

# Hepatitis C Update

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June 30, 2009

# The Numbers

- 130-170 million infections worldwide
- 2.2-3.0% of world's population
- Highest prevalence in Africa, Eastern Mediterranean
- By comparison: HIV Worldwide: 31 million (with about 25% coinfection)
- Mortality rates expected to rise in the next 10-20 years, even with widespread treatment

# Hepatitis C in the U.S.

- Prevalence of 1.6% between 1999-2002
- 4.1 million people, 80% chronic infections
- Principal cause of death from liver disease
- Leading indication for liver transplantation

# Current Screening Recommendations

- Any history of IV drug abuse, even once
- Intranasal drug users who share paraphernalia
- Blood transfusion or organ transplantation prior to 1992
- Unexplained elevations in aminotransferases
- Hemodialysis patients
- HIV-infected individuals

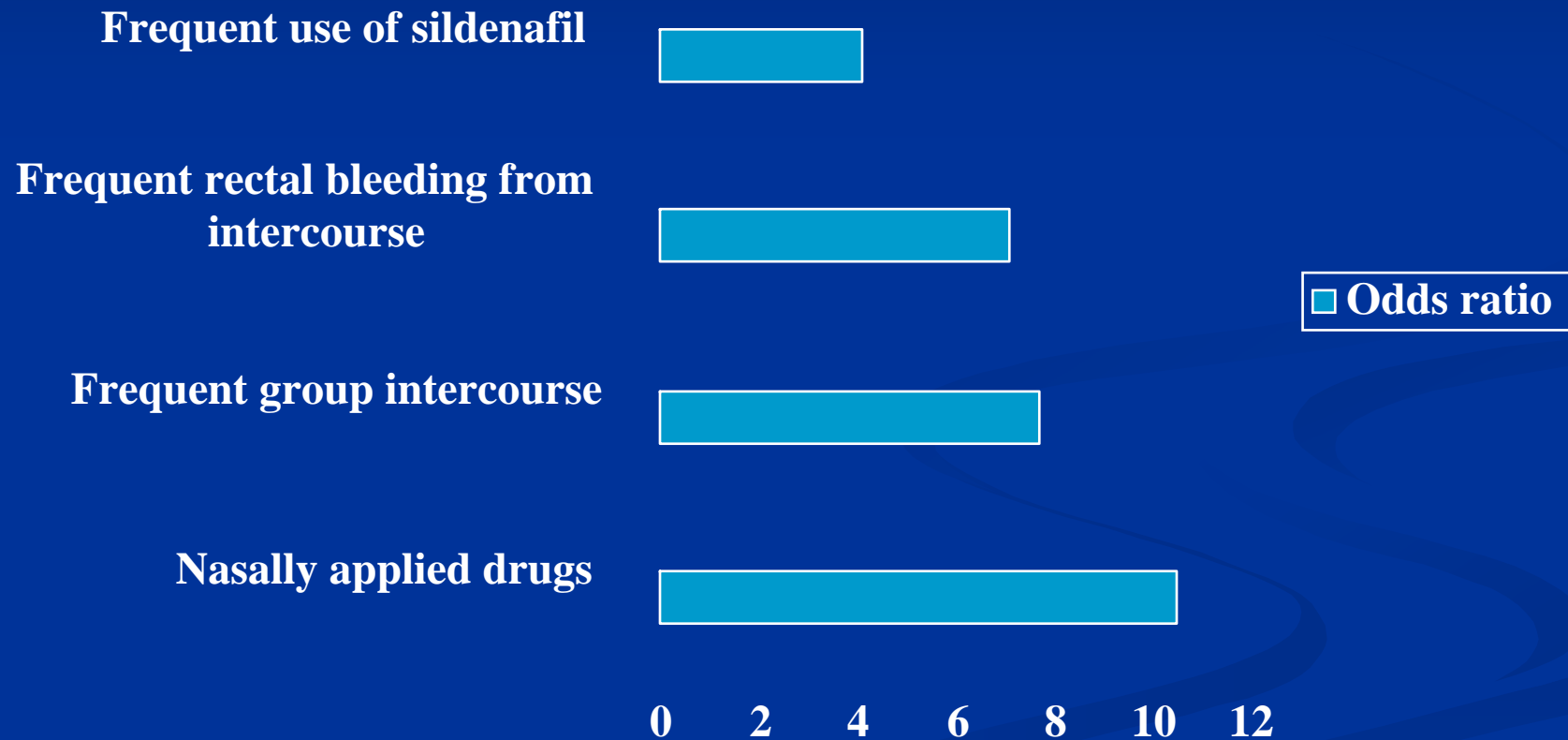
# What about MSM?

- Several cohort studies from Europe and the U.S. have recently identified sexually-transmitted HCV among MSM
- Almost exclusively HIV+ MSM with high STD rates including syphilis and LGV

# Risk factors for sexually-acquired HCV

- Greater number of sexual partners
  - (30 vs 11 in past year)
- Increased levels of high-risk sexual behaviors
  - Unprotected sex, rimming, fisting, group sex, use of sex toys
- Greater likelihood of shared intranasal or intranal drugs
- Greater lifetime incidence of STDs
- Sex in a group of more than two people was the strongest predictor

# Risk factors for HCV transmission in HIV+ MSM



Danta M et al., AIDS 2007 21:983-991

# HCV Natural History



Chicken livers with grapes and caramelized onions

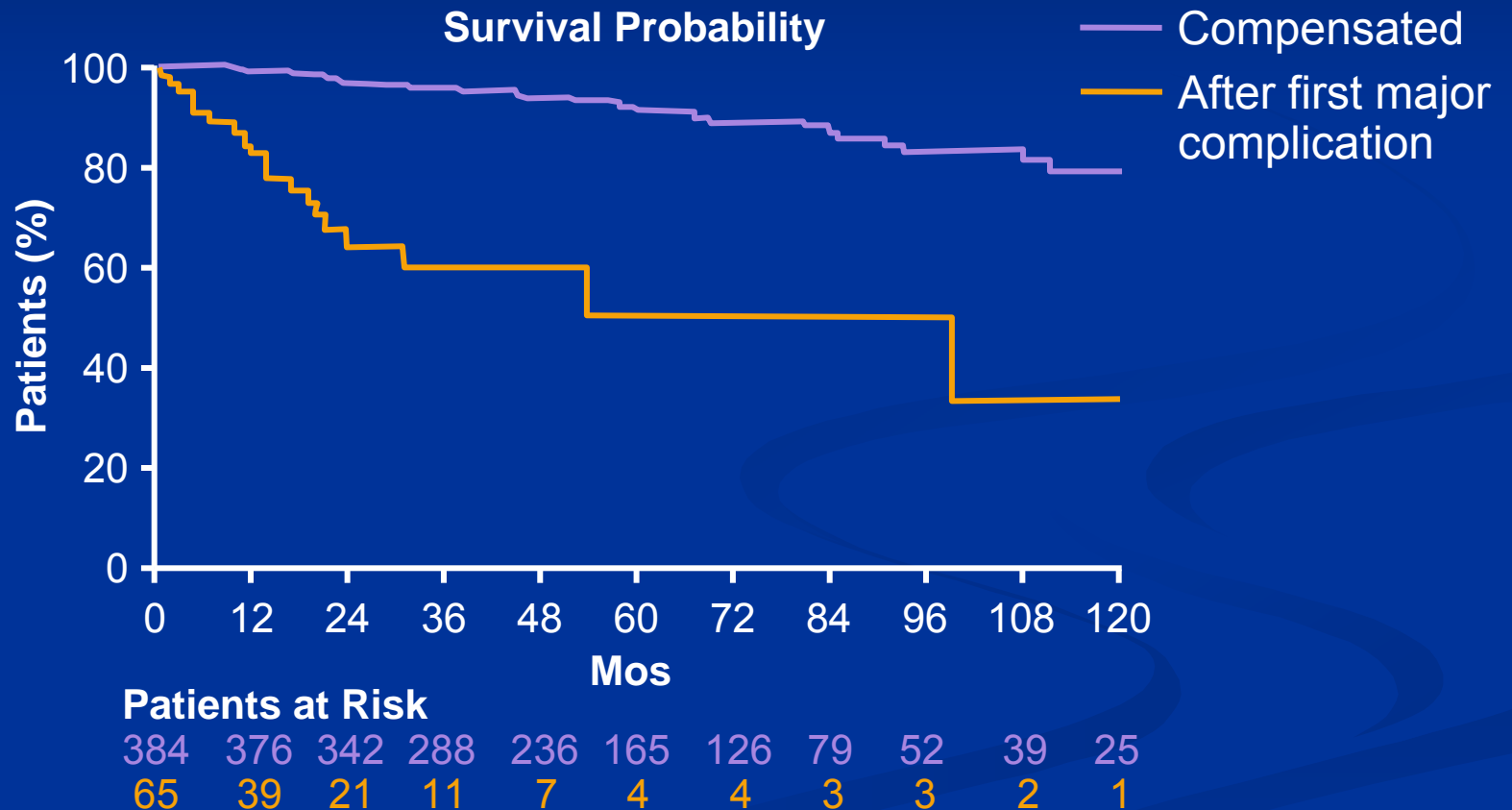
# HCV Natural History

- 25% of infections will develop acute hepatitis with jaundice
- Approximately 70% will develop chronic infection
- Roughly 20% of patients with chronic infection will develop cirrhosis
- Annual incidence of HCC in patients with cirrhosis is 1.6%

# Natural History of HCV-induced cirrhosis

- Annual rate of decompensation is about 4%
- Annual death rate among patients with decompensated cirrhosis is 15% in developed countries
- Annual death rate in patients with HCC is 80%

# Survival Probability in HCV Patients With Cirrhosis



From Gastroenterology, 112, Fattovich G, et al, Morbidity and mortality in compensated cirrhosis type C: A retrospective follow-up study of 384 patients, 463-472., 1997.

# Natural history of compensated hepatitis C virus-related cirrhosis in human immunodeficiency virus-infected patients

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## ABSTRACT

**Background:** Compensated HCV-related cirrhosis is a common finding in the HIV-infected population in areas where HCV/HIV coinfection is prevalent. There are scarce data on the clinical outcome of this condition. The aim of this study was to provide information about the incidence of hepatic decompensations, the mortality and the predictors thereof in HIV-infected patients with compensated HCV-related cirrhosis.

**Methods:** In this retrospective study, all 154 HIV and HCV-coinfected patients in whom a new diagnosis of compensated Child-Pugh-Turcotte (CPT) class A cirrhosis was made in the Infectious Diseases Units of seven hospitals, from January 1996 to September 2006, were included. Time from diagnosis to the first hepatic decompensation and survival were evaluated.

**Results:** The median (Q1-Q3) follow-up of the population studied was 29.1 (14.9-51.2) months. Thirty-six (23.4%) patients developed a liver decompensation. The density of incidence of hepatic decompensations was 8.8 per one hundred person-years. The probability of decompensation at 3 and 5 years was 27 and 32%, respectively. Ascites was the most common first decompensation of cirrhosis, followed by hepatic encephalopathy (HE) and portal hypertensive gastrointestinal bleeding (58%, 17% and 17%, respectively). The factors independently associated [HR (95%CI)] with the emergence of liver decompensation were lack of HCV therapy during the follow-up [3.71 (1.25-10.99)], a baseline CD4 cell counts lower than 300/mm<sup>3</sup> [2.12 (1.06-4.23)], a CPT score of 5 versus 5 [4.38 (2.03-9.43)], and a diagnosis of cirrhosis based on clinical findings [3.81 (1.8-8.05)]. Fifteen (8.7%) patients died during the follow-up. Eleven (73%) of them died due to liver disease. HE was the cause of death in nine (81%) patients. The mortality rate due to liver failure was 2.44 deaths per one hundred person-years. The 3 and 5-year survival estimates were 91 and 82%, respectively. HE as the first liver decompensation [28.75 (8.25-141.51)] and a higher baseline CPT [5.59 (1.20-24.42)] score were independently associated with liver-related mortality.

**Conclusions:** Clinical liver events are more frequent in HIV/HCV-coinfected patients with compensated CPT class A cirrhosis than previously reported in HCV-monoinfected patients. Liver disease is the main cause of death in this population. Lower baseline CD4 cell counts, lack of therapy against HCV, and higher CPT score are the factors related to the occurrence of clinical liver events.

## BACKGROUND

- HIV infection accelerates the course of HCV-related liver damage to cirrhosis, end stage liver disease (ESLD) and death.
- The incidence of clinical liver events in large cohorts of HCV-monoinfected subjects are extremely low. The annual incidence of clinical decompensation were from 3.1% to 3.9%. In relation to liver-related death, previous data showed annual rate of 1.9%.
- Little information is available regarding the natural history of compensated cirrhosis in HIV/HCV-coinfected subjects.

## OBJECTIVES

To obtain information about the clinical outcome of HCV-related compensated cirrhosis in HIV-infected patients, as well as to analyze the predictors of liver decompensation and death in this population.

## PATIENTS AND METHODS

From January, 1996 to September, 2006, all the HIV/HCV-coinfected individuals that fulfilled the following inclusion criteria were analyzed: (I) Detectable plasma HCV-RNA at baseline; (II) A diagnosis of Child-Pugh-Turcotte (CPT) class A cirrhosis at or after the inclusion in the cohort, and (III) No decompensation of liver disease had emerged before entering the cohort. Individuals who presented a liver decompensation at the time of cirrhosis diagnosis were excluded from the study.

Patients were followed until death, lost to follow-up, liver transplantation or the censoring date (30th September 2006). Visits, including a clinical, strategic, immunologic and biochemical evaluation, were carried out at least every six months.

The diagnosis of liver cirrhosis was based on one of the following diagnostic methods:

- Histology: A fibrosis grade F4, according to the Knodell scoring system modified by Scheuer, in a liver biopsy.
  - A hepatic stiffness  $\geq 14.6$  kPa measured by transient elastometry (FibroscanTM; Echosens, Paris, France).
  - Clinical, laboratory and ultrasound data consistent with cirrhosis.
- Disorders included as a decompensated cirrhosis: ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatocellular carcinoma, non-obstructive jaundice and hepatic encephalopathy.

The development of the first episode of hepatic decompensation, the occurrence of death due to liver failure and that of death due to any cause was the endpoints analyzed in this study. Estimated survival functions were calculated using the Kaplan-Meier method, and survival curves were compared via log-rank test. Covariates with P value equal to or less than 0.1 on bivariate analysis were introduced in a Cox regression model.

## RESULTS

- One hundred and fifty-four HIV/HCV-coinfected individuals with compensated CPT class A cirrhosis were included in this study.
- The median (Q1-Q3) follow-up time was 29.1 (14.9-51.3) months. Thirty-six (23.4%) patients developed a first hepatic decompensation and 15 (9.7%) died. The density of incidence of first hepatic decompensations was 8.8 per one hundred person-years. The probability of developing a first decompensation at five years was 33%. Eleven (73%) patients died due to liver disease. The rates of death was 2.44 per one hundred person-years. The probability of staying alive at five years was 82%.

## RESULTS

### Characteristics of the population

Parameter	Value
Age (years)*	28.9 (37.7-44.5)
Former or active intravenous drug users (%)	133 (86)
HCV genotype 1 (%)	87 (57)
Age at HCV infection†	21 (19-27)
Duration of HCV infection (years)†	18 (14.2-23.9)
MELD‡	8 (1-10)
Child A5 score (%)	155 (79)
HCV therapy during the follow-up (%)	66 (43)
Sustained virologic response to HCV therapy during the follow-up (%)	59 (29)
CDC stage C (%)	53 (34)
Highly active antiretroviral therapy during the follow-up (%)	145 (94)
Baseline CD4 cell counts*	403 (255-572)
Patients with baseline undetectable plasma HIV viral load	157 (88)
% of follow-up with undetectable plasma HIV-RNA load	64.7 (20.6-87.8)
Diagnosis of cirrhosis (%)	
Liver biopsy	99 (64)
Transient elastometry	15 (10)
Other	46 (30)

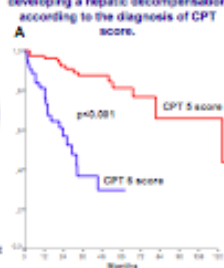
\*Median (interquartile range) †It could be assessed in 137 patients. ‡Available in 135 patients.

### Frequency of specific events as first liver decompensation

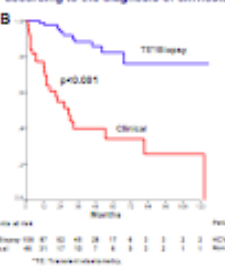


■ Ascites  
■ Hepatic encephalopathy  
■ Portal hypertensive gastrointestinal bleeding  
■ Hepatocellular carcinoma  
■ Jaundice

### (A) Probability of remaining free of developing a hepatic decompensation according to the diagnosis of CPT score.



### (B) Probability of remaining free of developing a hepatic decompensation according to the diagnosis of cirrhosis, and, (C) according to the HCV therapy.



## CONCLUSIONS

- In HIV/HCV-coinfected patients with CPT class A cirrhosis, clinical liver events are more common than previously reported in HCV-monoinfected subjects.
- Liver disease is the main cause of death in this population.
- Lower baseline CD4 cell counts, lack of therapy against HCV, and higher CPT score are the factors related to the occurrence of clinical liver events.
- Even among patients with CPT class A, CPT score is a strong predictor of hepatic decompensation and liver-related death.

### Predictors of the emergence of the first hepatic decompensation

Variable	No. (%)	p univariate	Hazard ratio (95% CI)	p multivariate
Age (years)				
<30	16 (10.6)			
≥30	22 (28.2)	0.217	-	-
Gender				
Male	29 (33.1)			
Female	7 (23.3)	0.207	-	-
HCV therapy				
Yes	4 (3.6)			
No	32 (26.5)	<0.001	3.71 (1.25-10.99)	0.006
HIV coinfection				
No	32 (26.5)			
Yes	4 (3.6)	0.65	-	0.409
HCV coinfection				
No	34 (22.5)			
Yes	2 (36.7)	0.3	-	-
CDC stage				
A or B	22 (21.7)			
C	14 (28.4)	0.233	-	-
Daily alcohol intake > 50 g/day				
No	18 (16.7)			
Yes	17 (38)	<0.001	-	0.193
Risk category				
No intravenous drug users	4 (36.4)			
Intravenous drug users	28 (27)	0.612	-	0.262
Child score				
5	16 (13.6)			
6	21 (45.6)	<0.001	4.38 (2.03-9.43)	<0.001
MELD score				
≤8	12 (16.6)			
>8	24 (31.2)	<0.001	-	0.381
HAART during the follow-up				
No	3 (30.3)			
Yes	33 (23.6)	0.449	-	-
Diagnosis of cirrhosis				
Clinical	24 (34.5)			
TS/Biopsy	11 (16.2)	<0.001	3.81 (1.8-8.05)	<0.001
CD4 gain after HAART				
>350	22 (26.5)			
≤350	14 (16.1)	<0.001	3.12 (1.03-9.24)	0.032
% of follow-up with plasma HIV-RNA load below the detection level				
>50	24 (31.6)			
≤50	11 (13.6)	0.028	-	0.462

### Predictors of death due to liver failure

Variable	No. (%)	p univariate	Hazard ratio (95% CI)	p multivariate
Age (years)				
<30	3 (7.3)			
≥30	8 (19.5)	0.262	-	-
Diagnosis of cirrhosis				
Clinical	7 (13.2)			
TS/Biopsy	4 (13.7)	0.023	-	0.037
HCV therapy				
No	2 (3.6)			
Yes	9 (15.2)	0.038	-	0.247
HIV coinfection				
No	9 (15.2)			
Yes	4 (20)	0.286	-	-
HCV coinfection				
No	9 (15.6)			
Yes	2 (8.7)	0.603	-	0.138
Daily alcohol intake > 50 g/day				
No	3 (11.1)			
Yes	6 (17.6)	0.667	-	0.374
Child score				
5	4 (11.7)			
6	7 (19.2)	<0.001	5.59 (1.20-24.42)	0.022
MELD score				
≤8	3 (5.6)			
>8	6 (17.8)	0.481	-	-
HAART during the follow-up				
No	1 (11.1)			
Yes	10 (18.8)	0.094	-	0.343
HE as the first decompensation				
No	7 (18.7)			
Yes	4 (20)	<0.001	23.75 (8.25-141.51)	<0.001
Baseline CD4 cell count				
<350	6 (8.6)			
≥350	6 (15.9)	0.042	-	0.072
% of follow-up with plasma HIV-RNA load below the detection level				
>50	7 (16.6)			
≤50	4 (11.7)	0.283	-	-

†E: Transient elastometry; ‡HE: hepatic encephalopathy

# Compensated Cirrhosis in Co-infected Patients

- 156 patients with compensated cirrhosis
- 36 (23%) experienced a decompensation
- 9/100 patient years
- Ascites most common, followed by hepatic encephalopathy and portal hypertensive GI bleeding
- 15 deaths (9.7%), 11 (73%) from liver disease
- 5-year survival rate 82%

# After first decompensation

- Survival significantly worse in co-infected vs. mono-infected patients:

	HIV/HCV	HCV alone
1 year	54%	74%
2 years	40%	61%
5 years	<b>25%</b>	44%

Pineda J et al. *Hepatology* 2005 41:779-789

# HCV Epidemiologic Questions

- Should we undertake routine screening, and should we routinely treat?
  - In favor:
    - Treatment is cost effective
    - Potential for cure, with decreased risk of sequelae of chronic infection
    - High cost of treatment of ESLD and OTLT
  - Against:
    - High cost of screening entire population
    - Additional tests also expensive
    - Many patients will not develop severe complications

# Complications of HCV



Head cheese and liver sausage

# Selected Complications of HCV

- Cognitive dysfunction
- Reductions in Quality of Life
- Type 2 DM

# HCV-related cognitive dysfunction

- May affect 1/3 of patients, even without cirrhosis
- Independent of indices of liver inflammation
- Patients may present with subtle memory or concentration deficits, or personality changes

# HCV-associated cognitive dysfunction: possible etiologies

- Underlying psychiatric disease
- Substance abuse
- High stress levels
- Direct viral effects
- Chronic inflammation

# Cognitive Dysfunction

- Hepatitis C-related dysfunction results in difficulties particularly affecting:
  - Short-term memory
  - Attention
  - Processing speed
- Degree of impairment correlates with degree of fibrosis
- Other underlying medical conditions exacerbate the impairment
- HIV/HCV coinfecting patients are more impaired than mono-infected patients

# Subtle cognitive impairment

- Comparison of 66 pts with HCV vs. 14 with other chronic liver diseases
- 82% impaired on measure of sustained attention
- Trend towards worse performance among patients with HCV vs. those with other liver diseases

Hilsabeck, et al. Neuropsychological impairment in patients with chronic hepatitis C. *Hepatology* 35:440-446 2002.

# Abnormal cerebral metabolism and cognitive impairments

- 25 HCV pts with histologically mild liver disease studied with cerebral proton MRS
- Patients showed impairments in working memory and attention compared to controls
- Higher myo-inositol/creatinine scores in frontal white matter in patients vs. controls
  - Significant correlation between MRS activity and prolonged working memory reaction times

Forton DM, et al. Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study. *J Hepatol* 49(3):316:322, 2008

# Cognitive dysfunction: mono-infection vs. coinfection

HCV alone (N = 47)

HCV/HIV (N = 29)

	HCV alone (N = 47)			HCV/HIV (N = 29)		
	Median	Range	% Impairment	Median	Range	% Impairment
TMT A	29.0	16-75	25.5	34.0	11-58	20.7
TMT B	66.0	36-247	27.7*	73.0	40-359	17.2
SDMT	47.0	13-37	31.9*	44.0	12-40	41.4*
Symbol Search <sup>a</sup>	30.0	17-62	22.2*	27.5	21-72	16.0

SDMT, Symbol Digit Modalities Test; TMT, Trail Making Test.

<sup>a</sup>There were no significant differences between the groups on the four cognitive measures (median).

\* $P < 0.025$  for comparison between patient groups and normal population.

Perry W, Carlson MD, et al. AIDS 19(S3) 2005

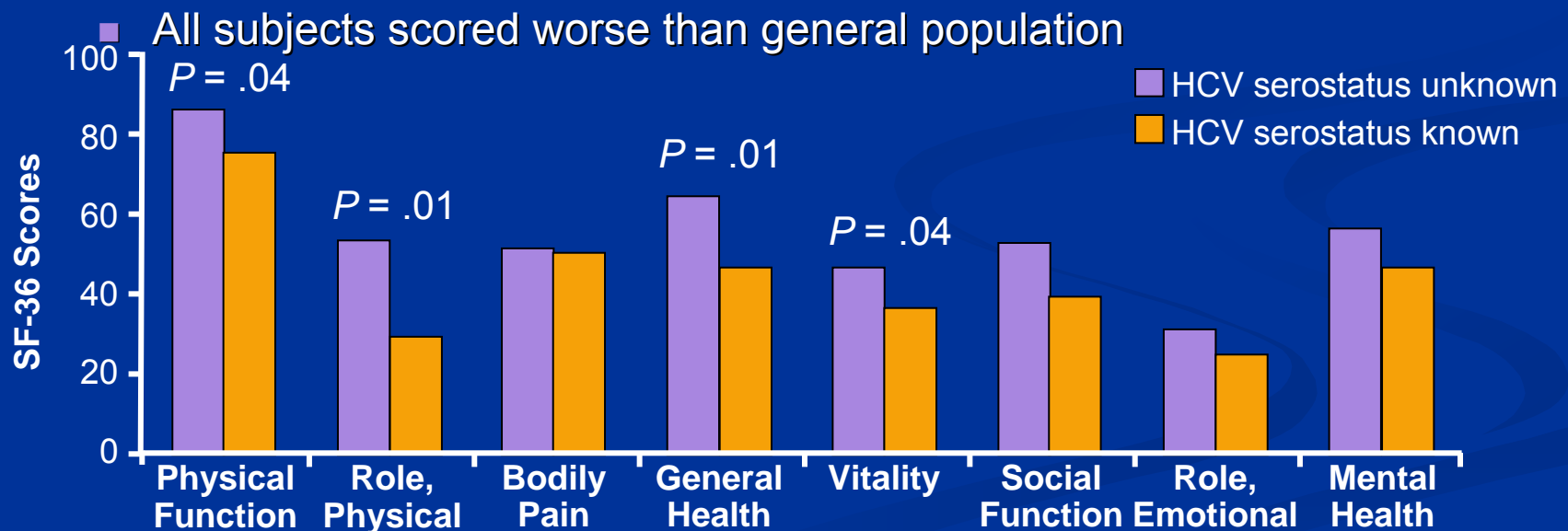
# Hepatitis C and Quality of Life

- Liver disease-specific instruments measuring QoL:
  - HCV-specific SF-36
    - Mental component score and physical component score added to make SF-36 more specific to HCV<sup>[1]</sup>
  - Chronic Liver Disease Questionnaire
  - Liver Disease Quality of Life Questionnaire
  - Hepatitis Quality of Life Questionnaire
  - Gastrointestinal Quality of Life Instrument

1. Ware JE Jr, et al. Hepatology. 1999;30:550-555.

# Lower QoL Scores in Patients Aware of HCV Serostatus

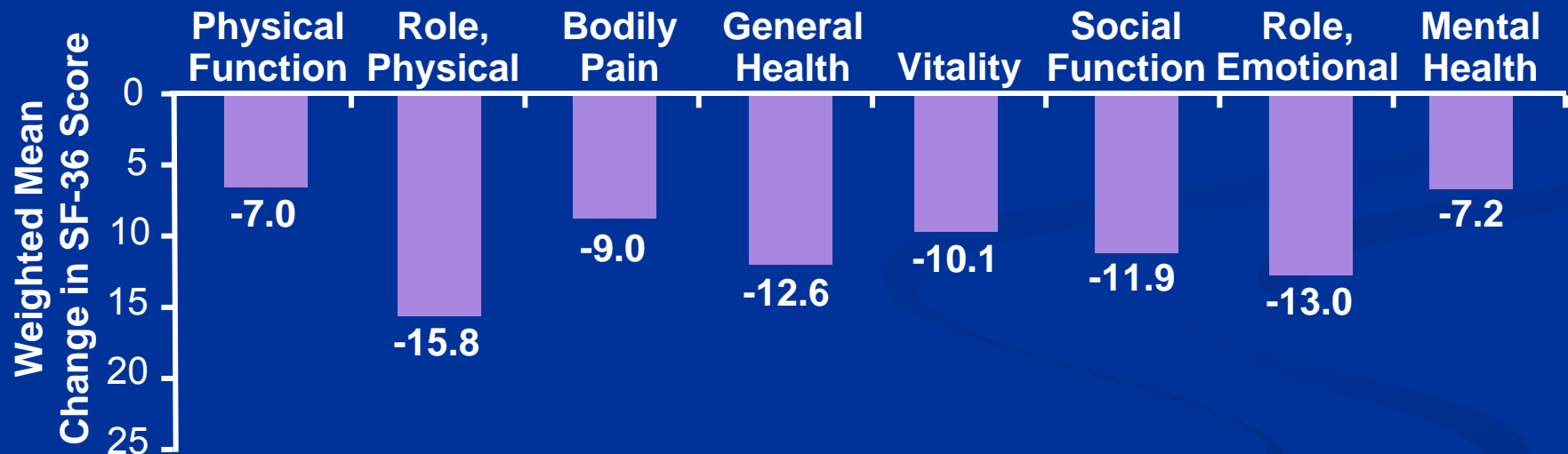
- 98 HCV-infected IVDU underwent SF-36 testing
  - 76% aware of HCV serostatus
- HCV patients aware of the diagnosis had worse QoL scores than those unaware of the diagnosis



Health-Related Quality of Life in Active Injecting Drug Users With and Without Chronic Hepatitis C Virus Infection, Dalgard AJ, et al. Hepatology. 2004;39:74-80.

# QoL Reductions Without Significant Liver Disease

- Systematic review of 15 studies comparing QoL in patients with compensated HCV vs healthy controls



- HCV may diminish QoL in the absence of clinically significant liver disease through extrahepatic somatic symptoms, extrahepatic disorders, or cognitive dysfunction

Spiegel BMR, et al. Hepatology. 2005;41:790-800.

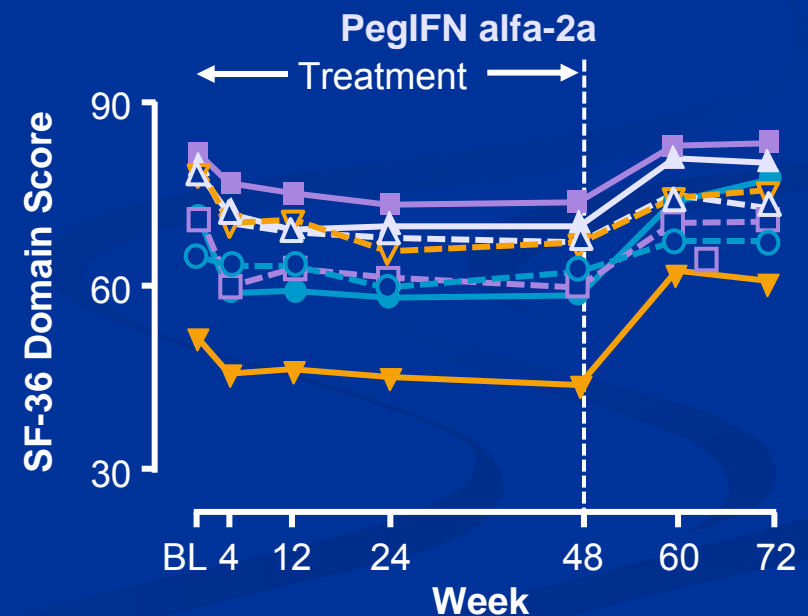
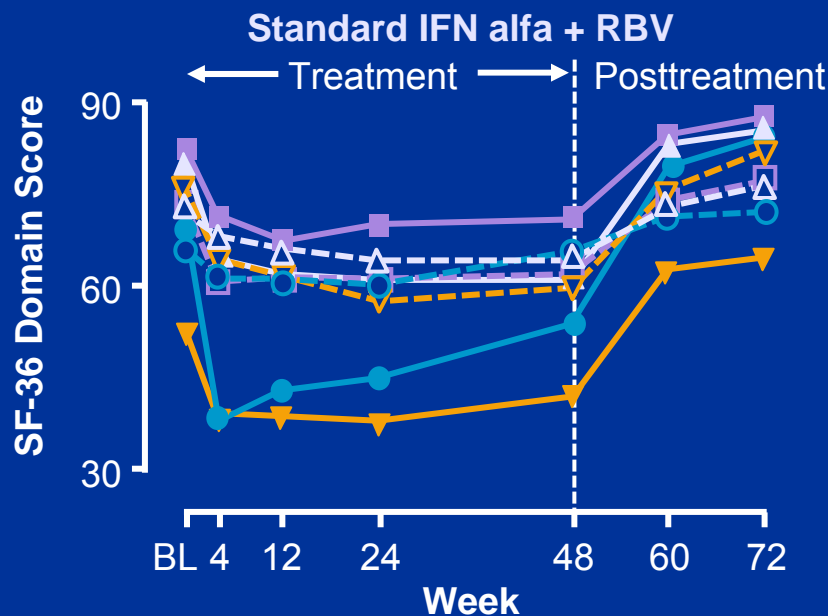
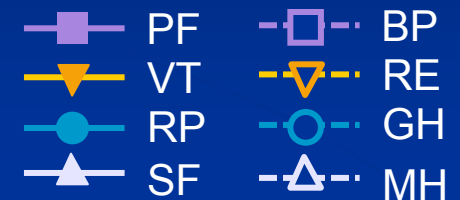
# Worse QoL in HCV/HIV- Coinfected Patients vs HIV- Monoinfected Patients

- QoL, depression, and fatigue compared between 105 HCV/HIV-coinfected patients vs 379 HIV patients in British Columbia
- Lower QoL, higher incidence of depression and fatigue in coinfecting patients thought to be explained by sociodemographic factors
  - Coinfected patients more likely female, injection drug users, unemployed, and living in unstable housing

	<b>HCV/HIV Coinfected (n = 105)</b>	<b>HIV Monoinfected (n = 379)</b>	<b><i>P</i> Value</b>
Female sex	18%	3%	< .001
Injection drug user	79%	5%	< .001
Unemployed	91%	49%	< .001
Unstable housing	19%	1%	< .001

# QoL Scores Decline in Pts Receiving HCV Therapy

- 412 HCV-infected pts randomized to open-label treatment with pegIFN alfa-2a vs IFN alfa-2b + RBV



Perrillo R, et al. Comparison of quality of life, work productivity and medical resource utilization of peginterferon alpha 2a vs the combination of interferon alpha 2b plus ribavirin as initial treatment in patients with chronic hepatitis C. *J Viral Hepat.* 2004;11:157-165.

# Greater QoL Reductions in HCV vs HBV Pts Receiving PegIFN alfa-2a

- Pooled data analyzed from 5 studies of pegIFN alfa-2a monotherapy in HCV compared with 2 studies in chronic HBV infection
- Lower incidence of common IFN-related AEs and a significantly lower incidence of depression in HBV pts
- Greater QoL reductions as assessed with SF-36 in HCV pts vs HBV pts
  - Scores returned to baseline levels after 24-wk follow-up period in both pt groups

Mean Reductions in On-Treatment SF-36 Composite Scores From BL to Wk 48	HBV (n = 448)	HCV (n = 791)	P Value
Physical component score	-1.1	-2.5	< .001
Mental component score	-1.7	-2.4	NS

# HCV Pts Achieving SVR Show Improved QoL vs Untreated Patients

- 912 pts randomized to IFN alfa-2b + RBV for 24 or 48 wks or placebo
- QoL scores from subset of pts achieving SVR analyzed with SF-36 QoL survey
  - At BL, pts scored lower in 5/8 categories vs general population
  - At end of follow-up, pts achieving SVR scored similarly in all but 1 QoL categories vs general population
    - General health remained lower ( $P < .05$ )

# Hepatitis C and DM

- HCV induces insulin resistance directly
- Insulin resistance has been closely linked to fibrosis, though also associated in pre-fibrotic stages
- One meta-analysis showed a 1.8 fold excess risk of DM II among HCV-positive compared with HBV-positive patients

# Prevalence of DM in HCV- and non-HCV-associated liver diseases

Author	Study population	HCV (%)	Non-HCV (%)
Allison	Cirrhosis (100)	50	9
Grimbert	Chronic liver disease (304)	24	9
Mason	Viral hepatitis (1117)	21	12
Caronia	Virus-related cirrhosis (1232)	23.6	9.4

# Interaction of Insulin Resistance, Steatosis, and Inflammation

## STEATOSIS

Increased FFAs; decreased adiponectin; activation of lipogenesis; diet (lipid, glucose)



## INFLAMMATION

Increased proinflammatory cytokines; ROS; activation of JNK; IKK; increased SOCS proteins



Visceral Fat  
Metabolic Syndrome  
Chronic HCV infection



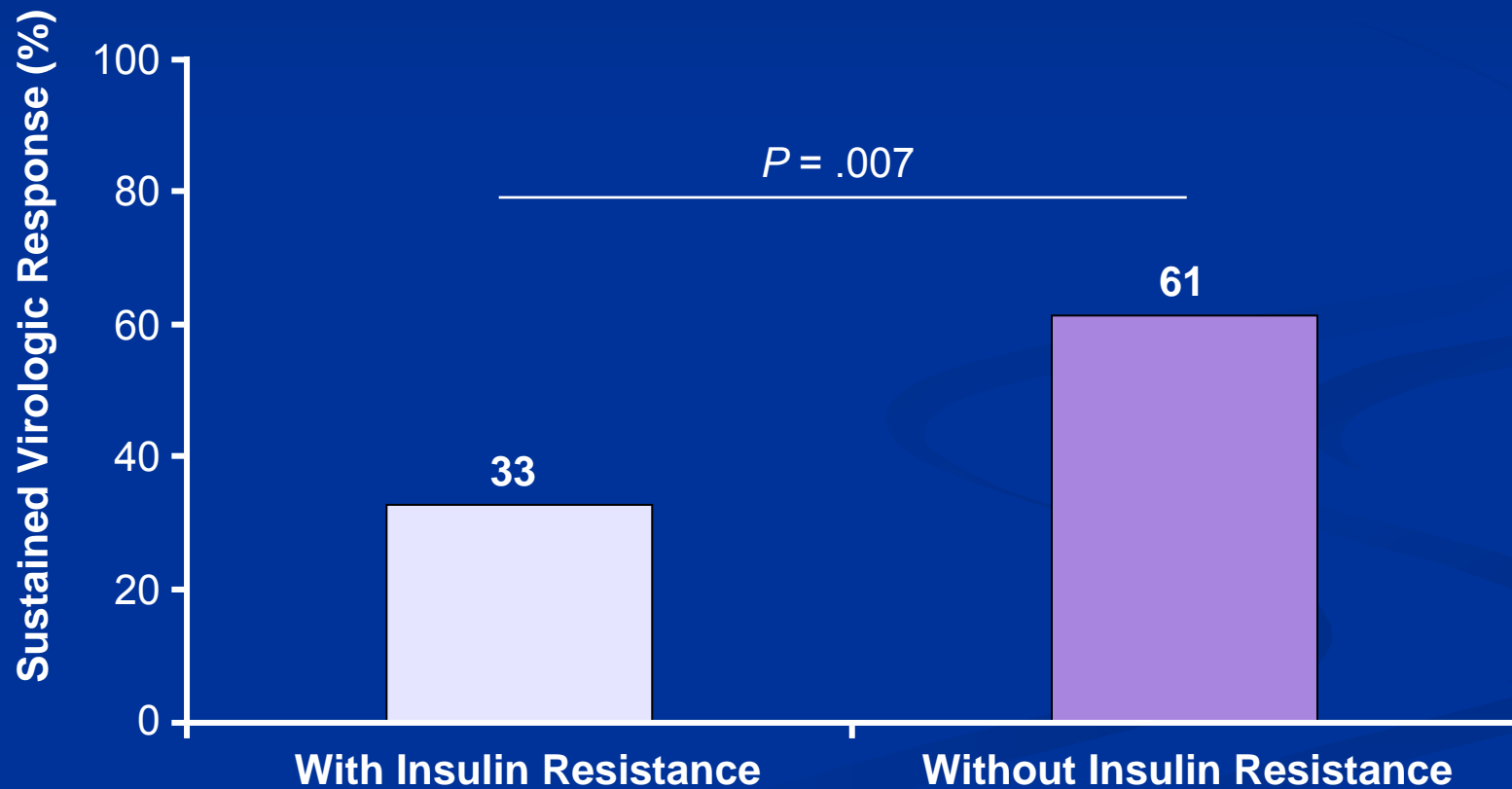
## INSULIN RESISTANCE

Downreg and serine phosphorylation of IRS proteins; Increased FFA, acylCoA, DAG; activation of PKC, JNK

# Consequences of HCV and Type 2 DM

- Type 2 DM and insulin resistance are independent predictors of more rapid progression of liver fibrosis and impaired response to antiviral treatment
- Patients with cirrhosis and Type 2 DM have increased risk of hepatocellular carcinoma, and increased susceptibility to hepatic encephalopathy

# Evidence: Insulin Resistance and SVR in HCV Genotype 1 Patients



# Candidate Selection



Monkfish liver sashimi

# Areas of consideration

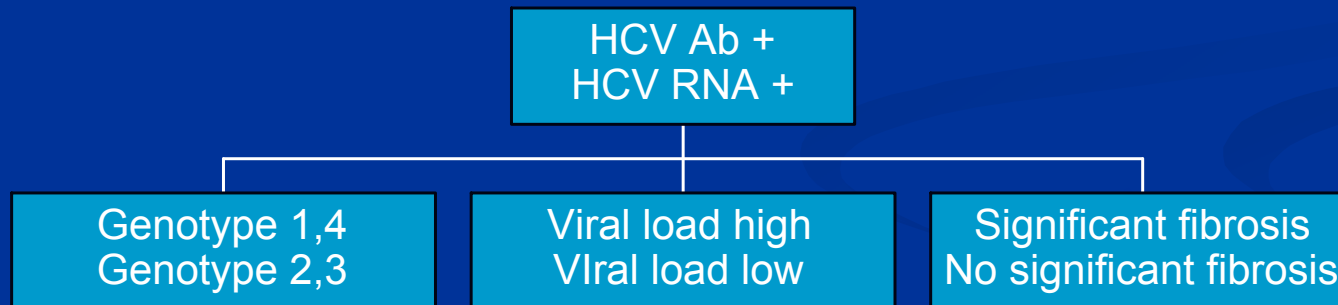
- HCV genotype and viral load
- Liver fibrosis
- Patient motivation
- Patient factors:
  - Depression
  - Substance Abuse

# Lab Testing

- Tests indicated for HCV:
  - CBC
  - LFTs
  - Urinalysis
  - Lipid panel
  - Serum glucose
  - Hep A, B serologies
  - PT
  - TSH
  - AFP (for patients with cirrhosis)
  - ANA screen
  - Ferritin
  - Anti-smooth muscle Ab

# Evaluation prior to treatment

Algorithm for Hepatitis C evaluation



# Liver fibrosis

- Imaging techniques: elastometry (FibroScan)
- Serum biochemical indices:
  - Fibrotest
  - APRI
  - SHASTA
  - FIB-4
  - Hyaluronic Acid

# Role of Biopsy

- Provides information about:
  - Necroinflammatory activity (grade)
  - Extent of fibrosis and presence or absence of cirrhosis (stage)
- Histological scoring systems:
  - IASL
  - Batts-Ludwig
  - Metavir
  - Ishak

# Role of Biopsy

- Gives information about two common non-HCV conditions that may impede treatment response:
  - Steatosis
  - Excess hepatocellular iron
- Identification of either of these features does not preclude treatment but provides additional information regarding likelihood of response

# Risk Factors for Rapid Progression of Fibrosis

- Older age at infection
- Male gender
- Excessive alcohol consumption
- Immunocompromised state
- Steatosis
- Diabetes
- High ALT levels

# Rationale for treatment without biopsy

Fairly high response rates to PEG IFN/RBV

- Faster progression of HCV-related liver disease in coinfecting patients
- Opportunity to assess viral response at 4 and 12 weeks identifies who will respond to ongoing therapy

## Case study: Mr. S

37 yo male with hx chronic LBP, major depression, remote drug/alcohol abuse and HIV/HCV coinfection with chronic transaminitis. HIV controlled on ART. HCV genotype 1a, HCV RNA 14,342. Liver biopsy April 2008 shows Grade 0, Stage 0 disease.

What do you counsel this patient?

# If no fibrosis, can treatment be delayed?

- 184 co-infected patients with at least 2 biopsies (median interval, 2.9 years)
- 10 excluded for cirrhosis on initial biopsy
- No or minimal fibrosis on initial bx in 136 patients (77%)
- 41 (24%) with significant fibrosis progression (2 or more stages)
- 26 (15%) with cirrhosis on either biopsy

# Progression of fibrosis

First Bx Stage

Second Bx Fibrosis Stage

	0	1	2	3	4	5	6
0	45	20	12	2	2	3	1
1	8	20	12	7	2	0	2
2	1	2	11	2	0	0	1
3	0	0	1	8	3	5	2
4	0	0	0	0	0	0	2

# Conclusions

- Progression of fibrosis over relatively short period of time is more common in co-infected (24%) vs. mono-infected patients (8-12%)
- Repeat biopsy at 3-5 years in mono-infected patients is probably adequate
- Biopsy not a sensitive method of identifying individuals at risk of subsequent fibrosis progression
- AST at initial biopsy more predictive of progression

# Case study: Mr. S

Would you recommend a repeat biopsy? If so, when?

Immediate follow up: biopsy repeated 6/09 because of patient anxiety; now shows Grade 3-4, Stage 2 disease!

# Case study: Mr. J

53 yo male with AIDS, history multiple recent pneumonias, poor ART adherence, recurrent IVDA (heroin and cocaine), on methadone maintenance, 30 mg/day. Last used IV drugs 2 months ago. Also has a history of intermittently controlled bipolar disorder. Going to school and raising his young daughter. Has refused HCV work up, aside from lab studies, several times in the past. Now complaining of intermittent sedation and confusion/delirium.

Exam shows cachexia, mild asterixis.

Labs: CD4 222/16%, HIV VL 68,400 on meds X 3 weeks, HCV genotype 1b, HCV RNA 233,645, AST 154, ALT 59, Albumin 1.8, Total bilirubin 2.2, INR 1.37, AFP 19, WBCs 3.9, Hgb 9.2, Plts 93.

Liver biopsy: Grade 4, Stage 4 disease

# Case study: Mr. J

- Is ongoing substance abuse a contraindication to treatment?
- If so, how long should a patient be drug-free prior to consideration for treatment?
- What about methadone maintenance?
- Any other treatment contraindications?

# Absolute Contraindications to therapy

- Decompensated liver disease: Child-Pugh-Turcotte Class B or C
- Advanced cardiopulmonary disease
- Renal failure
- Pregnancy
- Baseline hematologic abnormalities:
  - Hgb < 9
  - ANC < 1000
  - Plts < 50,000
- Uncontrolled Major Depression

# NIH Consensus Conference Statement

- All patients with chronic hepatitis C are potential candidates for antiviral therapy
- Treatment is recommended for patients with an increased risk of developing cirrhosis

# NIH Consensus Conference Statement

“HCV therapy has been successful even when the patients have not abstained from continued drug or alcohol use....Thus it is recommended that treatment of active injection drug use in and of itself not be used to exclude such patients from antiviral therapy.”

NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002.  
Available at: <http://consensus.nih.gov/2002/2002HepatitisC2002116html.htm>.

# Treating Patients with Ongoing Substance Abuse

- NIH Guidelines indicate that HCV treatment is possible in the setting of drug use
  - Participation in support groups, methadone clinics encouraged
  - Methadone maintenance *not* a contraindication
- Ongoing alcohol use can affect response to HCV therapy
  - Level of safe alcohol use not determined
  - Abstinence from alcohol during HCV therapy encouraged to maintain adherence

# Treating Patients with Active Substance Abuse

- Observational study of 184 providers treating:
  - 244 patients with active opiate abuse or on opiate substitution
  - 578 former users
  - 1031 non-users
- Rates of adherence and SVR were similar in all 3 groups
- QoL actually less impaired in active users/those on substitution therapy

# Treatment Response Patterns and Terminology



Cornmeal mush with liver

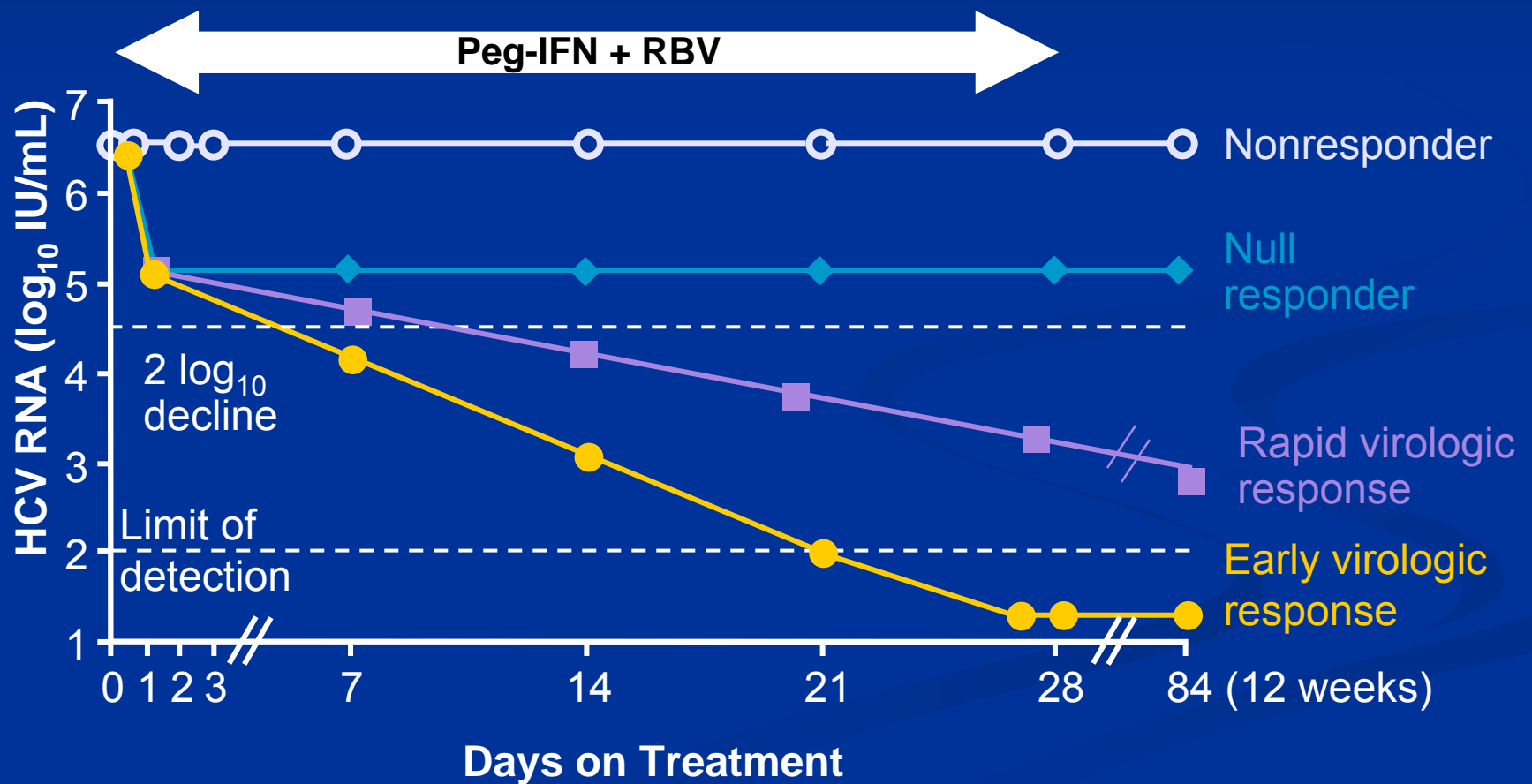
# Treatment Definitions

<b>Nonresponse</b>	Failure to achieve HCV RNA reduction at any time point during therapy
<b>RVR</b>	HCV RNA undetectable by Week 4
<b>EVR</b>	$\geq 2 \log_{10}$ decline in HCV RNA by Week 12
<b>Null Response</b>	HCV RNA decline $< 2 \log_{10}$ IU/mL by Week 12
<b>Partial Virologic Response</b>	$\geq 2 \log_{10}$ decline in HCV RNA by Week 12, but HCV RNA detectable at Week 24

Pawlotsky JM. Hepatology. 2002;36(suppl 1):S65-S73.

Sethi A, et al. Clin Liver Dis. 2005;9:453-471.

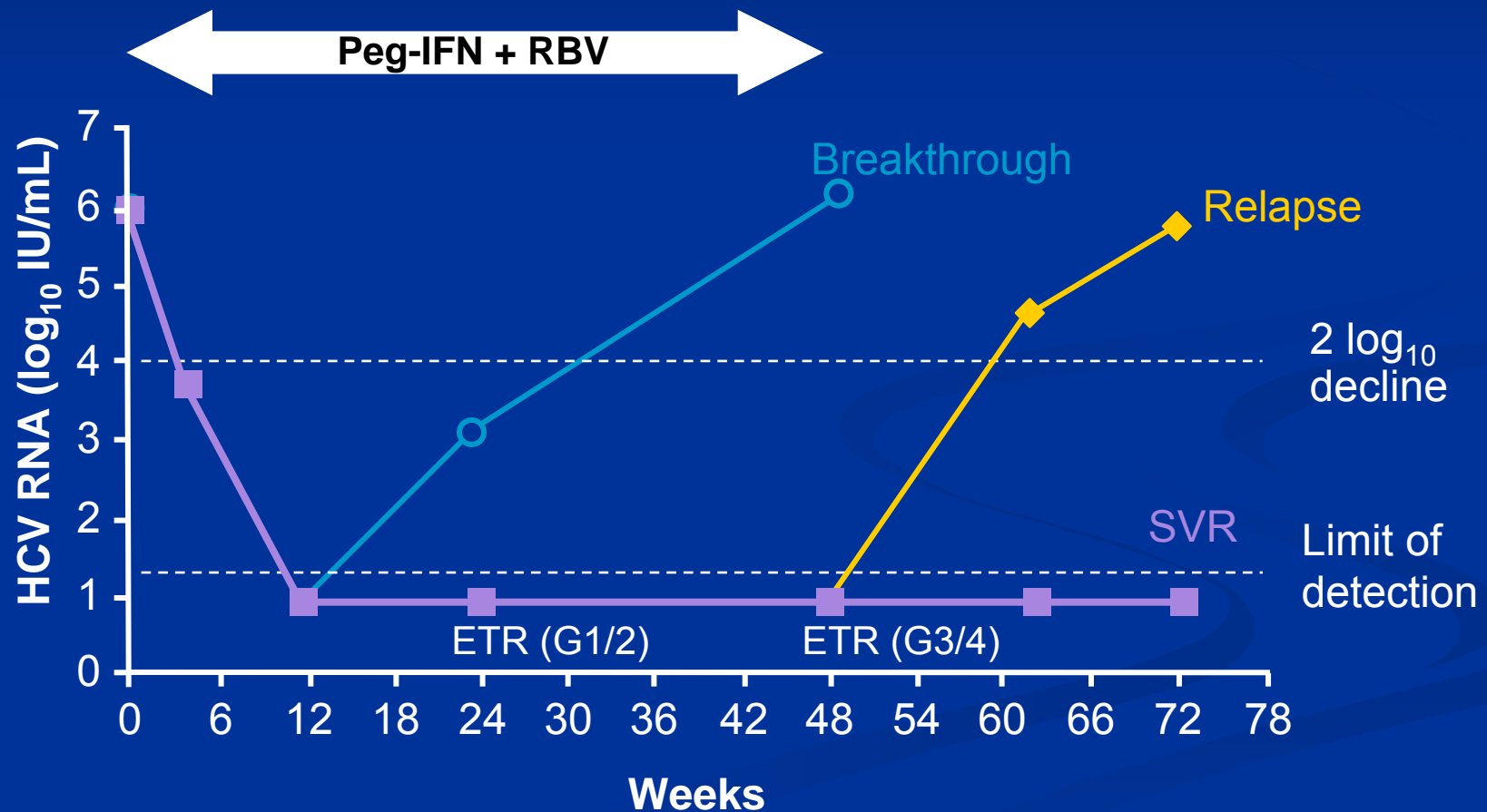
# Early Patterns of Response to Initial HCV Therapy



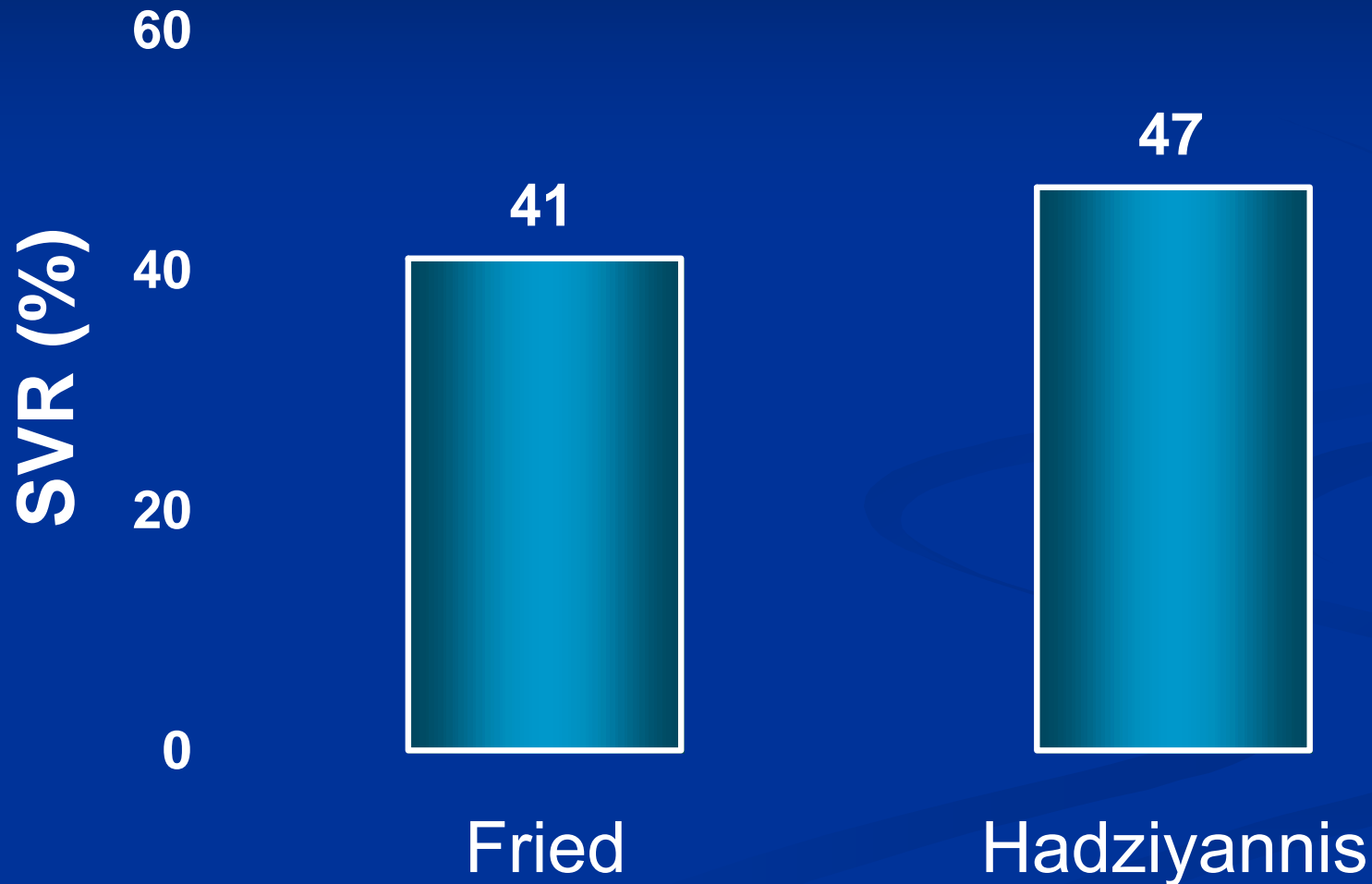
# Definitions of Response to Treatment

<b>ETR</b>	Undetectable HCV RNA at end of treatment
<b>Virologic Breakthrough</b>	Decline in HCV RNA to undetectable levels followed by rebound of detectable HCV RNA despite continued treatment
<b>SVR</b>	HCV RNA negativity 24 weeks after treatment end
<b>Relapse</b>	End of treatment response followed by rebound of detectable HCV RNA after treatment discontinuation

# Different Virologic Responses to HCV Therapy After Week 12



# PEG IFN alfa 2a and Ribavirin SVR by Genotype 1, HVL



Fried MW, NEJM, 2002

Hadziyannis S Ann Intern Med 2004

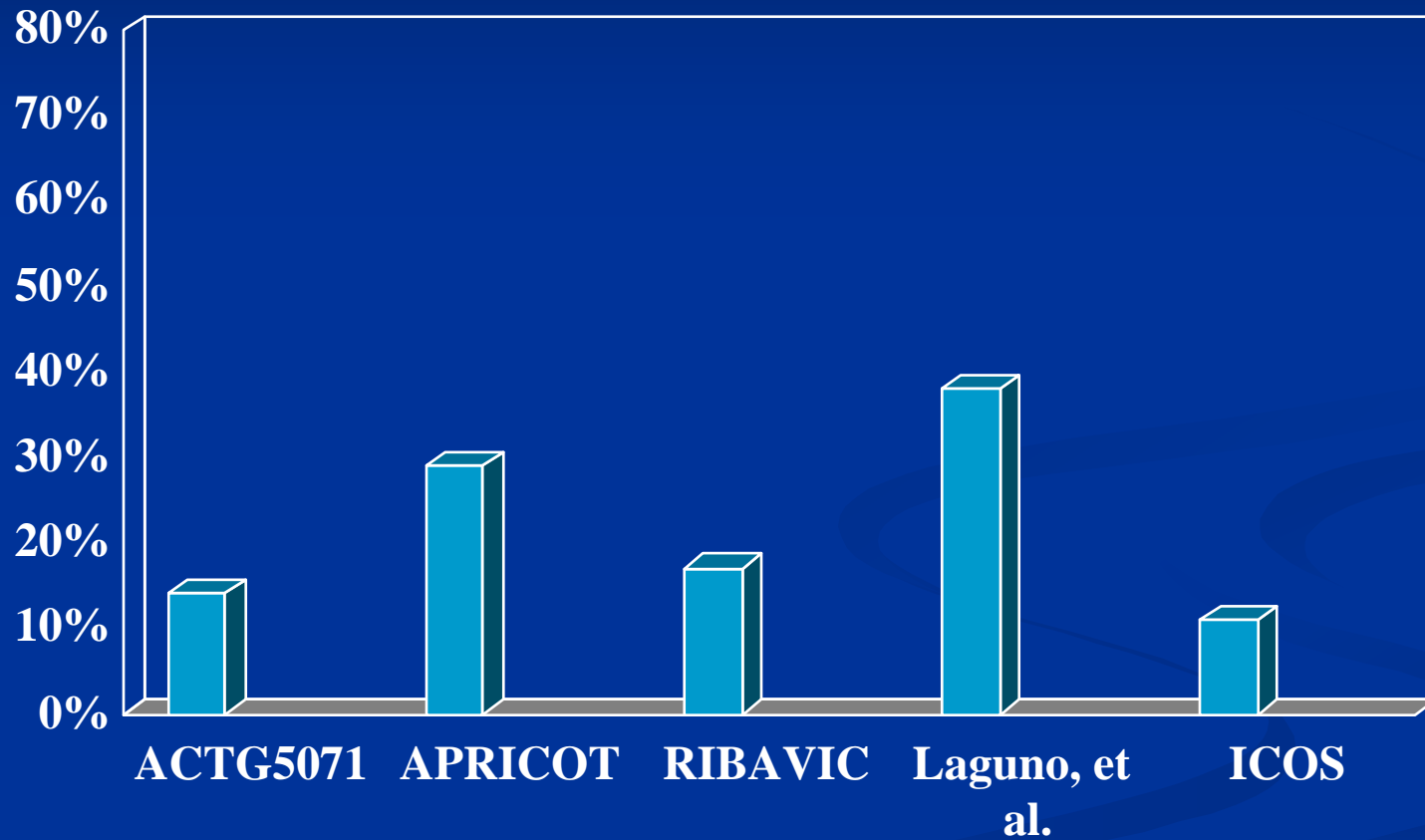
# PEG IFN alfa 2b and Ribavirin SVR by Genotype 1, HVL



Jacobson IM, Hepatology, 2007

Manns M Lancet 2001

# Response rates from major trials: Geotypes 1 & 4



Treatment either PEG-IFN $\alpha$ -2a or PEG-IFN $\alpha$ -2b + Ribavirin

# Predictors of SVR: fixed factors

- Most important:
  - Genotype 2 or 3
  - Low viral load (<800,000)
- Less important:
  - Age (Older patients ↓ response)
  - Weight (Greater BMI ↓ response)
  - Race (AA ↓ response)
  - Liver fibrosis (Stage 3-4 ↓ response)

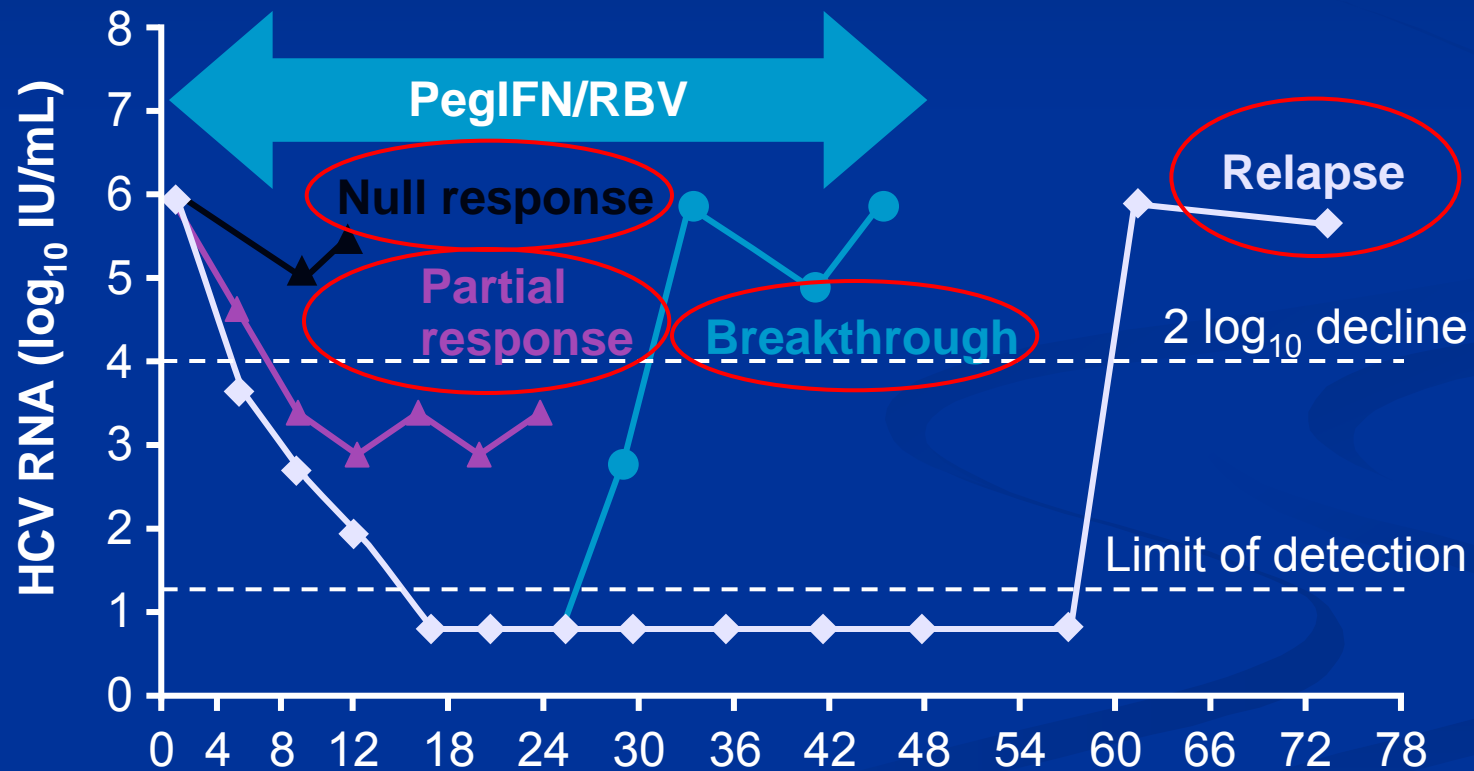
# Predictors of SVR: variable factors

- Adherence: 80/80/80 rule
- Active heavy alcohol use
  - However, patients who used alcohol and completed treatment had comparable SVR rates to non-drinkers
- Insulin resistance
- Steatosis/steatohepatitis

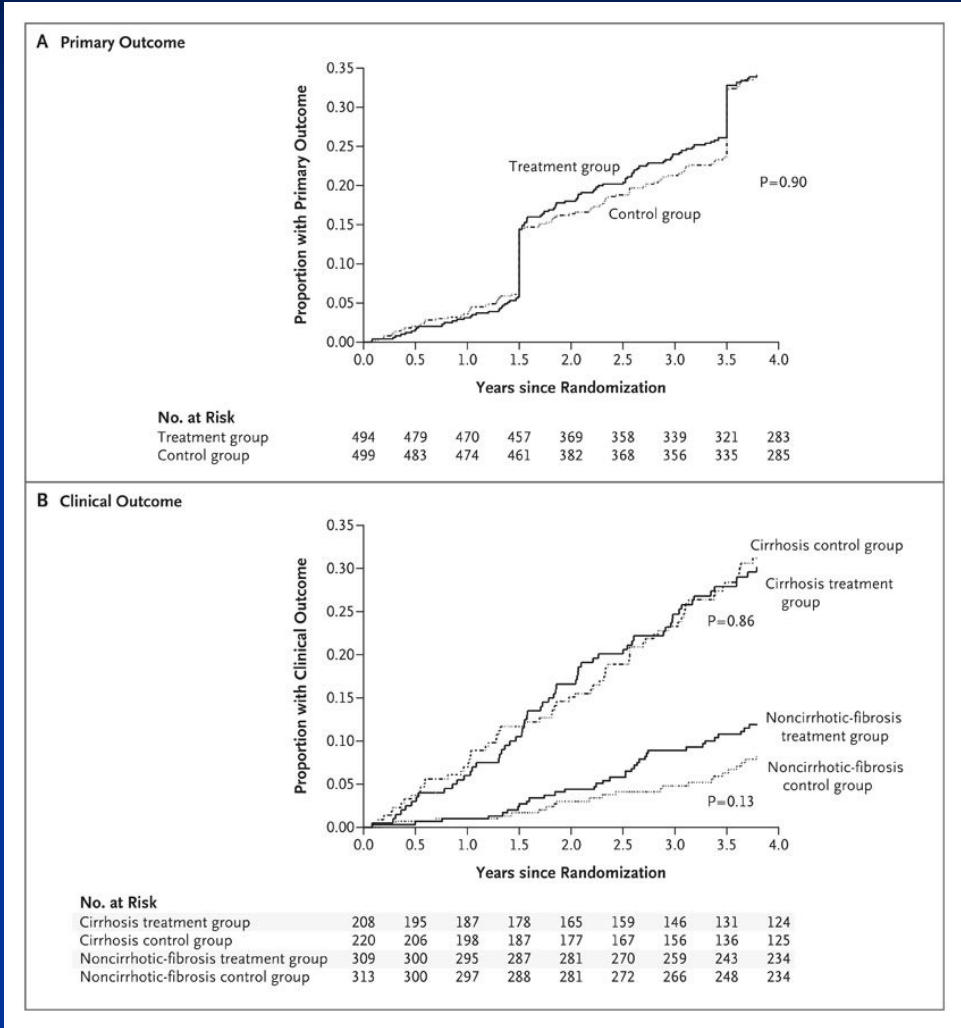
# Maintenance Tx: HALT-C Trial

- 1050 patients with chronic HCV and advanced fibrosis without SVR to PEGIFN/RBV randomly assigned to receive low-dose PEGIFN alfa 2a (90 mcg/wk) or no treatment for 3.5 years
- Primary end point was progression of liver disease, indicated by death, HCC, hepatic decompensation, or increase in Ishak score by 2 or more points

# Suboptimal virologic responses



# Kaplan-Meier Analysis of Time to the Primary Outcome and the First Clinical Outcome



Di Bisceglie AM et al. N Engl J Med 2008;359:2429-2441



The NEW ENGLAND  
JOURNAL of MEDICINE

# HALT-C Summary

- Despite improvements in aminotransferases and liver histology, long term therapy with peginterferon did not reduce rates of disease progression in patients with chronic HCV and advanced fibrosis who did not respond to initial treatment with P/R

# Post-treatment

QuickTime™ and a  
decompressor  
are needed to see this picture.

Haggis with neets and tatties

# Case study: Mr. F

47 yo male with HIV/HCV coinfection, genotype 1a, HCV RNA 58,925. Biopsy showed grade 1-2, stage 1-2 disease. Treated with standard IFN  $\alpha$  2a and low-dose RBV in 2000, with SVR documented by repeat HCV RNA 6 months following end of treatment. CD4 during treatment  $\cong$  500. Has been on and off ART, with most recent CD4 of 180, HIV RNA <50. Ongoing alcohol abuse, drinks 6-12 beers/night. HCV RNA rechecked for chronic transaminitis with ongoing alcohol abuse intermittent cocaine use.

Current labs:

AST/ALT: 103/123, remainder of LFTs normal

HCV RNA: 1,026,060

Is this a relapse, or a reinfection?

# Does treatment confer ongoing immunity?

- 211 coinfecting patients
- 16 episodes of recurrent viremia after SVR
- 8 available for analysis
- 6/8 with divergent paired sequences indicating reinfection with new strain
- Reinfection related to ongoing high-risk sexual activity

# Does treatment confer ongoing immunity?

- 51 viremic IDUs treated with IFN or PEG-IFN alpha 2a or 2b
- 28 (55%) achieved SVR
- 13/28 (46%) used illicit injection drugs in the 1.1 mean years of follow up
- 25/28 (89%) remained HCV RNA neg
  - 1 died of HCC
  - 1 lost to follow up
- 1 with recurrent viremia

# Case study: Mr. F

- Recurrent HCV viremia likely reinfection secondary to unprotected sex or cocaine abuse

# HCV Drugs in Development



Chopped liver

# The “STAT-C” Concept

- “Specifically Targeted Antiviral Therapy for HCV”
- Will be added to, not instead of, ‘reference therapy’ (PEGIFN/RBV)
- Will result in higher response rates
- May allow for shorter durations of treatment
- Genotypic and phenotypic resistance testing will become common

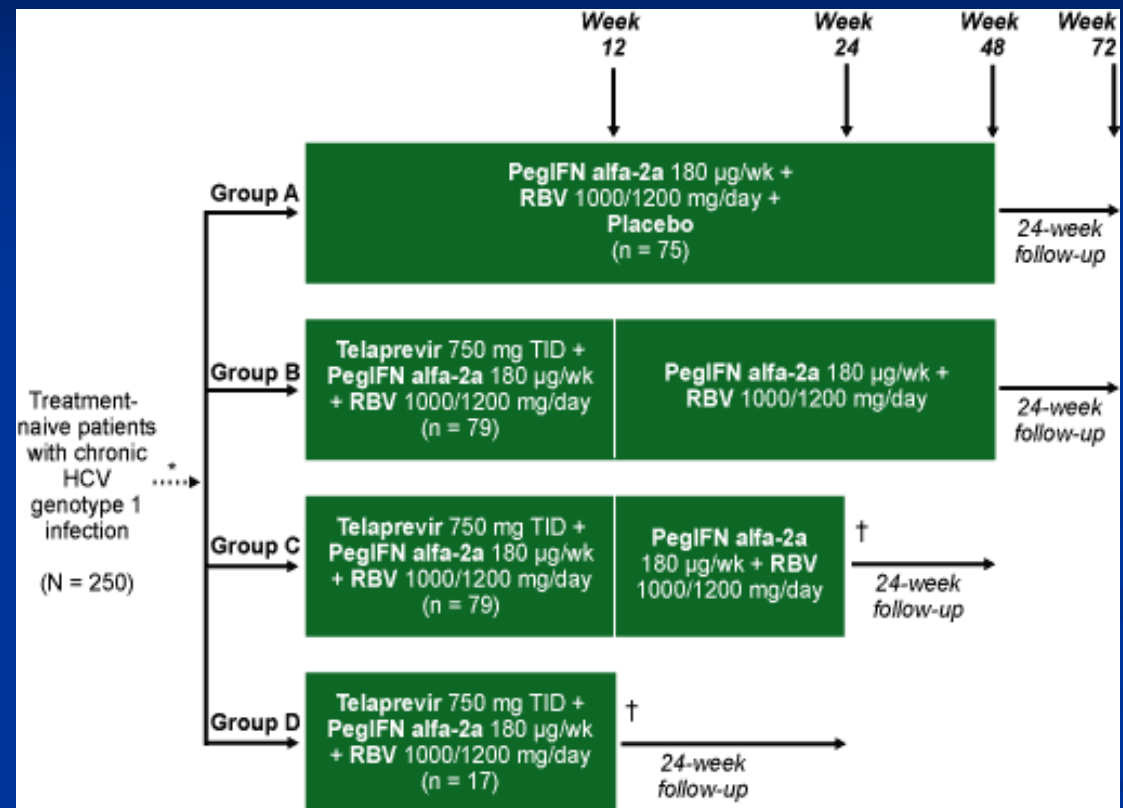
# STAT-C Drugs

- Protease and polymerase inhibitors will be the first approved
  - 2 protease inhibitors currently in Phase 3 trials
- Once several STAT-C agents become available, may allow for PEGIFN/RBV sparing regimens

# Telaprevir (VX-950)

- NS3 protease inhibitor produces dramatic HCV RNA suppression over a 14-day course (4-5.5 log), either alone or in combination with PEG-IFN
- Viral rebound during monotherapy follows replication of variants with high-level telaprevir resistance

# Telaprevir: PROVE1



PegIFN, peginterferon; RBV, ribavirin; TID, 3 times daily.

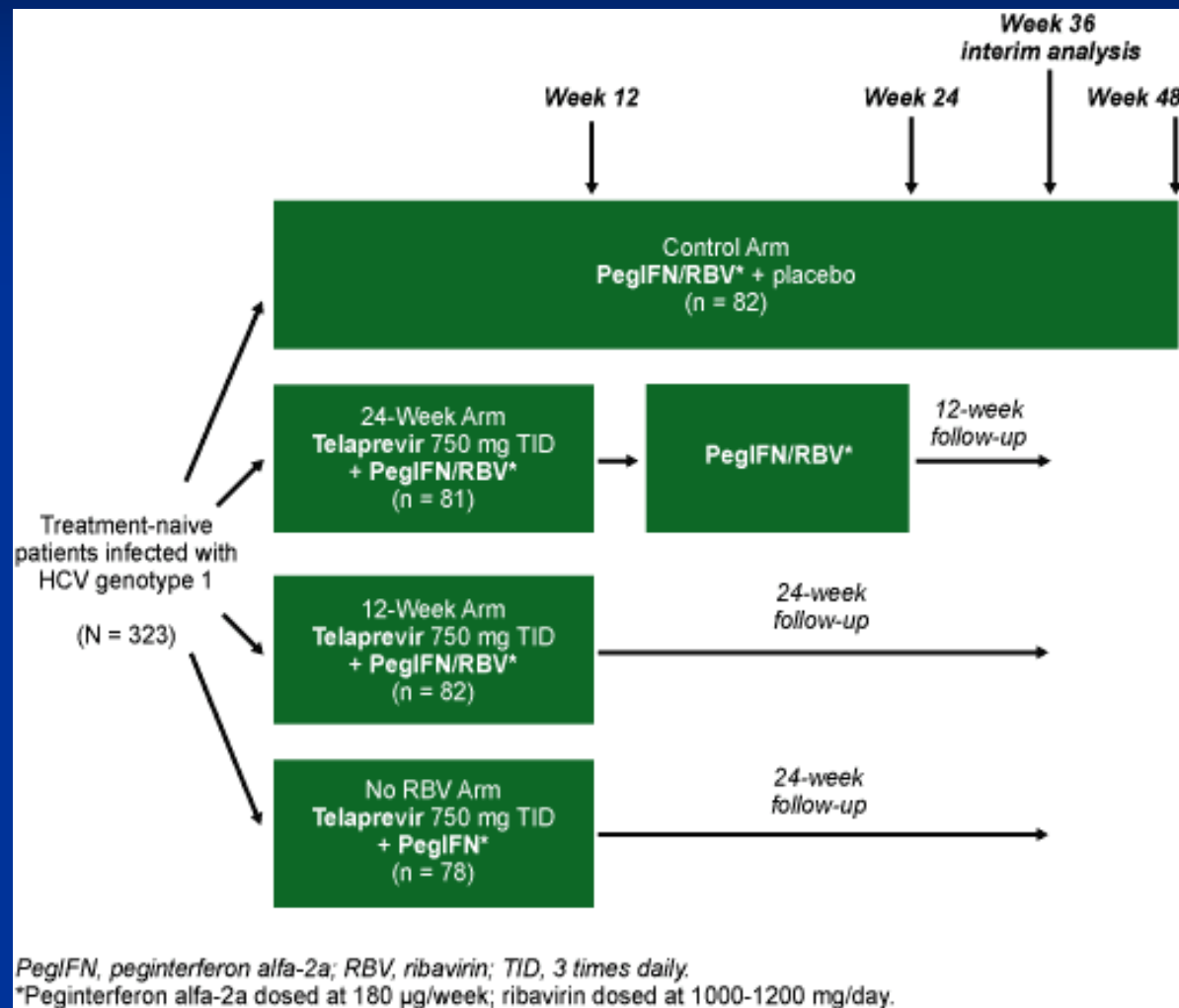
\*Patients received telaprevir 1250-mg loading dose or placebo based on the arm to which they were randomized.

†Patients must achieve undetectable HCV RNA at Week 4 (< 10 IU/mL) and at last test before stopping therapy at 12 or 24 weeks.

# PROVE1 Results

Response, n (%)	Group A: Control (n = 75)	Group B: 12 + 36 = 48 weeks (n = 79)	Group C: 12 + 12 = 24 weeks (n = 79)	Group D: 12 weeks (n = 17)
SVR	NA	NA	48 (61)	6 (35)
ETR	34 (45)	51 (65)	NA	NA
Lost to follow up	NA	NA	8 (10)	1 (6)

# Telaprevir: PROVE2



# PROVE2 Results

Undetectable HCV RNA	Controls (n = 82)	24-week arm (n = 81)	12-week arm (n = 82)	No RBV arm (n = 78)
Week 4	13	69*	80*	51*
Week 12	41	73*	79*	62*
SVR	Ongoing	65	59	29

\*P < .001

Zeuzem S, et al. PROVE2 interim analysis. 58th AASLD November 2-6 2007

# PROVE3 Phase 2b Trial

- Patients with genotype 1 chronic HCV infection who failed prior therapy with PEGIFN/RBV
  - Null responders
  - Relapsers
  - Breakthroughs
- 453 patients, analyzed by ITT

# PROVE3 rates of sustained virologic response at 12 wks

	TVR12/PR24	TVR24/PR48	PR48
Non-responders	39% (n=66)	38% (n=64)	9% (n=68)
Relapsers	69% (n=42)	76% (n=41)	20% (n=41)
Breakthroughs	57% (n=7)	50% (n=8)	40% (n=5)
Total	<b>51%</b> (n= 115)	<b>52%</b> (n=113)	<b>14%</b> (n=114)

# PROVE3 Other Results

- Relapse rates:
  - 13% (10/76 patients) in 48-week arm
  - 30% (26/87) in the 142% (14/14) ~~142% (14/14)~~
  - 53% (18/34) in the control arm
- Completers' analysis showed 4% relapse rate in 48 week arm vs. 52% in control arm
- 5% discontinuation rate secondary to rash
- Rates of anemia same in all groups

# Telaprevir

- Ongoing Phase III trial:
  - >1000 patients at >100 U.S. centers
  - Telaprevir + PEG-IFN + RBV for 24 weeks, vs. PEG-IFN + RBV for 48 weeks
  - Results expected 2010

# Boceprevir

- NS3 serine protease inhibitor
- Also results in dramatic reductions in HCV viral load

# SPRINT-1: Boceprevir + P/R

- Phase IIb study combining boceprevir plus P/R for either 28 or 48 weeks, compared to P/R alone
- Study also evaluated low- vs. standard-dose RBV, and 4-week P/R lead-in phase vs. no lead-in

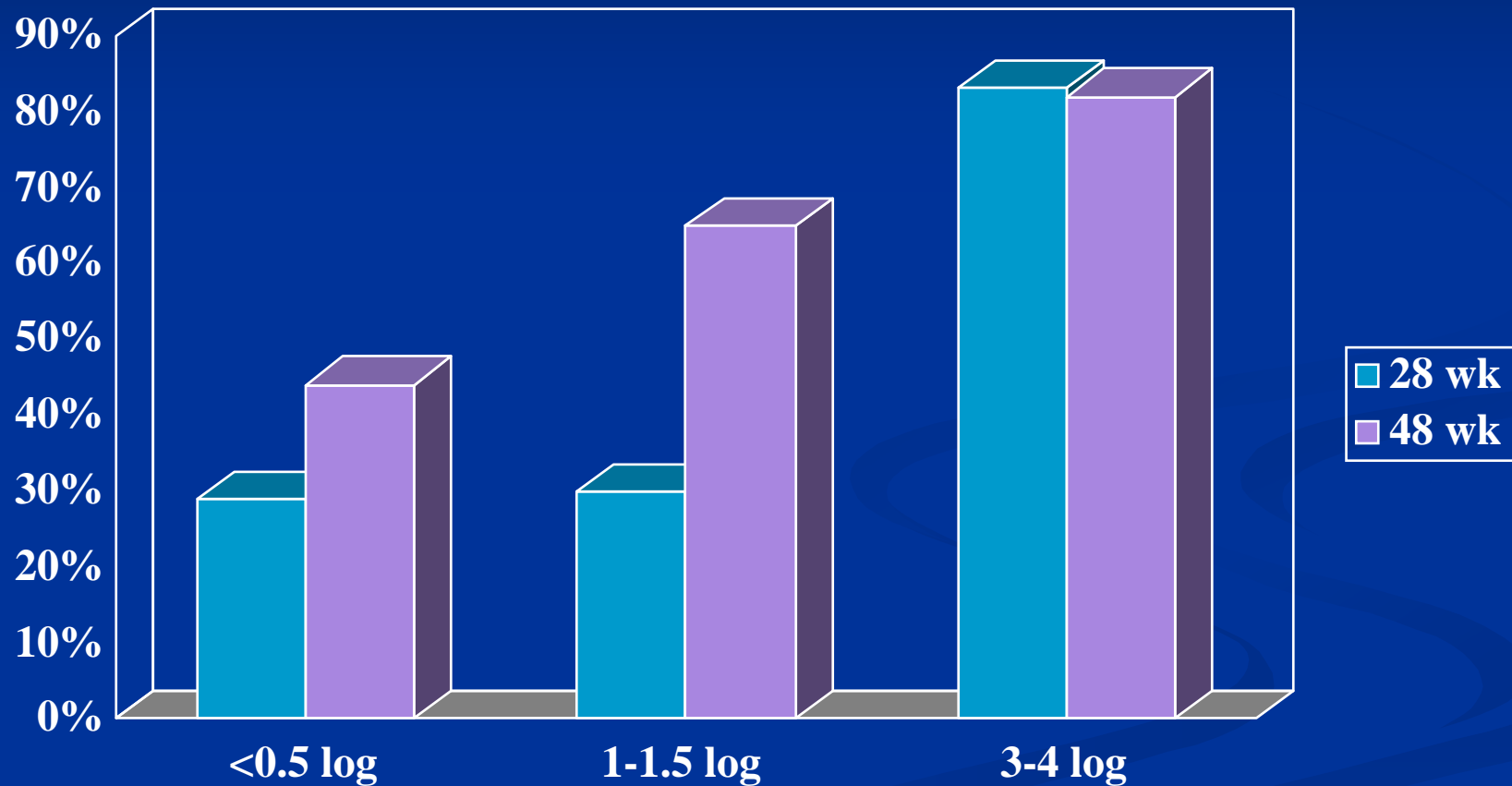
Kwo P, et al. HCV SPRINT-1 final results: SVR 24 from a phase II study of boceprevir plus peginterferon alfa-2b/ribavirin in treatment-naïve subjects with genotype 1 chronic hepatitis C. Program and abstracts of the 44th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2009; Copenhagen, Denmark. Abstract 4.

# SPRINT-1 Results

	28 wk with lead-in	48 wk with lead-in	28 wk no lead-in	48 wk no lead-in	Controls
SVR	56%	75%	54%	67%	38%
Relapse	24%	3%	30%	7%	24%

Kwo P, et al. HCV SPRINT-1 final results: SVR 24 from a phase II study of boceprevir plus peginterferon alfa-2b/ribavirin in treatment-naive subjects with genotype 1 chronic hepatitis C. Program and abstracts of the 44th Annual Meeting of the European Association for the Study of the Liver; April 22-26, 2009; Copenhagen, Denmark. Abstract 4.

# Response rates based on VL reduction at 4 weeks



Kwo P, et al. HCV SPRINT-1 final results: SVR 24 from a phase II study of boceprevir plus peginterferon alfa-2b/ribavirin in treatment-naive subjects with genotype 1 chronic hepatitis C. EASL, 2009; Copenhagen, Denmark. Abstract 4.

# Boceprevir and Anemia

- Additional 1g/dL drop in Hgb seen in boceprevir arm
- Use of stimulating factors lowered discontinuation rates
- 50% of patients in boceprevir plus full dose RBV arms received erythropoietin vs. 26% of controls
- Other adverse events similar in both arms

# Other Pipeline Drugs

## Albinterferon alfa-2b: long-acting IFN

- Much longer 1/2-life will allow for Q2-week or even Q4-week dosing
- Somewhat disappointing results show similar response rates in treatment-naïve and treatment-experienced patients
- “Quality of life” higher in the Albinterferon group

## ■ R1626: Polymerase inhibitor

- Phase IIb study: when combined with P/R, 74% of geno 1 pts reached undetectable HCV RNA at 4 wks vs. 5% controls
- High rates of grade 4 neutropenia, rare infections
- Now on hold because of heme effects

# Other Pipeline Drugs

- GI 5005: novel immunotherapeutic agent
  - Heat-activated *Saccharomyces cerevisiae* yeast expresses the HCV NS3 protease and core proteins
  - Subcut drug given weekly boosts viral clearance
  - Favorable phase 2 data presented at AASLD 2008

# Other Pipeline Drugs: Multiple Classes

- Monoclonal Abs
- TLR9 agonists
- NS5A inhibitors
- Antiphospholipids
- Cyclophilin inhibitors
- Pancaspase inhibitors
- Glucosidase I inhibitors
- IRES inhibitors
- Polymerase inhibitors
- Protease inhibitors
- Therapeutic vaccines
- Immunomodulators

# Hepatitis C Treatment: the near future

- PEG-IFN and RBV are going nowhere
- Look for more side effects, not less, as more drugs are combined
- Combination therapy may allow for a mercifully shorter treatment duration

# Hepatitis C treatment: long-term

- Combo therapy from several classes simultaneously with:
  - Fewer side effects
  - More oral meds
  - Higher cure rates

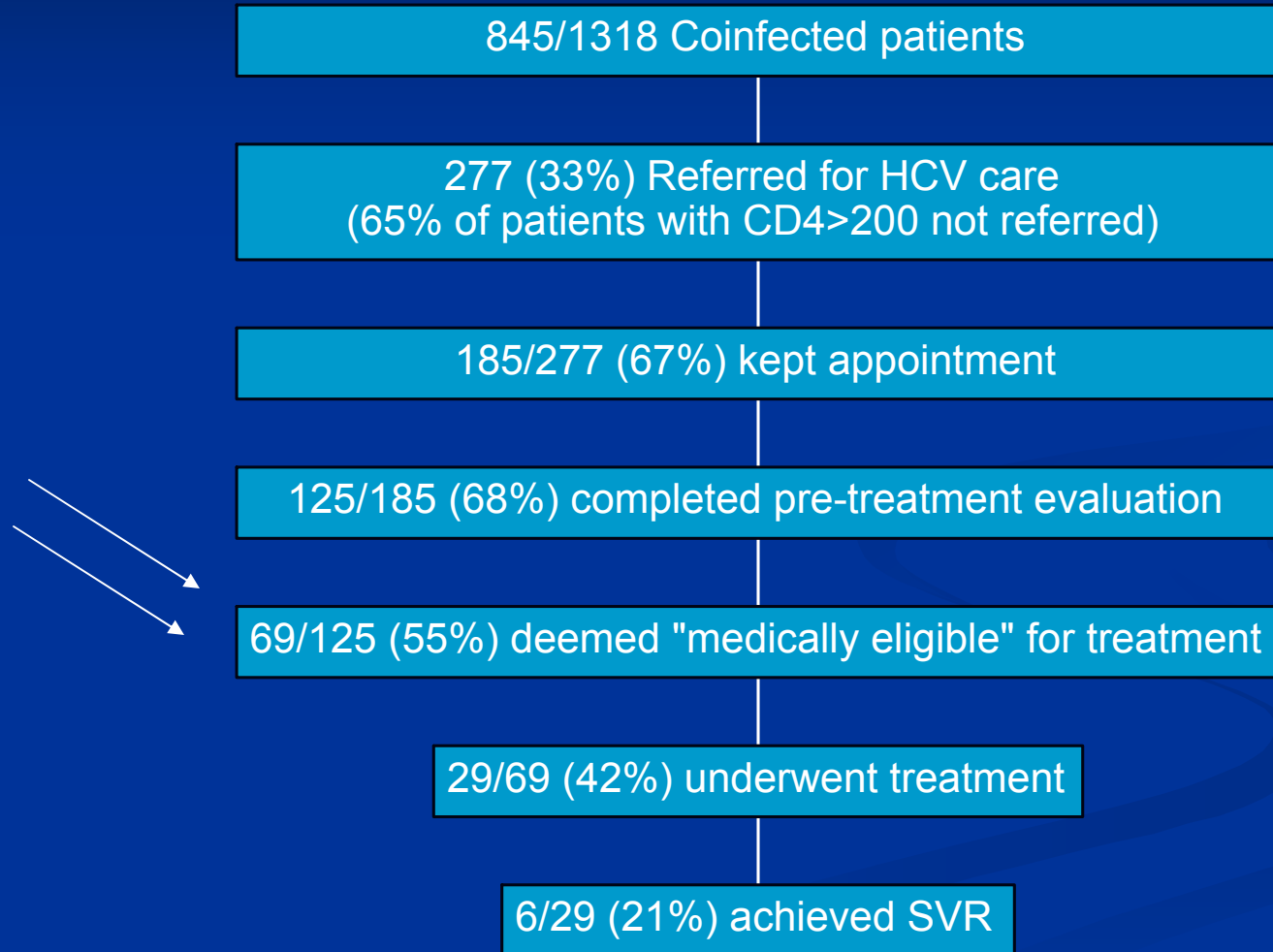
# Denver Health HIV PCC Treatment Experience



Liver pâté

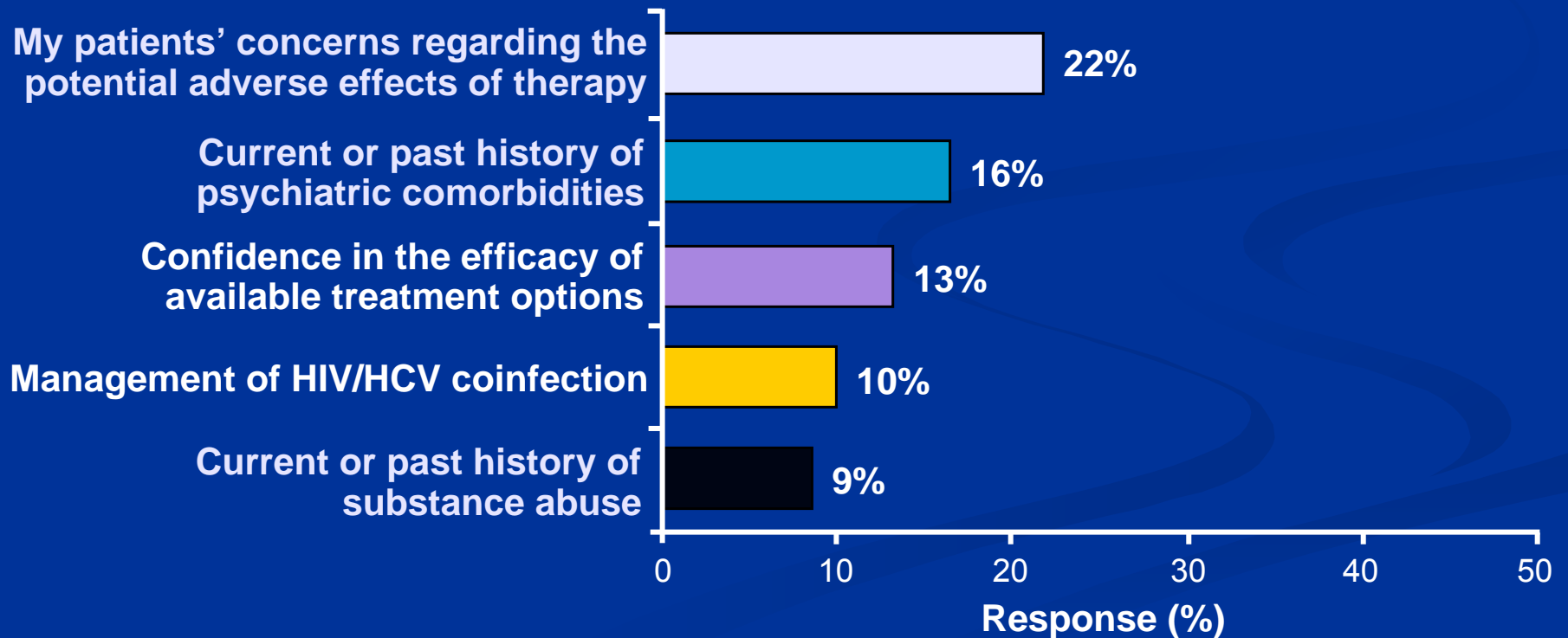
# Why Take Over HCV Treatment?

## Johns Hopkins Clinic Experience



# Barriers to Successful HCV Therapy

Question: What is the number 1 barrier to *initiating treatment* for a patient with chronic hepatitis C?





# HIV PCC Patients

Pt #	Gen	VL	Grade	Stag	Dispo
1	1b	125K	2	3	Treat: RNA <615 @ 12 & 24 weeks. Went to prison and treatment stopped
2	1a	3 mil	4	4	Child C, referred for OTLT. Deceased.
3	2b	2 mil	2	1	Treat: VL <615 @ 12 wks, ETR, SVR
4	1a	220K	3	2	Null responder; will begin consensus IFN
5	1a	1 mil	2	2	Stopped treatment 2/2 psychiatric side effects
6	1a	200K	2	3-4	Completing treatment. VL <615 at 12 weeks. Severe leukopenia despite neupogen and dose reduction
7	1b	2.75 mil	2-3	4	Attempted treatment; failed secondary to severe depression and alcoholism
8	1a	14,342	0	0	relapse Repeat bx 6/09 shows Gr. 3-4, Stage 2!

# Hepatitis C Update: Summary

- HCV-related liver disease is a source of tremendous morbidity and mortality in the co-infected population
- Cognitive dysfunction is an insidious and common complication of chronic infection
- HCV infection associated with significant declines in QoL, even after adjustment for many cofounders
- Diabetes and insulin resistance are common in patients with chronic HCV, and impact response to treatment

# Hepatitis C Update: Summary

- We are not managing HCV aggressively:
  - 2002 NIH consensus statement encourages consideration of most patients for treatment, including patients with ongoing alcohol and/or substance abuse
- Consider treating those at highest risk for complications of chronic liver disease
- Don't look for an excuse not to treat

# Hepatitis C Update: Summary

- Multiple drugs are in development, but Interferons and ribavirin will remain the backbone of therapy for the foreseeable future
- Treatment duration can be tailored according to genotype and RVR, with therapy ranging from 12-72 weeks
- Failure to achieve an RVR at 12 weeks is the most accurate predictor of not achieving SVR
- Approximately half of patients do not respond or relapse after current therapy. Newer agents will be needed to address this failure

# Great internet resources for providers undertaking hepatitis treatment

- [www.clinicaloptions.com](http://www.clinicaloptions.com)
- [www.hivandhepatitis.com](http://www.hivandhepatitis.com)
- [www.hcvadvocate.org](http://www.hcvadvocate.org)

**End**