

# Hepatitis C in Texas

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## Screening, Therapeutic Options & The Role of Expert Networks in Management

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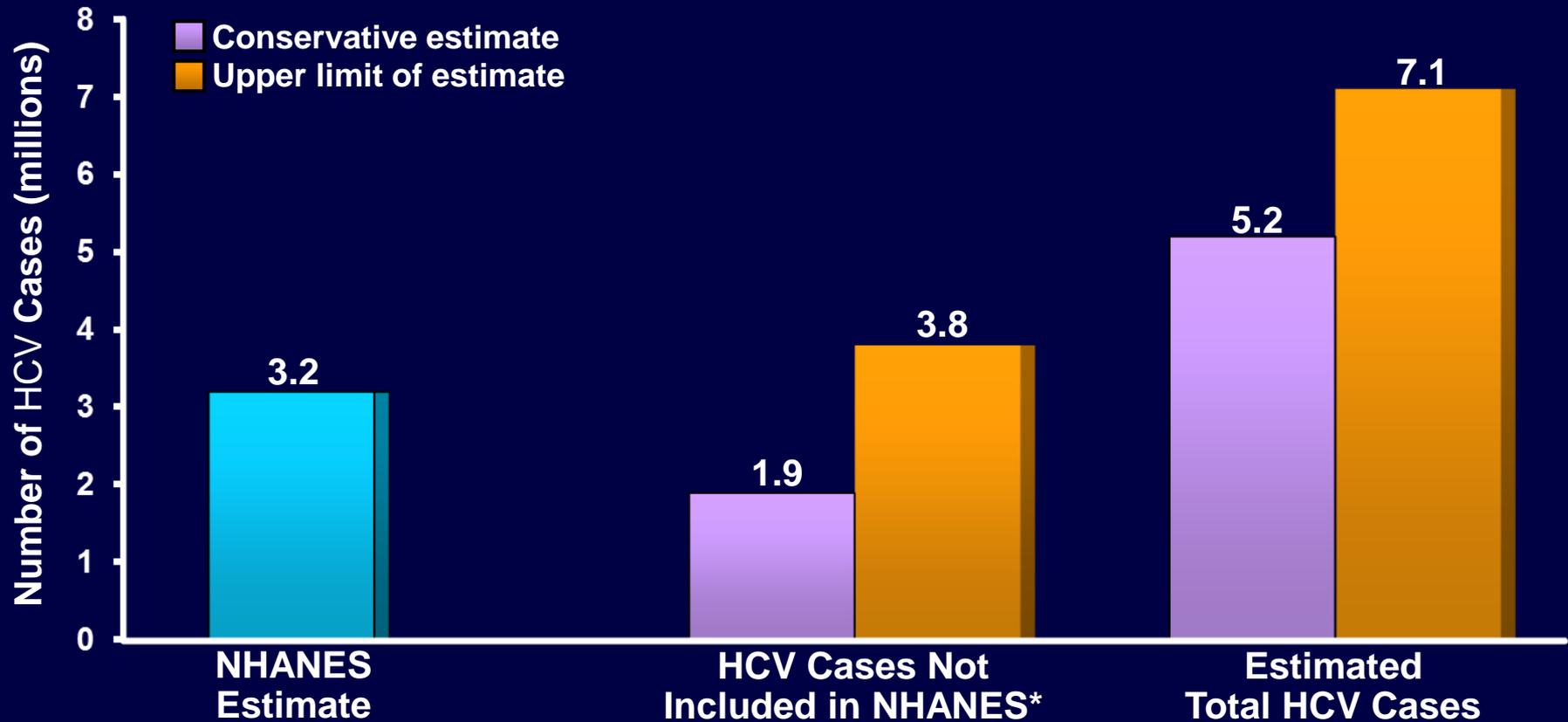
# Learning Objectives

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*After this lecture, you will:*

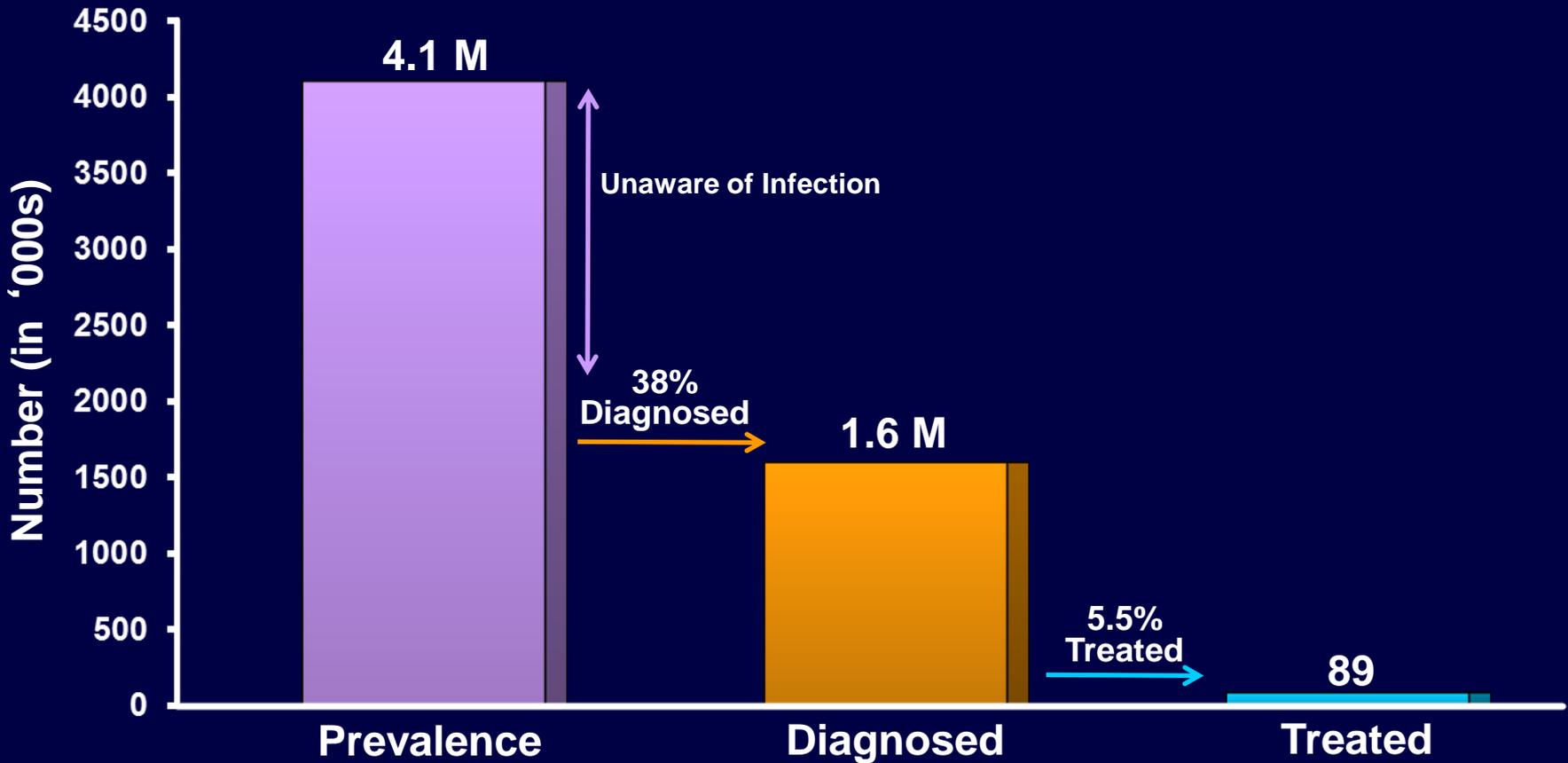
- Be familiar with the prevalence of HCV in the USA and in Texas
- Understand the impact of HCV on health and mortality
- Be familiar with drug targets and antiviral agents to treat HCV infection
- Recognize the potential impact of expert networks in managing complex diseases

# USA – People with Chronic HCV



\*Homeless (n=142,761-337,6100); incarcerated (n=372,754-664,826); veterans (n=1,237,461-2,452,006); active military (n=6805); healthcare workers (n=64,809-259,234); nursing home residents (n=63,609); chronic hemodialysis (n=20,578); hemophiliacs (n=12,971-17,000).

# Chronic HCV in the US: Underdiagnosed and Untreated

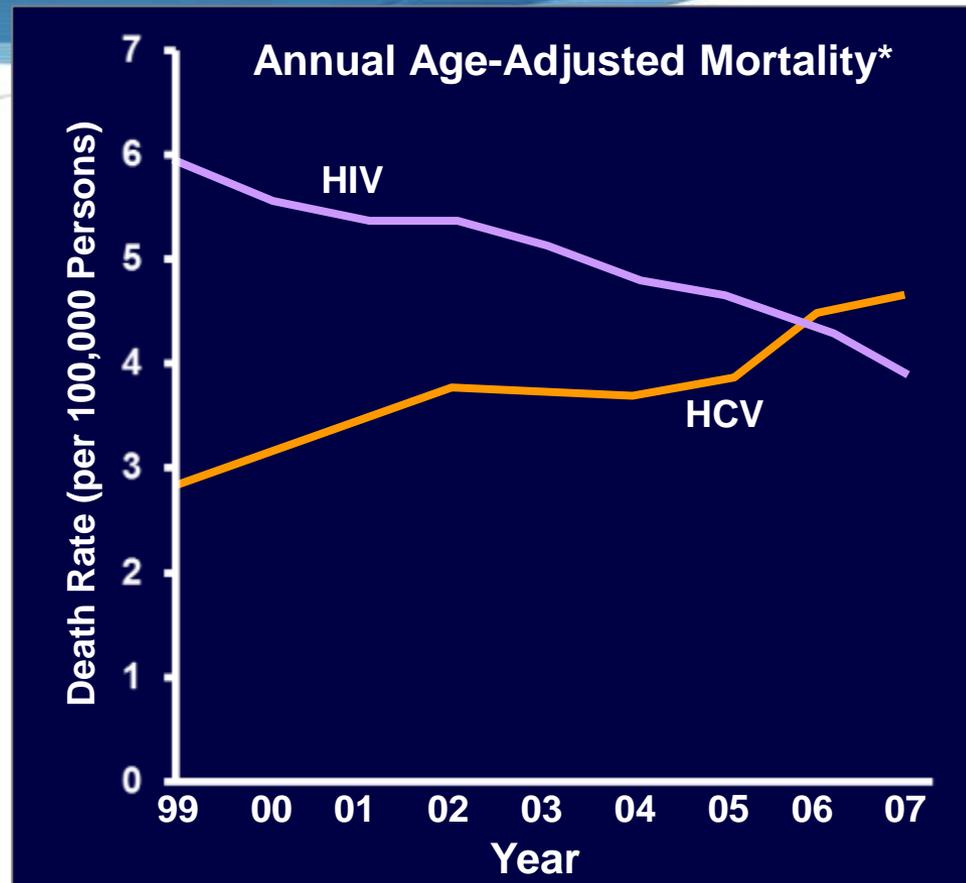


Estimated treatment rate is based on Q2 and Q4 2011 chart audits.

# HCV and HIV Mortality in the USA

1999-2007

- US multiple-cause mortality data (NCHS, 50 states plus DC)
  - Death certificate data
  - Approximately 21.8 million deaths
- Change in age-adjusted mortality rates (per 100,000 person-years)
  - HCV: increased 0.18 ( $P=0.002$ )
  - HIV: decreased 0.21 ( $P=0.001$ )
- New policy initiatives are needed to detect and link HCV patients to care and treatment



NCHS: National Center for Health Statistics.

\*A record listing >1 type of infection was counted for each type of infection.

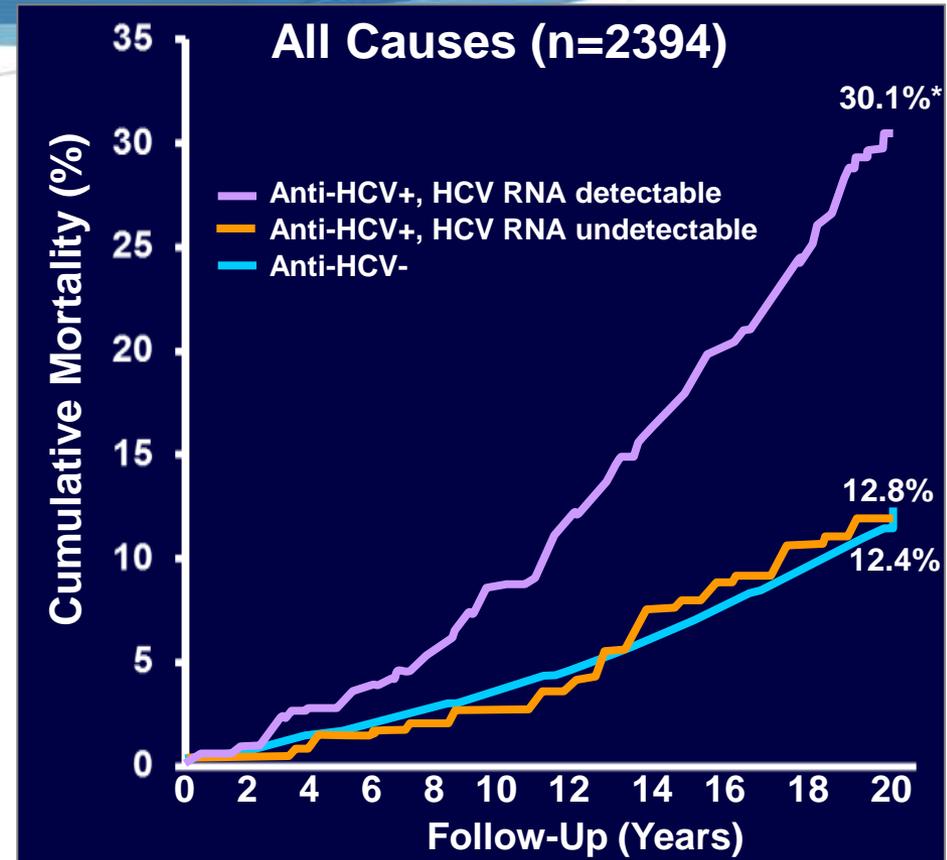
# REVEAL-HCV Study: Risk of Chronic HCV on Hepatic and Extrahepatic Deaths

- Community based, long-term, prospective study
  - Residents from 7 townships in Taiwan (n=23,820; Ages: 30 to 65 years)
- Current analysis (n=19,636 HBsAg-negative)
  - Anti-HCV seronegative (n=18,541)
  - Anti-HCV seropositive (n=1,095)
    - Detectable HCV RNA: 69.4%
- Deaths: 2,394 over 317,742 person-years of follow-up
  - Average follow-up: 16.2 years
  - Overall mortality: 753.4 per 100,000 person-years

**REVEAL: Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer. Enrollment 1991-1992. Last follow-up: 12/2008.**

# REVEAL-HCV: All Causes Mortality

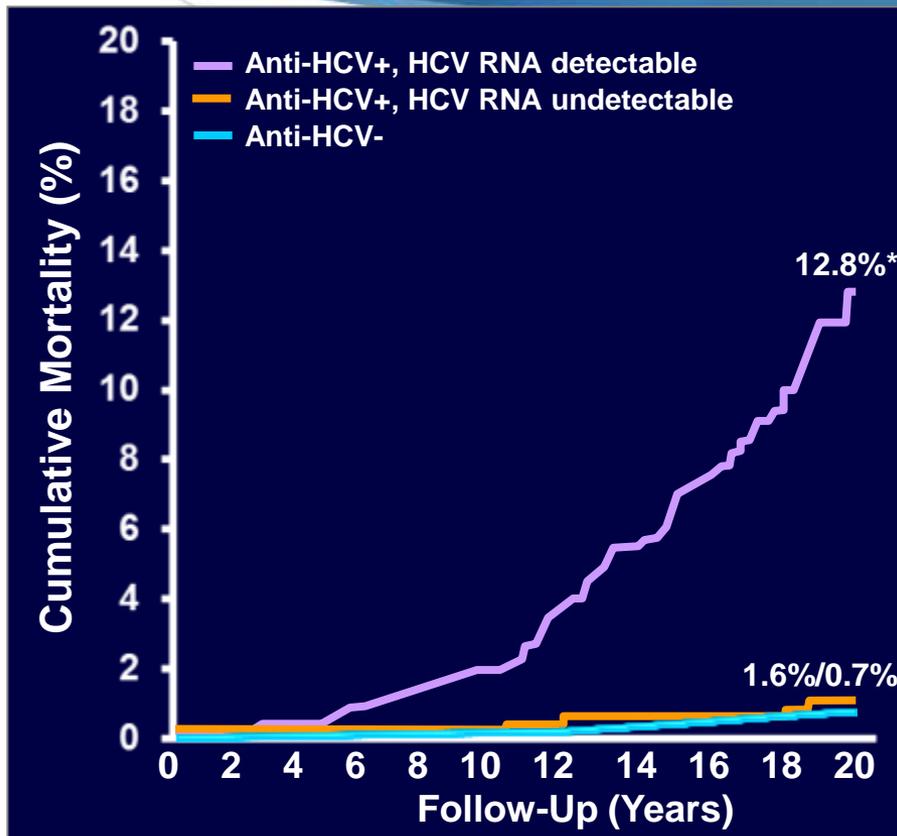
- Risk of dying from all causes, hepatic diseases, and extrahepatic diseases
  - Significantly higher in anti-HCV seropositives with detectable HCV RNA levels ( $P < 0.001$ )



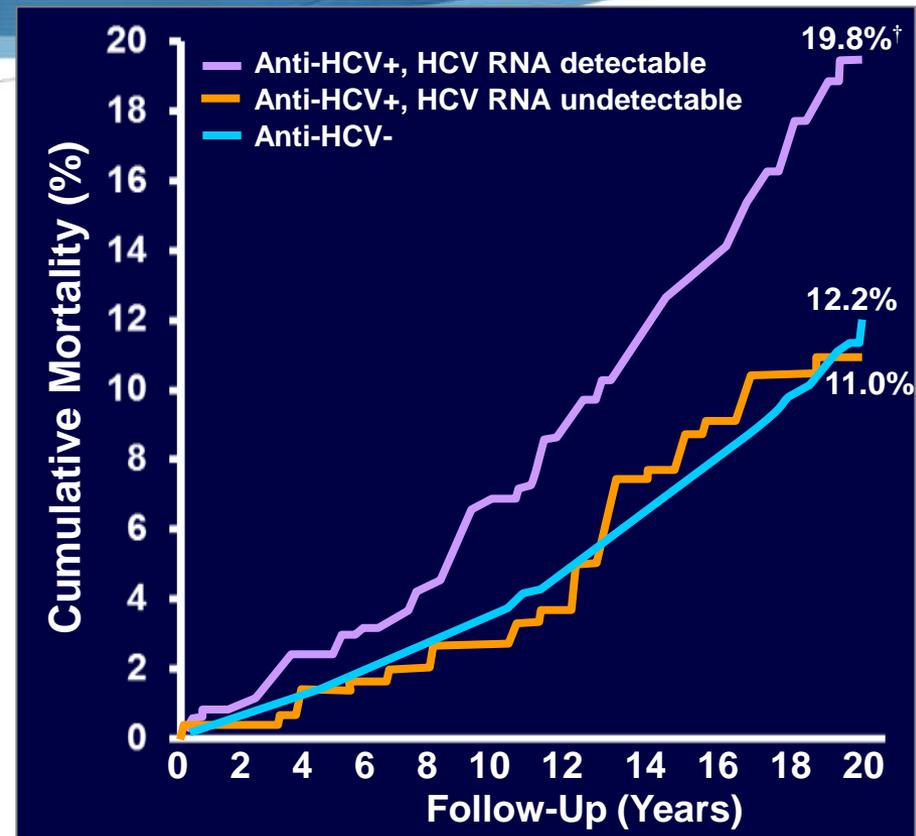
\* $P < 0.001$  for comparison among all 3 groups and  $P < 0.001$  for HCV RNA detectable versus undetectable.

# REVEAL-HCV Study Mortality: Hepatic Diseases and Extrahepatic Diseases

## Hepatic Diseases (n=195)



## Extrahepatic Diseases (n=2199)

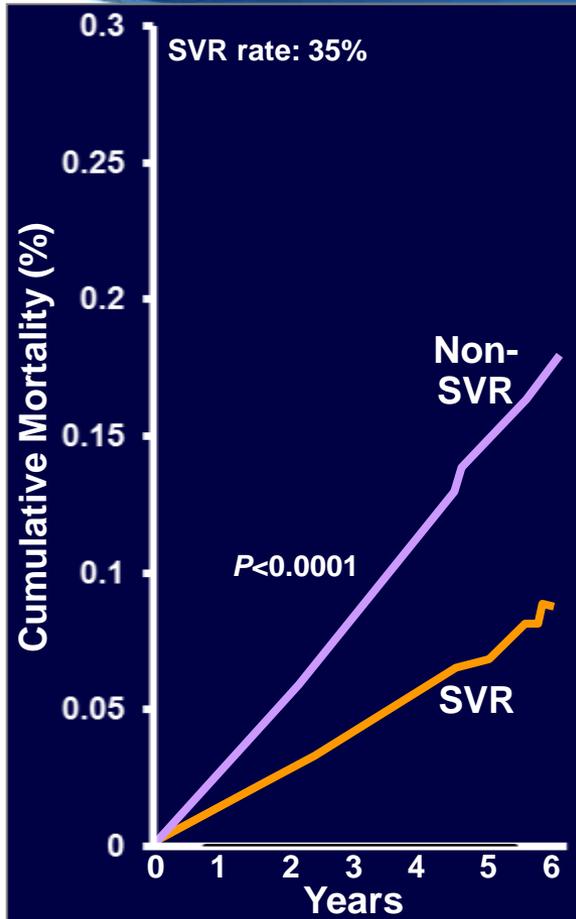


\* $P < 0.001$  for comparison among all 3 groups and  $P < 0.001$  for HCV RNA detectable versus undetectable.

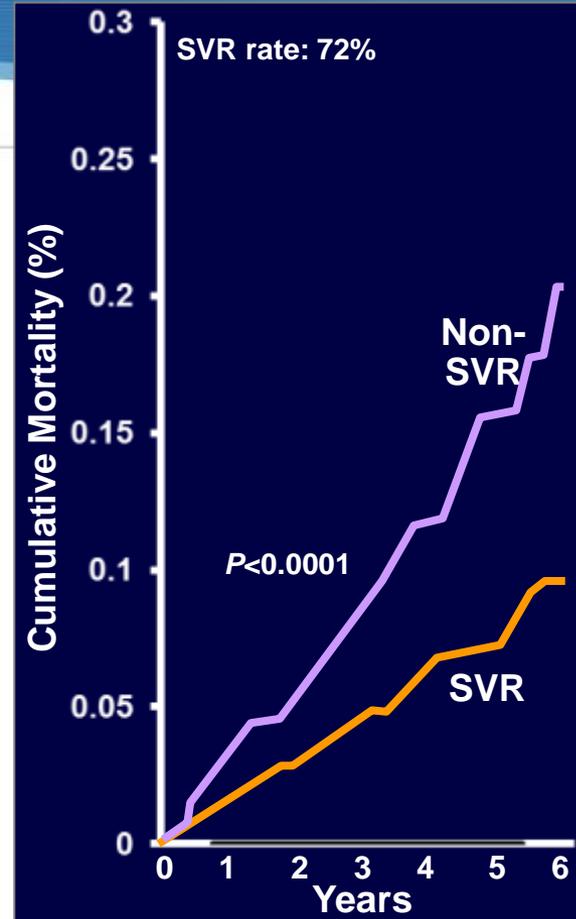
† $P < 0.001$  for comparison among all 3 groups and  $P = 0.002$  for HCV RNA detectable versus undetectable.

# SVR is Significantly Associated With Reduction in All-Cause Mortality

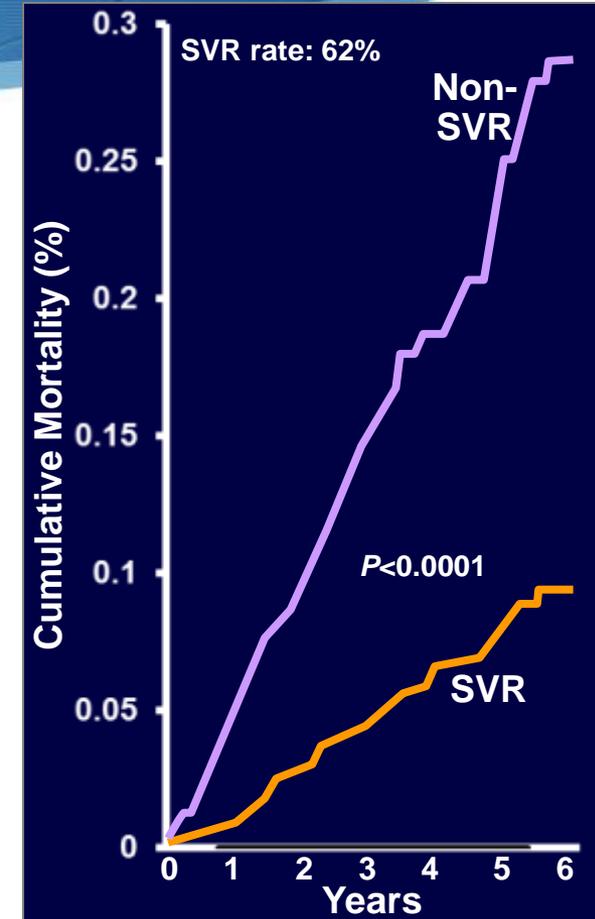
Genotype 1  
(n=12,166)



Genotype 2  
(n=2904)



Genotype 3  
(n=1794)

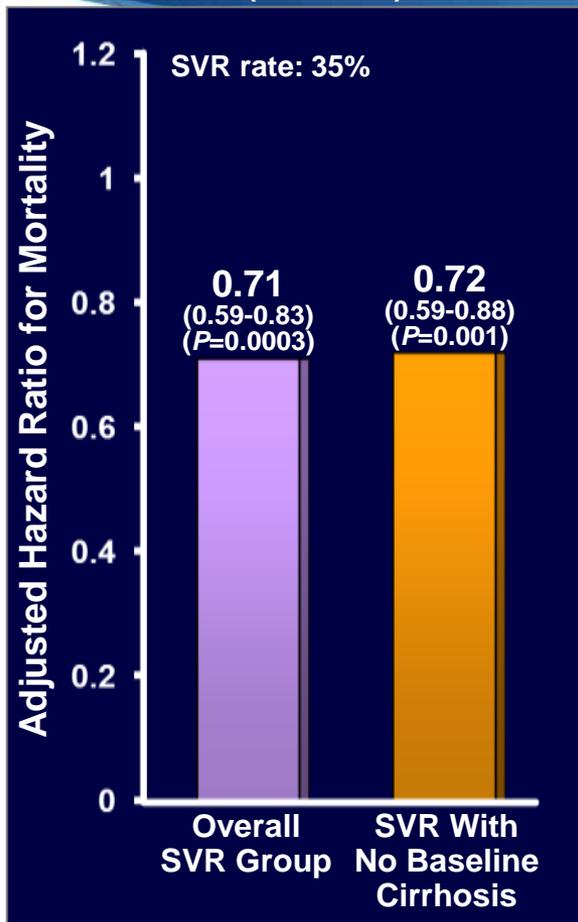


Retrospective analysis of veterans who received pegIFN + RBV at any VA medical facility (2001-2008).

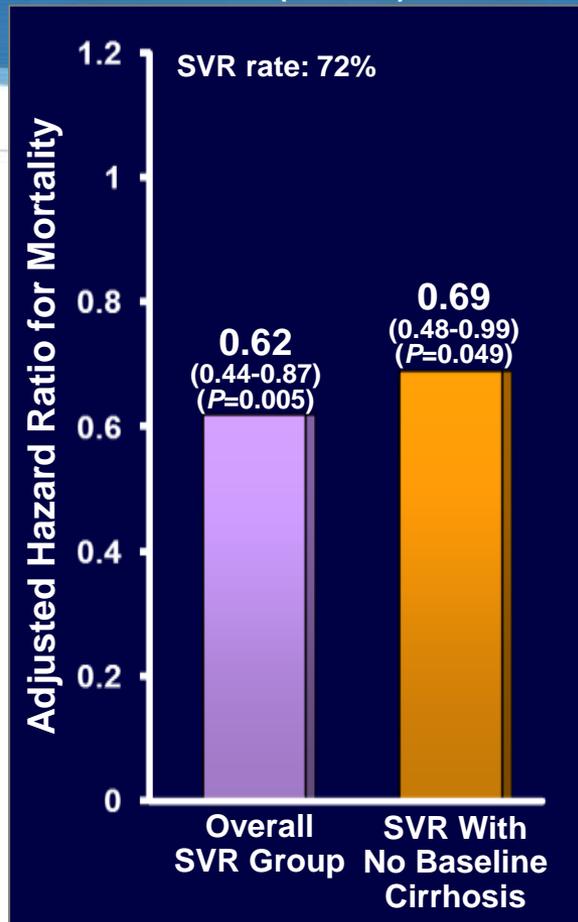
Backus LI, et al. *Clin Gastroenterol Hepatol.* 2011;9:509-516.

# SVR Reduces All-Cause Mortality Even in Absence of Cirrhosis

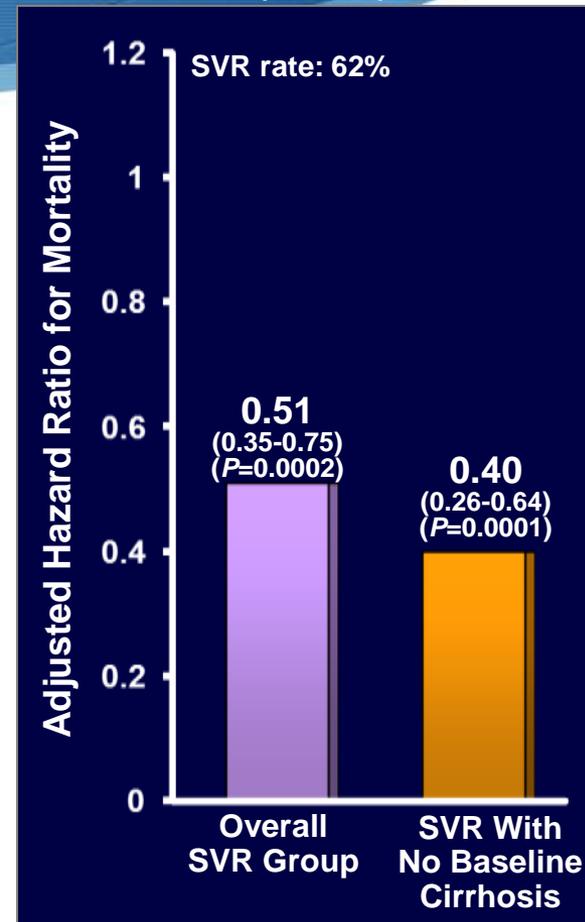
**Genotype 1**  
(n=12,166)



**Genotype 2**  
(n=2904)



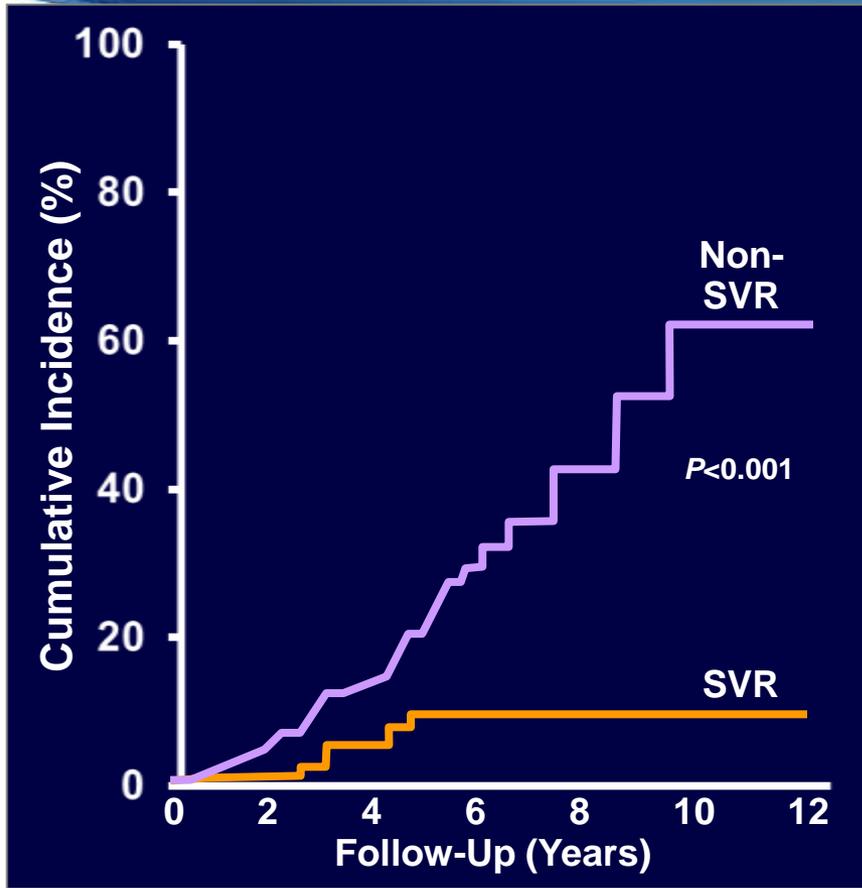
**Genotype 3**  
(n=1794)



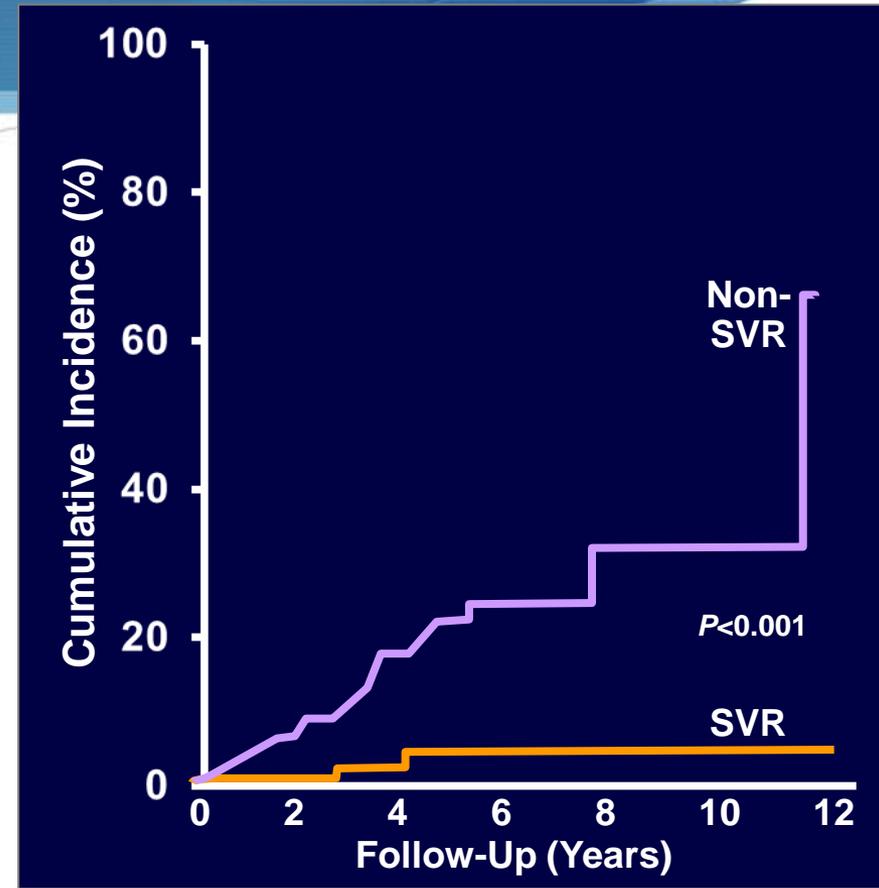
Retrospective analysis of veterans who received pegIFN + RBV at any VA medical facility (2001-2008).

# Impact of SVR on HCC and Liver-Related Complications

## HCC



## Liver-Related Complications



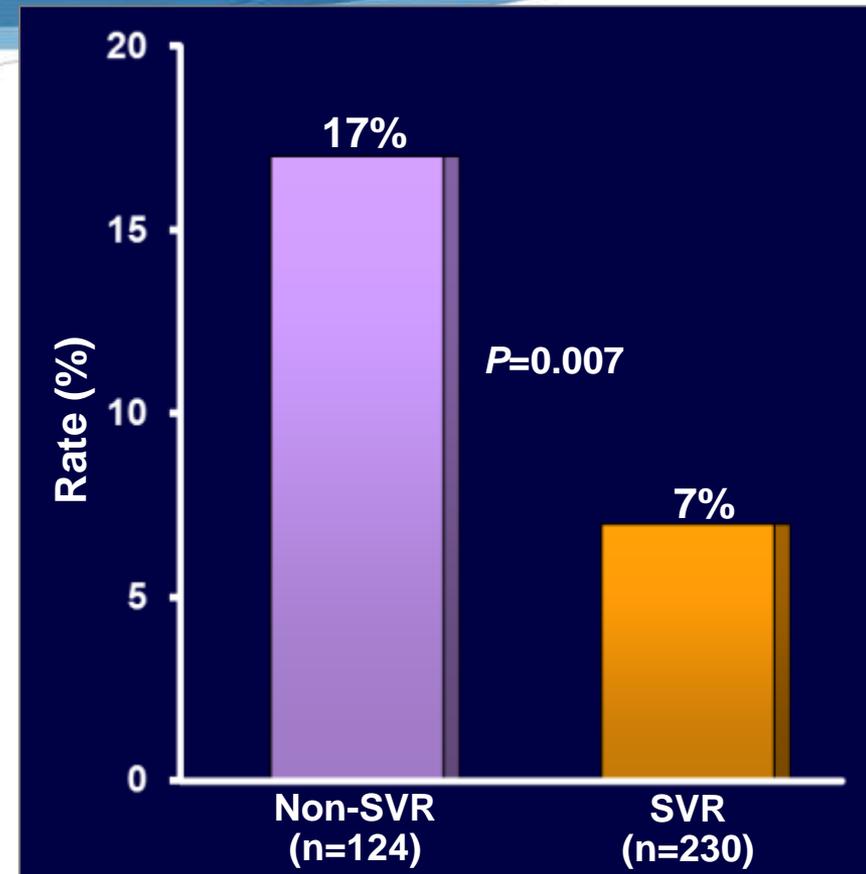
Single-center cohort. Non-SVR in 67% of patients treated with pegIFN + RBV. Median follow-up: 3.5 years. Total patients (n=307). Number of events: HCC (n=46); liver-related complications (n=31).

# MIST Study Cohort: SVR Reduces Development of New-Onset Insulin Resistance

- Extended follow-up sub-study of the MIST study
  - Non-diabetic, white HCV-infected patients treated with PR (n=399)
    - Male: 58%
    - Age: 51.8 years
    - BMI >25 kg/m<sup>2</sup>: 46%
    - Genotype 1/4: 50%
    - Fibrosis stage  $\geq$ 4: 29%
    - HOMA score: 1.15
  - SVR rate: 63%
  - New-onset insulin resistance (matched measurements)

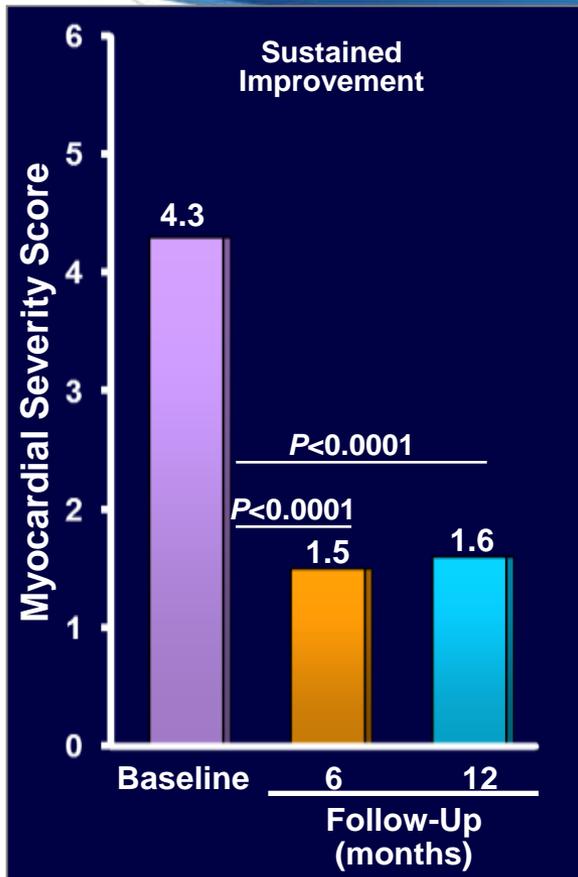
Japanese cohort with no overt ischemic or valvular disease.  
Abnormal myocardial injury score:  $\geq$ 3 on thallium-201 myocardial scintigraphy.

## Rate of De-Novo Insulin Resistance

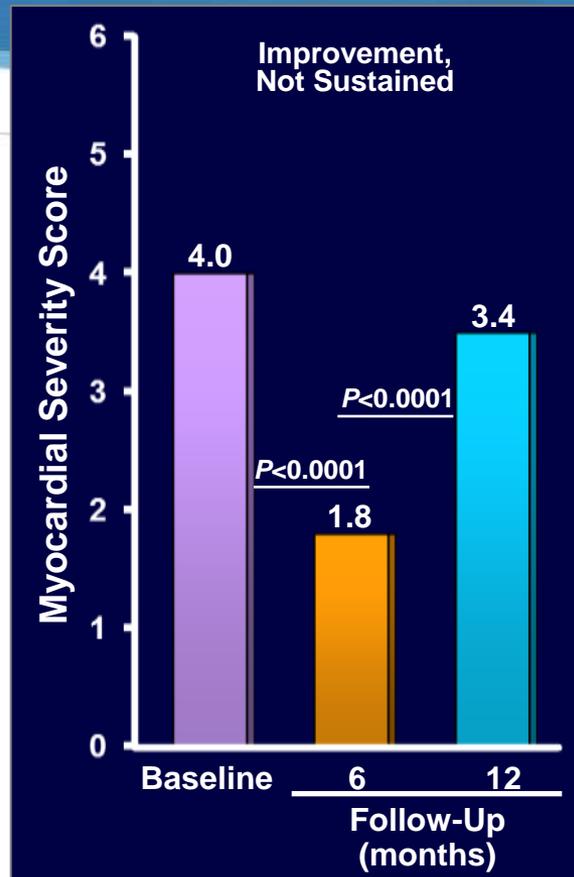


# SVR Provided Sustained Improvement in Myocardial Injury

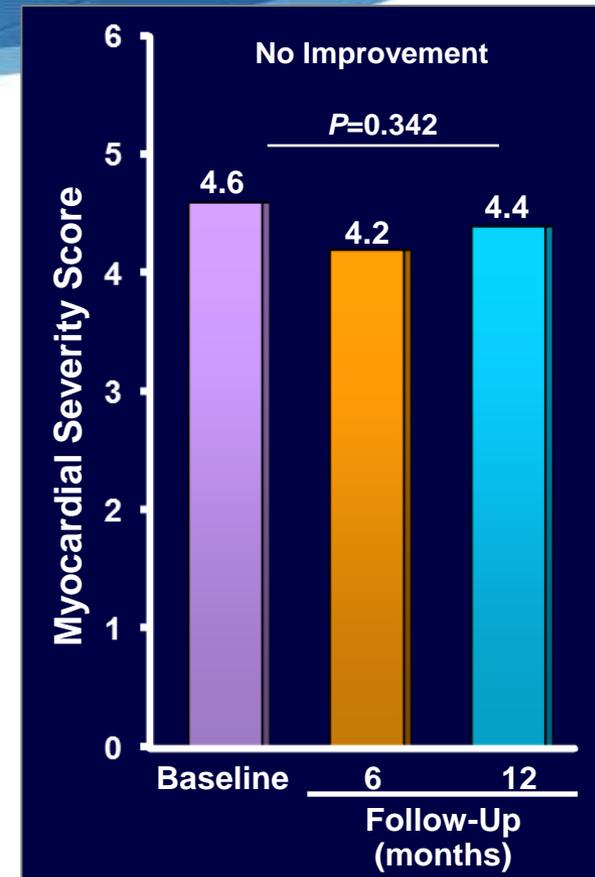
SVR  
(n=62)



Relapse  
(n=48)



No Response  
(n=45)



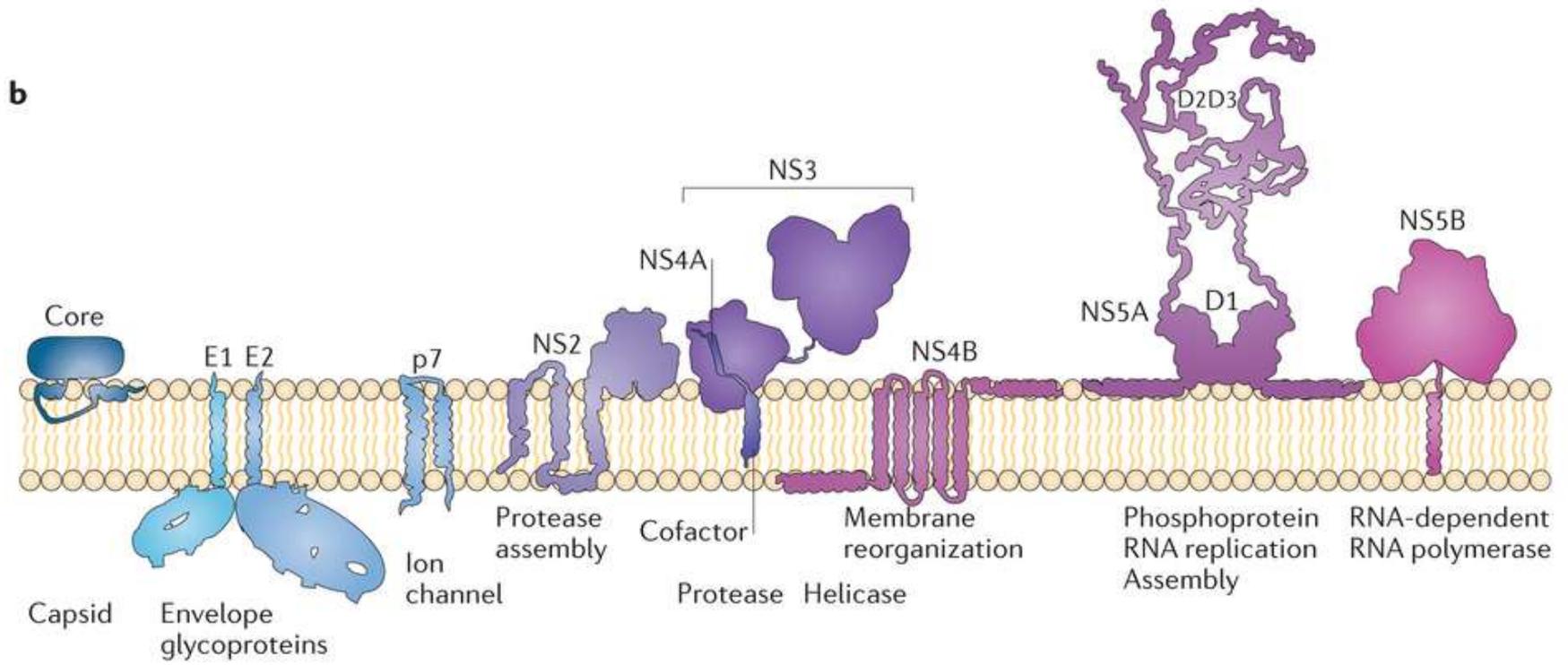
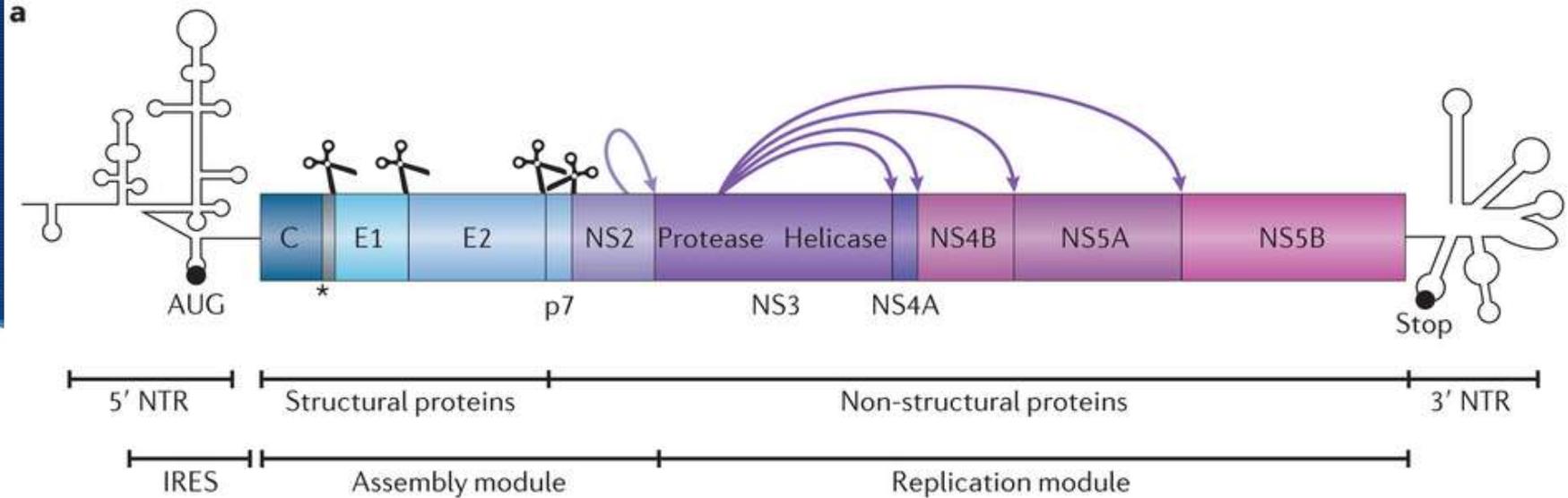
Japanese cohort with no overt ischemic or valvular disease.  
Abnormal myocardial injury score:  $\geq 3$  on thallium-201 myocardial scintigraphy.

# Antiviral Therapy

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## *Now and Future*

- Available: interferon, ribavirin, protease inhibitor
  - Efficacy: 50-70%
- Coming soon: new protease, first polymerase
  - P/R for genotype 1 & 4
  - Oral therapy for genotype 2 & 3
- Coming later: all oral therapy for all genotypes
  - Efficacy: at least 90%



# NEUTRINO Study: Sofosbuvir + PR in Treatment-Naïve, HCV Genotype 1, 4, 5, and 6

## Phase 3

Open-label  
Treatment-Naïve  
Genotype 1, 4, 5, and 6



Sofosbuvir (nucleotide NS5B polymerase Inhibitor).

No upper limit to age or BMI.

Opioid substitution permitted.

Platelets  $\geq 90,000/\text{mm}^3$ , neutrophils  $\geq 1500/\text{mm}^3$  or  $1000/\text{mm}^3$  (blacks).

Cirrhosis permitted (17% enrolled).

Primary efficacy endpoint: SVR12.

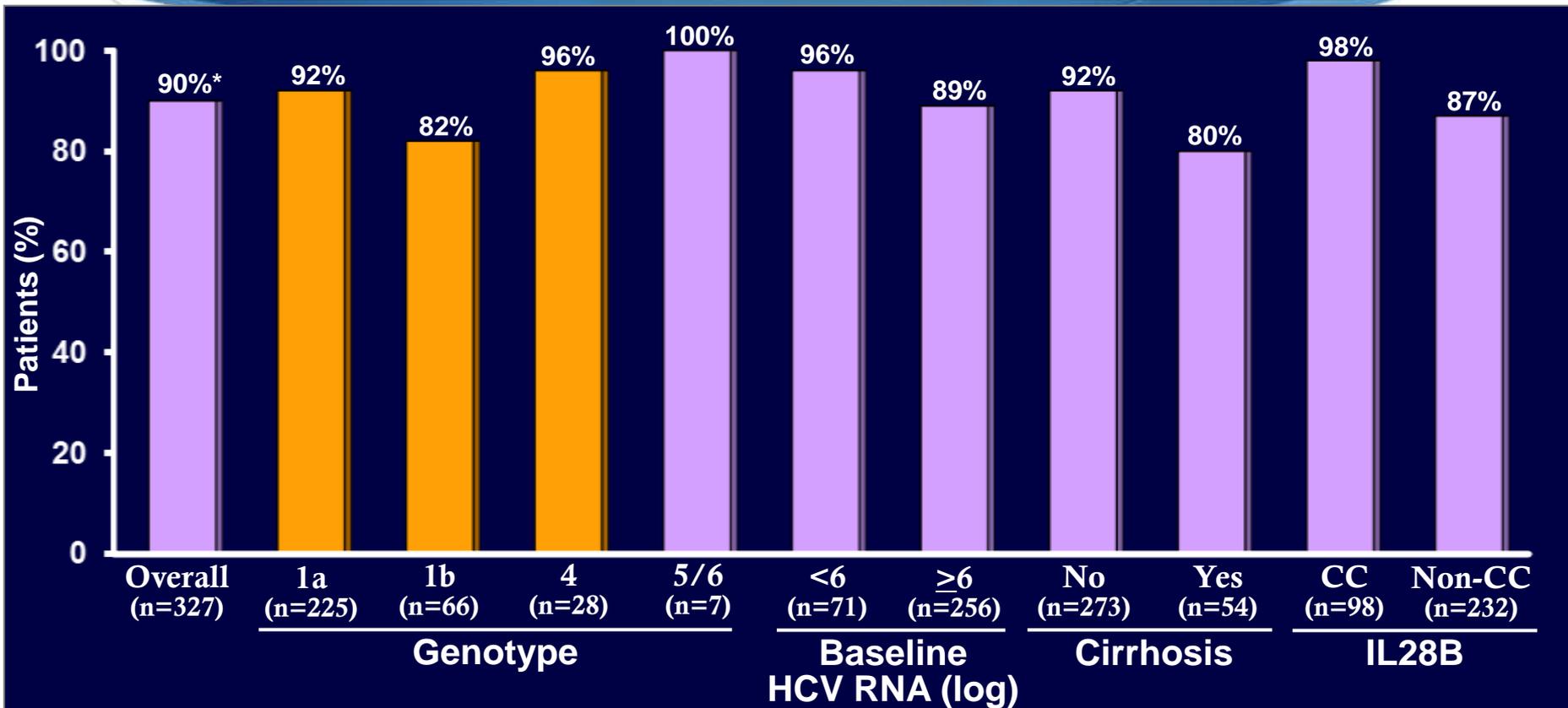
Prespecified comparison to historical SVR control rate of 60%.

Lawitz E, et al. *J Hepatol.* 2013;58(suppl 1):S567. Abstract 1411.

Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1887.

# NEUTRINO Study: SVR12 Rates by Prespecified Subgroups

Sofosbuvir 400 mg qd + PR (12 weeks)



\* $P < 0.001$  versus historical SVR rate of 60%.

# NEUTRINO Study: Resistance and Safety

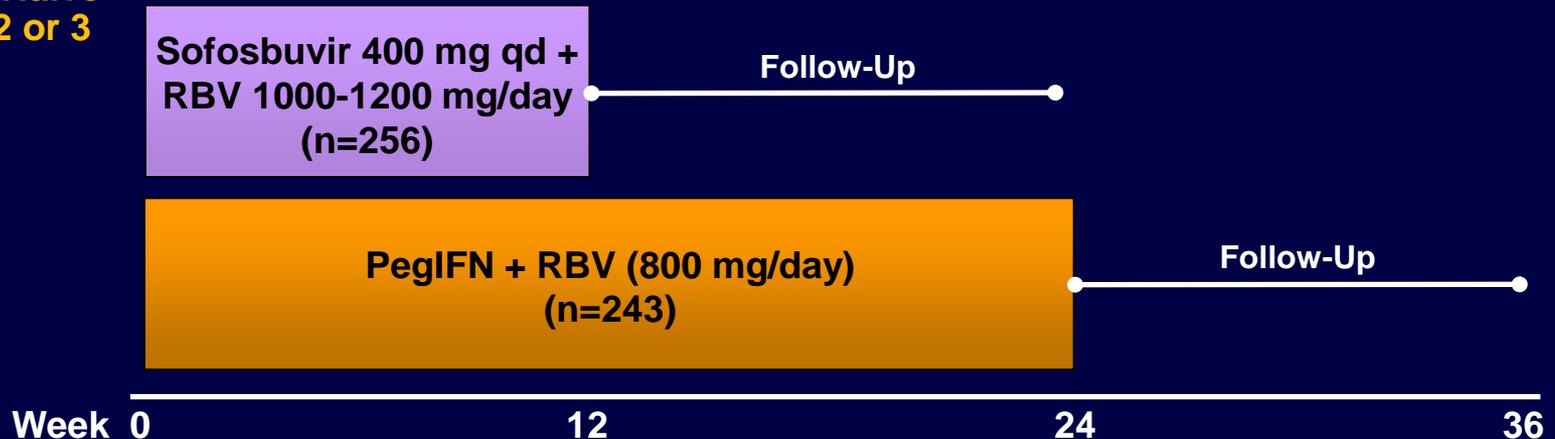
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- No resistance detected in sofosbuvir + PR virologic failures
  - 1 relapse patient who discontinued therapy
- Safety of sofosbuvir + PR
  - Well tolerated and no additive effects over PR
  - Most common adverse events
    - Fatigue (59%), headache (36%), nausea (34%), insomnia (25%), anemia (21%), rash (18%)
  - Safety profile consistent with ribavirin
    - Hemoglobin <10 g/dL: 23%; <8.5 g/dL: 2%

# FISSION Trial: Sofosbuvir + RBV in Treatment-Naïve, HCV Genotype 2 or 3

## Phase 3

Open-label  
Treatment-Naïve  
Genotype 2 or 3



Sofosbuvir (nucleotide NS5B polymerase inhibitor).

No upper limit to age or BMI.

Opioid substitution permitted.

Platelet  $>75,000/\text{mm}^3$  (cirrhotic: 20% maximum).

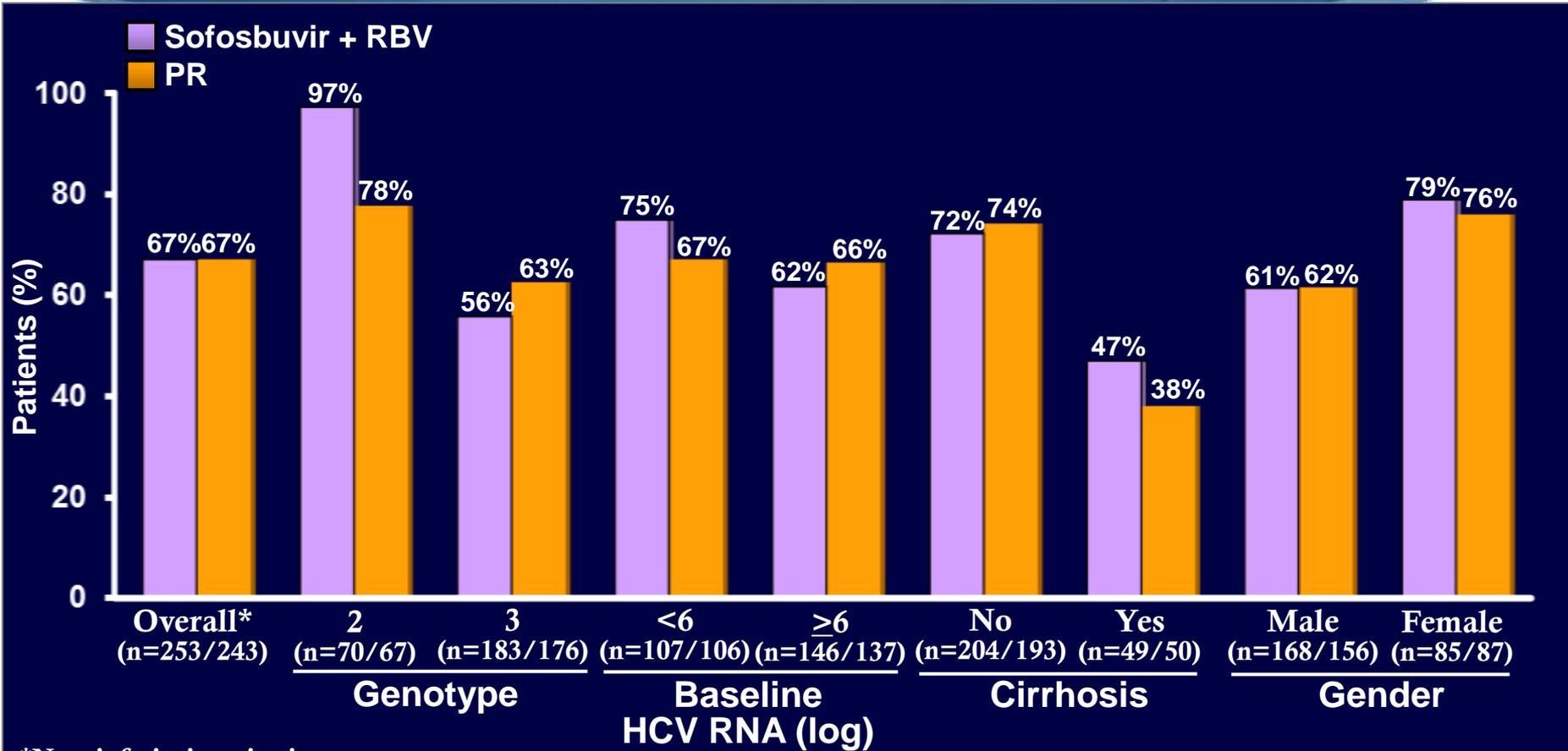
Stratified by genotype, HCV RNA, and cirrhosis.

Primary efficacy endpoint: SVR12 (non-inferiority margin: 15%).

Gane E, et al. *J Hepatol.* 2013;58(suppl 1):S3. Abstract 5.

Lawitz E, et al. *N Engl J Med.* 2013;368:1878-1887.

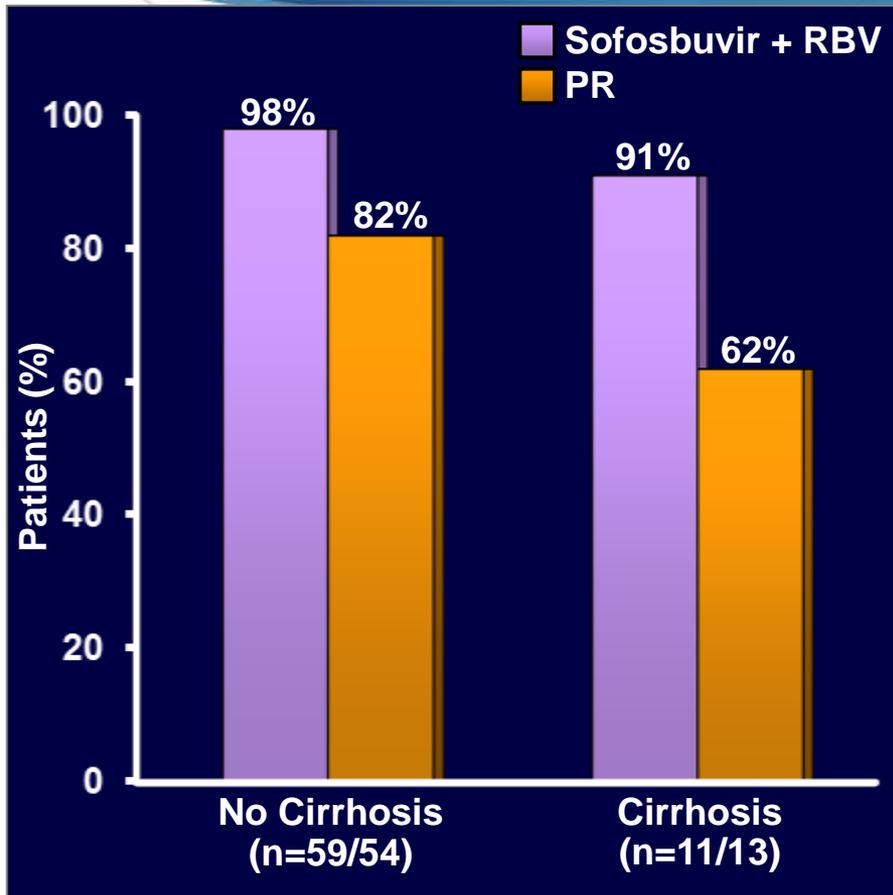
# FISSION Trial: SVR12 Rates by Prespecified Subgroups



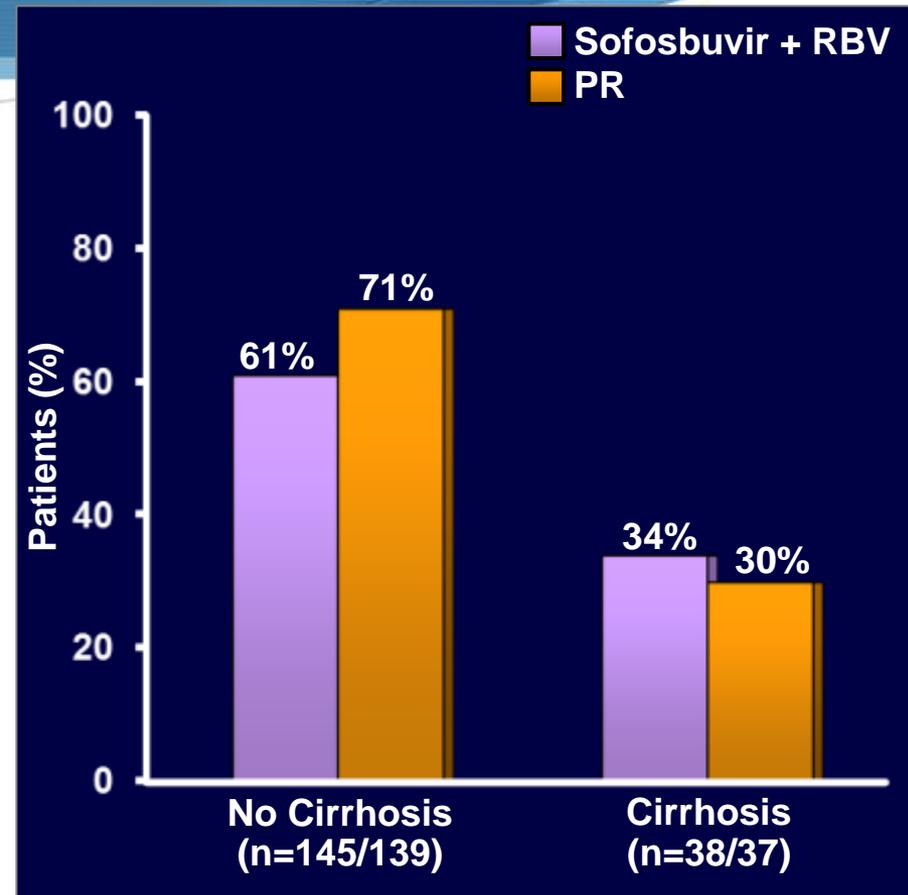
\*Non-inferiority criteria met.

# FISSION Trial: SVR12 Rates by Genotype and Cirrhosis

## Genotype 2



## Genotype 3



# FISSION Trial: Resistance and Safety

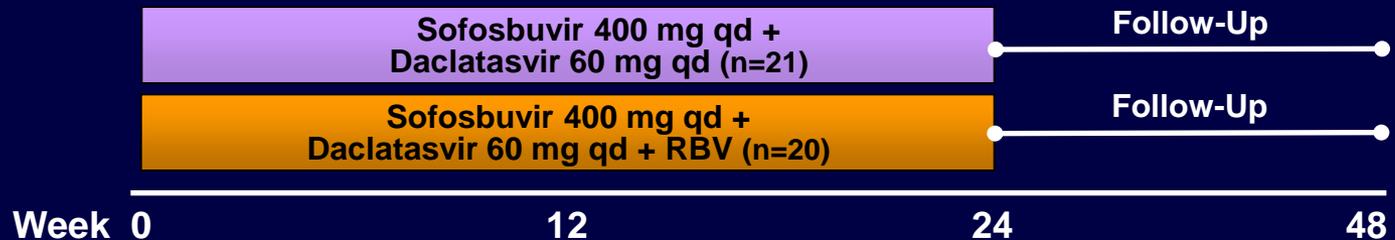
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- No resistance detected in sofosbuvir + RBV virologic failures
  - Relapse in all but 1 virologic failure (compliance)
- Safety of sofosbuvir + RBV
  - Well tolerated and few adverse events
  - Most common adverse events
    - Fatigue (36%), headache (25%), nausea (18%), insomnia (12%)

# Study 040: Sofosbuvir + Daclatasvir $\pm$ RBV in Previous Telaprevir or Boceprevir Failures

## Phase 2a

Prior Nonresponse, Relapse, or Breakthrough with Telaprevir or Boceprevir With PR Genotype 1



Sofosbuvir (nucleotide NS5B polymerase inhibitor).

Daclatasvir (NS5A replication complex inhibitor).

HCV RNA  $\geq 10^5$  IU/mL.

No upper limit to age or BMI.

METAVIR score: F0-F1 (12%),  $\geq$ F2 (88%).

NS3 polymorphisms conferring resistance to boceprevir or telaprevir as baseline: 46%

NS5A polymorphisms conferring resistance to daclatasvir: 7%

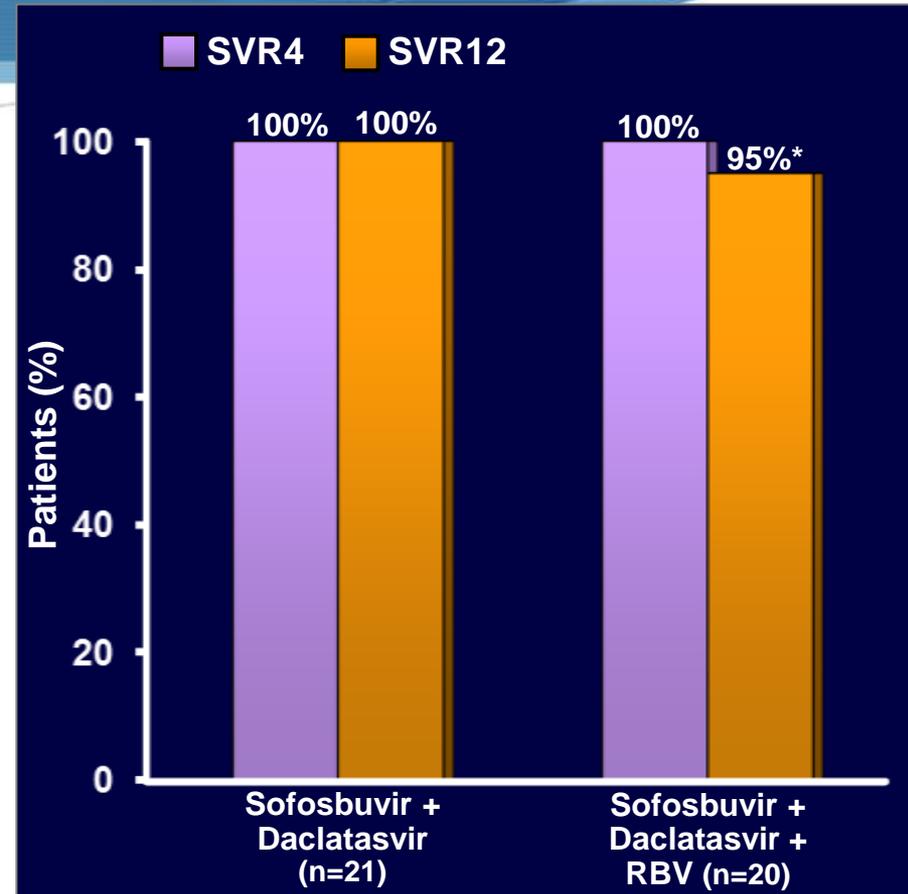
Excluded: patients who discontinued telaprevir or boceprevir due to an adverse event.

Primary efficacy endpoint: SVR12.

# Study 040 (24-Week Treatment): SVR4 and SVR12 Rates

## Genotype 1

- No virologic failures
- Neither baseline NS3 PI resistance nor use of RBV influenced response
- Sofosbuvir + daclatasvir  $\pm$  RBV was well tolerated
  - No discontinuations
  - Most common adverse events (without RBV)
    - Fatigue (29%), headache (33%), arthralgia (14%)
- No grade 3/4 elevations in ALT, AST, or total bilirubin
- Anemia (hemoglobin <9 g/dL): 0%

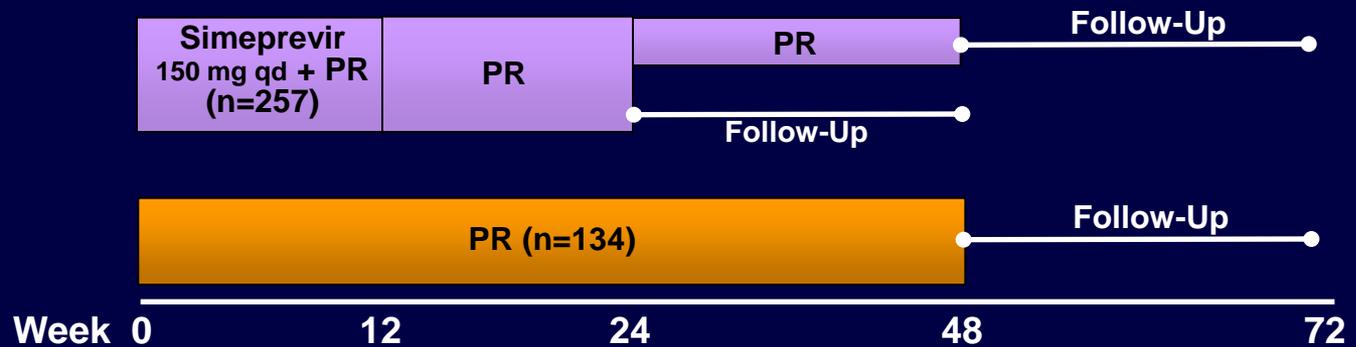


\*1 patient missing at post-treatment 12 weeks, HCV RNA undetectable at post-treatment week 24

# QUEST-2 Trial: Simeprevir + PR in Treatment-Naïve, HCV Genotype 1

## Phase 3

### Treatment-naïve Genotype 1



Simeprevir (NS3/4A protease inhibitor).

HCV RNA  $\geq 10,000$  IU/mL.

PR: pegIFN (alpha 2a or 2b) + RBV (weight-based dosing: 1000-1200 mg).

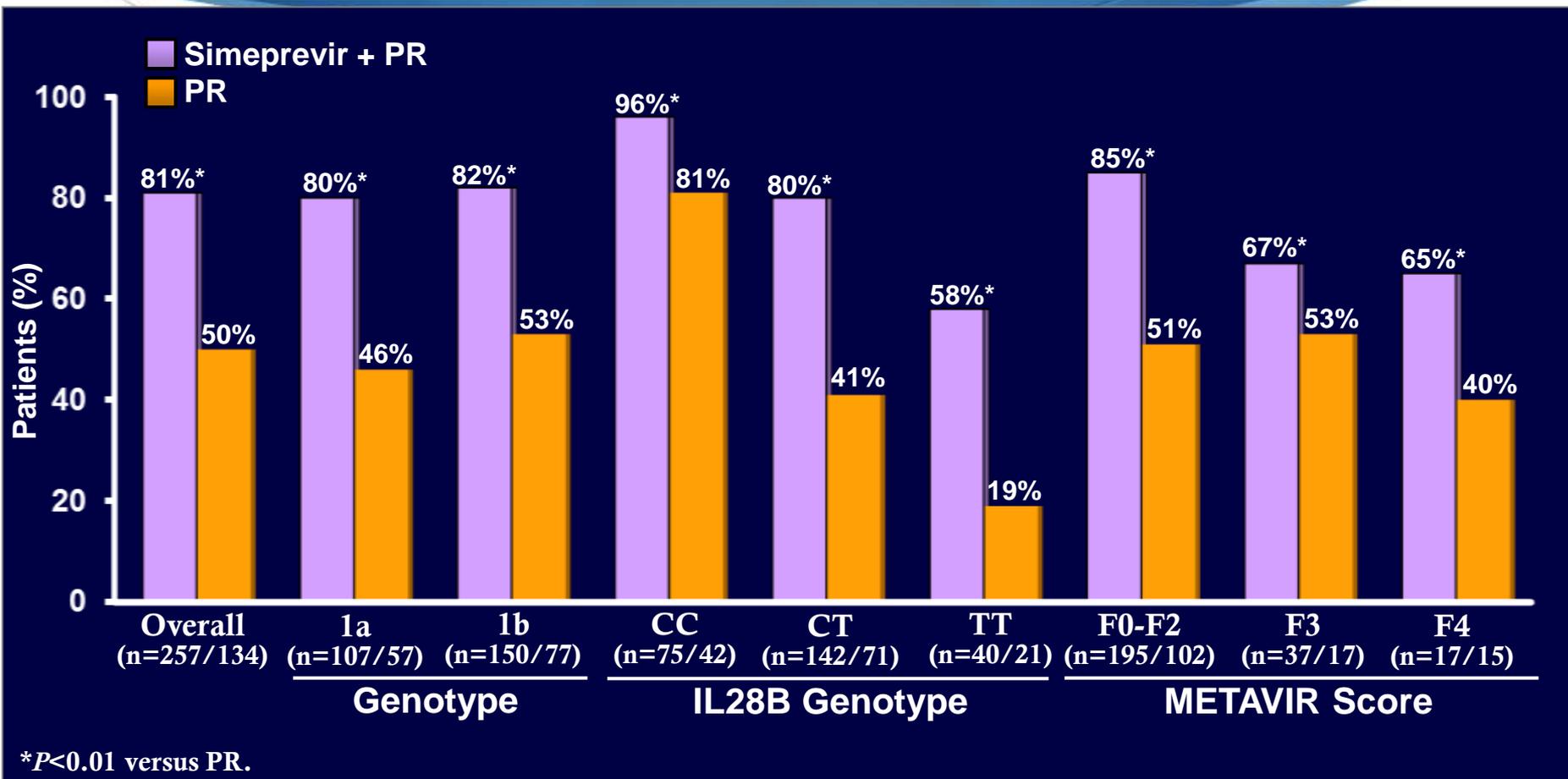
Patients stratified by HCV subtype and IL28B genotype.

Response-guided therapy criteria: HCV RNA  $< 25$  IU/mL at week 4 and undetectable at week 12.

METAVIR score: F0-F1 (50%);  $\geq$ F2 (50%).

Primary efficacy endpoint: SVR12.

# QUEST-2 Trial: SVR12 Rates by Prespecified Subgroups



# QUEST-2 Trial: Resistance and Safety

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- NS3 PI mutations were detected at the time of failure in 98% of simeprevir-treated patients who did not achieve an SVR
  - Genotype 1: mainly R155 alone
  - Genotype 1b: mainly D168V or Q80R + D168E
- Simeprevir + PR was well tolerated
  - Simeprevir treatment discontinuations due to adverse events: 1.6%
- Adverse event profile of simeprevir + PR was similar to the PR arm
  - Headache, pyrexia, fatigue, influenza-like illness, rash, anemia, pruritus

# Texas

Texas Rank	National Rank	City	Population	Area	Pop. Density
1	4	Houston	2,099,451	600	3,501
2	7	San Antonio	1,327,407	461	2,880
3	9	Dallas	1,197,816	341	3,518
4	14	Austin	790,390	298	2,653
5	16	Fort Worth	741,206	340	2,181
6	19	El Paso	649,121	255	2,544
7	50	Arlington	465,438	96	3,811
8	60	Corpus Christi	305,215	161	1,901
9	71	Plano	259,841	72	3,629
10	81	Laredo	236,091	89	2,656
11	84	Lubbock	229,573	122	1,876
12	87	Garland	226,876	57	3,973
13	94	Irving	216,290	67	3,228
14	121	Amarillo	190,695	100	1,917
15	133	Grand Prairie	175,396	72	2,433
16	134	Brownsville	175,023	132	1,323
17	162	Pasadena	149,043	43	3,482
18	178	Mesquite	139,824	46	3,040
19	187	McKinney	131,117	62	2,108
20	188	McAllen	129,877	48	2,689



ECHO Whale



PCA Espanola



Baton Rouge



Pecos Valley MC



DOH Las Cruces



SBRT-First Choice South Vc



Memorial HDX7000



LAS VEGAS ECFH



# Effectiveness

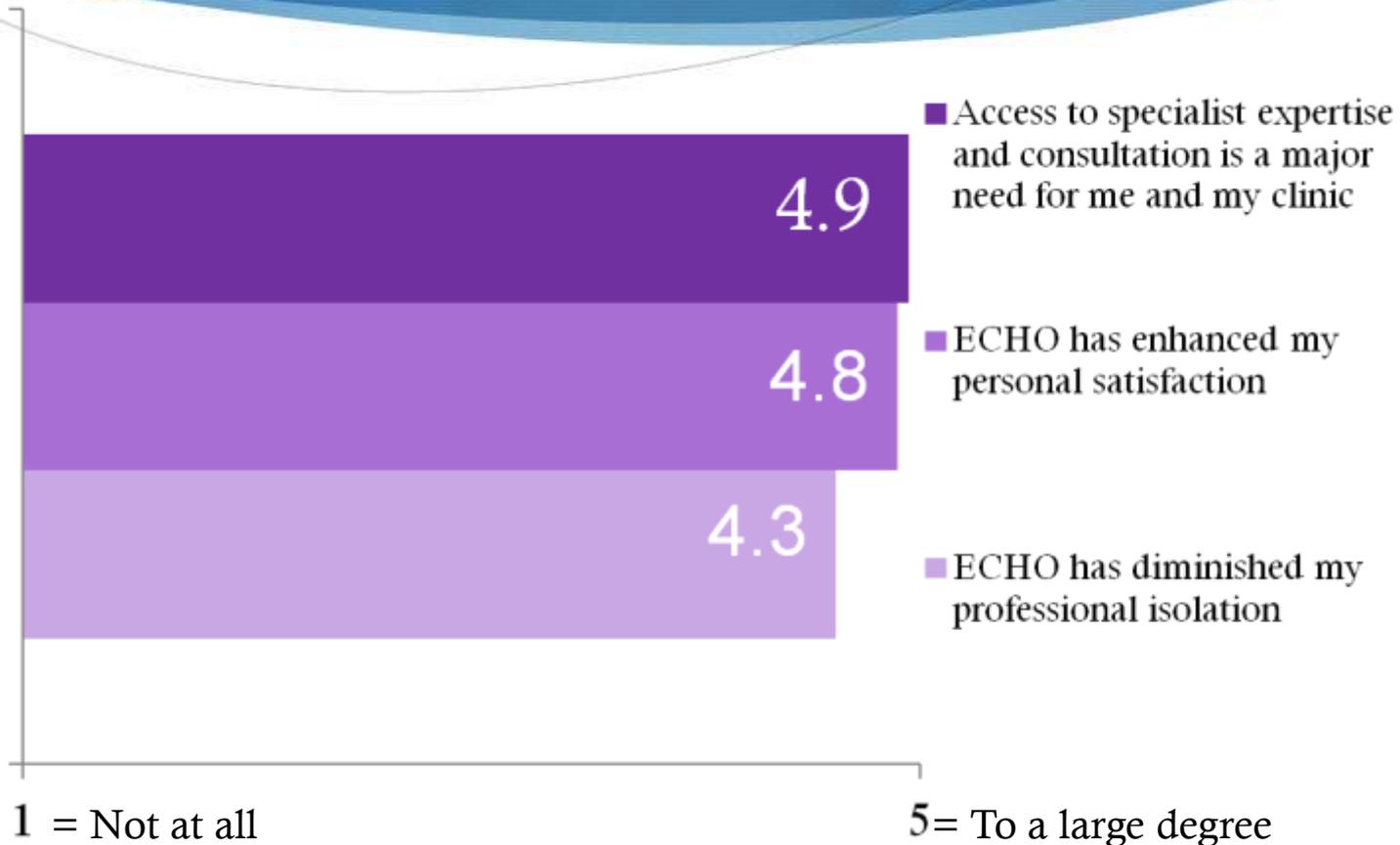
**Table 2. Sustained Virologic Response According to Genotype and Site of Treatment.\***

HCV Genotype	ECHO Sites <i>no. of patients with response/total no. (%)</i>	UNM HCV Clinic	Difference between ECHO Sites and UNM HCV Clinic <i>percentage points (95% CI)</i>	P Value
All genotypes	152/261 (58.2)	84/146 (57.5)	0.7 (-9.2 to 10.7)	0.89
Genotype 1	73/147 (49.7)	38/83 (45.8)	3.9 (-9.5 to 17.0)	0.57
Genotype 2 or 3	78/112 (69.6)	42/59 (71.2)	-1.5 (-15.2 to 13.3)	0.83

- >500 HCV Telehealth Clinics
- >5,000 patients entered HCV treatment
- 27,000 CMEs/CEUs issued – no cost to providers
- Reimbursement

# Physician Competence

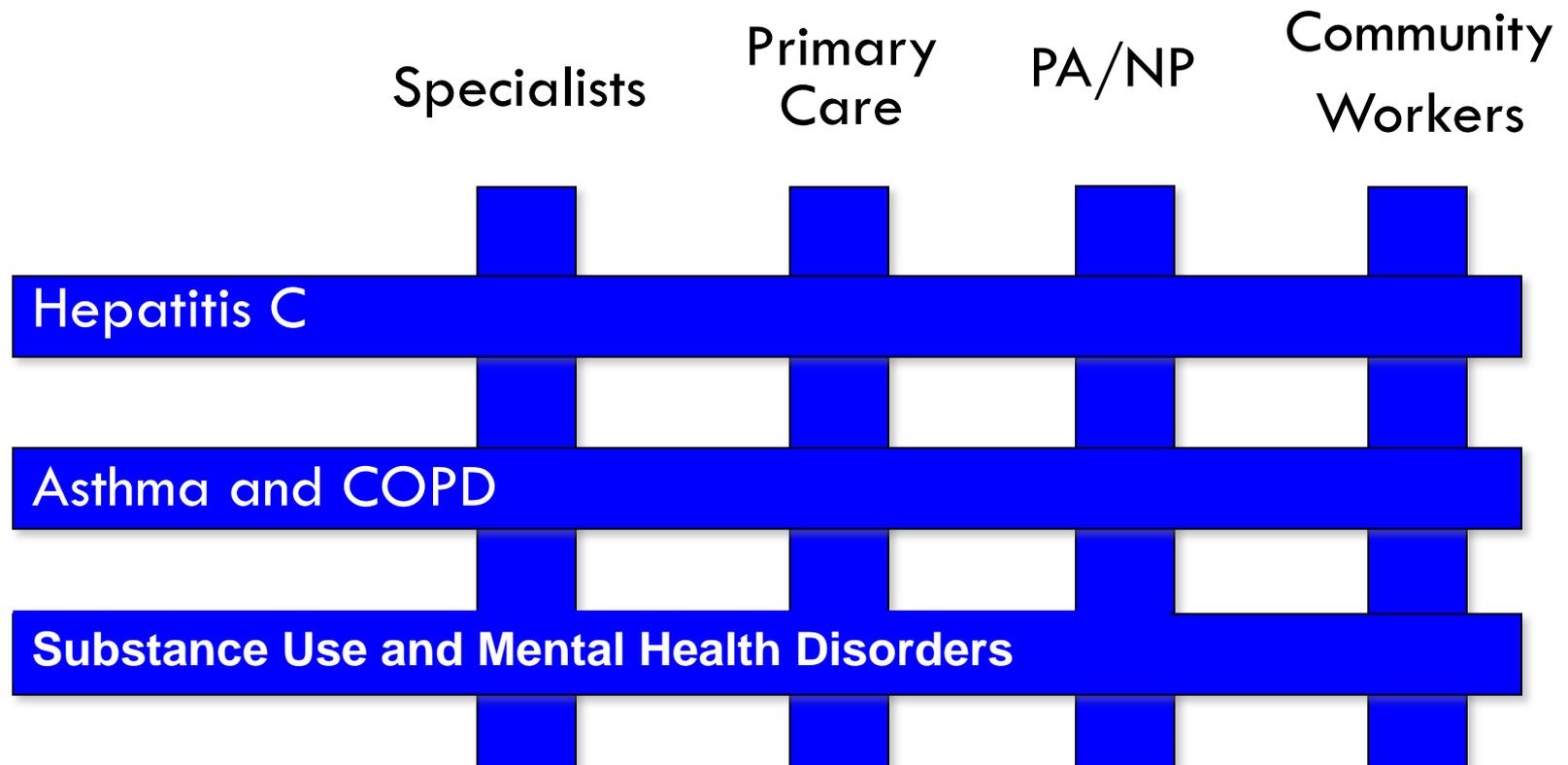
## *Annual Survey of Clinicians Participating in ECHO*



# FORCE MULTIPLIER

*Use Community Providers*

Pareto Principle – 80/20 Rule



# ECHO model of Disease Management

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- Liver (tiers of care)
  - High complexity – cirrhosis, tumors, transplant (specialists)
  - Moderate complexity – HCV (primary care)
  - Low complexity – Fatty liver (community workers, dietary, community activists, volunteers)
- Other specialties
  - Pediatric hepatology
  - Surgery (tumor boards)
  - HIV and other infectious diseases
  - Psychiatry, drug abuse, pain management
  - Asthma and COPD
  - Heart failure

# Summary

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- HCV is a common infection
  - 3-7 million infected individuals in the USA
  - 400,000 in Texas
- HCV infection is associated with increased mortality
  - A cure reverses the trend
- HCV has three potential antiviral targets
  - Drugs against all three targets have been developed
  - Two new drugs are expected in 2013
- Expert networks are an effective method of improving health outcomes by enhancing local resources