HCV Case Study

Treat Now or Wait for New Therapies

Program Disclosure

- This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the sponsorship of Annenberg Center for Health Sciences at Eisenhower and the Chronic Liver Disease Foundation. Annenberg Center for Health Sciences at Eisenhower is accredited by the ACCME to provide continuing medical education for physicians.

- This program is supported by educational grants from Kadmon and Merck Pharmaceuticals.

Learning Objectives

- Describe current data on approved and experimental DAA's used in combination with Pegylated Interferon and Ribavirin

- Define the benefits and risks of treating now versus delaying therapy for different patient populations

Glenn: Patient Characteristics

- 55 year old male
- Shift worker
- History/risk factors
  - BMI=34
  - Hypertension and dyslipidemia
  - Moderate drinker/cigarette smoker
- Concomitant medications
  - Simvastatin 20 mg/day
  - Lisinopril 10 mg/day

Glenn: Baseline Labs

• Hemoglobin	15.6 g/dL
• Neutrophils	1400 cells/mm^3
• Platelets	210,000 cells/mm^3
• AST/ALT	55/75 IU/L
• Albumin	4.1 g/dL
• Bilirubin	0.7 mg/dL

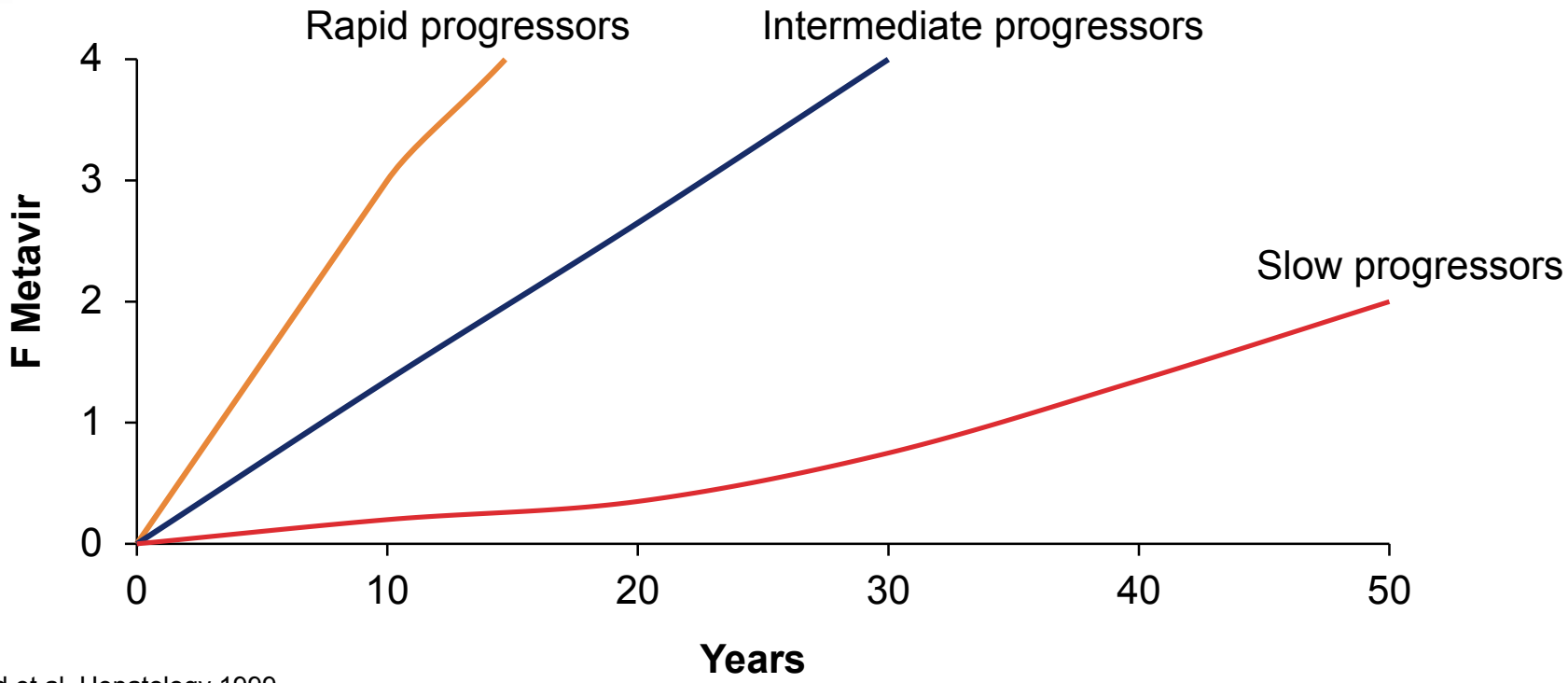
Glenn: Disease Characteristics

- Treatment naïve
- Genotype 1a
- *IL28B* CC
- METAVIR F3
- BL viral load 1,300,000 IU/mL

Clinical Decision 1

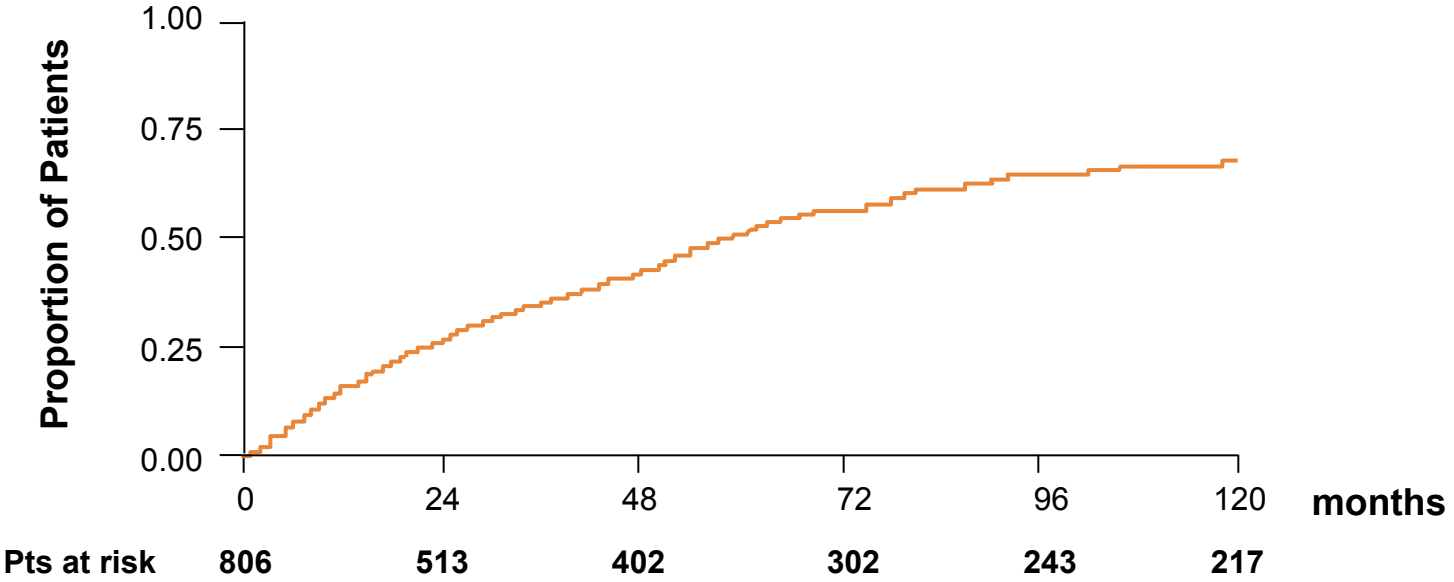
- How would you manage this patient?
  1. Continue to monitor patient but do not start treatment
  2. Start patient on first generation protease inhibitor/PEG-IFN/RBV

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



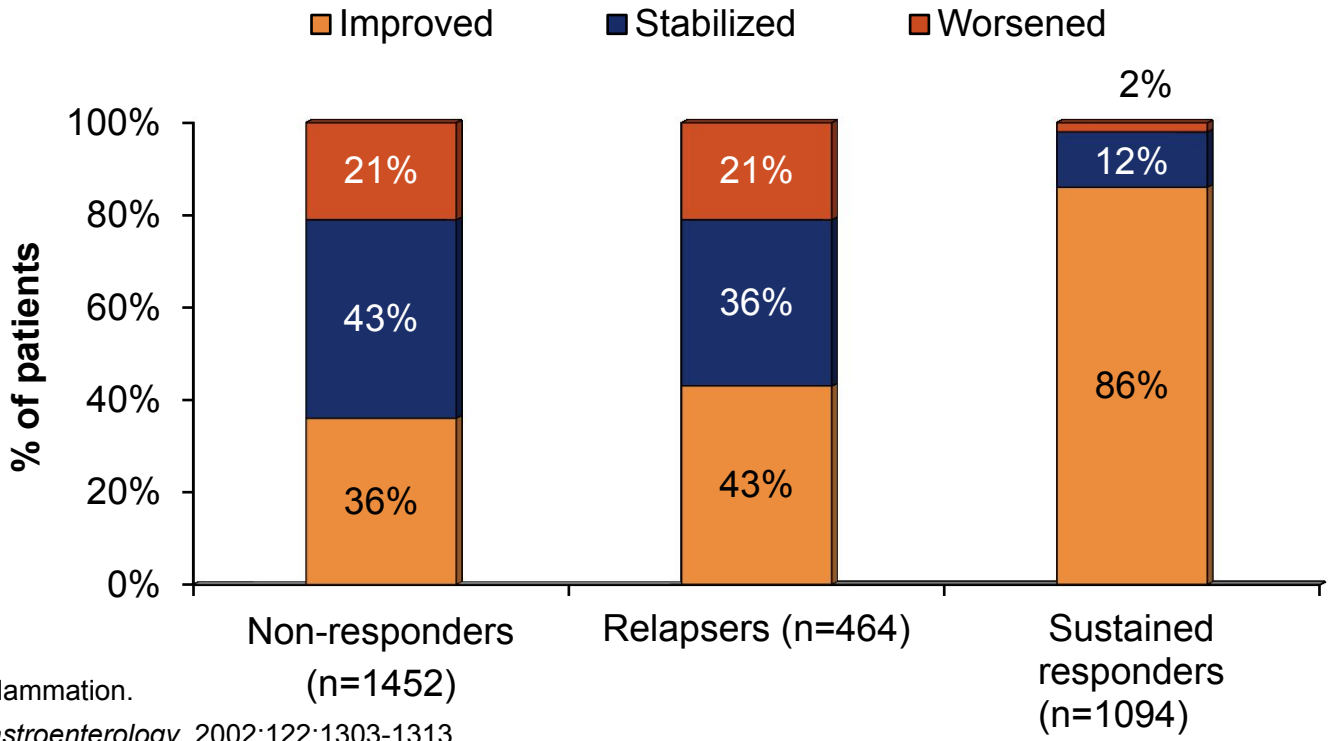
Poynard et al, Hepatology 1999

Cumulative Proportion of Patients Transitioning from Compensated to Decompensated Stage Over Time



D'Amico G et al. *J Hepatol.* 2006;44:217-231.

Impact According to Response of 10 Different Treatment Regimens on Evolution of Activity* in 3010 Patients with Paired Biopsies



*Necrosis and Inflammation.

Poynard et al. *Gastroenterology*, 2002;122:1303-1313.

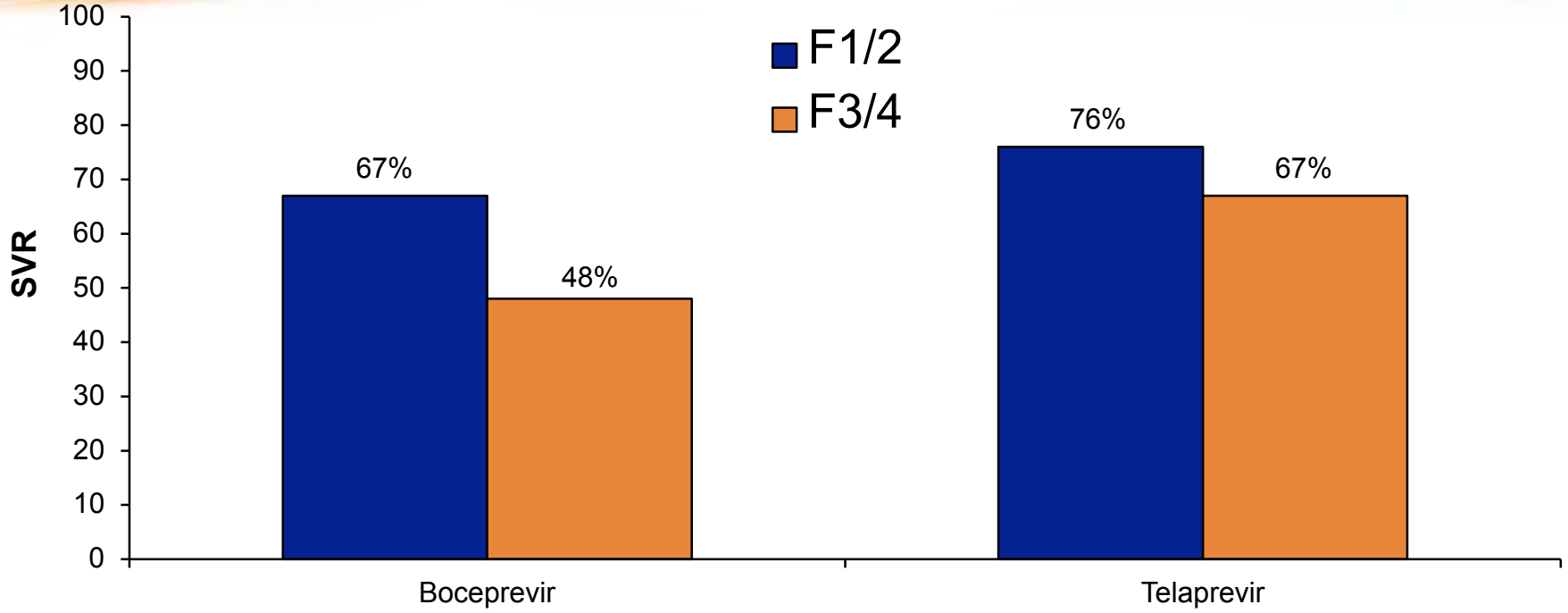
ADVANCE: *IL28B* Genotype Effect on Telaprevir Therapy

	In Patients Tested for *IL28B* (%)				In All ADVANCE Patients
	CC	CT	TT	Total	
T12PR*	**90**	71	73	78	75
T8PR**	87	58	59	67	69
PR	64	25	23	38	44

*T12PR = T+PR12 weeks, then PR12 or 36 weeks depending on eRVR status
**T8PR = T+PR8 weeks, then PR16 or 40 weeks depending on eRVR status

Jacobson et al. EASL 2011

SVR Rates in F1/2 vs F3/4 Naïve Patients



Jacobson IM et al, NEJM, 2011; 364: 2405-2416

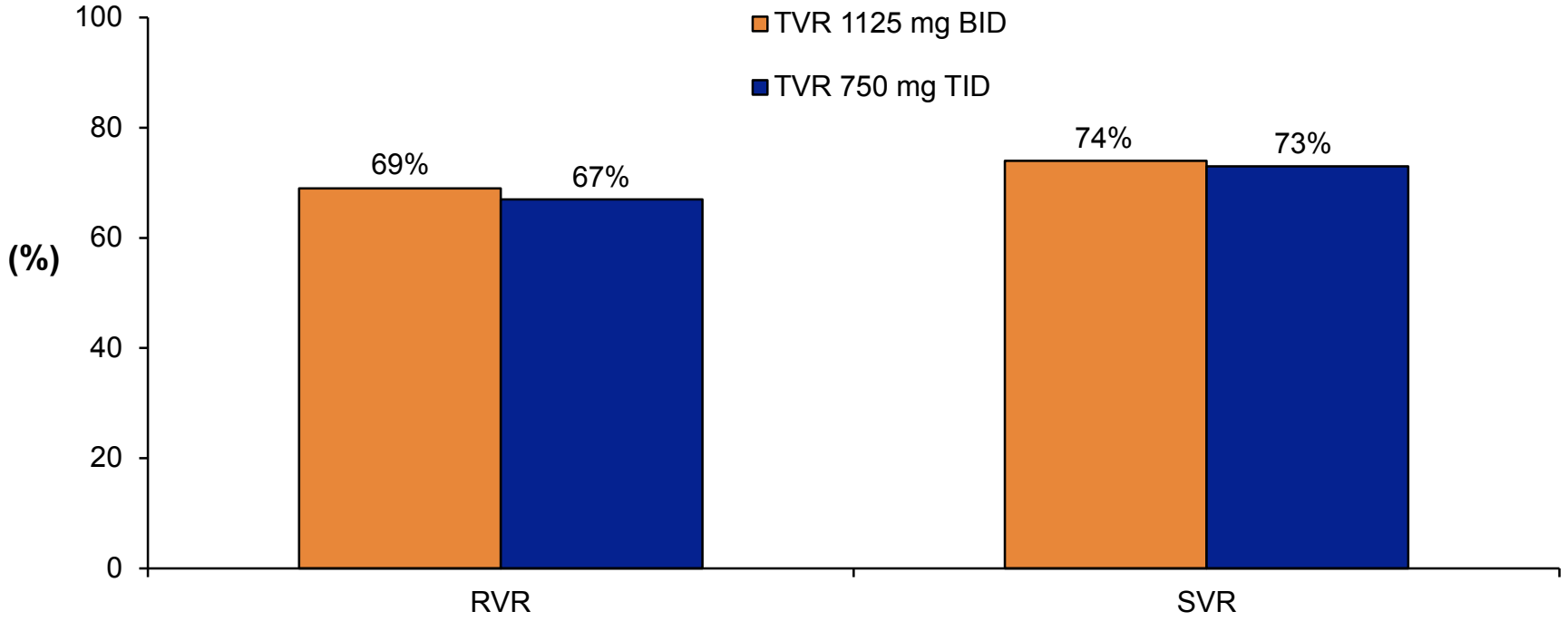
Poordad F et al, NEJM, 2011; 364: 1195-1206

OPTIMIZE Trial: Telaprevir BID vs TID

- PR + TVR 1125 mg BID versus 750 mg TID
- Response-guided therapy
- 740 patients
- 29% bridging fibrosis or cirrhosis
- 57% G1a, *IL28B* CC 29%

Buti M et al, Abstract LB-8, AASLD 2012

OPTIMIZE Trial: Results



Buti M et al, Abstract LB-8, AASLD 2012

Should Glenn Be Treated Now?

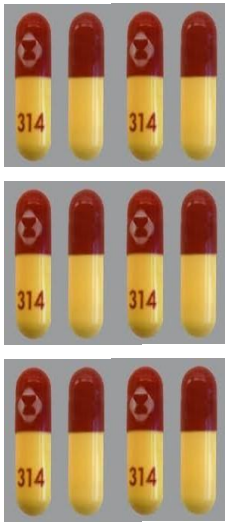
- F3 disease – risk of progression with waiting
- *IL28B* CC
- Potential BID option is attractive

The Case for Waiting

- Multiple issues with current therapy
  - Compliance – pill burden
  - Co-morbidities
  - Adverse effects
  - New treatments on the horizon

Compliance

Pill Burden



BOC = 18/d
RBV 4-7/d

TVR = 12/d
RBV 4-7/d

Food Requirement

Co-Morbidities

- Cardiac Risk Factors
  - Hypertension, hyperlipidemia, smoker
- Pre Treatment
  - DDI – Statin with TVR/BOC likely just stop it
- On Treatment
  - Anemia management consider pre-treatment cardiac testing

Drugs with the Potential to Interact with First Generation Protease Inhibitors are Commonly Used by HCV Patients

Drug Name	Percent	Drug Name	Percent
Zolpidem *	17.4	Diazepam	7.9
Codeine	16.0	Bupropion *	7.2
Prednisone	15.4	Trazodone	7.1
Tramadol *	14.3	Fluconazole	6.8
Citalopram	13.5	Sertraline	6.4
Fluticasone	13.1	Clarithromycin	6.1
Methylprednisolone	13	Sildenafil (Viagra)	5.4
Alprazolam *	11.8	Clonazepam	5.3
Amlodipine *	10.2	Simvastatin	5.2
Escitalopram *	8.1	Venlafaxine	5.0

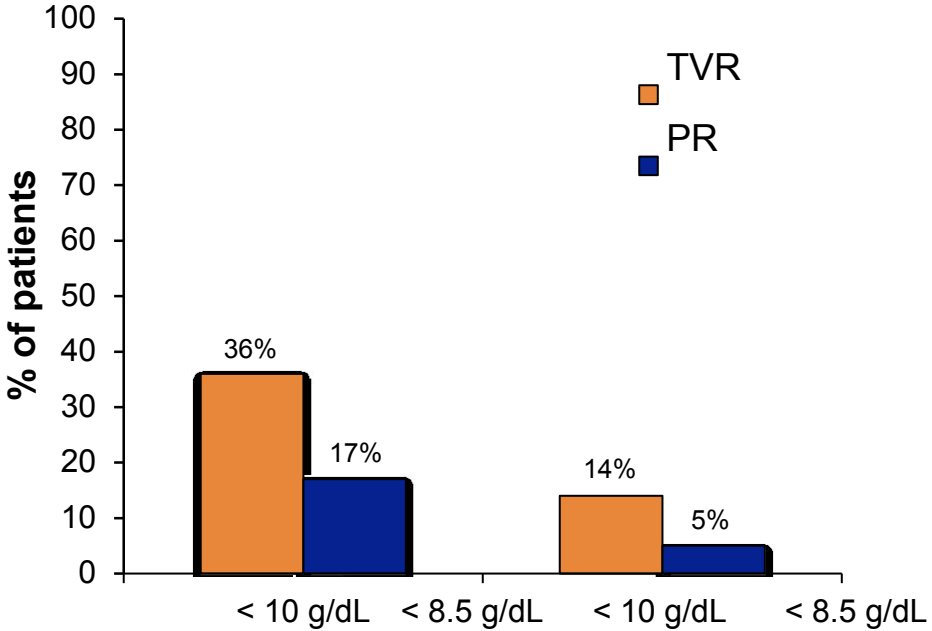
Mayer et al, Abstract #136, AASLD 2012

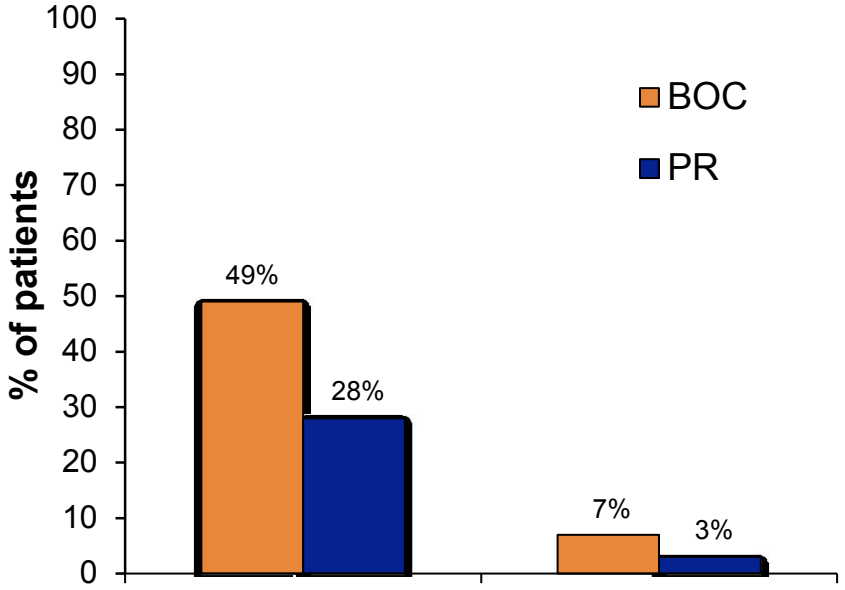
* One of the 20 most frequently filled

New Drug-Drug Interaction Data at AASLD 2012:HCV Protease Inhibitors

- No clinically significant interactions
  - Boceprevir
    - Prednisone (abstract #1896)
    - Omeprazole (abstract #1808)
    - Ethinyl estrodiol/norethidrone (abstract #1901)
  - Simeprevir (TMC-435)
    - Cyclosporine/tacrolimus (abstract #80)
    - Ethinyl estrodiol/norethidrone (abstract #773)

Anemia is a Known Side Effect with First Generation Protease Inhibitor Based Therapies



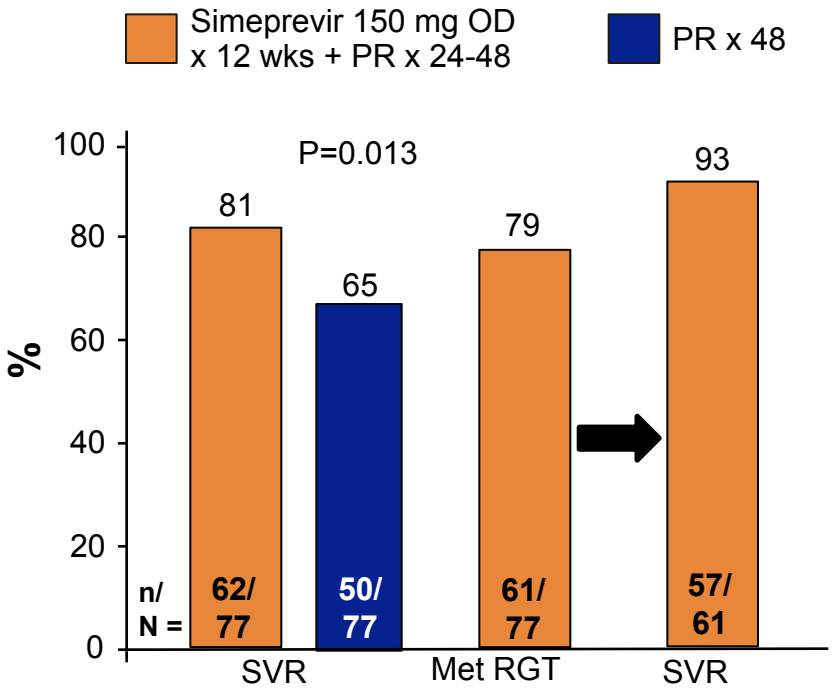


Telaprevir (INCIVEK™) Prescribing Information. Vertex Pharmaceuticals Incorporated, Cambridge, MA. October, 2012.

Boceprevir (VICTRELIS™) Prescribing Information. Merck Sharp & Dohme Corp., Whitehouse Station, NJ, November 2012.

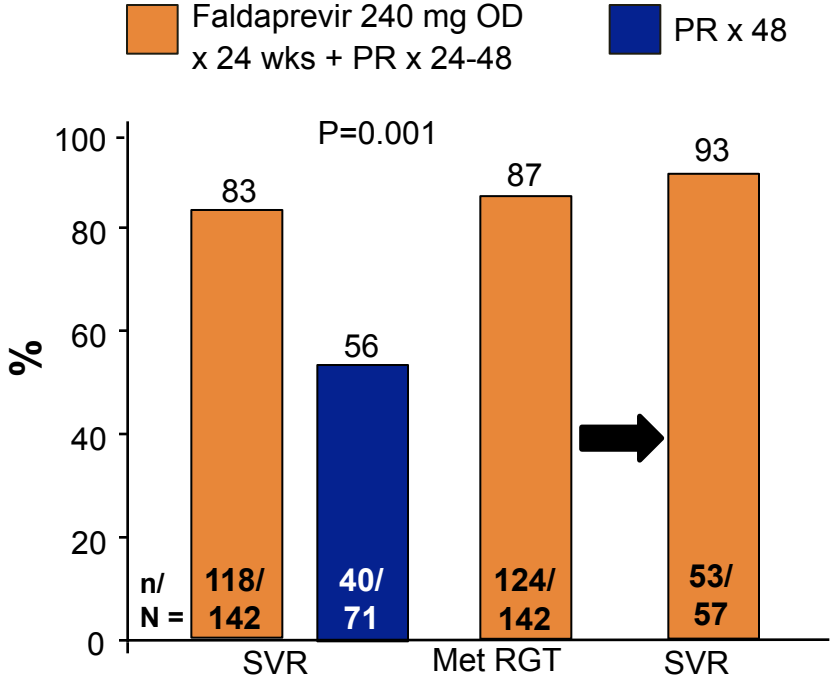
Future Options for Waiting? (Short-Term)

PILLAR (G1 Naïve)[1]



1. Fried et al. AASLD 2011

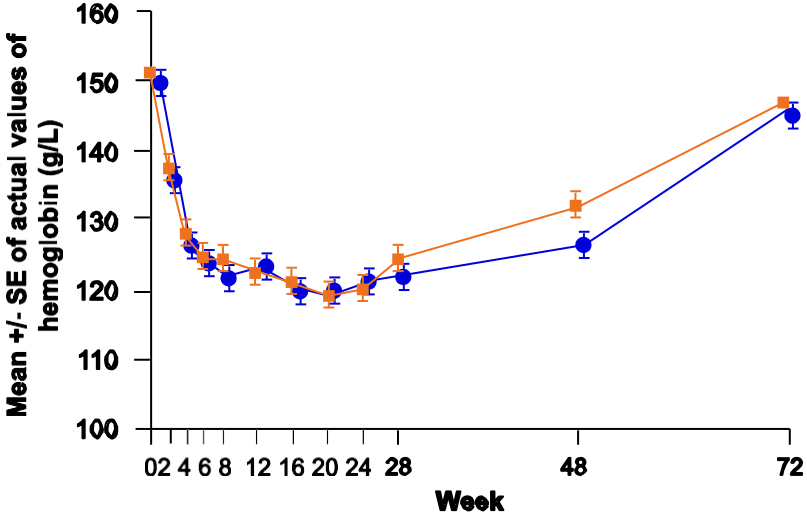
SILEN C1 (G1 Naïve)[2]



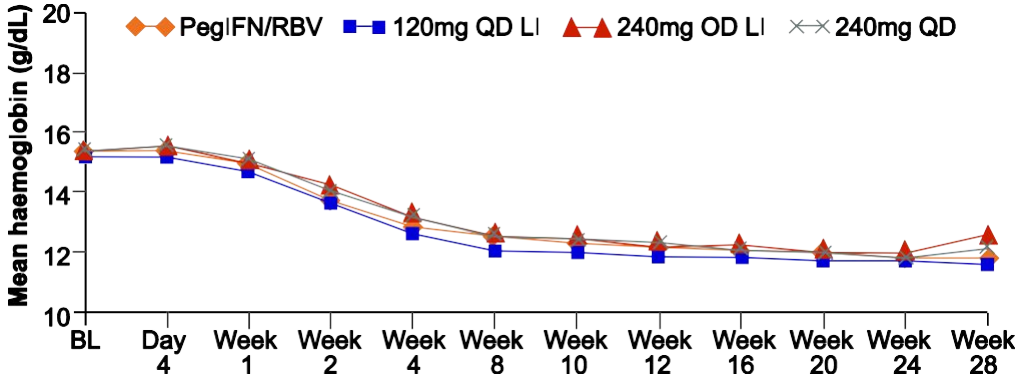
2. Sulkowski et al. EASL 2011

No Incremental Decline in Hemoglobin or Neutrophils with Simeprevir or Faldaprevir

Anemia with Simeprevir + P/R[1]



Anemia with Faldaprevir + P/R[2]



1. Jacobson et al, IDSA, 2012

2. Sulkowski et al, EASL 2011

Select Oral Directing Acting Antivirals in Development for the Treatment of Chronic Hepatitis C, 2012

Compound	Sponsor	Activity
ABT-267	Abbott	NS5A inhibitor
ABT-333	Abbott	Non-nucleoside NS5B polymerase inhibitor
ABT-450	Abbott	NS3/4A protease inhibitor
Faldaprevir (BI201335)	Boehringer Ingelheim	NS3/4A protease inhibitor
BI207127	Boehringer Ingelheim	Non-nucleoside NS5B polymerase inhibitor

Select Oral Directing Acting Antivirals in Development for the Treatment of Chronic Hepatitis C, 2012 (cont)

Compound	Sponsor	Activity
Asunaprevir (BMS-650032)	Bristol-Myers Squibb	NS3 protease inhibitor
Daclatasvir (BMS-790052)	Bristol-Myers Squibb	NS5A replication complex inhibitor
BMS-791325	Bristol-Myers Squibb	Non-nucleoside NS5B polymerase inhibitor
Sofosbuvir (GS-7977)	Gilead	Uridine nucleotide analog NS5B polymerase inhibitor
GS-5885	Gilead	NS5A protein inhibitor

Not all-inclusive, but indicates drugs covered in this presentation

Should Glenn Delay Treatment?

- *IL28B* CC ~80% chance of shortened therapy
  - 80-90% chance of SVR
- F3 disease – risk of progression with waiting
- No clear issues with IFN
- Seems anxious and willing to be treated now
- I would suggest treatment

Glenn: On Treatment Response

- Glenn was started on TVR/PEG/RBV
- TW4 and TW12
  - HCV RNA undetectable

Clinical Decision 2

- Which regimen should Glenn receive?

1. 12 weeks TVR/PEG/RBV
2. 12 weeks TVR/PEG/RBV + 12 weeks PEG/RBV
3. 12 weeks TVR/PEG/RBV + 24 weeks PEG/RBV
4. 12 weeks TVR/PEG/RBV + 36 weeks PEG/RBV
5. 24 weeks TVR/PEG/RBV

Recommended Treatment Duration

Treatment-Naïve and Prior Relapse Patients			
HCV-RNA	**Triple Therapy TVR/Peg-IFN/RBV**	**Dual Therapy Peg-IFN/RBV**	**Total Treatment Duration**
Undetectable at TW4 and TW12	**First 12 weeks**	**Additional 12 weeks**	**24 weeks**
Detectable (≤1000 IU/mL) at TW4 and/or TW12	First 12 weeks	Additional 36 weeks	48 weeks

Telaprevir (INCIVEK™) Prescribing Information. Vertex Pharmaceuticals Incorporated, Cambridge, MA. October, 2012.

HCV-RNA Levels and Lab Assays

- "Undetectable" (or "target not detected") result is required for assessing RGT eligibility
- Below LLOQ but still "detectable" is not sufficient to shorten therapy—ie, patient should continue for full 48 wks

LLOQ Values for Various Assays*

Assay Name	LLOQ
Roche COBAS® AmpliPrep/COBAS® Taqman® HCV Test	43 IU/mL
Roche COBAS® Taqman® HCV Test, v2.0	25 IU/mL†
Abbott RealTime HCV Assay	12 IU/mL

*Package Inserts state the "the assay should have a lower limit of HCV-RNA quantification ≤ 25 IU/mL and a limit of HCV-RNA detection of approximately 10-15 IU/mL.
† Usually considered 25 IU/mL, but 23 IU/mL per FDA-approved label.

COBAS® AmpliPrep/COBAS® Taqman® HCV Test. Roche Molecular Diagnostics. Accessed July 19, 2011. Harrington PR, et al. Hepatology. 2012;55: 1046-1057. United States Food and Drug and Drug Administration (FDA), FDA Division of Antiviral Products; June 30, 2011.

Conclusions

- Many chronic hepatitis C patients are good candidates for treatment today
- The HCV pipeline is promising with potential new treatment modalities in the near future
- Physicians should carefully consider individual patient characteristics when deciding whether to initiate or delay treatment