Treatment Initiation and Monitoring in HIV/HCV Co-infected Patients

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HCV Epidemiology

- NHANES IV 1999-2002[1]
  - 1.6% of the US *household* population (incarcerated and homeless not included) positive for HCV antibodies
  - Estimated persons ever infected: 4,060,000
  - Estimated persons with chronic infection: 3,200,000
  - Risk factors: injection drug use, blood transfusion before 1992, higher number of sexual partners
- 15% to 40% prevalence of HCV in US prison population[2]
  - 300,000-400,000 HCV-positive incarcerated at any time

1. Armstrong GL, et al. Ann Intern Med. 2006;144:705-715.
2. Murray OJ, et al. Correct Care. 2007;21:1,16-18.

HCV/HIV Coinfection

- In US and Europe, ~ 33% of all HIV-infected persons are HCV coinfected
- HIV coinfection exacerbates natural history of HCV infection
  - Higher levels of HCV viremia
  - Less likely to clear HCV following acute HCV infection
  - More rapid progression of HCV-related liver disease
  - Less likely to clear HCV in response to treatment

Sulkowski MS. J Hepatol. 2008;48:353-367.

Effect of HCV Coinfection on HIV Infection

- Some studies report impaired immune reconstitution on ART
  - However, effect is inconsistent and likely not clinically relevant[1]
- Patients more likely to experience hepatotoxicity on ART
- Patients 5x more likely to be admitted to hospital for liver complications[2]
- D:A:D study: liver disease second leading cause of death, after AIDS and before CV disease[3]
- With effective treatment of HIV, HCV has emerged as significant cause of morbidity and mortality

1. Sulkowski MS. J Hepatol. 2008;48:353-367. 2. Gebo KA, et al. J Acquir Immune Defic Syndr. 2003;34:165-173. 3. Weber R, et al. Arch Intern Med. 2006;166:1632-1641.

Counseling for Patients Who Are HCV Positive

- Avoid sharing toothbrushes and dental and shaving equipment; cover bleeding wounds to prevent contact of blood with others
- Stop using illicit drugs or avoid reusing or sharing syringes, needle or other paraphernalia; clean injection sites and dispose of sharps appropriately
- Do not get tattooed
- Do not donate blood, body organs, other tissues, or semen
- Limit alcohol intake

Weinbaum C, et al. MMWR. 2003; 52(No.RR-1)

Selecting Patients for HCV Treatment

- HCV antibody test positive
- Quantitative HCV RNA: confirms infection; gives information about potential response to therapy
- Genotype: gives information about potential response to therapy and duration of therapy
- Medical history, CBC, metabolic panel, PT/PTT, thyroid studies, pregnancy test for women
  - Anemia, low platelets, chronic renal disease are relative contraindications to therapy
  - Uncontrolled thyroid disease, autoimmune disease, or uncontrolled coronary artery disease are absolute contraindications to therapy
  - Ribavirin is a potent teratogen; pregnancy or inadequate contraception is an absolute contraindication to therapy

Ghany M, et al. Hepatol. 2009;49:1335-1374. Soriano V, et al. AIDS. 2007; 21:1073-1089.

Assessment of Alcohol and Substance Abuse

- Ongoing Alcohol use? Amount?
- Ongoing Substance Abuse? Amount?
- How much use is acceptable?
- What are individual clinic protocols?

Evaluating and Modifying Obesity

- Obesity is associated with nonalcoholic fatty liver disease and steatosis
- Insulin resistance may diminish response to interferon
- ? Weight criteria for treatment initiation
- ? What are individual clinic protocols?

Indicators of Decompensated Cirrhosis

- Development of ascites
- Variceal hemmorhage
- Hepatic encephalopathy*
- Jaundice
- Hepatocellular carcinoma*
  - Screen via ultrasound every 6 months for patients with cirrhosis or bridging fibrosis
  - * can occur even in incomplete cirrhosis

Morgan T, Hepatitis Annual Update 2009.
clinicaloptions.com – accessed 3.12.11

Evaluation of Liver Status and Transplantation Referral

- Prognosis via MELD (Model for end stage liver disease) score should be assessed periodically
- Calculator available at:
- http://www.mayoclinic.org/mel/mayomodel6.html
- Score greater than 10 indicates need for possible liver transplantation referral

Factor Predicting Favorable Response

- HCV Genotype2,3
- HCV RNA level <400,000
- IL-28B genotype CC
- Non-African American race
- Absence of bridging fibrosis or cirrhosis
- Body weight <75 kg
- Age <40
- Baseline ALT > 3x ULN

Mental Health Assessment

- Mental Health Referral
- CES-D or PHQ-9 questionnaires

Factors Favoring Initiation of Therapy

- Patient motivation
- Biopsy with chronic hepatitis and greater than portal fibrosis
- Cryoglobulinemic vasculitis or kidney disease
- Stable HIV disease
- Compensated liver disease
- Acceptable hematologic parameters
- Serum creatinine <1.5

Absolute Contraindications to Therapy

- Uncontrolled active major psychiatric illness
- Hepatic decompensation (hepatic encephalopathy, coagulopathy, or ascites)
- Uncontrolled HIV with advanced immunosuppression (CD4 < 100 cells/mm3)
- Known allergy or severe adverse reaction to interferon and/or ribavirin

Absolute Contraindications to Therapy

- Women who are pregnant, nursing, or are of child-bearing potential and not able to practice contraception
- Men who have pregnant partners or partners of child-bearing potential and unwilling to practice contraception during treatment and for 6 months after treatment ends
- Active, untreated autoimmune disease (e.g., systemic lupus erythematosis) known to be exacerbated by peginterferon and ribavirin
- Ribavirin is contraindicated if the creatinine clearance is less than 50 cc/min

Relative Contraindications to Treatment

- Significant hematologic abnormality: hemoglobin < 10.0 g/dl, absolute neutrophil count < 1,000/µl, or platelet count < 50,000/µl
- CD4 <200 cells/mm3
- Uncontrolled diabetes mellitus
- Patients concurrently receiving zidovudine

Relative Contraindications to Treatment

- Autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis)
- Active substance use or ongoing alcohol use if interference with adherence is anticipated
- Untreated mental health disorder
- Hemoglobinopathies (e.g., thalassemia major and sickle cell anemia)
- Sarcoidosis
- Solid organ transplantation patients

Overcoming Barriers to Treatment Initiation

- Substance Abuse Counselors
- Opioid Dependence Treatment
- Patient Education
- Peer-Based Counseling
- Group Counseling
- Clinic Based Injections

Selecting Patients for Treatment

- Control other chronic diseases (asthma, hypertension, diabetes)
- If on antiretroviral therapy for HIV, should not be receiving zidovudine, stavudine, or didanosine
- Assess for depression
  - Interferon therapy is associated with depression and suicide has been reported in patients receiving interferon for HCV therapy

Ghany M, et al. Hepatol. 2009;49:1335-1374. Soriano V, et al. AIDS. 2007; 21:1073-1089.

Selecting Patients for Treatment

- Need to differentiate between nonsignificant fibrosis and significant fibrosis
- International Association for the Study of the Liver scoring system for staging liver fibrosis

Stage	0	1	2	3	4
Score	None	Mild	Moderate	Severe	Cirrhosis
Significance	Nonsignificant		Significant		

- Assess liver fibrosis; options include
  - Liver biopsy
  - Noninvasive markers of hepatic fibrosis
  - Transient elastography

Ghany M, et al. Hepatol. 2009;49:1335-1374. Soriano V, et al. AIDS. 2007;21:1073-1089.

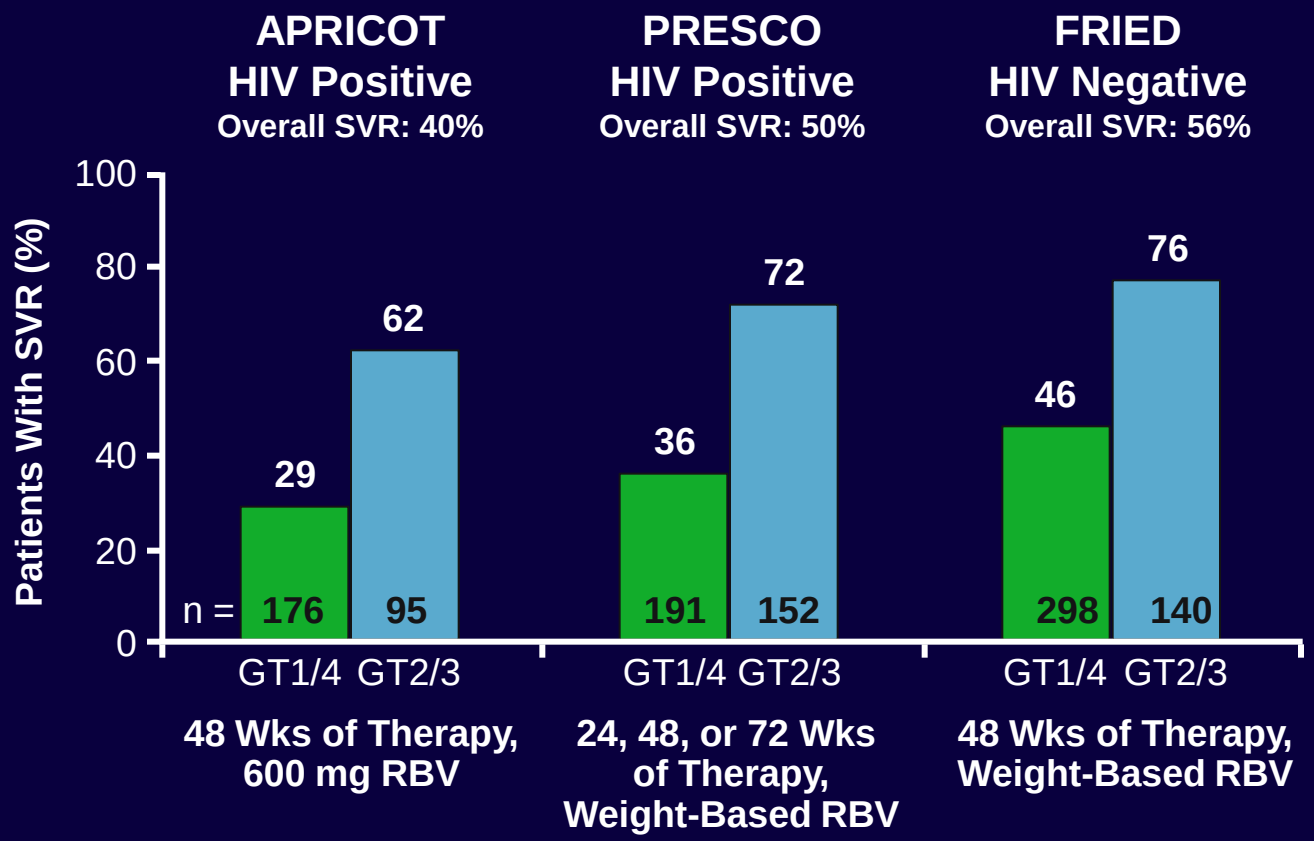
PegIFN/RBV: Current Standard-of-Care Treatment for HCV-infected Patients

Medication	Dosing
PegIFN	
PegIFN alfa-2a	180 µg SQ q7d
PegIFN alfa-2b	1.5 µg/kg SQ q7d
Weight-based RBV	
▪ < 75 kg	1000 mg PO divided BID
▪ > 75 kg	1200 mg PO divided BID
▪ Genotype 2 and 3	800 mg PO divided BID

Response Terminology

Term	Time Point	HCV RNA Level
Rapid virologic response (RVR)	Wk 4 of therapy	Undetectable
Early virologic response (EVR)	Wk 12 of therapy	≥ 2 $\log_{10}$ IU decrease from baseline
Complete early virologic response (cEVR)	Wk 12 of therapy	Undetectable
Slow to respond	Wk 24 of therapy	Undetectable (but with detectable HCV RNA at Wk 12)
End of treatment response (EOT or ETR)	End of therapy	Undetectable
Sustained virologic response (SVR)	6 mos posttherapy	Undetectable

HCV Response Rates in HIV+ and HIV- Patients Treated With PegIFN/RBV



Soriano V, et al. Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV–HIV International Panel AIDS. 2007;21:1073-1089.

Sequencing HCV and HIV Treatment

- If HIV treatment is indicated, treat HIV infection first
- Consider treating HCV first if
  - CD4+ count > 500 cells/mm^3 and antiretroviral therapy is not being initiated
  - Patient cannot tolerate antiretroviral therapy due to hepatotoxicity, since HCV coinfection may increase likelihood of antiretroviral therapy–associated hepatotoxicity

Monitoring HCV During Treatment

- CBC and differential blood count every 2-4 wks
- TSH every 12 wks
- Pregnancy test (female)
- HCV RNA
  - 4 wks (RVR)
  - 12 wks (EVR, cEVR)
  - 24 wks (STR)

Ghany M, et al. Hepatol. 2009;49:1335-1374.

Managing Adverse Effects: PegIFN/RBV

- When initiating pegIFN/RBV, tell patients what to expect prior to starting therapy
- In all cases, consider coaching and encouragement particularly if response looks promising

RBV	Surveillance/Treatment
Anemia	▪ Monitor CBC frequently ▪ Ask about fatigue, SOB, chest pain ▪ If Hb < 10 g/dL, use erythropoietin (preferred) or reduce RBV dose

Managing Adverse Effects: PegIFN

PegIFN	Surveillance/Treatment
Depression	▪ Assess mood prior to treatment and during treatment ▪ Ask about mood, sleep, suicidal thoughts ▪ Consider SSRI to treat baseline or new depression ▪ Ask mental health services to follow high-risk patients during HCV treatment
Decreased WBC and platelets	▪ Monitor CBC frequently ▪ Ask about symptoms of infection or bleeding ▪ Reduce dose of interferon
Influenzalike symptoms	▪ Acetaminophen ▪ Hydration ▪ Reduce dose of interferon
Dry, itchy skin	▪ Moisturizing lotion ▪ Antihistamines
GI upset	▪ Antiemetics ▪ Dietary supplements ▪ Appetite stimulants
Hair loss	▪ Encouragement
Insomnia	▪ Diphenhydramine or other sleep aid
Injection-site reactions	▪ Alternate injection sites; stomach and thighs are good places to inject ▪ Inject at 45-90 degree angle to skin ▪ Warm interferon in hand prior to injecting

Safety Considerations When Managing HCV/HIV-Coinfected Patients

- RBV-related anemia more common in HCV/HIV-coinfected patients than in HCV-monoinfected patients
  - Particularly common in patients also receiving the antiretroviral, zidovudine
- RBV potentiates the toxic effects of the antiretrovirals, didanosine and stavudine
  - Mediated by mitochondrial toxicity
  - Can result in fatal lactic acidosis and pancreatitis
  - Combination contraindicated

Soriano V. AIDS. 2007;21:1073-1089.

Drug/Toxicity Links

- Anemia – Ribavirin
- Thrombocytopenia – Pegylated Interferon
- Neutropenia – Pegylated Interferon

Management of Treatment Related Anemia

- For Symptomatic Anemia or Hgb <10 g/dL

- STEP 1:
  - Reduce Ribavirin by 200 mg for patient receiving 800-1200 mg/d
  - Reduce Ribavirin dose by 400 mf for patients receiving 1400 mg/d

- STEP 2:
  - Reduce Ribavirin by another 200 mg for patients who have not responded 2 weeks after dose reduction (provided current dose is 800mg/d or greater)

Management of Treatment Related Anemia – Special Situations

- Immediately reduce ribavirin dose to 600 mg/d for the following situations:
  - A sharp decline in hemoglobin in the first 4 weeks of treatment
  - Moderate to severe symptoms of anemia
  - High Cardiovascular Risk
- Dose should not be reduced below 600 mg/d

Management of Treatment Related Anemia – Special Situations

- Ribavirin dose should remain at reduced level if patient is not receiving erythrocyte-stimulating agents
- If the patient is given an erythrocyte-stimulating agent, the ribavirin dose can be slowly increased when Hgb approaches or exceeds 10 g/dL
- If Hgb persist at a level less than 8.5 g/dL despite dose reduction and erythrocyte stimulating factors, ribavirin should be discontinued

Use of Erythrocyte-Stimulating Agents

- Dosing:
- Epoetin alfa – 40,000 IU SC/ week
- Darbepoetin alfa 200 mcg SC every other week
- **Goal: 1g/dL or more increase in Hgb in 2 weeks**
  - If goal not achieved, change epoetin alfa to 60,000 IU/week, darbepoetin to 300 mcg/ every other week

Use of Erythrocyte-Stimulating Agents

- Outcome goal:
- Hgb between 10-12 g/dL but not exceeding 12 g/dL
  - Hgb of >13 g/dL resulting from erythrocyte stimulating agents has been linked to increased mortality and cardiovascular complications
- Some experts will maintain the use of erythrocyte stimulating agents and slowly increase ribavirin dose when Hgb is between 10-12 g/dL

Management of Thrombocytopenia

- Primary strategy is pegylated interferon dose reduction
- Therapy should be discontinued for platelet count less than 25,000 cell/mm^3

Management of Neutropenia

- Primary strategy is peginterferon dose reduction
- Permanent discontinuation rarely necessary, but temporary discontinuation necessary for:
  - ANC < 400 cells/mm^3
  - Active bacterial infection AND ANC < 500 cell/mm^3
- Permanent discontinuation for neutropenia which is refractory to peginterferon dose reduction and filgrastim (G-CSF)

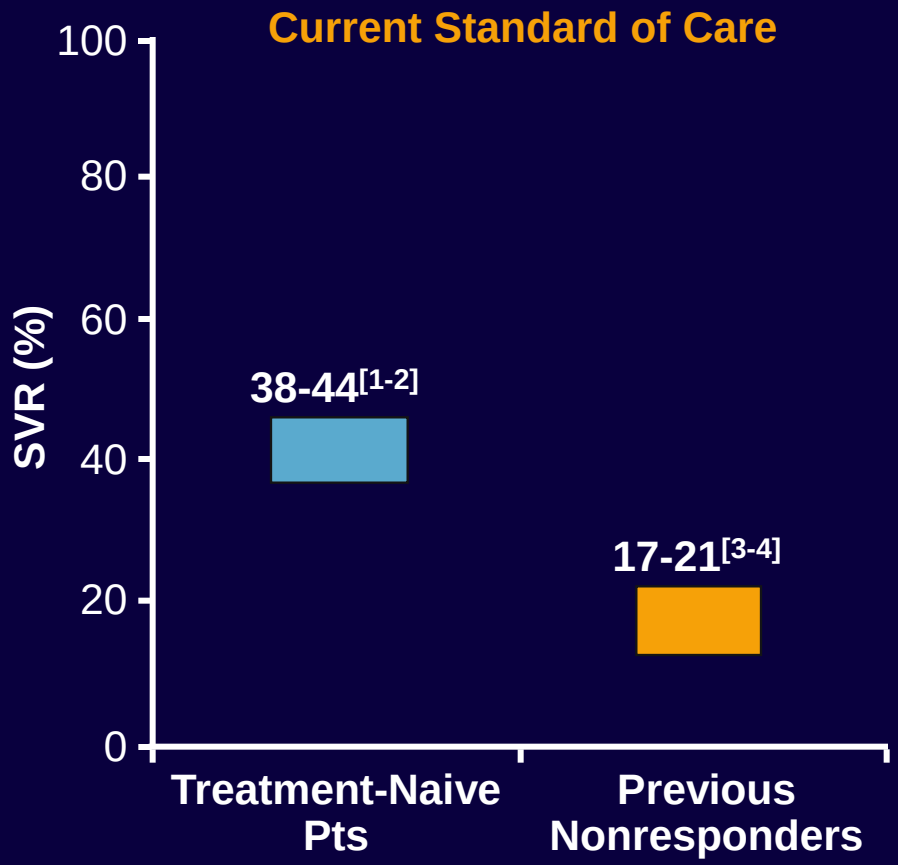
Use of Filgrastim (G-CSF)

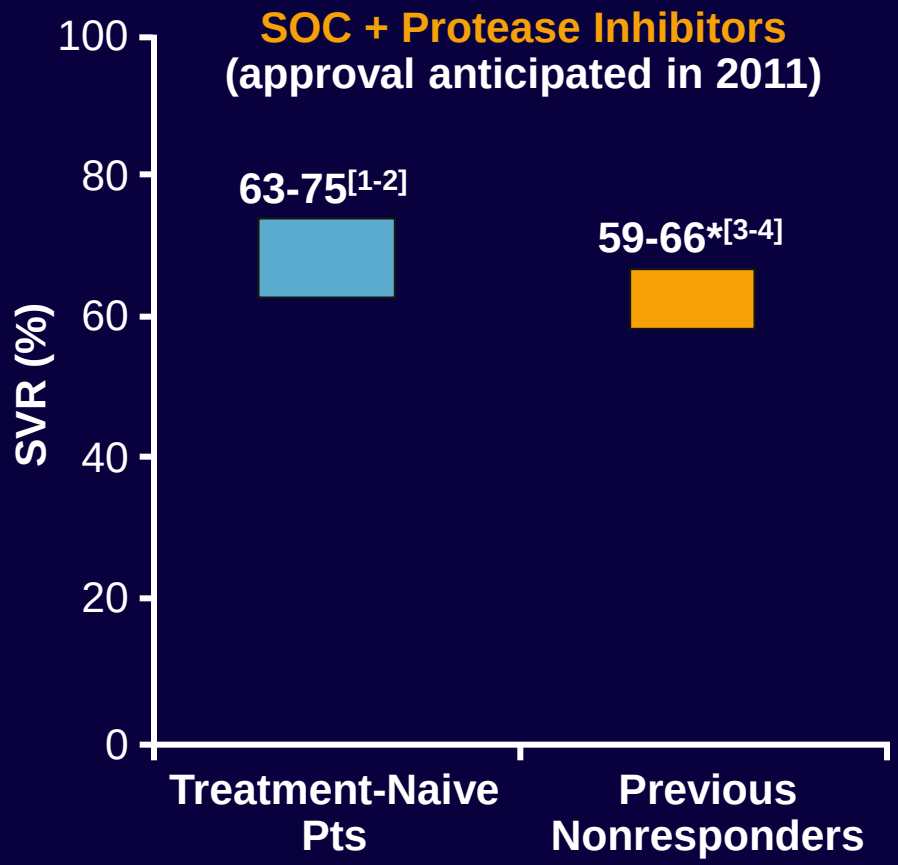
- For ANC <500 cells/mm^3
- Neutropenia which dose not respond to level 1 peginterferon dose reduction
- G-CSF 300 mcg SC once or twice weekly
- Monitor ANC at least 1-2X weekly
- Redose based on response
- G-CSF may need dosed 2-3x/week in some cases to maintain ANC >500 cells/mm^3
- Hold G-CSF for ANC > 750 cells/mm^3

What Is New in HCV Evaluation and Treatment

- *IL28B* haplotype testing
  - Predicts response rate to pegIFN/RBV
  - Commercially available
- Protease inhibitors for genotype 1 HCV
  - FDA approved first HCV protease inhibitors in May 2011
  - HCV protease inhibitors in combination with pegIFN and RBV may increase response rate and potentially decrease length of therapy in genotype 1 patients

SVR Rates With BOC and TVR in GT1 Treatment-Naive and -Experienced Pts



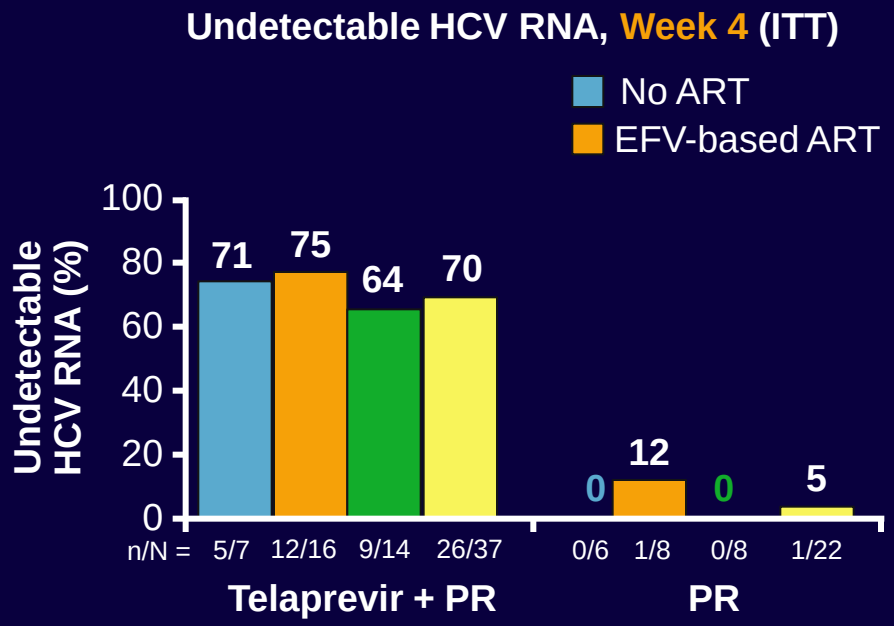


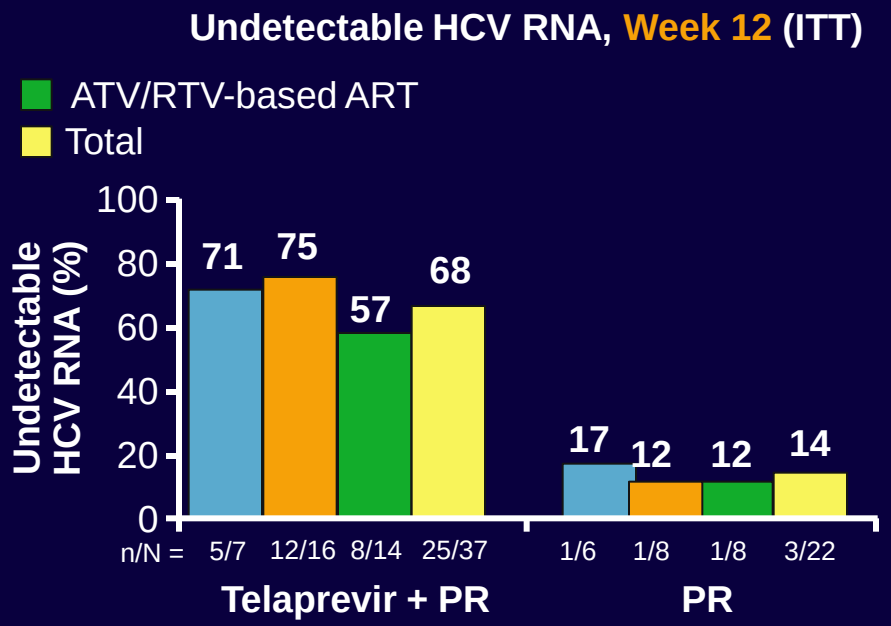
*Overall rates in protease inhibitor–containing arms, not stratified by type of prior nonresponse.

1. Poordad F, et al. N Engl J Med. 2011;364:1195-1206. 2. Jacobson IM, et al. AASLD 2010. Abstract 211. 3. Bacon BR, et al. N Engl J Med. 2011;364:1207-1217. 4. REALIZE Study. EASL 2011. Abstract 5.

Study 110: High Rates of Early Response With TVR + PR in Coinfected Patients

- Similar efficacy results observed with or without concurrent ART
- Nausea, pruritus, dizziness, fever more common with TVR vs placebo
- Pharmacokinetic interactions with ATV or EFV not clinically significant





Sulkowski M, et al. CROI 2011. Abstract 146LB. Graphics used with permission.

Key Points About HCV Protease Inhibitors

- FDA approved in May 2011
- Only tested in genotype 1
- Will be used in combination with pegIFN and RBV
- Expected to reduce total duration of treatment and increase SVR in significant number of patients
- Will also increase adverse effects and regimen complexity
- Drug interactions with many antiretroviral drugs

Summary

- HCV and HCV/HIV coinfection are common
- Targeted screening for those at high risk of HCV infection is an effective means of diagnosis
- All HCV-positive patients should receive education regarding prevention of transmission of HCV to others
- HCV infection treatment in the setting of HIV coinfection requires careful patient selection and treatment monitoring