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Do We Need New HCV Drugs? YES

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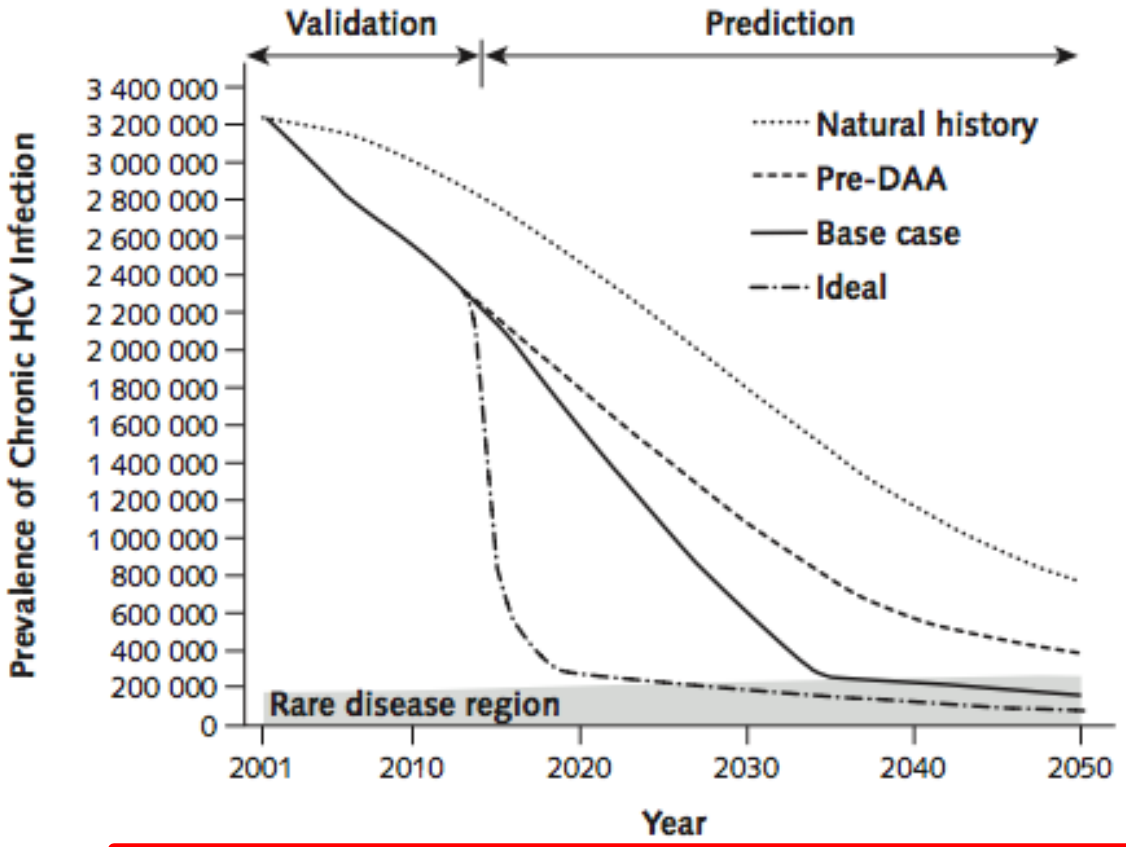
IT'S HOW MEDICINE SHOULD BE®

Disclosures

- Consultation: AbbVie, Abbott, Merck, Gilead, BMS
- Research (paid to Rush): AbbVie, Abbott, Shire, Intercept, GenFit

HCV Projected To Be A Rare Disease By 2036

Estimated HCV prevalence in the US from 2001-2050

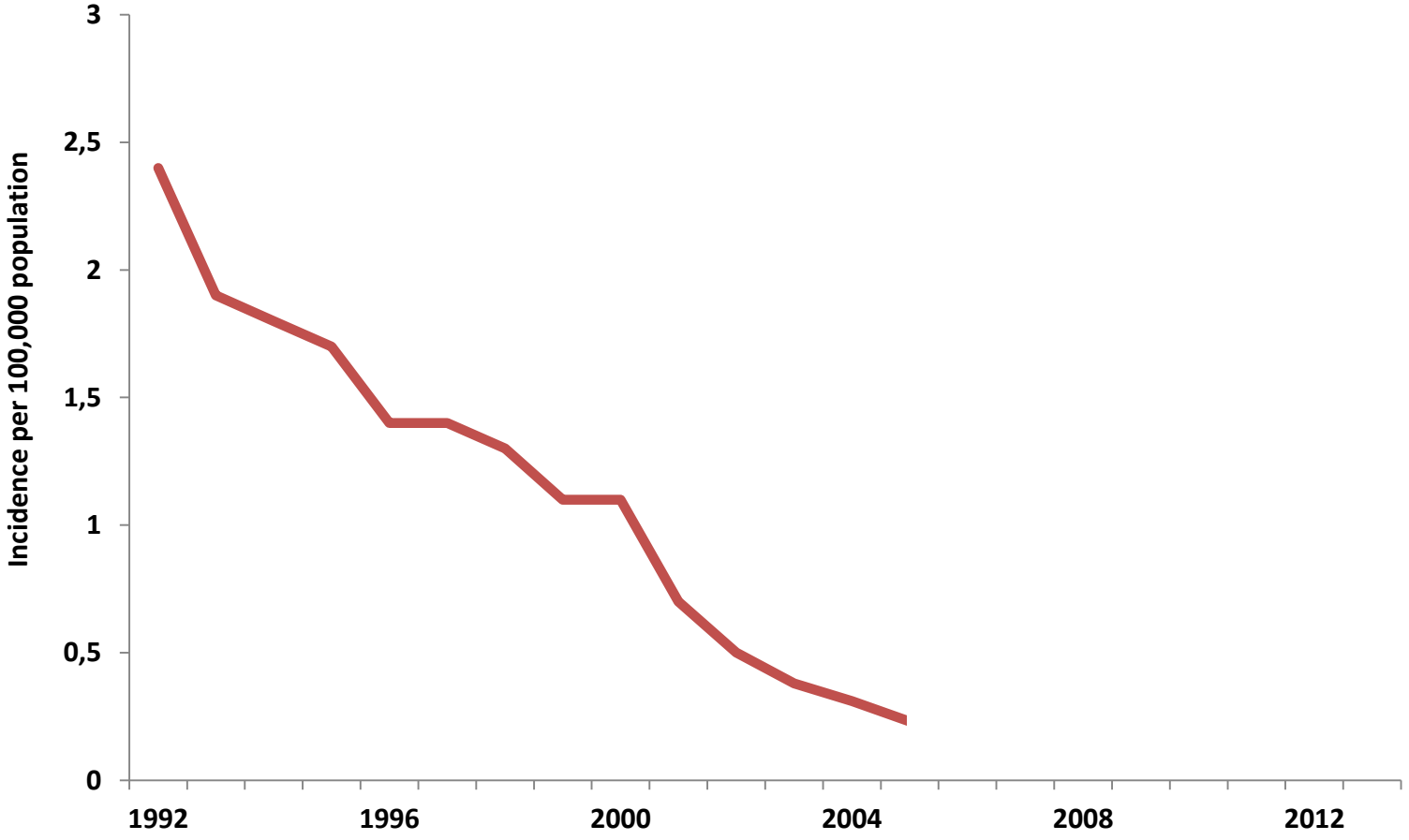


"Our study underscores the need for **more aggressive screening strategies** to reduce the burden of HCV infection."

Why develop drugs for a disease that's been cured?

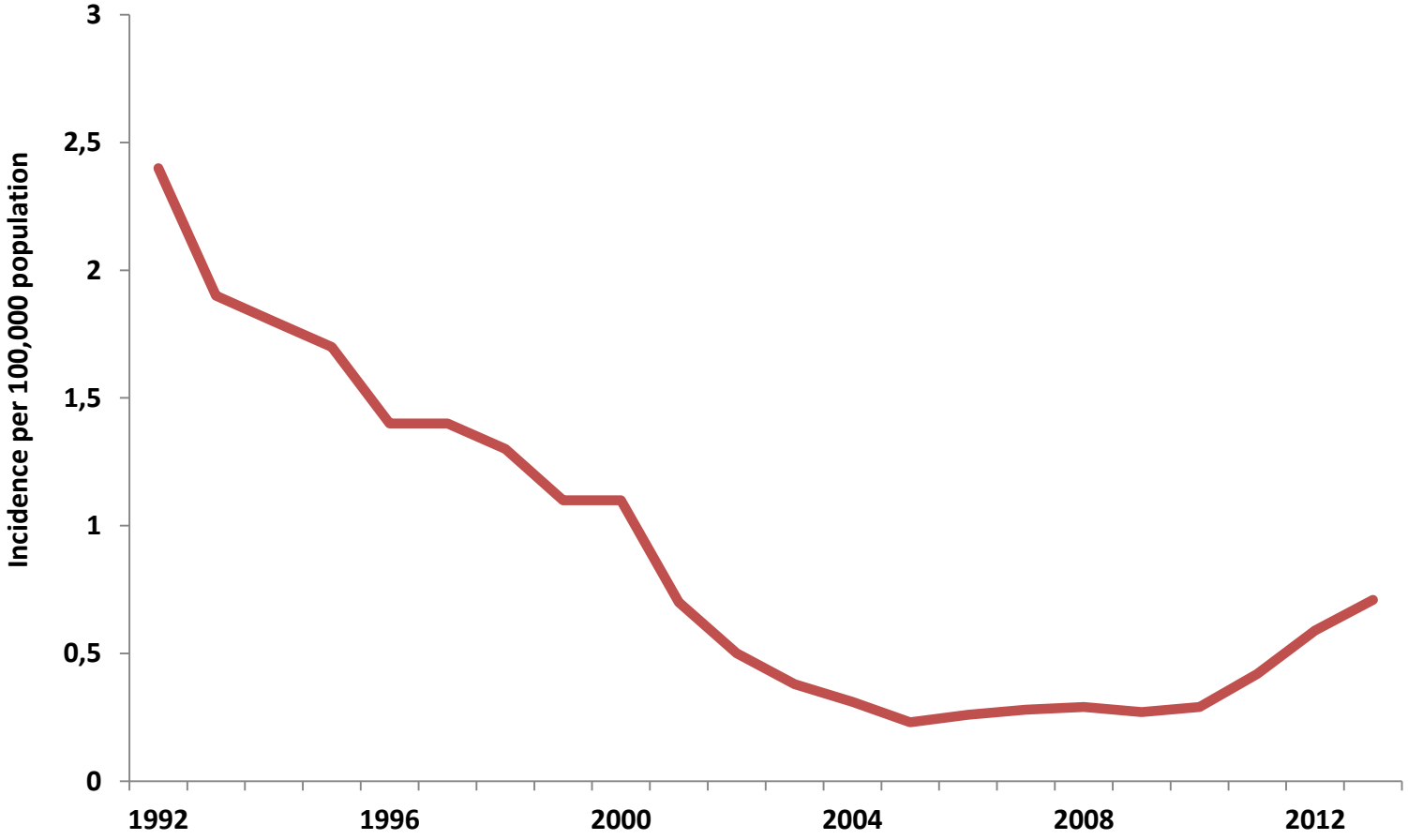
Ann Intern Med. 2014;161:170-180

Incidence of Acute HCV in the US: 1992-2005



MMWR. 2015;62(53):1-122.

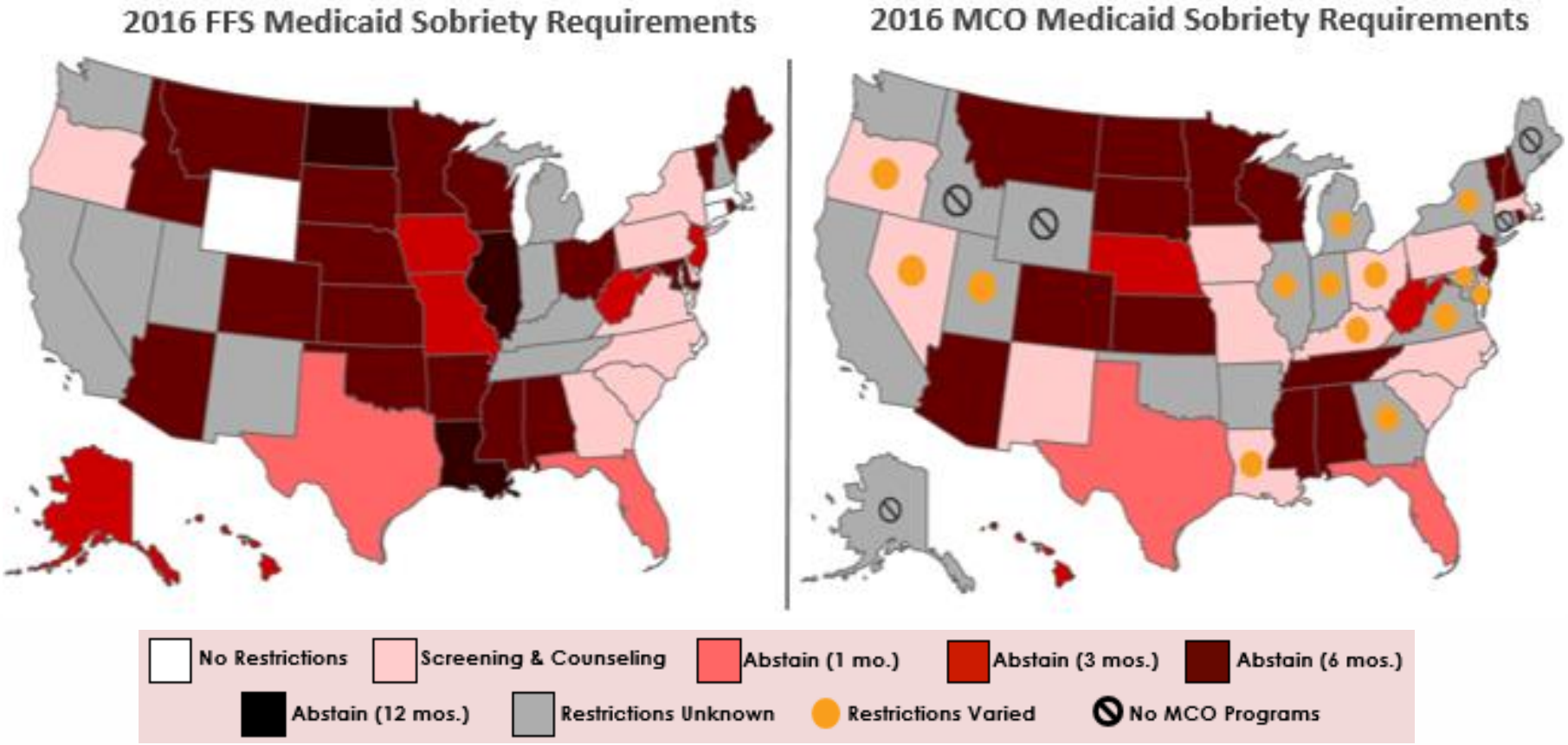
Incidence of Acute HCV in the US: 1992-2013



MMWR. 2015;62(53):1-122.

Pts Using Drugs/Alcohol Denied Access to HCV Treatment in Some Settings

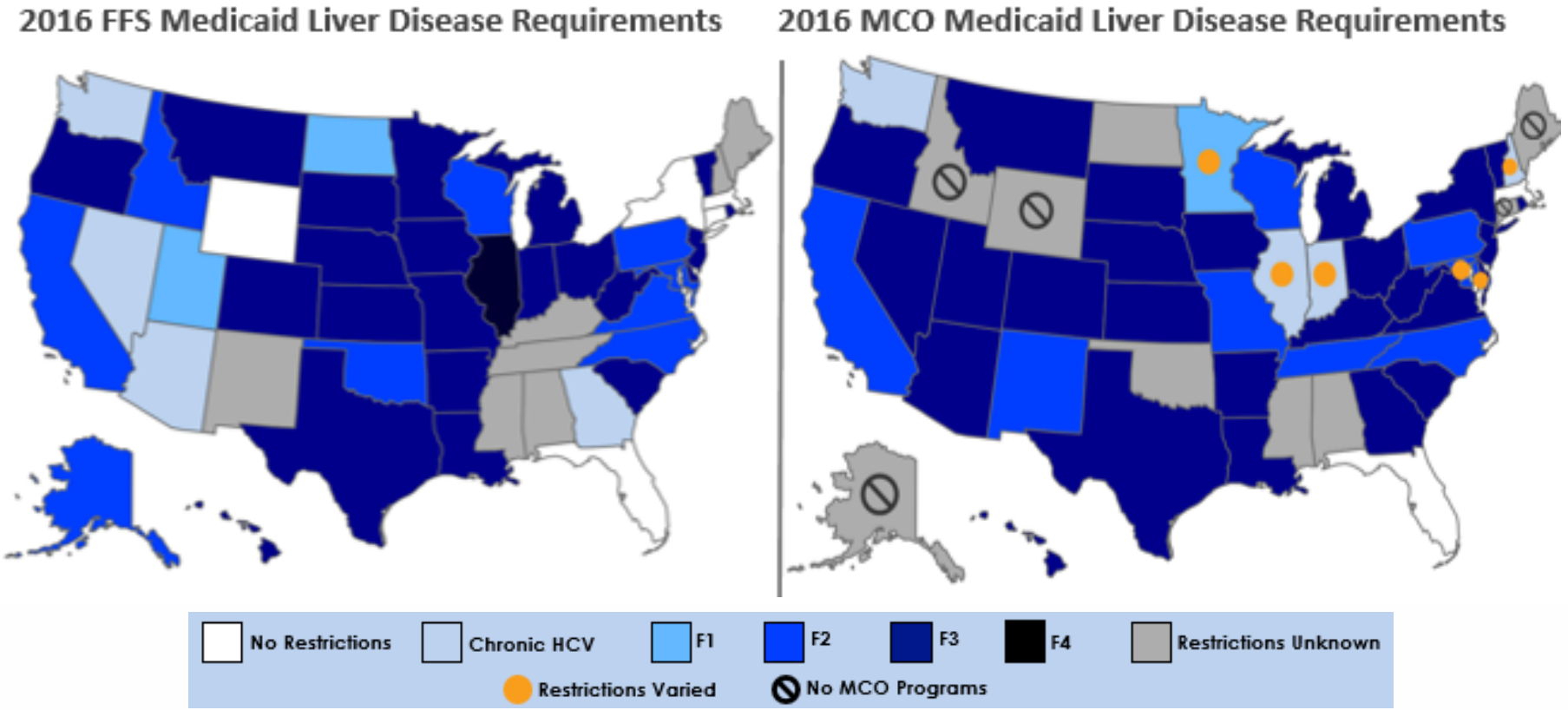
- Medicaid reimbursement criteria for DAAs based on required drug/alcohol abstinence period



Greenwald R, et al. CHLPI/NVHR Summary Report. 2016.

Pts With Minimal Liver Disease Denied HCV Treatment Access in Many Settings

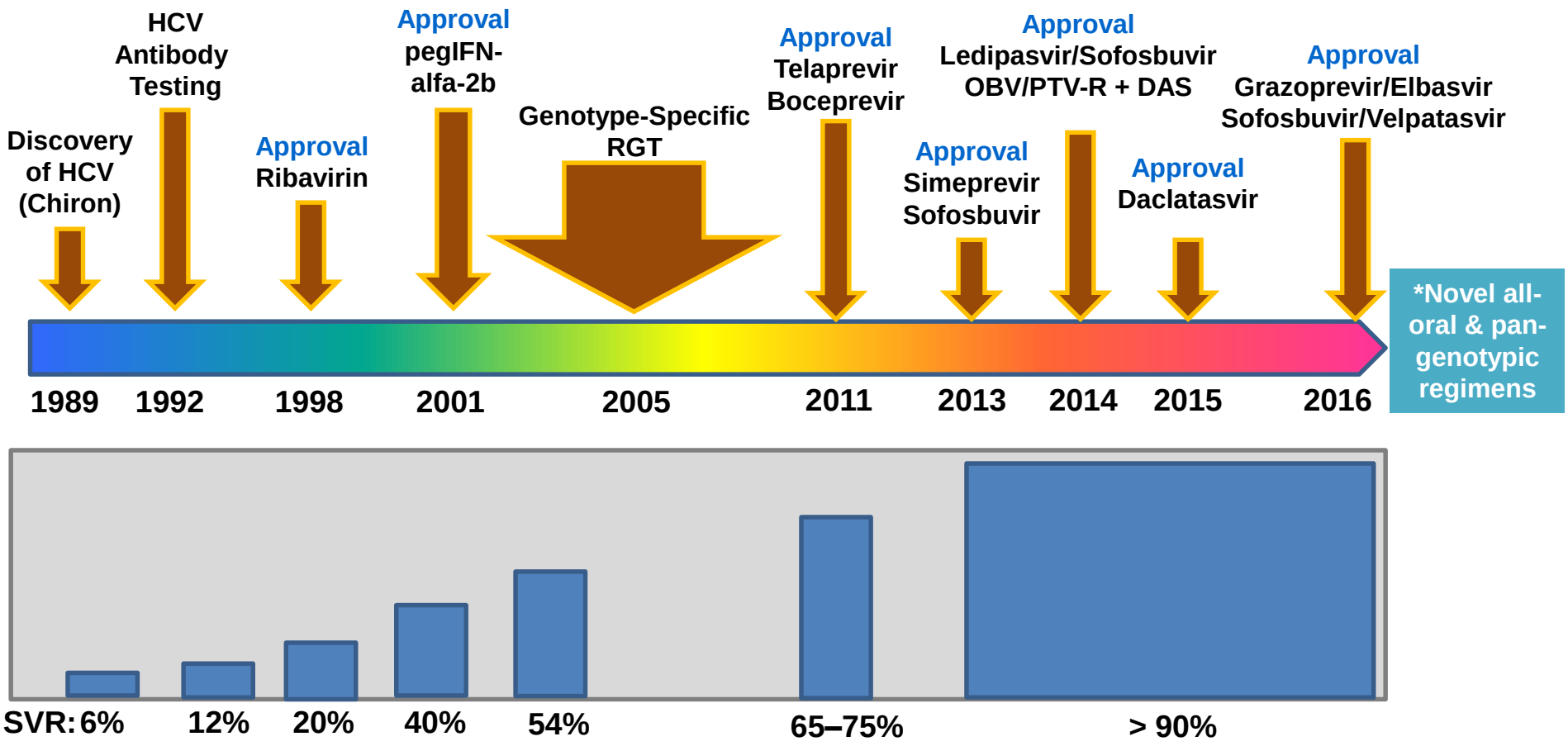
- Medicaid reimbursement criteria for DAAs based on documented liver fibrosis stage required for reimbursement



Greenwald R, et al. CHLPI/NVHR Summary Report. 2016.

History and Evolving Landscape of HCV Therapy

Why develop drugs if the current therapy works?



pegIFN-alfa 2b = peg-interferon alfa-2b; RGT = response-guided therapy; OBV/PTV-R + DAS = ombitasvir/paritaprevir and ritonavir + dasabuvir (or 3D).

Houghton M. *Liver Int*. 2009;29(Suppl 1):82-88; Carithers RL, et al. *Hepatology*. 1997;26(3 Suppl 1):S83-S88; Zeuzem S, et al. *N Engl J Med*. 2000;343(23): 1666-1672; Poynard T, et al. *Lancet*. 1998;352(9138):1426-1432; McHutchison JG, et al. *N Engl J Med*. 1998;339(21):1485-1492; Lindsay KL, et al. *Hepatology*. 2001;34(2):395-403; Fried MW, et al. *N Engl J Med*. 2002;347(13):975-982; Manns MP, et al. *Lancet*. 2001;58(9286):958-965; Poordad F, et al. *N Engl J Med*. 2011;364(13):1195-1206; Jacobson IM, et al. *N Engl J Med*. 2011;364(25):2405-2416; Lawitz E, et al. *N Engl J Med*. 2013;368(20):1878-1887; Jacobson IM, et al. *Lancet*. 2014;384(9941):403-413; Afdhal N, et al. *N Engl J Med*. 2014;370(20):1889-1898; Nelson DR, et al. *Hepatology*. 2015;61(4):1127-1135; Zeusem S, et al. *Ann Intern Med*. 2015;163(1):1-13; Feld JJ, et al. *N Engl J Med*. 2015;373(27):2599-2607.; Foster GR, et al. *N Engl J Med*. 2015;373(27):2608-2617.

Does Difficult To Treat Still Exist?

Historic	First wave DAA	2nd Wave DAA	Future ?
Age >65			
BMI			
HIV	HIV	DDIs	
Black		Renal failure	
Cirrhosis	Cirrhosis	Decompensated	Decompensated
Treatment experienced	TE		
High viral load	HVL		
IL28B TT	Post-OLT	RAV	DAA failure
Genotype 1		Genotype 3	
			ACCESS

Traditional Factors Have Lost Impact

Baseline Characteristics on SVR: PrOD ± RBV

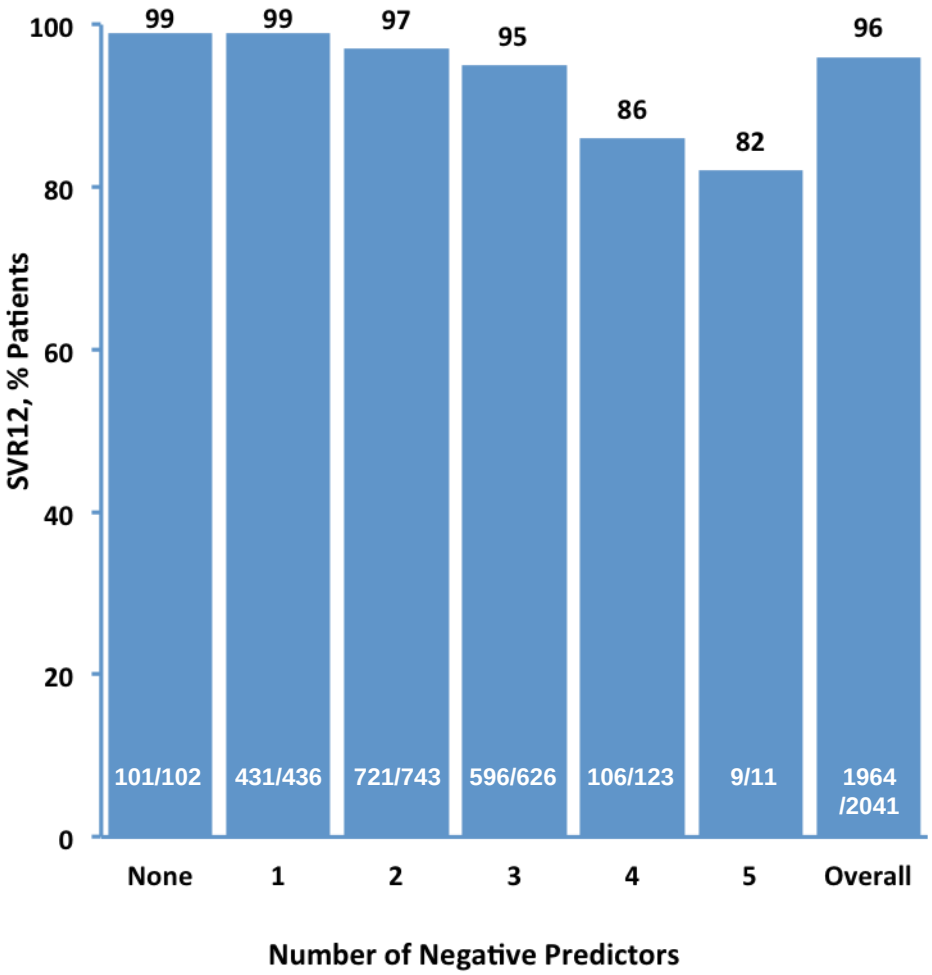
Multivariate Stepwise Regression Analysis of Baseline Factors of All Treated Patients

	P value		*P* value
HCV GT1a	<.001	Fibrosis Stage	NS
Weight	.007	Cirrhosis	NS
Hispanic /Latino Ethnicity	.013	Albumin	NS
IL28B TT Genotype	.034	Platelet Count	NS
HCV RNA	.041	Treatment Regimen (3D + RBV)	NS
Treatment Experienced	NS	Treatment Duration	NS
IL28B CT Genotype	NS	History of Diabetes	NS
Age	NS	History of Depression /Bipolar Disorder	NS
Sex	NS	History of Bleeding Disorders	NS
Race	NS	Former Injection Drug Use	NS
BMI	NS	Geographic Region	NS

Multivariate Stepwise Regression Analysis of Baseline Factors for Label-recommended Regimen

	Odds Ratio	*P* value
BMI	0.874	.001
HCV GT1a	0.066	.008

0=100%
1= 98%
2= 95%



Negative predictors: HCV GT1a, weight ≥75kg, IL28B TT, Hispanic/Latino, HCV RNA ≥800,000 IU/mL

Reau N, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. P0781.

1. Not Everyone can be cured

Difficult To Treat

Historic	First wave DAA	2nd Wave DAA	Future
Age >65			
BMI			
HIV	HIV	DDIs	
Black		Renal failure	
Cirrhosis	Ci s	Decompensated	*Decompensated*
Treat experie			
High viral l	VL		
IL28B TT	Post-OLT	RAV	DAA failure
Genotype 1		Genotype 3	Genotype 3 +RAS
			ACCESS

Rare- but how do we re-treat patients who fail DAAs?

Summary of Phase 3 studies of IFN-free therapy in GT 1 patients published NEJM 2014*

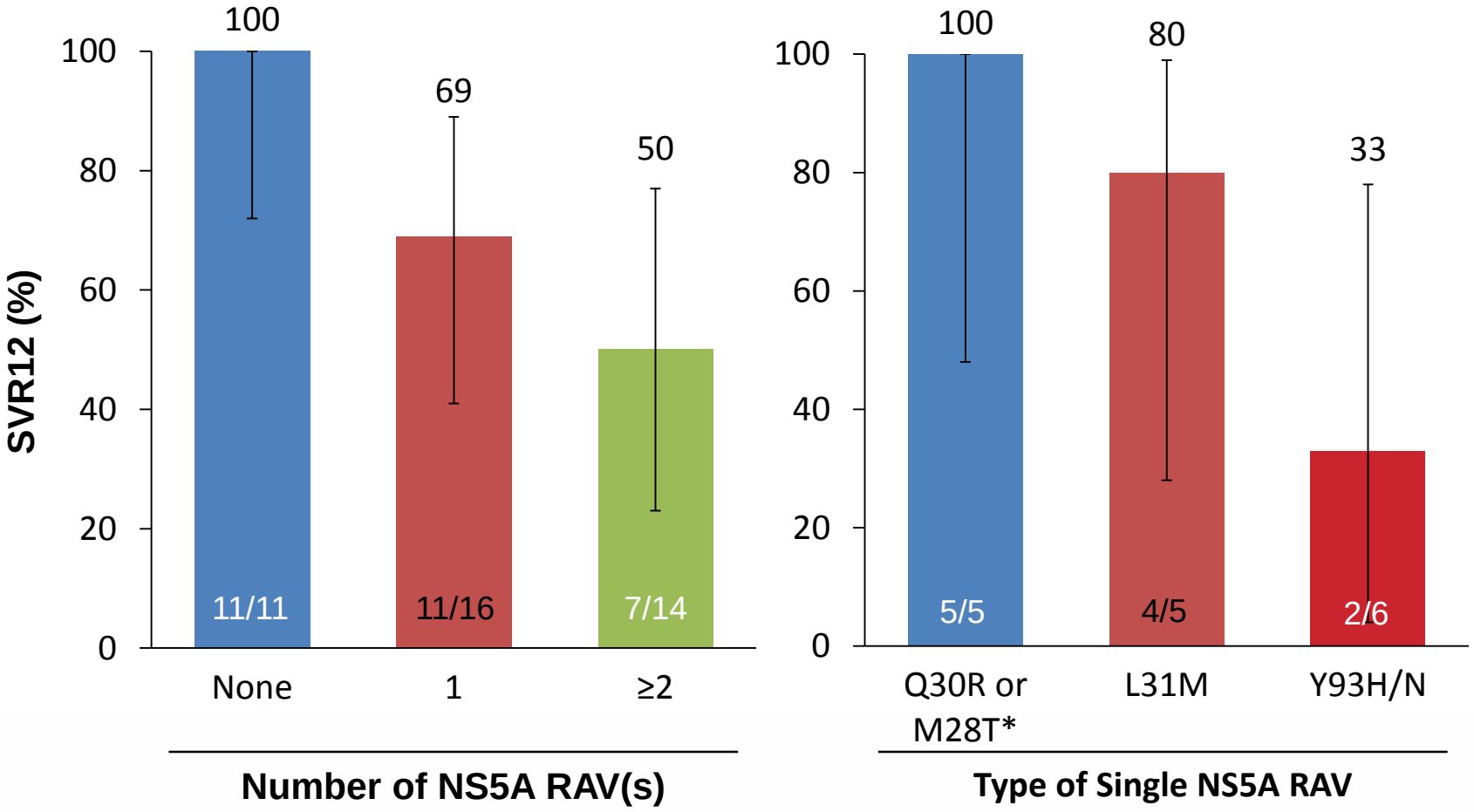
Trial	Regimen
ION-1	LDV/SOF ± RBV
ION-2	LDV/SOF ± RBV
ION-3	LDV/SOF ± RBV
SAPPHIRE-I	OMV/PTV/RTV + DSV + RBV
SAPPHIRE-II	OMV/PTV/RTV + DSV + RBV
PEARL-III	OMV/PTV/RTV + DSV + RBV
PEARL-IV	OMV/PTV/RTV + DSV + RBV
TURQUOISE-II	OMV/PTV/RTV + DSV + RBV

Liang J, Ghany MG. N Engl J Med 2014;370:2043–7

*Included treatment-naïve and -experienced patients ± cirrhosis.

RAS -> Some could Respond to Current Therapy

LDV/SOF x 24 Weeks After Failing 8-12 weeks LDV/SOF

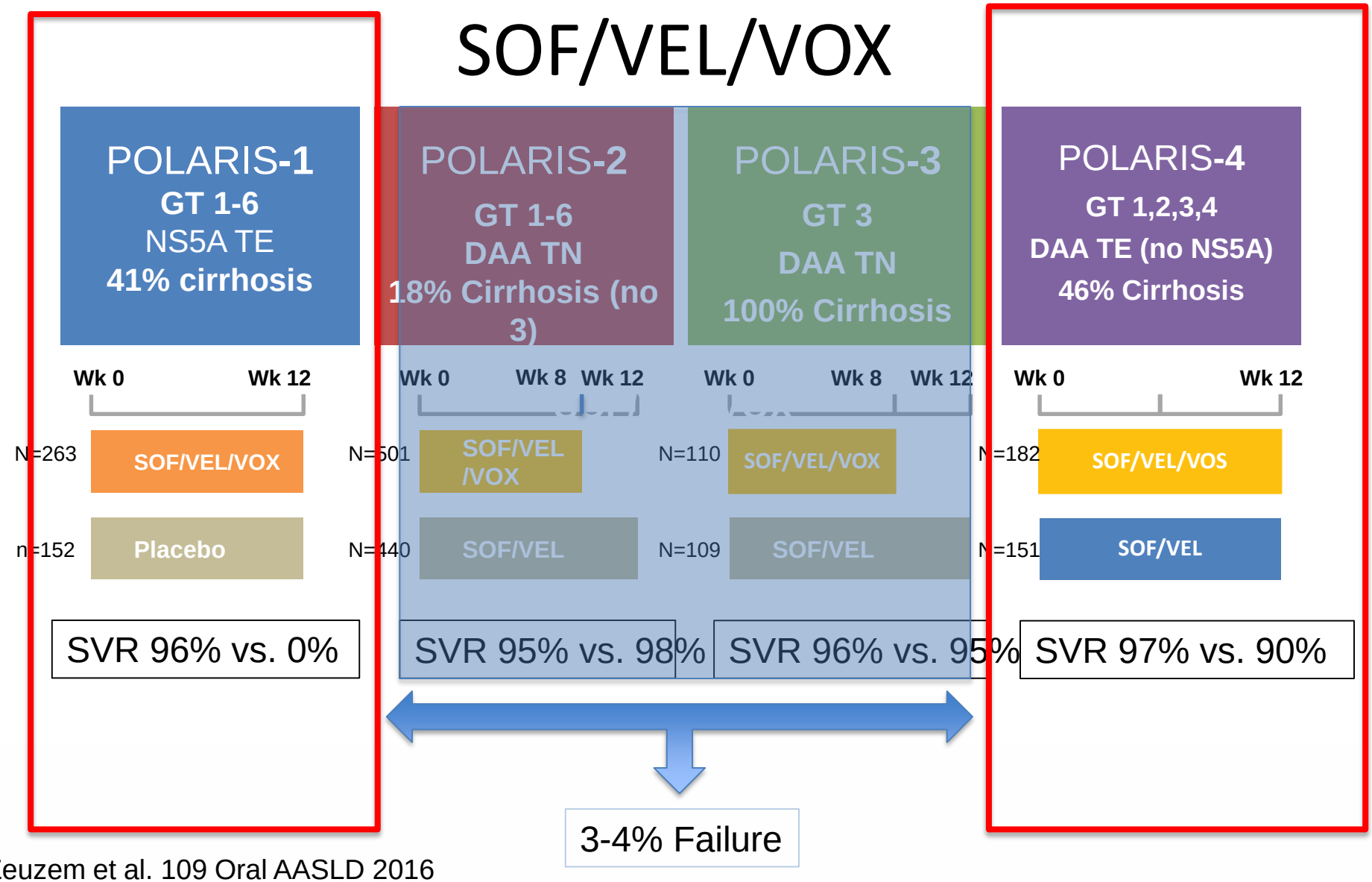


*M28T (n=1).

Lawitz E, et al. EASL 2015. Abstract O005.

The POLARIS Phase 3 Program

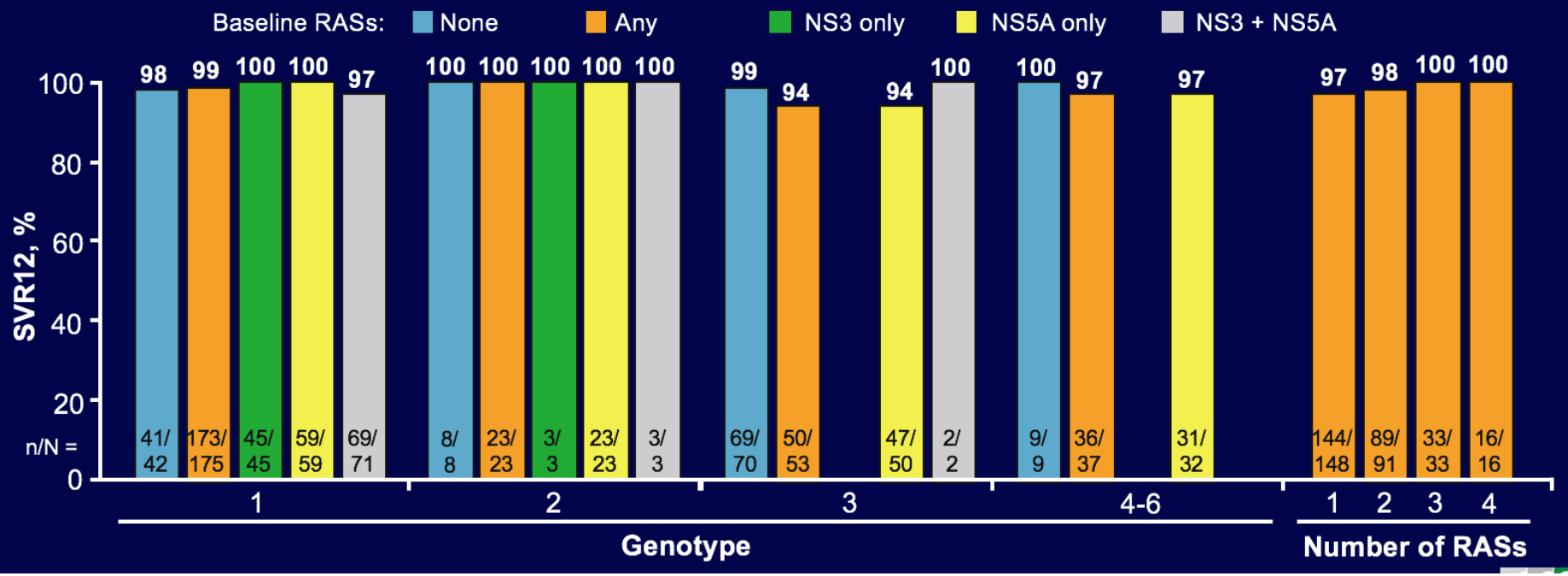
SOF/VEL/VOX



Zeuzem et al. 109 Oral AASLD 2016
Bourliere et al.194 Oral AASLD 2016

POLARIS-1 and -4: Impact of Baseline RASs on 12-wk SOF/VEL/VOX in DAA-experienced Pts

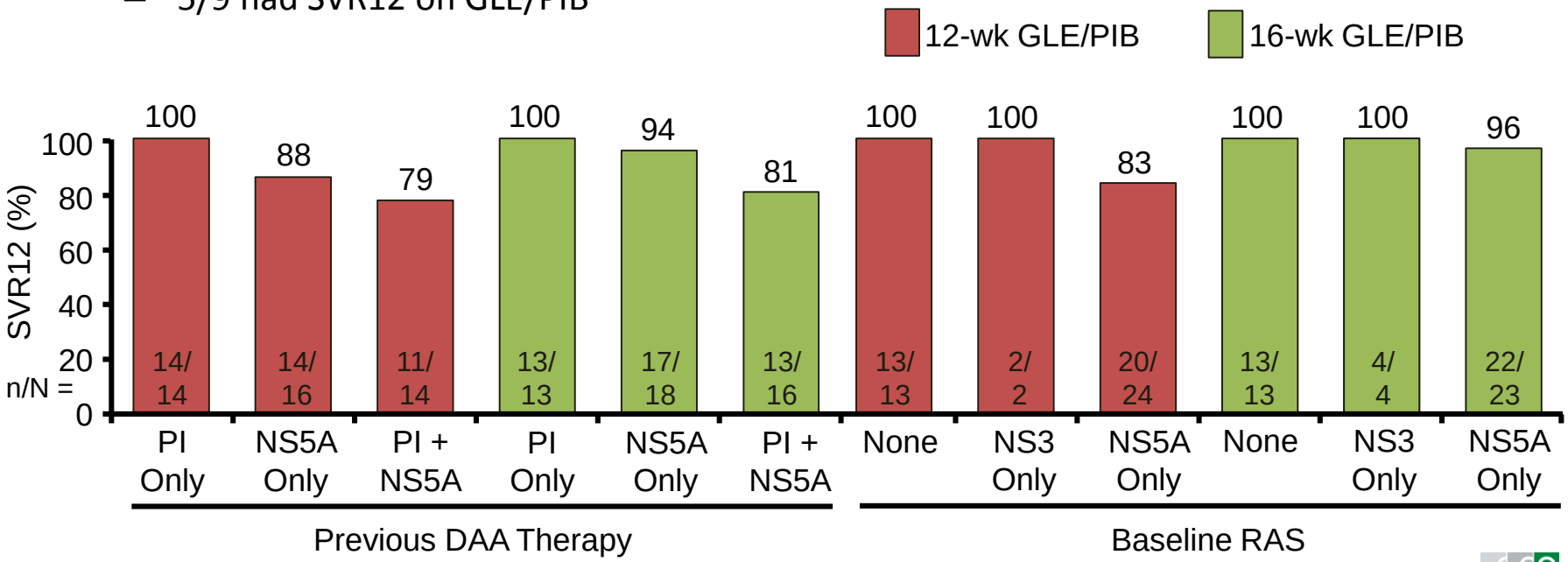
- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors



Sarrazin, et al. EASL 2017. Abstract THU-248.

MAGELLAN-1: GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with both NS3 and NS5a RASs, 9/9 had previous failure with PI + NS5A
  - 5/9 had SVR12 on GLE/PIB

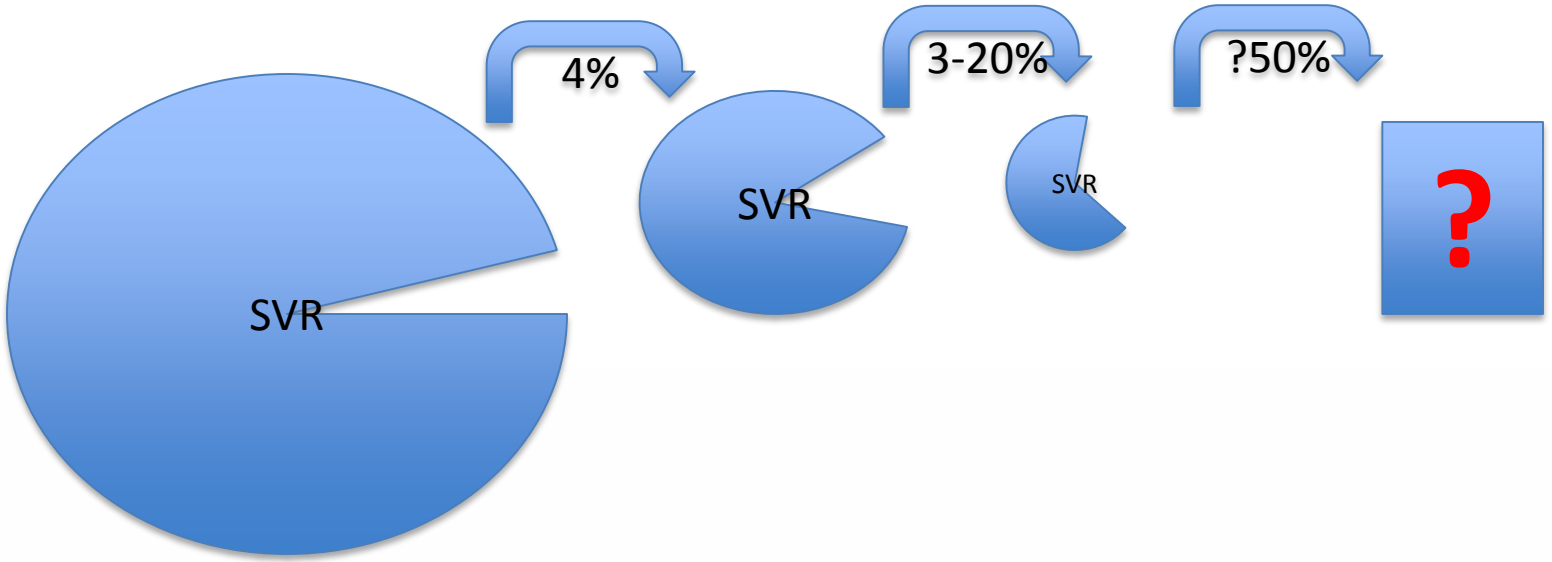


Slide credit: clinicaloptions.com

Poordad F, et al. EASL 2017. Abstract PS-156.

How Do We Treat 2nd Generation Failures?

- RAS testing might not identify high risk patients
- G/P failures had complicated resistance patterns that current salvage might not cover



There is more to difficult than TE

Recommended Therapies for Patients with Renal Impairment

Severity	Creatinine Clearance	Therapy	Genotype
Mild to Moderate	30 – 80 mL / min	LDV/SOF SOF/VEL PrOD GZP/EBV	1, 4 – 6 1 – 6 1, 4 1, 4
Severe or ESRD	<30 mL/min	GZP/EBV PrOD Peg-IFN + RBV	1, 4 1 2, 3, 5, 6

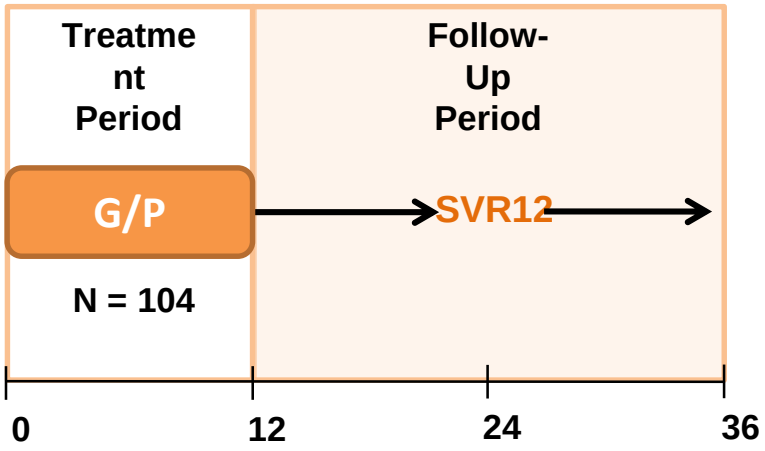
Do investigational therapies show promise for patients with severe renal impairment?

Expedition-4 Glecaprevir/Pibrentasvir HCV GT 1-6 Patients with Renal Impairment

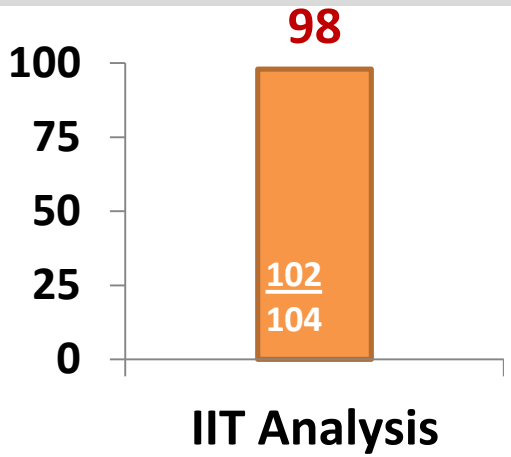
Study Design

Key Inclusion Criteria:

- HCV GT 1 – 6
- CKD 4 – 5
- ±cirrhosis
- TN or TE*



SVR12: Intent-to-Treat Analysis



88% of patients had CKD Stage 5 and 82% were on hemodialysis

* TE defined as IFN/pegIFN ± RBV or SOF + RBV ± pegIFN therapies
TN = treatment naïve; TE = treatment experienced
Gane E, et al. AASLD 2016. Boston, MA. Abstract #LB-11.

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Severe or ESRD	<30 mL/min	GZP/EBV ~~PrOD~~ G/P ~~Peg-IFN + RBV~~	1, 4 1 1-6

What about ESRD+decompensated cirrhosis

http://www.hcvguidelines.org/full-report/unique-patient-populations-patients-renal-impairment

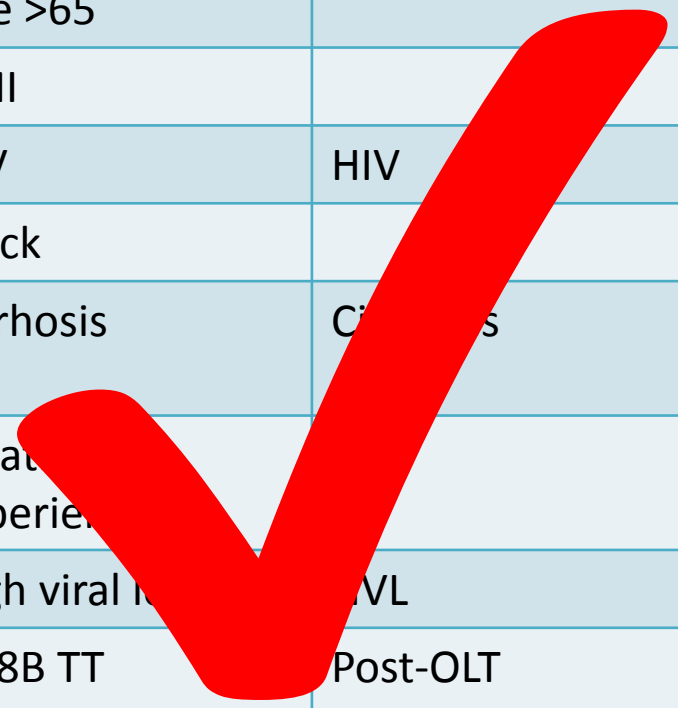
Difficult To Treat

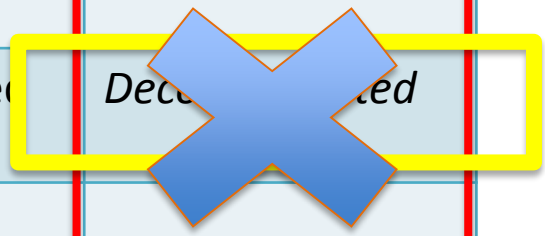
Historic	First wave DAA	2nd Wave DAA	Future
Age >65			
BMI			
HIV	HIV	DDIs	
Black		Renal failure	
Cirrhosis	Ci s	Decompensate	*Decompensated*
Treat experie			
High viral l	VL		
IL28B TT	Post-OLT	RAV	DAA failure
Genotype 1		Genotype 3	Genotype 3 +RAV
			ACCESS

Bigger Fish To Fry

Difficult To Treat

Historic	First wave DAA	2nd Wave DAA	Future
Age >65			
BMI			
HIV	HIV	DDIs	
Black		Renal failure	
Cirrhosis	Ci s	Decompensate	*Dec ted*
Treat experie			
High viral l VL			
IL28B TT	Post-OLT	RAV	DAA failure
Genotype 1		Genotype 3	Genotype 3 +RAV
			ACCESS





2. New Population Needs New Treaters

- Next wave of chronic HCV
  - PWID/OST
  - MSM
  - Underinsured
  - Marginal Medical Literacy
- HCV therapy will move to the medical home

Strategies to Optimize Therapy

- **Simplify the regimen**
- **Decrease toxicity**
- **Shorten duration**
- **Improve efficacy**

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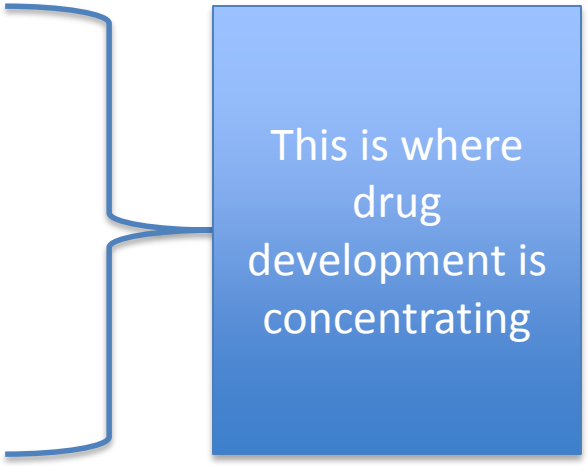

One Size Fits All

1. Expand Provider Pool
2. Lesson Paperwork
3. Eliminate Thought

SIMPLE

Simple
Independent of patient and viral characteristics

Ultra-SHORT

Rules
Rules
Rules

- Cirrhosis
- Genotype
- Sub Genotype
- Viral Load
- RAS
- DDIs

Difficult To Treat

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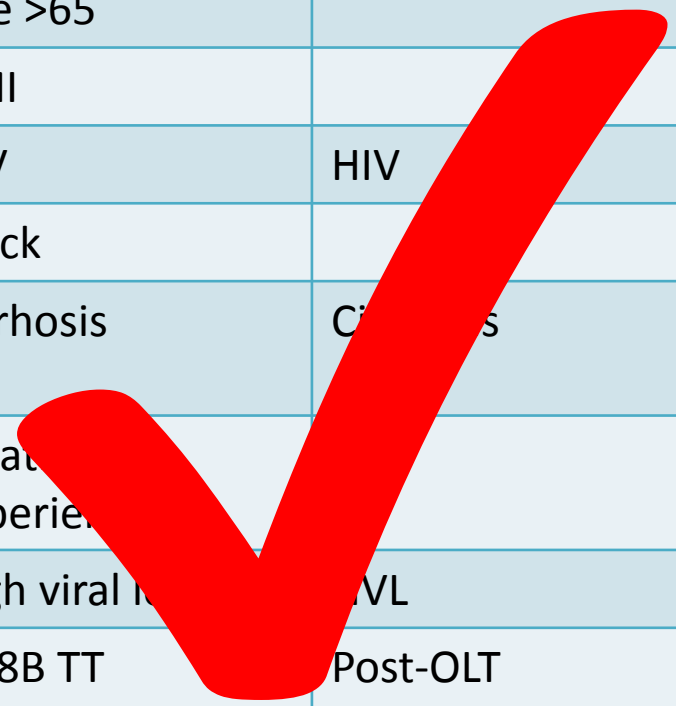


3. Confidence to be Cost Effective

- Shortening therapy lowers price

Clinical Question

- Does 8 weeks of LDV/SOF achieve SVR rates equal to ION-3?
- Are US providers using this therapy for TN, G1, non-cirrhotic with HCV PCR < 6 millions?

Guidelines: Is 8 Weeks An Option?

AASLD

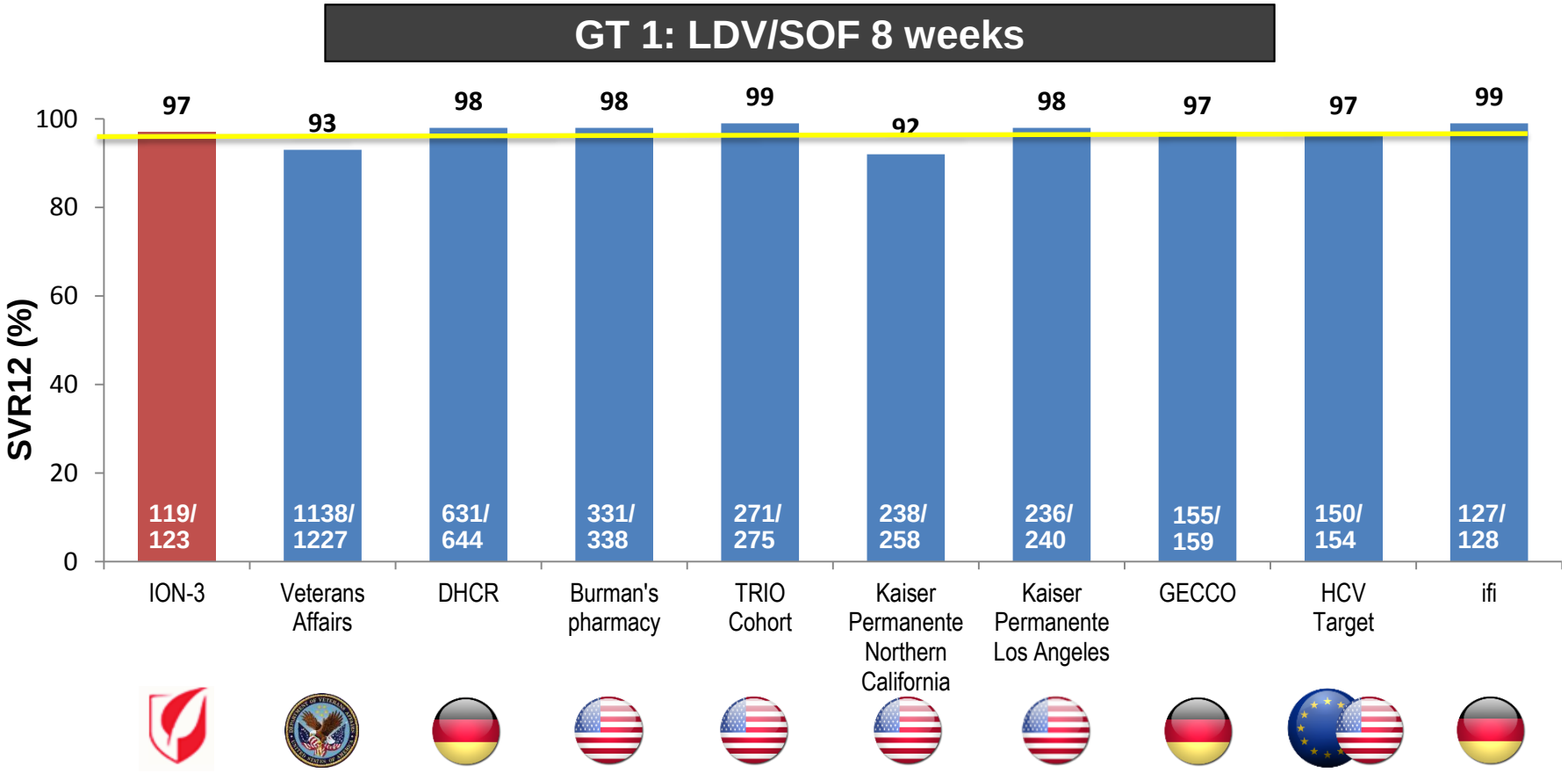
- Treatment Naïve, Non-cirrhotic
- Done at the discretion of the practitioner
- Not Recommended
  - HIV-infected patients
  - African-American patients,
  - IL28B polymorphism CT or TT.

EASL

- Treatment can be shortened to 8 weeks in treatment-naïve patients without cirrhosis if their baseline HCV RNA level is below 6 million (6.8 Log) IU/ml.
- This should be done with caution in patients with F3 fibrosis (**B1**).

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j. jhep.2016.09.001
www.HCVguidelines.org assessed 3/23/2017

SVR12 in ION-3 Compared to Real-World Cohorts



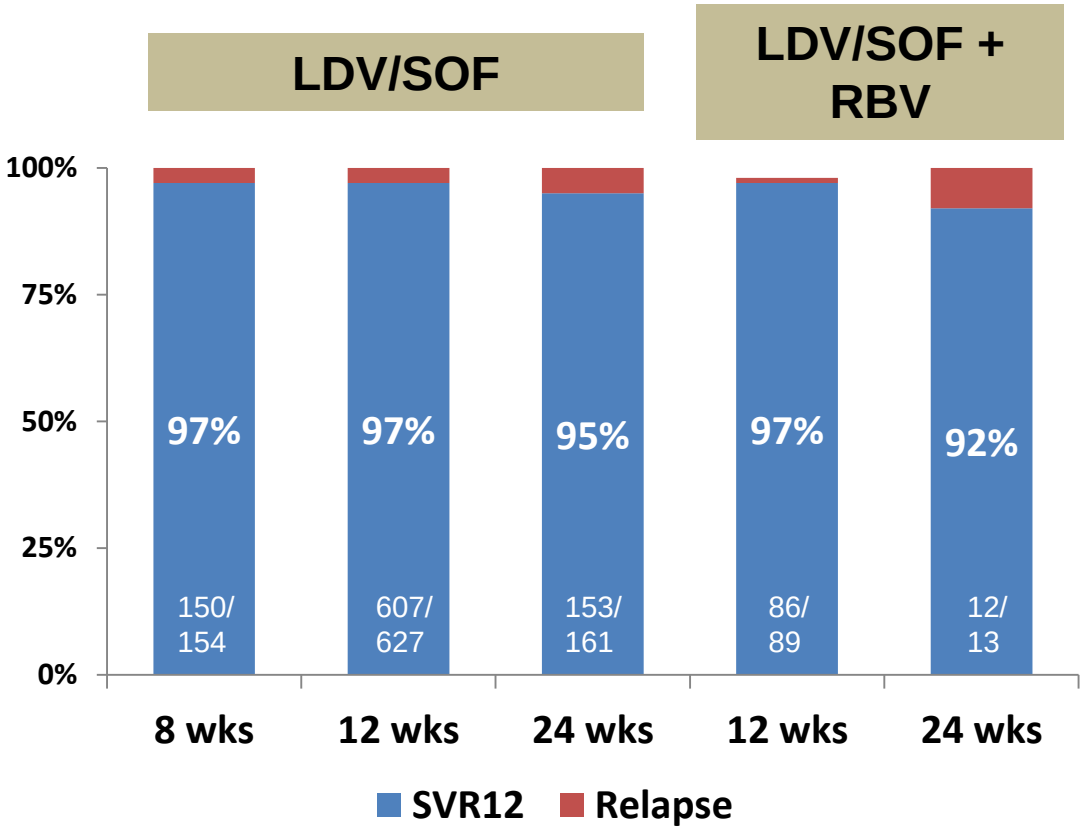
Kowdley. **ION-3**. NEJM *
Backus, **VA**, Hepatology 2016 ***
Afdhal. **TRIO**. LBP-519 ***
Buggisch. **IFI**. SAT-243 ***
Latt. **Kaiser**. SAT-227 **
Qureshi. **Burman's**. SAT-192 **
Terrault. **HCV-TARGET**. AASLD 2015 **
EASL 16 **
Curry. **GECCO**. AASLD 2015 ***
Buggisch. **DHC-R**. SAT-241 ***
Lai. **Kaiser**. SAT-177 ***

Real-World Data across >3,000 patients treated with LDV/SOF 8 weeks achieved high and comparable SVR to LDV/SOF 12 weeks

*Post hoc analysis ** Per Protocol *** ITT analysis ; patients were primarily treatment-naive non-cirrhotic patients with BL viral load < 6 million IU/mL

Real-World Efficacy of LDV/SOF ± RBV: HCV-TARGET

N (%)	HCV GT1 Patients (N = 1,270)
Treatment Status	
Naïve	674 (53)
Experienced	596 (47)
DAA Experienced	167 (13)
Cirrhosis	479 (38)
Decompensated	170 (13)
Liver Transplant	129 (10)
HIV	39 (3)



87% of G1, TN NC with HCV RNA <6 million IU/ mL;
35% received an 8-wk regimen -> 8-wk regimen is underutilized

Terrault N, et al. AASLD 2015; San Francisco, CA. Abstract 94.

4. Competition: Access and Price

The economic impact of competition

- **Competition affects market outcomes**
- More competition, more players, more dynamic entry and exit, and more intense rivalry for customers tend to deliver better market outcomes
- Outcomes include lower prices and better access to services for consumers

http://www.eldis.org/go/home&id=55701&type=Document#.WT2u91KZPK0

Medicine is a unique market

- Prices can not be easily discounted once a product comes to market
  - Drug development may be the only way to impact price until a generic is produced
- The “consumer” is not the entity who uses the drug
- Pricing is not transparent
- Each new agent upsets the balance

Difficult To Treat

Historic	First wave DAA	2nd Wave DAA	Future
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Cirrhosis	Ci s	Decompensated	*Decompensated*
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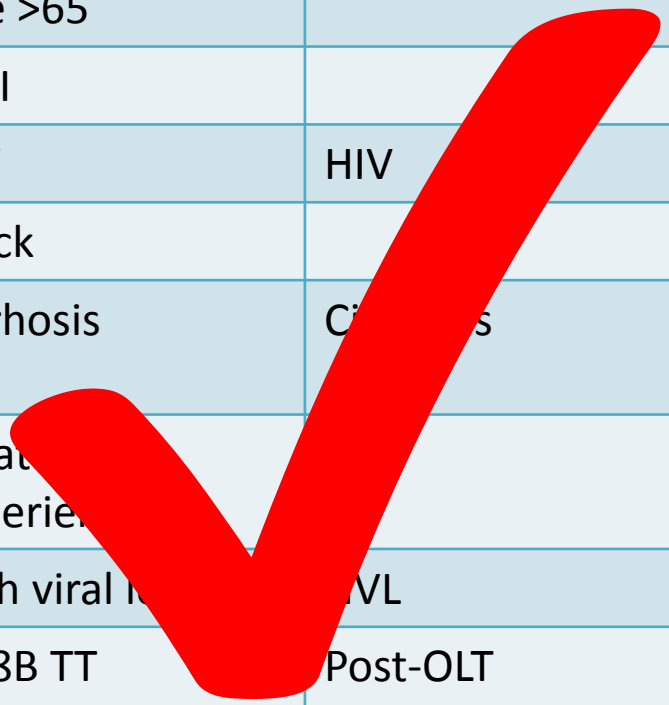
			ACCESS



Conclusions

1. Despite a cure, HCV is here to stay
2. Not all patients can be cured
3. New treaters entering work force need simple rules
4. Pricing still limits access which limits eradication