

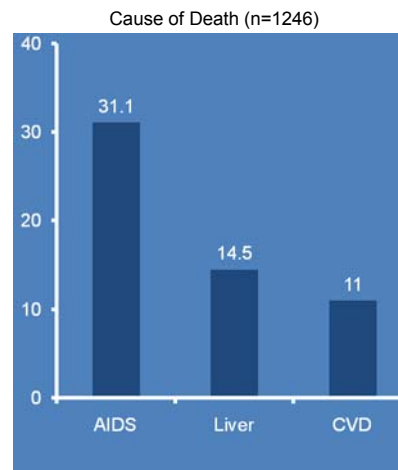
# HIV/HCV Coinfection

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Updated April 10, 2009

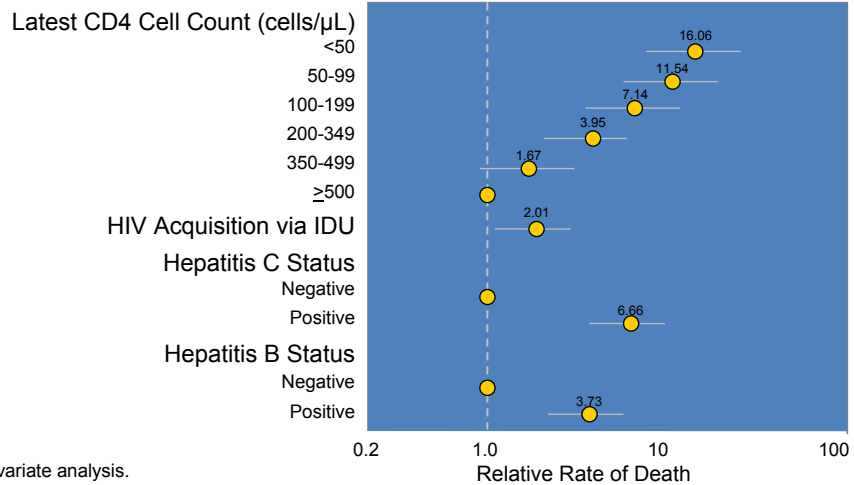
## Liver Disease is a Leading Cause of Death in HIV-Infected Patients

- 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/mm<sup>3</sup>
  - HIV RNA undetectable at death, 55%



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

## Independent Predictors of Liver-Related Death

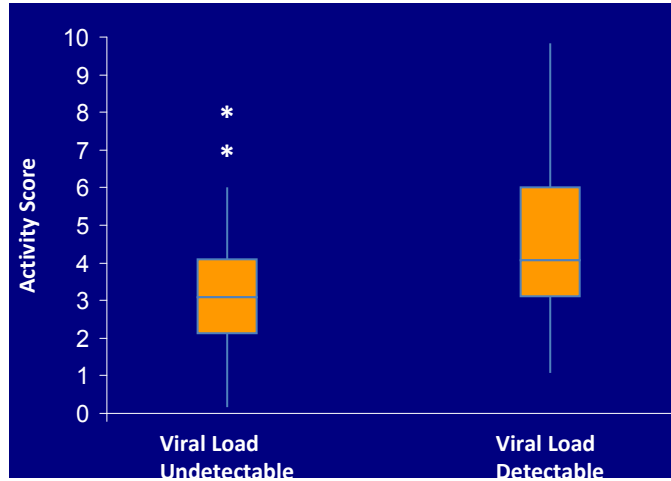


Multivariate analysis.  
Not shown: Age per 5 years (1.32).  
Weber R, et al 2006

## 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

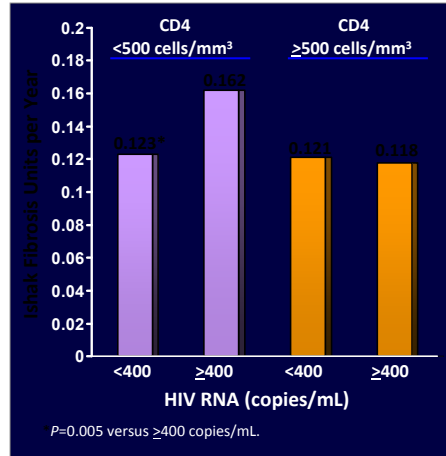
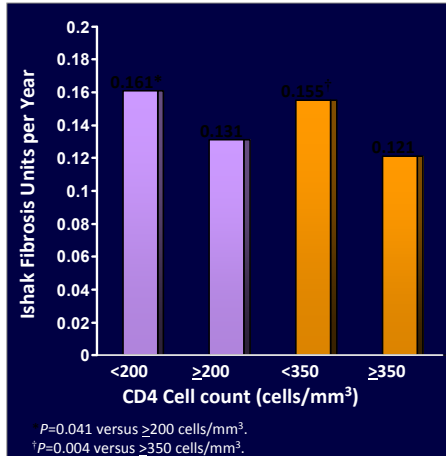
## HIV Suppression is Associated with Less Hepatic Necroinflammatory Activity



Mehta SH, et al. *Hepatology*. 2005.

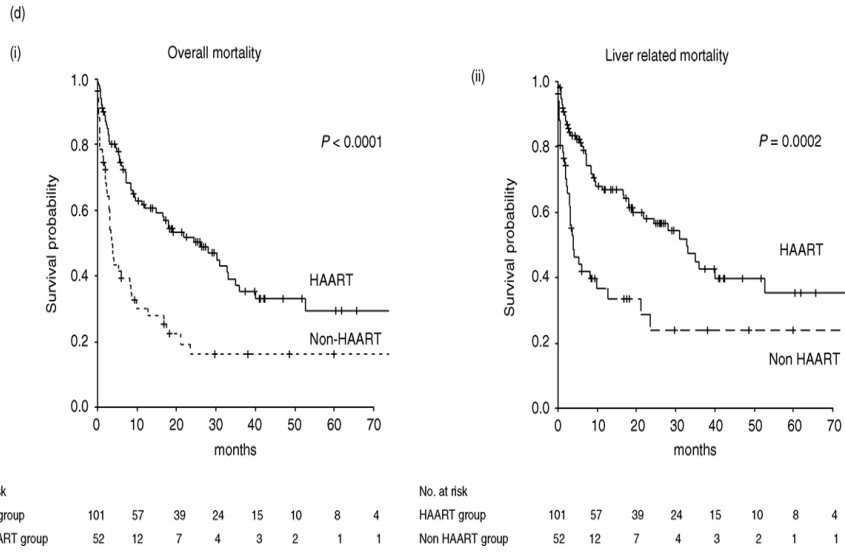
## Impact of HIV RNA, CD4, or Both on HCV-Related Fibrosis Progression Rate

CD4 and HIV RNA Levels Affect Risk of Fibrosis Progression

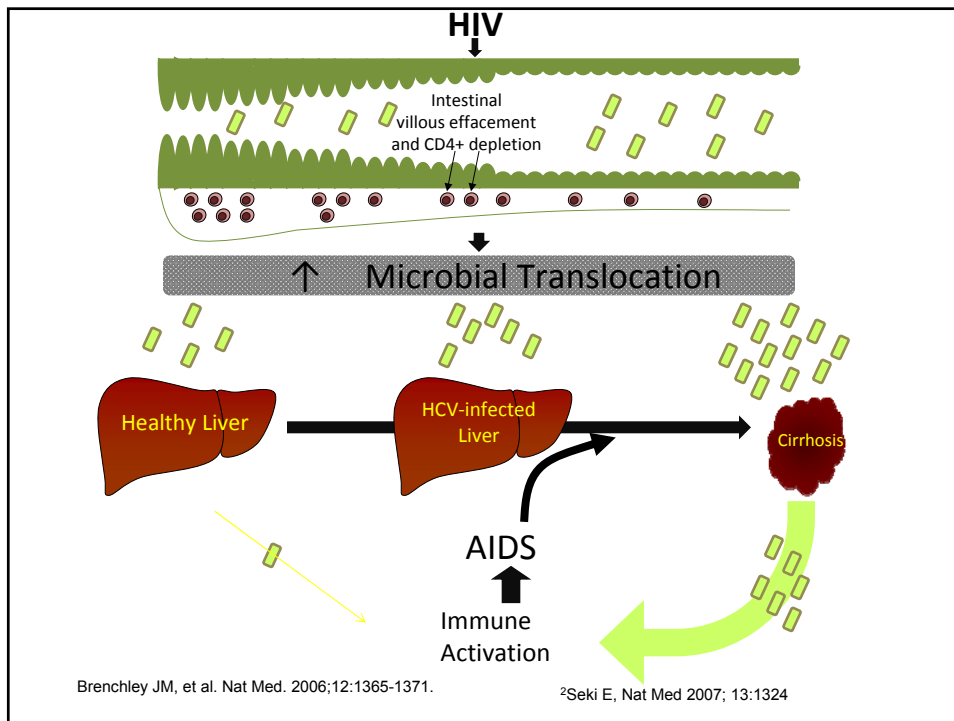


Brau N, et al. *J Hepatol*. 2006;44:47-55.

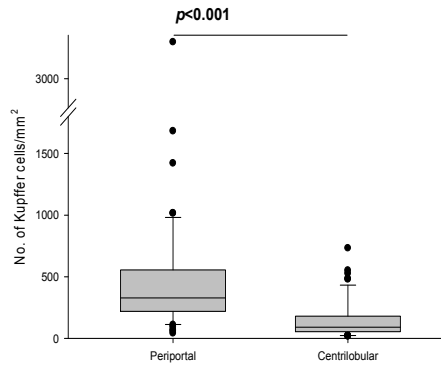
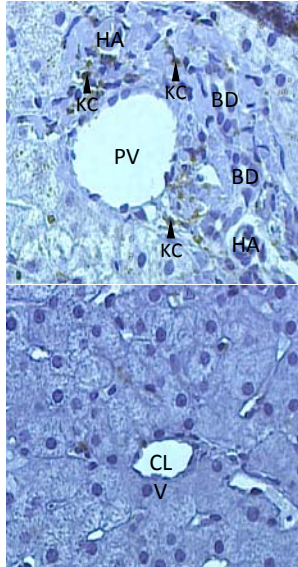
# ART Improves Survival in ESLD



AIDS: Volume 20(1)2 January 2006 p 49-57



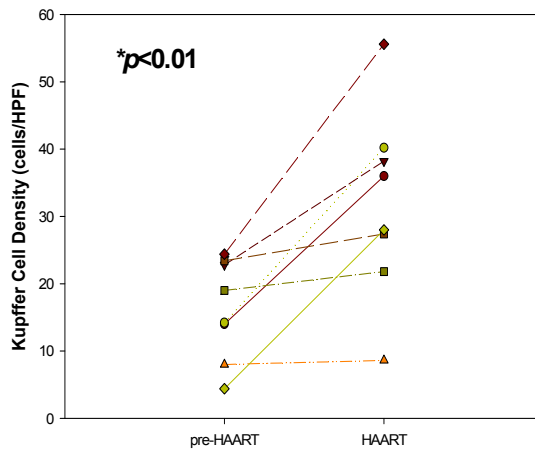
## Kupffer Cell Density is Greatest at the Point of Contact with Microbial Products



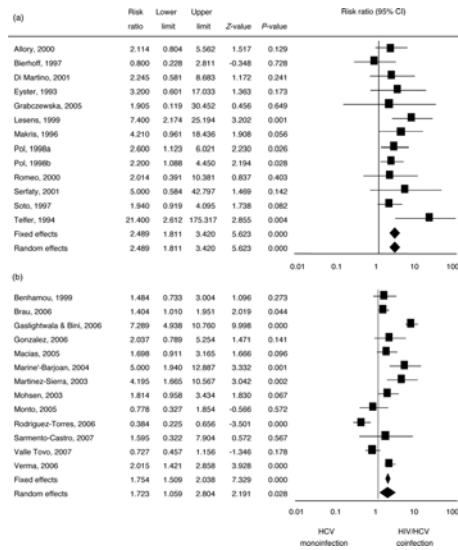
Balogopal A et al. KUPFFER CELL DENSITY PARALLELS CD4+ T CELL COUNT IN HIV INFECTION AND WITH HAART. PO-172; Monday 3/23/2009

## Kupffer Cell Density is Decreased with Low CD4 count and Increased following ART-related CD4 Cell Restoration

Kupffer Cell Density on HAART



## Impact of HIV in the Era of HAART: A Meta-analysis

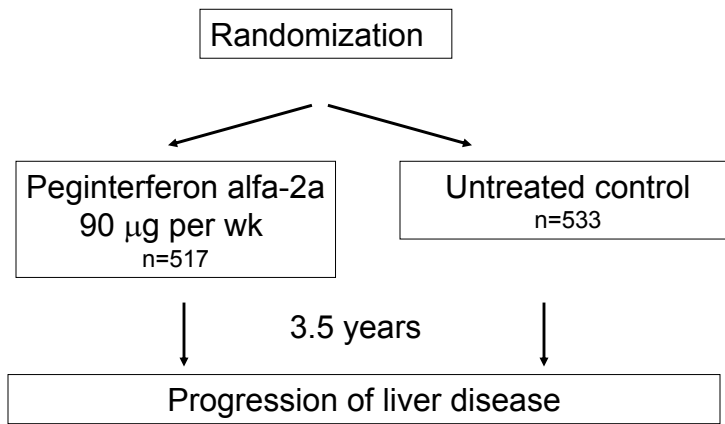


Thein HH et al. AIDS:22(15)1 October 2008: 1979-1991

## Goals of HCV Therapy

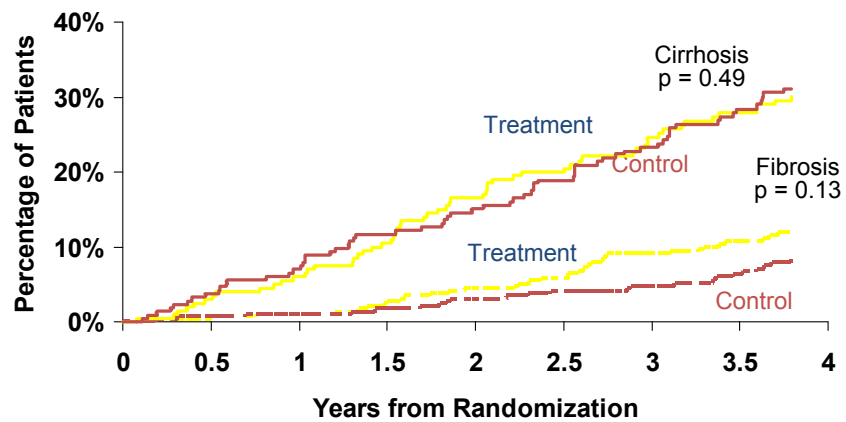
- Achieve viral eradication
  - Undetectable HCV RNA level 6 months after the end of treatment
- Manage ART associated liver injury
- Prevent liver disease progression (No SVR)
  - Fibrosis and necro-inflammation
  - ESLD
  - Hepatocellular carcinoma

# HALT-C TRIAL DESIGN



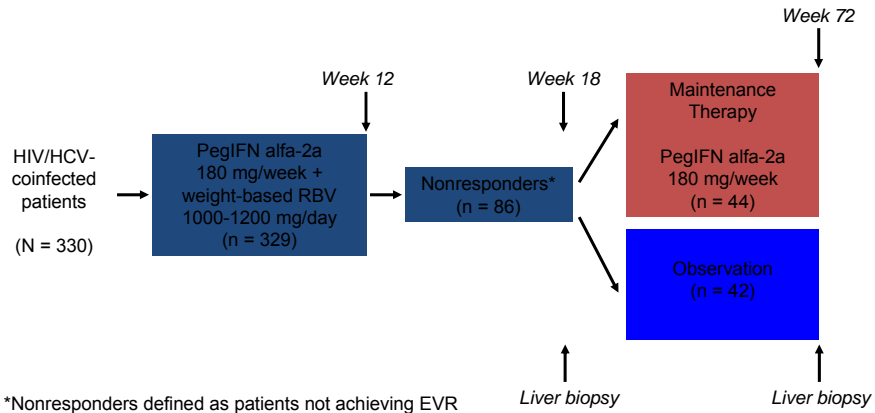
Di Bisceglie Hepatology 2007; 46:290A

## Time to First Clinical Outcome



Di Bisceglie Hepatology 2007; 46:290A

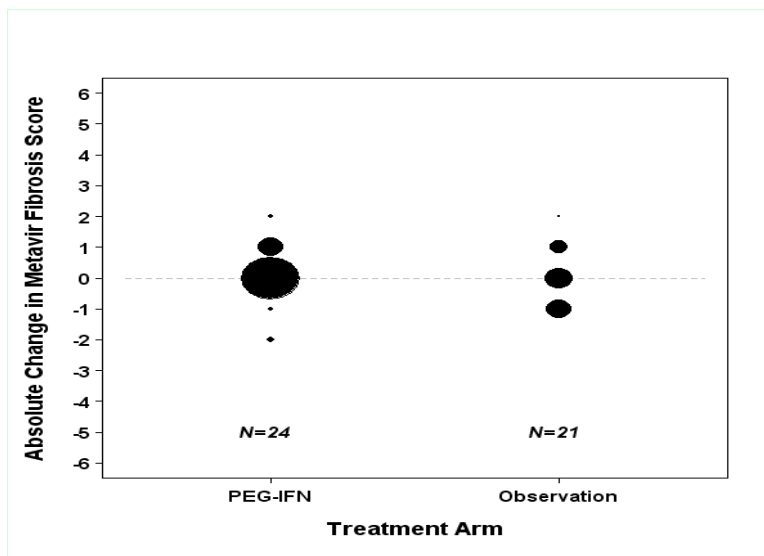
# ACTG 5178 (SLAM-C): PegIFN for HCV/HIV Nonresponders



\*Nonresponders defined as patients not achieving EVR (undetectable HCV RNA < 600 IU or 2 log<sub>10</sub> drop by Week 12).

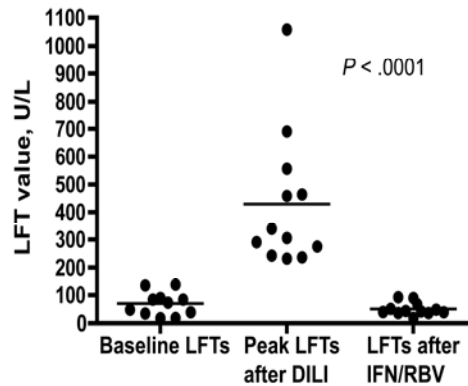
Sherman KE, et al. CROI 2008. Abstract 59.

## Interim Analysis: 45 Subjects with Paired Liver Biopsy



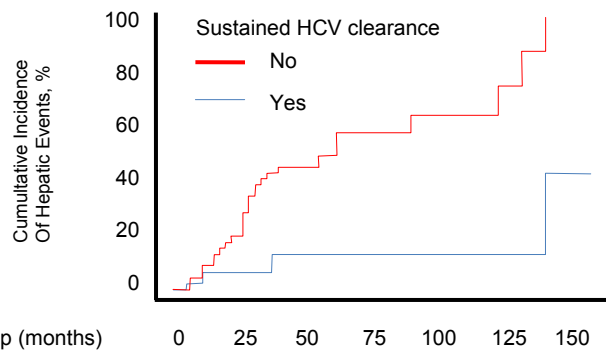
## HCV Treatment May Reduce Risk of Hepatotoxicity

- 12 pts – AIDS and symptomatic grade 3/4 LEE
  - 7 recurrent LEE
  - Fibrosis, 2.9 (Knodell)
- IFN + RBV
- Start ART ~ 12 weeks
  - Maintained adequate ALT levels
  - F/U 26.4 months
  - Only 1 HCV RNA response



McGovern BH et al. Clin Infect Dis 2007;45:1386

## SVR Reduces the Likelihood of HAART-associated Hepatotoxicity



No. of patients	89	38	11	7	6	3	0
— (Red)	89	38	11	7	6	3	0
— (Blue)	43	25	5	4	4	4	1

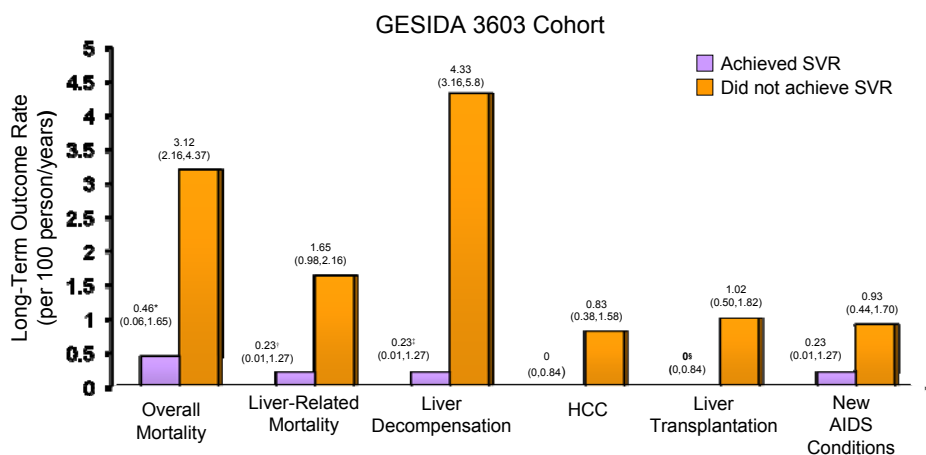
Labarga et al. J Infect Dis. 2007 Sep 1;196(5):670-6.

## 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



\*P=0.003, †P=0.028, ‡P<0.001, and §P=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. 15<sup>th</sup> CROI. Boston, 2008. Abstract 60.

## Sustained Virologic Response in HIV/HCV-Coinfected Patients

	Sustained Virologic Response at Week 72 (%)		
	<u>Overall</u>	<u>Genotype 1</u>	<u>Genotype 2/3</u>
<b>AACTG 5071<sup>1</sup></b>			
IFN/RBV (n=67)	12	6	33
Peg-IFN/RBV (n=66)	27	14	73
<b>APRICOT<sup>2</sup></b>			
IFN/RBV (n=285)	12	7	20
Peg-IFN/RBV (n=289)	40	29	62
Peg-IFN (n=286)	20	14	36
<b>RIBAVIC<sup>3</sup></b>			
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 8-72, respectively. Ribavirin dose was fixed at 800 mg/day for APRICOT and RIBAVIC.

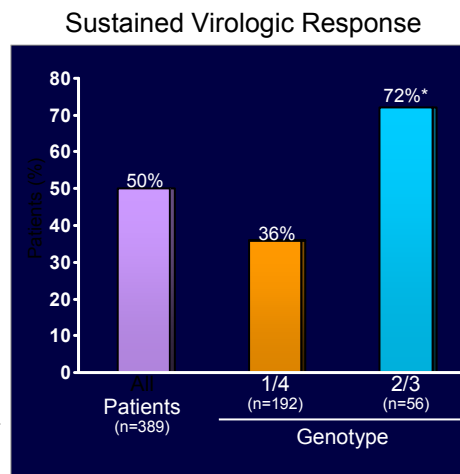
<sup>1</sup>Chung R, et al. *N Engl J Med.* 2004;351:451-459.

<sup>2</sup>Torriani FJ, et al. *N Engl J Med.* 2004;351:438-450.

<sup>3</sup>Carrat R, et al. *JAMA.* 2004;292:2839-2848.

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

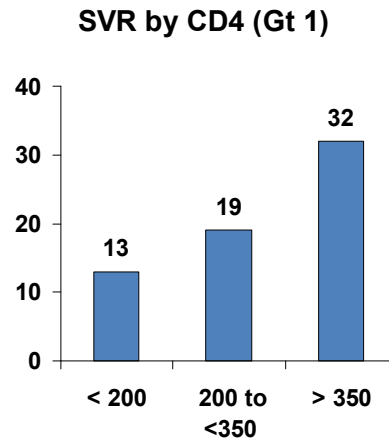
- Prospective, open-label study
  - Spain
  - Not randomized
  - All CD4 >300 cells/mm<sup>3</sup>
  - No didanosine
  - Weight-based ribavirin
    - <75 kg: 1000 mg/day
    - >75 kg: 1200 mg/day
- Independent predictors of SVR
  - HCV genotype 2/3
  - Lower baseline HCV RNA level
  - Negative HCV RNA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



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

## HIV and ART: Impact on SVR

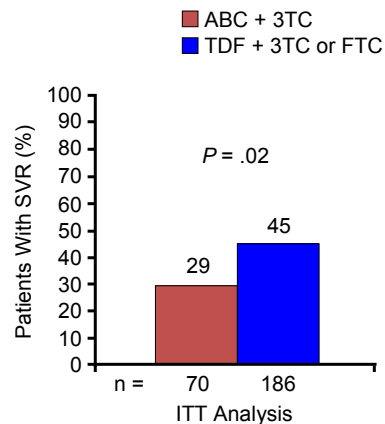
- CD4 > 350 cells/mm<sup>3</sup> – trend toward higher SVR rate for genotype 1
- PIs and NNRTIs
  - APRICOT: PI or NNRTI associated with increased SVR ( $p = .034$ )
- NRTIs
  - Didanosine → mitochondrial toxicity
  - Zidovudine → anemia
  - Abacavir → decreased viral response?



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

## Abacavir may be Associated with Reduced Viral Response Rates

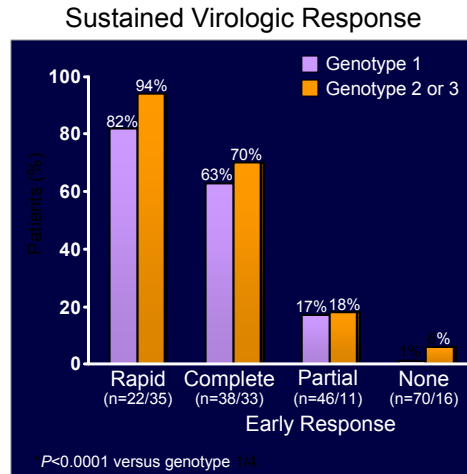
- Possible drug-drug interaction
- RIBAVIC – retrospective analysis
  - ABC use associated with no EVR (OR 4.9, 1.5 - 16)
- Retrospective analysis of 256 patients
  - In multivariate analysis, TDF associated with 2.6-fold increased likelihood of SVR vs abacavir ( $P = .03$ )
  - RBV < 13.2 mg/kg/d



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. 15<sup>th</sup> CROI. Boston, 2008. Abstract 1073.

## RIBAVIC: Week 4 and 12 Response

- 323 coinfecting pts – PEG or standard IFN alfa-2b/RBV (JAMA 2004)
  - Week 4
    - HCV RNA  $> 460,000$  IU/mL  $\rightarrow$  NPV 100% (no SVR)
    - $\Delta$  HCV RNA  $< 2 \log_{10}$  IU/mL or negative  $\rightarrow$  NPV 94.2%
  - Week 12
    - HCV RNA  $> 39,000$  IU/mL  $\rightarrow$  NPV 100% (no SVR)
    - $\Delta$  HCV RNA  $< 2 \log_{10}$  IU/mL or negative  $\rightarrow$  NPV 99.3%
- Stop therapy at week 4
  - Limit toxicity and expense

Payan C et al. Gut online 22 Mar 2007

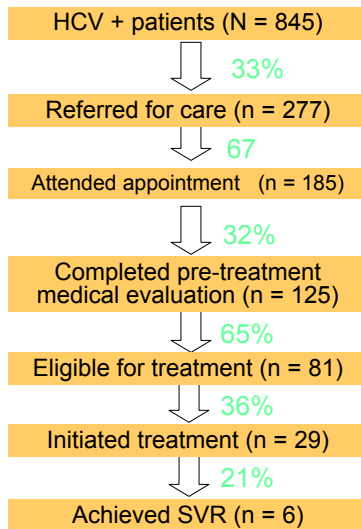
## HIV/HCV-infected Patients have Significant Medical and Psychiatric Comorbidities

	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)



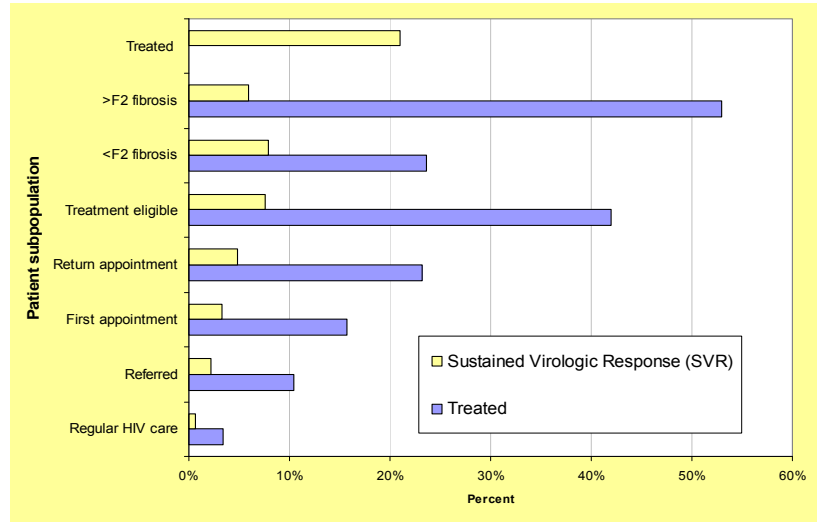
Referral associated with:

- ↑ALT levels
- Undetectable HIV RNA
- CD4+ > 350 cell/mm<sup>3</sup>
- Receiving care for psychiatric condition
- No active drug use

1%

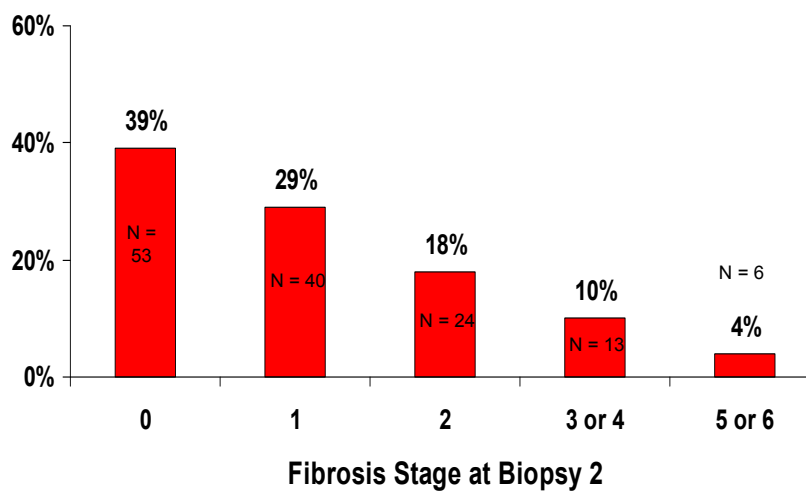
Mehta et al. AIDS 2006

## 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



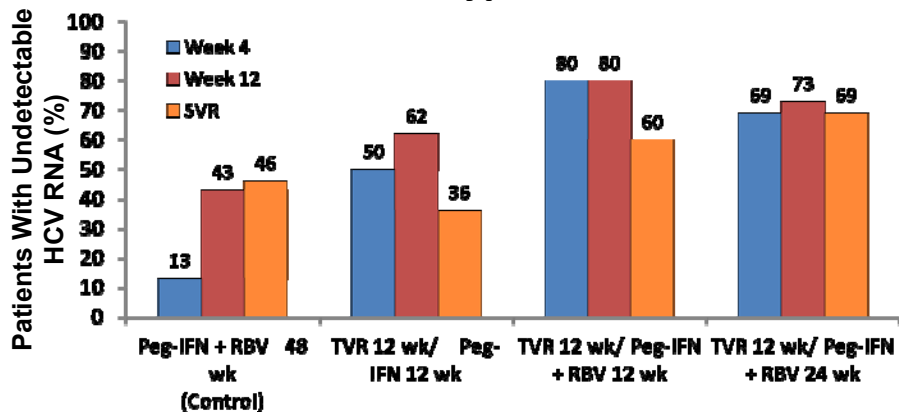
- 2014: Protease + polymerase +/- other agents (+/- Peg-IFN +/- RBV)

## **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

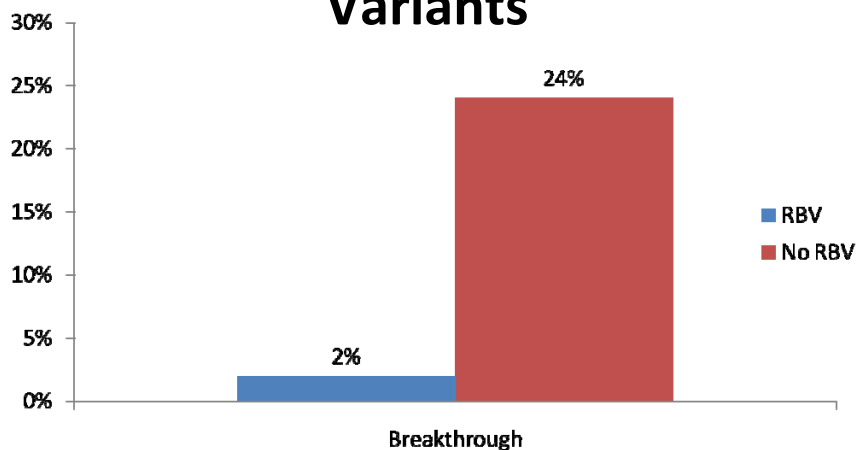
Sherman KE. Development of novel agents for the treatment of chronic hepatitis C infection: Summary of the FDA Antiviral Products Advisory Committee recommendations. Hepatology. 2007 Dec;46(6):2014-20

## 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	56	39
Severe	7	1
Nausea	53	31
Severe	2	0
Diarrhea	37	27
Severe	1	0

Jacobson IM et al. AASLD 2007. Abstract 177.

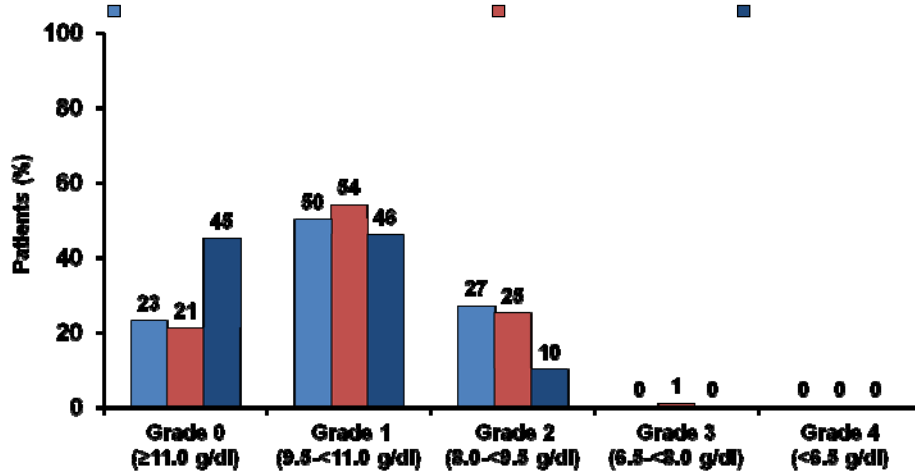
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## SPRINT-1: Boceprevir + Peg-IFN + RBV

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



† Epoetin-alfa use allowed; 48% in P/R lead-in, 45% in P/R/boceprevir, 25% in P/R control  
 ‡ Boceprevir added to treatment regimen after 4 week lead-in of PEG-IFN  $\alpha$ -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, ddI 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