

HEPATITIS WEB STUDY  HEPATITIS C ONLINE

Treatment of Chronic HCV Genotype 5 or 6

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Treatment of Chronic HCV Genotype 5 or 6

- Background and Definitions
- Initial Treatment and Retreatment of Prior Relapsers
- Retreatment of Prior Nonresponders
- Issues and Controversies
- Future Therapies
- Summary

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 5 OR 6

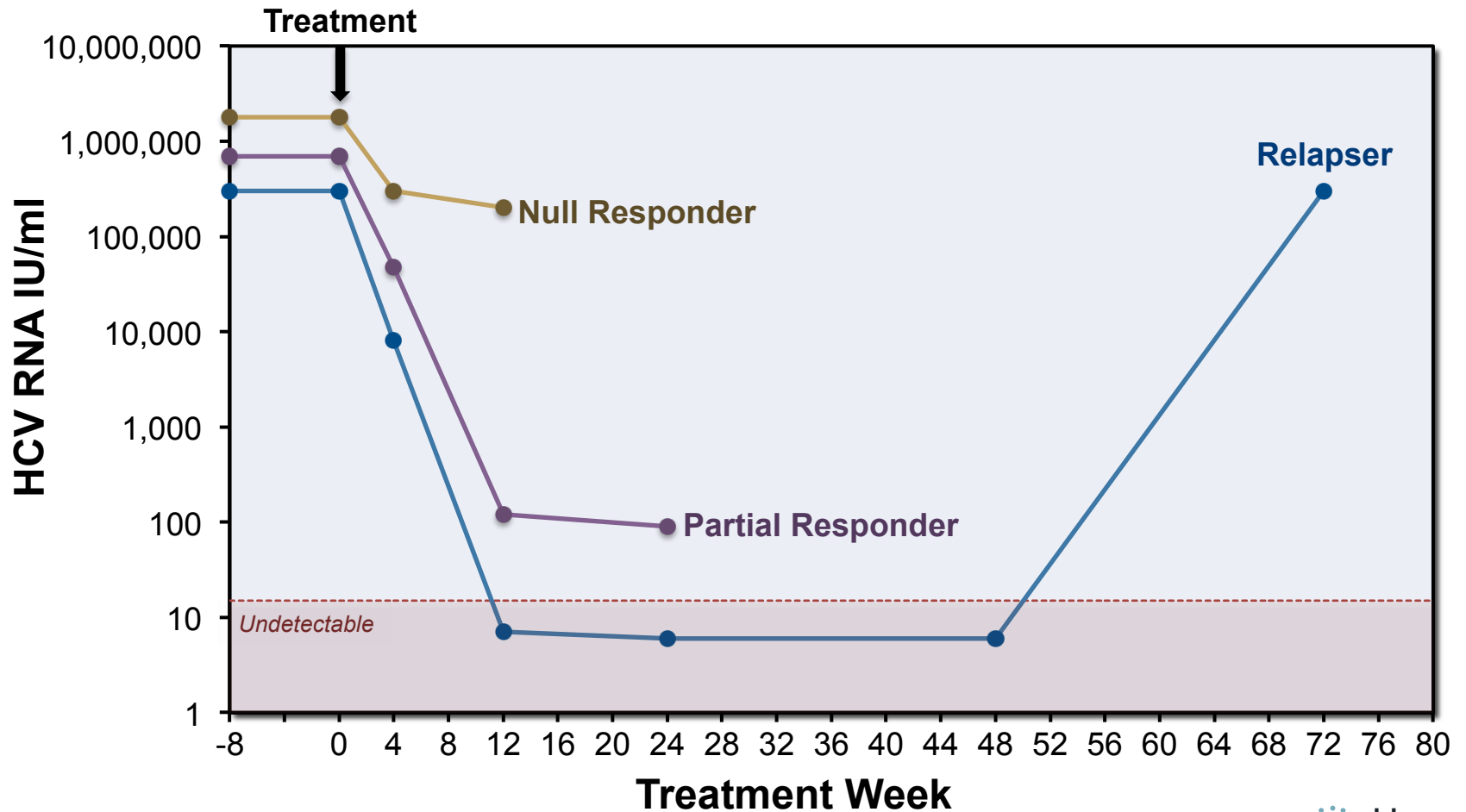
Background and Definitions

Hepatitis C Genotype 5 or 6 Background

- HCV infects ~ 5 million people in the US today
- Fewer than 2% of HCV infections in US caused by GT 5 or 6
- GT5 infection endemic in South Africa and very rare in US
- GT6 important in Vietnam, SE China, and other countries in Southeast Asia
- Historically SVR rates for GT 5,6 with PEG-based therapy between GT1 and GT 2,3

Virologic Responses with HCV Therapy Relapser and Nonresponder (Null and Partial)

Different Types of Virologic Failure with HCV Therapy



AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations

Criteria for Interferon Ineligible

Interferon Ineligible is defined as one or more of the following:

- Intolerance to interferon
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to peginterferon or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/ μ L, a baseline platelet count below 90,000/ μ L or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 5 OR 6
Treatment-Naïve and Prior Relapsers

AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations Initial Therapy for Patients with Genotype 5 or 6 Chronic HCV

Patients with GT 5 or 6 HCV: Initial Treatment & Retreatment of Relapsers*

Recommended Therapy, Interferon Eligible

Sofosbuvir + Peginterferon + Ribavirin x 12 weeks

Alternative Therapy, Interferon Eligible

Peginterferon + Ribavirin x 48 weeks

Not Recommended

Monotherapy with Peginterferon, Ribavirin, or a Direct Acting Antiviral Agent

Telaprevir- or Boceprevir-based Regimens

*Patients previously treated with peginterferon plus ribavirin and had relapse

Treatment-Naïve & Prior Relapsers with GT 5 or 6 Chronic HCV

Key Studies that Support Treatment Recommendations

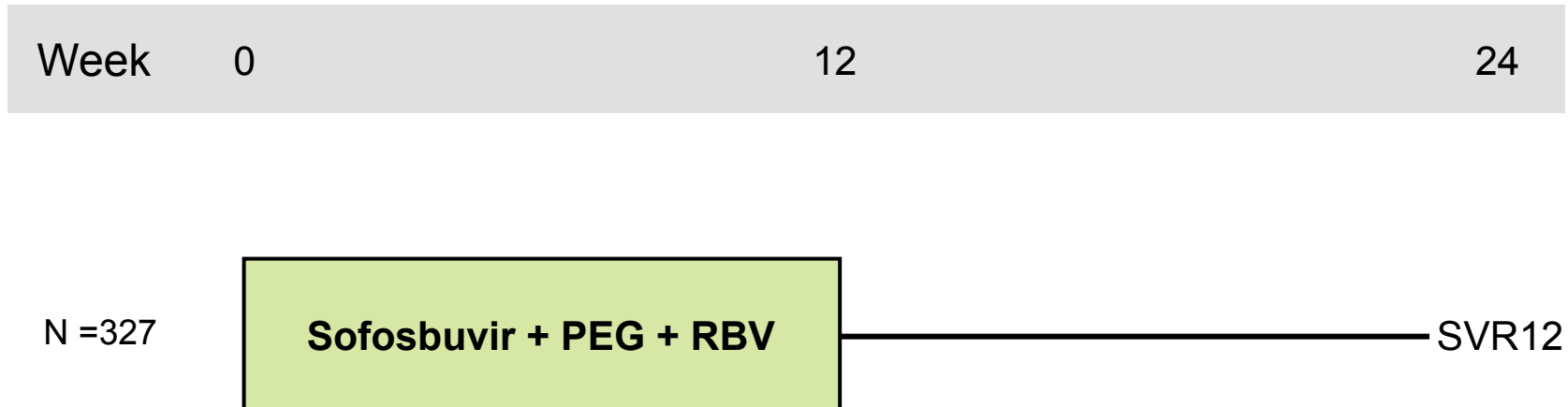
- **Sofosbuvir + Peginterferon + Ribavirin**
 - NEUTRINO
 - ATOMIC

Sofosbuvir + PEG + RBV: Treatment-Naive HCV GT 1,4,5,6 NEUTRINO Trial: Features

NEUTRINO Trial: Features

- **Design:** Single-arm, open-label, phase 3 trial of triple therapy with sofosbuvir + peginterferon + ribavirin in HCV genotypes 1, 4, 5, or 6
- **Setting:** 56 sites in United States, enrolled June-August 2012
- **Entry Criteria**
 - Treatment-naïve, chronic HCV monoinfection
 - HCV RNA \geq 10,000 IU/ml
 - HCV Genotypes 1, 4, 5, or 6
- **Primary End-Point:** SVR12

Sofosbuvir + PEG + RBV: Treatment-Naive HCV GT 1,4,5,6 NEUTRINO Trial: Design



Drug Dosing

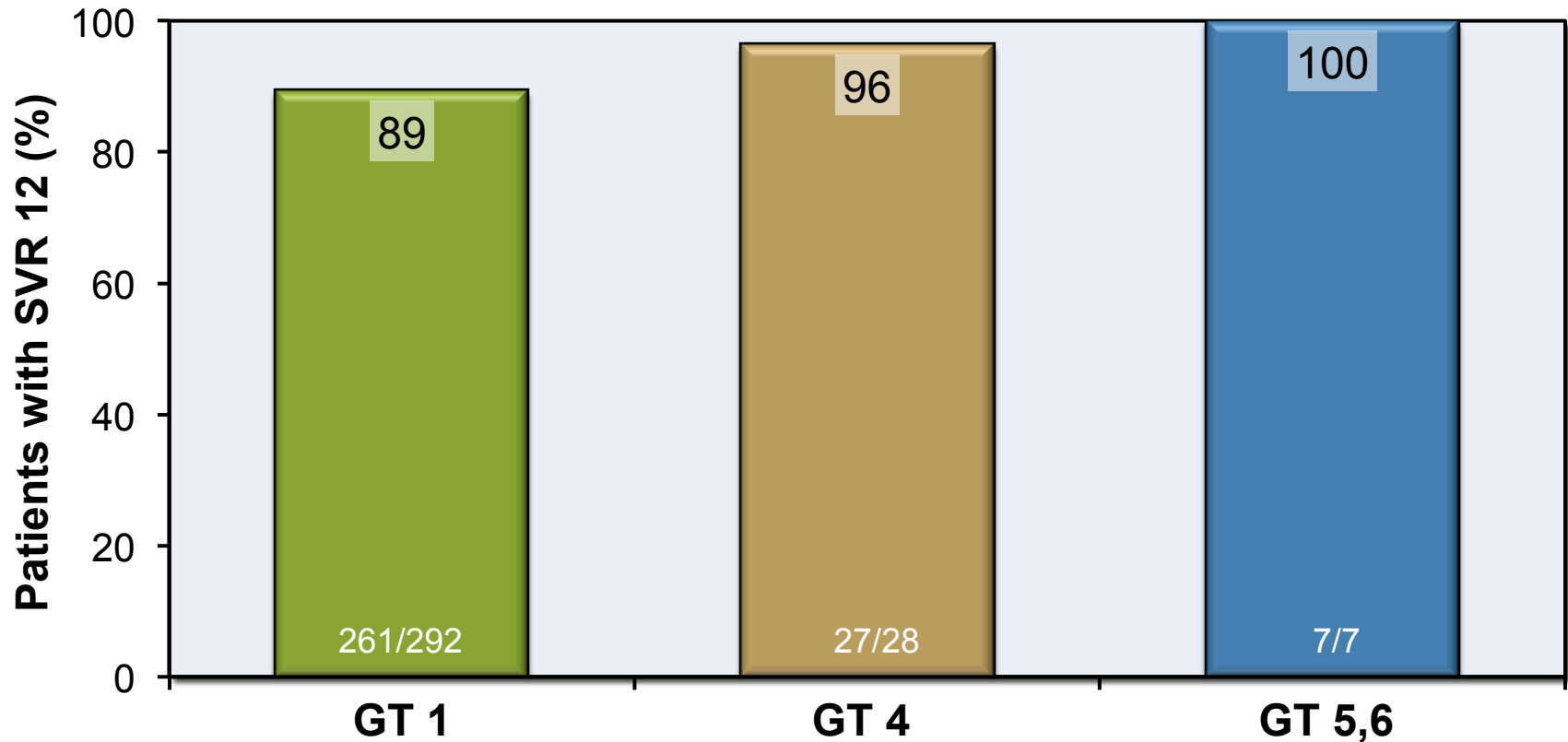
Sofosbuvir: 400 mg once daily

Peginterferon alfa-2a: 180 µg once weekly

Ribavirin (weight-based and in 2 divided doses): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Sofosbuvir + PEG + RBV: Treatment-Naive HCV GT 1,4,5,6 NEUTRINO Trial: Results

NEUTRINO: SVR 12 by Genotype



GT = genotype

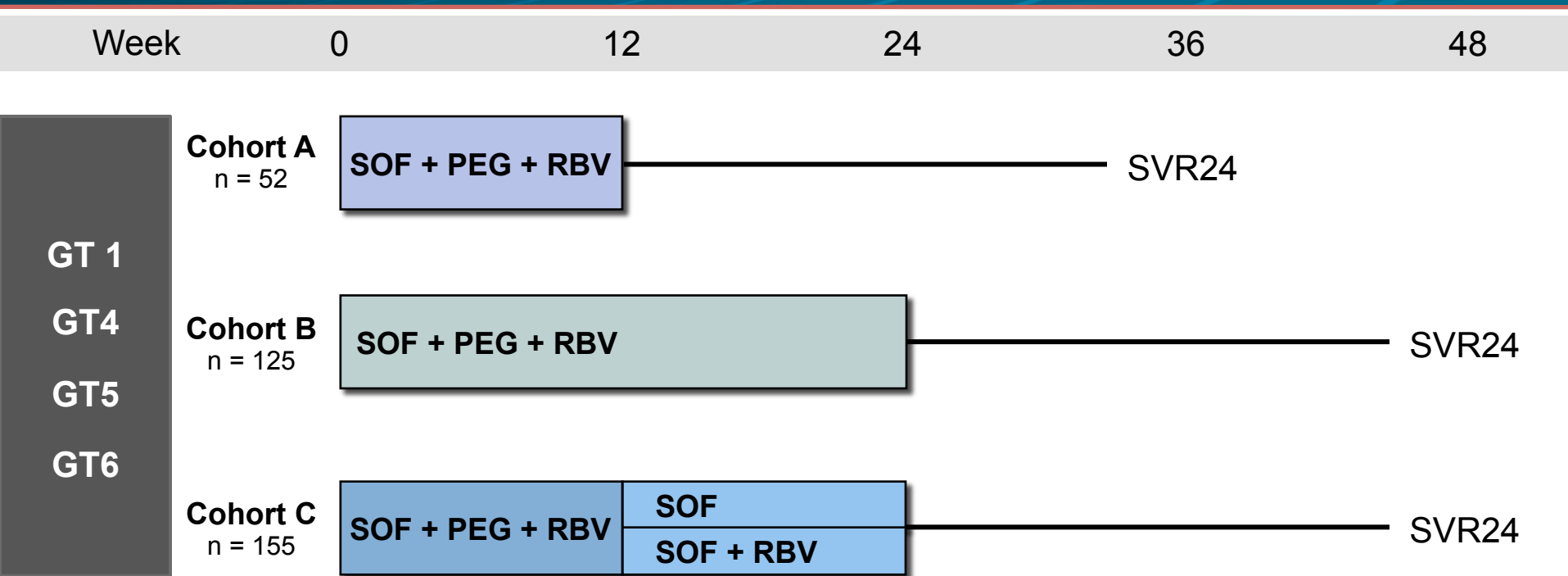
Source: Lawitz E, et al. N Engl J Med. 2013;368:1878-87.

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1,4,5,6 ATOMIC Trial: Study Overview

ATOMIC Trial: Features

- **Design:** Randomized, open-label, phase 2 trial investigating effectiveness and required duration of sofosbuvir, peginterferon, and ribavirin in treatment-naïve patients with GT 1, 4, 5, or 6
- **Setting:** 42 centers in United States and Puerto Rico
- **Entry Criteria**
 - Chronic HCV infection with HCV genotype 1, 4, 5, or 6
 - Treatment-naïve
 - Age 18 or older
 - HCV RNA \geq 50,000 IU/mL
 - Absence of cirrhosis
 - Absence of coinfection with HBV or HIV
 - BMI \leq 18 kg/m²
- **Primary End-Point:** SVR24

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1,4,5,6 ATOMIC Trial: Design



Drug Dosing

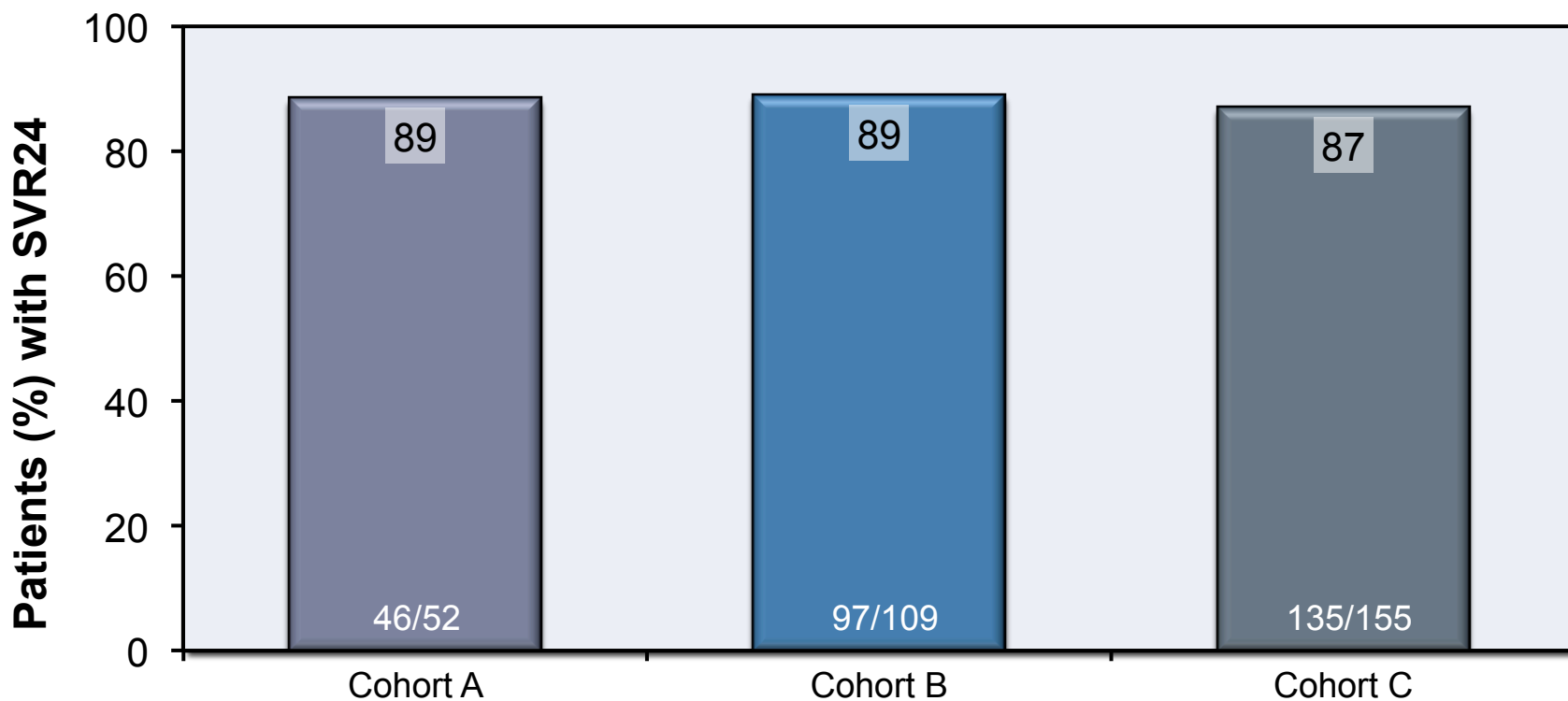
Sofosbuvir (SOF): 400 mg once daily

Ribavirin (RBV) weight-based and divided bid: 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Peginterferon alfa-2a (PEG): 180 µg once weekly

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1,4,5,6 ATOMIC Trial: Results, by Cohort (Regimen)

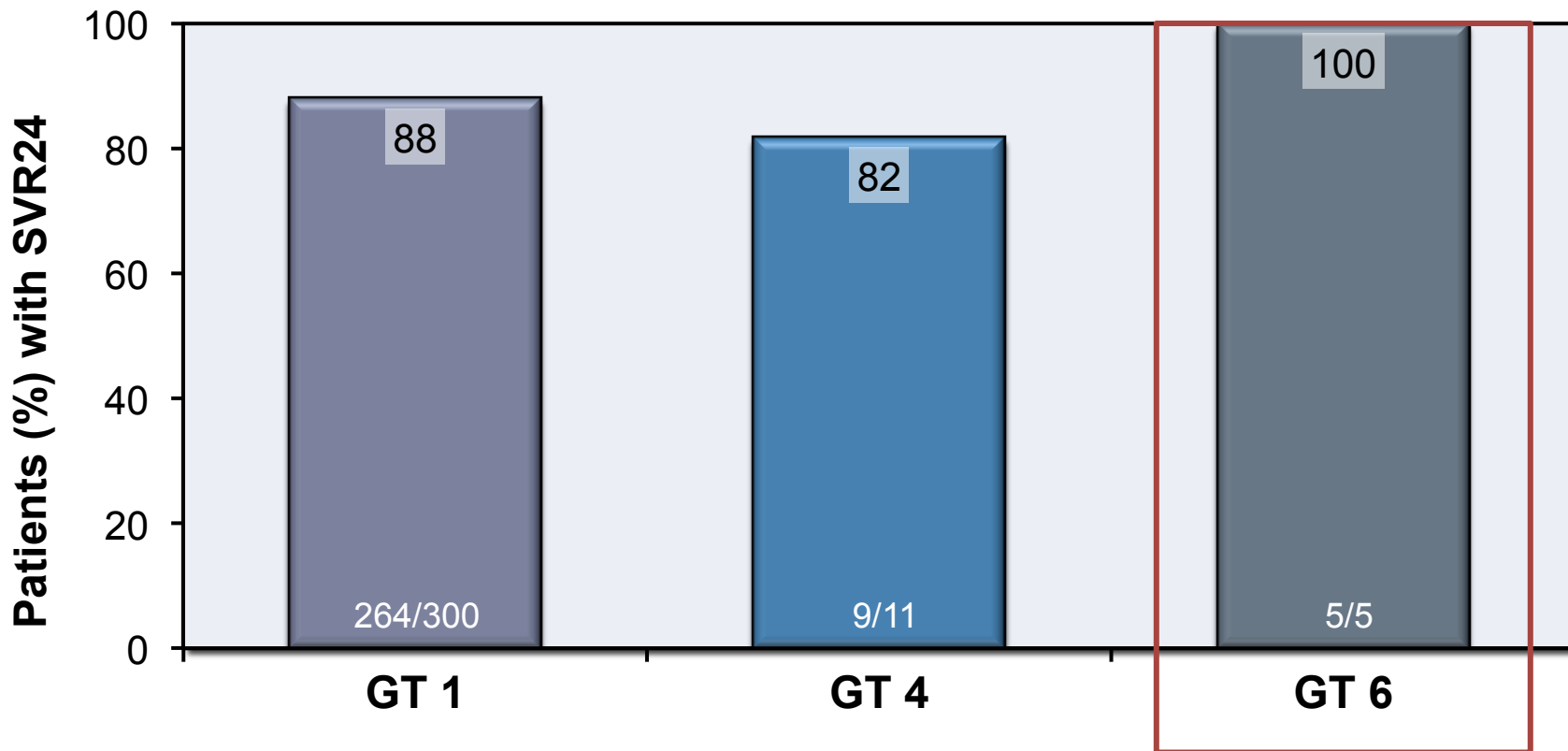
ATOMIC: SVR 24 by Cohort (Regimen)



Patients with Genotype 1, 4, or 6

Sofosbuvir + Peginterferon + Ribavirin in Genotypes 1,4,5,6 ATOMIC Trial: Results, by Cohort (Regimen)

ATOMIC: SVR 24 by Genotype



- Notes: (1) No patients with Genotype 5 enrolled in study
(2) All patients with Genotype 4 or 6 received 24 weeks of SOF + PEG + RBV
(3) The 2 patients with Genotype 4 and failure resulted from lost to follow-up at end of treatment

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 5 OR 6

Retreatment of Prior Nonresponders

AASLD/IDSA/IAS-USA 2014 HCV Treatment Recommendations

Retreatment of Patients with Genotype 5 or 6 Chronic HCV

Patients with GT 5 or 6 HCV: Retreatment of Prior Nonresponders*

Recommended Therapy^

Sofosbuvir + Peginterferon + Ribavirin x 12 weeks

Alternative Therapy

None

Not Recommended

Peginterferon + Ribavirin +/- [Boceprevir or Simeprevir or Telaprevir]

Monotherapy with Peginterferon, Ribavirin, or a Direct-Acting Antiviral Agent

Treatment of Decompensated Cirrhosis with Peginterferon

^Expert consultation is recommended to determine the optimal duration of therapy

*Patients who experienced nonresponse (partial or null) with Peginterferon plus Ribavirin therapy

Treatment Experienced Nonresponders with GT5 or 6 Chronic HCV

Lack of Retreatment Studies

- Sparse retreatment data for patients with genotypes 5 and 6
- EMEA has approved SOF for Genotype 5 and 6 from this limited treatment data
- US FDA has not included Genotype 5 and 6 in the PI for SOF
- High response rates (SVR = Cure) are inferred from this limited data set

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPES 5 OR 6

Issues and Controversies

Issues and Controversies

- Cost of Therapy
- When to Defer Therapy
 - Decisions on when to warehouse?
- Degree of Liver Fibrosis
 - How to stage?

How is cost of therapy impacting treatment decisions?

Hepatitis C Genotype 5 or 6

Estimated Medication Costs for Treatment-Naïve & Prior Relapsers

Patients with GT 5 or 6 HCV: Initial Treatment & Retreatment of Relapsers	
Regimen and Duration	Regimen Cost
Recommended Therapy	
Sofosbuvir + Peginterferon + Ribavirin x 12 weeks	\$97,000
Alternative Therapy	
Peginterferon + Ribavirin x 48 weeks	\$48,000

Hepatitis C Genotype 5 or 6

Estimated Medication Costs for Retreatment of Nonresponders

Patients with GT 5 or 6 HCV: Retreatment of Nonresponders

Regimen and Duration	Regimen Cost
Recommended Therapy	
Sofosbuvir + Peginterferon + Ribavirin x 12 weeks*	\$97,000

*Note: expert consultation recommended to determine the optimal duration of retreatment of nonresponders in patients with genotypes 5 or 6 and thus treatment duration may extend past 12 weeks and cost may exceed \$97,000

When to defer therapy?

Factors Favoring Treat Now for GT 5 or 6

- Advanced Fibrosis (F3-F4)
 - Platelet count < 150,000/uL
 - Large spleen and/or portal vein (Over 12 rule = Spleen >12 cm or PV > 12 mm)
 - Esophageal varices
- Synthetic dysfunction, low albumin, high INR
- Systemic disease
 - Cryoglobulinemia (+RhF)
- Highly motivated patients/symptoms
- Patients with Increased Mortality Risk
 - All cause
 - HCC risk

HEPATITIS C: GENOTYPES 5 OR 6

Future Treatment Options

Future Regimens for GT 5 or 6

- **Ledipasvir-Sofosbuvir (fixed dose combination)**
 - Ledipasvir: NS5A replication inhibitor
 - Sofosbuvir: NS5b polymerase inhibitor
- **MK-5172 + MK-8742 (fixed dose combination in development)**
 - MK-5172: NS3/4A protease inhibitor
 - MK-8742: NS5A replication inhibitor

Future Regimens for GT 5 or 6

- **Ledipasvir-Sofosbuvir (with or without ribavirin)**
 - Phase 2 trial with GT 4 or 5 in treatment naïve and experienced
 - Phase 2 trial includes GT 6 in treatment naïve and experienced
- **MK-5172 + MK-8742 (fixed dose combination in development)**
 - C-EDGE Program

HEPATITIS C: GENOTYPES 5 OR 6

Summary Points

Summary Points for Treatment of Chronic HCV GT 5 or 6

- Infection with GT 5 and 6 accounts for <2% of HCV infections in US
- GT5 highly prevalent in South Africa
- GT6 important in Southeast Asia and especially in the Vietnamese population in the US
- SOF + PEG + RBV recommended for treatment-naïve and relapsers
- Consider SOF + RBV for 24 weeks in interferon ineligible
- Expert consultation recommended for retreatment of nonresponders

This slide deck is from the University of Washington's *Hepatitis C Online* and *Hepatitis Web Study* projects.

Hepatitis C Online
www.hepatitisc.uw.edu

Hepatitis Web Study
<http://depts.washington.edu/hepstudy/>

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