2018

NCSCG 4TH ANNUAL POST-AASLD SYMPOSIUM

Rehoboth McKinley Christian Health Care Services

Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Northern California Society for Clinical Gastroenterology.

Northern California Society for Clinical Gastroenterology

Advances in the Management of Chronic Hepatitis C

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Outline

- Disease burden – changing epidemiology
- Current treatment
  - Advances and retreatment
- Benefits of SVR
  - Effect on HCC
- Transplantation and HCV+ organs

HCV Case

- A 61 year-old Caucasian man who was recently diagnosed with HCV after routine age cohort screening is referred to you for treatment.
- Feels well, works full time, denies any symptoms suggestive of decompensated liver disease
- Treatment-naïve an anxious to be cured.
- Comorbidities: BMI 33, HbA1c 7.7 and HDL 30.
- Habits: 4-5 drinks per week; no cigs/THC

Case: Pre-Treatment Evaluation

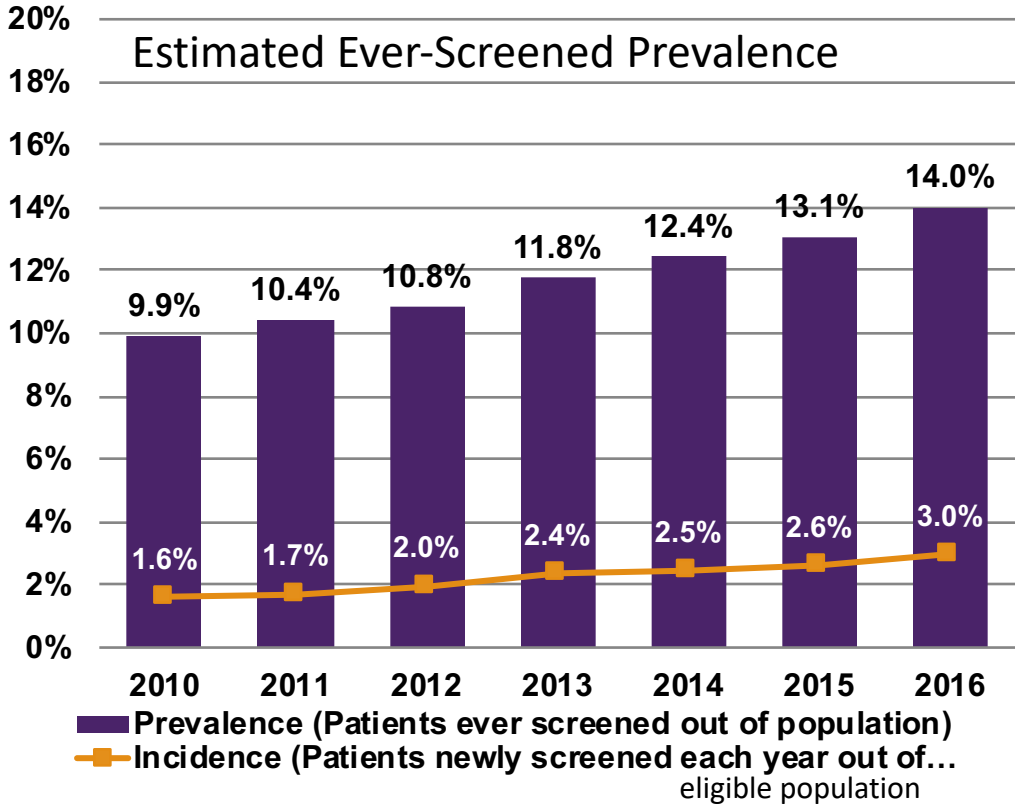
- Labs:
  - HCV RNA 1,200,000 IU/mL
  - HCV genotype 3a
  - Alb 3.7, INR 1.0, Cr 1.3, total bilirubin 1.2
  - AST 64, ALT 72
  - Plt 150,000
- Ultrasound shows a smooth liver with heterogeneous echogenicity, no masses; borderline enlarged spleen (13 cm)

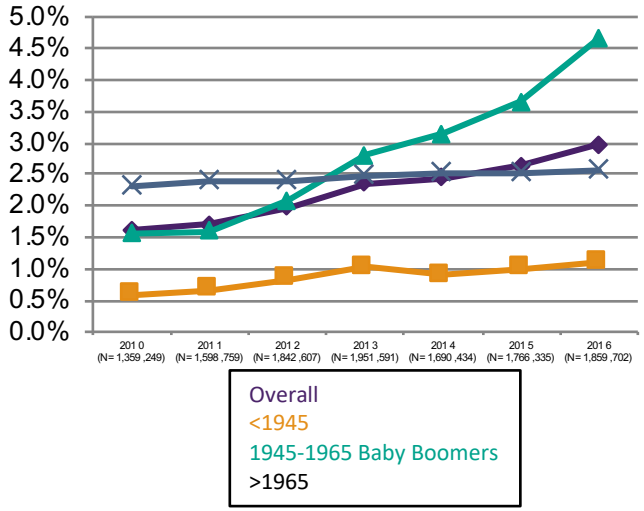
Case: Next Steps

- What additional testing would you order for this patient?
- What are the current treatment options available for this patient?
- What additional treatment options may become available in the next 2 years?
- How would you follow this patient after SVR?

HCV Disease Burden Cascade of Care

How are we doing with identifying HCV-infected persons?





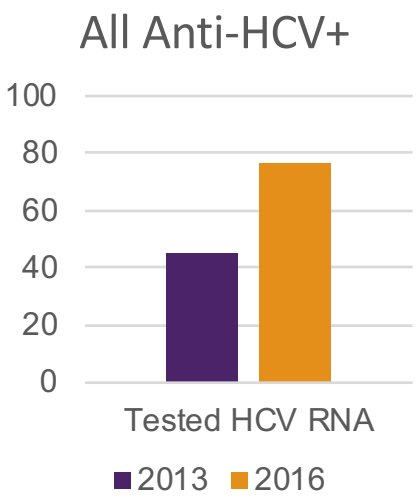
Key messages: Annual HCV screening rates are trending upwards but are still low in the US, despite recent CDC age-based recommendations

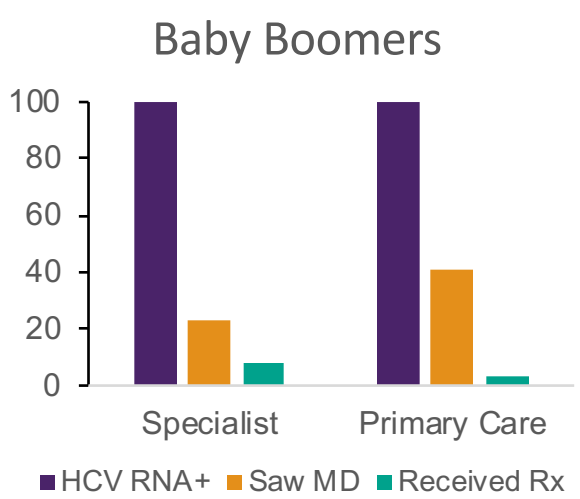
Optum database

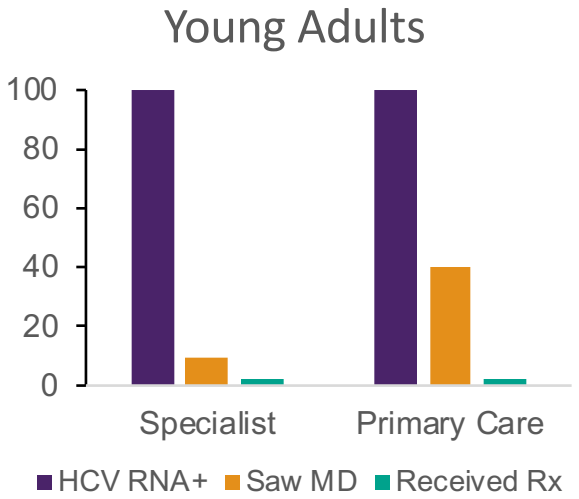
Linkage to care remains a problem

Data from 17.15 Million patients from 2 large commercial labs → inferred referral & treatment

Reau et al. AASLD 2018, Abstract 1567





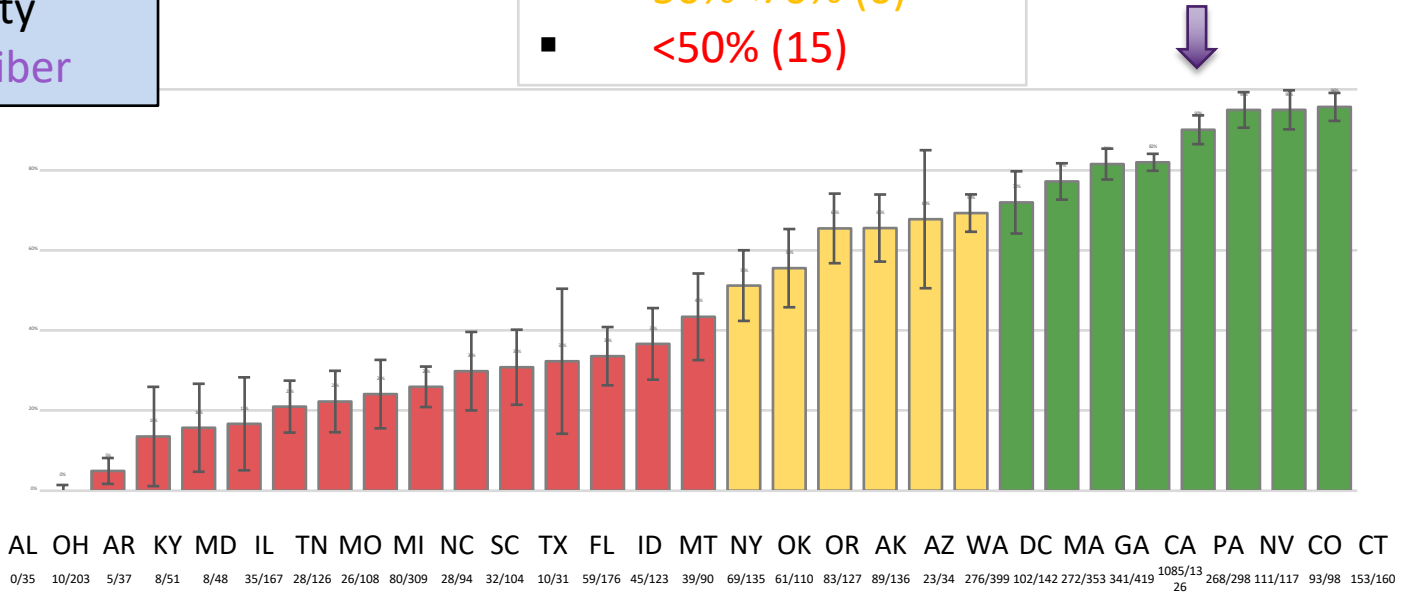


- Despite increased HCV RNA testing (45→77%), poor linkage to optimal care
- Low linkage to specialists (esp. young adults); Increased linkage rates to PCP but VERY low treatment uptake (esp. for baby boomers)

Barriers persist for Medicaid patients

Restrictions:
- Fibrosis
- Sobriety
- Prescriber

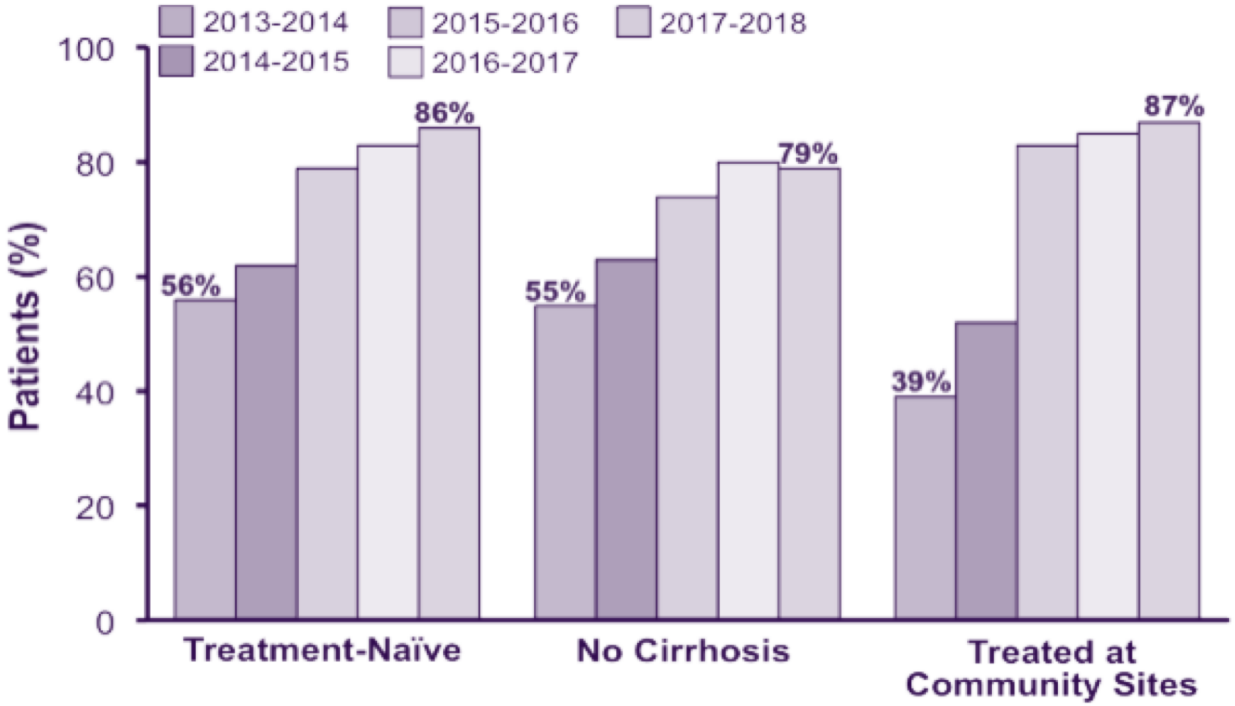
Start Rates by State
- ≥70% (8)
- 50%<70% (6)
- <50% (15)



Younossi et al, AASLD 2018, Abstract 0147

Trends in HCV Treatment

- TRIO database, N=19,944 DAA prescriptions 2013-2018



From 2013-2018, significant change to:

- Treatment naïve (vs. experienced)
- No cirrhosis (vs cirrhosis)
- Community site treatment (vs academic)

Tsai N, AASLD 2018, Abstract 613

Treatment Advances and Real World Treatment Efficacy

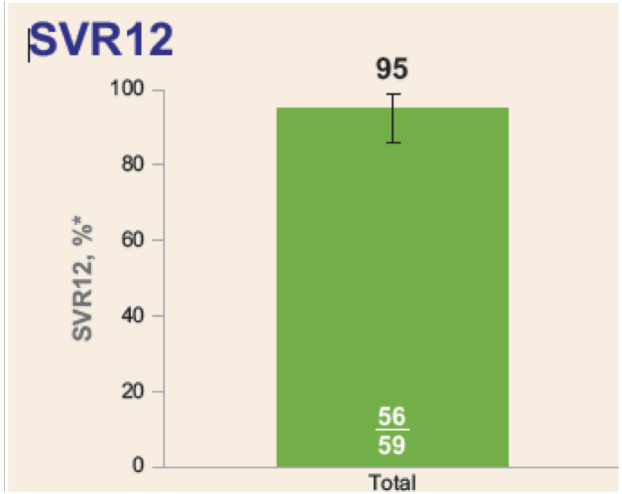
SOF/VEL in Patients on Dialysis

Open label phase 2 study, N=59

SOF/VEL once daily for 12 wks

Key eligibility criteria:

- **Undergoing hemodialysis or peritoneal dialysis**
- **Any HCV genotype**
- **Treatment naïve or experienced**
- **With or without compensated cirrhosis**



3 patients did not achieve SVR12

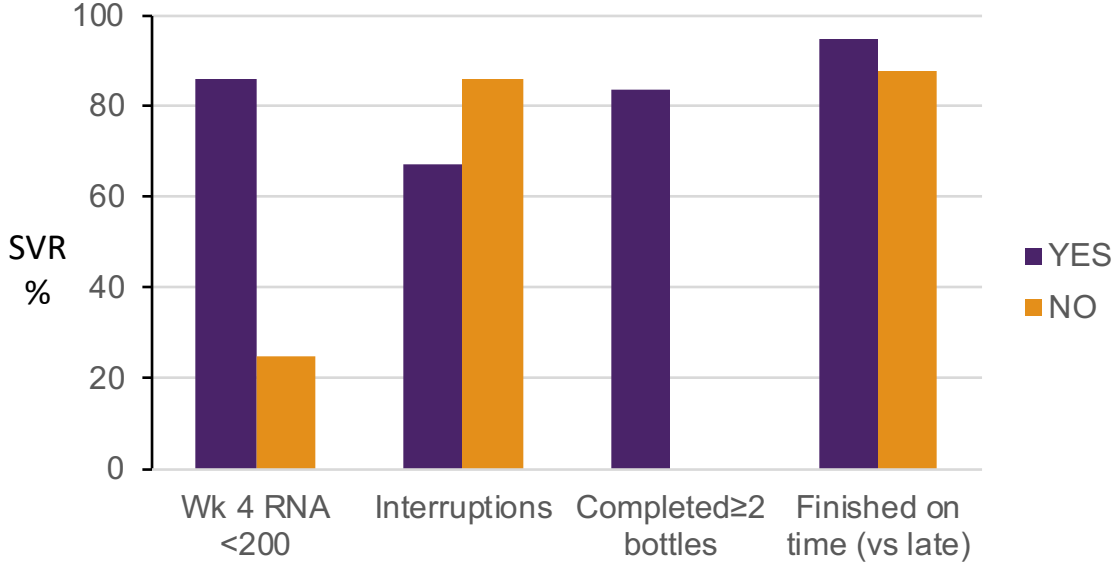
- N=1, HCV GT 3 and cirrhosis relapsed
- N=1 with noncompliance relapsed
- 1 died of suicide after treatment end (SVR4)

No treatment-related adverse events

Borgia SM, AASLD LB-15

Anchor Study: SOF/VEL in PWIDs

Active injection drug use within 3 m treated with SOF/VEL x 12w, n=66



- 78% achieved SVR
- SVR lower if
  - HCV RNA>200 IU/mL at week4
  - <8 weeks of therapy total
- Finishing late – even 14d late – no effect on SVR

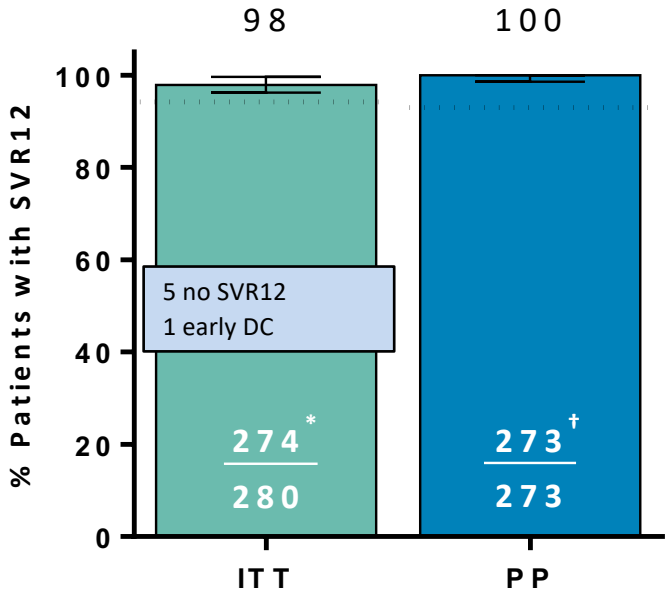
- High SVR rates despite imperfect adherence
- Missed doses and finishing late had little effect on SVR

Kattakhuzy et al AASLD 2018, Abstract 18

GLE/PIB for 8 weeks with Cirrhosis

EXPEDITION 8

Characteristic	N=302 (%)
Genotype 1a/1b 2 4/5/6	 34/ 49% 9% 5/ <1/ 3%
CPT Score 5 6	 90% 9%
BL NS5A polymorphisms	36%



- No virologic failures
- No safety concern

- Extension to include genotype 3 with compensated cirrhosis ongoing

Brown et al. AASLD 2018, LB-7

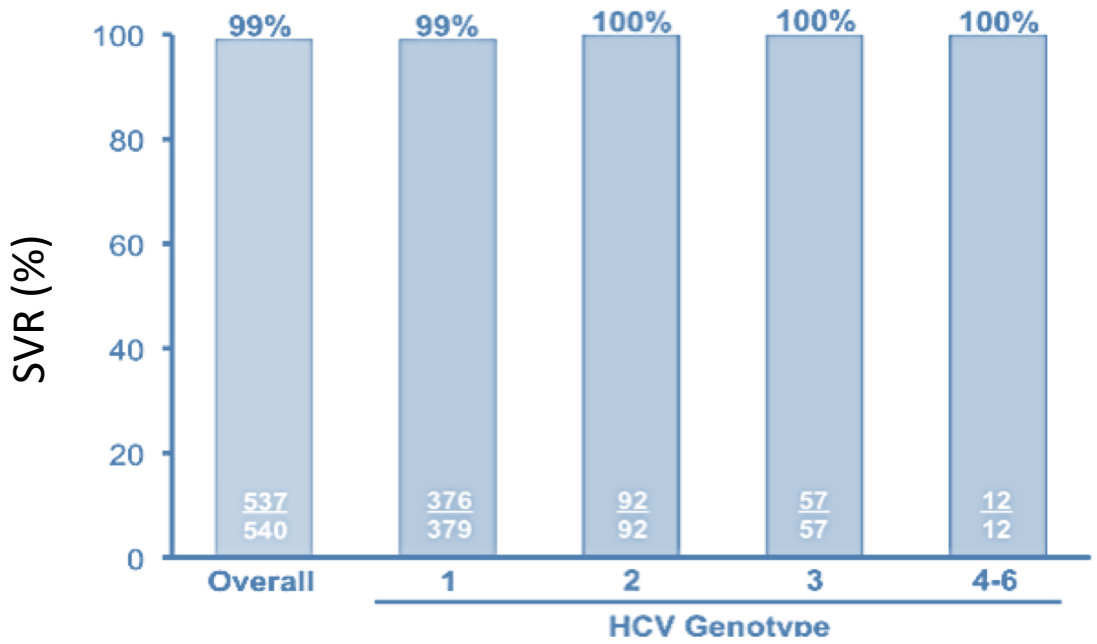
GLE-PIB for 8 Wks in Treatment Naïve Patients

TRIO real world data

Prescription database
N=560, 2017-2018

Baseline characteristics:
CKD stage 4-5 (5%)
Fe (11%)
Genotypes (GT1 54%)

Overall PP SVR= 99%

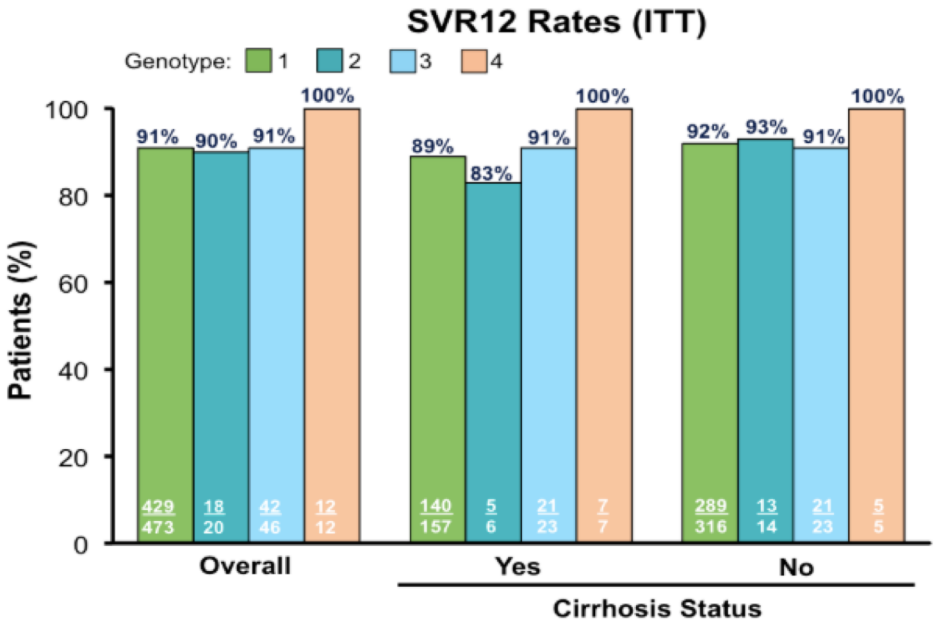


SVR rates in real world = those of clinical trials

S Flamm, AASLD Abstract 632

SOF/VEL/VOX in Prior DAA Failures: VA Experience

SOF/VEL/VOX in N=573 after DAA failure



High overall efficacy

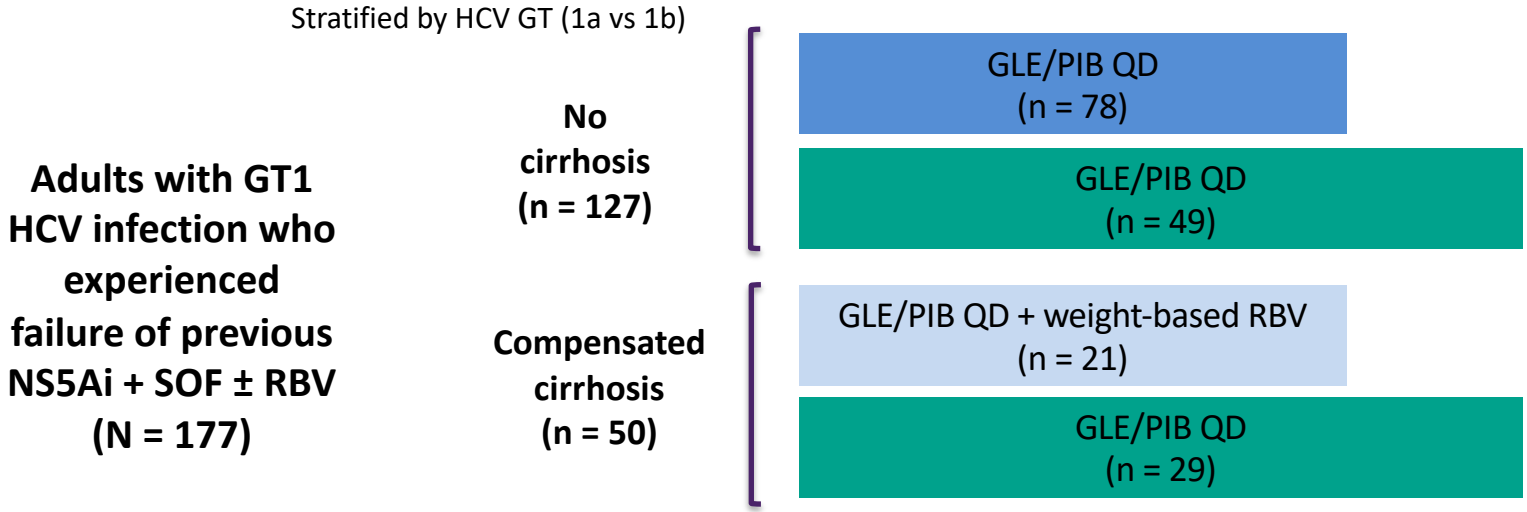
- G1 >95% SVR regardless of past class (1a vs 1b?)
- G3 > 93% SVR regardless of past class
- G4 100% SVR across all subgroups

Lower SVR with SOF/VEL/VOX after SOF/VEL → modest sample size but may want to consider alt. regimen

Belperio et al AASLD 2018, Abstract 227

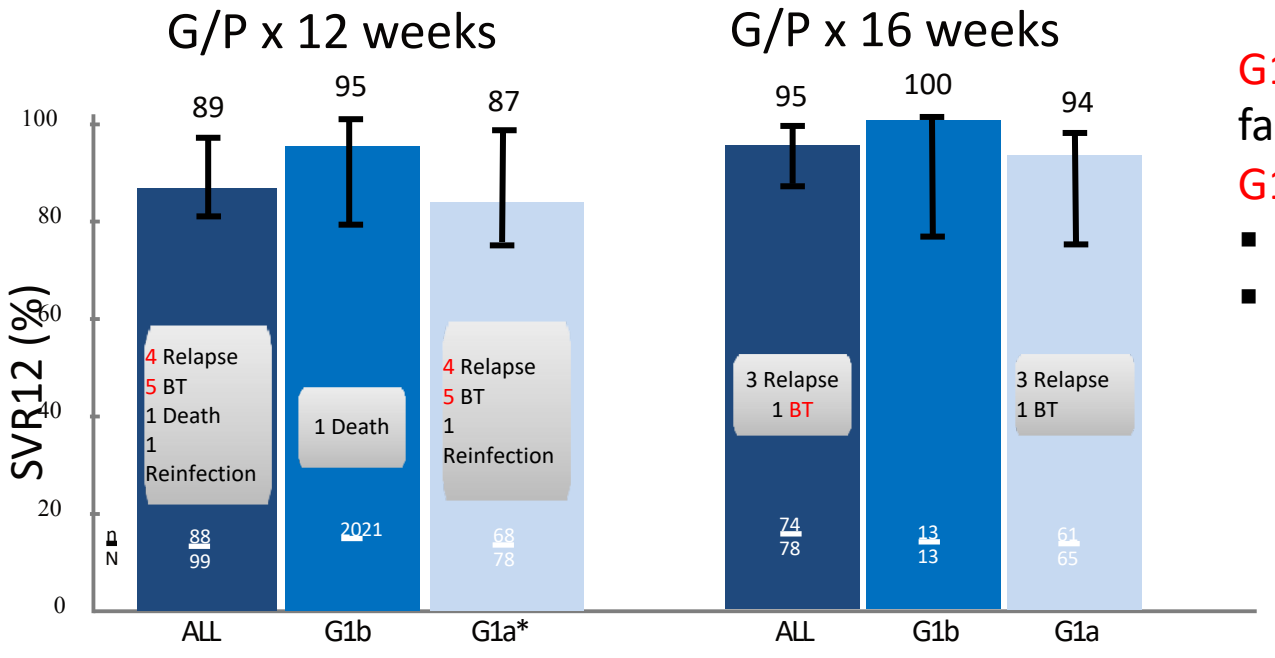
GLE/PIB ± RBV for Genotype 1 HCV After Failure of NS5A Inhibitor + SOF ± RBV

- Multicenter, randomized, open-label phase IIIb study
  - Primary endpoint: SVR12



Sulkowski. AASLD 2018. Abstr 226.

GLE/PIB ± RBV for Genotype 1 HCV After Failure of NS5A Inhibitor + SOF ± RBV



- Effective for G1b (12 or 16w)
- G1a requires 16w with no benefit from RBV but failures may be challenging

G1b (n=34): no virological failures

G1a failures:

- Breakthrough (n=6)
- Relapse (n=7)
  - NS5A RAS at BL
  - Emergent (4/7) & NS5A RAS

* includes 4 non1a/non-1b genotype
BT, Breakthrough;

Sulkowski et al. AASLD 2018, Abstract 226

Case: 61yo male, cirrhosis, G3

- Treated with SOF/VEL for 12 weeks and achieves SVR12
- 18 months after clearing virus, he was found to have a 1.9 cm lesion on surveillance ultrasound.
- MRI shows a 2.2 cm hypervascular mass with contrast washout and pseudocapsule, LIRADS 5 (definitely hepatocellular carcinoma).

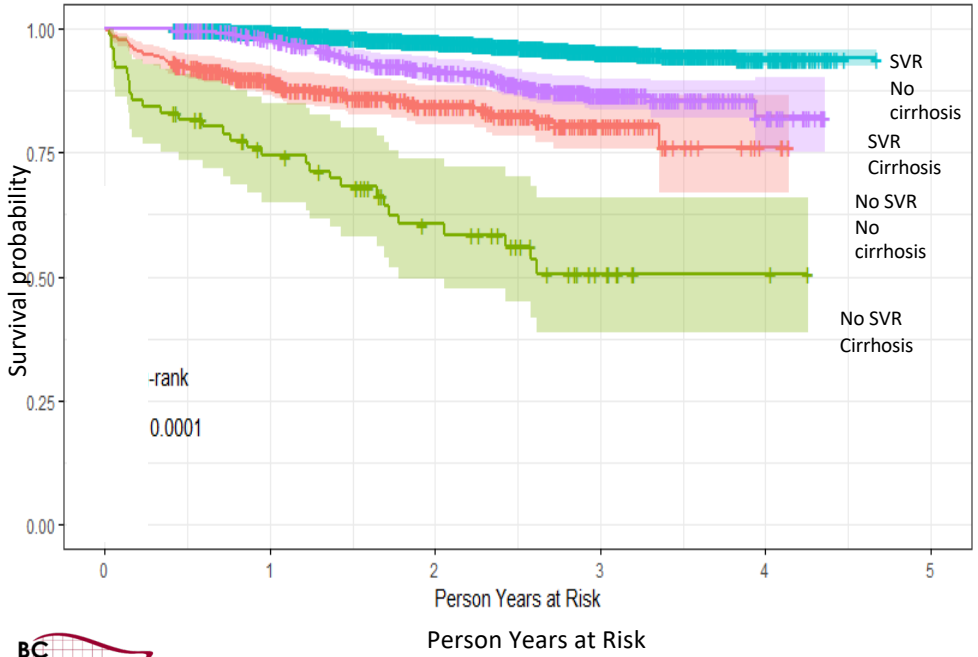
Case: HCC Post-SVR

- What do you tell him about the relationship between HCV (or its treatment) and his new diagnosis of HCC?
- He elects to pursue liver transplantation. How do you counsel him on the potential use of an HCV+ organ?

Benefits of SVR

Benefits of SVR – Overall Survival

- **Centralized HCV testing in BC - Patients who filled ≥1 script for HCV therapy**



Person Years at Risk

Multivariable model for effect of SVR from DAAs on mortality

	Adjusted Hazards Ratio (95%CI)*		
	All N=7126	**No Cirrhosis N=6466**	**Cirrhosis N=660**
No SVR, DAA	**Ref**	**Ref**	**Ref**
SVR, DAA	**0.14 (0.11-0.18)**	**0.13 (0.1-0.18)**	**0.14 (0.08-0.22)**

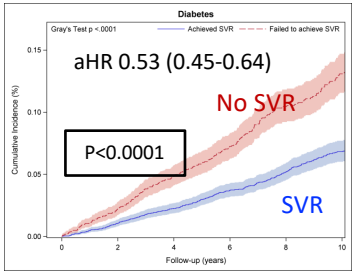
~85% reduction in mortality!

BC HTC British Columbia Hepatitis Testers Cohort

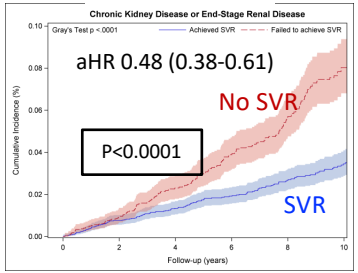
Janjua et al, AASLD 2018, Abstract 0145

Increasing Evidence of Non-Liver Benefits of SVR

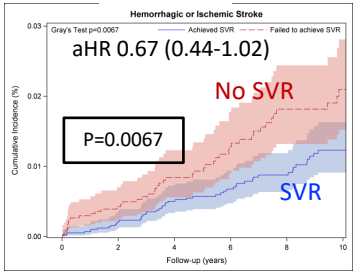
Diabetes



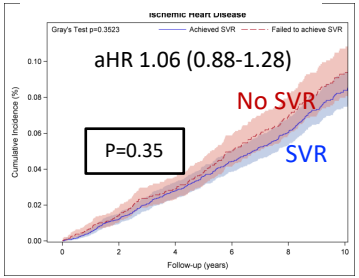
CKD/ESRD



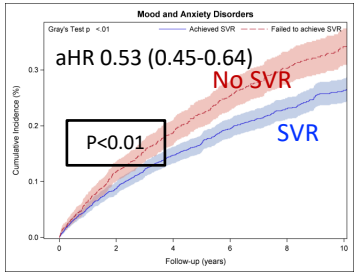
Stroke



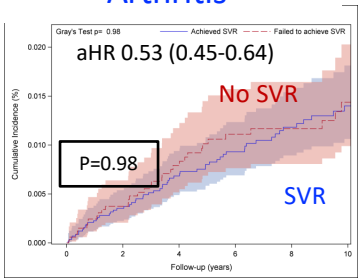
Ischemic Heart Disease



Mood & Anxiety Disorders



Rheumatoid Arthritis



BC HTC British Columbia Hepatitis Testers Cohort

Reduced incidence of multiple extra-hepatic manifestations of HCV with SVR

Rossi et al, AASLD 2018, Abstract 0148

Benefits of SVR: Reversal of Decompensation

- 204 CP-B(81%)/C(19%) patients were included and followed for median (IQR) of 1.16 (0.56-1.84) years.

Outcome at Last Follow Up

All Patients

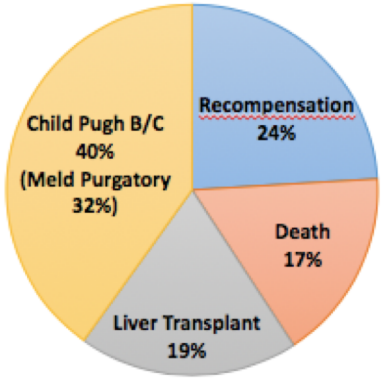


Table 2.Multivariable Predictors of Recompensation

Predictors of Interest	OR	95% CI	P-Value
Ascites	0.22	0.09-0.53	<0.001
Bilirubin (ref <2)			
2-3	0.24	0.09-0.67	<0.001
>3	0.31	0.09-1.08	0.066
Platelets (per 10 unit)	1.10	1.00-1.20	0.044
ALT (per 10 unit)	1.15	1.04-1.28	0.006

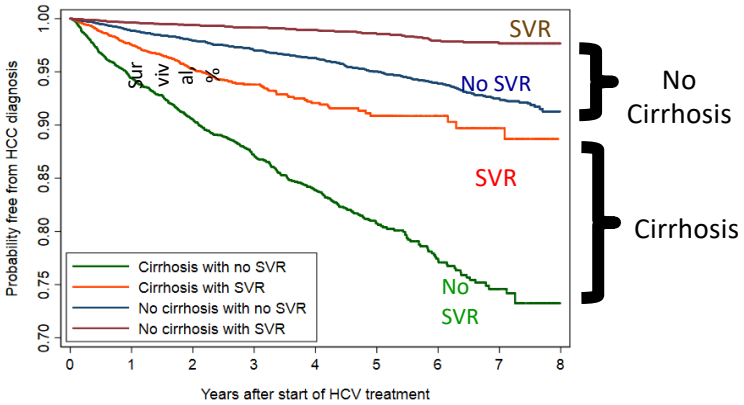
Variables evaluated in univariable but not significant in multivariable analysis: hepatic encephalopathy, hepatocellular carcinoma, sodium, albumin, SVR, use of ribavirin and Hispanic ethnicity.

- **1 in 4 with CP-B/C cirrhosis achieve recompensation within 1 yr**
- **Predictors = less severe portal hypertension and more active inflammatory disease (higher ALT).**

Radhakrishnan K, AASLD, Abstract XXX

Risk of HCC post-SVR

VA: 45,810 HCV therapy with 1,297 HCC in 3.1 yr F/U



Other factors: Age, sex, race, BMI, HCV gt, plt, AST/ALT, INR

Follow-up of Gilead treatment trials n=6808

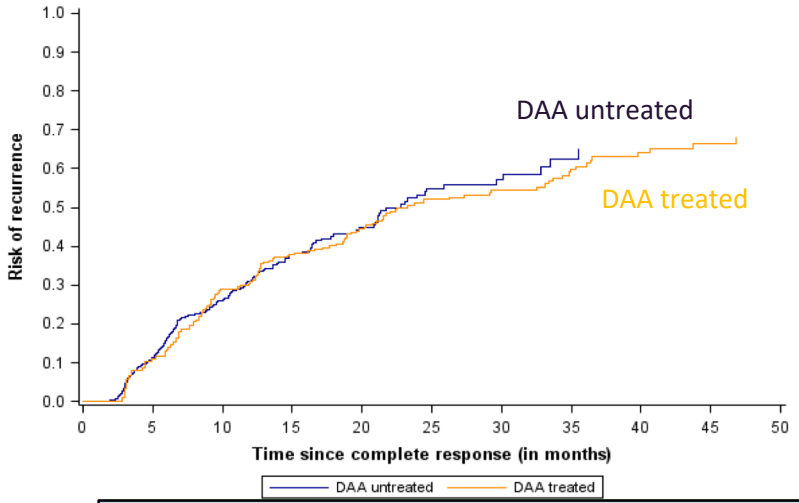
	No Cirrhosis n=4592	Compensated Cirrhosis n=1913	Decompensated Cirrhosis n=292	Overall N=6803*
PY of follow-up	11,013	4925	741	16,710
No. of observed events	8	64	30	102
Exposure-adjusted incidence rate, /100 PY	0.07	1.30	4.05	0.61

- **SVR near-eliminates HCC risk in those without cirrhosis**
- **Reduces but does not eliminate the risk in those with cirrhosis**
- **High risk persists with decompensated cirrhosis**

Ioannou AASLD 2018, Abstract 0094, Reddy et al, Abstract 635

Do DAAs Increase the Risk of HCC Recurrence?

- 31 N American sites – HCC with curative treatment then DAA (n=304) or no treatment (n=491) → HCC recurrence



Median f/u – 10.4 (5.3-20.8) months
Recurrence – 128 after DAA
– 289 no DAA

Binary exposure:

- **aHR for DAA exposure – 0.32 (0.25-0.40)**

As time dependent exposure:

- **aHR for DAA exposure - 0.90 (0.70-1.16)**

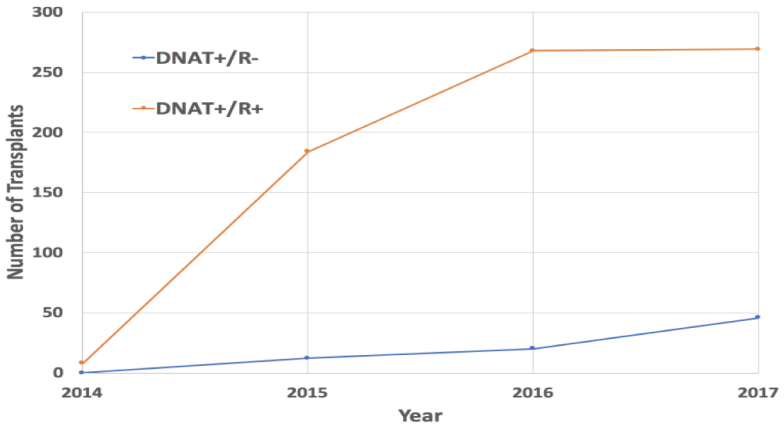
Adjusted for age, sex, CP score, AFP, tumor burden and type of HCC therapy

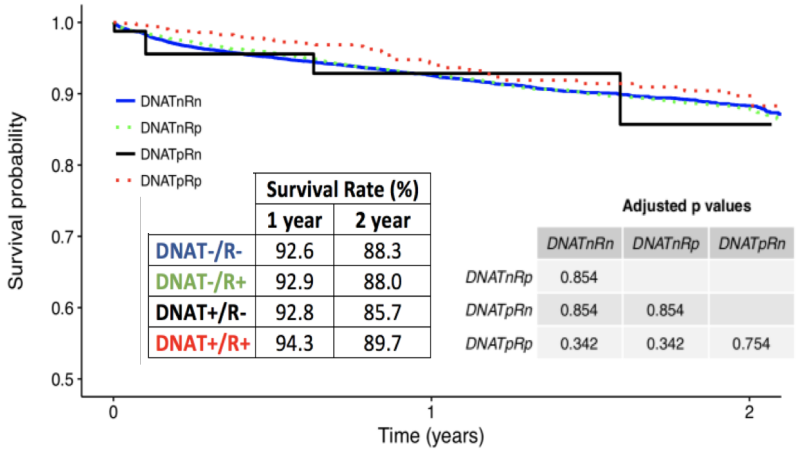
No increased risk of HCC recurrence or aggressive HCC with DAA treatment post-HCC cure

Singal et al AASLD 2018, Abstract 0092

Increasing use of HCV-infected organs

- **Increasing use of HCV NAT+ donors for transplant – both to HCV+ recipients and now recently HCV- recipients**





	Survival Rate (%)	
	1 year	2 year
DNAT-/R-	92.6	88.3
DNAT-/R+	92.9	88.0
DNAT+/R-	92.8	85.7
DNAT+/R+	94.3	89.7

Adjusted p values

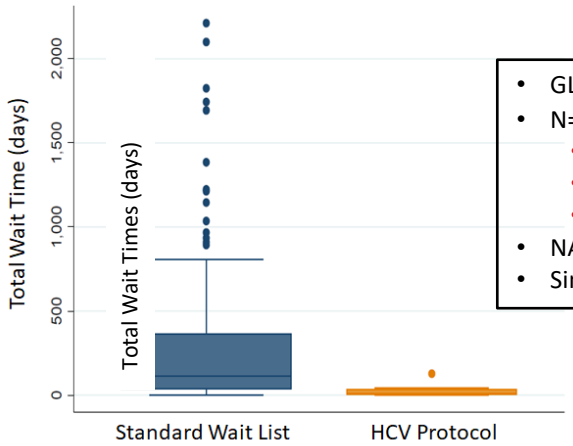
	DNATnRn	DNATnRp	DNATpRn
DNATnRp	0.854		
DNATpRn	0.854	0.854	
DNATpRp	0.342	0.342	0.754

Increasing use of HCV-infected organs for transplantation with similar outcomes to those in HCV-uninfected organs at 1 and 2 yrs

Paul et al, AASLD 2018, Abstract 0249

HCV+ donors to HCV- recipients

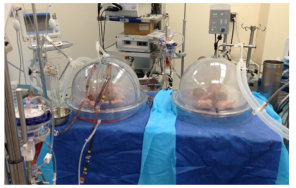
Cardiac: Reduced wait times



- GLE/PIB x 8w on call to OR
- N=25
  - SVR12 – 12
  - SVR4 – 5
  - Others undetectable
- NAT-/Ab+ → no viremia
- Similar results Vanderbilt

HCV+ Donor

Ex Vivo Lung Perfusion x 6 h (reduce HCV RNA)



HCV- Recipient (n=20)

SOF/VEL x 12w – median 21d post-OLTx
2 of 8 relapse
High level resistance
1 early FCH

- **Non-liver transplants using organs from HCV+ recipients reduce wait times**
- **Treatment failures associated with high level viral resistance**
- **Promising but needs to be done carefully with adequate planning and guaranteed access to DAA therapies**

Bethea et al. AASLD 2018, Abstract 0007, Feld et al, Abstract 0223, O'Dell Abstract 0225

Summary - HCV

- Barriers to HCV elimination: identification of infected persons and linkage to an HCV treater
- Majority of treated patients are treatment naïve and without cirrhosis – several excellent DAA options; confirmed by real world data
- G/P for 8 weeks can be considered for compensated cirrhosis G1,2, 4-6
- Retreatment highly effective for those who fail but groups with higher risk of failure are emerging
- Continuing demonstration of the benefits of SVR including on liver and non-liver outcomes
- DAA do not increase risk of HCC recurrence or severity
- Transplantation using HCV+ donors in liver and non-liver recipients is occurring – some caution needed

Acknowledgements

- AASLD Hepatitis Debrief
- CCO Hepatitis AASLD Viral Hepatitis Review
- Simply Speaking AASLD review
- All the AASLD presenters who provided slides