HEPATITIS C TREATMENT IN 2015

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Liver Disease & Hepatitis Program

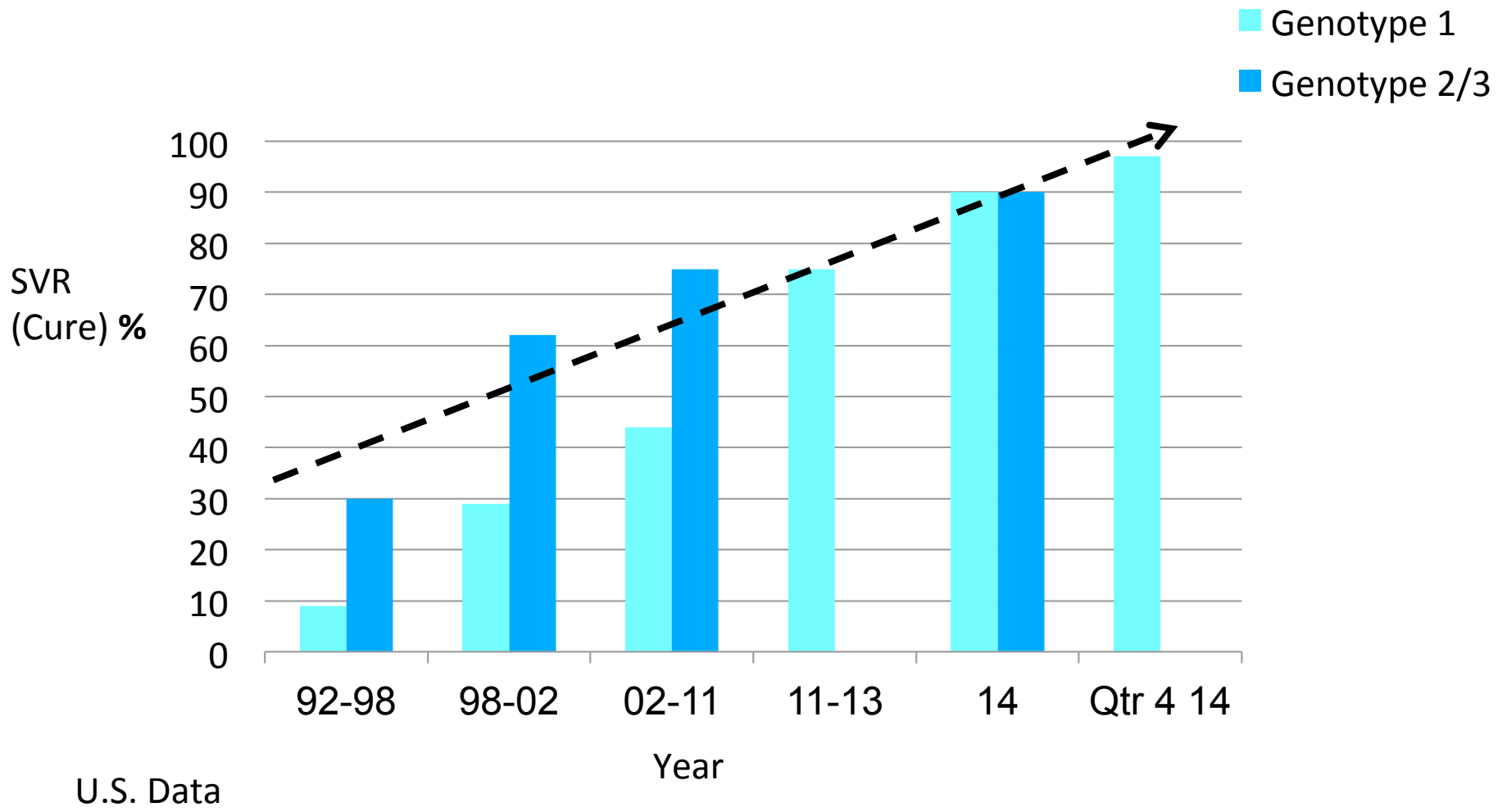
Disclosure

- The ANTHC Liver Disease & Hepatitis Program is conducting an investigator-sponsored observational study of Alaska Native/American Indian persons receiving sofosbuvir-based treatment for hepatitis C infection. This study is funded in-part by a contract with Gilead Sciences.

Objectives

- Recognize that hepatitis C treatment has improved
- Identify drugs used now to treat hepatitis C
- Recognize positive effect of sustained virologic response (SVR) on risk of liver transplant, hepatocellular carcinoma (HCC) and death
- Explain Fibroscan imaging and its role in non-invasive monitoring of liver fibrosis

History of Hepatitis C Treatment Response



U.S. Data

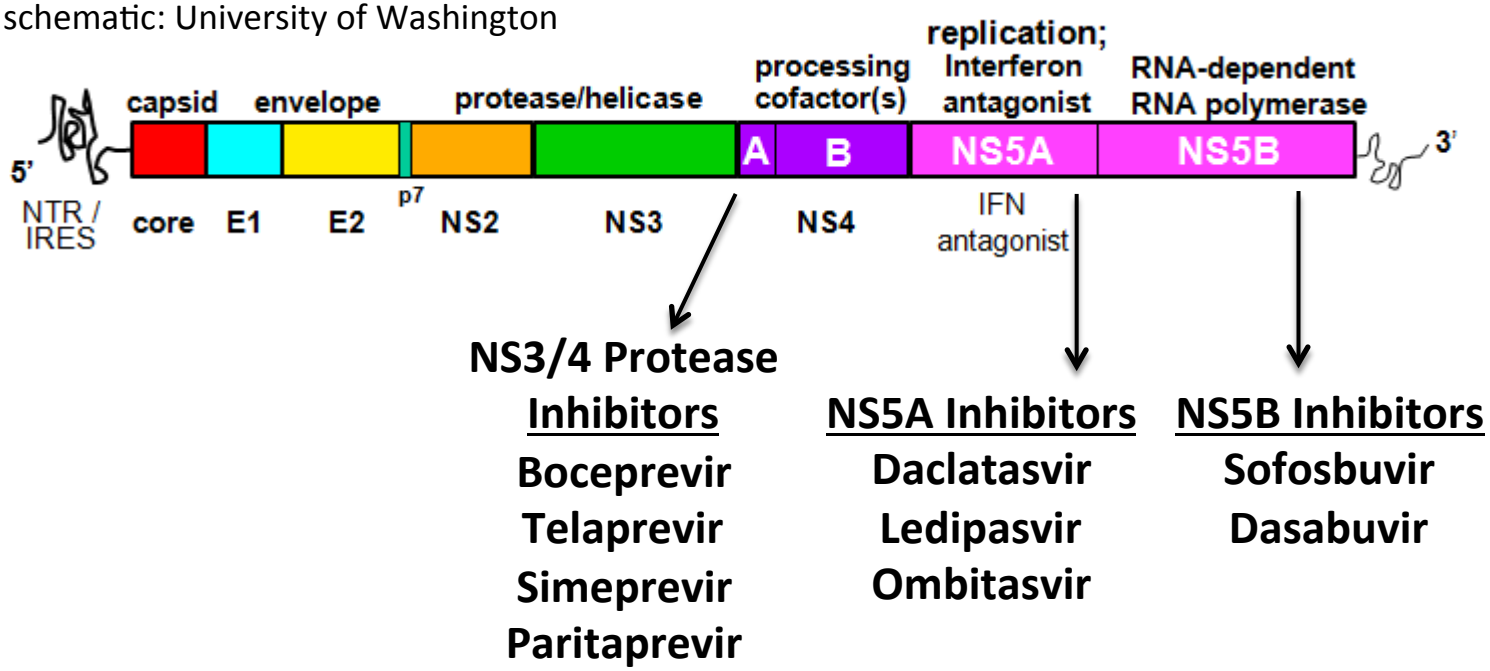
"This probably won't work, but we do have medications that will take care of the side effects."

Revolutionary changes started in 2013

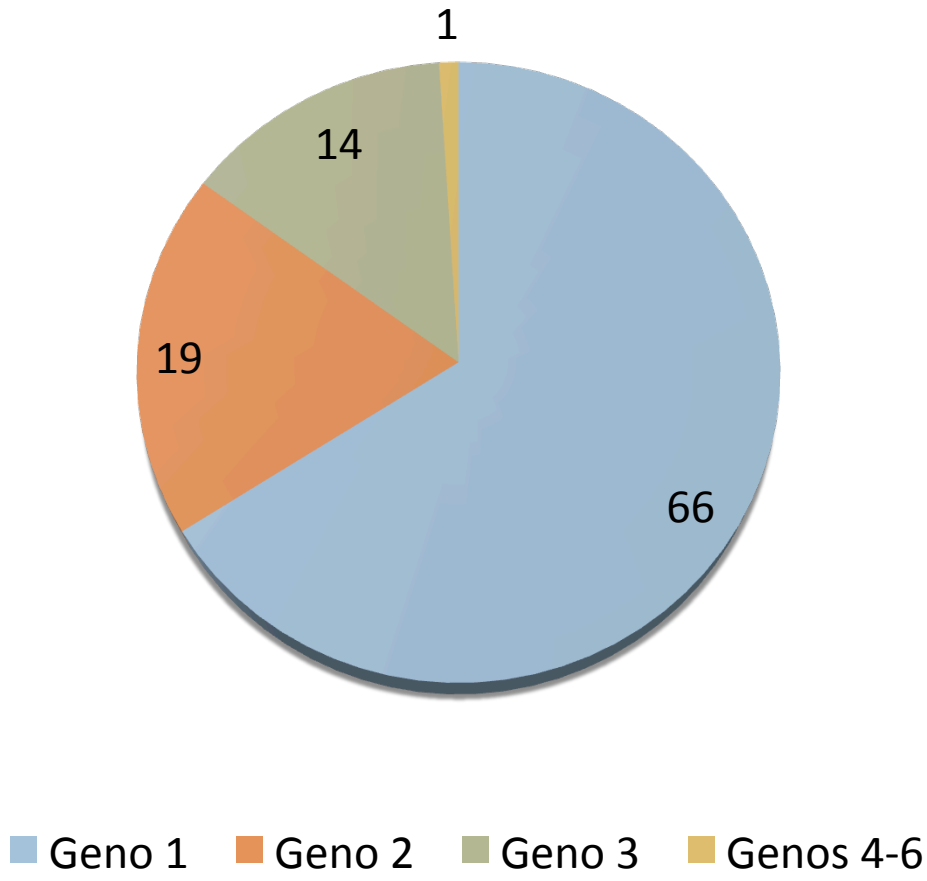
- Interferon-free
- Fewer side effects
- Shorter duration of treatment
- Higher cure rates

Where Direct Acting Anti-Virals (DAAs) Target the Hepatitis C Virus

Virus schematic: University of Washington



Genotypes



Treatment Options Genotype 1: Direct Acting Anti-viral Combinations

Ledipasvir/Sofosbuvir (Harvoni®)

- Ledipasvir (LDV) 90mg
  - NS5A inhibitor
  - Antiviral activity against HCV GT 1a and 1b
- Sofosbuvir (SOF) 400mg
  - NS5B polymerase inhibitor
  - Potent antiviral activity against HCV GT 1-6

Side effects: fatigue and headache

Ledipasvir/Sofosbuvir (Harvoni®) for Genotype 1

- Minimal side effects
- Pregnancy Category B
- Take with or without food
- Interactions with acid-suppressing medications
- Do not take with St. John's wort or rifampin
- Safe for mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, or C)
- Safe for mild to moderate renal impairment (GFR ≥ 30)
- Manufacturer's price $94,500 for 12 week treatment

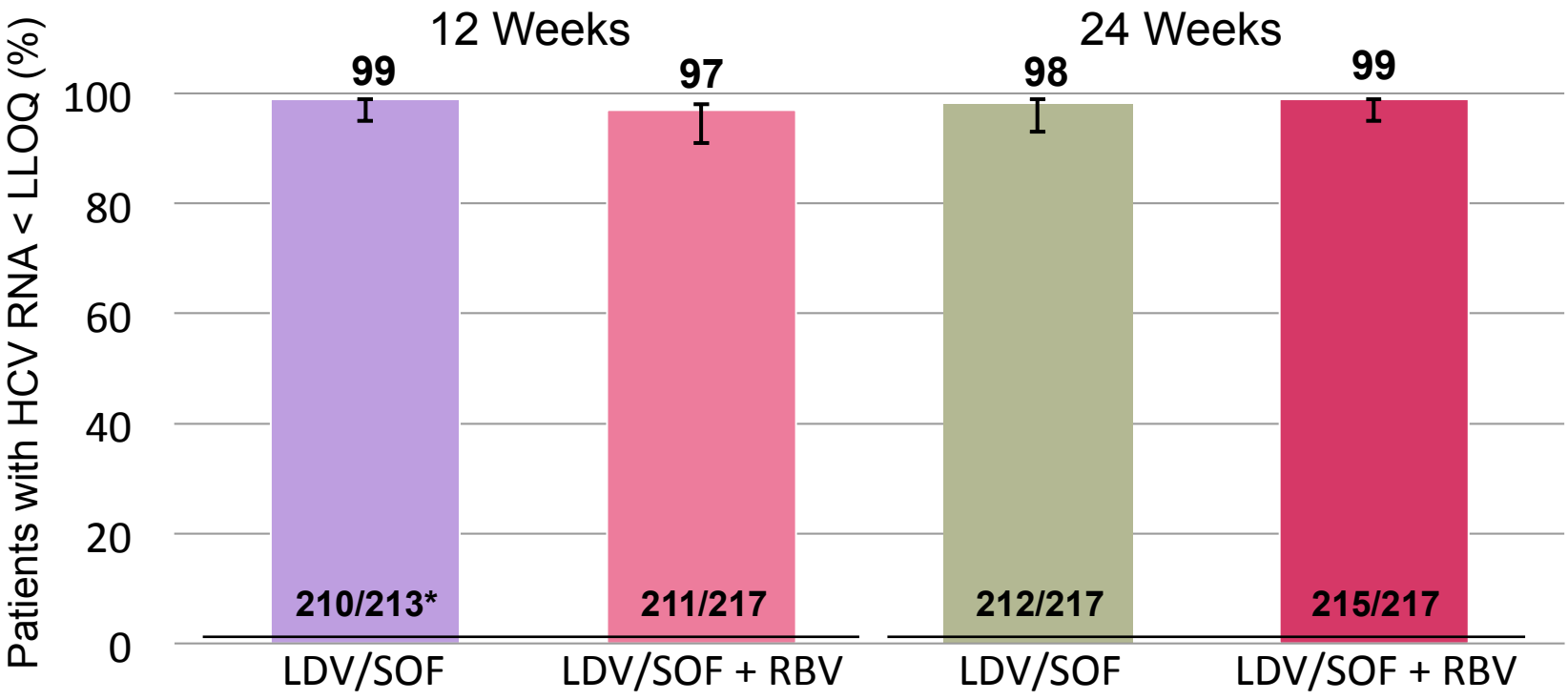
FDA Indications
Ledipasvir/Sofosbuvir (Harvoni®)

Patient Population	Recommended Treatment Duration
Treatment-naïve with or without cirrhosis	12 weeks*
Treatment-experienced without cirrhosis	12 weeks
Treatment-experienced with cirrhosis	24 weeks

* 8 weeks can be considered in treatment-naive patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL

LDV/SOF Overall Results

ION-1 (GT 1, Treatment-Naive, LDV/SOF±RBV x 12 or 24 weeks)

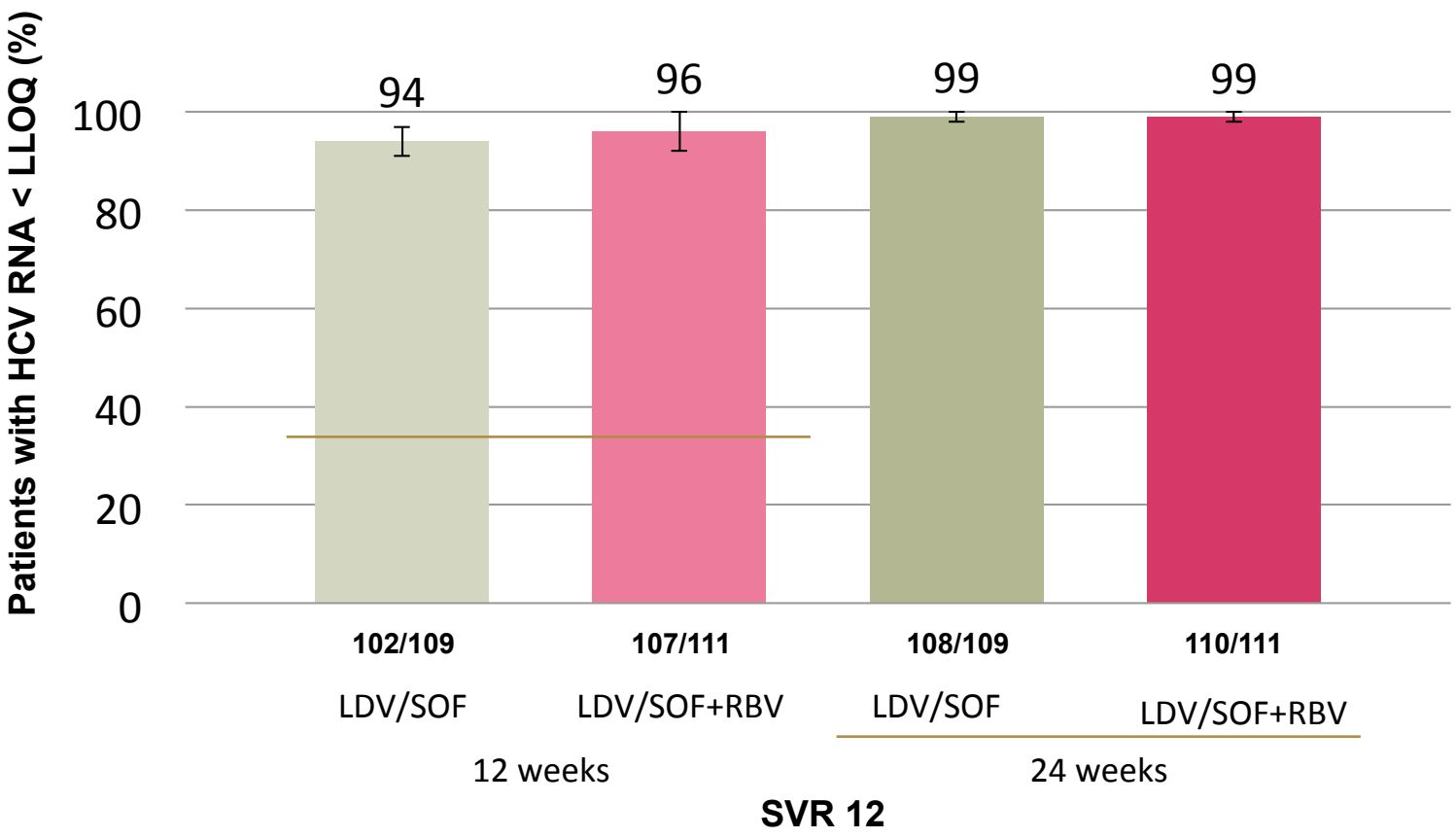


*excluding one subject with genotype 4 infection
Error bars represent 95% confidence intervals.

Afdhal N, et al. *N Engl J Med* 2014; 370:1889-98. Data on File, Gilead Sciences, Inc.

LDV/SOF Overall Results

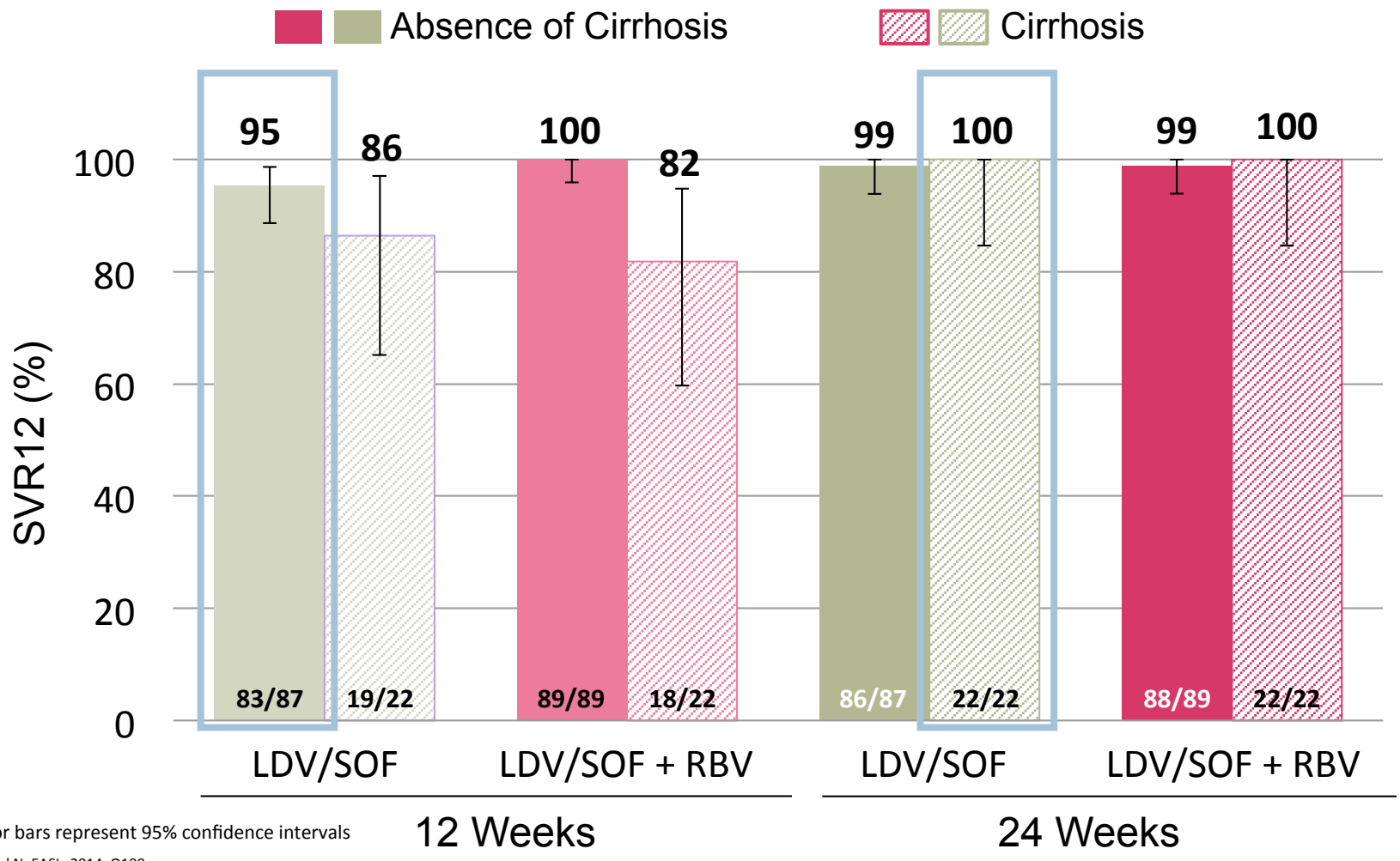
ION-2 (GT 1, Treatment-Experienced, LDV/SOF±RBV x 12 or 24 weeks)



Afdhal N, EASL, 2014, O109
Afdhal N, et al. *N Engl J Med* 2014;370:1483-1493

SVR12: No Cirrhosis vs. Cirrhosis

ION-2 (GT 1, Treatment-Experienced, LDV/SOF±RBV x 12 or 24 weeks)

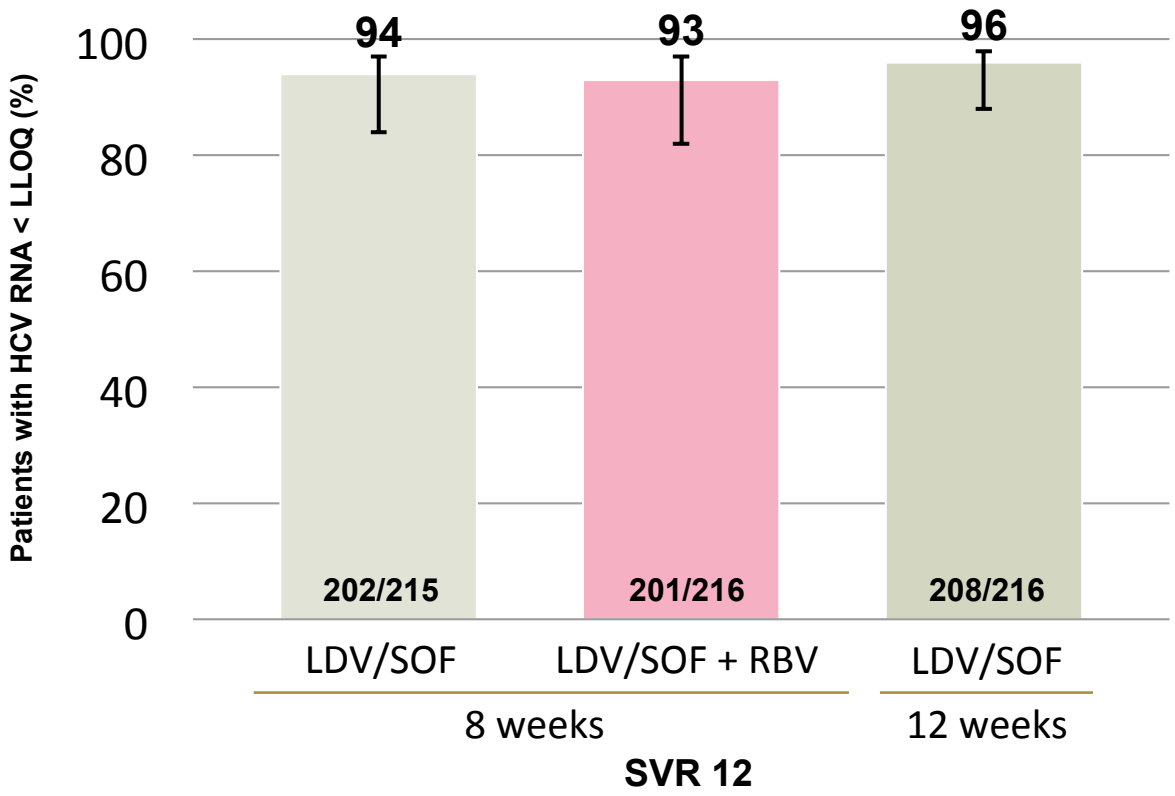


Error bars represent 95% confidence intervals

Afdhal N, EASL, 2014, O109
Afdhal N, et al. *N Engl J Med* 2014;370:1483-1493

LDV/SOF Treatment Duration

ION-3 (GT 1, Treatment-Naive, Non-Cirrhotic, LDV/SOF±RBV x 8 or 12 weeks)

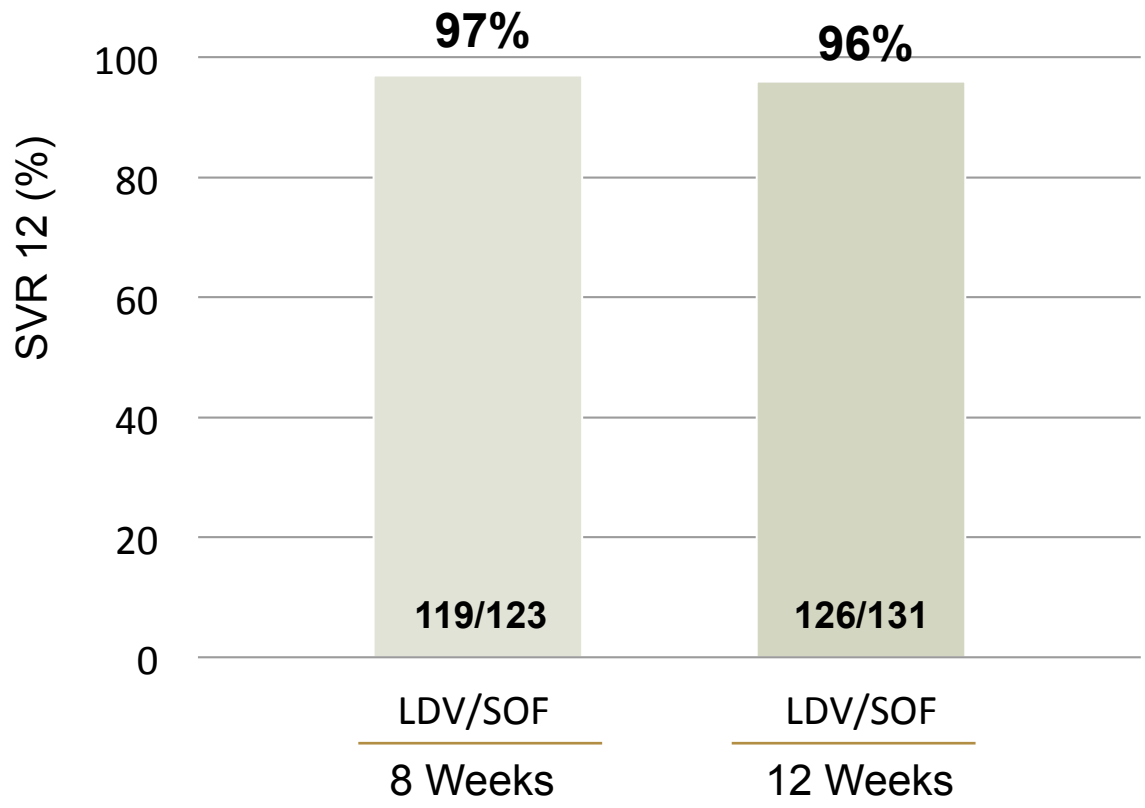


Error bars represent 95% confidence intervals

Kowdley K, et al. *N Engl J Med* 2014;370:1879-1888
Data on File, Gilead Sciences, Inc. Data on File, Gilead Sciences, Inc.

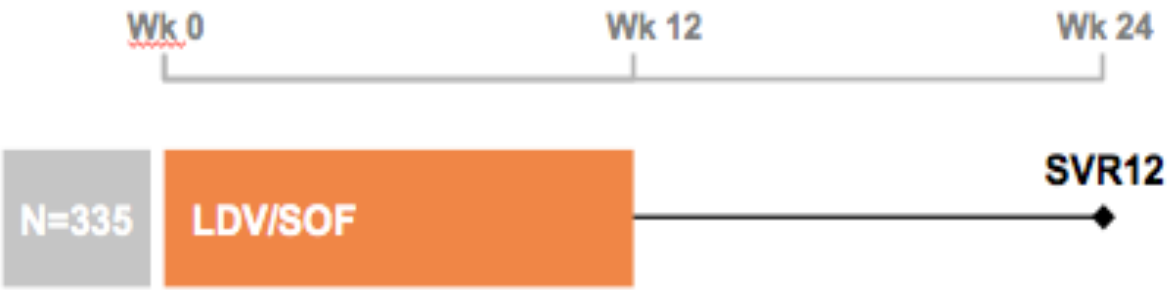
Baseline HCV RNA < 6 Million IU/mL

ION-3 (GT 1, Treatment-Naive, Non-Cirrhotic, LDV/SOF±RBV x 8 or 12 weeks)



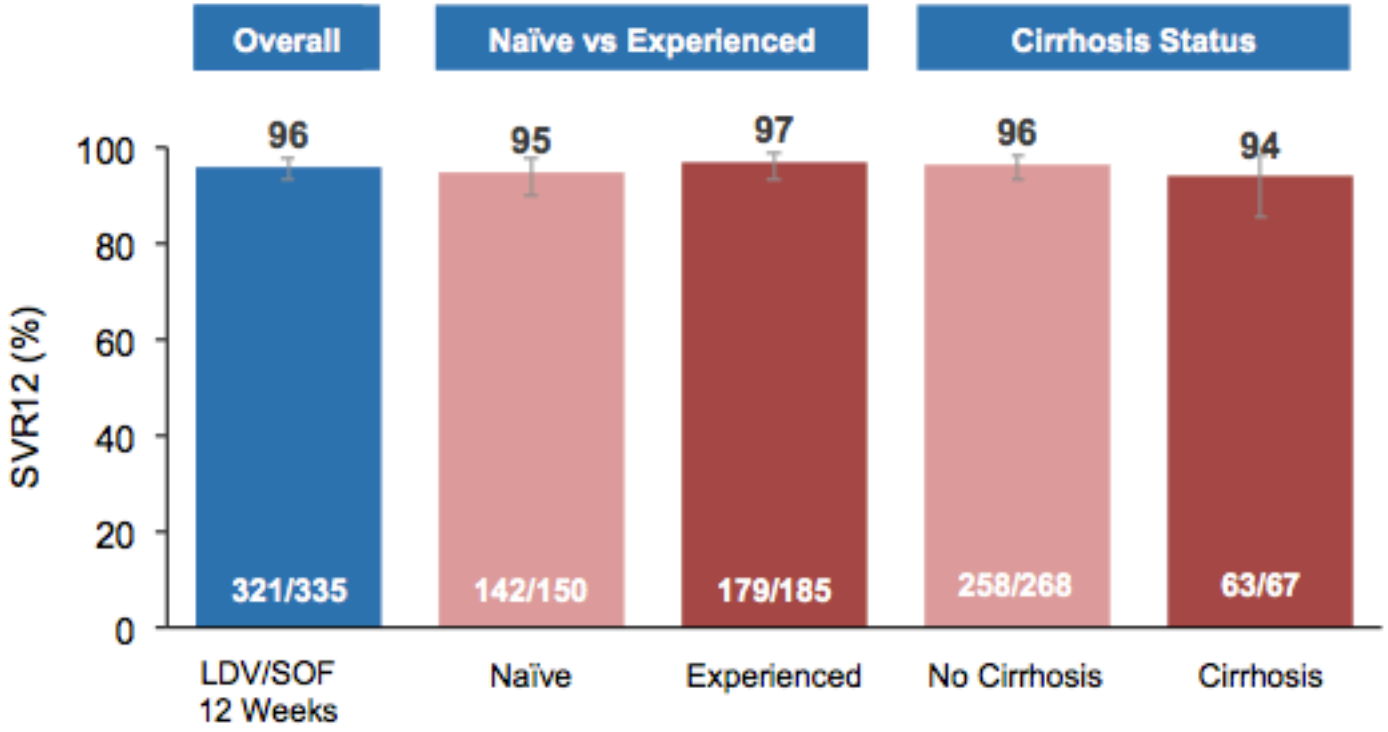
Data on File, Gilead Sciences, Inc.

Harvoni HIV/HCV ION-4 Study Design



- Phase 3, multicenter, open-label study (NCT02073656)
- HCV GT 1 or 4 patients in US, Canada, and New Zealand
- Broad inclusion criteria
  - HCV treatment-naïve or treatment-experienced
  - 20% with compensated cirrhosis
  - Platelets ≥50,000/mm^3; hemoglobin ≥10 mg/dL, CrCl ≥60 mL/min
  - HIV-1 positive, HIV RNA <50 copies/mL; CD4 cell count >100 cells/mm^3
- ART regimens included emtricitabine and tenofovir disoproxil fumarate plus efavirenz, raltegravir, or rilpivirine

Harvoni® HIV/HCV ION-4 Study SVR 12 Results

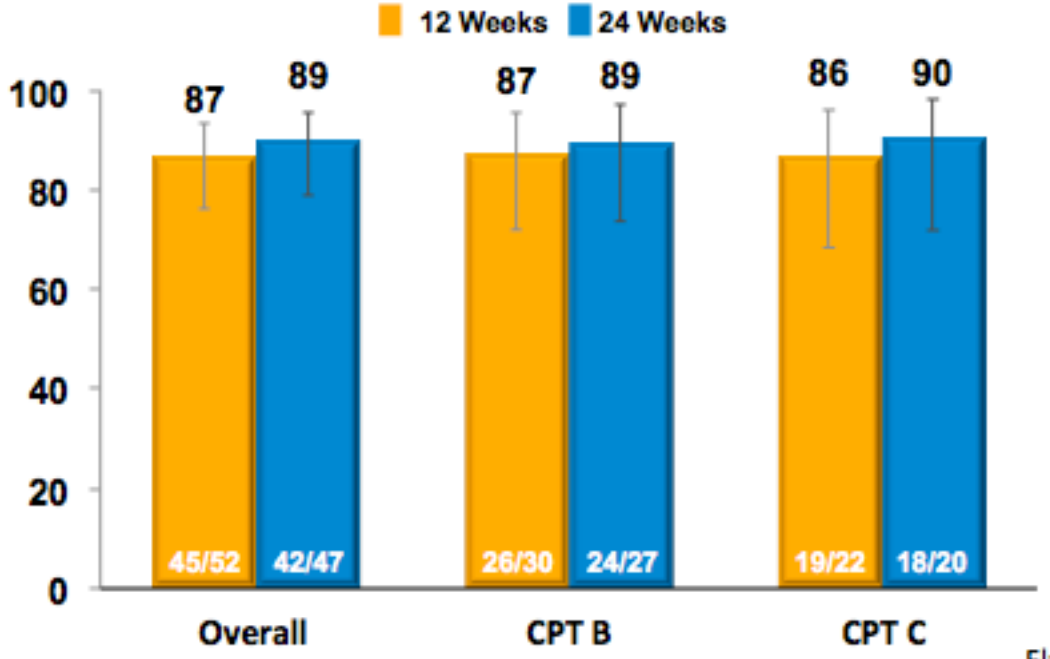


Error bars represent 95% confidence intervals.

Treatment of Persons with Decompensated Cirrhosis

Ledipasvir/Sofosbuvir + RBV in Patients with Decompensated Cirrhosis: Preliminary Results of a Prospective, Multicenter Study

- Randomized to SOF + LDV + RBV (600 mg w/escalation) for 12 or 24 weeks
- Patients with GT 1 or 4 and decompensated cirrhosis
  - Most patients with MELD > 10 (MELD= 16-20 in 10-46%)
  - Median Albumin= 2.6- 3.0 g/L; Median platelets = 71-88 K

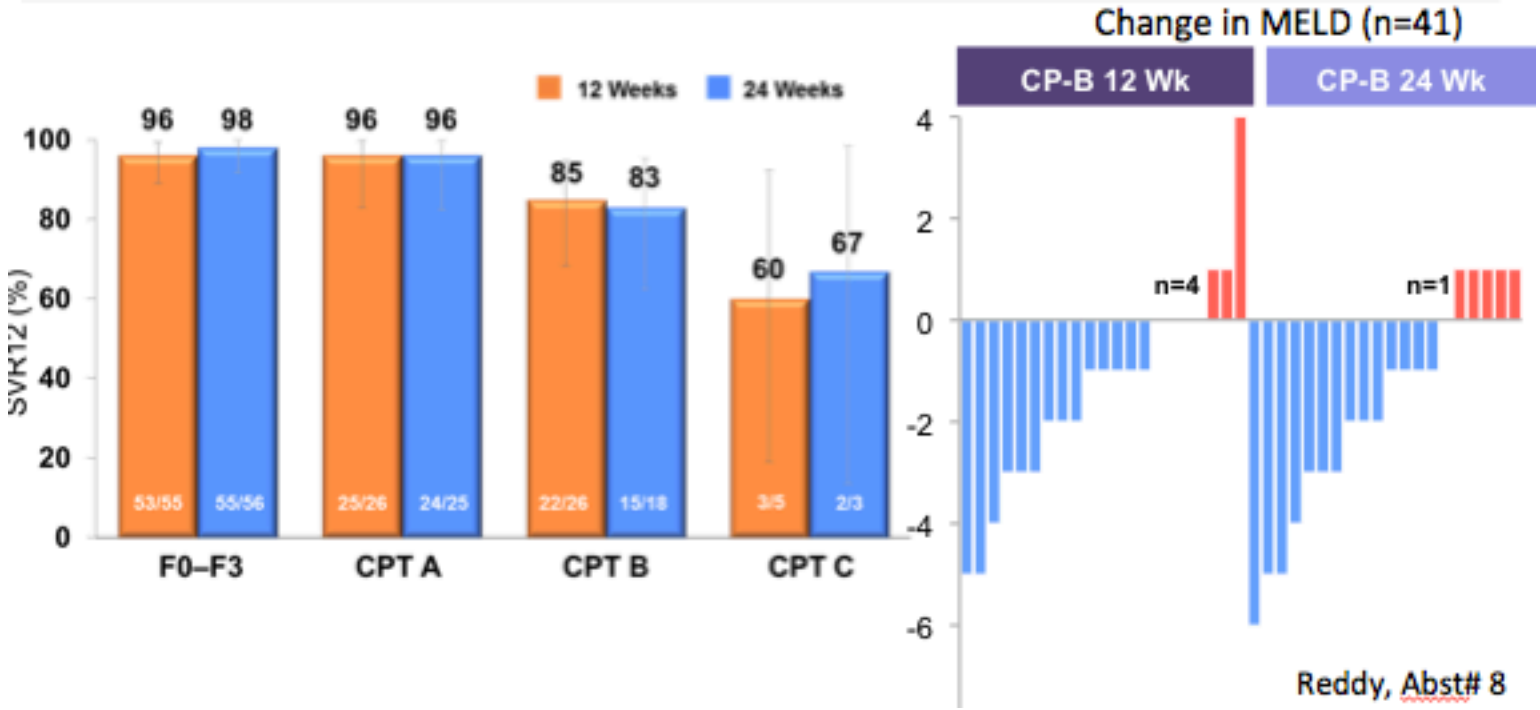


Flamm, Abst# 239

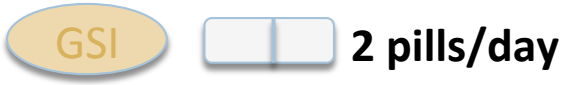
…and Post-Transplant

Ledipasvir/Sofosbuvir + RBV in Patients with in Patients With Post-Transplant Recurrence: Preliminary Results of a Multicenter Study

- **Randomized to SOF + LDV + RBV (600 mg w/escalation) for 12 or 24 weeks**
- **Post-transplant patients with GT 1 or 4, Included F0-F3 and cirrhotics**
  - **Most cirrhotic patients with MELD > 10 (60%),**
  - **Median platelets=79-108K, Median albumin= 2.4-3.7 g/dl**
- **Improvements in MELD, bilirubin, and albumin noted**



Simeprevir/Sofosbuvir for Genotype 1



- Simeprevir (Olysio®)
  - NS3/4A protease inhibitor
  - Multiple potentially significant drug interactions
- Sofosbuvir (Sovaldi®)
  - NS5B polymerase inhibitor
- Approved by FDA for combination use in November 2014
- Combined manufacturers' price > $150,000 for 12 weeks

Side Effects: Photosensitivity, rash, fatigue, headache, nausea, insomnia, pruritis, dizziness, diarrhea

FDA Indications Simeprevir/Sofosbuvir

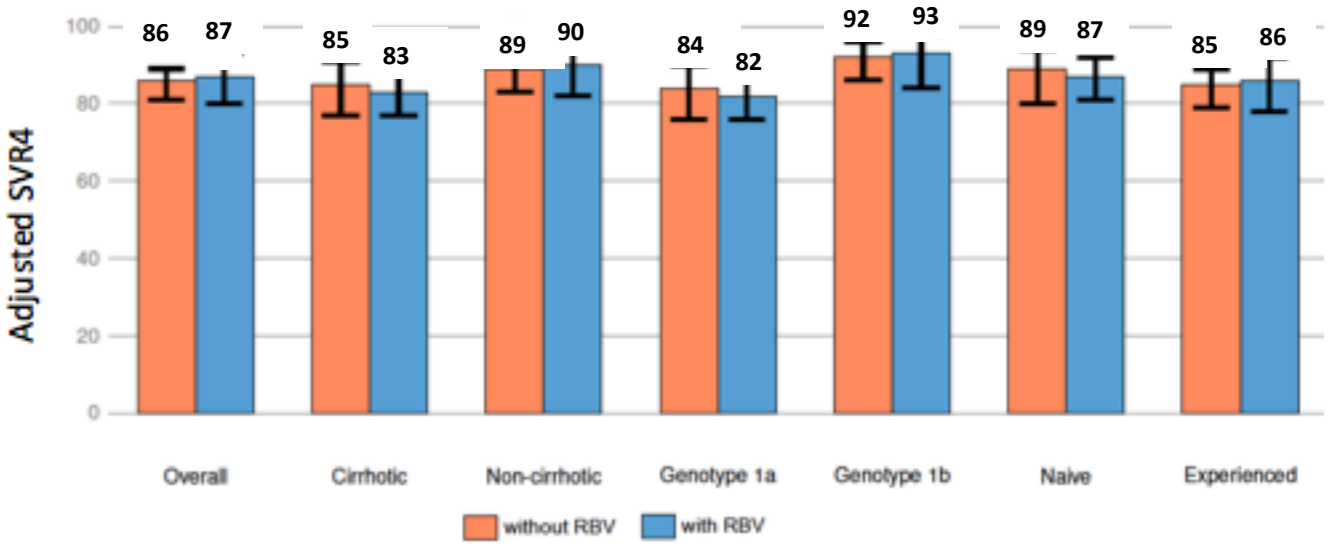
Patient Population	Treatment duration
Genotype 1a & 1b without cirrhosis*	12 weeks
Genotype 1a & 1b with cirrhosis*	24 weeks

* Includes treatment-naïve and treatment experienced

Simeprevir and Sofosbuvir

Safety and Efficacy of Sofosbuvir-Containing Regimens for Hepatitis C: Real-World Experience in a Diverse, Longitudinal Observational Cohort

- HCV-TARGET cohort: Medical records centrally abstracted for safety and efficacy data
- 51 enrolling sites (38 Academic and 13 Community practices)
- High rate of SOF/SMV use, Well-tolerated; 2.3% discontinued due to AE
- SVR 4 (adjusted for baseline factors) similar SVR +/- RBV
- Negative predictors of SVR4: Prior triple therapy failure, Geno 1a, Prior decompensation



Jensen, Abst# 45; Sulkowski, Abst# 955

Viekira Pak®
(Ombitasvir/Parataprevir/Ritonavir plus Dasabuvir)

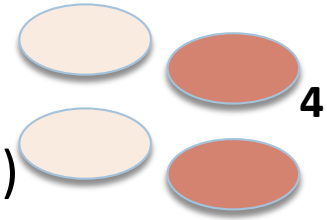
- Ombitasvir
  - NS5A inhibitor
- Paritaprevir
  - NS3/4A protease inhibitor
- Ritonavir
  - CYP3A inhibitor (boosts protease inhibitor)
- Dasabuvir
  - NS5B palm polymerase inhibitor

Side effects: nausea, pruritus, insomnia (without ribavirin) and fatigue, nausea, pruritus, rash, insomnia and asthenia (with ribavirin)

FDA Indications Viekira Pak®

Patient Population	Treatment	Duration
Genotype 1a without cirrhosis	Viekira Pak + ribavirin	12 weeks
Genotype 1a, with cirrhosis	Viekira Pak + ribavirin	24 weeks
Genotype 1b, without cirrhosis	Viekira Pak	12 weeks
Genotype 1b, with cirrhosis	Viekira Pak + ribavirin	12 weeks

Viekira Pak® +/- Ribavirin for Genotype 1



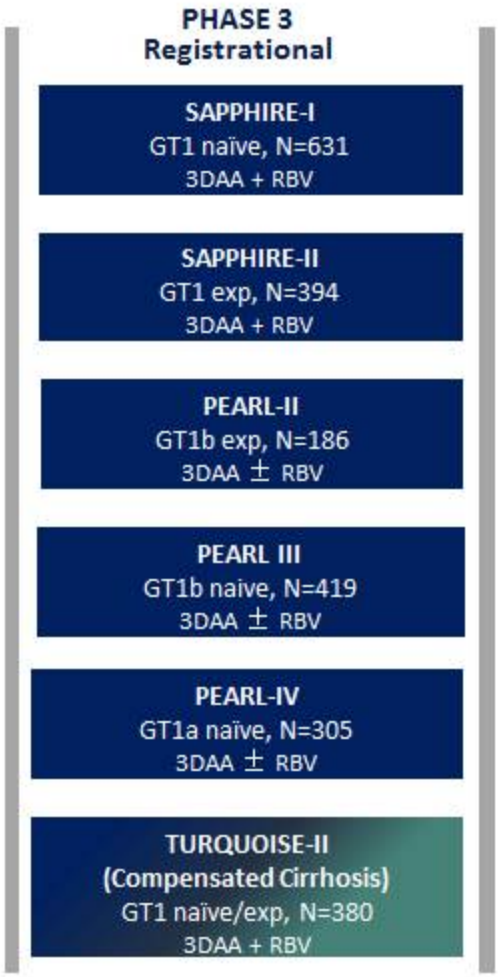
4 -10 pills/day

- 4 pills/day without ribavirin
- Additional 5-6 pills with ribavirin (weight-based)
- Pregnancy Category B without ribavirin
- Take with food
- Many drugs contraindicated with Viekira Pak
- Additional drugs interact with and require dose changes when coadministered with Viekira pak
- Not recommended in moderate cirrhosis (Child Pugh B)
- Contraindicated in severe cirrhosis (Child Pugh C)
- Safe for mild, moderate or severe renal impairment (without ribavirin)
- Manufacturer's price $83,319 for 12 weeks

Ribavirin

- Anti-viral medication for HCV since 1998
- Exact mechanism of action unknown
- Pregnancy category X
- Must use birth control during treatment and for 6 months after treatment
- Adds 5 – 6 pills/day to treatment
- Dose reduction required for CrCl < 50
- Causes hemolytic anemia
- S/Es: fatigue, headaches, arthralgias, insomnia, alopecia, nausea/vomiting, diarrhea, anorexia, pruritus, cough, thrombocytopenia and neutropenia
- Manufacturer's price $3000-$4000/12 weeks

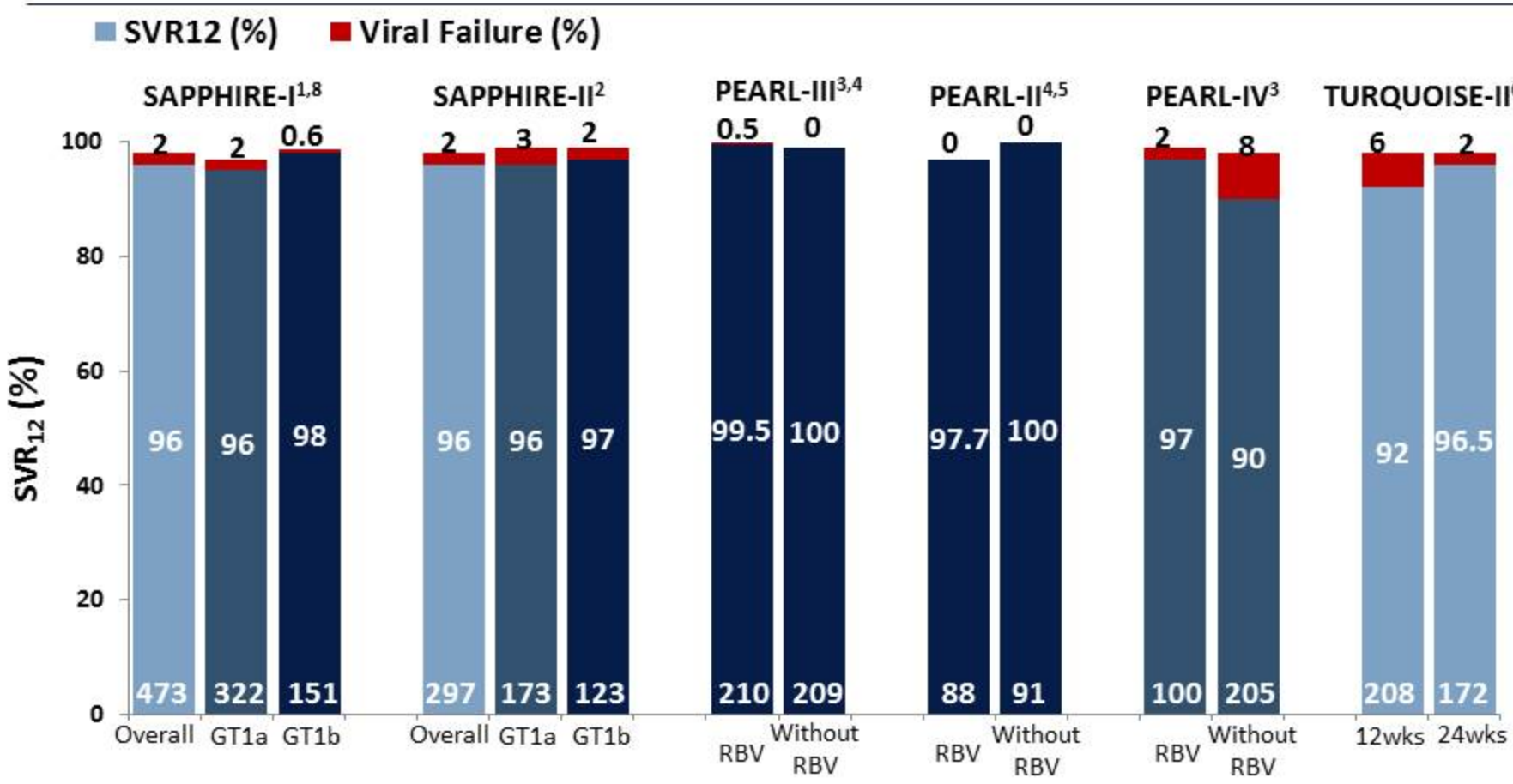
Viekira Pak Phase 3 Program—Registrational Trials



Abbreviations: 3DAA, OBV/PTV/r +DSV; DAA, Direct Acting Antivirals; DSV, dasabuvir; Exp, PegIFN/RBV experienced; GT, genotype; OBV, ombitasvir; PTV, paritaprevir; PegIFN, pegylated interferon; r, ritonavir; RBV, ribavirin.

Reference: www.clinicaltrials.gov

Viekira Pak Phase 3 Program—Registrational Trials
Summary of Results



Cirrhosis	✗	✗	✗	✗	✗	✓ ✓
Treatment	Naive	Experienced	Naive	Experienced	Naive	Naïve / experienced
Subtype	GT1a/b	GT1a/b	GT1b	GT1b	GT1a	GT1a/b

* The side-by-side graphs are to simplify presentation; direct comparison across trials should not be made due to differing trial designs.

1.Feld J, *et al. NEJM* 2014; 2. Zeuzem S, *et al. NEJM;* 2014;
3. Ferenci P, *et al. NEJM* 2014; . 4. Bernstein D, *et al.* UEGW 2014. P0048;
5.Andreone, *et al.* Gastro 2014; 6. Poordad F, *et al. NEJM* 2014;.
7. Wedemeyer H, *et al.* UEGW 2014. P0625; 8. Feld J, *et al.* ID Week 2014

Genotype 2 and 3 Treatment

FDA Approved Treatment for Genotypes 2 and 3: Sofosbuvir (Sovaldi) + Ribavirin

Sofosbuvir

- NS5B Inhibitor
- Approved by the FDA in Dec 2013

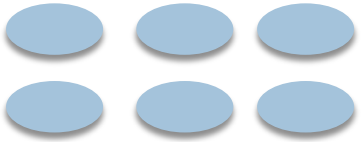
Ribavirin

- Anti-viral used in HCV treatment since 1998
- Pregnancy category X

Side effects: fatigue, headache, insomnia, loss of appetite, anemia

Sofosbuvir (Sovaldi®) and Ribavirin

1 sofosbuvir/day + 5-6 ribavirin/day

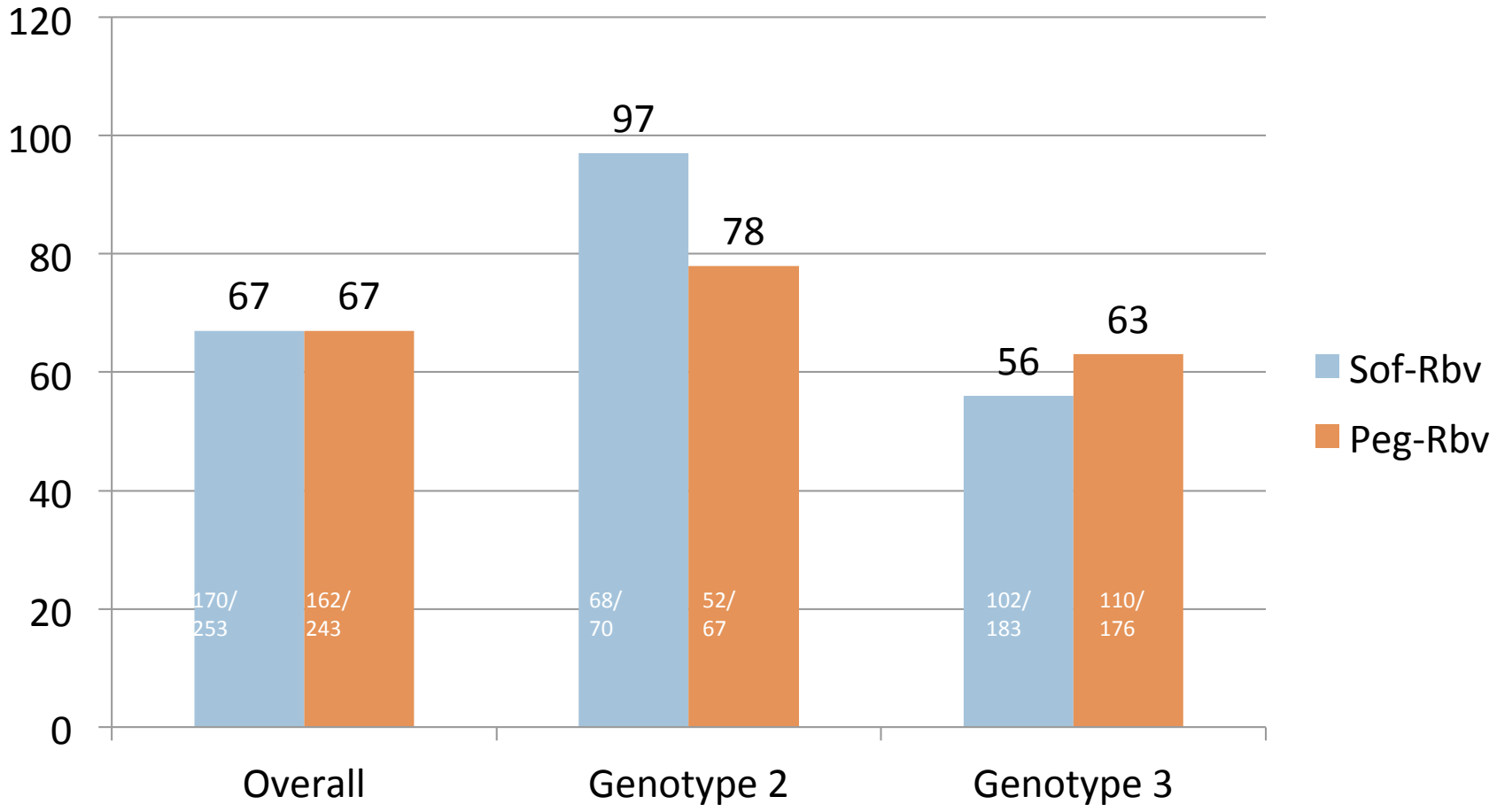


- Sofosbuvir can be taken with or without food
- Ribavirin should be taken BID with food
- Must use birth control during treatment and for 6 months after treatment

FDA Indications Genotypes 2 & 3

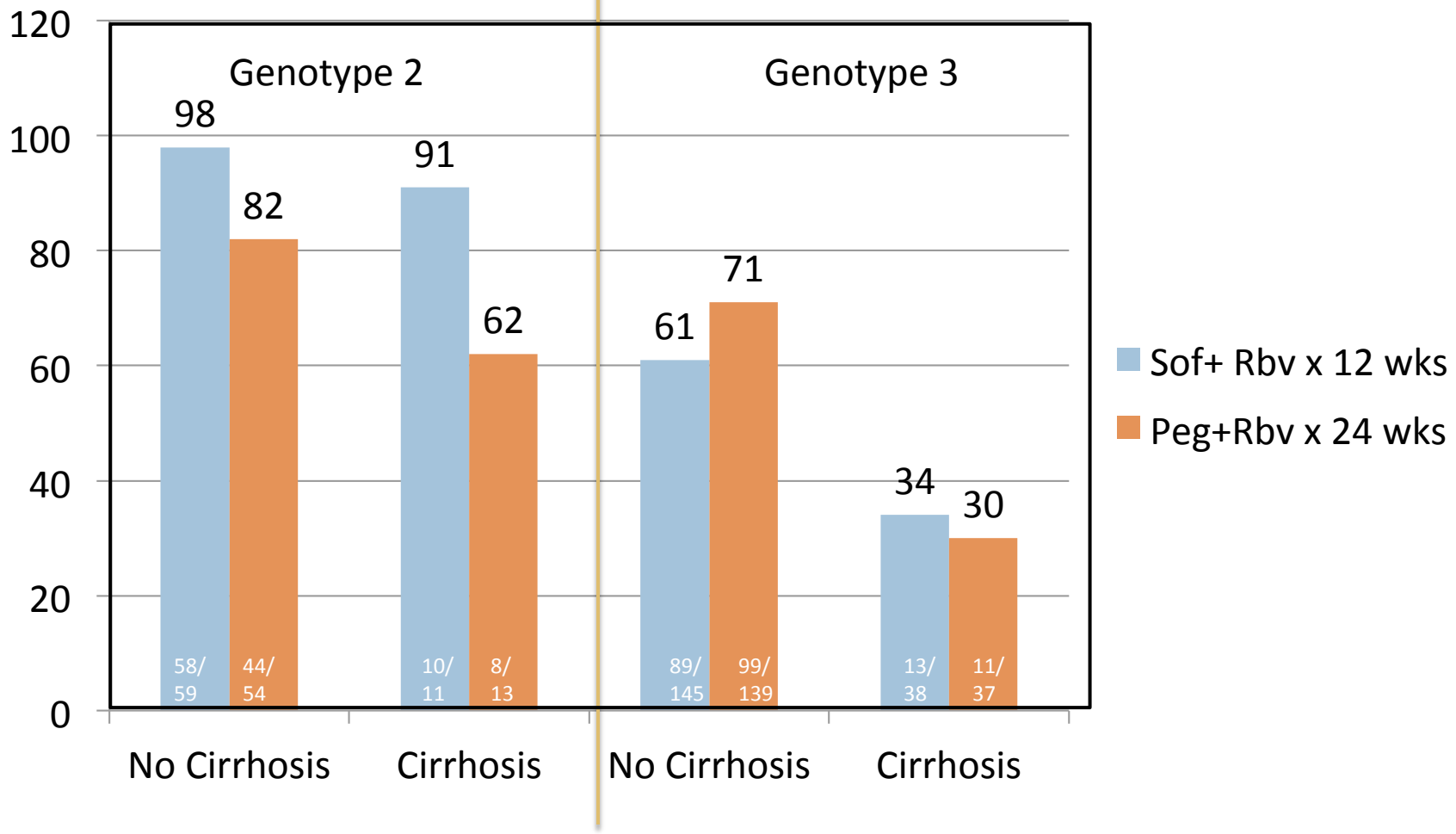
HCV and HCV/ HIV Co-Infection	Treatment	Duration
Genotype 2	Sofosbuvir (Sof) + Ribavirin (Rib)	12 weeks
Genotype 3	Sof + Rib	24 weeks

FISSION SVR 12 Results
Sofosbuvir + Ribavirin x 12 weeks
Treatment-Naive



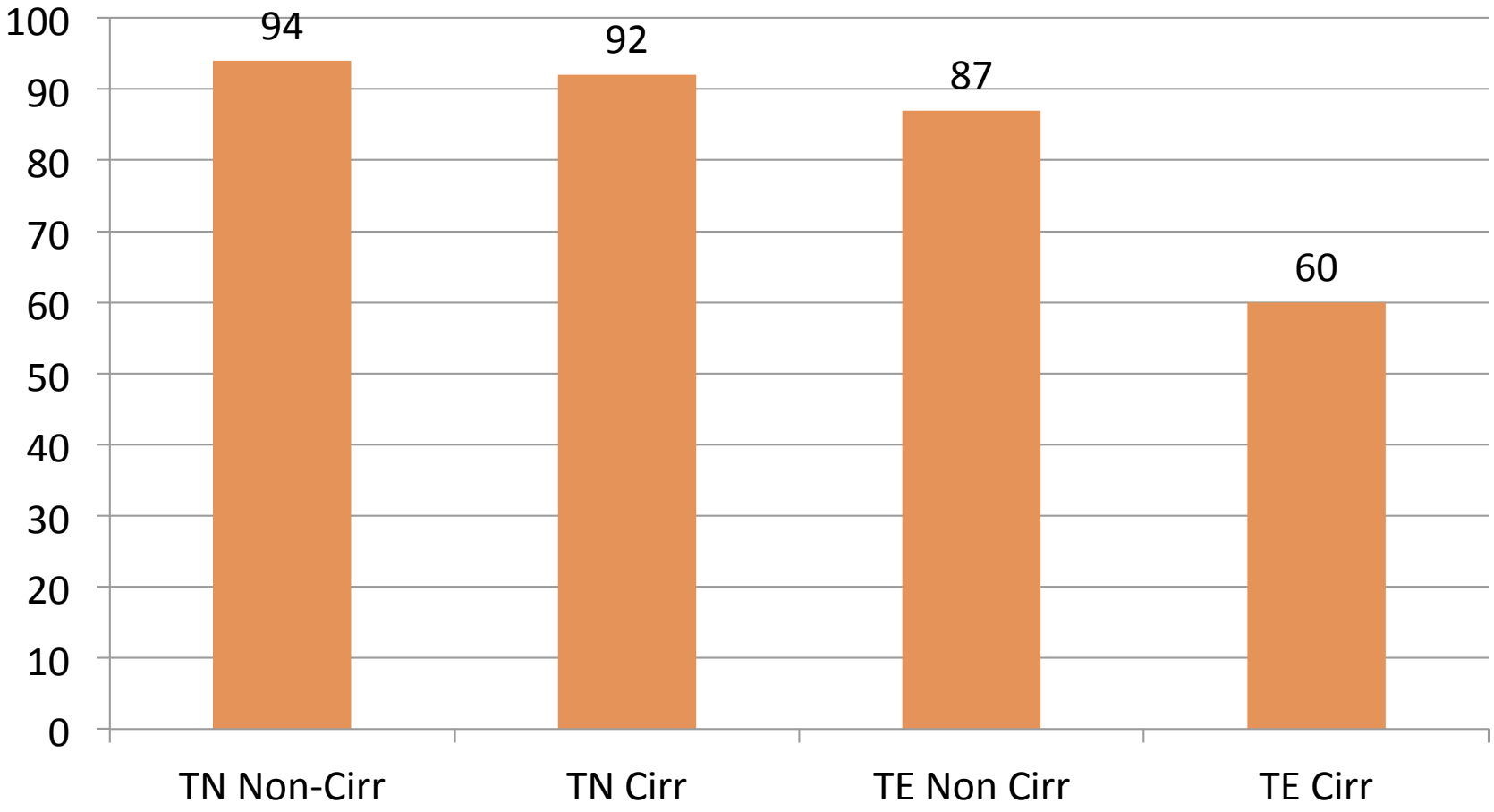
Lawitz, E. et al. NEJM; April 23, 2013

FISSION - SVR12 for Genotype 2 & 3 Cirrhosis vs. Non-Cirrhosis



Gane E, et al. EASL 2013. Amsterdam, The Netherlands. Oral #5

Valence SVR Results: Genotype 3 Sofosbuvir + Ribavirin x 24 weeks



Alternative Treatment for Genotype 3

Genotype	Treatment/ Duration	SVR
3	Sof + Peginterferon (Peg) + Rib x 12 weeks	97% TN (38/39)

New treatment of daclatasvir + sofosbuvir for genotype 3 expected to be FDA approved by mid 2015.

Benefits of Hepatitis C Treatment

- Sustained virologic response (SVR) results in a 90% reduction in cirrhosis and 70% reduction in liver cancer [1,2,3]

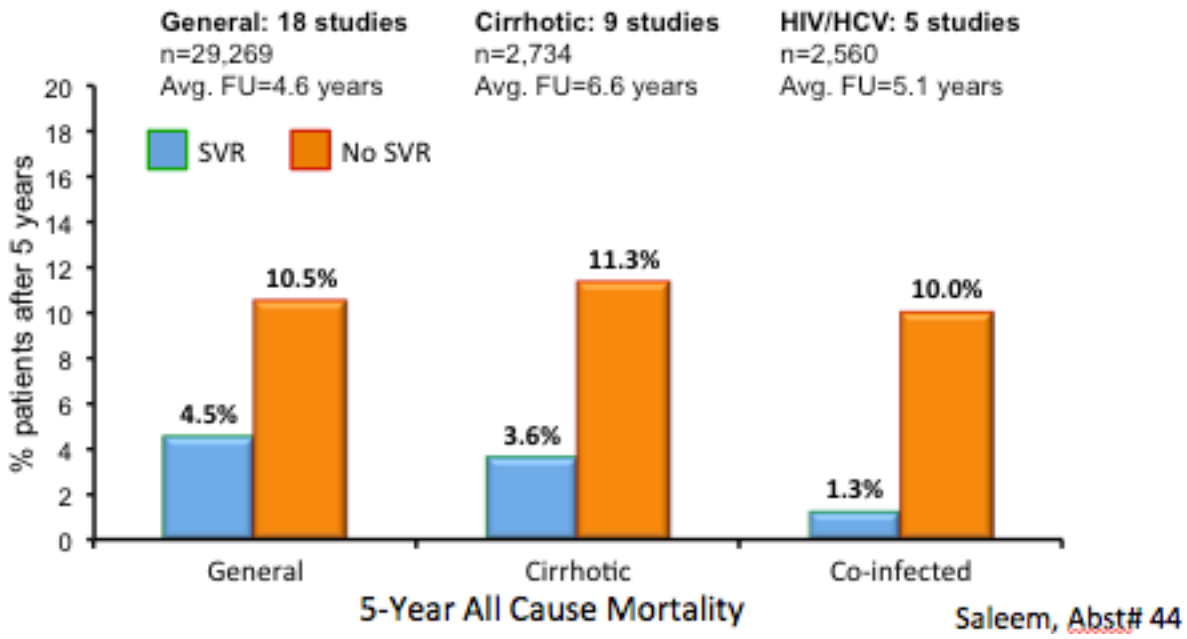
[1]Morgan, RL, et al. Ann Intern Med. 2013;158 (5 Pt 1):329-337.

[2]van der Meer, et al. JAMA. 2012;308(24):2584-2593.

[3]Veldt, BJ et al. Ann Intern Med. 2007;147(10):677-684.

Effect of SVR on Risk of Liver Transplant, HCC, and Death

- **Meta-analysis of 129 studies w/over 23,000 patients**
- **Estimated relative reductions in risk of liver transplant, HCC, all-cause mortality for SVR vs non-SVR after antiviral therapy**
- **RR substantially reduced for all groups with SVR**



Saleem, Abst# 44

Hepatitis C Treatment Coverage in AK

Medicare Part D
Pharmacy carriers have different drug formularies, Requires prior authorization

Private Insurance
Most require prior authorization
Some only cover F3-F4 fibrosis

AK Marketplace Insurance Plans
Moda, Premera

Cover *F3-F4 Fibrosis Only

AK Medicaid
Requires drug testing
Covers *F3-F4 fibrosis only
Viekira Pak (no CP B or C** cirrhosis)

VA
Is covering treatment. Has treatment criteria.

Uninsured
Apply to Patient Assistance Programs (See next slides)

*F3-F4 Fibrosis = Advanced fibrosis of the liver (bridging fibrosis or cirrhosis)
**CP B or C = Child Pugh classification of moderate or severe cirrhosis

Pharmaceutical Supported Patient Assistance Programs

Gilead Support Path 1-855-769-7284

http://www.mysupportpath.com

Abbvie ProCeed 1-844-277-6233

https://www.viekira.com/proceed-program

Janssen 1-855-565-9746

http://www.janssenprescriptionassistance.com/olysio-cost-assistance

Moderiba (Ribavirin) 1-844-663-3742

http://www.moderiba.com/patient-support/financial

Other Patient Assistance Programs

Partnership for Prescription Assistance 1-888-477-2669

www.pparx.org

Patient Access Network Foundation 1-866-316-7263

www.panfoundation.org

Chronic Disease Fund 1-877-968-7233

www.cdfund.org

Needymeds.org 1-800-503-6897

www.needymeds.org

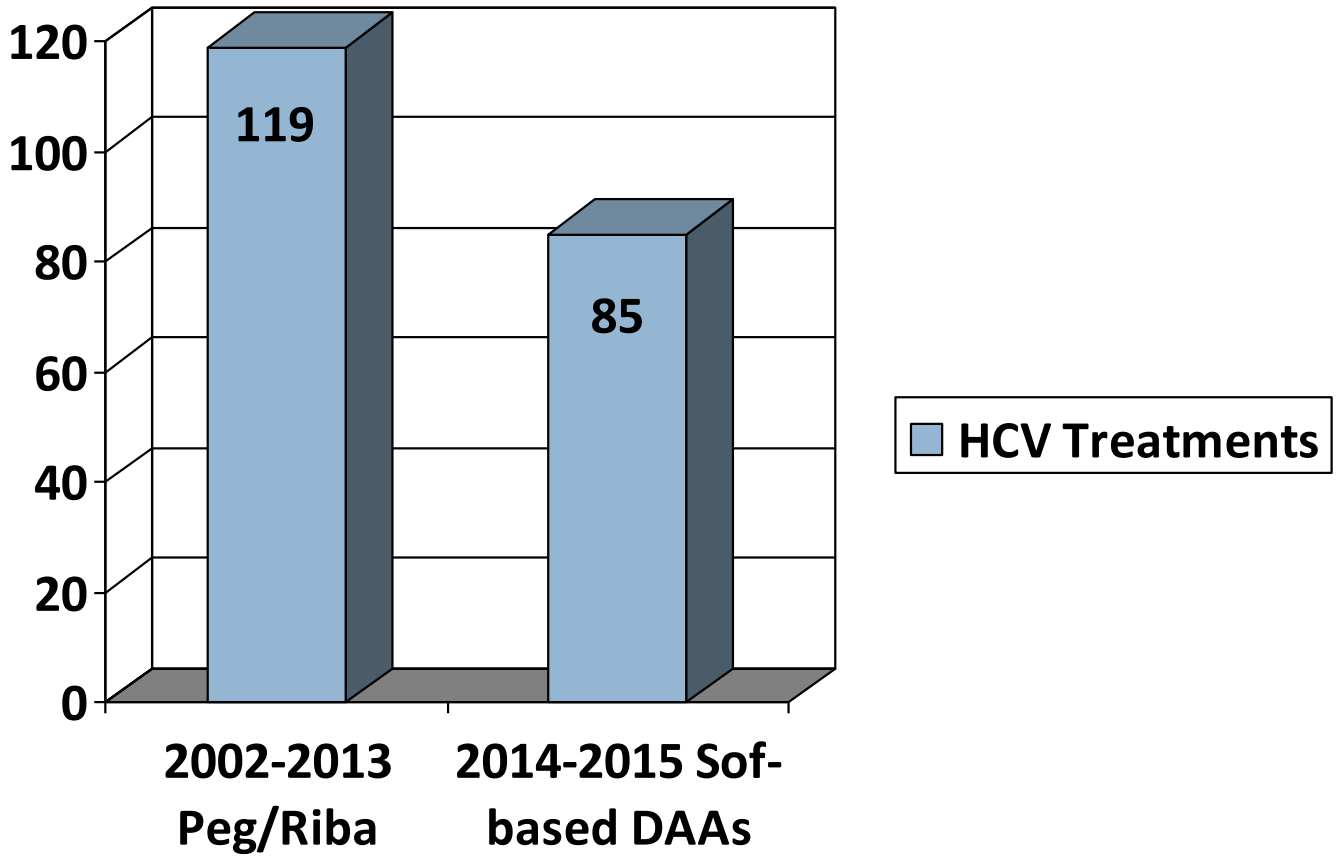
Hepatitis C Treatment Options 2015

Genotype	FDA Approved Treatments
1	Ledipasvir/sofosbuvir (Harvoni®) or Simeprevir (Olysio®) combined with sofosbuvir (Sovaldi®) or Abbvie 3D regimen (Viekira pak®) +/- ribavirin
2	Sofosbuvir + ribavirin x 12 weeks
3	Sofosbuvir + ribavirin x 24 weeks

Genotypes 4,5,6	Refer to AASLD/IDSA Guidelines

AASLD/IDSA Guidelines: Recommendations for Testing, Managing and Treating
Hepatitis C, revised 12/19/14. Available at: www.hcvguidelines.org

ANTHC Hepatitis C Treatment History



Results of 274 HCV Treatment Courses

Treatment Regimen	Number of Persons Treated	Number Completing Therapy (incl # who did not meet response criteria to continue)	% with SVR[4]
Interferon alone (1992-1998)	18	3	3/18 (16.7%)
Interferon/Ribavirin (1998-2002)	37	11	11/37 (29.7%)
Peginterferon/Rbv[1] (2002-2013)	119	61	61/119 (51.3%)
Peginterferon/Rbv/ Protease Inhibitor[2] (2011/2012 G1 only)	15	12	9/15 (60%)
FDA Approved Sofosbuvir-Based DAAs[3] (2014 to present)	85 (50 still on treatment)	35 (17 not to SVR12 testing yet)	15/18 (83%)

[1]Ribavirin
[2]Protease Inhibitor of Telaprevir or Boceprevir
[3]Direct Acting Antiviral Agents
[4]Sustained Viral Response or "Cure"

Hepatitis C Living in Bethel Service Unit

- 33* Chronic HCV (PCR positive) – Consider Treatment:
  - 24 Genotype 1s
  - 6 Genotype 2,3
  - 3 Unknown Genotype

  23 with Other Status:
  - 2 on treatment
  - 3 treated/recovered
  - 7 recovered
  - 11 pending confirmation or recovery – need further testing

*15 live in Bethel

In Summary, Hepatitis C Treatment…

- Duration is shorter
- Has fewer side effects
- Is much more effective
- Can prevent complications of liver failure, hepatocellular carcinoma, and liver-related death

- Is much easier (for patient and provider)

Liver Disease/Hepatitis Program Website

http://www.anthctoday.org/community/hep/index.html

- Patient Information
- Provider Information
- Hepatitis C Treatment
- Publications
- LiverConnect – Past presentations
- The website is constantly updated as new treatments are FDA approved

LiverConnect Videoteleconference

- 2nd Tuesdays, 8-9am Alaska Standard Time
- Case study presentations from hub/rural providers wanted and welcome!!!
- CEUs (1.0 for each session)
- Contact Sharon Corbett to join: 907-729-1588
- Questions: Email liverconnect@anthc.org or contact Julia Plotnik, RN 907-729-1581 or Jim Gove, RN 907-729-1568