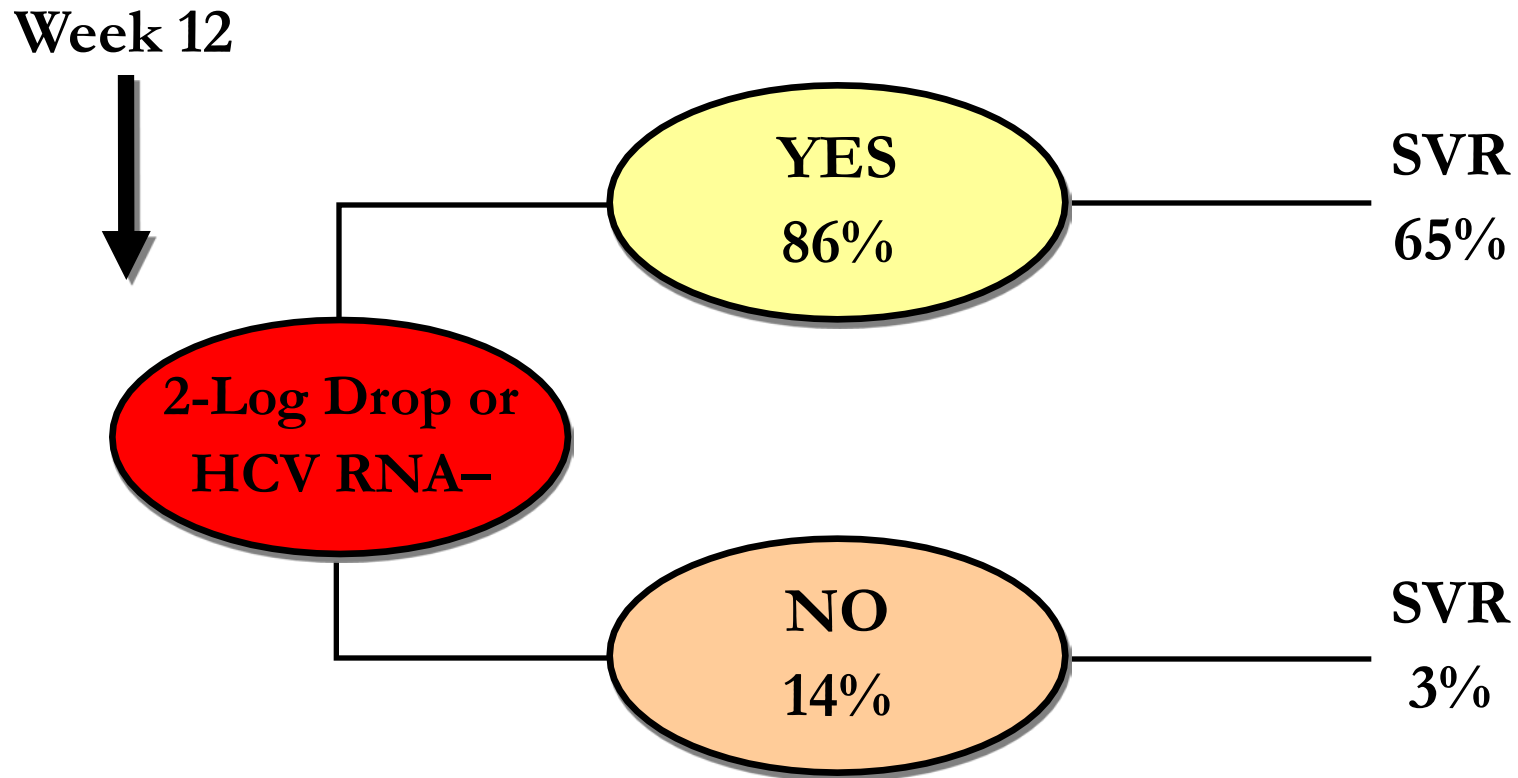
Fried MW, et al. *N Engl J Med.* 2002;347:975. Manns MP, et al. *Lancet.* 2001;358:958.



Standard Interferon-Based Therapy: Response to Treatment

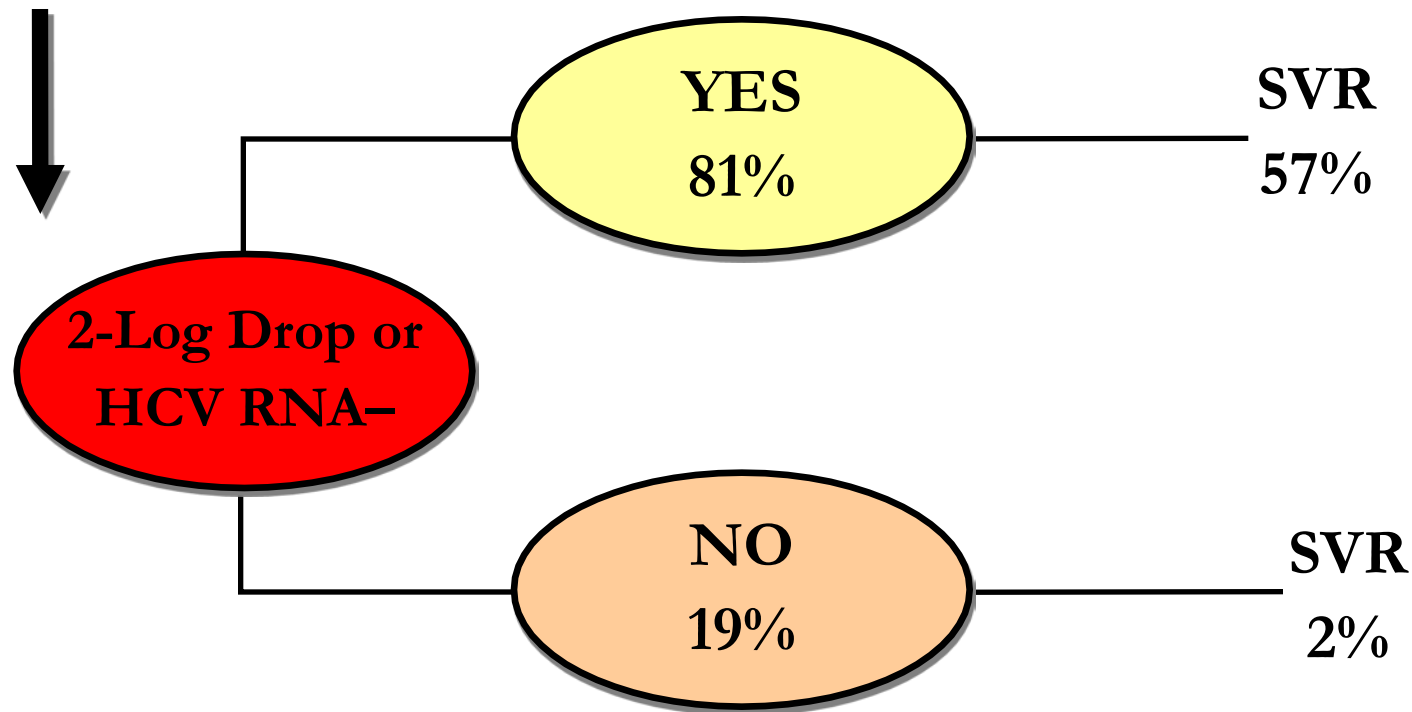
- If viral load does not drop by a factor of at least 2 logs within the first 12 weeks of treatment, therapy should be discontinued.
 - e.g., viral load of 1,000,000 IU/mL must decrease to 10,000 IU/mL to indicate an early viral response.
- Early viral response (EVR) predicts sustained viral response (SVR)

Early Virologic Response to PegIFN alfa-2a + Ribavirin



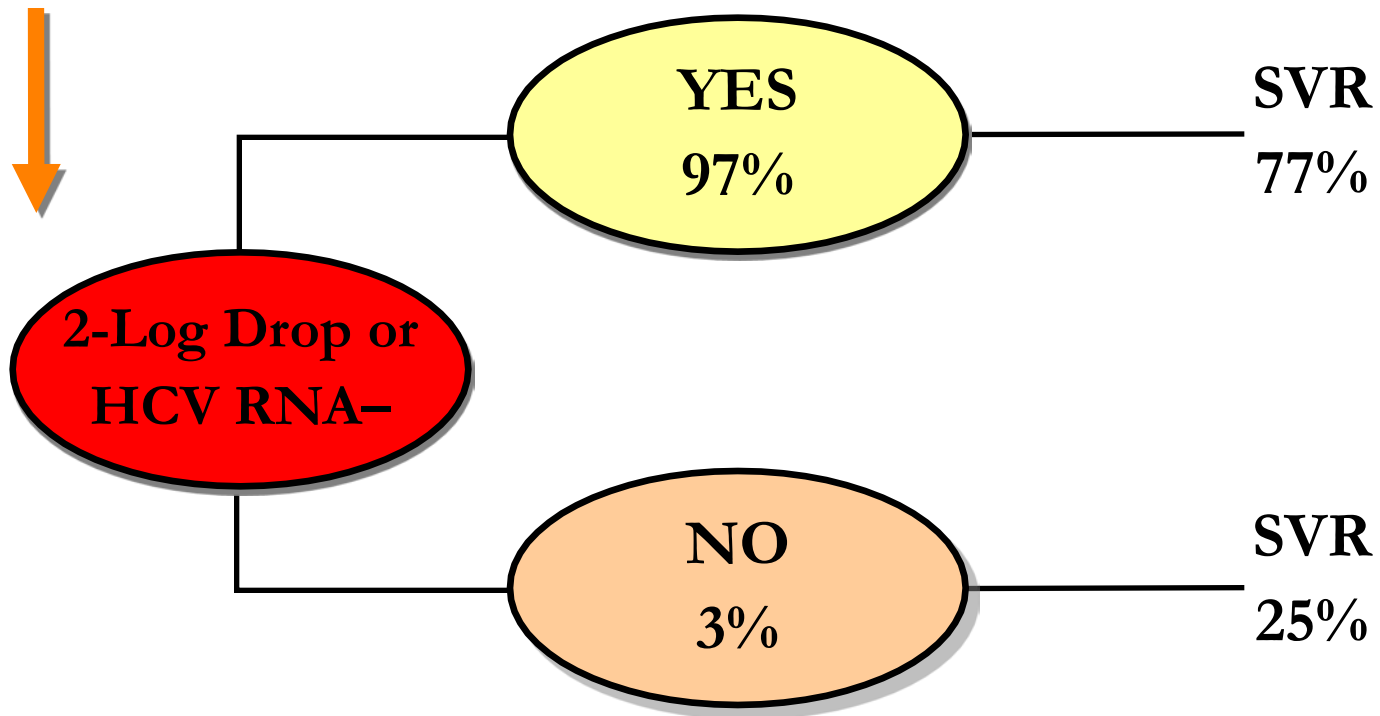
Early Virologic Response to PegIFN alfa-2a + Riba, Genotype 1

Week 12



Early Virologic Response to PegIFN alfa-2a + Riba, Genotypes 2/3

Week 12



Predictors of Response

The Old and the New

Old

- genotype 2/3
- absence of fibrosis
- low viral load
- younger age
- female gender
- lower weight

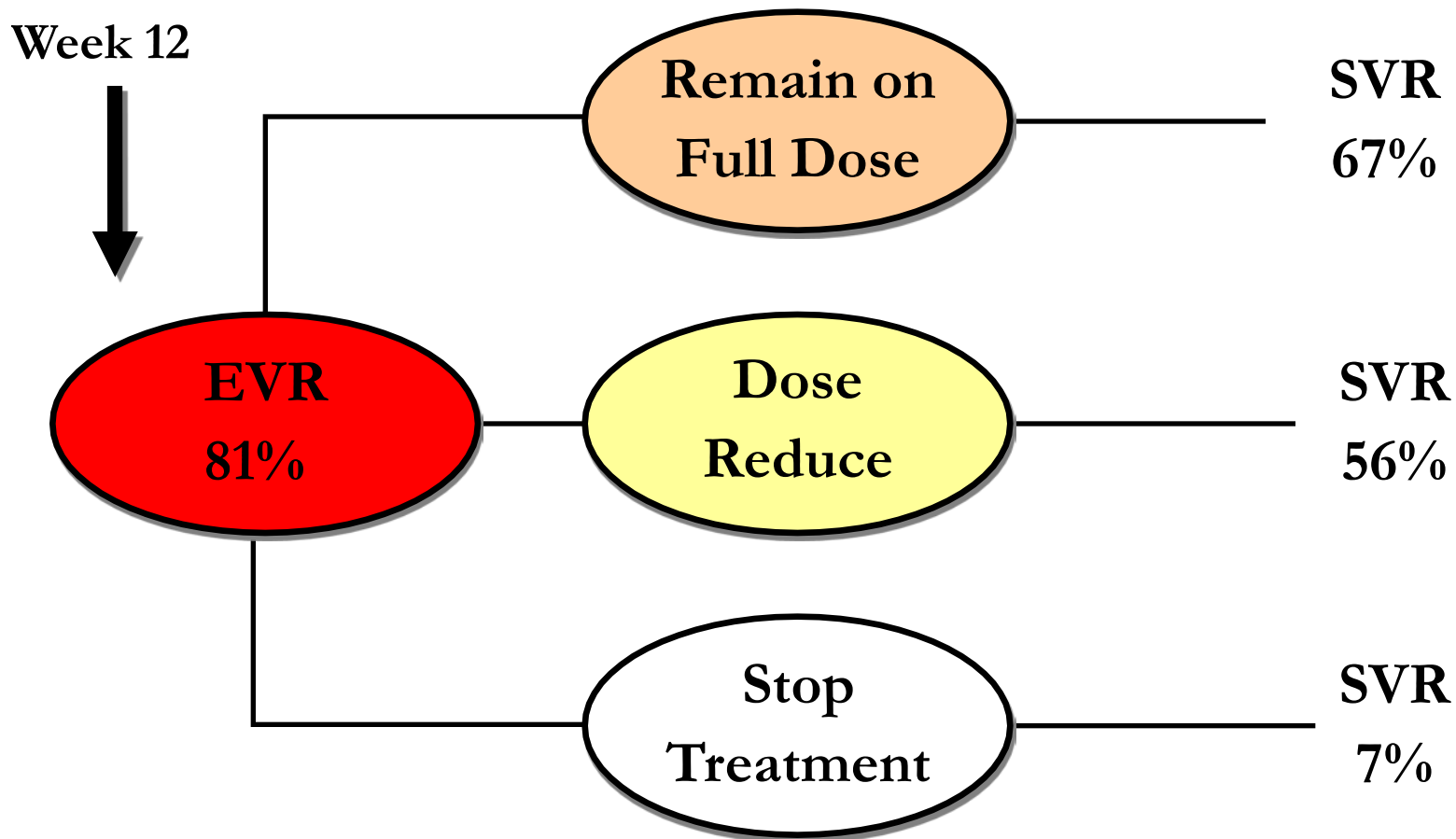
New

- ❖ genotype 2/3
- ❖ lack of steatosis
- ❖ adherence
- ❖ early viral response
- ❖ ribavirin dosage
- ❖ ethnicity
- ❖ 4-week viral clearance

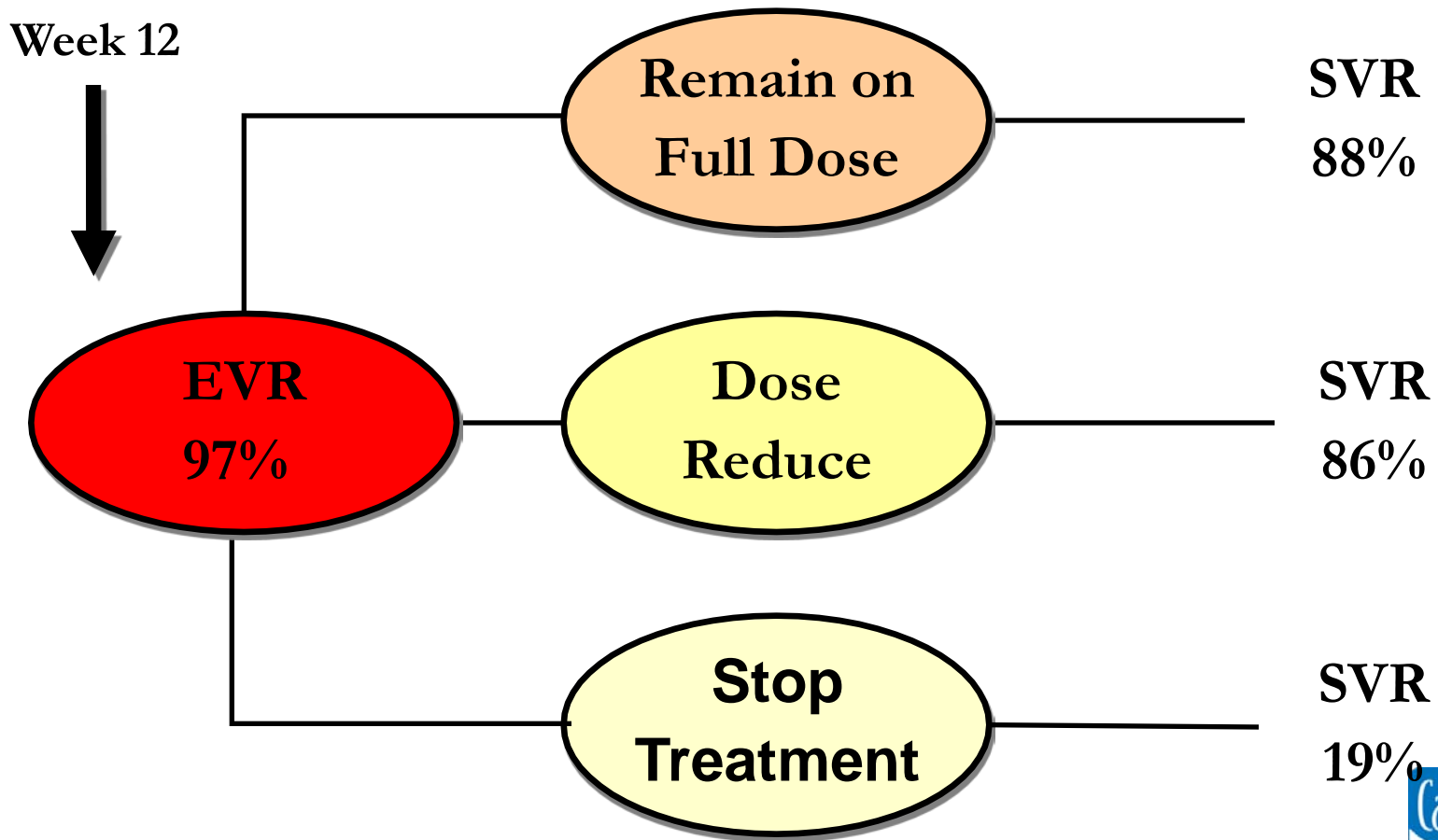
Therapy of HCV in African-Americans

- SVR lower regardless of treatment regimen
 - **pegIFN/riba, genotype 1: 26% vs. 39% in Caucasians**
- several potential factors:
 - **genetic differences**
 - **genotype 1**
 - **higher BMI**
 - **more dose reductions for neutropenia (37%)**
 - **virus relatively refractory to interferon by kinetic studies; receptor-independent**
 - **perhaps related to cell signaling differences**

Adherence to Therapy with PegIFN alfa-2a+Riba, Genotype 1



Adherence to Therapy with PegIFN alfa-2a+Riba, Genotypes 2/3



Improving Treatment Adherence

- **The patient**
 - address depression/substance abuse first
 - patient education – HCV disease, treatment regimen, consequences of non-adherence
 - support systems – family/peers/RNs/NPs/PAs
- **The regimen**
 - pill organizers/reminders
 - accessible refills
- **The side effects**
 - be proactive/educate
 - easy access to staff
 - antidepressants
 - erythropoietin



Interferon: Side Effects and Adverse Events

- flu-like symptoms
 - headache
 - fatigue or asthenia
 - myalgia, arthralgia
 - fever, chills
- nausea
- diarrhea
- psychiatric symptoms
 - depression
 - insomnia
- alopecia
- injection-site reaction
- leukocytopenia
- thyroiditis
- autoimmunity
- thrombocytopenia

Life-Threatening Complications of Interferon Therapy

- survey of 11,241 patients treated with interferon in Italy¹
 - 5 patients died (0.04%)
 - 2 suicide attempts
 - 4 seizures (other studies as high as 1%)
 - treatment may be riskier than liver biopsy
- 68,276 biopsies 1973-83 in Italy²
 - 3 cirrhotic patients and 3 patients with tumors died (deaths < 1/10,000)

1 Fattovich et al J Hepatol 1996;24,38

2 Piccinino et al J of Hep, 1986;2:165



Life Threatening Complications of Interferon Therapy (cont.)

- incidence of depression during interferon therapy:
 - 24% depressive symptoms and 12% with major depression on 3MU TIW
 - 45% major depression on 20MU/m² for 5d/wk
 - 29-31% developed depression with pegylated interferon

¹ Castera et al, Hepatology 2002;35:978

² Musselman et al NEJM 2001;344:961

³ Manns et al, Lancet 2001;358:958



Ribavirin: Side Effects and Adverse Events

- usually mild
- includes cough, shortness of breath, itching, rash, and reduced appetite
- serious adverse events associated with ribavirin:
 - hemolytic anemia
 - birth defects

Anemia Associated with HCV Combination Therapy

- anemia occurs to some degree in every patient treated with combination antiviral therapy¹
 - risk factors for severe anemia – female, older, impaired renal function, iron deficiency
- hemoglobin decreases 2-3 g/dL within the first 4 weeks of pegIFN/ribavirin²
- 9%-22% of patients require dose modification due to changes in hemoglobin^{1, 3}
- 36% of treatment discontinuations are secondary to anemia⁴

¹ Russo MW, et al. *Gastroenterology*. 2003;124:1711. ² De Franceschi, et al. *Hepatology*. 2000;31:997.

³ Rebetol PI. Kenilworth, NJ: Schering Corp; 2001.

⁴ Gaeta GB, et al. *Aliment Pharmacol Ther*. 2002;16:1633.



Consequences of Hematologic Side Effects of Combination Therapy

- **anemia**
 - fatigue, impaired QoL and reduced adherence
 - theoretic risk of myocardial ischemia, other cardiovascular abnormalities
 - ↓ RBV dose = ↓ SVR
- **neutropenia**
 - ↓ pegIFN dose
 - theoretic risk of predisposing to infection
- **thrombocytopenia**
 - ↓ pegIFN dose
 - theoretic risk of predisposing to bleeding

Prevalence of Neuropsychiatric Effects with PegIFN/Riba

pegIFN α -2a/RBV¹

- irritability, anxiety, nervousness: 33%
- insomnia: 30%
- depression: 20%
- concentration impairment: 10%
- mood alteration: 5%

pegIFN α -2b/RBV²

- insomnia: 40%
- depression: 31%
- anxiety, emotional lability, irritability: 47%
- concentration impairment: 17%
- agitation: 8%
- nervousness: 6%

1. Pegasys PI. Nutley, NJ: Roche Pharmaceuticals; 2002.
2. PEG-Intron PI. Kenilworth, NJ: Schering Corp; 2001.



Depression and HCV

- Depression is present in persons with HCV in greater numbers than in the general population.
- Because of the risk new-onset depression, worsening of pre-existing depression, or reactivation of clinical depression associated with interferon-based therapy, depression must be carefully evaluated and managed.
- Active suicidal ideation is a contraindication to interferon-based therapy.

Psychiatric Issues & Interferon-Based HCV Treatment

- pegIFN is associated with psychiatric adverse effects
 - most common reason for treatment discontinuation ^{1,2}
 - depression is leading cause of treatment nonadherence for all medical conditions
- etiology of IFN-induced depression is likely related to alterations in serotonin pathway³
- patients with psychiatric history are more susceptible to IFN-induced depression

¹ PEG-Intron PI. Kenilworth, NJ: Schering Corp; 2001. ² Pegasys PI. Nutley, NJ: Roche Pharmaceuticals; 2002.
³ Zdilar D, et al. *Hepatology*. 2000;31:1207.



Depression and PegIFN/Riba

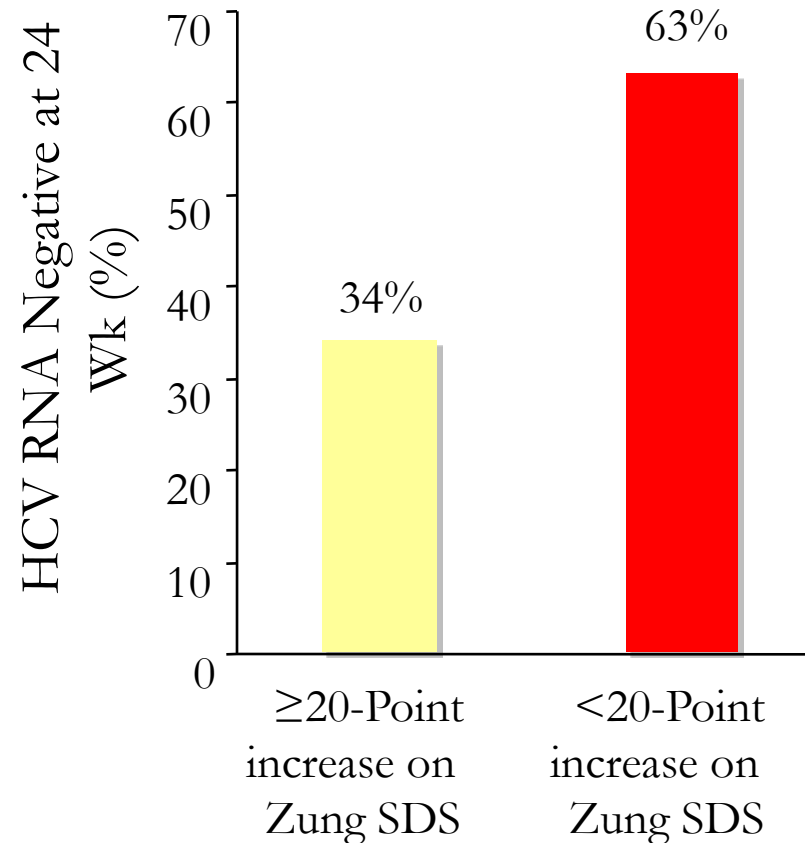
- 24-week prospective cohort of PEG IFN a-2b + fixed or weight-based RBV study
- Mean Zung Self-Rating Depression Scale (SDS) score depression rating increased from 41.8 at baseline to maximum 55.6 during 24 weeks of treatment
- 38% developed clinically significant symptoms of moderate-to-severe depression (SDS >60); 11% met criteria for major depression

Depression and PegIFN/Riba, cont.

- factors correlating with clinically significant depression
 - weight-based RBV dosing (OR 2.43)
 - past history of depression (OR 3.3)
 - baseline SDS predicted clinically significant depression
 - OR 2.0 for each 5-point increase in baseline SDS

Depression and HCV Clearance

- Prospective cohort (n = 102) from larger study of pegIFN a-2b + fixed or weight-based ribavirin
- Increased depressive symptoms associated with reduced viral clearance (p = 0.006)



Depression and HCV Treatment: Practical Considerations

- take psychiatric history
- treat/stabilize pre-existing neuropsychiatric conditions before starting pegIFN/ribavirin
- consider evaluating patients for depression every week during first 2 months of anti-HCV therapy, then at least every 2-4 weeks
- consider
 - antidepressants
 - pegIFN dose reduction/discontinuation
 - other management as appropriate
- develop relationship with mental health providers



Depression Screening Tools

- Beck Depression Inventory
 - restandardized (BDI-II)
 - better for medical patients because it emphasizes cognitive over somatic symptoms
 - completed by patient
- Center for Epidemiologic Studies-Depression Scale (CES-D)
 - older
 - used in research but not renormed
 - derived from items on Zung, Beck, and MMPI
 - less specific

Depression Screening Tools (cont.)

- Hamilton Depression Scale
 - **clinician-administered**
- structured clinical interview for DSM-IV
 - **follows DSM-IV but is cumbersome**
 - **used only in research, but clinical version available**
- symptom check list 90-R
 - **general symptom checklist, revised version**
- Zung self-rating depression scale
- Hospital Depression and Anxiety Scale-D
 - **good for establishing presence of psychiatric disease**

Interferon-Based Therapy in the Setting of HIV/HCV Coinfection

Effects of HCV on HIV Disease

- HCV probably has little if any effect on HIV progression or response to HAART, but this is controversial
- HCV adversely impacts HIV management
 - **increased toxicity of anti-HIV therapy**
 - nucleoside RTIs most common
 - hepatotoxicity of protease inhibitors not increased
 - side effects of HCV, IFN/Riba, HAART are additive
 - **potential interaction of ribavirin with ddI and d4T**

Interferon-Based Therapy in the Setting of HIV/HCV Coinfection

Effects of HIV on HCV Disease

- HIV accelerates HCV disease progression
 - increases the relative risks for cirrhosis
 - increases relative risk for hepatocellular carcinoma

Anti-HCV Treatment Efficacy in HIV/HCV Coinfection

- Apricot (Dieterich - 868 subjects, 95 ctrs, 19 countries)
 - Peg+R 40% SVR (29% genotype 1, 62% geno 2/3)
 - Peg 20% SVR (14% genotype 1, 36% geno 2/3)
 - IFN+R 12% SVR (7% genotype 1, 20% geno 2/3)
- Ribaviric (Perrone - 416 subjects, 39% F3/4, 41% dropout)
 - Peg+R 27% SVR (16% genotype 1, 43% geno 2/3)
 - IFN+R 19% SVR ??

Anti-HCV Treatment Efficacy in HIV/HCV Coinfection, cont.

- ACTG 5071 (Chung - mostly US, 134 subjects)
 - Peg+R 27% SVR (14% genotype 1, 73% geno 2/3)
 - IFN+R 12% SVR (6% genotype 1, 33% geno 2/3)

CONCLUSIONS

- HIV/HCV coinfecting patients can be successfully treated
 - responses are 10-15% lower than in non-coinfecting pts
- EVR rules hold in coinfecting patients



Treatment Options in the Setting of Mild Hepatitis C

- no antiviral therapy
- watchful waiting with biopsy every 3 years with treatment for patients found to have cirrhosis
- watchful waiting with biopsy every 3 years with treatment for patients found to have moderate hepatitis
- antiviral treatment now

Watchful Waiting

- periodic liver biopsy for mild disease
- avoids treatment
- entails periodic liver biopsy
- as patients age, likelihood of response decreases
- potential progression between biopsies