Chronic Hepatitis C Natural History and Current Treatment 2013

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Consulting: Cumberland, Novartis

AND

My presentation may possibly include discussion of off-label use of DAAs

Outline of this talk

- Review Hep C 101: basic statistics
- Review the CDC Baby Boomer Directive
- Provide an overview to current Rx with the new DAAs
- Give a glimpse of the future, which happens to be just around the corner

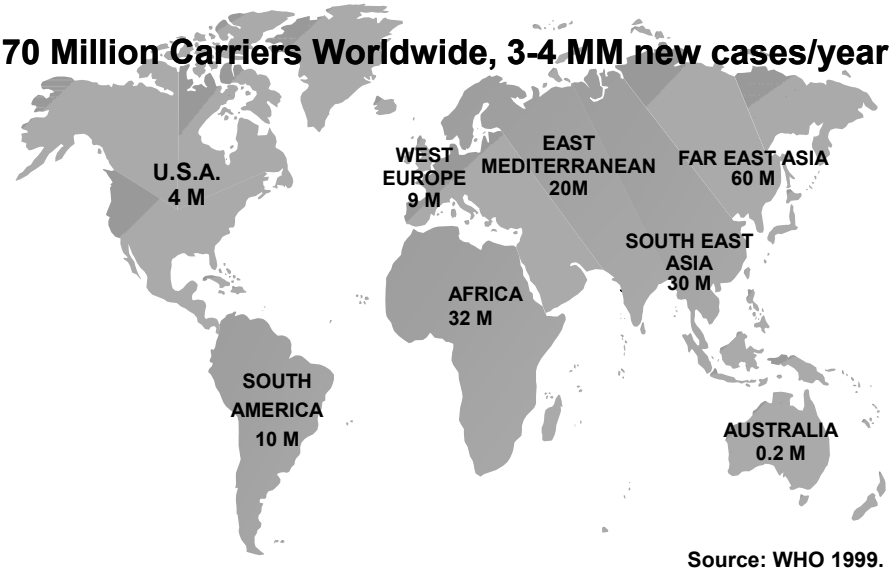
Hepatitis C Virus (HCV)

- Discovered in 1989 as a small RNA blood-borne virus with a large reservoir of chronic carriers worldwide
- Major cause of post-transfusion hepatitis prior to 1992
- Major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide
- Prevalence is 1.8% of the US population, 4 million
- 1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002.

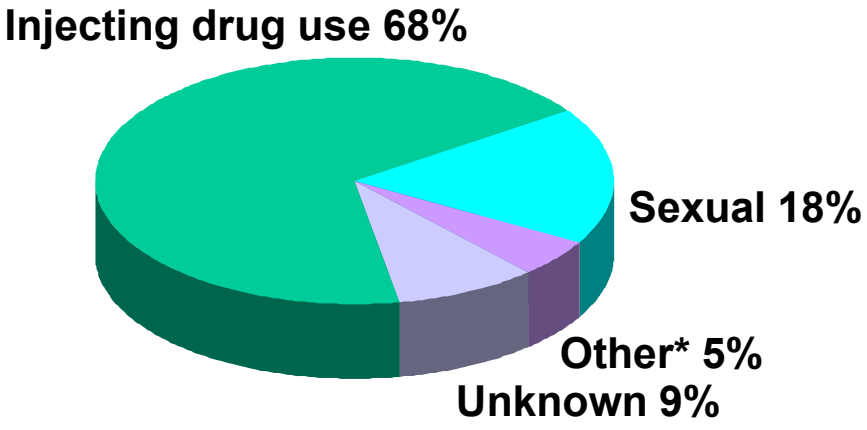
Hepatitis C: A Global Health Problem

170 Million Carriers Worldwide, 3-4 MM new cases/year



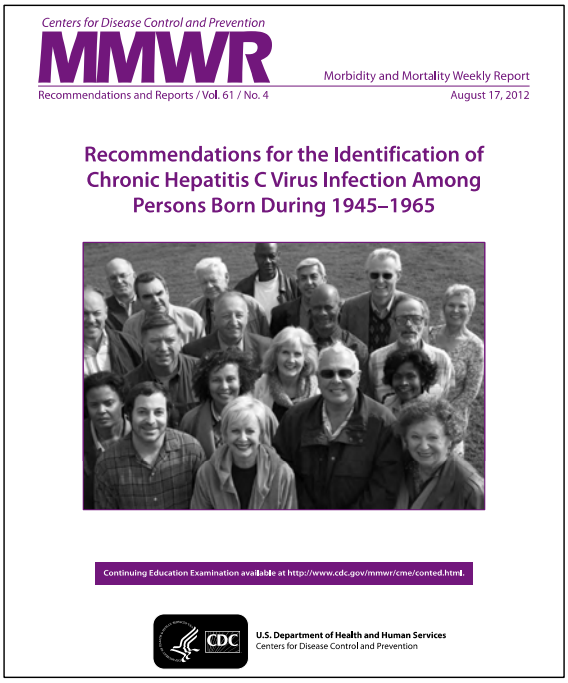
Source: WHO 1999.

Sources of Infection for Hepatitis C (1995-2000)



*Nosocomial; Health-care work; Perinatal

Adapted from Hepatitis Slide Kit http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/ Accessed 01/18/03. Alter MJ. Hepatology 2002;36:S93-S98.

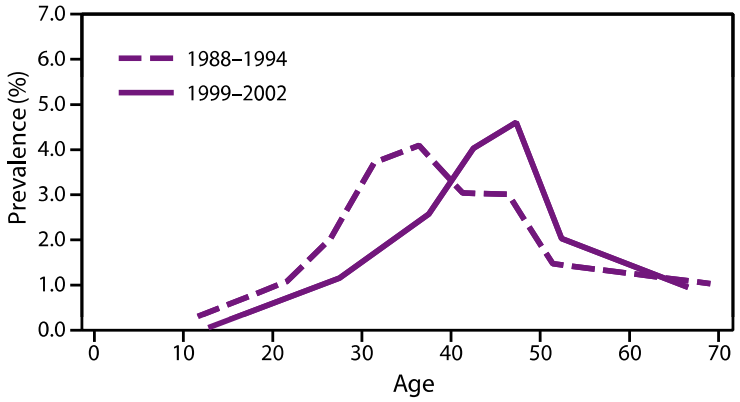


Recommendations for Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945-1965

- Adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

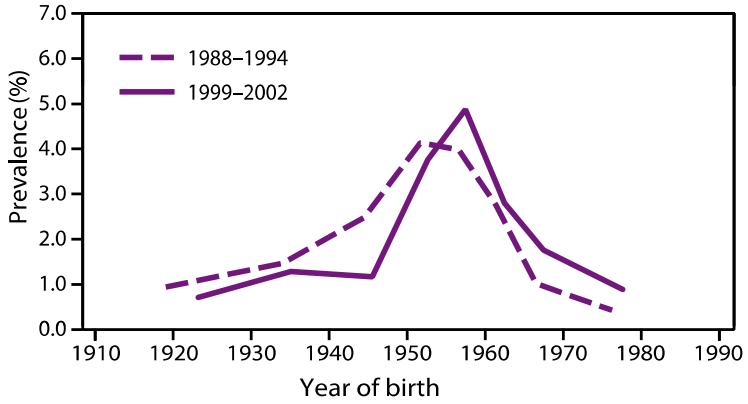
MMWR /August 17, 2012 / Vo1. 61 / No.4

FIGURE 1. Prevalence of hepatitis C virus antibody, by age at time of survey — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002



Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Internal Med 2006;144:705–14. Modified and reprinted with permission from Annals of Internal Medicine.

FIGURE 2. Prevalence of hepatitis C virus antibody, by year of birth — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002



Source: Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Internal Med 2006;144:705–14. Modified and reprinted with permission from Annals of Internal Medicine.

TABLE 1. Number and prevalence of persons born during 1945–1970 positive for anti-HCV and with chronic HCV infection, by birth cohort — National Health and Nutrition Examination Survey, United States, 1999–2008

Birth cohort	U.S. population (in millions)*	Anti-HCV No. (in millions)	Anti-HCV (Weighted %)†	Chronic HCV infection No. (in millions)§	Chronic HCV infection (%)
1945–1965	84.2	2.74	(3.25)	2.06	76.6
1950–1970	89.2	2.89	(3.24)	2.17	80.6
1945–1970	105.1	3.15	(3.00)	2.36	87.3
1950–1965	68.3	2.47	(3.61)	1.85	69.9
1950–1960	45.6	1.83	(4.01)	1.37	52.3
1945–1949	13.2	0.21	(1.58)	0.16	6.7
1966–1970	20.9	0.41	(1.94)	0.30	10.8

Abbreviations: HCV = hepatitis C virus; anti-HCV = antibody to hepatitis C virus.
* Source: U.S. Census Bureau. 2010 Census: Single years of age and sex: summary file 1, table PCT12. Available at http://factfinder2.census.gov/faces/tableservices/jsf/pages/productview.xhtml?pid=DEC_10_SF1_PCT12&prodType=table. Accessed April 27, 2012.
† Not adjusted by age or other covariates.
§ An estimated 75% of anti-HCV–positive persons have chronic HCV infection. (Source: Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. [Practice Guideline.] Hepatology 2009;49(4):1335–74.)

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TABLE 2. Prevalence of anti-HCV among three birth cohorts, by sex and race/ethnicity* — National Health and Nutrition Examination Survey, United States, 1999–2008

Characteristic	Anti-HCV (weighted %) 1945–1965	1950–1970	1945–1970
Sex			
Male	4.34	4.12	3.89
Female	2.19	2.34	2.14
Race/ethnicity			
White, non-Hispanic	2.89	3.01	2.77
Black, non-Hispanic	6.42	5.73	5.60
Mexican American	3.26	2.56	2.71

Abbreviation: anti-HCV = antibody to hepatitis C virus.
* Not adjusted by age or other covariates.

by non-Hispanic white males (4.05%) and Mexican-American males (3.41%).

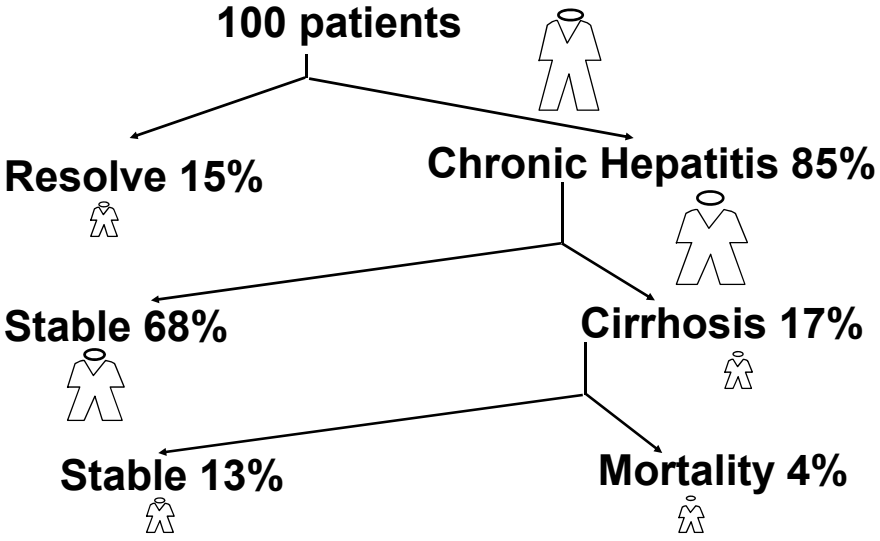
Complicating health outcomes among HCV-infected persons born during 1945–1965 are a lack of health insurance (31.5%) and use of alcohol (3). Of all anti-HCV positive

Summary of new CDC Recs

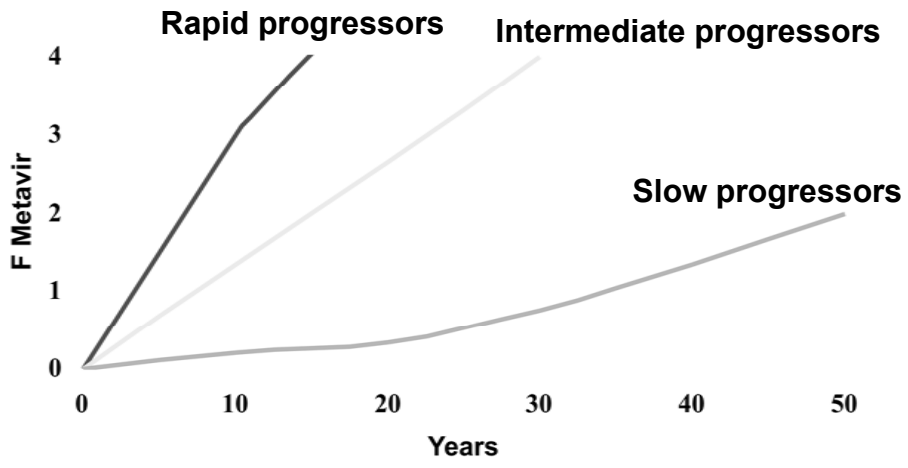
- Current estimates are ca. 4 million Americans with HCV
- Between 45 and 85% of HCV infected are unaware of it
- Risk-based strategies have failed
- Baby boomers (1945-1965) represent 27% of the population but 75% of those infected
- 1990-2015: estimated 4-fold increase in the number of patients diagnosed with HCV in the United States

NIH Consensus Development Conference Panel Statement Management of Hepatitis C, 2002.

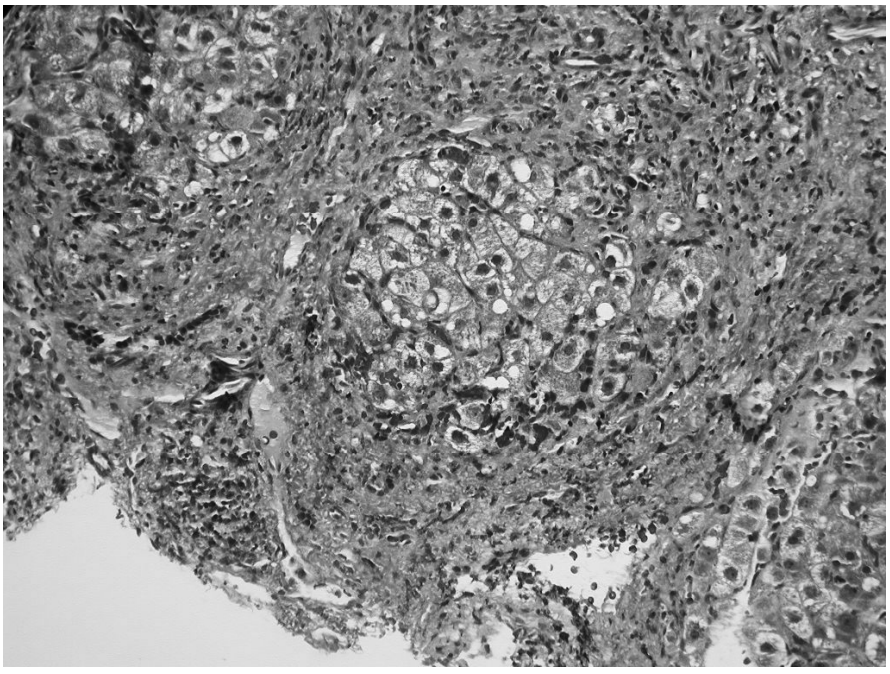
Natural History Hepatitis C



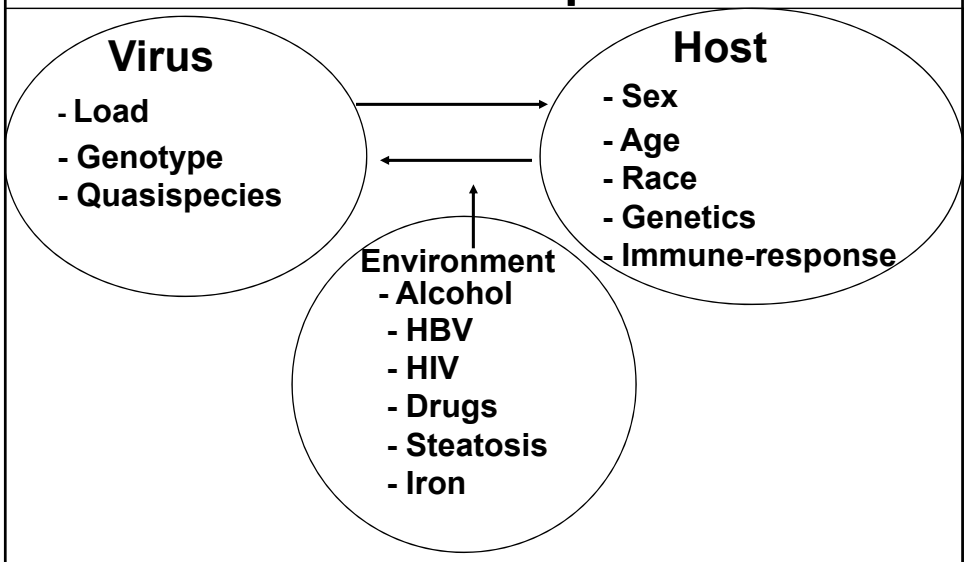
Modeling of Liver Fibrosis in Chronic Hepatitis C, n=1157 Patients



Poynard et al, Hepatology 1999

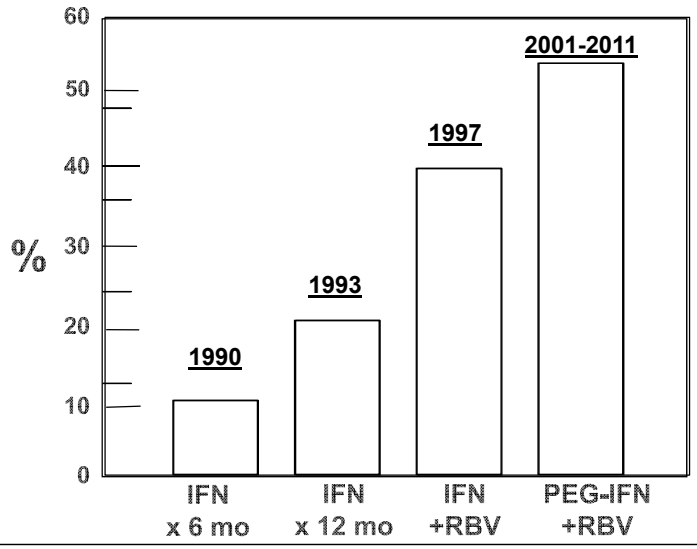


Factors Which Might Influence The Outcome Of Hepatitis C

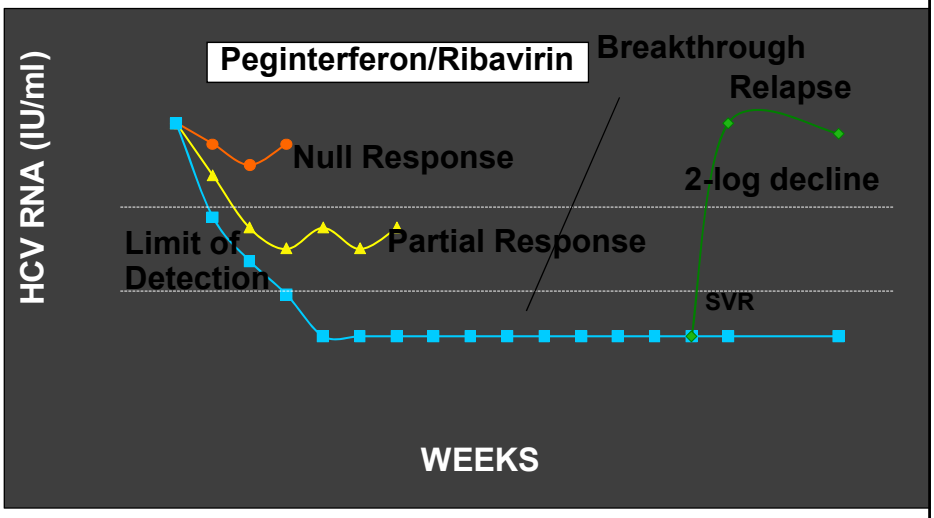


Alberti. J of Hepatology, 1999.

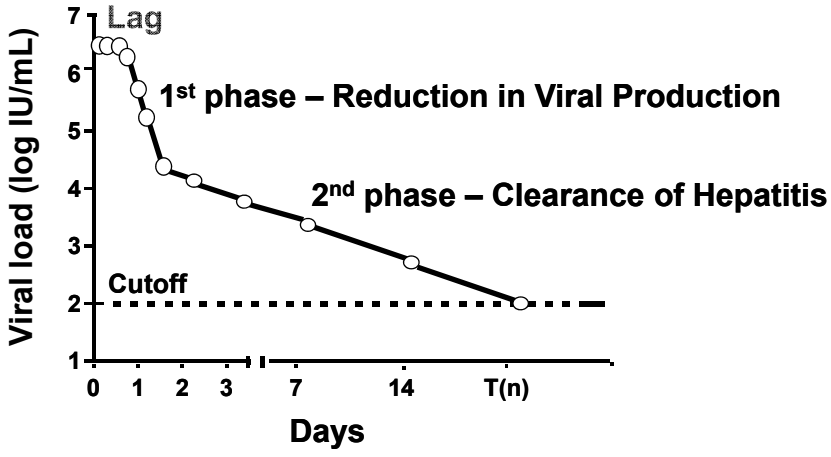
Advances in HCV Therapy
Average SVR



Treatment of Chronic HCV
Type of Response



HCV Kinetics: Key to Viral Clearance

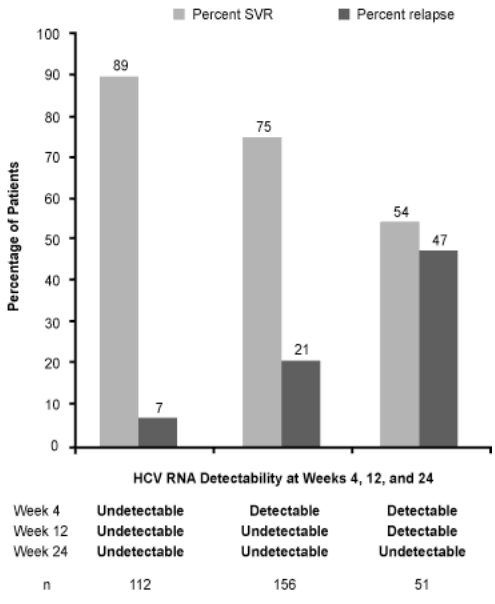


Neumann et al. Science. 1998;282:103.

Virological Response Terms

- EVR = minimum 2 $\log_{10}$ decrease in HCV RNA during first 12 wk of therapy
- ETR = undetectable HCV RNA at the completion of therapy
- SVR = persistently undetectable HCV RNA for ≥6 months following completion of therapy
- RVR = negative at wk 4
- eRVR = extended RVR, neg wk 4 + wk 12, 20
- VRVR = negative at wk 1

Genotype 1: Relationship of SVR rate and time to undetectable HCV RNA.



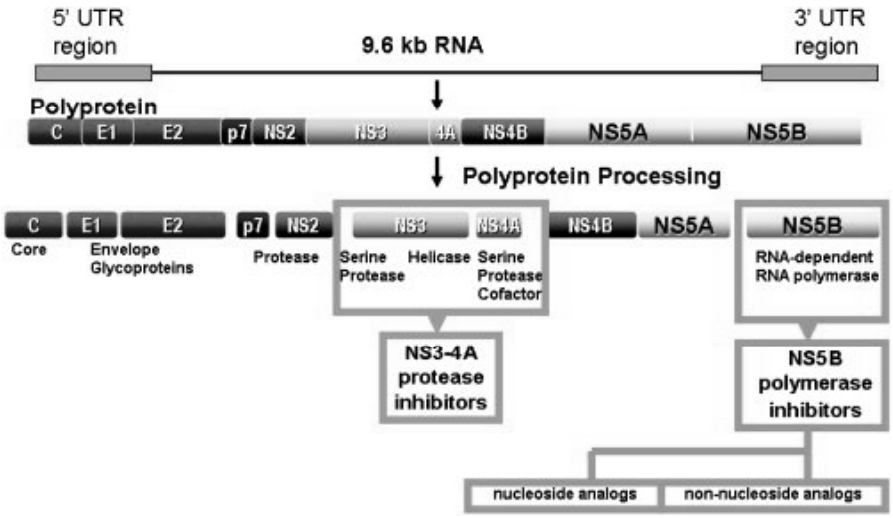
Likelihood of RVR:
34% low VL
vs. 23% with high VL

Both viral load and early response make a difference

Overall response of Genotype 1: ca. 40%
But ca. 25% in A-A patients

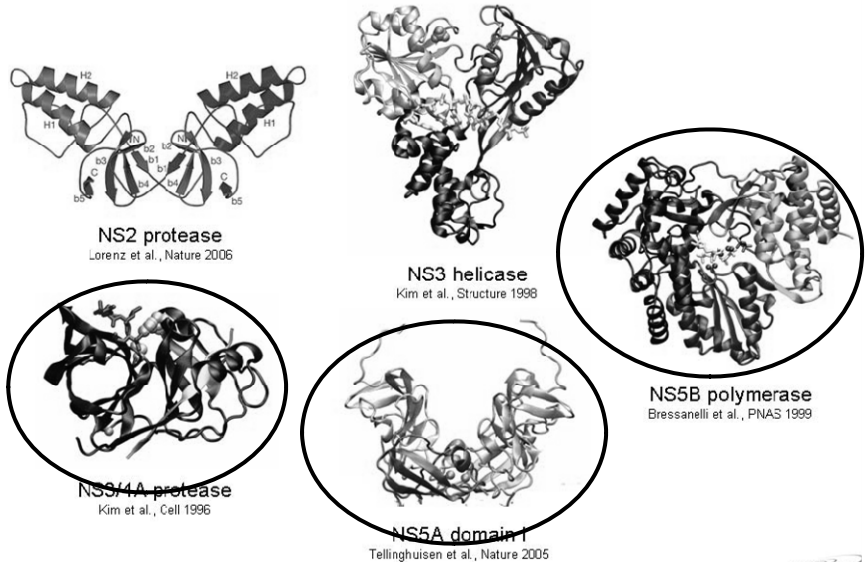
Ferenci et al Data based on Pegasys licensing trial

HCV Polyprotein Processing and Viral Protein Function



McGovern B, Abu Dayyeh B, and Chung RT. Hepatology. 2008; 48:1700-12

Potential HCV Targets



Adapted from Bartenschlager RJ. Presented at 43rd EASL Milan, Italy, April 2008.

Graveyard for HCV Compounds is Filling Up Quickly!

ISIS 14803
(Antisense)

UT-231B
(Imino sugar)

Heptazyme
(Ribozyme)

VX-497
(IMPDH inhibitor)

ANA975
(TLR agonist)

BILN 2061
(Protease)

JTK-003
(Polymerase)

HCV-796
(Polymerase)

NM-283
(Polymerase)

R803
(Polymerase)

CPG 10101
(TLR agonist)

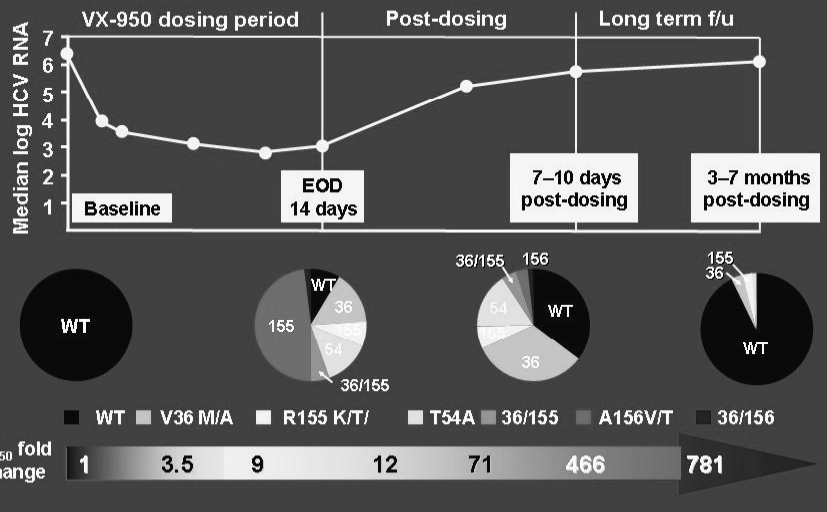
ACH-806/GS-9132
(NS4a)

R7025
(Interferon-alpha)

Courtesy of Nelson D.

Data have not been reviewed or approved by FDA.

Emergence of Resistance Underlies Breakthrough and Plateau Response



Data have not been reviewed or approved by FDA.

Sarrazin C, et al. *Gastroenterol.* 2007;132:1767-1777.

Back Up

Major HCV Therapy Trials 2006-2011

MERCK: Boceprevir, Victrelis®
SPRINT-1: Naïve, Phase 2: Boceprevir: dose finding
SPRINT-2: Naïve, Phase 3: Boceprevir: RGT/Blacks/Non-Black
RESPOND-2: Experienced, Phase 3: Boceprevir, length Rx experienced
VERTEX: Telaprevir, Incivek®
PROVE-1: Naïve, Phase 2: Telaprevir, dose/duration
PROVE-2: Naïve, Phase 2: Telaprevir, leave off RBV?
ADVANCE: Naïve 8 vs 12 wk, Phase 3: Telaprevir, shorten Rx to 8 wk
ILLUMINATE: Naïve RGT, Phase 3: Telaprevir: RGT: 24 vs. 48
REALIZE: Experienced, Phase 3: Telaprevir: Lead-in

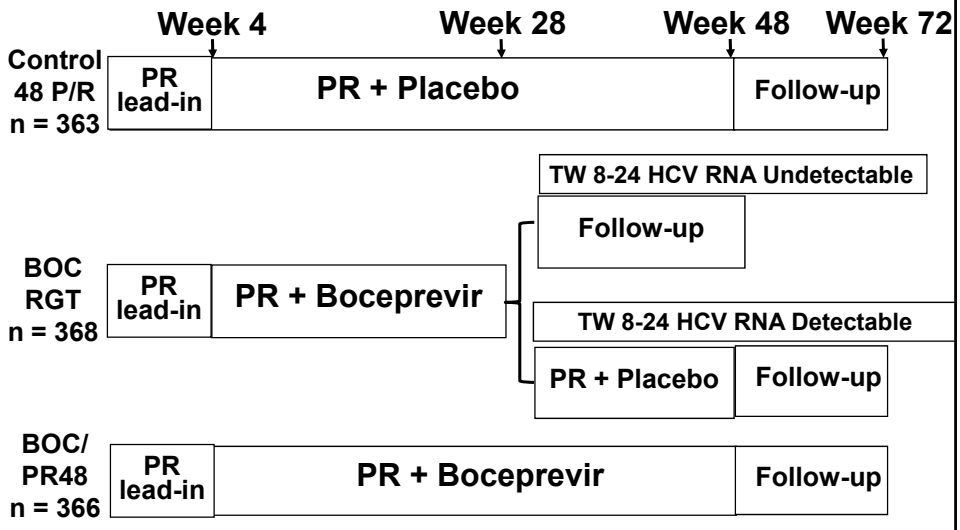
Add on to SOC: Phase 2 Trials of HCV NS3-4A protease inhibitors in HCV-1

Response	PROVE1 (24 wks)	PROVE2 (24 wks)	SPRINT-1 (28 wks) (no leadin/leadin)	SPRINT-1 (48 wks) (no leadin/leadin)	SOC Peg/RBV (48 wks)
RVR	81%	69%	39%	37%	8-15%
SVR	61%	68%	54/56%	67/75%	38-48%

- **PROVE1: TPV + Peg-2a / RBV × 12 wks then Peg/ RBV × 12 wks if RVR (24W)**
- **PROVE2: TPV + Peg-2a / RBV × 12 wks then Peg RBV × 12 wks (24W)**
- **SPRINT-1: Boceprevir + Peg-2b + RBV for 24/28 weeks or 44/48 weeks with or without a 4-wk lead in period of PEG-2b + RBV**

McHutchison J, et al. NEJM 2009;360:1827-38
Hezode C et al, NEJM 2009;360:1839-50
Kwo P, et al. Lancet 2010; 376:705-16

SPRINT-2: Boceprevir in G1 Naïve CHC

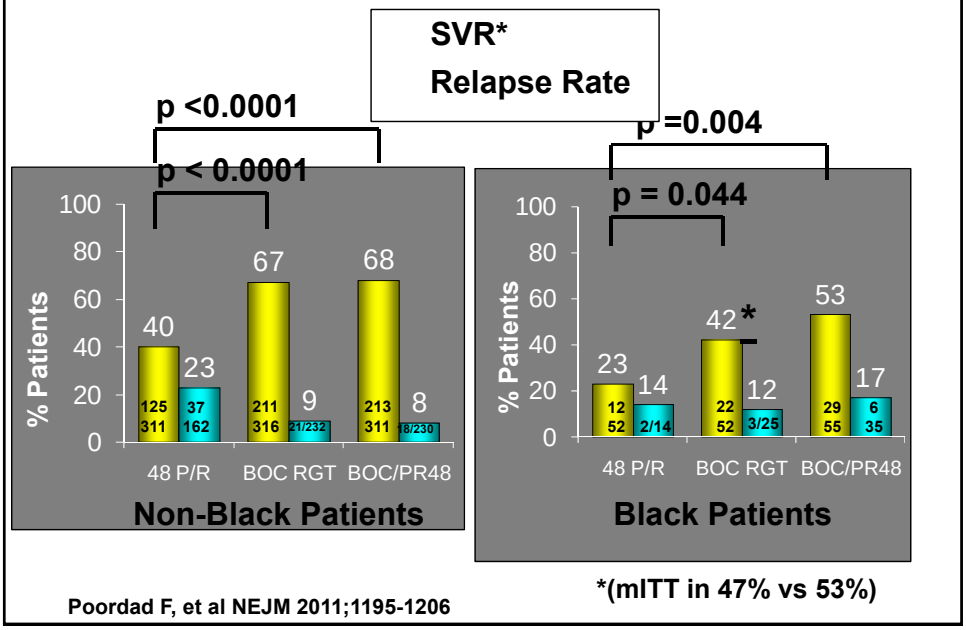


Peginterferon (P) administered subcutaneously at 1.5 µg/kg once weekly, plus ribavirin (R) using weight-based dosing of 600-1400 mg/day in a divided daily dose

Boceprevir dose of 800 mg thrice daily

Poordad F et al. NEJM 2011;364:1195-1206

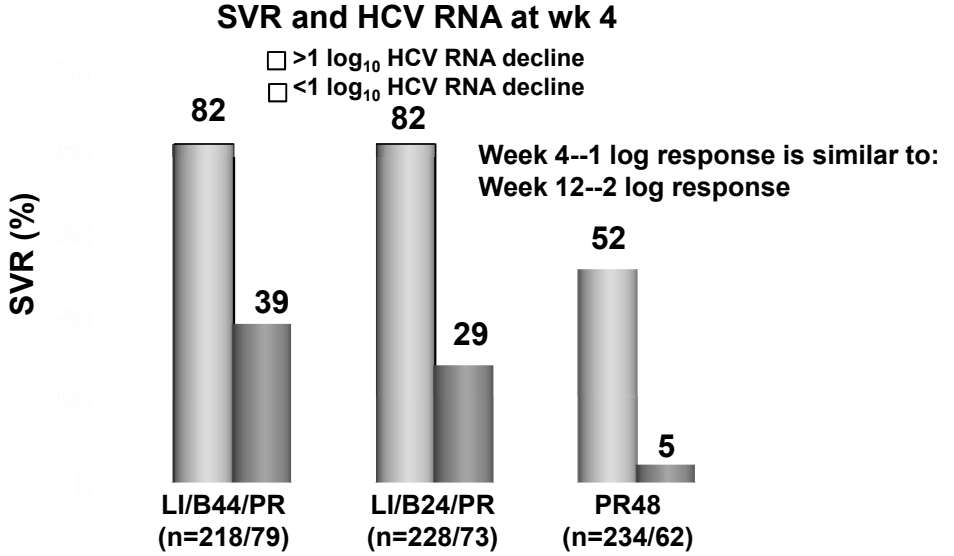
SPRINT-2: SVR and Relapse Rates (ITT)



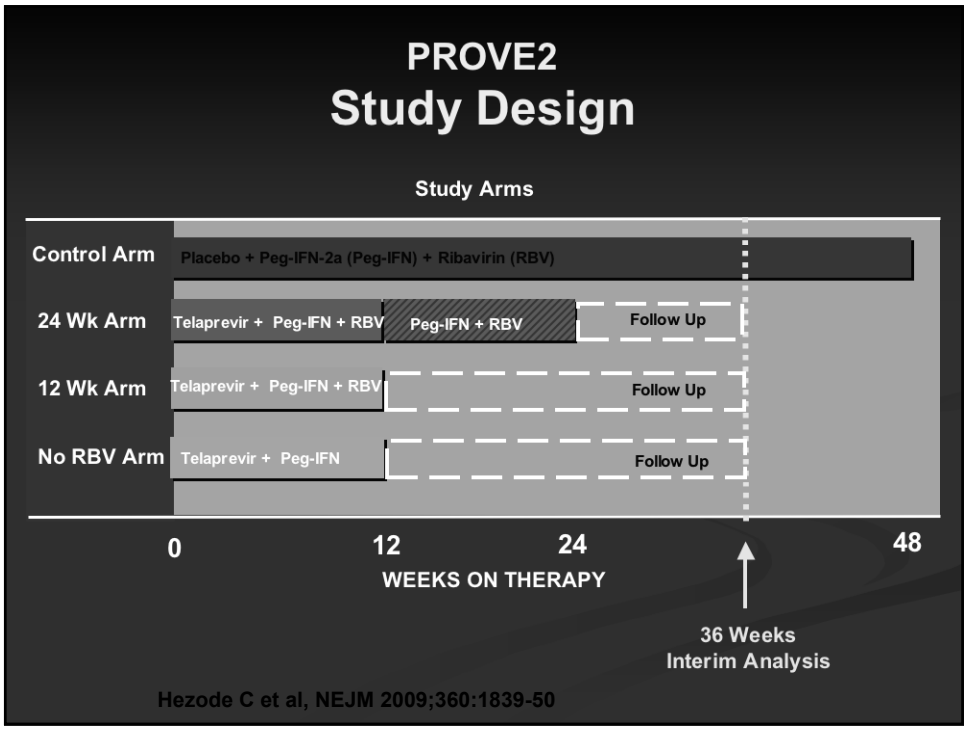
*(mITT in 47% vs 53%)

Poordad F, et al NEJM 2011;1195-1206

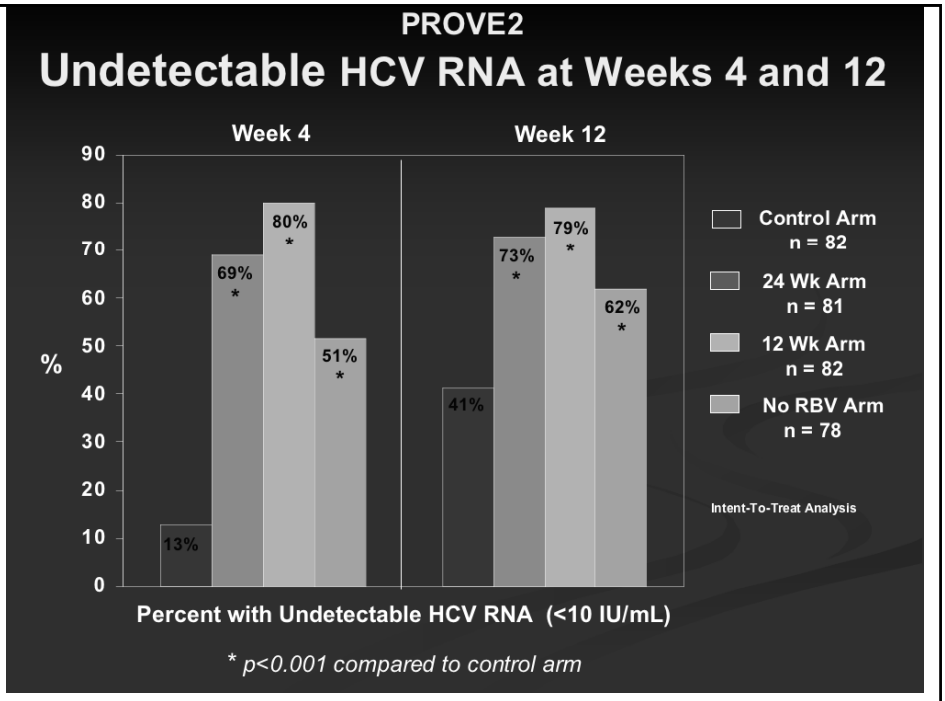
SPRINT-2 Study Outcomes Based on Week 4 Lead-In (Nonblack Patients)



RAVs: resistance-associated variants. Boceprevir RAVs determined with population sequencing.
Poordad F, et al. NEJM 2011;364:1195-1206



Hezode C et al, NEJM 2009;360:1839-50



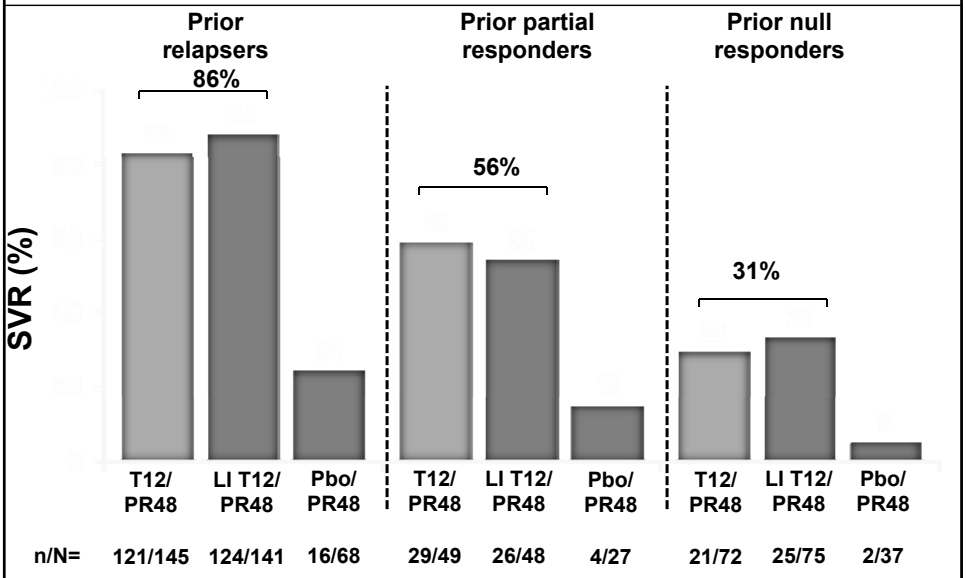
Hezode C et al, NEJM 2009;360:1839-50

ADVANCE: Most Common Adverse Events

% of Patients with	T12PR N=363	T8PR N=364	PR (control) N=361
Any Adverse Event*	99	99	98
Fatigue	57	58	57
Pruritus	**50**	**45**	**36**
Headache	41	43	39
Nausea	**43**	**40**	**31**
Rash	**37**	**35**	**24**
Anemia	**37**	**39**	**19**
Insomnia	32	32	31
Diarrhea	**28**	**32**	**22**
Influenza-like illness	28	29	28
Pyrexia	26	30	24

Shaded areas: 10% or greater incidence in either TVR groups vs control

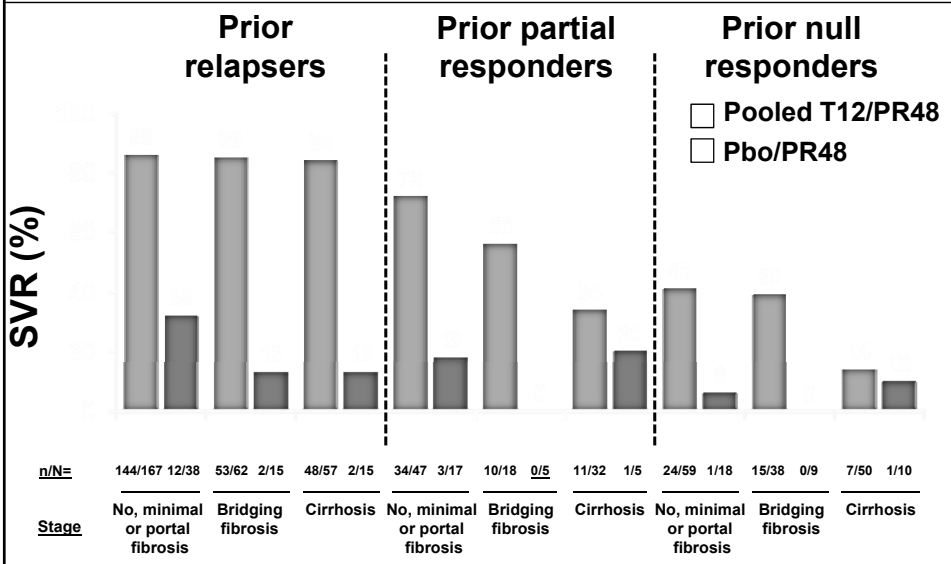
REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



Zeuzem S, et al.EASL:2011, Oral Presentation 5.

*p<0.001 vs Pbo/PR48

REALIZE: SVR by Baseline Fibrosis Stage and Prior Response



Zeuzem S, et al.EASL:2011, Oral Presentation 5.

Conclusions: HCV Therapy as of 2011

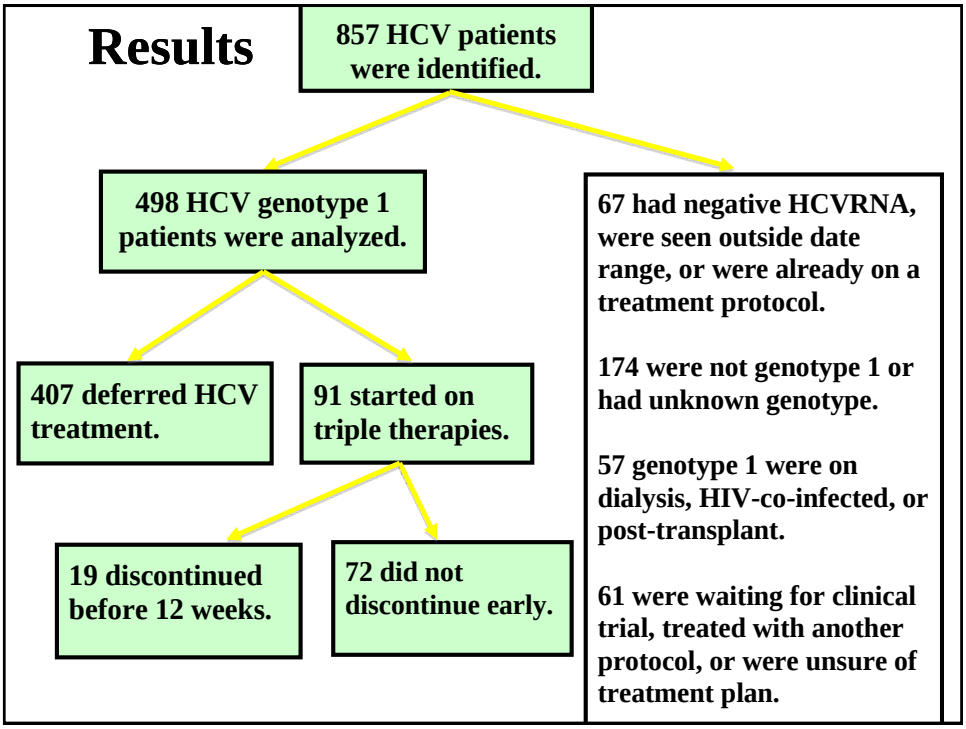
Durability of therapy

- SVR is a cure
- Tailor therapy to early viral response: RGT is effective

Protease inhibitors

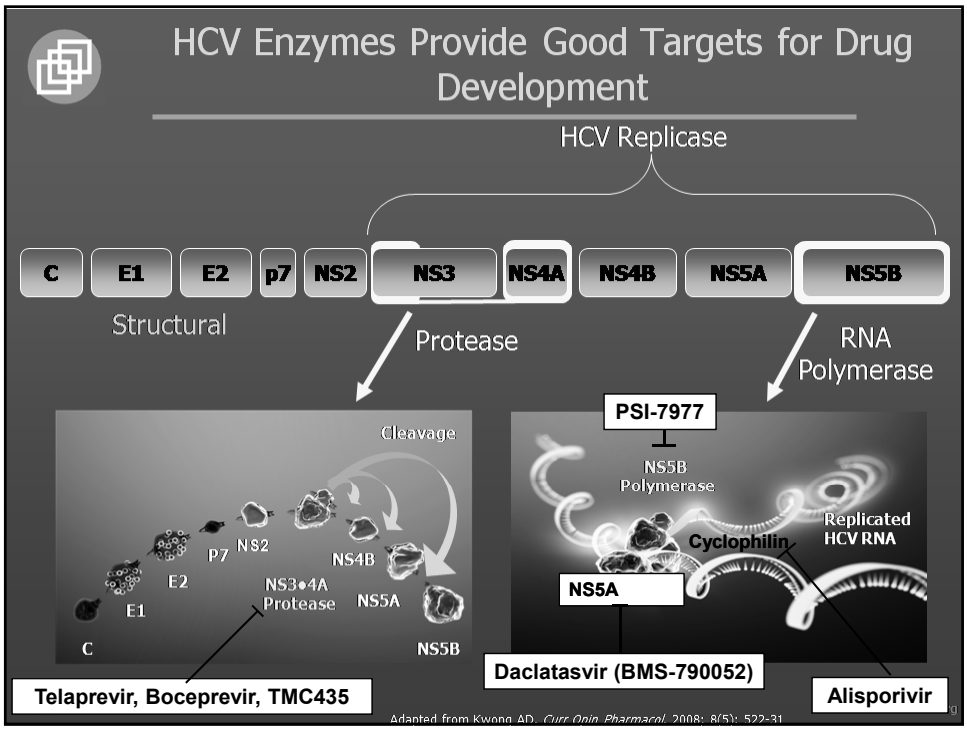
- High rates of RVR in naive patients, ca. 65%
  - Can shorten Rx to 24-28 weeks Rx for RVR's
  - Treatment-limiting adverse effects include rash, diarrhea
- More side effects, limiting responses but few relapses
- Virological failure occurs with mutations, ? significance
- Cirrhosis, high VL, genotype less predictive; 1b > 1a
- Prior IFN/RBV response determines 3-drug response
- Need IFN and RBV so far!!
- Watch for earlier and more severe anemia!

Results



Discussion

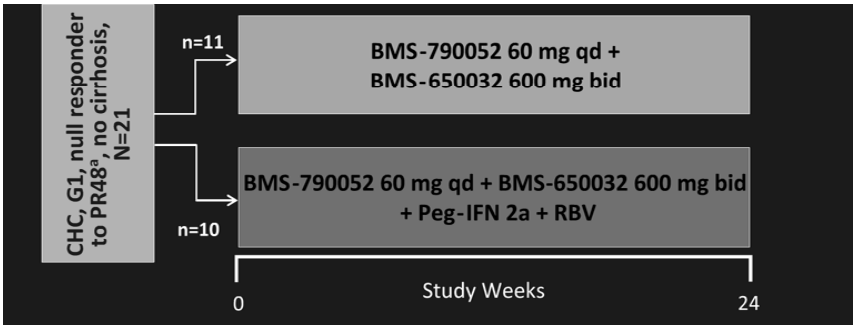
- Triple therapy initiation rate was only 18%
- Reasons to defer triple therapy included medical and psych contraindications, too early or too late
- Probably more HCV patients in academic practices have advanced fibrosis and/or are prior treatment non-responders. “Hard-to-treat”
- Triple therapy discontinuation rate (20.8%) higher than the 7-9% reported in clinical trials



Examples of > 80% SVR Rates in Phase II, DAA + PegIFN + RBV Trials in HCV GT1, Rx Naive Patients

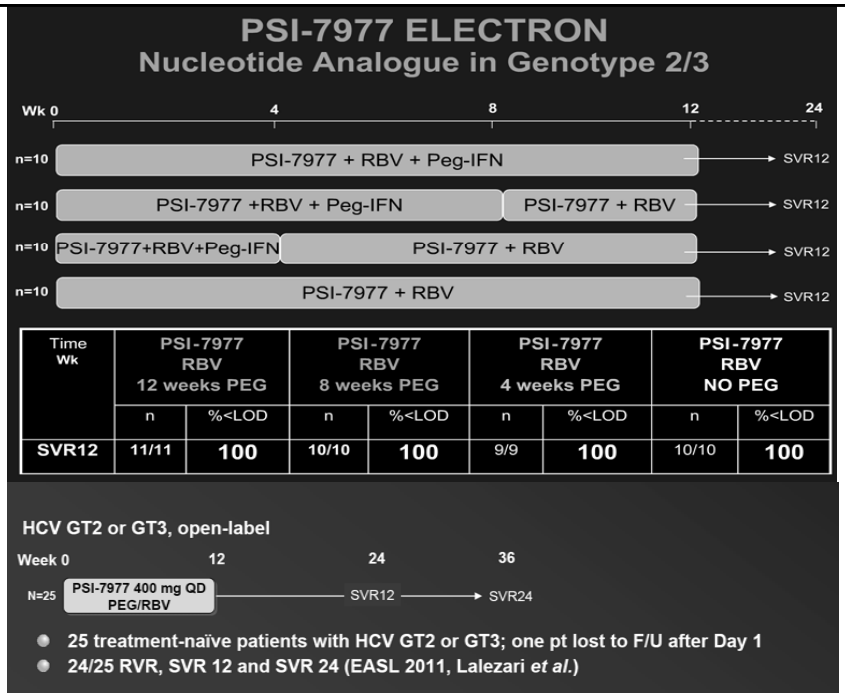
Direct Acting Antiviral	Target	SVR rates (DAA /PR vs. PR)	Unique Features
Daclatasvir 10 mg, 48 wk, N=12	NS5A Replication Complex	92% vs. 25%	First in class Once daily dosing No new side effects
TMC435, 150 mg X 24 wk, N=79	NS3/4A protease	86% vs. 65%	Macrocyclic Higher resistance barrier Once daily dosing
PSI-7977 400 mg, 24 wk, N=47	NS5B polymerase	91% vs. < 50%	Pangenotypic Once daily dosing No resistance observed

Phase 2a Study of Double or Quadruple Therapy of Null Responder, Genotype 1 HCV Infection with Daclatasvir (BMS-790052) and Asunaprevir (BMS-650032) +/- PR



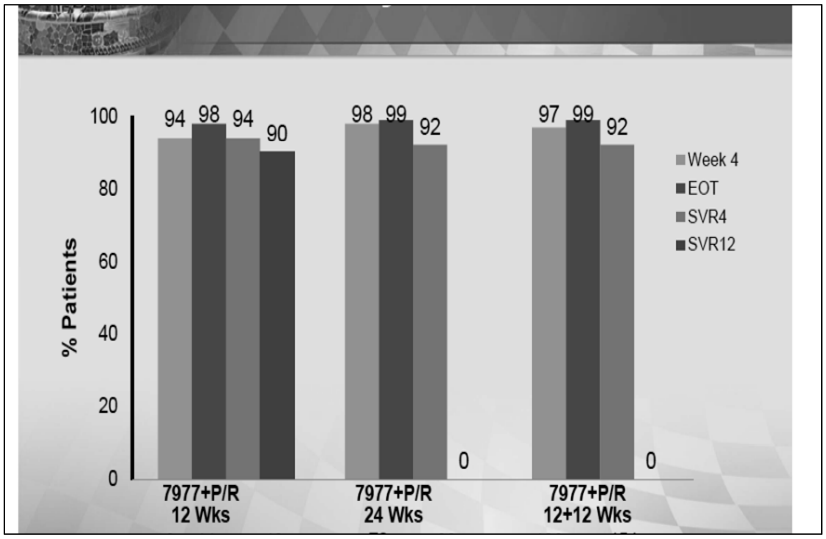
	IL28B CT/TT	1a/1b	RVR	EOT	SVR12
PI + NS5A	90.4%	9/2	63.6%	45%	36%
Quad		9/1	60%	100%	100%

Lok, AS, et al, NEJM, 2012; 366:216



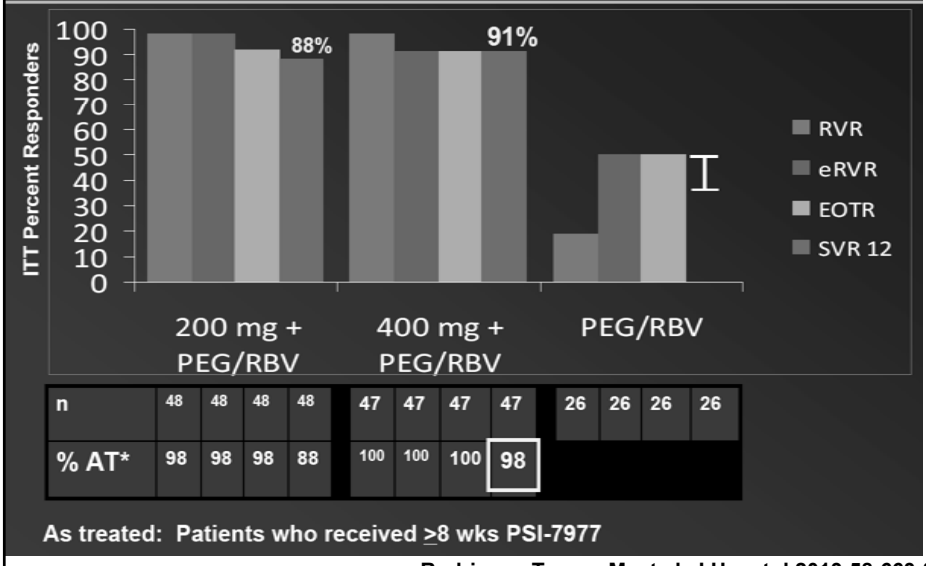
Rodriguez-Torres, M, et al. J Hepatol 2013;58:663-8.

The ATOMIC Study; 7977 plus P/R for geno 1 HCV



Rodriguez-Torres, M, et al. J Hepatol 2013;58:663-8.

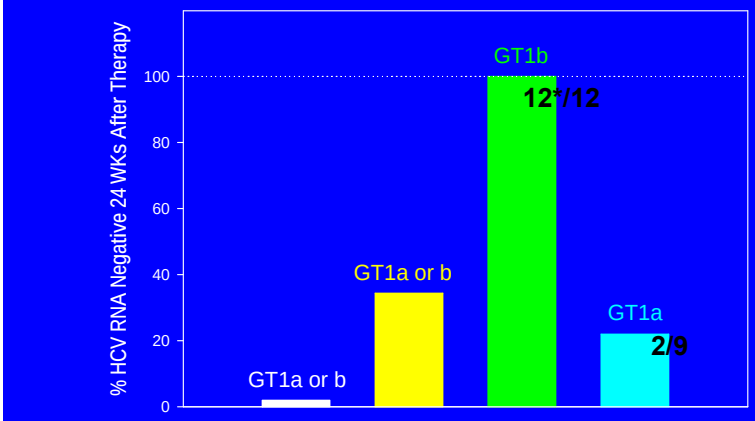
RESULTS: 98% SVR in subjects who received at least 8 weeks of PSI-7977 400 mg QD + PEG/RBV



As treated: Patients who received ≥8 wks PSI-7977

Rodriguez-Torres, M, et al. J Hepatol 2013;58:663-8.

Cure of Genotype 1b, Prior Null-Responder HCV Infections with an Interferon-Free Regimen



Zeuzem, S., et al, N. Engl. J. Med., 2011, 364:2417
Lok, A.S., et al , NEJM, 2012; 366:216
Chayama, K. et al, Hepatology, 2011; 54:1428A

*One patient completed only 8 weeks RX but still HCV RNA negative 24 wks later

Summary: Current State of Play 2013

- Triple therapy is superior to Peg/RBV
- But is not successful in many patients with established cirrhosis
- Interferon/RBV still needed so far
- New agents hold great promise/not here yet
- We will be able to treat all sorts of HCV patients within the next 3 years: HIV, cirrhosis, post-transplantation

Unanswered Questions

- 2nd generation agents are not yet here but seem amazing
- Will they work as well in the 'hard to treat?'
- How will we treat HIV/HCV? Or transplant patients?
- When will we have an approved IFN-free regimen?
- What will be the cost of a 'sure cure?'

Public Health Concerns

- Medications very expensive, currently up to $70,000 for a course of treatment
- No vaccination available
- Large number of unrecognized cases, probably around 50%
- Need to develop strategies to identify new cases
- Increasing numbers with end-stage liver disease being recognized: HCC
- Large burden on health care system

Taking the CDC Recs to Heart

- CDC recs represent a watershed
- How to implement them?
- How about employee screening for HCV?
- HIPAA considerations?
- The drugs will soon be available, fall 2013?
- Conquering Hep C is in sight!!

Ohio State Liver Care/Transplant Group

Chronic/end stage liver disease, hepatitis B and C, clinical trials, drug-induced liver injury, acute liver failure.

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