# Chronic Hepatitis C Natural History and Current Treatment 2013

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## Financial Disclosures

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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.

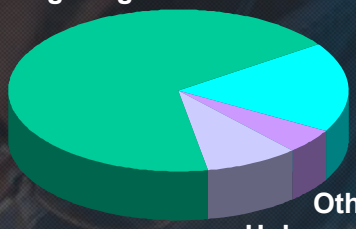
## Hepatitis C: A Global Health Problem

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


Source: WHO 1999.

## Sources of Infection for Hepatitis C (1995-2000)

Injecting drug use 68%



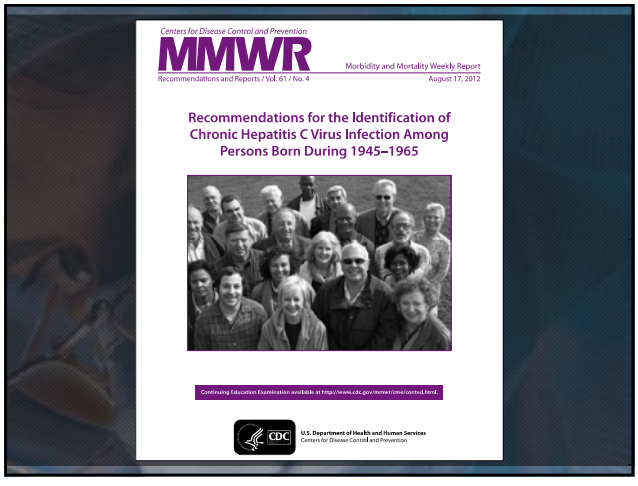
Sexual 18%

Other* 5%

Unknown 9%

*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.



Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Recommendations and Reports / Vol. 61 / No. 4 August 17, 2012

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

Continuing Education Examination available at http://www.cdc.gov/mmwr/cme/conted.html.

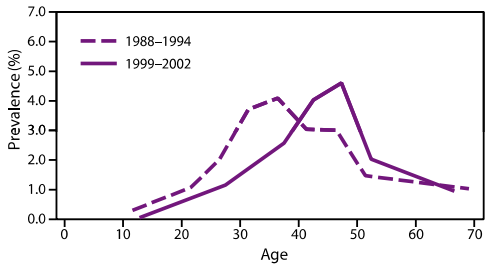
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

## 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

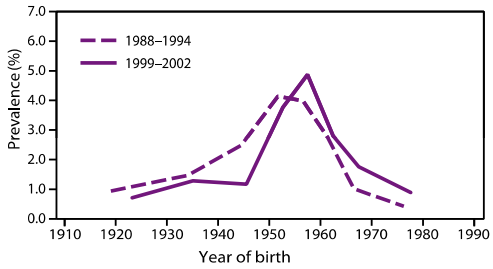
**FIGURE 1. Prevalence of hepatitis C virus antibody, by age at time of survey — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002**




**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**

| | | Anti-HCV | | Chronic HCV infection | |
|---|---|---|---|---|---|
| Birth cohort | U.S. population (in millions)* | No. (in millions) | (Weighted %)† | No. (in millions)§ | (%) |
| 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.)



...nas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and ...t of hepatitis C: an update. [Practice Guideline.] Hepatology 2009;49(4):1335–74.)

...cause ...antial ...years ...born ...–1965 ...direct ...s at a ...cation ...n. The ...death ...th the ...Data ...ups in ...–1965 ...as the ...nd the ...of the CDC

**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**

| | Anti-HCV (weighted %) | | |
|---|---|---|---|
| Characteristic | 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%).

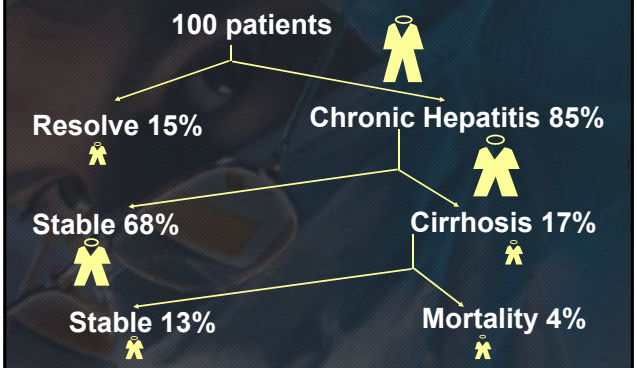
Complicating health outcomes among HCV-infected persons born during 1945–1965 are a lack of health insurance (31.5%) and use of alcohol (3). Of all anti-HCV–positive

## Summary of new CDC Recs

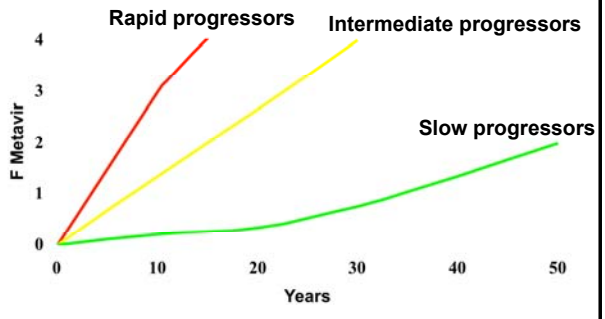
- Current estimates are ca. 4 million Americans with HCV
- Between 45 and 85% of HCV infected are unaware of it
- Risk-based strategies have failed
- Baby boomers (1945-1965) represent 27% of the population but 75% of those infected
- 1990-2015: estimated 4-fold increase in the number of patients diagnosed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

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

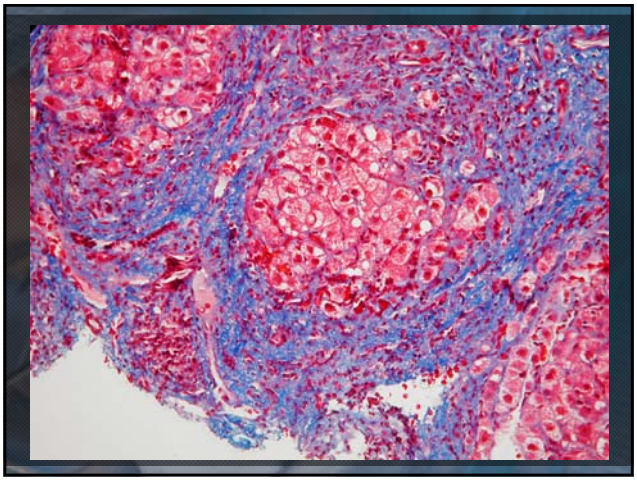
## Natural History Hepatitis C



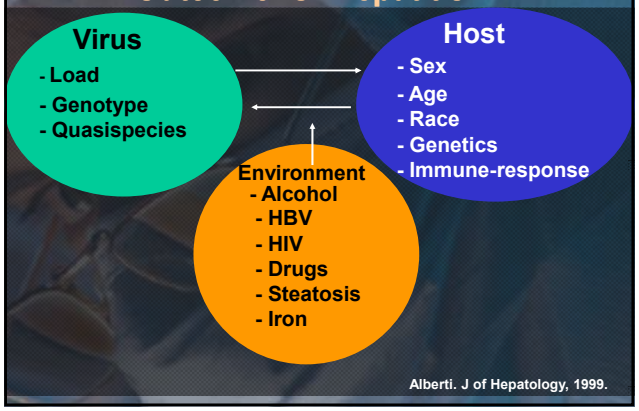

## Modeling of Liver Fibrosis in Chronic Hepatitis C, n=1157 Patients




Poynard et al, Hepatology 1999

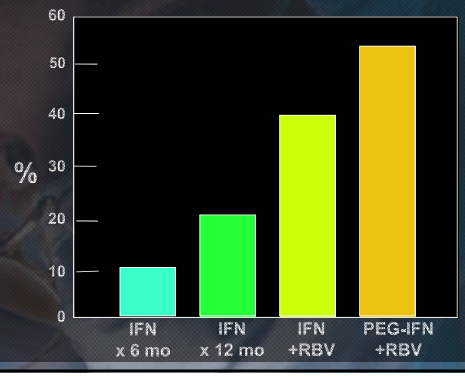


## Factors Which Might Influence The Outcome Of Hepatitis C

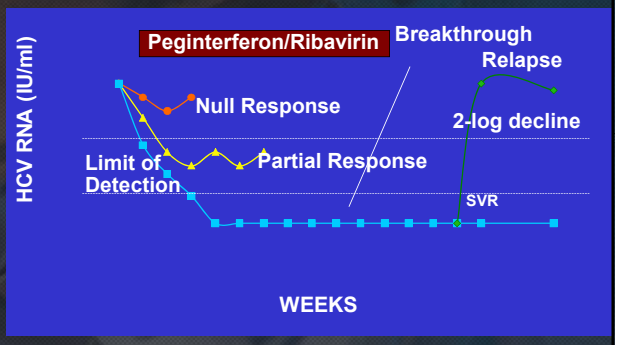



Alberti. J of Hepatology, 1999.

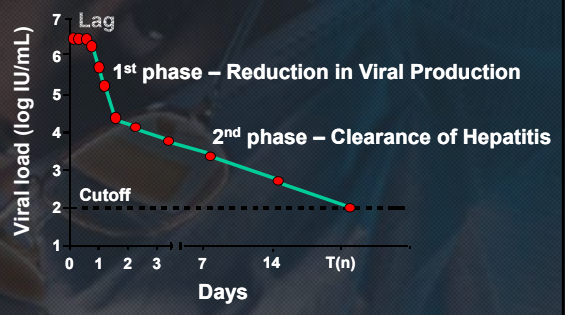
## Advances in HCV Therapy
*Average SVR*




## Treatment of Chronic HCV
*Type of Response*




## HCV Kinetics: Key to Viral Clearance

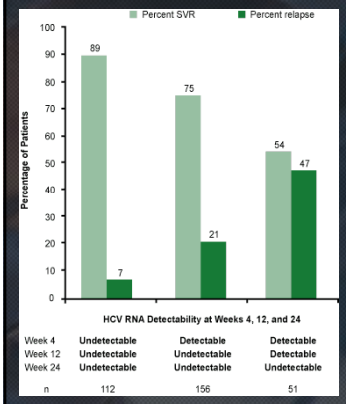



Neumann et al. Science. 1998;282:103.

## 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.



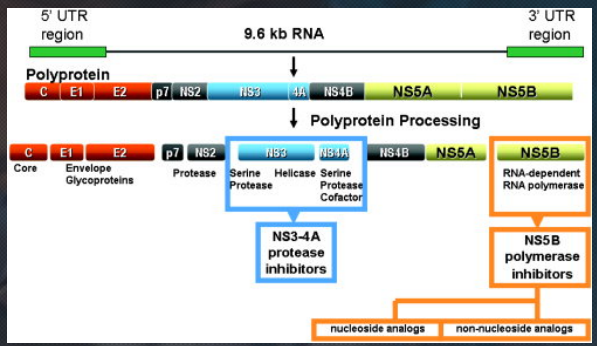

**Likelihood of RVR: 34% low VL vs. 23% with high VL**

**Both viral load and early response make a difference**

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

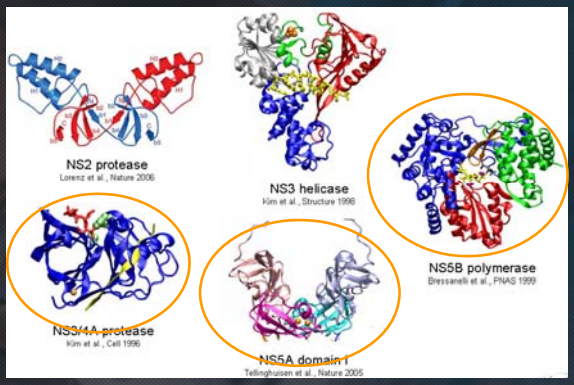
Ferenci et al Data based on Pegasys licensing trial

## 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)

CPG 10101 (TLR agonist)

ACH-806/GS-9132 (NS4a)

R7025 (Interferon-alpha )

BILN 2061 (Protease)

JTK-003 (Polymerase)

HCV-796 (Polymerase)

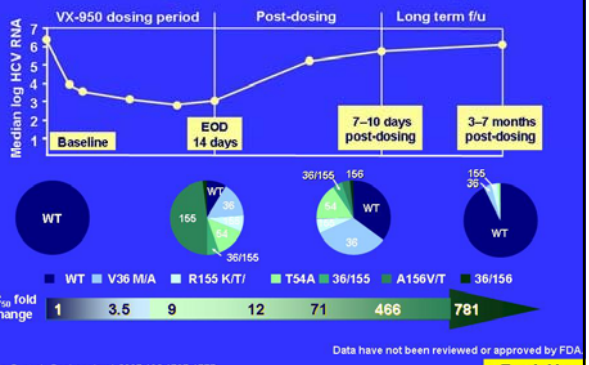
NM-283 (Polymerase)

R803 (Polymerase)

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

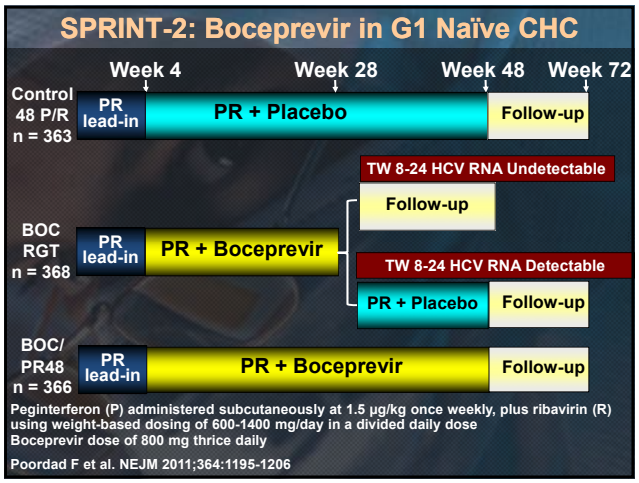
| Response | PROVE1 (24 wks) | PROVE2 (24 wks) | SPRINT-1 (28 wks) (no leadin/leadin) | SPRINT-1 (48 wks) (no leadin/leadin) | SOC Peg/RBV (48 wks) |
|---|---|---|---|---|---|
| RVR | 81% | 69% | 39% | 37% | 8-15% |
| SVR | 61% | 68% | 54/56% | 67/75% | 38-48% |

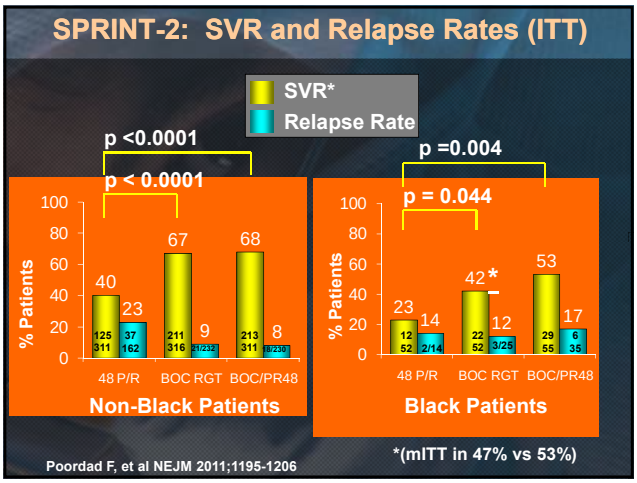
- **PROVE1: TPV + Peg-2a / RBV × 12 wks then Peg/ RBV × 12 wks if RVR (24W)**
- **PROVE2: TPV + Peg-2a / RBV × 12 wks then Peg RBV × 12 wks (24W)**
- **SPRINT-1: Boceprevir + Peg-2b + RBV for 24/28 weeks or 44/48 weeks with or without a 4-wk lead in period of PEG-2b + RBV**

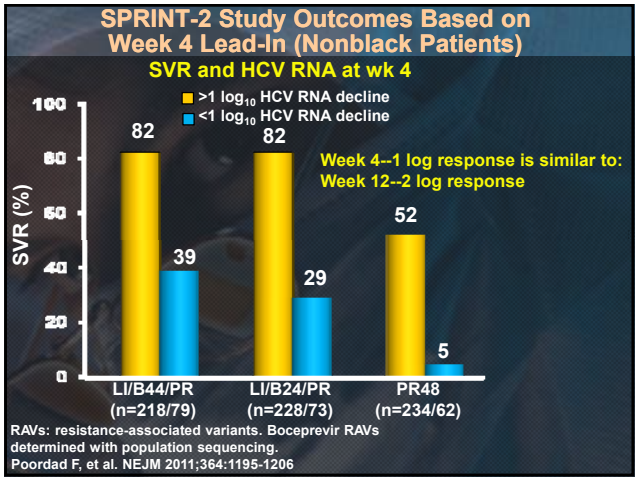
McHutchison J, et al. NEJM 2009;360:1827-38

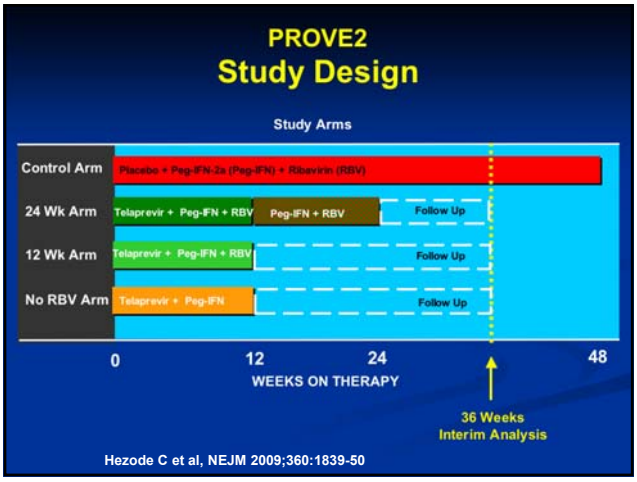
Hezode C et al, NEJM 2009;360:1839-50

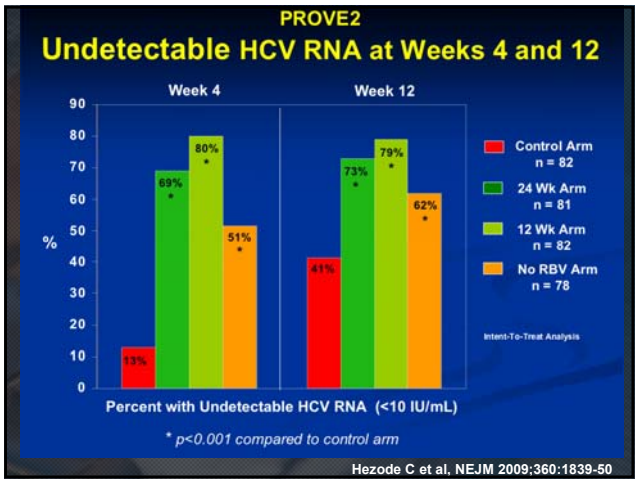
Kwo P, et al. Lancet 2010; 376:705-16


SPRINT-2: Boceprevir in G1 Naïve CHC
Week 4
Week 28
Week 48
Week 72
Control
48 P/R
n = 363
PR lead-in
PR + Placebo
Follow-up
TW 8-24 HCV RNA Undetectable
Follow-up
BOC
RGT
n = 368
PR lead-in
PR + Boceprevir
TW 8-24 HCV RNA Detectable
PR + Placebo
Follow-up
BOC/
PR48
n = 366
PR lead-in
PR + Boceprevir
Follow-up
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)
SVR*
Relapse Rate
p <0.0001
p < 0.0001
p =0.004
p = 0.044
% Patients
100
80
60
40
20
0
40
23
67
9
68
8
125/311
37/162
211/316
21/232
213/311
18/230
48 P/R
BOC RGT
BOC/PR48
Non-Black Patients
23
14
42*
12
53
17
12/52
2/14
22/52
3/25
29/55
6/35
48 P/R
BOC RGT
BOC/PR48
Black Patients
*(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)
SVR and HCV RNA at wk 4
>1 log10 HCV RNA decline
<1 log10 HCV RNA decline
SVR (%)
100
80
60
40
20
0
82
39
82
29
52
5
Week 4--1 log response is similar to: Week 12--2 log response
LI/B44/PR (n=218/79)
LI/B24/PR (n=228/73)
PR48 (n=234/62)
RAVs: resistance-associated variants. Boceprevir RAVs determined with population sequencing.
Poordad F, et al. NEJM 2011;364:1195-1206

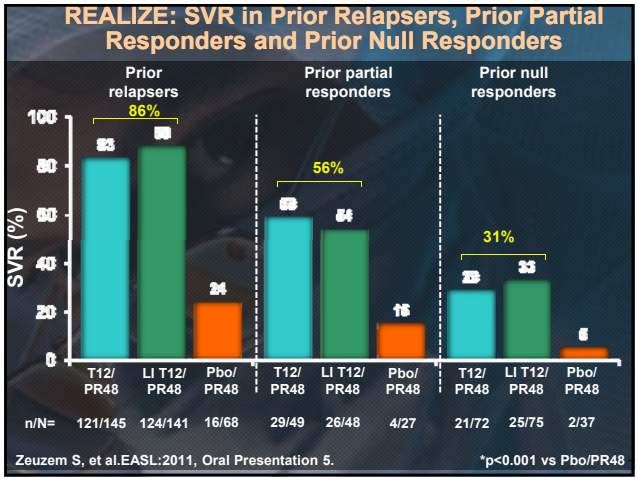

PROVE2
Study Design
Study Arms
Control Arm
Placebo + Peg-IFN-2a (Peg-IFN) + Ribavirin (RBV)
24 Wk Arm
Telaprevir + Peg-IFN + RBV
Peg-IFN + RBV
Follow Up
12 Wk Arm
Telaprevir + Peg-IFN + RBV
Follow Up
No RBV Arm
Telaprevir + Peg-IFN
Follow Up
0
12
24
48
WEEKS ON THERAPY
36 Weeks
Interim Analysis
Hezode C et al, NEJM 2009;360:1839-50

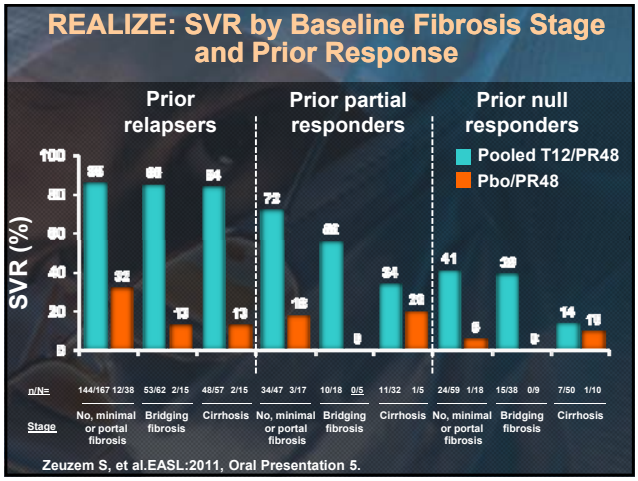



## ADVANCE: Most Common Adverse Events

| % 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

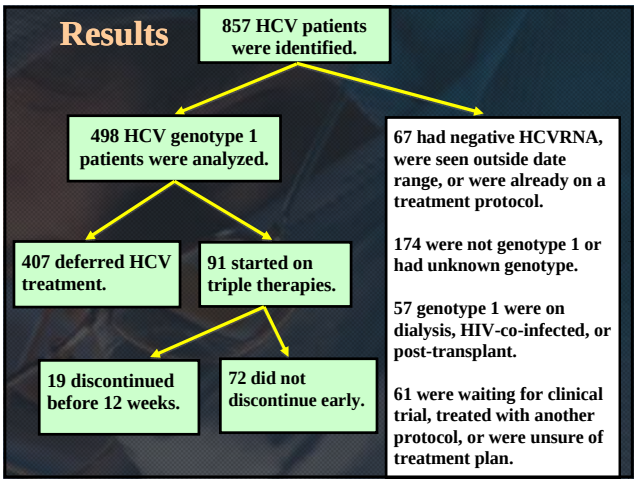


## Conclusions: HCV Therapy as of 2011

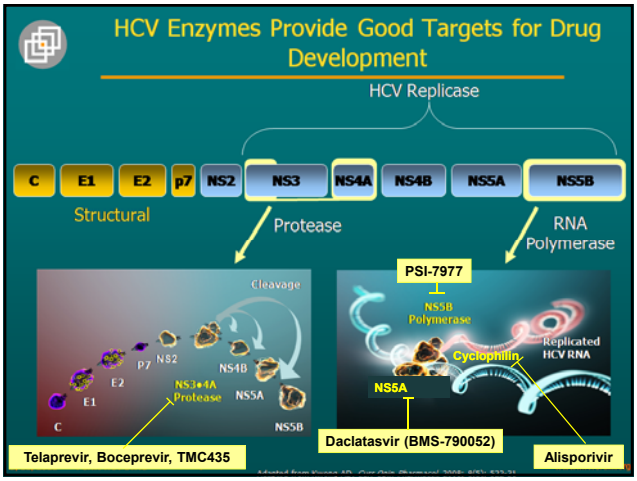
Durability of therapy
- SVR is a cure
- Tailor therapy to early viral response: RGT is effective

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!




## Discussion

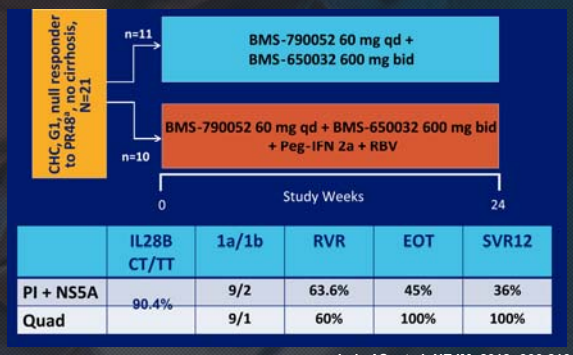
- Triple therapy initiation rate was only 18%
- Reasons to defer triple therapy included medical and psych contraindications, too early or too late
- Probably more HCV patients in academic practices have advanced fibrosis and/or are prior treatment non-responders. "Hard-to-treat"
- Triple therapy discontinuation 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<br>Once daily dosing<br>No new side effects |
| TMC435, 150 mg X 24 wk, N=79 | NS3/4A protease | 86% vs. 65% | Macrocyclic<br>Higher resistance barrier<br>Once daily dosing |
| PSI-7977 400 mg, 24 wk, N=47 | NS5B polymerase | 91% vs. < 50% | Pangenotypic<br>Once daily dosing<br>No resistance observed |

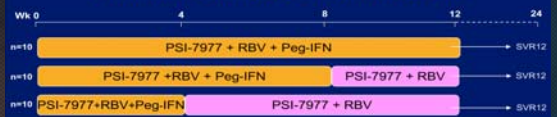
## Phase 2a Study of Double or Quadruple Therapy of Null Responder, Genotype 1 HCV Infection with Daclatasvir (BMS-790052) and Asunaprevir (BMS-650032) +/- PR




| | 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

## PSI-7977 ELECTRON
### Nucleotide Analogue in Genotype 2/3




| Time Wk | PSI-7977 RBV 12 weeks PEG | | PSI-7977 RBV 8 weeks PEG | | PSI-7977 RBV 4 weeks PEG | | PSI-7977 RBV NO PEG | |
|---|---|---|---|---|---|---|---|---|
| | n | %<LOD | n | %<LOD | n | %<LOD | n | %<LOD |
| SVR12 | 11/11 | 100 | 10/10 | 100 | 9/9 | 100 | 10/10 | 100 |

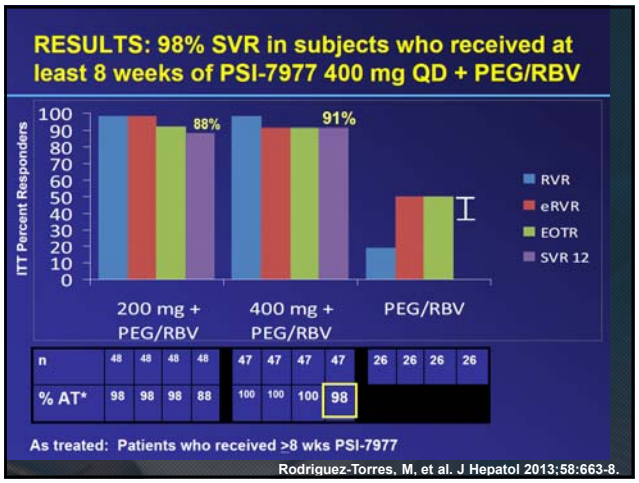
HCV GT2 or GT3, open-label

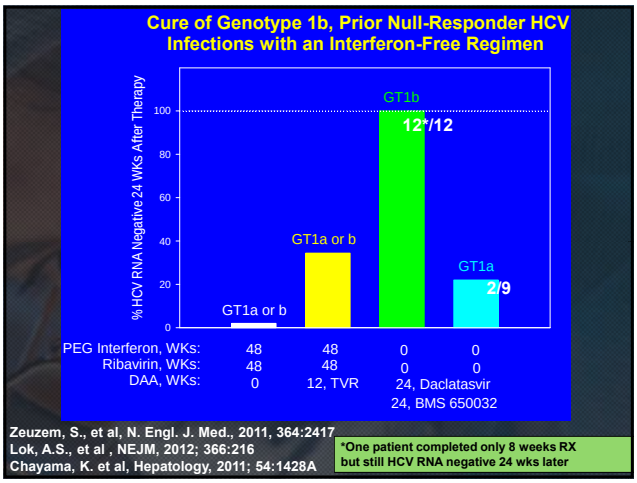

- 25 treatment-naive patients with HCV GT2 or GT3; one pt lost to F/U after Day 1
- 24/25 RVR, SVR 12 and SVR 24 (EASL 2011, Lalezari *et al.*)

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.




## 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.
Phone: 614-293-6255 Fax Referrals To: 614-293-8518
Long-Distance: 800-293-8965 After business hours, call: 800-293-5123