

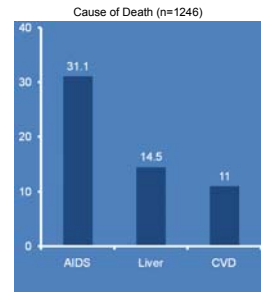
HIV/HCV Coinfection

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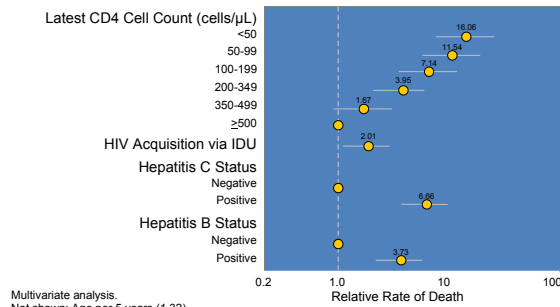
Liver Disease is a Leading Cause of Death in HIV-Infected Patients

- D:A:D study (n = 23,441)
 - HCV positive, 22.5 %
 - Active HBV infection, 6.8 %
 - HAART, 88.7 %
- Liver deaths (n = 181)
 - HAART, 97%
 - CD4 cell count at time of death, 196/mm³
 - HIV RNA undetectable at death, 55%



Weber R, et al. Arch Intern Med. 2006;166:1632-1641.

Independent Predictors of Liver-Related Death

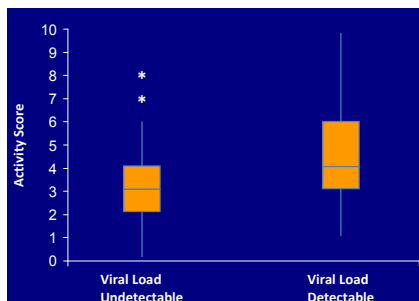


Multivariate analysis.
Not shown: Age per 5 years (1.32).
Weber R, et al 2006

Management of Liver Disease in HCV/HIV-infected Persons

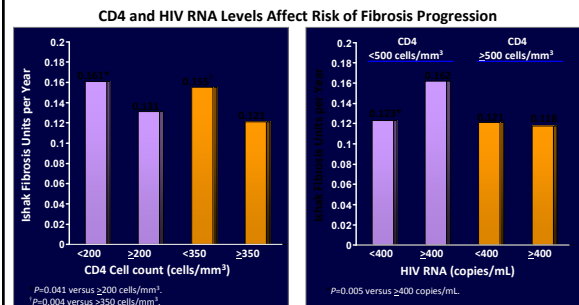
- Antiretroviral therapy
 - Improve inflammation
 - Reduce liver deaths?
- HCV treatment
 - SVR is beneficial
 - Response can be predicted early ~ 4 weeks
 - Treatment uptake of PegIFN/RBV is insufficient

HIV Suppression is Associated with Less Hepatic Necroinflammatory Activity

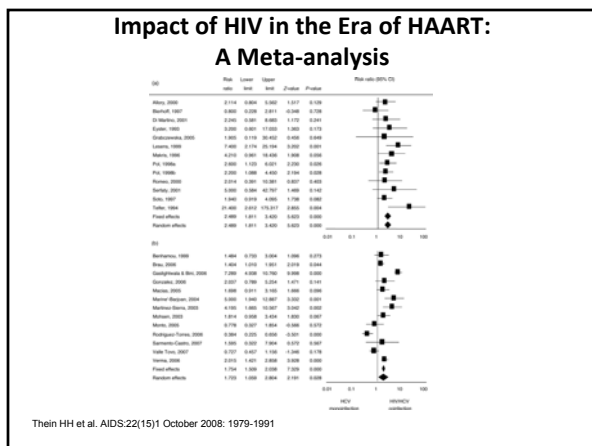
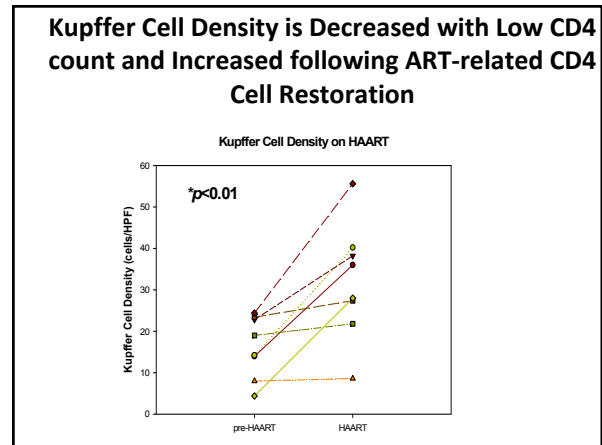
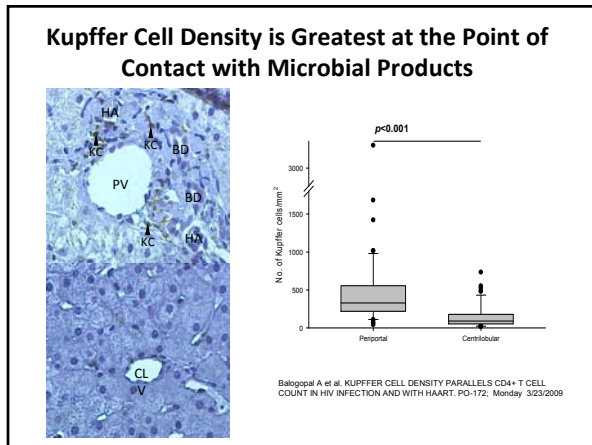
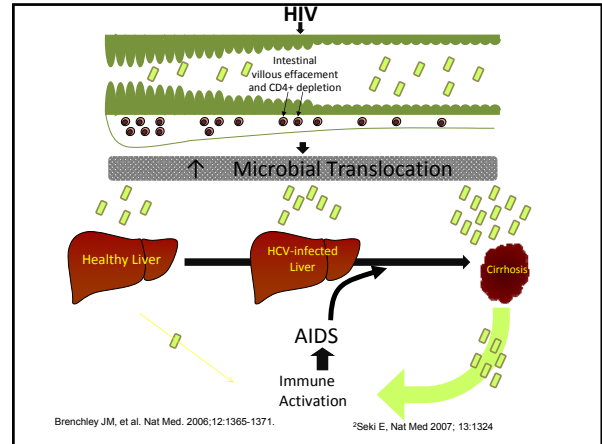
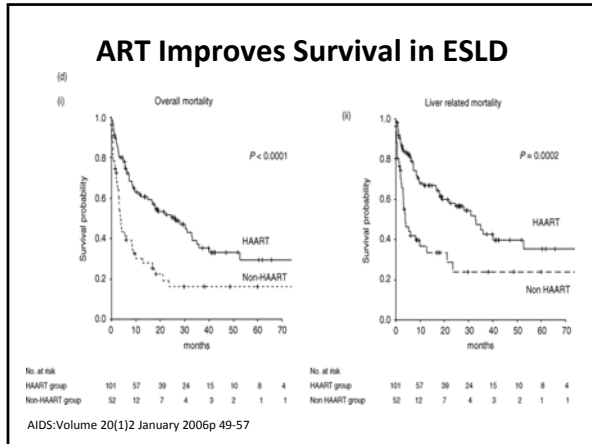


Mehta SH, et al. Hepatology, 2005.

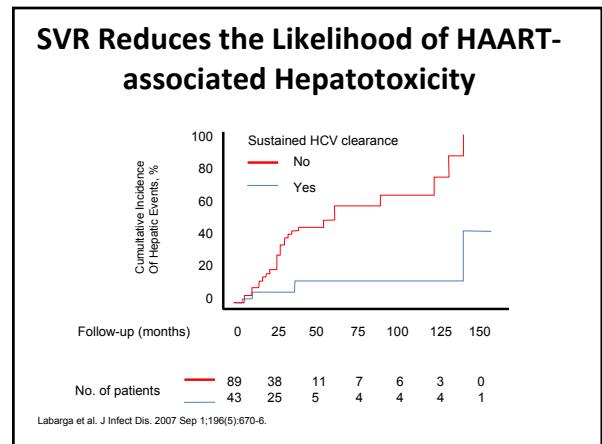
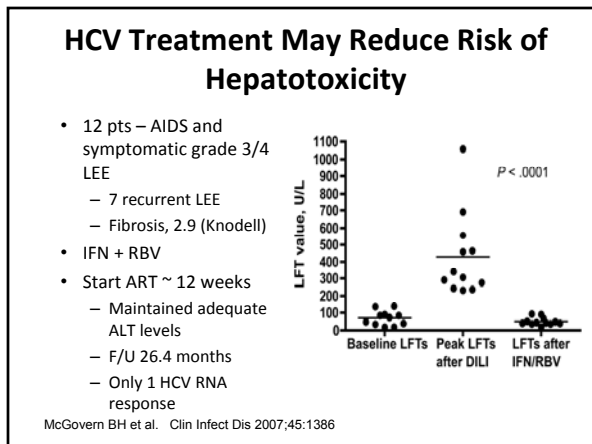
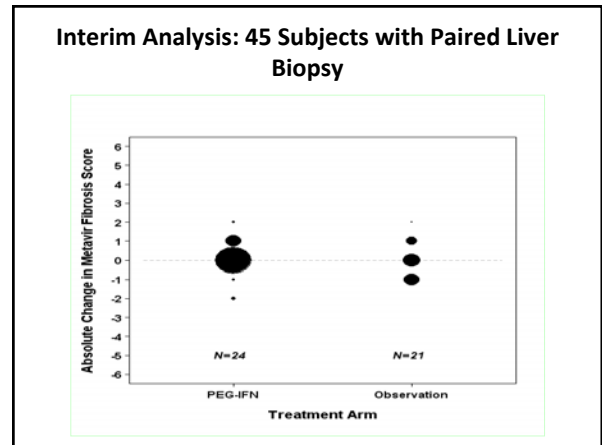
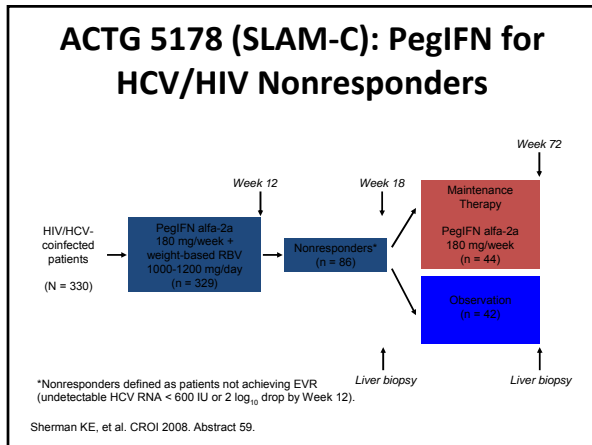
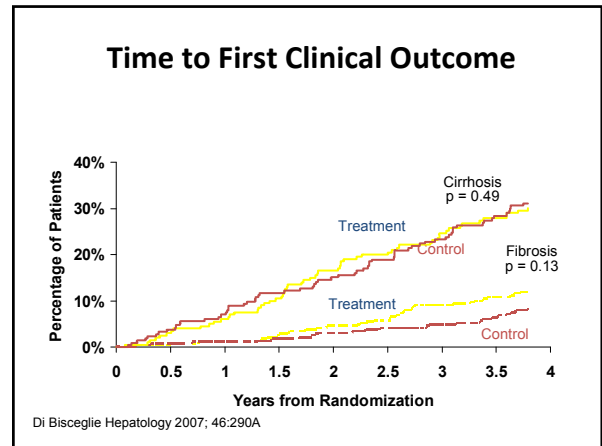
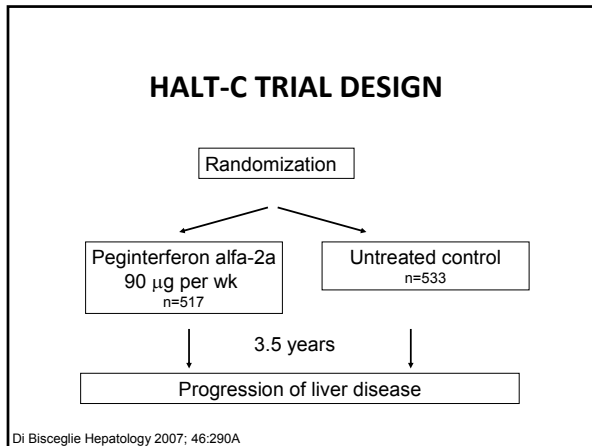
Impact of HIV RNA, CD4, or Both on HCV-Related Fibrosis Progression Rate



Brau N, et al. J Hepatol. 2006;44:47-55.



- ### Goals of HCV Therapy
- Achieve viral eradication
 - Undetectable HCV RNA level 6 months after the end of treatment
 - Manage ART associated liver injury
 - Prevent liver disease progression (No SVR)
 - Fibrosis and necro-inflammation
 - ESLD
 - Hepatocellular carcinoma

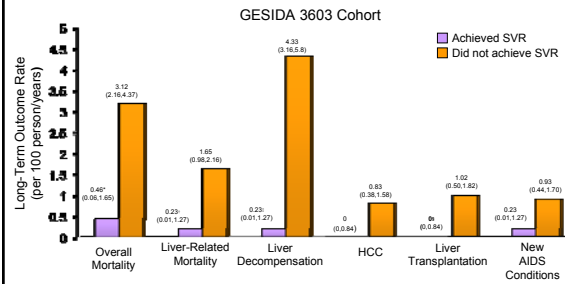


GESIDA Cohort: SVR Reduces Risk for Liver-Related Morbidity and Mortality

- 711 coinfecting patients
 - HIV RNA < 50, 52%
 - CD4 cell count, 544 (396 – 721)
 - F3/4, 39%
 - Median f/u, 19.7 – 22.1 months
- PegIFN + RBV, 82%
 - SVR = 31% (genotypes 1/4, 14%; 2/3, 46%)
- Outcomes
 - Liver failure, cancer, transplant
 - AIDS
 - Death

Berenguer J, Alvarez-Pellicer et al. CROI 2008, Abstract 60

Achieving Sustained Virologic Response: Impact on Long-Term Outcomes in HIV/HCV-Coinfection



¹P=0.003, ²P=0.028, ³P<0.001, and ⁴P=0.034 versus not attaining a sustained virologic response. n=711 HIV/HCV-coinfecting patients receiving interferon (peg or conventional) + ribavirin.

Berenguer J, et al. 15th CROI, Boston, 2008. Abstract 60.

Sustained Virologic Response in HIV/HCV-Coinfected Patients

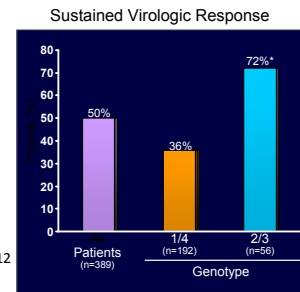
	Sustained Virologic Response at Week 72 (%)		
	Overall	Genotype 1	Genotype 2/3
AACTG 5071¹			
IFN/RBV (n=67)	12	6	33
Peg-IFN/RBV (n=66)	27	14	73
APRICOT²			
IFN/RBV (n=285)	12	7	20
Peg-IFN/RBV (n=289)	40	29	62
Peg-IFN (n=286)	20	14	36
RIBAVIC³			
IFN/RBV (n=207)	20	6	43
Peg-IFN/RBV (n=205)	27	17	44

AACTG 5071 ribavirin dose: 600, 800, and 1000 mg/day for weeks 1-2, 4-8, and 9-72, respectively. Ribavirin dose was fixed at 800 mg/day for APRICOT and RIBAVIC.

¹Chung R, et al. *N Engl J Med*. 2004;351:451-459.
²Torriani FJ, et al. *N Engl J Med*. 2004;351:438-450.
³Carrat R, et al. *JAMA*. 2004;292:2839-2848.

PRESCO Trial: Weight-Based Ribavirin Dosing in HIV/HCV-Coinfected Patients

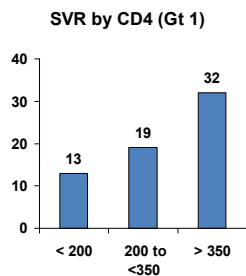
- Prospective, open-label study
 - Spain
 - Not randomized
 - All CD4 >300 cells/mm³
 - No didanosine
 - Weight-based ribavirin
 - <75 kg: 1000 mg/day
 - >75 kg: 1200 mg/day
- Independent predictors of SVR
 - HCV genotype 2/3
 - Lower baseline HCV RNA level
 - Negative HCV RNA level at week 12
- Anemia reasonable



Nunez M, et al. *AIDS Res Hum Retroviruses*, 2007;23:972-982.

HIV and ART: Impact on SVR

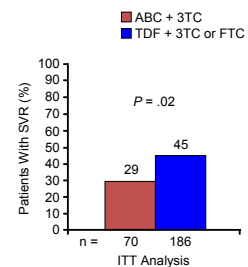
- CD4 > 350 cells/mm³ – trend toward higher SVR rate for genotype 1
- PIs and NNRTIs
 - APRICOT: PI or NNRTI associated with increased SVR (p = .034)
- NRTIs
 - Didanosine → mitochondrial toxicity
 - Zidovudine → anemia
 - Abacavir → decreased viral response?



Opravil M et al. *JAIDS* 2007;47:36-49

Abacavir may be Associated with Reduced Viral Response Rates

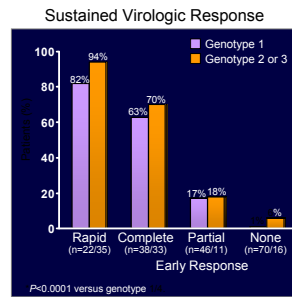
- Possible drug-drug interaction
- RIBAVIC – retrospective analysis
 - ABC use associated with no EVR (OR 4.9, 1.5 - 16)
- Retrospective analysis of 256 patients
 - In multivariate analysis, TDF associated with 2.6-fold increased likelihood of SVR vs abacavir (P = .03)
 - RBV < 13.2 mg/kg/d



Mira J, et al. CROI 2008. Abstract 1074.; Bani-Sadir et al. *JAIDS* 2007;123

HIV/HCV Coinfection: Predictive Value of Early and Rapid Virologic Response

- APRICOT study
 - PegIFN/RBV, n=271
- HCV RNA responses
 - Rapid (week 4 and 12 undetectable)
 - Early
 - Complete (week 4 detectable, week 12 undetectable)
 - Partial (week 4 and 12 detectable, $\geq 2 \log_{10}$ drop at week 12)
 - None (week 4 and 12 detectable, $< 2 \log_{10}$ drop at week 12)
- Rate of SVR highest with rapid response, regardless of HCV genotype



Rodriguez-Torres M, et al. 15th CROI. Boston, 2008. Abstract 1073.

RIBAVIC: Week 4 and 12 Response

- 323 coinfectd pts – PEG or standard IFN alfa-2b/RBV (JAMA 2004)
 - Week 4
 - HCV RNA > 460,000 IU/mL → NPV 100% (no SVR)
 - Δ HCV RNA < 2 log₁₀ IU/mL or negative → NPV 94.2%
 - Week 12
 - HCV RNA > 39,000 IU/mL → NPV 100% (no SVR)
 - Δ HCV RNA < 2 log₁₀ IU/mL or negative → NPV 99.3%
- Stop therapy at week 4
 - Limit toxicity and expense

Payan C et al. Gut online 22 Mar 2007

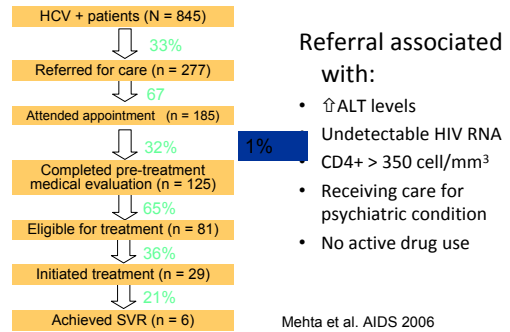
HIV/HCV-infected Patients have Significant Medical and Psychiatric Comorbidities

	HCV (n = 114,005)	HIV/HCV (n = 6,502)
Drug use	39%	56%
Alcohol use	44%	48%
Depression (major)	18%	23%
Bipolar	10%	10%
Anemia	12%	24%
Hepatitis B	3%	9%
CAD	13%	9%
Received HCV treatment	12%	7%

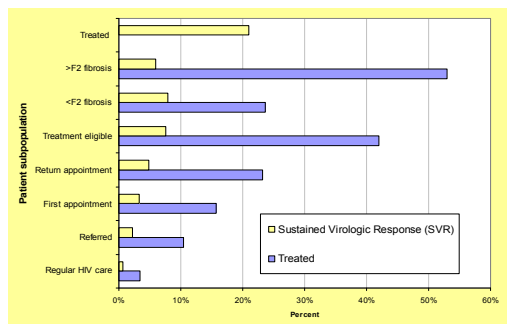
Butt A. Alimentary Pharmacology & Therapeutics Volume 24, Issue 4, Pages 585-591, 2006

Limited Effectiveness of HCV Treatment

Johns Hopkins HIV Clinic (1998-2003)

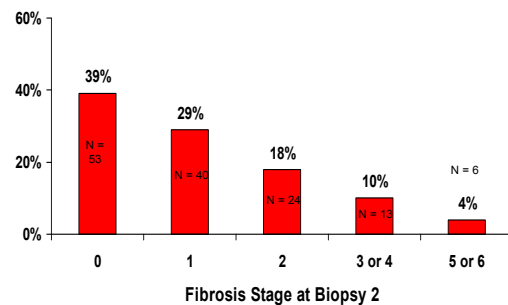


Coinfected Patients with F0/1 were Less Likely to be Treated: "Watch and Wait"



Histologic Outcome of "Watch and Wait" Approach in Coinfected Persons F0 or 1

n = 136



Emerging HCV Treatment Paradigm

- 2011: Peg-IFN + RBV + protease inhibitor
- ↓
- 2014: Protease + polymerase +/- other agents (+/- Peg-IFN +/- RBV)

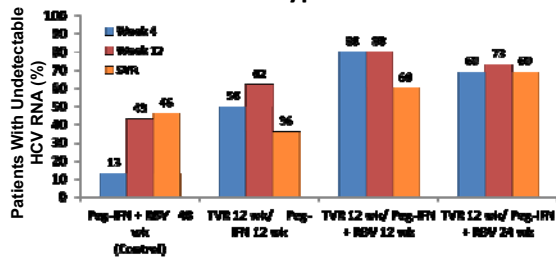
FDA Antiviral Products Advisory Committee Recommendations: HIV/HCV

- Strong recommendation that prior to initial drug approval, studies should be initiated in HCV/HIV coinfecting populations
 - Efficacy outcomes
 - Drug-drug interactions
 - Adherence
 - Toxicity
- Studies should inform, but not necessarily limit, approval to HCV-monoinfected populations

Sherman KE. Development of novel agents for the treatment of chronic hepatitis C infection: Summary of the FDA Antiviral Products Advisory Committee recommendations. Hepatology. 2007 Dec;46(6):2014-20

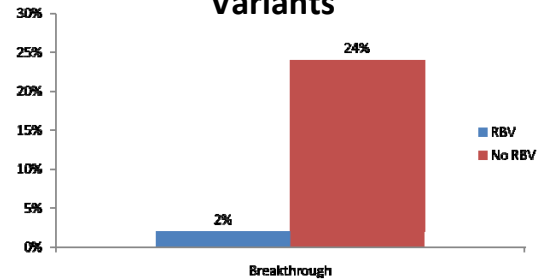
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PROVE 2: Telaprevir + Peg-IFN ± RBV in Treatment-Naive Patients With HCV Genotype 1



Zeuzem S et al. AASLD 2008. Abstract 243.

RBV Significantly Reduces Selection of PI Resistant HCV Variants



PROVE 1: Adverse Events

- Adverse events leading to discontinuation during Wk 1-12
 - TVR-containing arms: 13%
 - Control arm: 3%

Most Common Adverse Events (Through Wk 48)		
Adverse Event	TVR Arms (n = 175) %	Control Arm (n = 75) %
Rash Severe	56 7	39 1
Nausea Severe	53 2	31 0
Diarrhea Severe	37 1	27 0

Jacobson IM et al. AASLD 2007. Abstract 177.

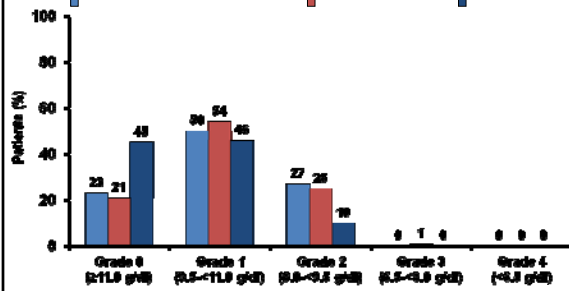
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SPRINT-1: Boceprevir + Peg-IFN + RBV

Treatment arm	Sustained Virologic Response (%)	Virologic Breakthrough (%)
No lead-in, 28 wks	55	7
Peg-IFN+ RBV lead-in, 28 wks	56	4
No lead-in, 48 wks	66	11
Peg-IFN+ RBV lead-in, 48 wks	74	5
Control (Peg-IFN+ RBV 48 wks)	38	0

Kwo P et al. AASLD 2008. Abstract LB16.

Boceprevir + Peg-IFN + RBV: Hemoglobin Reductions



¹ Epoetin-alfa use allowed; 48% in P/R lead-in, 45% in P/R/boceprevir, 25% in P/R control
² Boceprevir added to treatment regimen after 4 week lead-in of PEG-IFN α-2b + ribavirin.
 Kwo P et al. EASL 2008. Abstract 995.

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PegIFN/RBV: A Simplified Approach to HCV/HIV

- Is HIV under control?
- Are there significant comorbid conditions that preclude therapy?
- If child-bearing potential, willing to use birth control?
- If eligible: HCV RNA, HCV genotype, consider biopsy or non-invasive staging, education
- Stop ZDV, ddl and/or ABC(?)
- Treat PegIFN + RBV (1000 – 1200 mg/d)
- Maximize adherence (direct administration)
- HCV RNA at week 4 and 12
 - Stop for insufficient response
 - < 1 log wk 4 and < 2 log wk 12