

HEPATITIS WEB STUDY  HEPATITIS C ONLINE

Treatment of Chronic HCV Genotype 4

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Treatment of Chronic HCV Genotype 4

- 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 4

Background and Definitions

Treatment of Chronic HCV Genotype 4 Background

- HCV infects ~ 5 million people in the US today
- Genotype 4 accounts for about 1-2% of HCV infections in US
- Genotype 4 very important in Egypt, Saudi Arabia, North Africa, and Southern Europe and immigrants from these regions
- Approximately 70% of patients with genotype 4 HCV have moderate to severe steatosis with or without sinusoidal fibrosis (similar to GT3)
- Historic SVR rates with IFN-based therapy between GT1 and GT 2,3

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4

Initial Treatment

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

Genotype 4 Chronic HCV: Initial Treatment

Genotype 4 HCV: Initial Treatment

Recommended Regimens

Ledipasvir-Sofosbuvir x 12 weeks

Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks

Sofosbuvir + Ribavirin x 24 weeks

Alternative Regimen, Patients Eligible to Receive Interferon

Sofosbuvir + Ribavirin + Peginterferon x 12 weeks

Treatment-Naïve & Prior Relapsers with GT4 Chronic HCV

Key Studies that Support Treatment Recommendations

- **Ledipasvir-Sofosbuvir**
 - NIAID Synergy (Genotype 4)
- **Ombitasvir-Paritaprevir-Ritonavir**
 - PEARL-I
- **Sofosbuvir + Ribavirin**
 - Egyptian Ancestry
- **Sofosbuvir + Ribavirin + Peginterferon**
 - NEUTRINO

Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Features

Week

0

12

24

Genotype 4

Treatment Naïve (n = 13)

Treatment Experienced (n = 8)

n = 21

Ledipasvir-Sofosbuvir

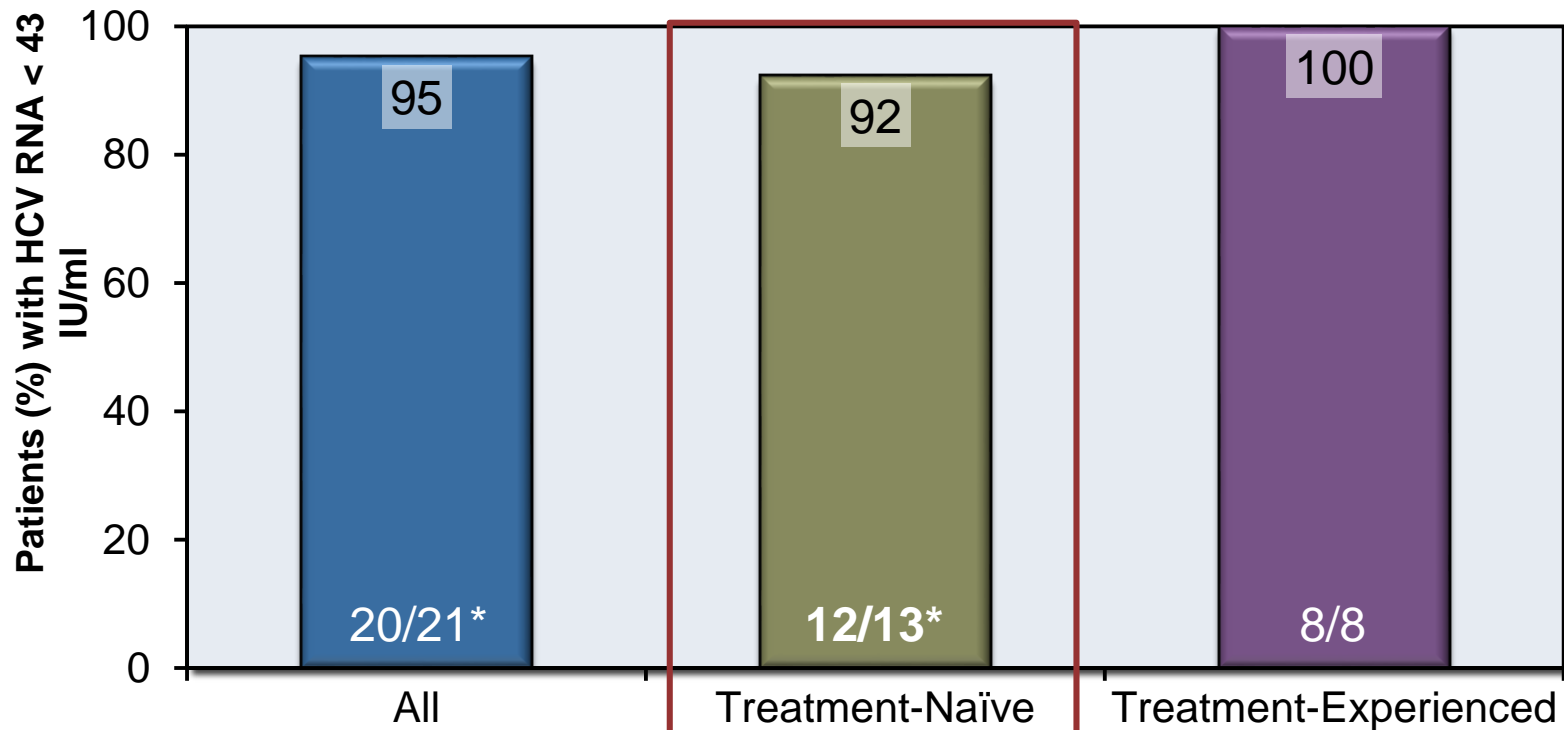
SVR12

Drug Dosing

Ledipasvir-sofosbuvir (90/400 mg): fixed dose combination; one pill once daily

Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Results

NIH SYNERGY: SVR 12, Intent to Treat Analysis



Ledipasvir-Sofosbuvir Treated Patients

*1 patient did not complete 12 weeks of treatment due to drug non-adherence

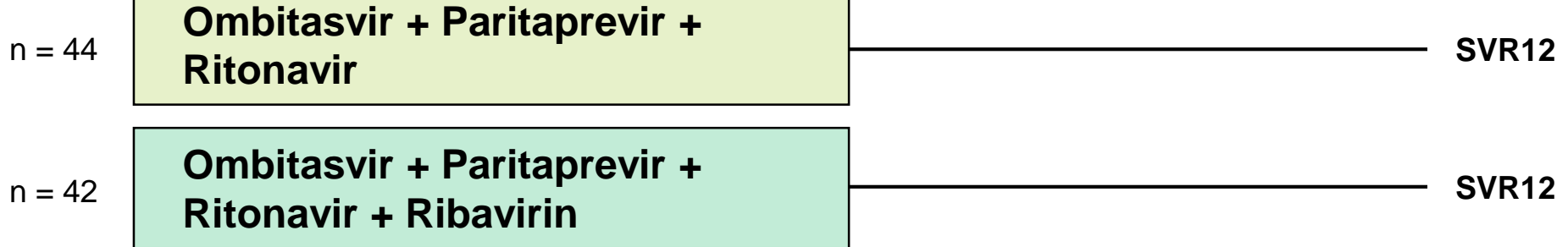
Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4 PEARL-I: Regimens

Week 0

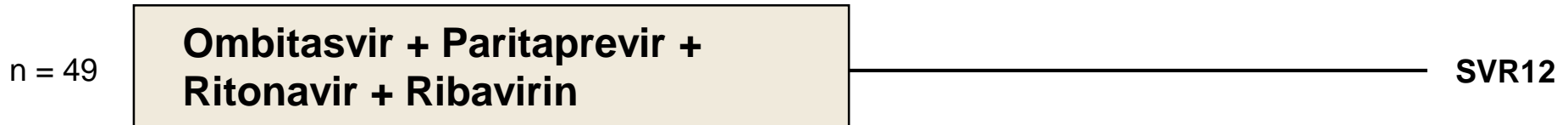
12

24

HCV Treatment Naïve GT4



HCV Treatment Experienced GT4



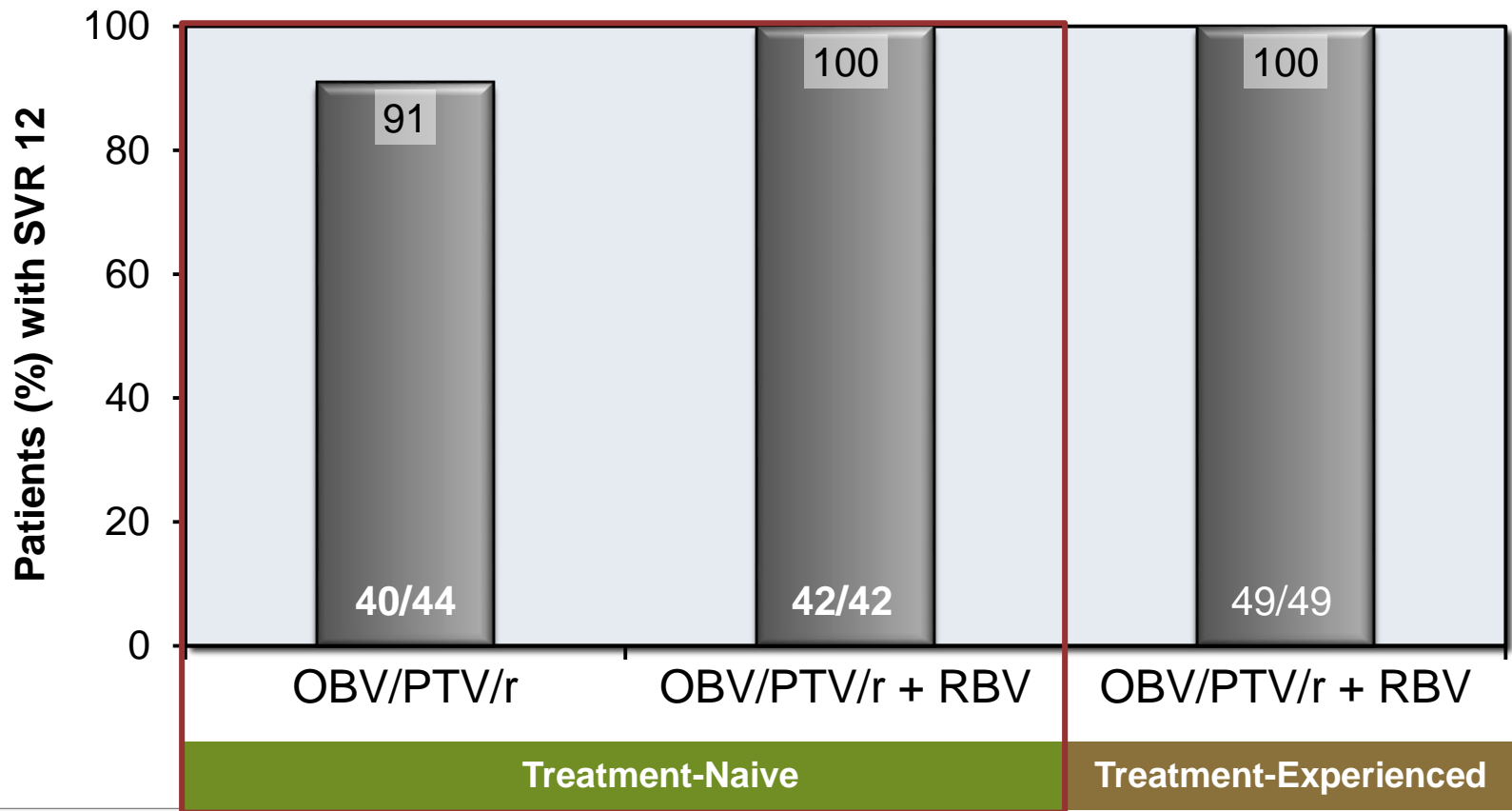
Drug Dosing

Ombitasvir (25 mg once daily), Paritaprevir (150 mg once daily), Ritonavir (100 mg once daily)

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

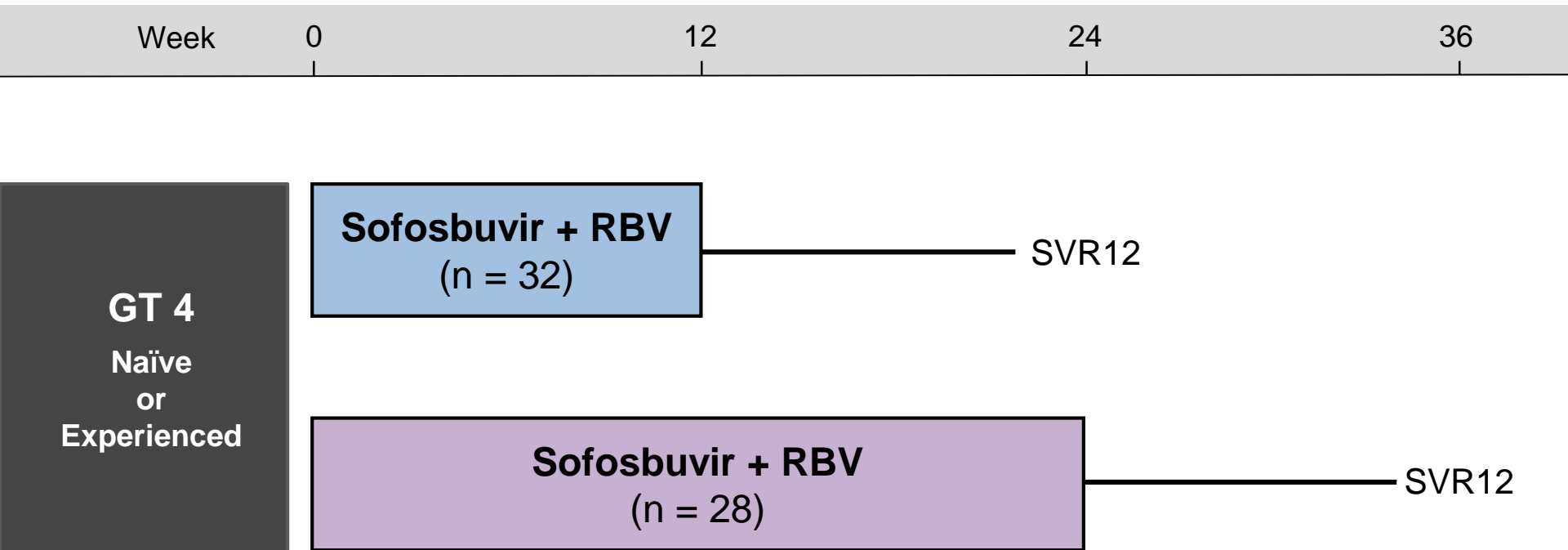
Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4 PEARL-I: Results

PEARL-I: SVR 12 Rates (HCV RNA <25 IU/mL)



OBV/PTV/r = Ombitasvir-Paritaprevir-Ritonavir; RBV = ribavirin

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Design



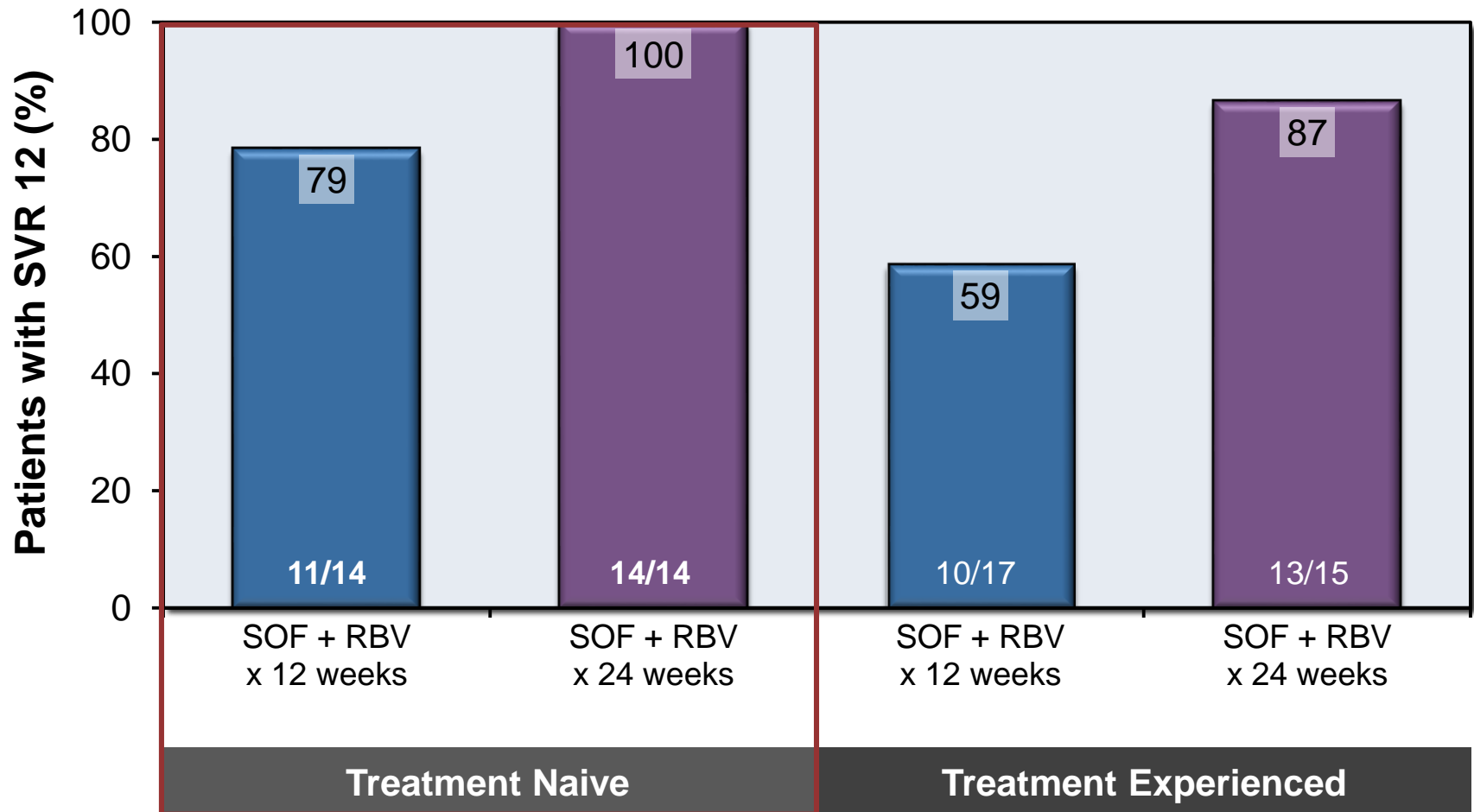
Drug Dosing

Sofosbuvir: 400 mg once daily

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

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Results

SVR 12 by Regimen Duration and Treatment Experience



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

Week

0

12

24

Total N = 327
(N = 28 for GT 4)

Sofosbuvir + PEG + RBV

SVR12

Drug Dosing

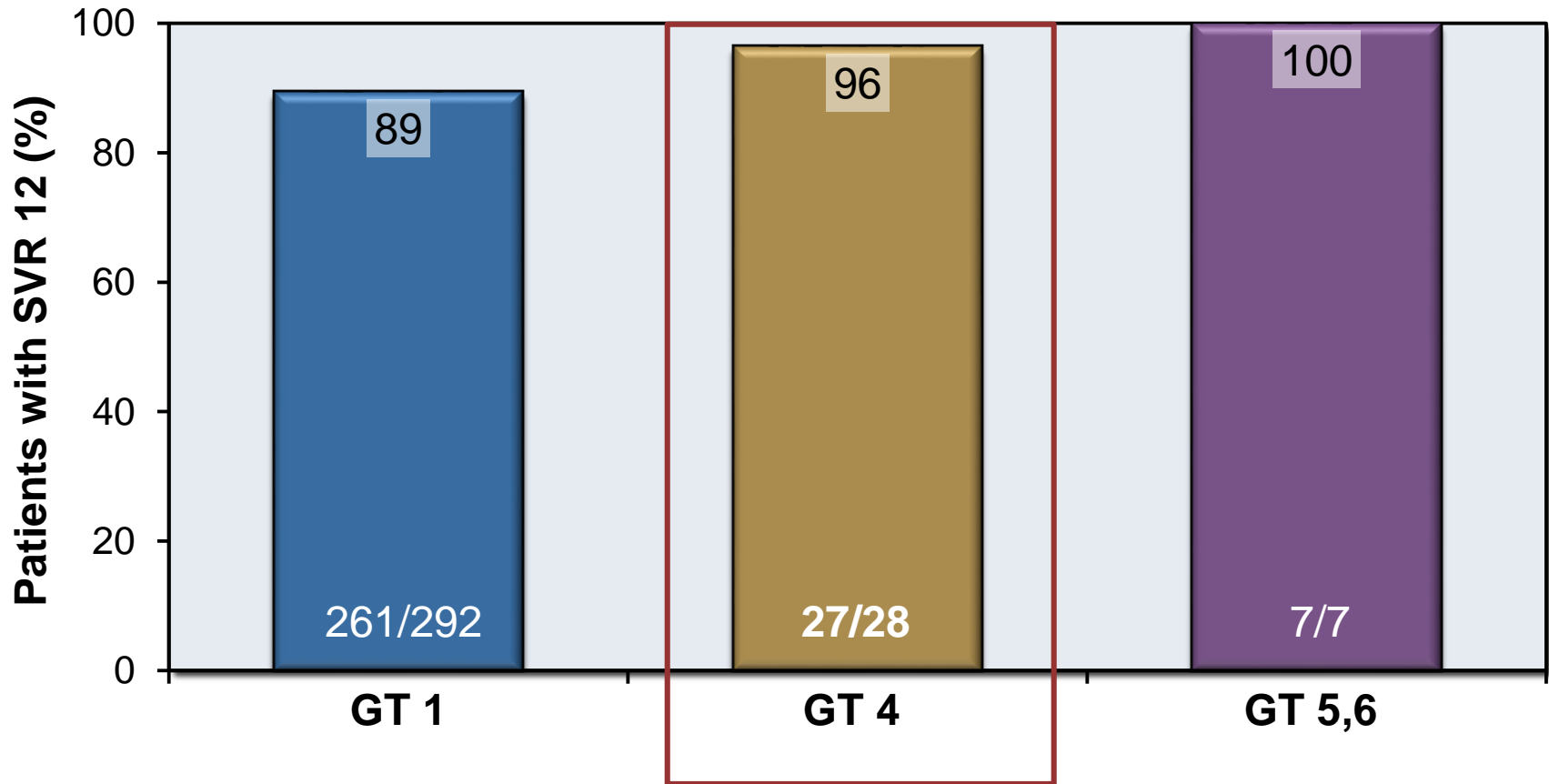
Sofosbuvir: 400 mg once daily

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.

TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4
Retreatment of Persons in Whom Prior Therapy Failed

AASLD/IDSA/IAS-USA 2015 HCV Treatment Recommendations

Genotype 4 Chronic HCV: Retreatment, Prior Failure with PR

Genotype 4 HCV: Retreatment, Prior Failure with Peginterferon + Ribavirin

Recommended Regimens

Ledipasvir-Sofosbuvir x 12 weeks

Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks

Sofosbuvir + Ribavirin + Peginterferon x 12 weeks

Sofosbuvir + Ribavirin x 24 weeks

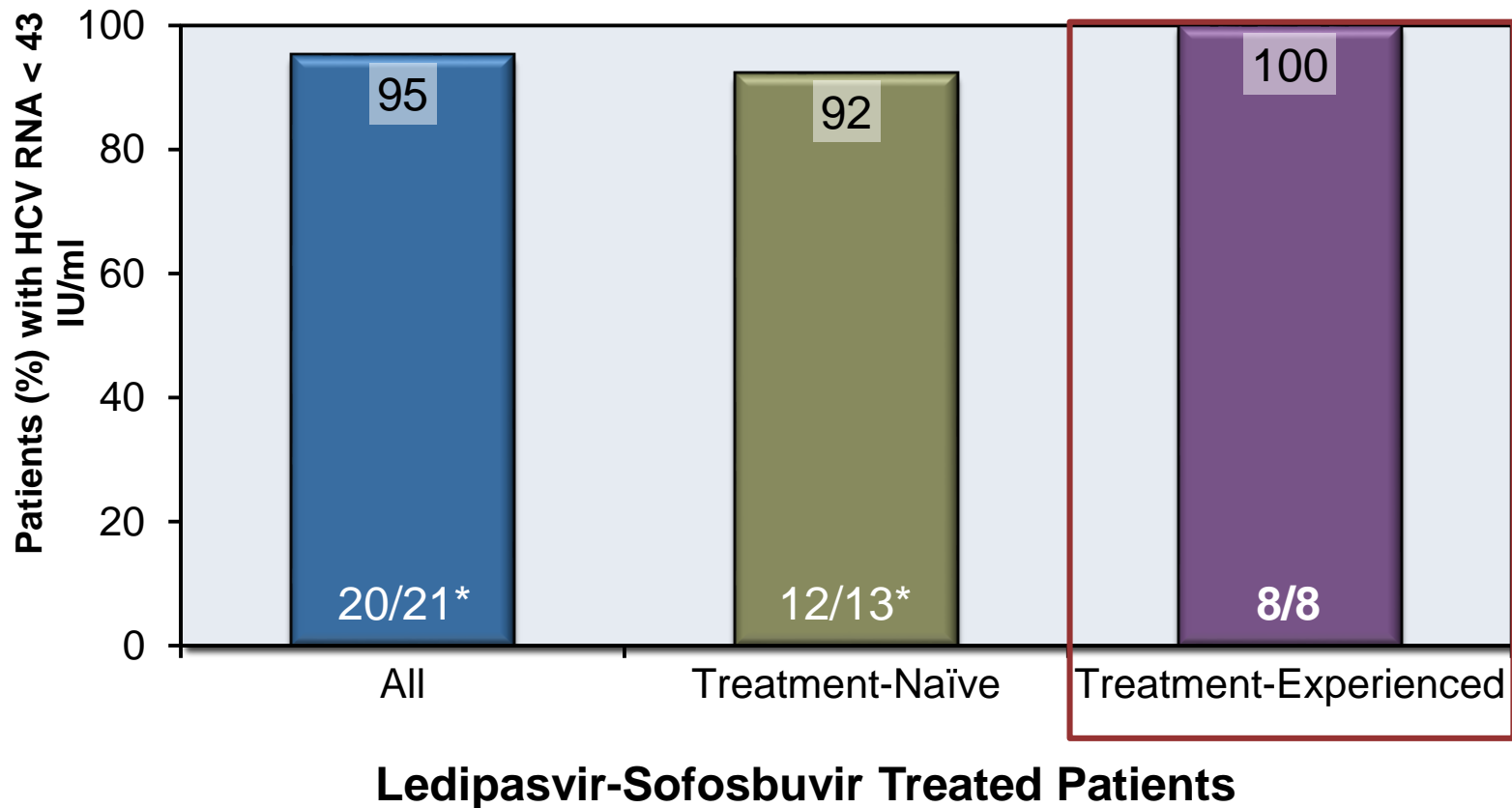
Retreatment of GT4 Chronic HCV

Key Studies that Support Treatment Recommendations

- **Ledipasvir-Sofosbuvir**
 - NIAID Synergy (Genotype 4)
- **Ombitasvir-Paritaprevir-Ritonavir**
 - PEARL-I
- **Sofosbuvir + Ribavirin + Peginterferon**
 - NEUTRINO (data for treatment-naïve patients)
- **Sofosbuvir + Ribavirin**
 - Egyptian Ancestry

Ledipasvir-Sofosbuvir in Genotype 4 NIAID SYNERGY (GT4) Trial: Results

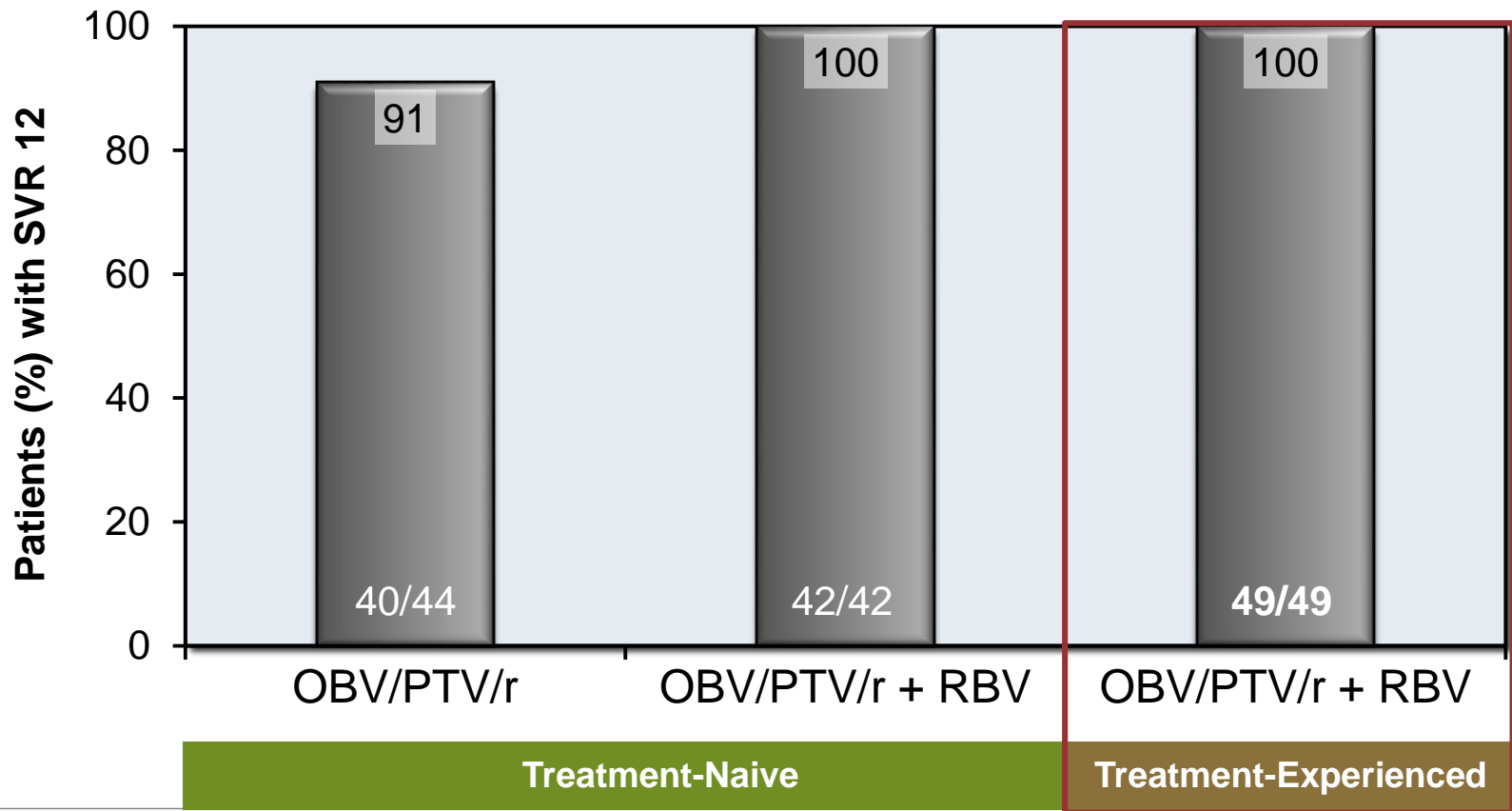
NIH SYNERGY: SVR 12, Intent to Treat Analysis



*1 patient did not complete 12 weeks of treatment due to drug non-adherence

Ombitasvir + Paritaprevir + Ritonavir +/- RBV in HCV GT4 PEARL-I: Results

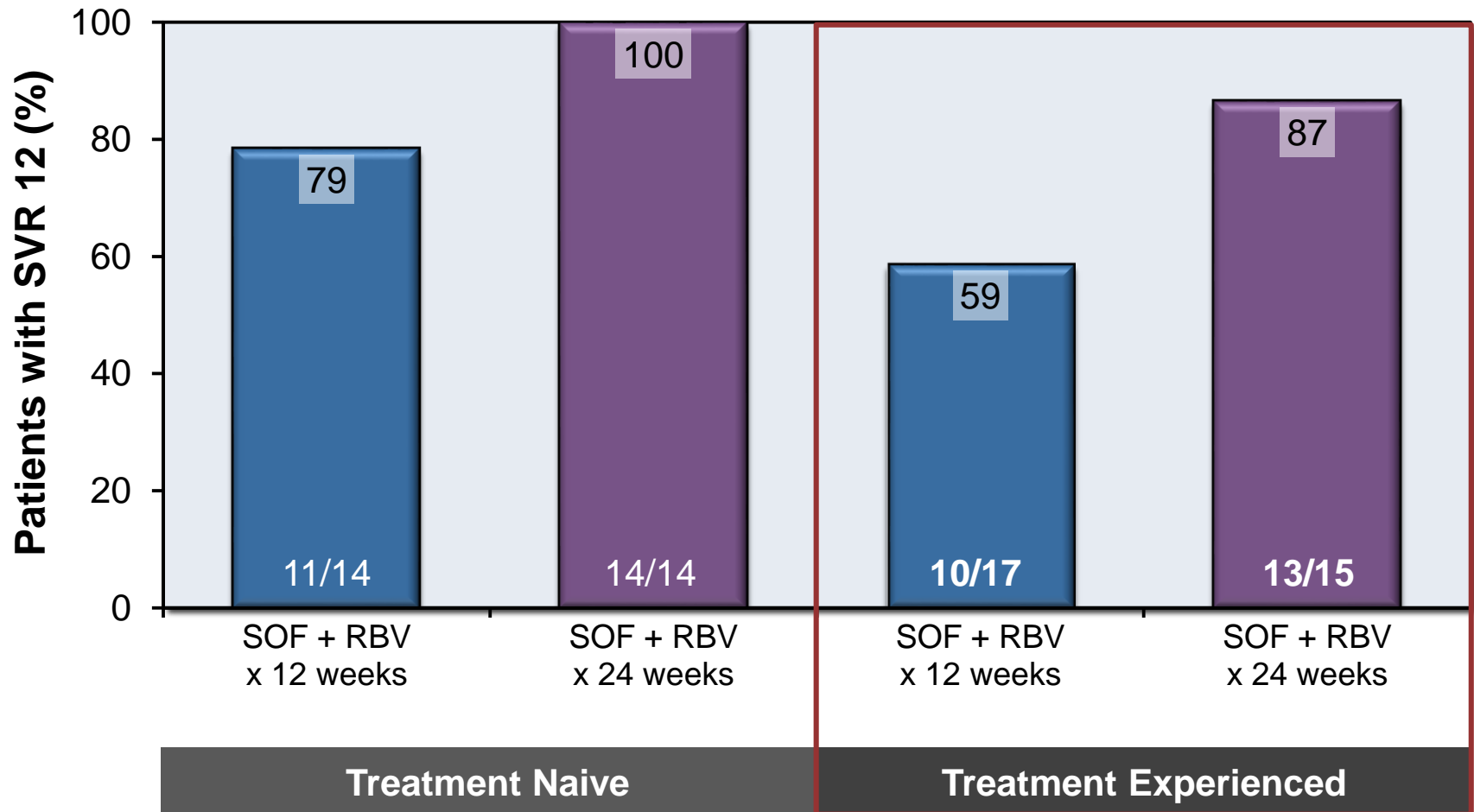
PEARL-I: SVR 12 Rates (HCV RNA <25 IU/mL)



OBV/PTV/r = Ombitasvir-Paritaprevir-Ritonavir; RBV = ribavirin

Sofosbuvir and Ribavirin in HCV Genotype 4 Egyptian Ancestry Trial: Results

SVR 12 by Regimen Duration and Treatment Experience



TREATMENT OF CHRONIC HEPATITIS C: GENOTYPE 4

Issues and Controversies

Issues and Controversies

- Cost of Therapy
 - ❖ What is real cost?
 - ❖ Cost per cure?
 - ❖ Discounts
- When to Defer or Decline Therapy
 - ❖ Decisions on when to warehouse if any?
 - ❖ Noncompliance
 - ❖ Short life span
- (Non) Role of IL-28b Testing
- Is the Degree of Liver Fibrosis useful to allocate treatment
 - ❖ How to stage?

How is cost of therapy impacting treatment decisions?

Hepatitis C Genotype 4

Costs of Different Regimens for Treatment of Genotype 4

Estimated Medication Cost for Treatment of Genotype 4 Chronic HCV

Regimen and Duration	AWAC Regimen Cost
Ledipasvir-Sofosbuvir x 12 weeks	\$94,500
Ombitasvir-Paritaprevir-Ritonavir + Ribavirin x 12 weeks	\$77,000
Sofosbuvir + Ribavirin x 24 weeks	\$169,000
Sofosbuvir + Ribavirin + Peginterferon x 12 weeks	\$97,000

AWAC = Average Wholesale Acquisition Cost

Note: health care systems may receive substantial discounts

Should one decline or defer therapy?

Factors Favoring Treat Now for all GT4

- 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: GENOTYPE 4

Future Treatment Options

Future Regimens for GT-4

- **Daclatasvir + Sofosbuvir**
 - Daclatasvir: NS5A replication inhibitor
 - Sofosbuvir: NS5B polymerase inhibitor
- **Sofosbuvir-Velpatasvir (GS-5816) Once Daily Fixed-Dose Combination**
 - Velpatasvir: NS5A replication inhibitor, second generation, pangenotypic
 - Sofosbuvir: NS5B polymerase inhibitor
 - ✧ **ASTRAL-1 Study¹: 116/116 (100%) with GT4 achieved SVR12**
- **Grazoprevir-Elbasvir Once Daily Fixed-Dose Combination:**
 - Grazoprevir: NS3/4A protease inhibitor
 - Elbasvir: NS5A replication inhibitor
 - ✧ **C-EDGE Study²: 16/16 (100%) with GT4 achieved SVR12**

¹Gilead Sciences

²Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.

Summary Points for Treatment of Chronic HCV GT-4

- HCV GT4 uncommon in US, but prevalent in Egypt, Saudi Arabia, North African, and southern Europe as well as immigrants from these regions to the US including Coptic population and horn of Africa (Sudan, Ethiopia, Somalia and Eritrea)
- For initial treatment of GT4 the recommended regimens are:
 - Ledipasvir-sofosbuvir x 12 weeks
 - Ombitasvir-paritaprevir-ritonavir + Ribavirin x 12 weeks
 - Sofosbuvir + Ribavirin x 24 weeks
- For retreatment of patients with GT4, the recommended regimens are the same as initial treatment with one additional regimen included:
 - Sofosbuvir + Ribavirin + Peginterferon x 12 weeks

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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