

Dilemmas in HIV and Hepatitis C Management

Brad Hare, MD

Assistant Clinical Professor of Medicine, UCSF
Medical Director, Positive Health Program, SFGH



Topics to Discuss

- HCV Background
- Assessment of liver fibrosis
- Optimal duration of treatment
- Management of treatment non-responders or relapsers
- Acute HCV
- HCC Screening

Primary Source: Care of patients coinfectd with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. Soriano, et al (AIDS 2007, 21:1073-1089).

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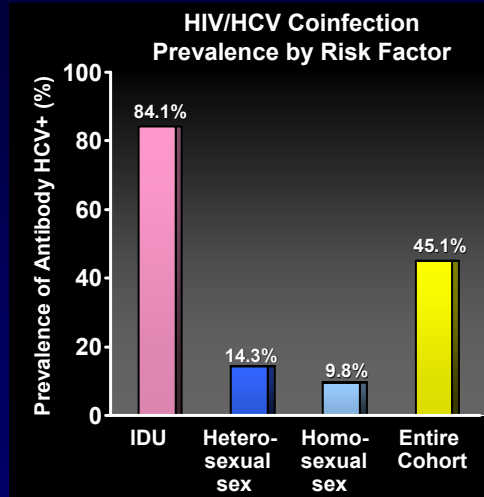
HCV in the United States

- **Incidence 230,000 infections/year in the 1980s**
 - 36,000/year in 1996
 - 28,000/year in 2000
- **Prevalence 3.9 million in US (1.8% of population or 4 times number of HIV infected individuals)**
- **40% of chronic liver disease is related to HCV**
- **10,000 deaths/year related to HCV**
- **Most frequent indication for liver transplant (30% of all liver transplants)**
 - Liver transplants for ESLD are going down in US

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Prevalence of HIV/HCV Coinfection

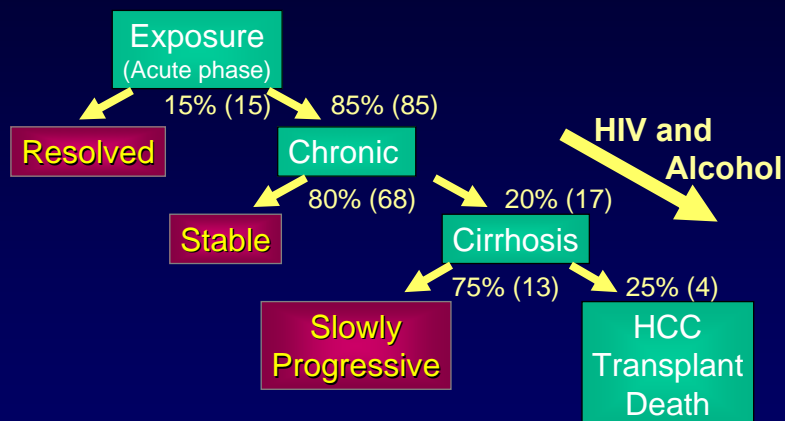
- Johns Hopkins HIV clinic
 - Urban setting
 - Prospective, longitudinal database
 - HCV-coinfection clinic established in 1997
- 1742 HIV-infected patients screened for HCV infection (1997-2000)
 - HCV+: 798 patients



Sulkowski MS, et al. *Hepatology*. 2000;32. Abstract 204.

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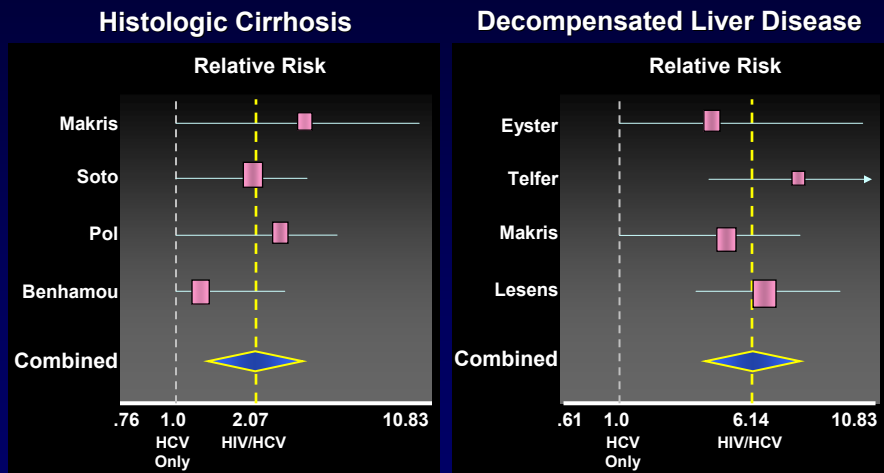
Natural History of HCV Infection



Alter MJ, *Semin Liver Dis*, 1995.
Management of Hepatitis C, NIH Consensus Statement, 1997.

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HIV Coinfection Increases the Risk of Cirrhosis and ESLD Due to HCV



Graham CS, et al. *Clin Infect Dis.* 2001;33:562-569.

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Case History: HCV Treatment

- A 38-year-old HIV/HCV co-infected man is evaluated for treatment of HCV.
- Labs
 - CD4 cell count 517 cells/mm³ (naïve to ARV Rx)
 - HCV genotype 1a
 - HCV RNA PCR = 2,800,000 copies/ml
 - ALT = 41; AST = 28; T bili = 0.3
 - Albumin = 3.8; INR = 1.0; Platelets = 156,000

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Case History: HCV Treatment

What would you do (recommend) to assess the degree of liver fibrosis?

1. Liver Biopsy
2. Standard imaging (e.g., CT, ultrasound)
3. Specialized imaging techniques (e.g., elastometry, Fibroscan)
4. Specialized biochemical markers (e.g., Fibrotest, FIB-4, etc)
5. Nothing – not necessary information at this time

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Role of Liver Biopsy

- **Pros**
 - May identify additional liver pathology
 - May motivate patient either to adhere to treatment or to defer treatment
 - Offers prognostic information
- **Cons**
 - Low risk of morbidity or complication from procedure
 - Limited resources – access to biopsy or cost
 - May not change your plan

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Progression of Liver Disease

- **67 HIV/HCV Coinfected patients with repeat liver biopsies a median of 2.8 years apart**
 - Staged by Ishak fibrosis score (0-6)
 - **28% of patients had at least a 2 stage worsening in fibrosis score between the biopsies**
 - Including 26% of patients who started with stage 0-1
 - **Fibrosis progression associated with HIV RNA >10,000 copies/mL and elevated AST**
 - Not associated with age, gender, race, CD4, ALT, ART use, EtOH, or IFN use

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Sulkowski M, CROI 2005 (Abstract #121).

Non-Invasive Assessment of Liver Fibrosis

- **Imaging Techniques**
 - Elastometry, FibroScan
- **Biochemical Markers**
 - FibroTest, SHASTA, FIB-4, others
- **Generally good at distinguishing between minimal fibrosis and advanced fibrosis**
- **Less able to discern differences in intermediate stages of fibrosis**
- **Biochemical markers less reliable in HIV**

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Case History: HCV Treatment

The patient decides on treatment. What do you use?

- 38-year-old HIV/HCV co-infected man.
Labs
 - CD4 cell count 517 cells/mm³ (naïve to ARV Rx)
 - HCV genotype 1a
 - HCV RNA PCR = 2,820,000 copies/ml
 - Liver Bx: Metavir Stage 3 fibrosis

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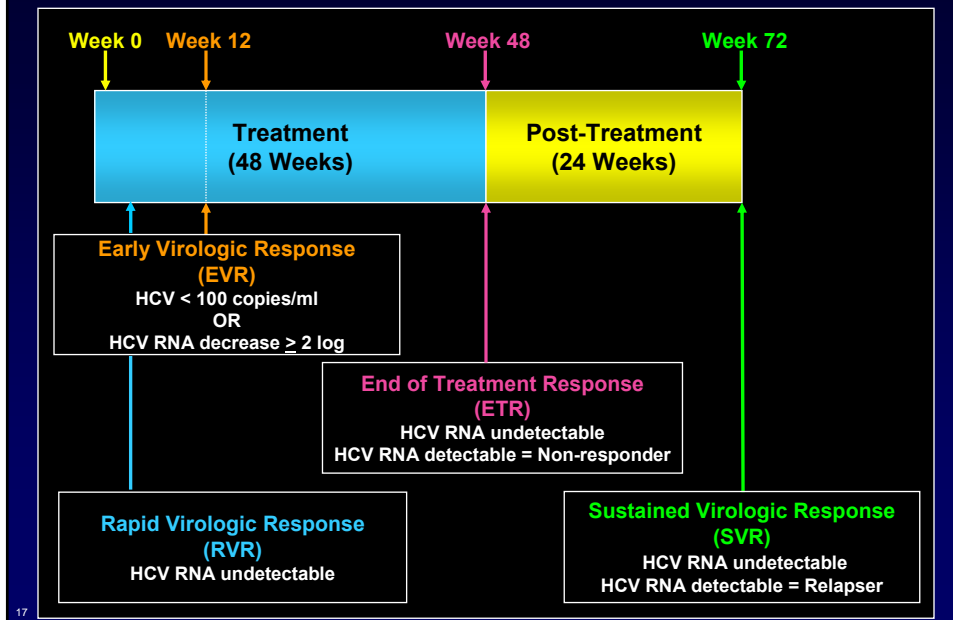
Case History: HCV Treatment

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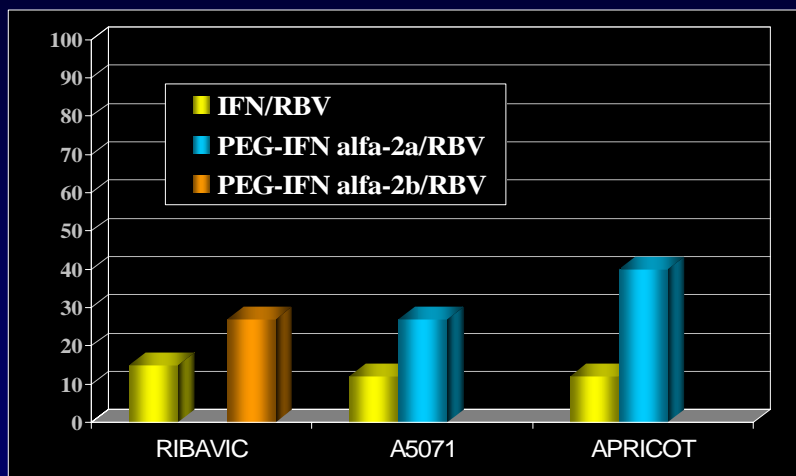
1. Interferon + Ribavirin x 48 weeks
2. Peginterferon + Ribavirin x 24 weeks
3. Peginterferon + Ribavirin x 48 weeks
4. Peginterferon + Ribavirin x 96 weeks

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HCV Therapy: Terminology



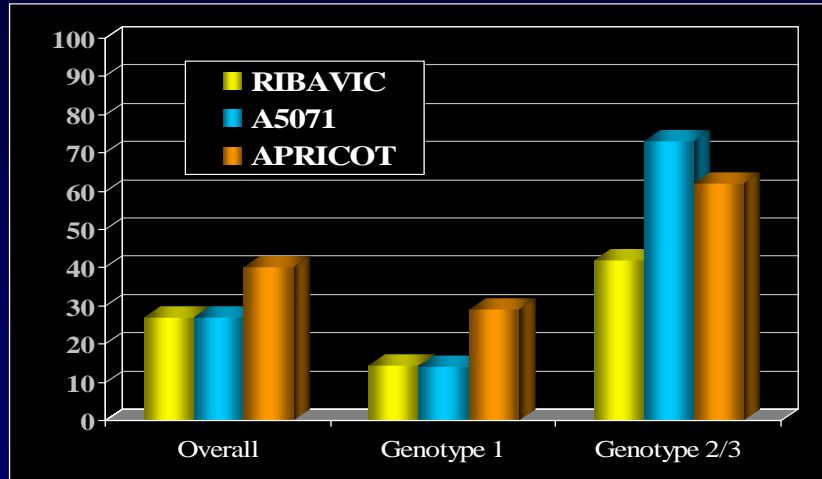
Sustained Virologic Responses in HIV/HCV Trials with PEG IFN (ITT)



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Perronne, CROI 2004; Chung, NEJM 2004; Torriani, NEJM 2004.

Sustained Virologic Responses to PEG IFN/RBV by HCV Genotype (ITT)



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Perronne, CROI 2004; Chung, NEJM 2004; Torriani, NEJM 2004.

Case History: HCV Rx

- The patient (HCV Genotype 1a) is started on Peginterferon alpha-2a plus Ribavirin.
 - His week-12 HCV RNA level is 1,300,000 copies/ml
 - Baseline pretreatment HCV RNA was 2,820,000

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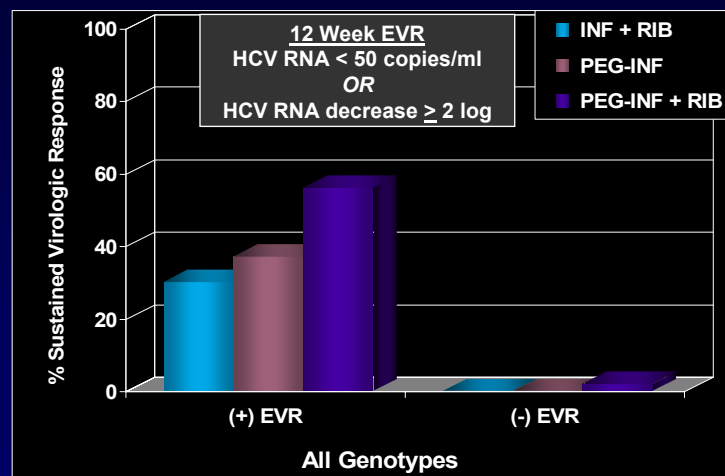
Case History: HCV Rx

What do you predict regarding the sustained virologic response (SVR) based on this 12 week HCV RNA value?

1. The 12 week early virologic response (EVR) does NOT reliably predict SVR in HIV-infected patients
2. He has approximately a 50% chance of having a SVR
3. He has approximately a 10% chance of having a SVR
4. He has less than 5% chance of having a SVR

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12 Week Early Virologic Response (EVR) Predicts SVR APRICOT TRIAL



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Torriani FJ, et al. N Engl J Med 2004;351:438-50.

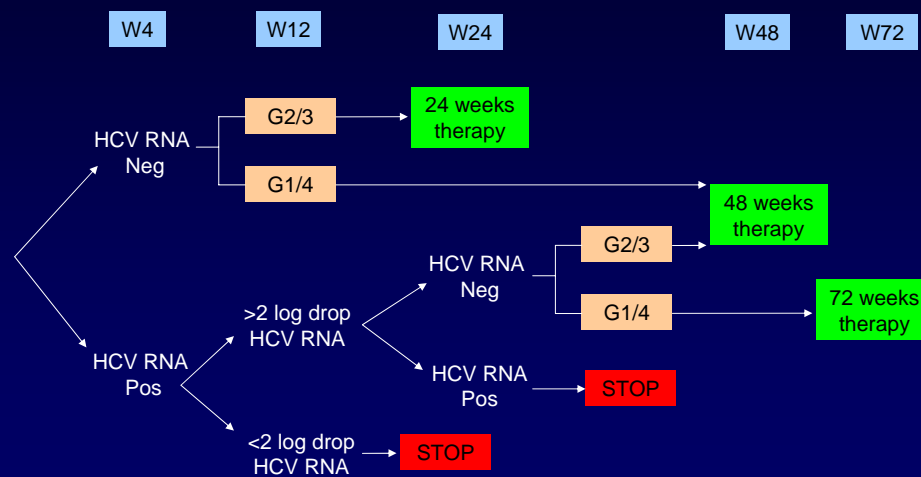
Rapid Virologic Response

- **Week 4 RVR is the strongest individual predictor of SVR**
 - **36/102 (35%) HIV/HCV Coinfected patients had RVR**
 - **Positive Predictive Value = 83%**
 - **Negative Predictive Value = 79%**

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Poordad, AASLD 2007.

Proposed Optimal Duration of Treatment



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Soriano, AIDS 2007.

Why Patients Fail HCV Therapy

- Noncompliance with treatment
- Inherently resistant to IFN
- Response not recognized
- Adverse events
 - Therapy stopped
 - Dose of pegIFN and/or RBV reduced
- Treatment not continued for a sufficient period of time

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Case History: Non-responder

The patient is interested in further treatment. What do you recommend?

- 38-year-old HIV/HCV co-infected man.
Labs
 - CD4 cell count 517 cells/mm³ (naïve to ARV Rx)
 - HCV genotype 1a
 - HCV RNA PCR = 2,820,000 copies/ml
 - Liver Bx: Metavir Stage 3 fibrosis
 - Non-responder to prior Peginterferon + Ribavirin

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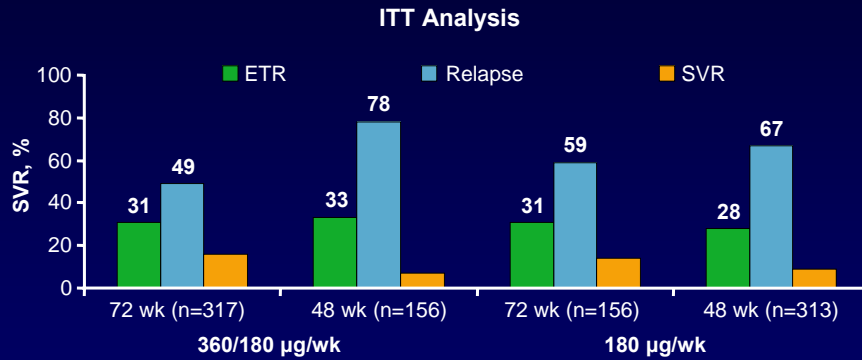
Case History: Non-responder

The patient is interested in further treatment. What do you recommend?

1. Re-treat with high dose Peginterferon (360 µg/week) + Ribavirin
2. Maintenance interferon
3. Consensus interferon
4. New oral HCV drug (e.g., protease inhibitor, polymerase inhibitor)
5. No treatment at this time – watch and wait

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Retreatment with High-Dose PegIFN alfa-2a: REPEAT



- SVR in pooled 72-wk vs 48 wk arms: 16% vs 8% ($P = .0006$; OR: 2.22; 95% CI: 1.40-3.52)

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Jensen D, et al. AASLD 2007. Abstract LB4.

Maintenance Interferon: HALT-C Final Results

- Low dose peginterferon alfa-2a arm (90 µg/week) vs control group had
 - Greater reductions in HCV RNA and ALT ($P < .0001$)
 - Greater reductions in necroinflammation ($P < .001$)
- No reduction in fibrosis or difference between arms
- No significant difference between arms in any primary outcome
 - 34.1% vs 33.8%; HR 1.01 (95% CI, 0.81-1.26)

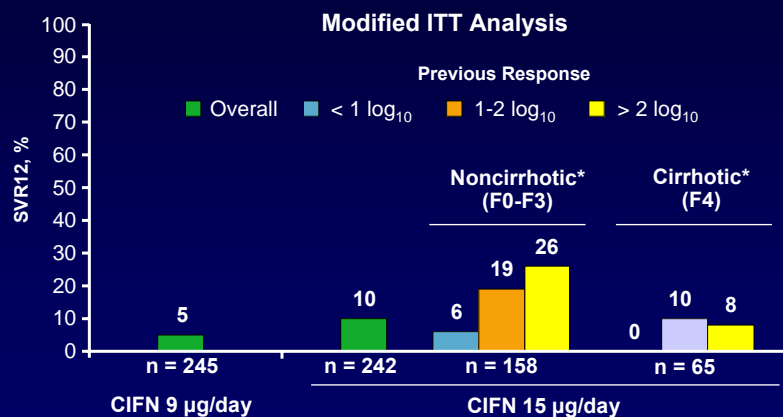
Study Arm	Baseline Fibrosis*	Any primary outcome, %	Death, %	HCC, %	CTP score ≥ 7 , %
Peginterferon alfa-2a 90 µg/week (n = 517)	3/4	36.6	2.6	2.6	3.2
	5/6	30.1	2.4	1.9	17.8
Control (n = 533)	3/4	35.5	0.6	1.6	3.2
	5/6	31.1	2.7	4.6	14.6

*Ishak Score

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Di Bisceglie A, et al. AASLD 2007. Abstract LB1.

Daily Consensus IFN: DIRECT



*Within 3 years of study entry.

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Bacon B, et al. AASLD 2007. Abstract 168.

Select HCV Antivirals in Development

Drug	Mechanism	Phase
Telaprevir (VX-950)	Protease Inhibitor	II/III
SCH 503034	Protease Inhibitor	II
BILN 2061	Protease Inhibitor	Withdrawn
ACH-806	NS4A Inhibitor	Withdrawn
Vaopicitabine (NM-283)	Polymerase Inhibitor	III
R1626	Polymerase Inhibitor	I
JTK 003/109	Polymerase Inhibitor	Withdrawn
BILB 1941	Polymerase Inhibitor	I
QU665	Helicase Inhibitor	Preclinical
DEBIO-025	Cyclophilin B Inhibitor	I

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Phased Deployment of New HCV Drugs

- **PHASE 1 (next 5 years)**
 - New Drugs + SOC trials in HIV/HCV
- **PHASE 2 (next 5 years)**
 - Shortening PEG/RBV treatment with New Drugs
 - Substitution of RBV with New Drugs
 - SOC + 1 or more new drugs for Non-Responders
- **PHASE 3 (6-10 years)**
 - Combinations of New Drugs without SOC

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Chung, R. CROI 2007. Abstract 162.

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Case History: Acute HCV

- A 34-year-old HIV infected injection drug user presents with jaundice and newly elevated LFTs.
- Labs
 - CD4 count 310 cells/mm³; HIV RNA < 75 on ARVs
 - HCV Ab positive (was negative 4 months earlier)
 - HCV genotype 1a; RNA 4,190,000 copies/ml
 - Repeat HCV RNA 3 months later is 1,200,000
 - ALT = 1190; AST = 824; Tbili = 5.0; INR = 1.1

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Case History: Acute HCV

She is diagnosed with acute HCV. What treatment would you offer her?

1. Peginterferon alone x 12 weeks
2. Peginterferon + Ribavirin x 24 weeks
3. Peginterferon + Ribavirin x 48 weeks
4. No treatment at this point

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Treatment of Acute Hepatitis C

Pros:

- Very high success rates in uncontrolled trials

Cons:

- 15% of patients may clear spontaneously and never need treatment
- Timing and duration of treatment are unclear

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Treatment of Acute Hepatitis C

- In HIV negatives, short courses of PEG-IFN with or without Ribavirin are associated with SVR rates of 71-98%
- Less well studied in HIV co-infected patients
 - Prospective study of 70 HIV+ patients in Germany with acute HCV
 - Some treated, some not. Some PEG-IFN monotherapy, some with RBV. Most for 24 weeks, some for 48 weeks
 - 11 untreated patients – 3 spontaneously cleared
 - 36 treated patients – 61% SVR

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Wiegand, Hepatology 2006. Kamal, Gastroenterology 2006. Jaeckel, NEJM 2001. Vogel ICAAC 2006.

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Case History: HCC Screening

- 49yo GWM. CD4 = 235, VL = 13,740. ARV naïve.
 - Speed user. Living in shelter.
 - HCV Ab positive. Baseline LFTs 2-5x ULN.
 - Cirrhotic – albumin 2.8; total bilirubin 2.4; INR 1.7; platelets 136k
 - HAV immune. HBsAb positive. HBsAg negative.

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Case History: HCC Screening

How would you screen him for hepatocellular carcinoma (HCC)?

1. No screening is necessary
2. Annual serum AFP only
3. Liver imaging every 6 months only
4. Both liver imaging and AFP every 6 months

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Hepatocellular Carcinoma (HCC)

- Early stage disease (<3cm tumor)
 - Surgical resection and transplantation can be curative
 - 5-year survival 50-60%
 - Recurrence of 70% at 5 years
- Late stage disease (>50% have advanced disease at dx)
 - 5-year survival is 0-17%
- Can occur in either HCV or HBV
 - HCV: Incidence of 1-4% per year in cirrhotics
 - HBV: Don't have to be cirrhotic and develops at younger age
 - Treatment of HBV has been shown to reduce incidence of HCC

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Pouti, AIDS 2004. Daniele, Gastroenterology 2004. Bruno, J Hepatology 2006.

Hepatocellular Carcinoma (HCC)

- Screening recommendations
 - Who:
 - Child's Class A Cirrhotics
 - Child's Class B&C Cirrhotics only if transplantation is available
 - Questionable: Non-cirrhotic HBV patients, especially >40yo
 - What test:
 - Liver imaging + AFP
 - Ultrasound is most common (very specific, but not sensitive), but CT or MRI are more sensitive for smaller tumors
 - AFP >400 considered "diagnostic" for HCC
 - How often:
 - Every 6 months
 - Suggestion of more frequently in HIV

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Bruix, J Hepatol 2001. Sherman, Seminars in Liver Dis 2005.