NORTHWEST AIDS EDUCATION AND TRAINING CENTER

HIV and Hepatitis C: Treatment

John Scott, MD, MSc
Asst Professor
University of Washington

Presentation prepared & presented by: John Scott, MD, MSc
Last Updated: Jul 2, 2012

NW AETC | echo

Outline

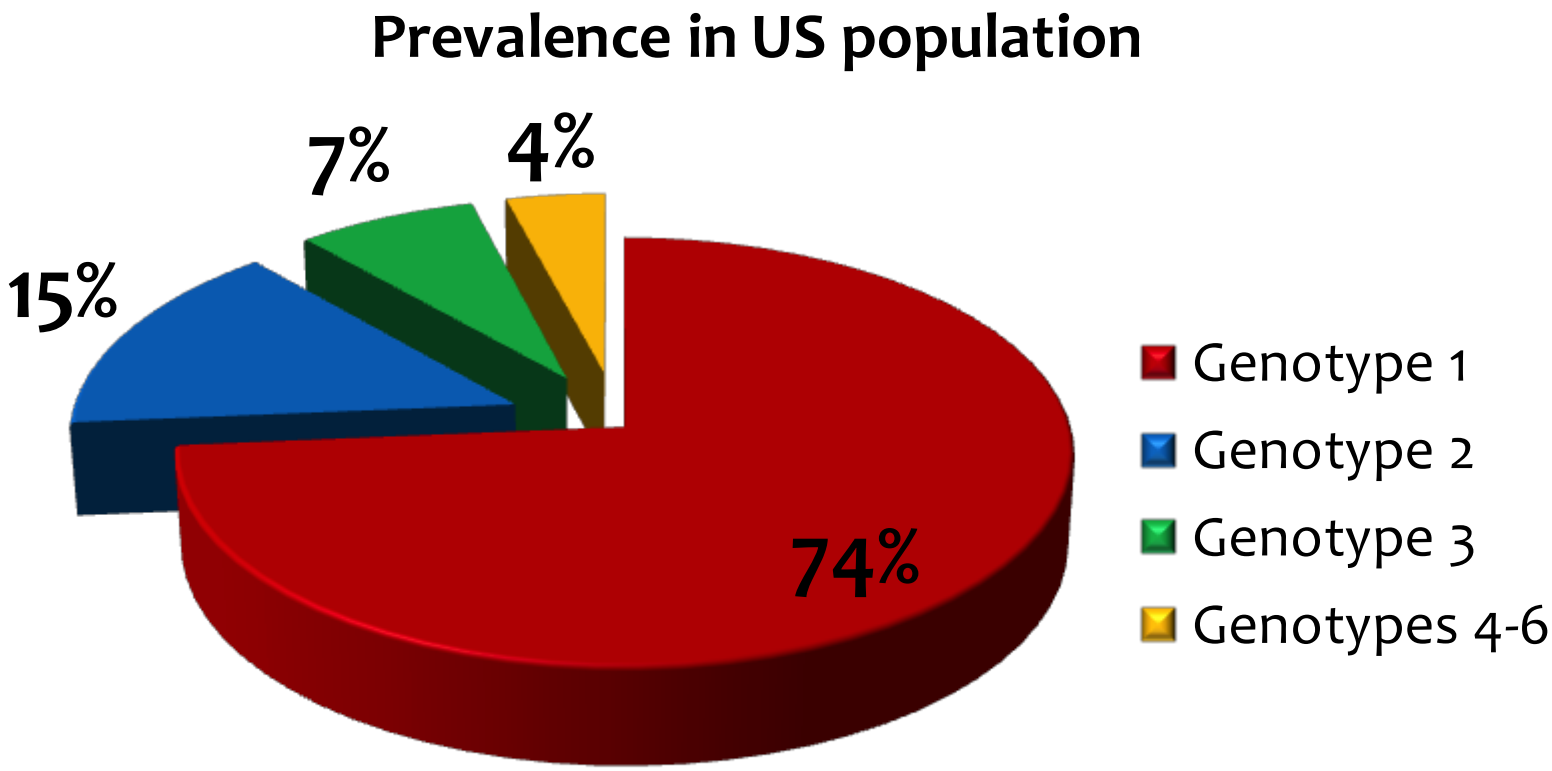
- **Hepatitis C**
  - Definitions of Viral Response
  - Standard of Care
  - DAAs in HIV/HCV

Hepatitis C: Definitions of Virologic Response

Rapid Virologic Response (RVR)	HCV RNA undetectable by Week 4
Extended RVR (eRVR)	HCV RNA undetectable at Weeks 4 & 12
Early Virologic Response (EVR)	≥ 2 $\log_{10}$ decline by Week 12
Partial Virologic Response	≥ 2 $\log_{10}$ decline by Week 12, HCV RNA detectable at Week 24
End of Treatment Response (ETR)	HCV undetectable at end of treatment
Sustained Virologic Response (SVR)	HCV undetectable 24 weeks ***after*** the end of treatment
Nonresponse	Failure to achieve undetectability at any time during therapy

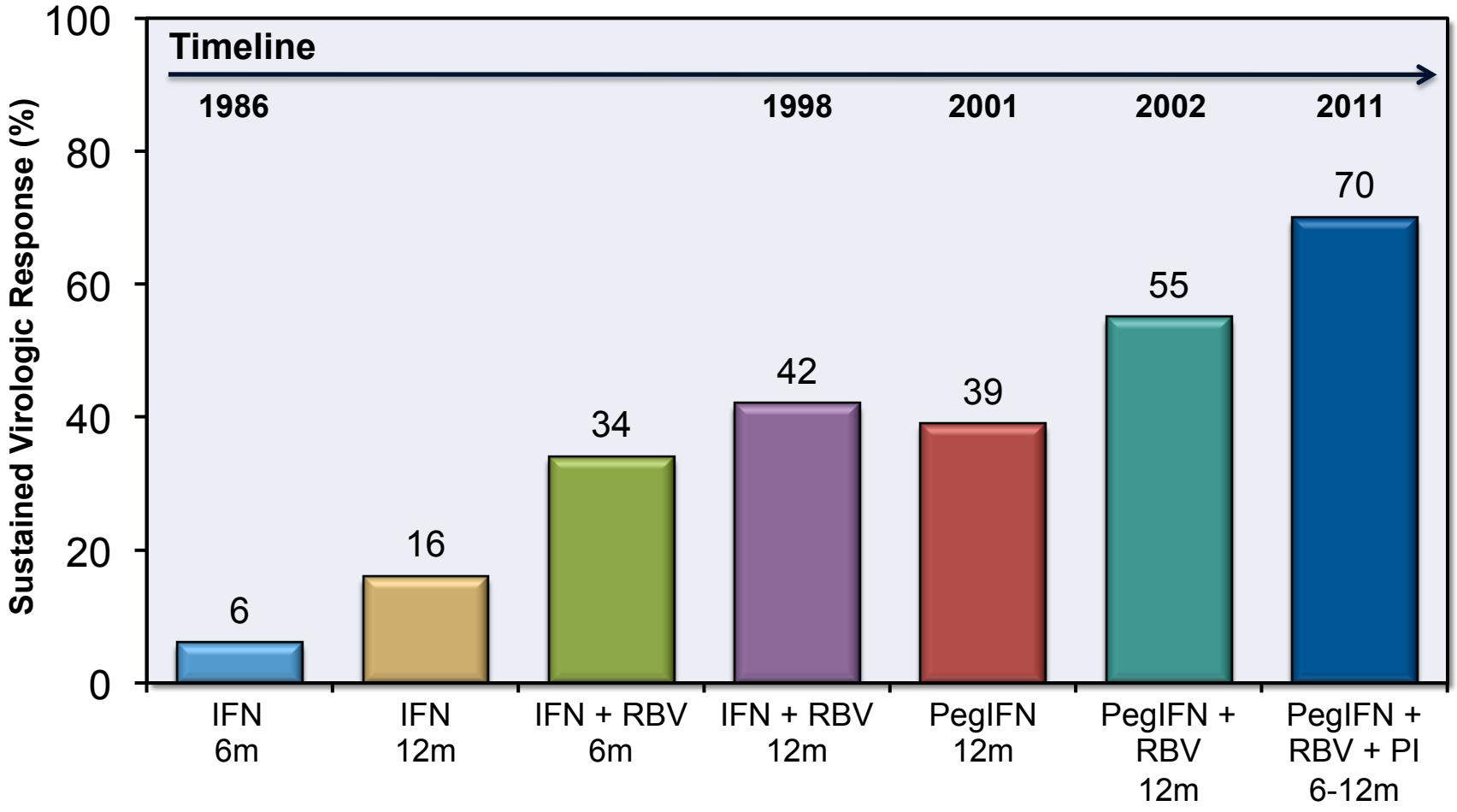
Pawlotsky JM *Hepatology* 2002;36(suppl 1): S65-73

Hepatitis C Genotypes



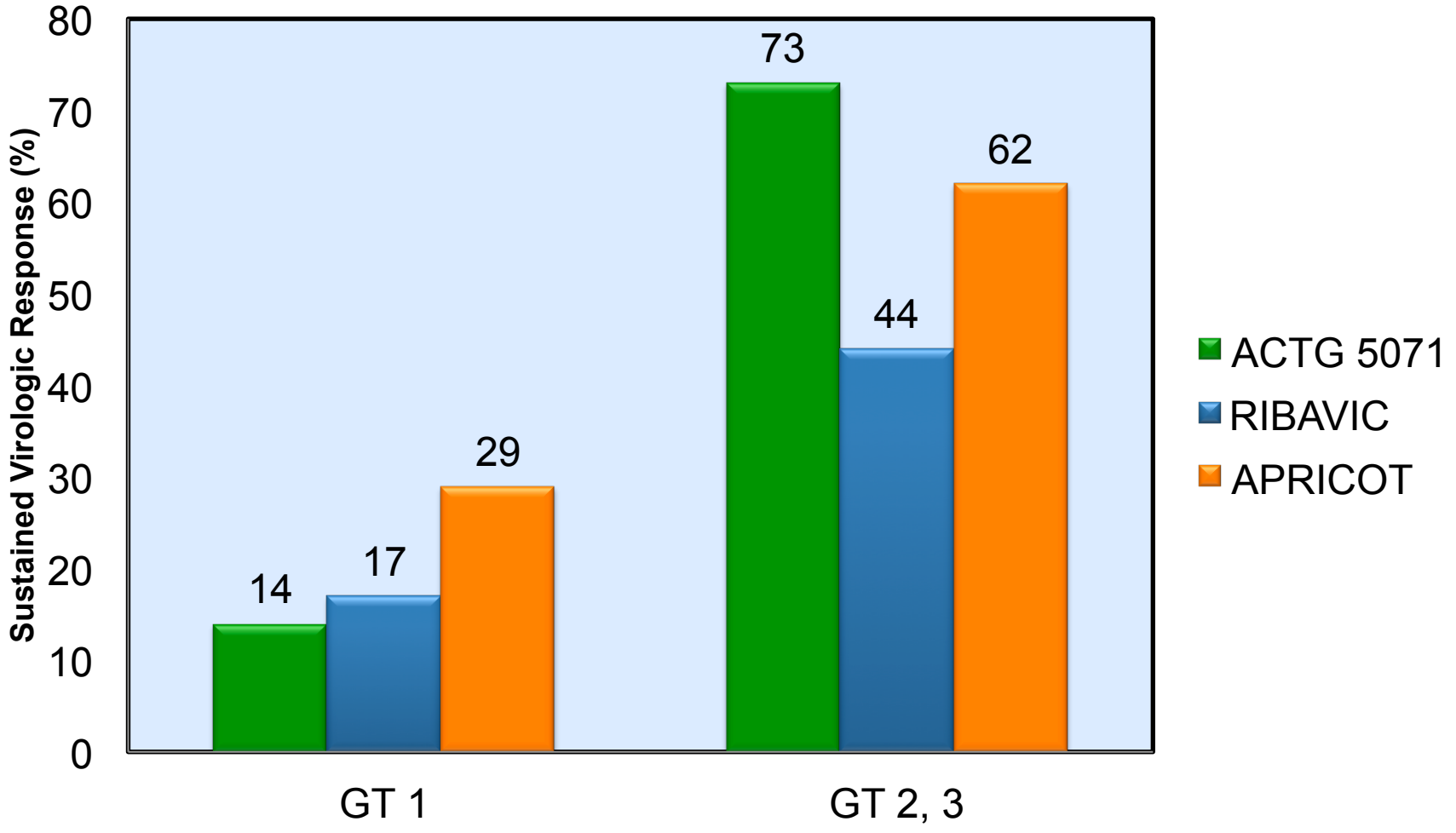
Alter MJ *et al. N Engl J Med* 1999; 341:556-62

Therapy for Hepatitis C: Historical Milestones



Above cure rates are in HIV- GT 1 pts

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.

Predicting Response: Adverse Predictors

- Genotype 1
- High viral level (>800k)
- Advanced fibrosis
- AA race
- *IL28B* genotype
- Steatosis and obesity
- Metabolic syndrome

AASLD guidelines, Thomas DL et al CID 2012 Apr;54(7):979-83

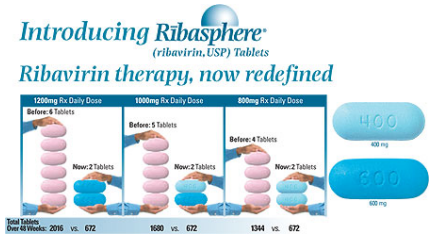
FDA approved HCV Therapy in HIV+

Peg-Interferon alfa

180 mcg SQ Qweek

Ribavirin

1000-1200 mg PO QD (divided BID)



Duration depends on genotype & response

- Genotype 1 or 4: **48 weeks**
- Genotype 2 or 3: **48 weeks**

Management of hepatitis C. NIH Consens State Sci Statements. 2002;19:1-46.
Manns M, et al. Lancet. 2001;358:958-965. Fried MW, et al.
N Engl J Med. 2002;347: 975-982.

NW AETC | echo

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) **q 8 hrs** 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.

NW AETC | echo

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.

Drugs that are contraindicated with DAAs

Boceprevir & Telaprevir	Clinical Comment
St. John's Wort	May lead to loss of virologic response
Rifampin	May lead to loss of virologic response
Alfuzosin	Increased alfuzosin concentrations can result in hypotension
Dihydroergotamine, ergonovine, ergotamine, methylergonovine	Potential for acute ergot toxicity (peripheral vasospasm or ischemia)
Cisapride	Potential for cardiac arrhythmias
Lovastatin, simvastatin (Atorvastatin with TVR also)	Potential for myopathy including rhabdomyolysis
Pimozide	Potential for cardiac arrhythmias
REVATIO® (sildenafil) or ADCIRCA® (tadalafil) for treatment of PAH	Potential for PDE5 inhibitor-associated AEs
Triazolam; midazolam (oral)	Prolonged or increased sedation or respiratory depression
Boceprevir	**Clinical Comment**
Carbamazepine, phenobarbital, phenytoin	May lead to loss of virologic response to BOC
Drosperinone (oral contraceptive)	Potential for hyperkalemia

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 = 59 HIV/HCV coinfected
- Phase 2a trial; randomized, placebo-controlled
- Chronic HCV; Genotype 1; HCV- treatment naïve
- Randomized to Telaprevir + PegIFN+ Ribavirin versus PegIFN + Ribavirin
- Part A: No ARV Rx; CD4 $\geq$ 500 cells/mm^3; HIV RNA $\leq$ 100,000 copies/ml
- Part B: ARV Rx; CD4 $\geq$ 300 cells/mm^3; HIV RNA $\leq$ 50 copies/ml
- Antiretroviral Regimens in Part B:
  (1) Tenofovir-Emtricitabine-Efavirenz
  (2) Tenofovir + (Emtricitabine or Lamivudine) + Ritonavir + Atazanavir

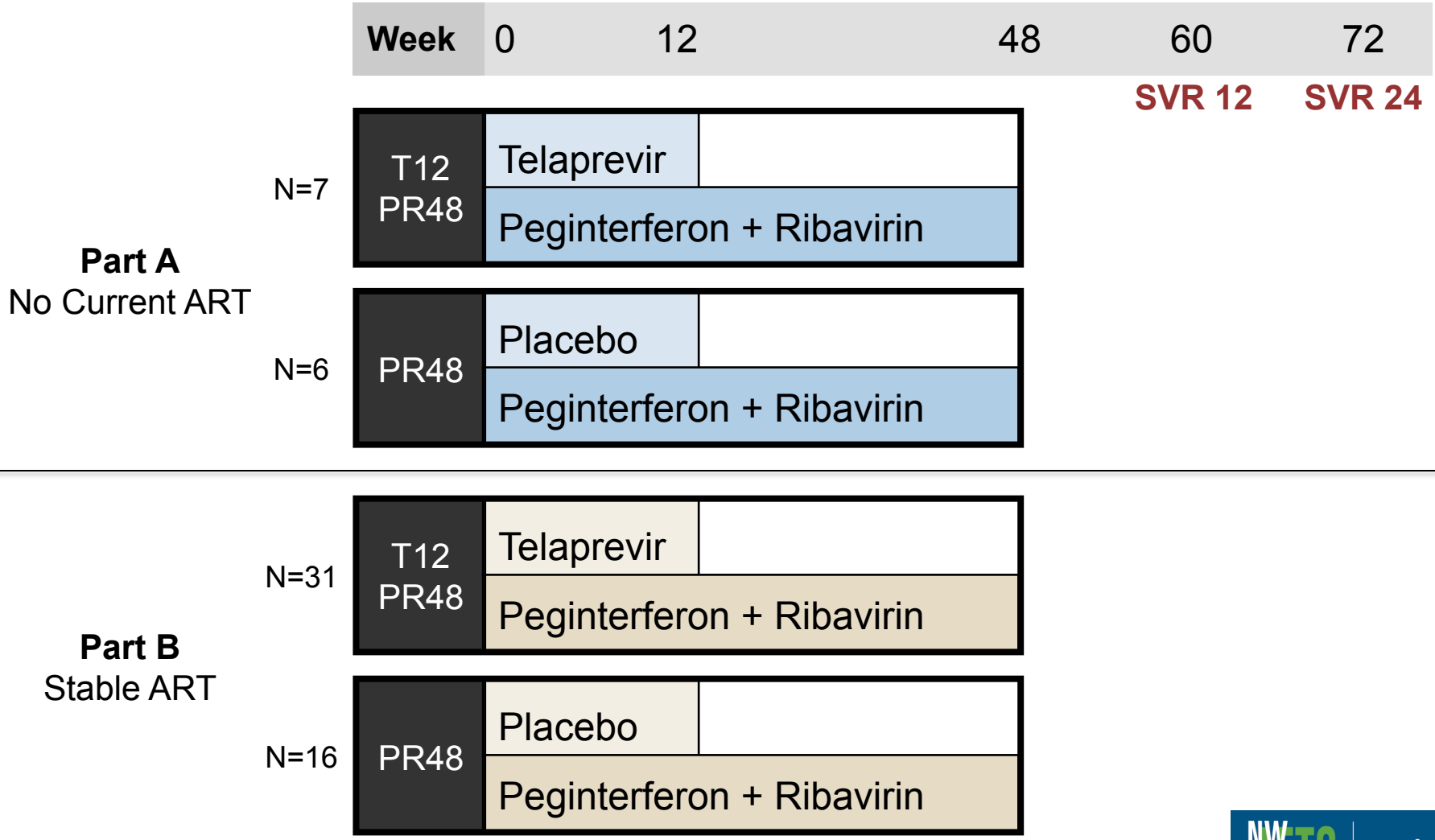
Drug Dosing

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 $\geq$ 75 kg)

Source: Dieterich D, et al. 19th CROI. 2012; Abstract 46.

Investigational

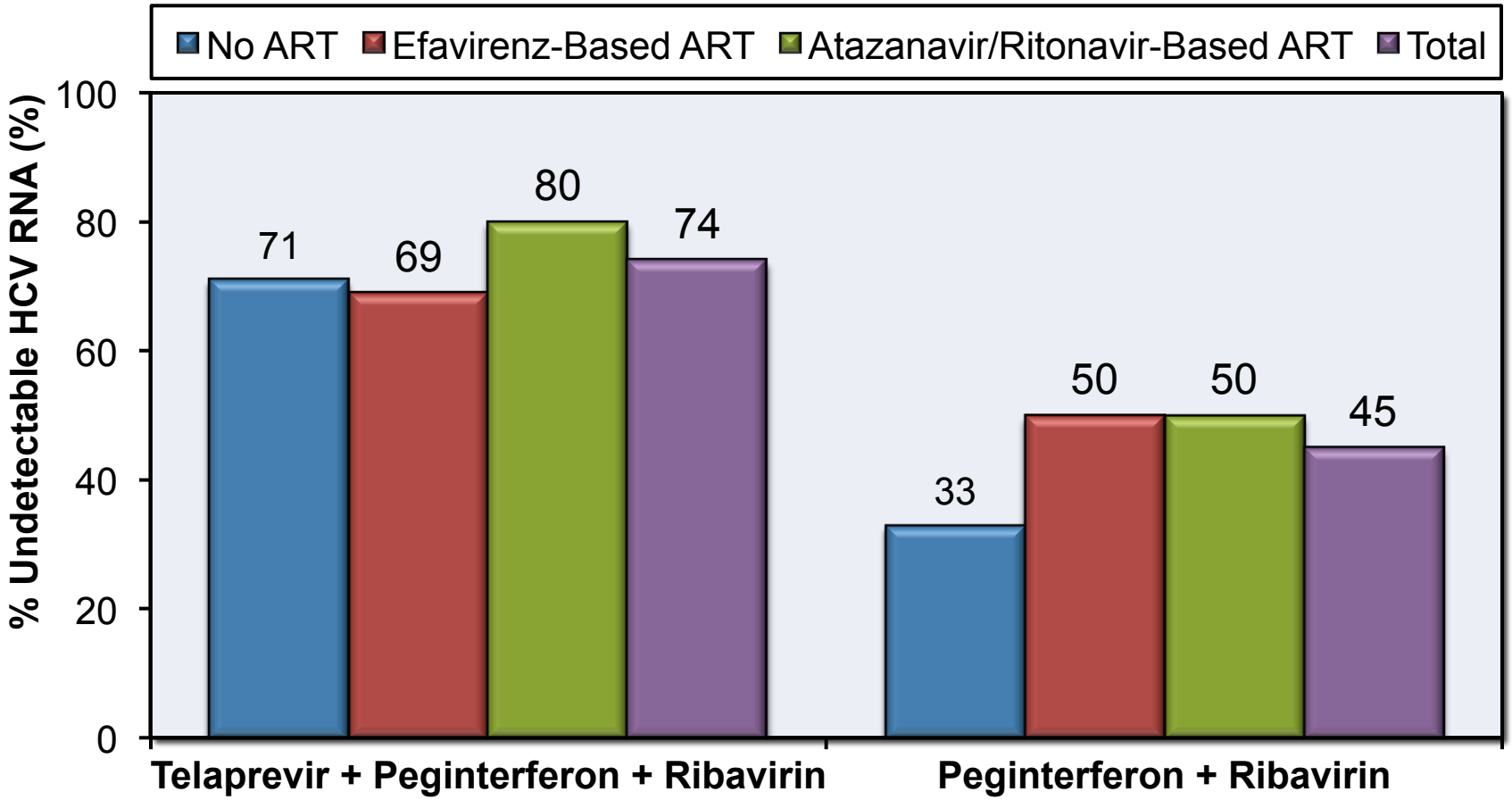
Telaprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Study 110: Design



Source: Dieterich D, et al. 19th CROI. 2012; Abstract 46.

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

Week 12 Post Treatment (SVR-12)



Source: Dieterich D, et al. 19th CROI. 2012; Abstract 46.

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: Dieterich D, et al. 19th CROI. 2012; Abstract 46.

Boceprevir in Treatment Naïve HIV/HCV

Interaction Between Boceprevir and Ritonavir-Boosted Protease Inhibitors in Healthy Volunteers

Impact of Boceprevir on Levels of Ritonavir-Boosted Protease Inhibitors			
Protease Inhibitor	**Cmin (trough)**	**Mean AUC**	**Cmax (peak)**
Atazanavir	↓ 49%	↓ 35%	↓ 25%
Darunavir	↓ 59%	↓ 44%	↓ 36%
Lopinavir	↓ 43%	↓ 34%	↓ 30%

Source: Hulskotte EGJ, et al. 19th CROI. 2012; Abstract 771LB.

For Consumers

Victrelis (boceprevir) and Ritonavir-Boosted HIV Protease Inhibitor Drugs - Drug Interactions

The U.S. Food and Drug Administration (FDA) is notifying healthcare professionals and patients that drug interactions between the hepatitis C virus (HCV) protease inhibitor Victrelis (boceprevir) and certain ritonavir-boosted human immunodeficiency virus (HIV) protease inhibitors (atazanavir, lopinavir, darunavir) can potentially reduce the effectiveness of these medicines when they are used together.

Patients should not stop taking any of their medicines without talking to their healthcare professional. Patients should contact their healthcare professional if they have any questions or concerns.

Healthcare professionals who have started patients infected with both chronic HCV and HIV on Victrelis and antiretroviral therapy containing a ritonavir-boosted protease inhibitor should closely monitor patients for HCV treatment response and for potential HCV and HIV virologic rebound.

Facts about Victrelis (boceprevir) and HIV protease inhibitors

- Victrelis is a hepatitis C virus (HCV) protease inhibitor used with the medicines peginterferon alfa and ribavirin to treat chronic (long-lasting) hepatitis C infection in adults who have not been treated before or who have failed previous treatment.
- HIV protease inhibitors are a class of anti-viral drugs used to treat HIV infection.
- Ritonavir is an HIV protease inhibitor used to "boost" other HIV protease inhibitors, increasing their levels in the blood and making them more effective.

A drug interaction study showed that taking boceprevir (Victrelis) with ritonavir (Norvir) in combination with atazanavir (Reyataz) or darunavir (Prezista), or with Kaletra (lopinavir/ritonavir) reduced the blood levels of the HIV medicines and boceprevir in the body (see Data Summary below). FDA will be updating the Victrelis drug label to include information about these drug interactions.

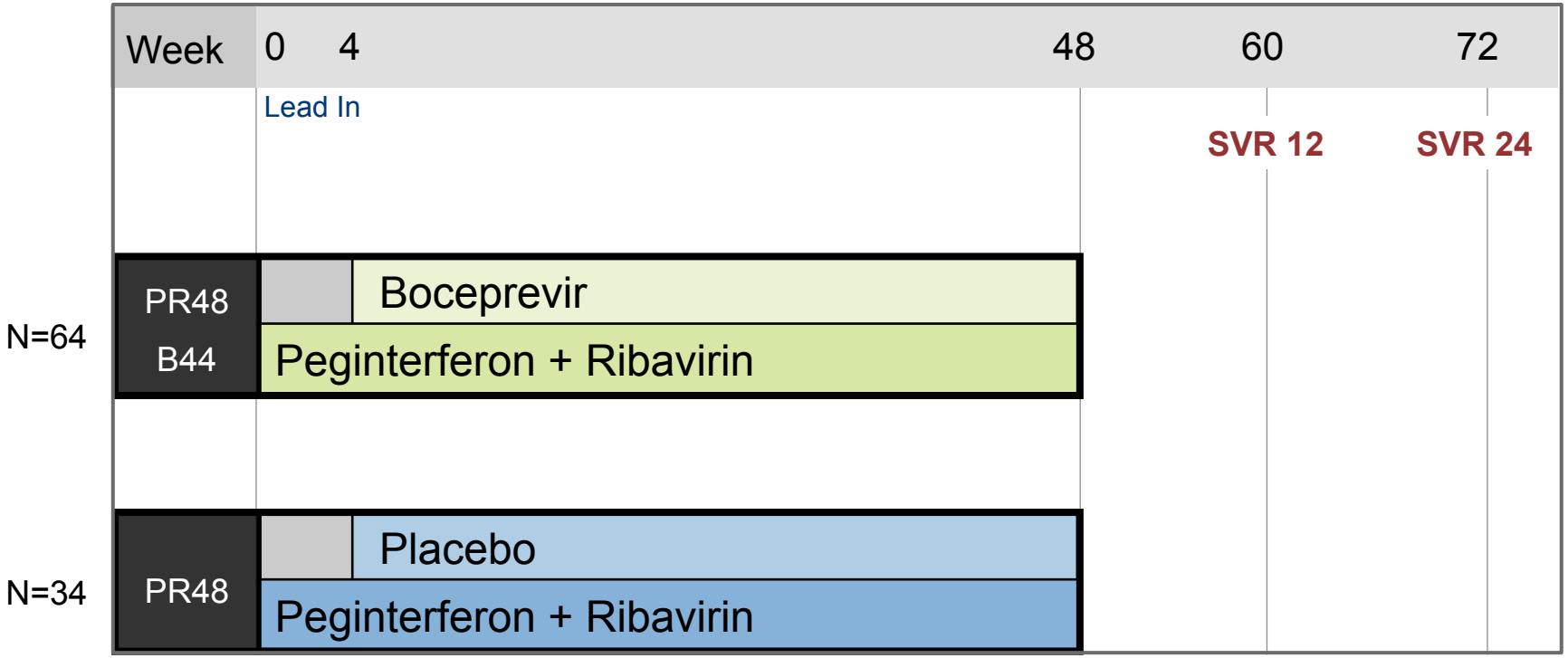
Merck and Company has issued a Dear Healthcare Professional letter (PDF - 67KB) with information about this drug interaction study.

Boceprevir with Antiretroviral Therapy
Study: Design

Study Features
Protocol - N = 100 HIV/HCV coinfected, Age 18-65 - Phase 2a trial; randomized, placebo-controlled - Chronic HCV; Genotype 1; HCV treatment naïve - CD4 ≥ 200 cells/mm^3; HIV RNA < 50 copies/ml on ARV therapy - Some ARVs Not Allowed: NNRTI, unboosted PI, ZDV, d4T, ddI - Randomized: (1:2) and all had 4-week lead in with Peginterferon + Ribavirin (1x) Peginterferon + Ribavirin (n =34) (2x) Boceprevir + Peginterferon + Ribavirin (n =64)
Drug Dosing Boeceprevir = 800 mg tid Peginterferon alfa-2b = 1.5 µg/kg/week Ribavirin = 600-1400 mg/d (weight based)

Source: Sulkowski M, et al. 19th CROI. 2012; Abstract 47.

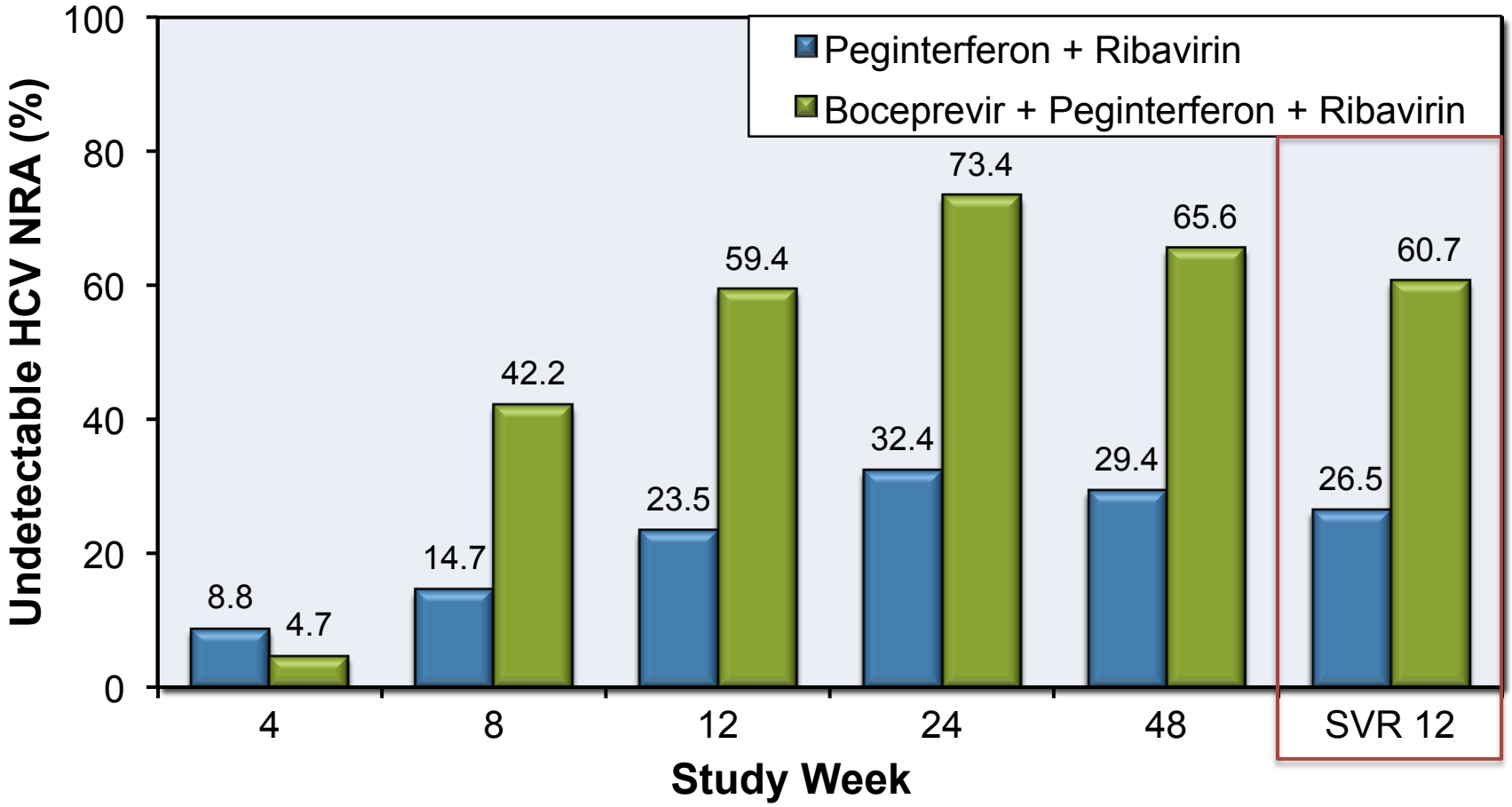
Boceprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Study: Design



Source: Sulkowski M, et al. 19th CROI. 2012; Abstract 47.

Boceprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection Study: Results

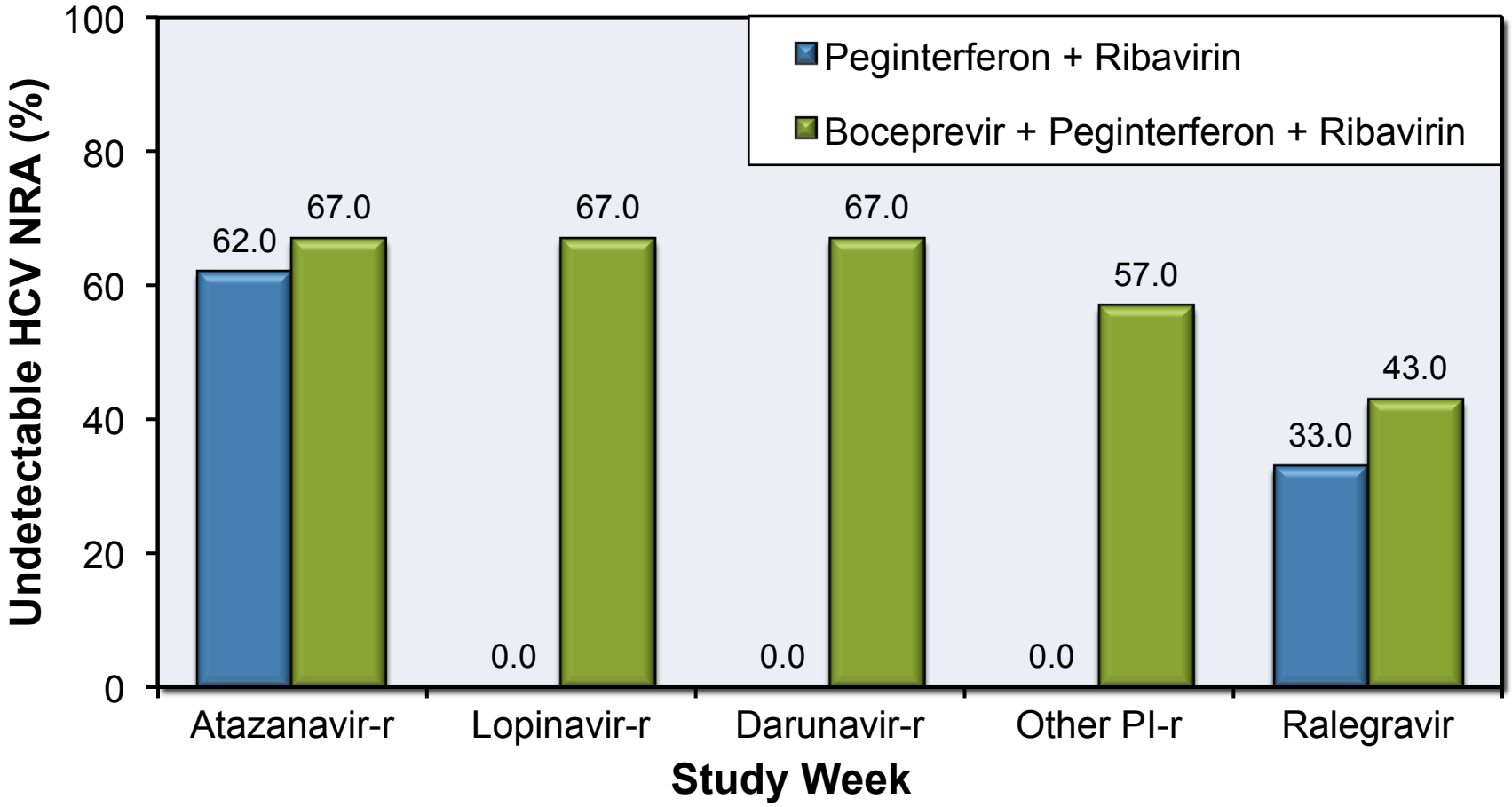
Treatment Response



Source: Sulkowski M, et al. 19th CROI. 2012; Abstract 47.

Boceprevir plus Peginterferon/Ribavirin in HIV/HCV Coinfection
Results: SVR-12 According to Antiretroviral Regimen

Treatment Response



Source: Sulkowski M, et al. 19th CROI. 2012; Abstract 47.

Boceprevir: Adverse Effects

	Boc/PR N=64	PR N=34
Serious AE	17%	21%
Study discontinuation due to AE	20%	9%
Anemia (serious AE)	3%	6%
Leading to discontinuation	2%	3%
Grade 3-4 (Hgb <8 g/dl)	5%	3%
EPO use	38%	21%
Blood transfusion	6%	6%
Neutropenia, Grade 3-4 (ANC <750)	27%	12%

HIV Breakthrough Viremia

- HIV Breakthrough Viremia (HIV RNA > 50 copies/ml on 2 consecutive visits)
  - Overall: 7 (7%) of 98 patients
  - Control Group (PR): 4 (12%) of 34
  - Boceprevir Group (B + PR): 3 (5%) of 64

Source: Sulkowski M, et al. 19th CROI. 2012; Abstract 47.

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)

NW AETC | echo

Take Home Points

- Interferon-based therapies have significant side effects
- Achieving cure (SVR) in Hepatitis C is possible, even in HIV patients, but requires intensive support, monitoring, and teamwork
- The Hepatitis C treatment landscape is rapidly changing with many new questions…

Stay tuned for <u>Interferon-free regimens</u> 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!!