NORTHWEST AIDS EDUCATION AND TRAINING CENTER

HIV and Hepatitis C: Advances in Treatment

John Scott, MD, MSc
Asst Professor
University of Washington

Presentation prepared & presented by: John Scott, MD, MSc
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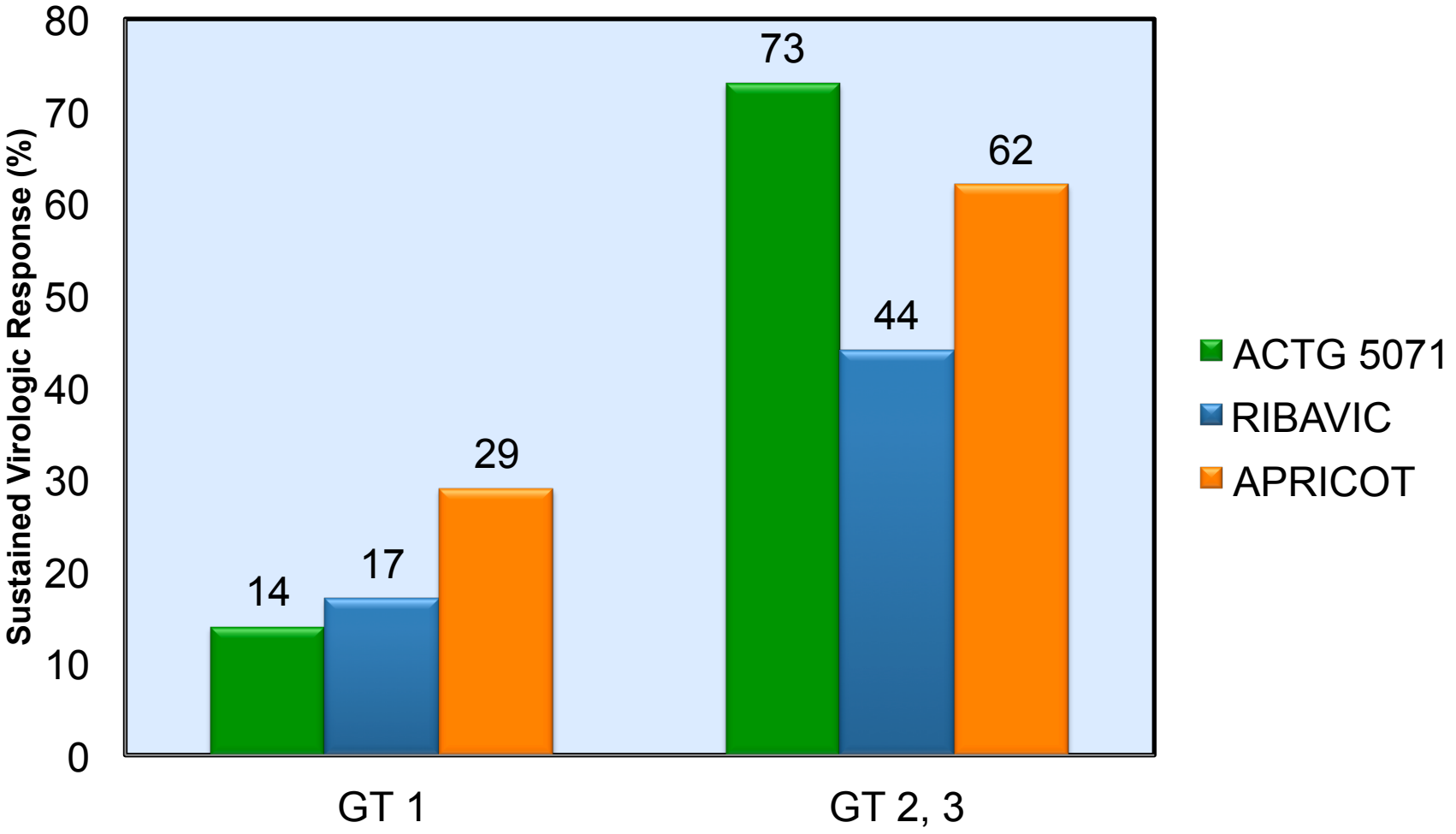
Outline

- **Hepatitis C**
  - Standard of Care
  - 1st generation DAAs in HIV/HCV
  - Polymerase inhibitors for HCV

Cure Rates for HIV/HCV Pts w/ PegIFN + Ribavirin



Chung RT. NEJM 2004; 351:451-9. Carrat F. JAMA 2004; 292:2839-48. Torriani F. NEJM 2004; 351:438-50.

Side Effects of Interferon/Ribavirin Therapy

- Cytopenias
- Depression, anxiety, insomnia
- Rashes
- Flu like syndrome
- Thyroid dysfunction
- Retinopathy
- Nausea, vomiting, diarrhea
- Cough

“Interferon Man”

Standard HCV therapy - Summary

- Genotype 1 is hardest to treat and 2 and 3 have much better treatment response
- Main toxicities of IFN/Ribavirin are hematologic, psychiatric, and ‘constitutional’
- Many factors helpful in predicting response
- In HIV-HCV co-infected patients SVR/cure rates can approach 50%

Telaprevir (*Incivek*)

- **Approval**
  - FDA Approved May 23, 2011
- **Indications**
  - In combination with Peginterferon-alfa and Ribavirin (PR)
  - Chronic HCV **genotype 1** infection, **HIV negative**
  - Adults (≥ 18 years of age) with compensated liver disease, including cirrhosis
  - Treatment-naïve or prior interferon-based treatment
- **Dosing**
  - 750 mg (two 375-mg tablets) **three times daily** with food (20 gm fat)
  - Treat with PR for 12 weeks (followed by additional 12 or 36 weeks PR)
- **Adverse Effects**
  - **Rash, anemia**, nausea, fatigue, headache, diarrhea, pruritis, and anal or rectal irritation and pain ('fire-rrhea')

Source: Telaprevir (Incivek) Prescribing Information. Vertex Pharmaceuticals.

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Boceprevir (*Victrelis*)

- **Approval**
  - FDA Approved May 13, 2011
- **Indications**
  - In combination with Peginterferon-alfa and Ribavirin
  - Chronic HCV **genotype 1** infection, **HIV negative**
  - Adults (≥ 18 years of age) with compensated liver disease, including cirrhosis
  - Treatment-naïve or failed prior interferon and ribavirin therapy
- **Boceprevir Dosing**
  - 800 mg (four 200-mg capsules) **3 times daily** with food (meal or light snack)
  - Boceprevir given for 24-44 weeks
  - Treat with PR for 28-48 weeks based on HCV RNA results (week 8 & 12)
- **Adverse Effects Attributable to Boceprevir**
  - **Anemia**, nausea, and **dysgeusia**

Source: Boceprevir (*Victrelis*) Prescribing Information. Merck & Co.

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Investigational

Telaprevir in Treatment Naïve HIV/HCV Study 110

Telaprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Study 110: Design

Study Features for Study 110

Protocol

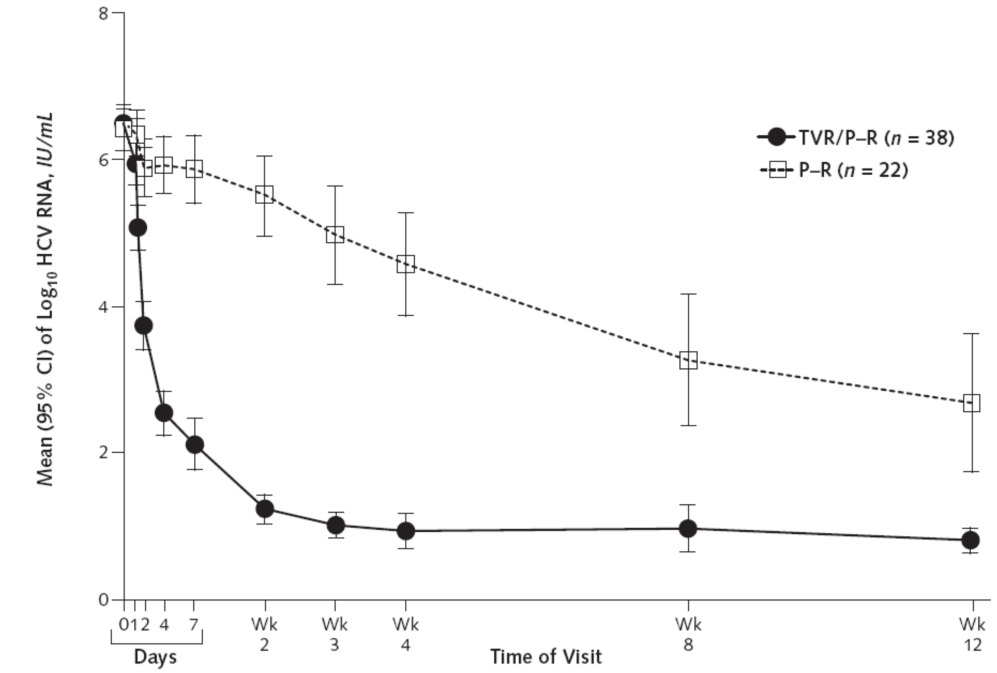
- N = 62 HIV/HCV coinfected (2 didn't receive study drug)
- Phase 2a trial; randomized, placebo-controlled
- Chronic HCV; Genotype 1; HCV- treatment naïve
- Randomized to Telaprevir + PegIFN+ Ribavirin versus PegIFN + Ribavirin
- Part A: no ARVs
- Antiretroviral Regimens in Part B:
  (1) Tenofovir-Emtricitabine-Efavirenz
  (2) Tenofovir + (Emtricitabine or Lamivudine) + Ritonavir + Atazanavir

Drug Dosing

Telaprevir = 750 mg tid (1125 mg tid with efavirenz)
Peginterferon alfa-2a = 180 µg weekly
Ribavirin = 800 mg/d or weight based in France and Germany
(1000 mg/d for wt < 75 kg; 1200 mg/d for wt ≥ 75 kg)

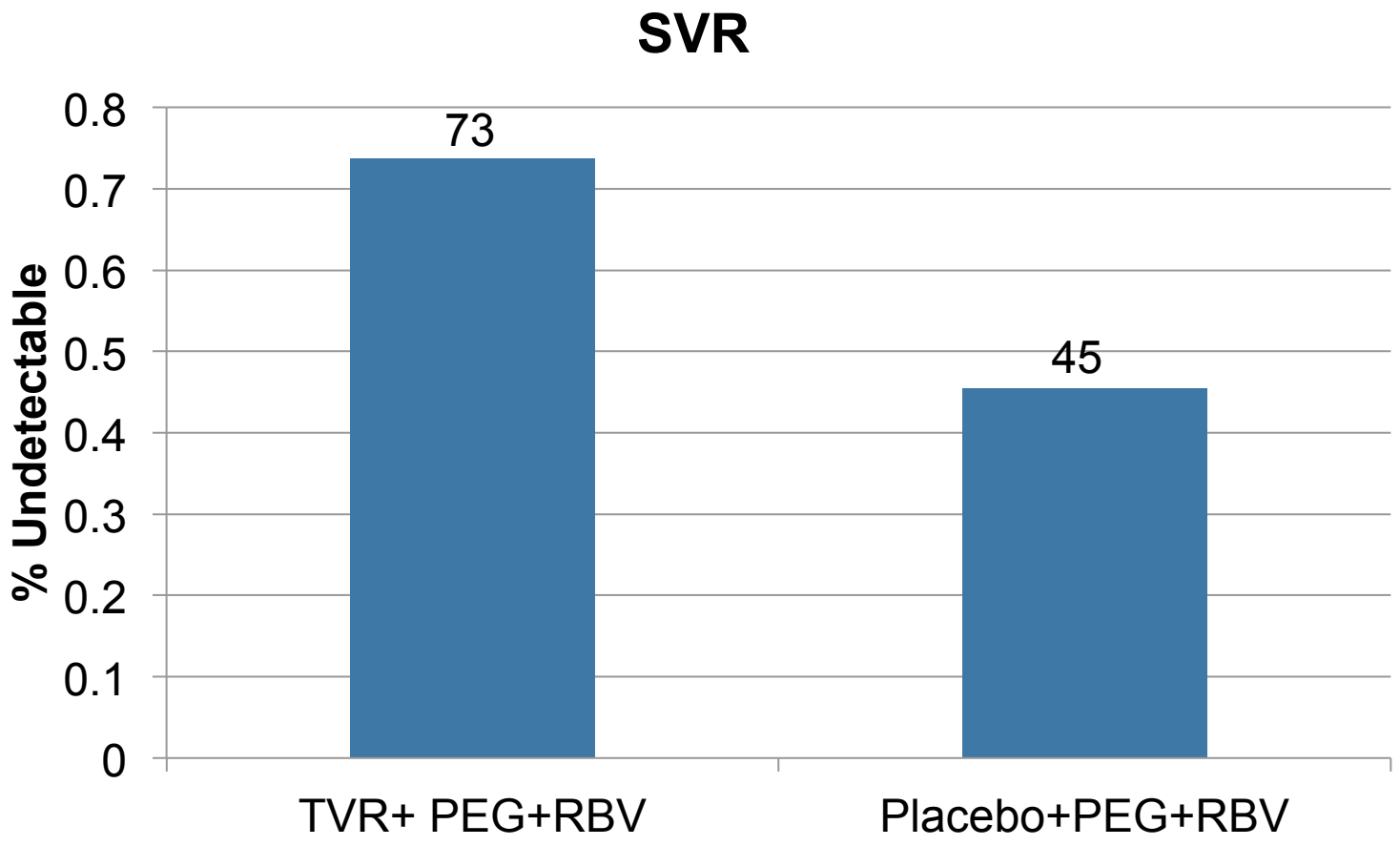
Source: Sulkowski M, et al. Ann Intern Med 2013; published online 17 May 2013.

HCV Kinetics on Treatment



Participants With HCV RNA Measures, *n*							
TVR/P–R	38	38	36	36	36	35	33
P–R	22	22	21	22	22	21	21

Study 110: Sustained Viral Response

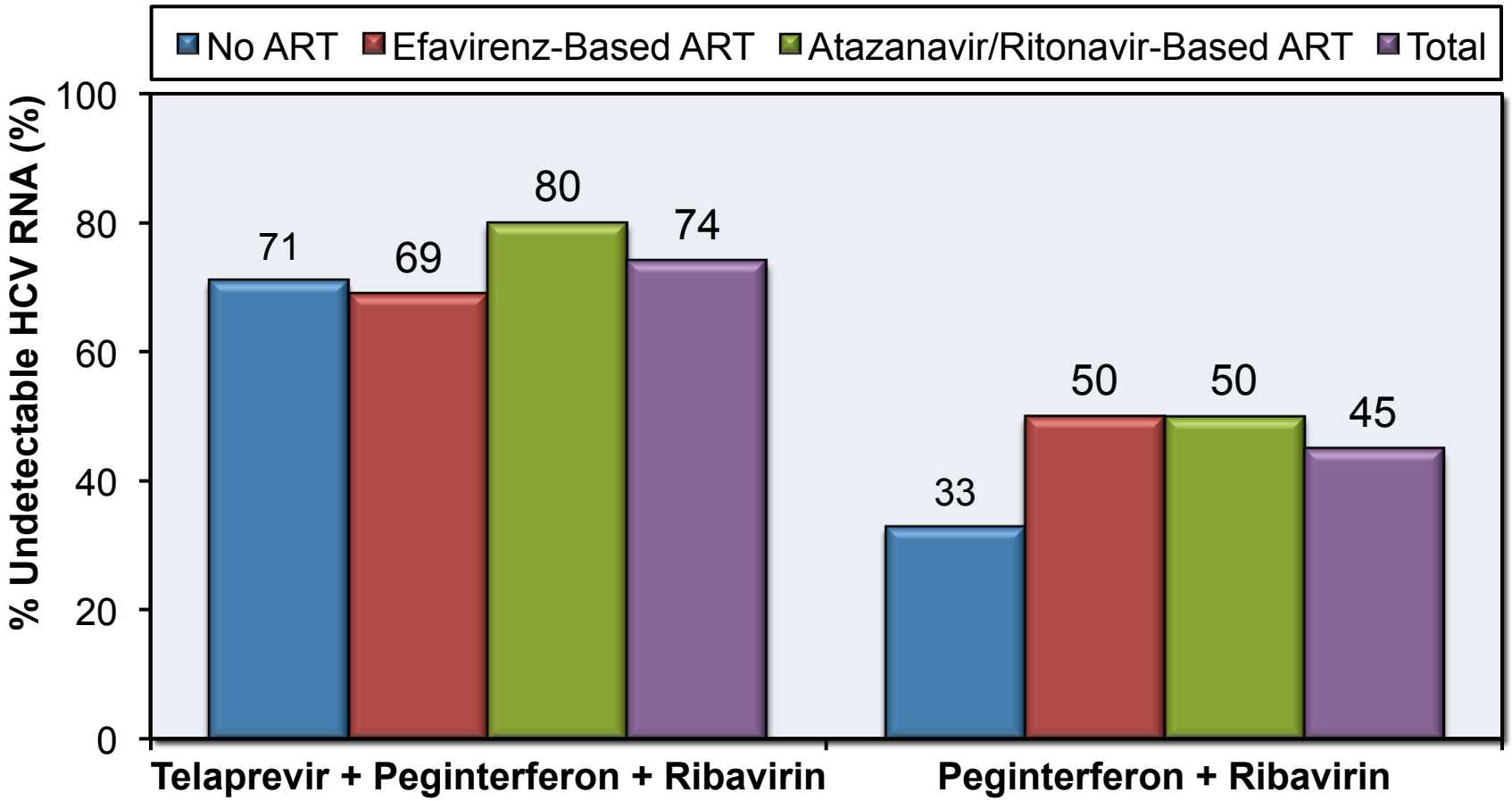


Source: Sulkowski M. Ann Intern Med 2013.

Investigational

Telaprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Study 110: Design

Week 12 Post Treatment (SVR-12)



Source: Sulkowski M. Ann Intern Med 2013.

Telaprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Study 110: Telaprevir-Related Adverse Effects

Adverse Event	Telaprevir/PR (N = 38) n (%)	PR (N = 22) n (%)
Pruritus	**16 (39)**	**2 (9)**
Nausea	13 (34)	5 (23)
Severe rash	0 (0)	0 (0)
Mild to moderate rash	13 (34)	5 (23)
Anemia	7 (18)	4 (18)
Grade 3 Hgb drop (7-8.9 g/dl)	11 (29)	5 (23)
Use of EPO	3 (8)	1 (5)
Blood transfusions	**4 (11)**	**1 (5)**

Source: Sulkowski M. Ann Intern Med 2013.

HHS Antiretroviral Therapy Guidelines: March 2012
Managing Patients Coinfected with HIV and HCV

Antiretroviral Regimen	Hepatitis C Therapy
Patients not on Antiretroviral Therapy	Use either boceprevir or teleprevir
Patients receiving: Raltegravir + 2-NRTIs	Use either boceprevir or teleprevir
Patients receiving: Atazanavir/ritonavir + 2-NRTIs	Use teleprevir at standard dose. Do not use boceprevir
Patients receiving: Efavirenz + 2-NRTIs	Use teleprevir at increased dose of 1125 mg every 7-9 hours. Do not use boceprevir.

Source: 2012 HHS Antiretroviral Therapy Guidelines. AIDS Info (www.aidsinfo.nih.gov)

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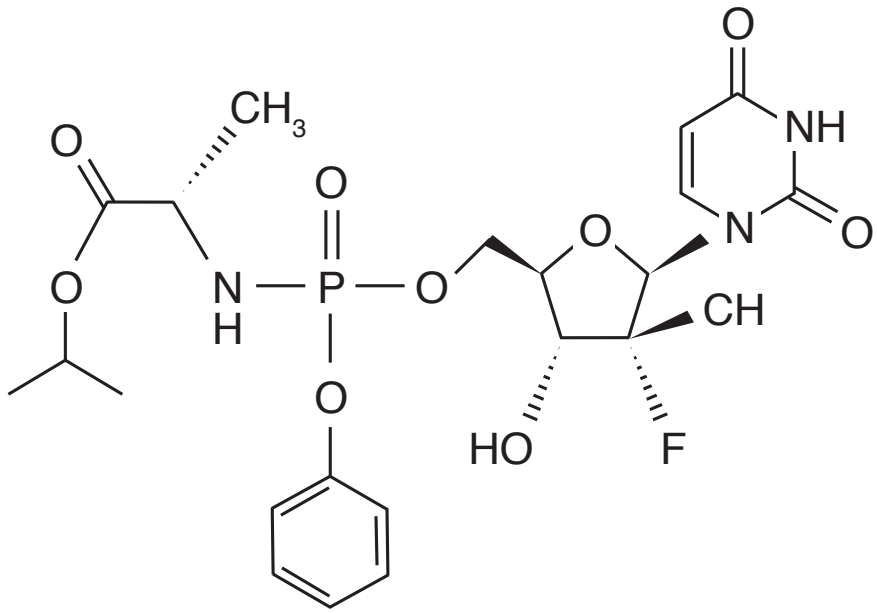
Sofosbuvir (GS 7977)

Sofosbuvir (SOF, GS 7977)

- Potent HCV-specific nucleotide analog (chain terminator)
- Safe and well tolerated
  - Once daily, no food effect
  - No significant drug interactions
  - No safety signals in preclinical/clinical studies
- High barrier to resistance
  - No virologic breakthrough to date
- Pangenotypic antiviral effect
- Safe and well tolerated in ~1500 patients in Phase 2 and Phase 3 studies



NEUTRINO Study: GT 1,4-6 naive

Study Design

-N=327 HCV GT 1, 4-6

-Naïve

-Phase 3

-Sofosbuvir (aka GS 7977) a nucleotide polymerase inhibitor

-Single group, open label

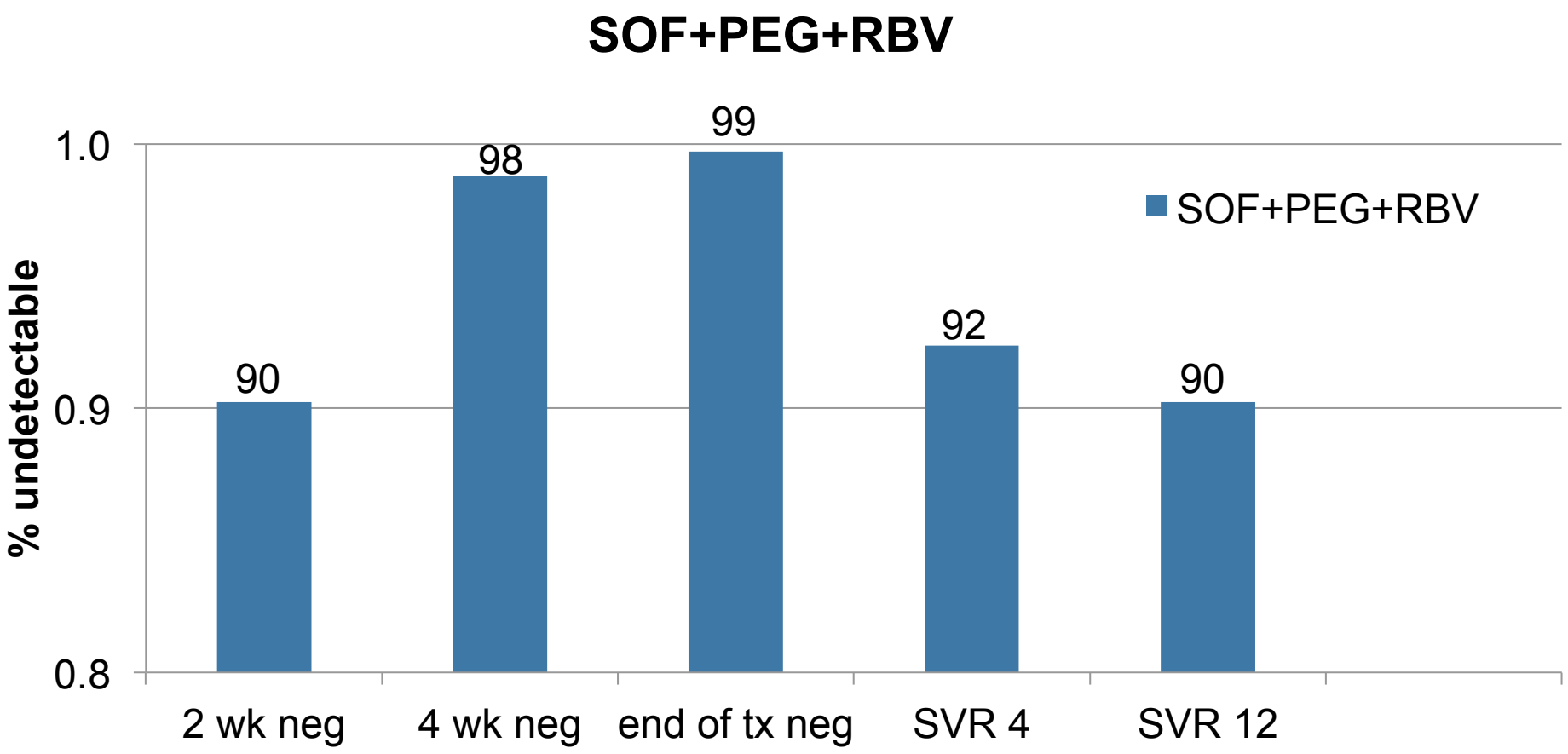
SOF 400 mg qd + RBV (wt based) + Pegasys 180 mcg SQ x 12 wks

Source: Lawitz E, et al. NEJM 2013;368: 1878-87.

Baseline Characteristics

Characteristic	SOF + RBV + PEG
Male	64%
Mean age	52
BMI	29
GT 1 GT 4 GT 5 GT 6	89% 9% <1% 2%
IL28 genotype CC CT TT	 29% 55% 16%
Cirrhosis	17%
Mean HCV RNA	6.4 log

Outcomes



Lawitz, et al. NEJM 2013;368:1978-87.

FISSION Study: GT 2,3 naive

Study Design

-N=499 HCV GT 2, 3

-Naïve, incl cirrhosis

-Phase 3

-Sofosbuvir (aka GS 7977) a nucleotide polymerase inhibitor

-Open label, randomized 1:1

-Stratification by HCV GT, RNA level, and cirrhosis

-Non-inferiority study

SOF 400 mg qd + RBV (wt based) x 12 wks (N=253)

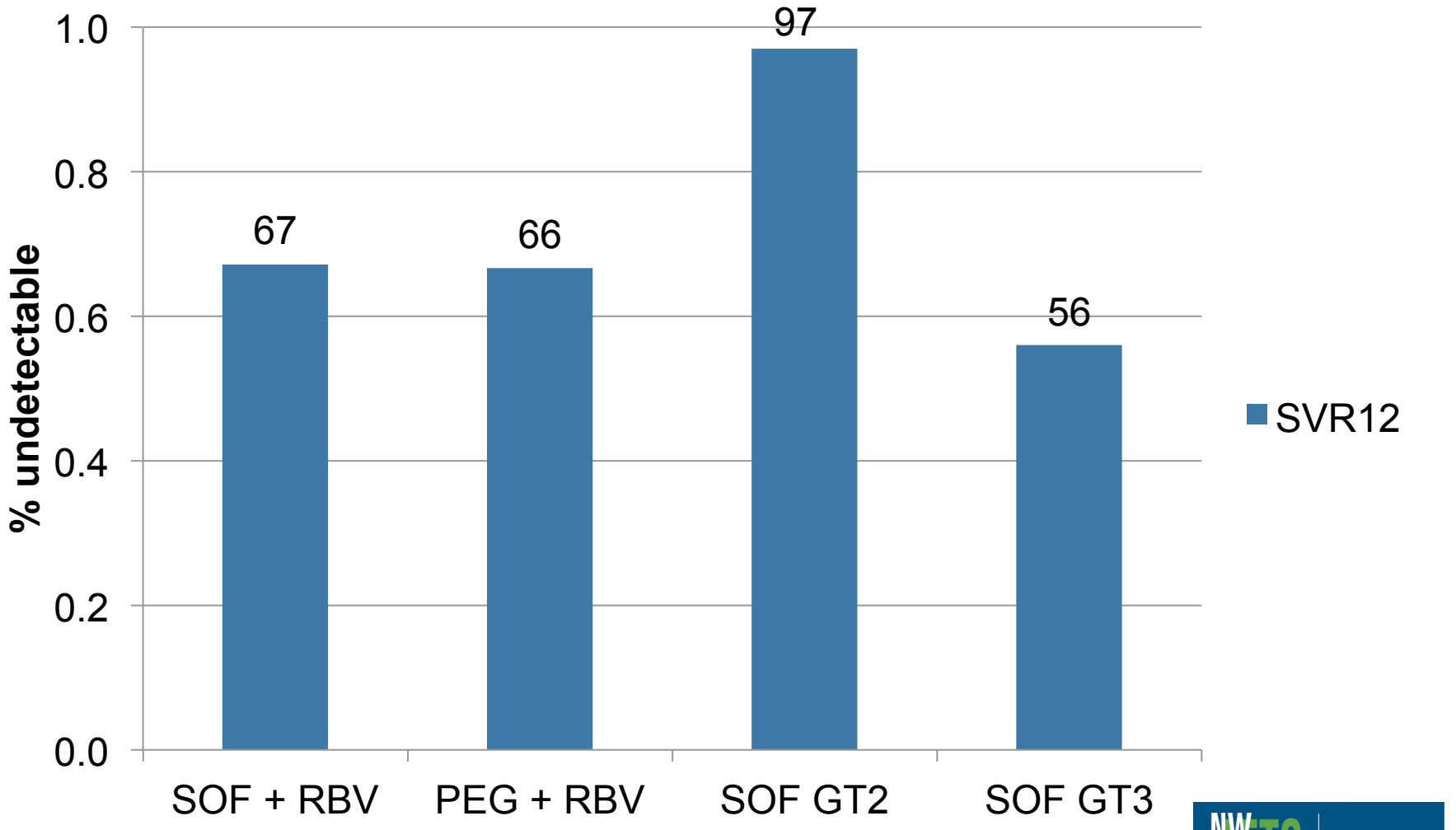
RBV (wt based) + PegIFN x 24 wks (N=243)

Source: Lawitz E, et al. NEJM 2013; 368:1978-87.

Baseline Characteristics

Characteristic	SOF + RBV	RBV + PegIFN
Male	67%	64%
Mean age	48%	48%
BMI	28	28
GT 2 GT 3	27% 71%	28% 72%
IL28 genotype CC CT TT	 42% 47% 10%	 44% 40% 16%
Cirrhosis	20%	21%
Mean HCV RNA	6.0 log	6.0 log

Outcomes



Lawitz, et al. NEJM 2013;368:1978-87.

Predictors of Response

- No significant differences between IL28 genotypes, cirrhosis, viral kinetics, racial group, or Hep C genotype

Adverse Events

- Usual RBV and IFN side effects
  - Fatigue, headache, nausea, insomnia, anemia
  - 23% had Hgb <10 g/dl, 2% <8.5 g/dl in GT1
  - 15% developed ANC b/t 500-750, 5% <500
  - Less cytopenias, depression, myalgias in IFN free group
- None of the relapsed pts developed S282T mutation
- Very few DDIs

Take Home Points

- Interferon-based therapies have significant side effects
- Telaprevir appears to be as safe and effective for HIV/HCV patients, but there are significant DDIs and side effects.
- Sofosbuvir appears to be promising antiviral, yet to be FDA approved. GT3 patients still hard to cure.
- The Hepatitis C treatment landscape is rapidly changing with many new questions…

Stay tuned for Interferon-free regimens in HIV/ HCV Co-infected patients

Web Resources

- http://hab.hrsa.gov/publications/hcvguide2011.pdf
- www.nlm.nih.gov/medlineplus/hepatitisc
- www.nwaetc.org
- www.hepwebstudy.org
- www.hivwebstudy.org
- www.clinicaloptions.com
- www.cdc.gov/hiv
- www.cdc.gov/hepatitis

THANK YOU!!