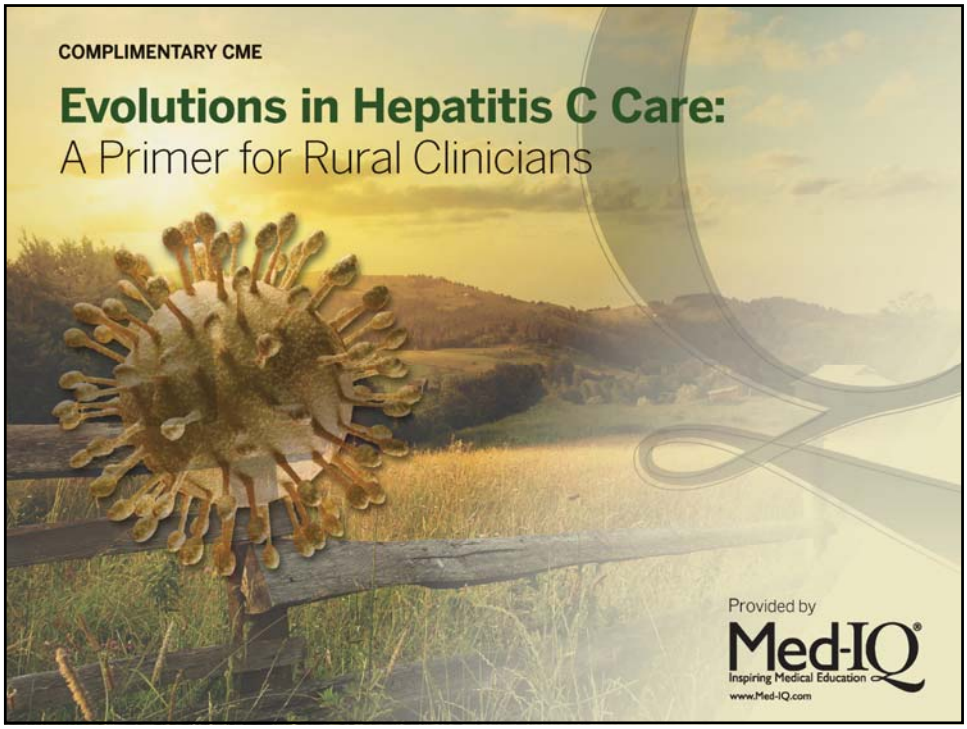
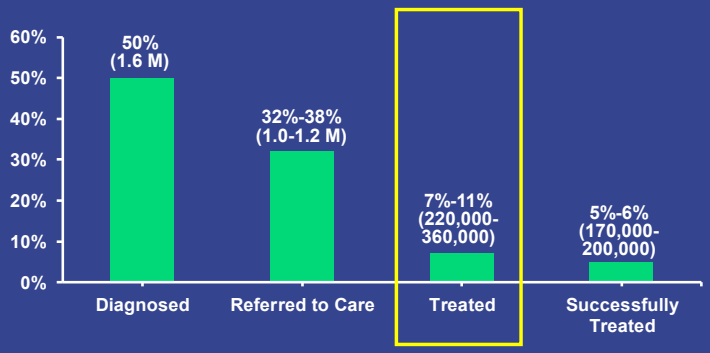


Learning Objectives

Upon completion, participants should be able to:

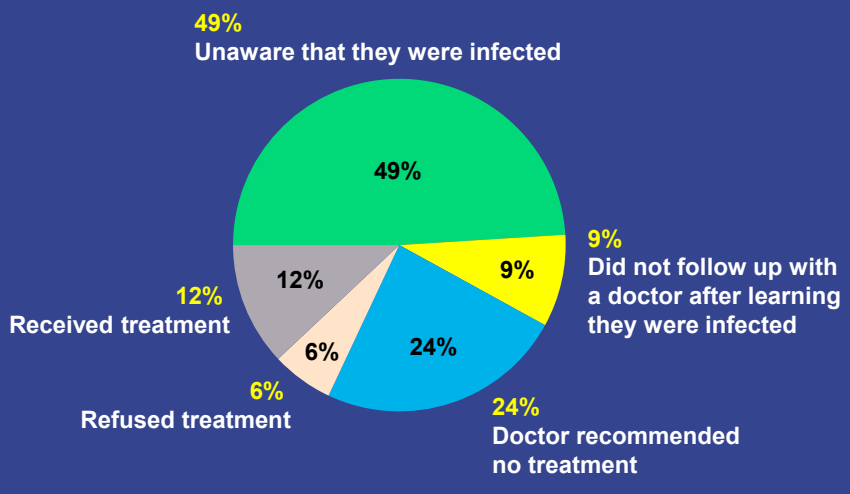
- Discuss the benefits and limitations of available direct-acting antiviral agents for the management of patients chronically infected with HCV
- Use patient characteristics and desires to appropriately and effectively choose HCV treatment strategies that maximize the potential of achieving a cure

Underdiagnosed and Undertreated



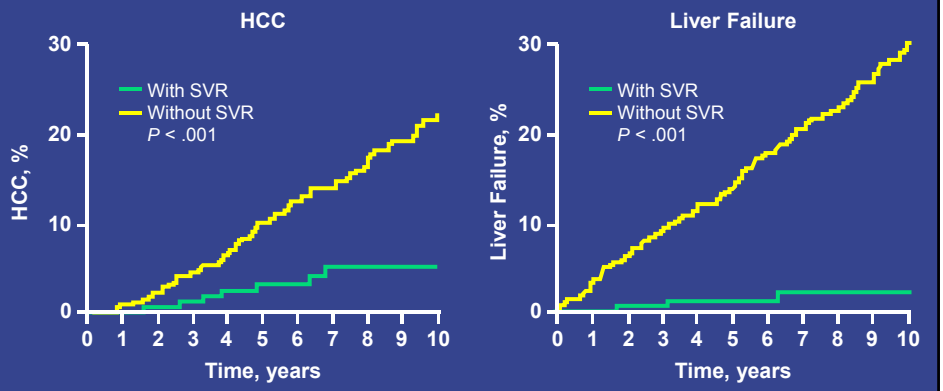
Holmberg SD, et al. *N Engl J Med*. 2013;368:1859-61.

Reasons for Lack of Treatment Among Patients With Chronic HCV



Adapted from Volk ML, et al. *Hepatology*. 2009;50:1750-5.

Clinical Benefits of SVR: Lower Rates of HCC, Liver Failure



- 530 Europeans and Canadians followed for a median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

HCC = hepatocellular carcinoma; SVR = sustained virologic response.

van der Meer AJ, et al. *JAMA*. 2012;308:2584-93.

How to Treat HCV

- GT1 is the most common type in the US
- Multiple, highly effective, oral-delivery antiviral regimens are available for HCV GTs
  - Interferon-α is no longer recommended
- New agents are direct-acting antivirals, which directly inhibit the life cycle of HCV

GT = genotype.

AASLD/IDSA. http://hcvguidelines.org.

How to Treat HCV

- Combinations of these pills can eradicate HCV from the body, resulting in undetectable HCV RNA levels 12 weeks after the completion of treatment
  - Termed an SVR, which is considered a viral cure

AASLD/IDSA. http://hcvguidelines.org.

Factors That Affect Treatment Decisions

- The most important predictors of achieving SVR:
  - HCV GT
  - Cirrhosis status
- These two factors also determine the appropriate combination of medications and duration of treatment

AASLD/IDSA. http://hcvguidelines.org.

Additional Treatment Considerations

Fibrosis	• Child-Pugh score • Cirrhosis • Cirrhosis with decompensation
Viral	• HCV GT • Viral load
Treatment history	• Treatment-naïve infection • Treatment-resistant infection • Prior treatments • RBV eligibility
Coinfection/ comorbidities	• HIV coinfection • Renal, cardiovascular, metabolic, etc. • Drug-drug interactions
Financial	• Insurance approval or coverage

RBV = ribavirin.

AASLD/IDSA. http://hcvguidelines.org.

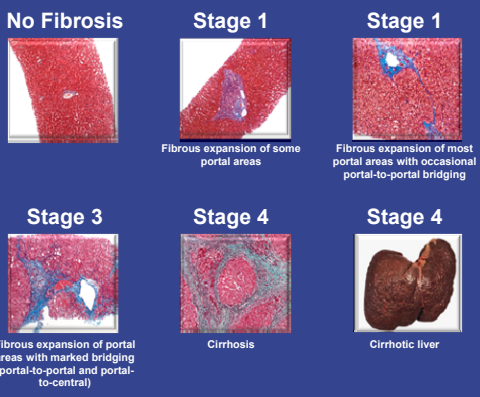
Importance of Assessing Fibrosis in HCV Treatment

- Determines urgency of therapy
- Selects patients with cirrhosis in need of additional screening for:
  - Varices
  - HCC
- Allows for the selection of proper treatment plan and duration of therapy
- May be used by many payers as a way to restrict access to therapy or prioritize therapy

AASLD/IDSA. http://hcvguidelines.org.

Liver Disease Staging Is Needed to Determine Advanced Fibrosis

- Noninvasive fibrosis markers are best at determining the likelihood a patient has:
  - No or little fibrosis (stage 0-1) OR
  - Advanced fibrosis (stage 3-4; bridging fibrosis to cirrhosis)
- If cirrhosis is present, patient requires HCC screening, EGD for varices, and counseling for liver harm reduction



EGD = esophagogastroduodenoscopy.

Foucher J, et al. *Gut*. 2006;55:403-8; Scott DR, et al. *Antivir Ther*. 2010;15:1-11.

Positive HCV Test Result: Next Steps

- Screen for immunity to hepatitis A virus (HAV antibody total) and hepatitis B virus (HBsAg, anti-HBs, and anti-HBc) and vaccinate if nonimmune
- Discuss risk of sexual transmission of HCV, which is low but not absent and which may not warrant barrier protection
  - Higher risk of sexual transmission among MSM, particularly those with HIV infection
- Assess alcohol use in all patients with HCV
  - There is no “safe” amount of alcohol consumption
  - Refer patients with risky use for alcohol treatment
- Screen children born to HCV-infected mothers

MSM = men who have sex with men.

AASLD/IDSA. http://hcvguidelines.org.

When and in Whom to Initiate Therapy

Recommendations for When and in Whom to Initiate Treatment

- Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owning to liver disease should be managed in consultation with an expert.
  Rating: Class I, Level A

- Critical changes:
  - Prioritization tables removed
  - Populations at risk of accelerated fibrosis progression mentioned:
    - GT3
    - HIV or hepatitis B virus coinfection
    - Nonalcoholic fatty liver disease

AASLD/IDSA. http://hcvguidelines.org.

What Makes a Regimen Recommended vs Alternative?

- Recommended—favored for most patients based on:
  - Optimal efficacy
  - Favorable tolerability and toxicity profiles
  - Shorter duration
  - Lower pill burden
- Alternative—have potential disadvantages:
  - Limted use in certain populations
  - Less supporting data

Alternative regimens may be the optimal regimen in select patients or situations.

AASLD/IDSA. http://hcvguidelines.org.

Treatment-Naïve Patients With GT1: Recommended vs Alternative

Treatment Naïve		LDV/SOF	DCV + SOF	SMV + SOF	PTV/r/OBV + DSV	EBR/GZR	VEL/SOF
1a	Noncirrhotic	12 wks	12 wks	12 wks	12 wks + R	No RAVs: 12 wks RAVs: 16 wks + R	12 wks
	Cirrhotic	12 wks	24 wks ± R	24 wks ± R	24 wks ± R	No RAVs: 12 wks RAVs: 16 wks + R	12 wks
1b	Noncirrhotic	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks
	Cirrhotic	12 wks	24 wks ± R	24 wks ± R	12 wks	12 wks	12 wks
Adverse events (occurring in ≥ 10% of patients)		Fatigue, headache, nausea	Fatigue, headache, nausea, rash, diarrhea	Fatigue, headache, nausea	Fatigue, headache, nausea, pruritus, insomnia	Fatigue, headache, nausea	Fatigue, headache, nausea, anemia

DCV = daclatasvir; DSV = dasabuvir; EBR = elbasvir; GBR = grazoprevir; LDV = ledipasvir; OBV = ombitasvir; PTV = paritaprevir; r = ritonavir; R = weight-based RBV; RAVs = EBR-specific NS5A RAVs (28, 30, 31, 93); SMV = simeprevir; SOF = sofosbuvir; VEL = velpatasvir.

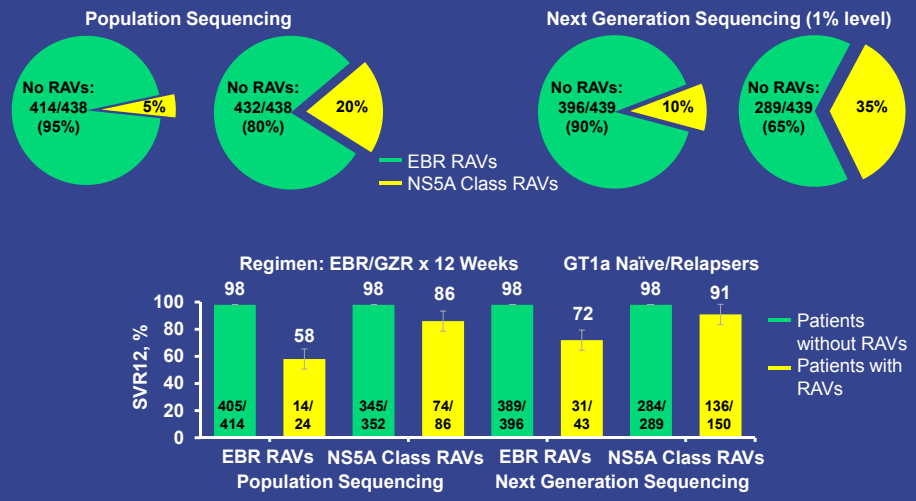
AASLD/IDSA. http://hcvguidelines.org.

Differentiators Among Regimens: Treatment-Naïve Patients

- LDV/SOF
  - 12 weeks without RBV for all treatment-naïve GT1 populations
- PTV/r/OBV + DSV
  - RBV for all GT1a populations
  - Extension to 24 weeks for GT1a cirrhotics
  - 12 weeks without RBV for all GT1b populations
- EBR/GZR
  - RAV testing recommended for all GT1a populations
    - Most will not have RAVs ➤ 12 weeks without RBV
  - 12 weeks without RBV for all GT1b populations
- VEL/SOF
  - 12 weeks without RBV for all GT1 populations (except those with decompensated cirrhosis)

AASLD/IDSA. http://hcvguidelines.org.

Effect of Baseline NS5A RAVs in GT1a Patients Treated With EBR/GZR

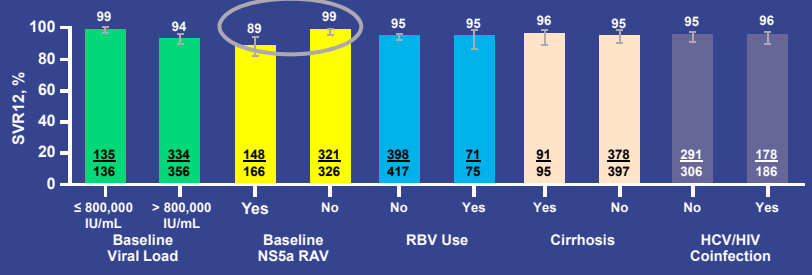


EBR RAVs = RAVs with > 5-fold shift in EBR EC50.

Jacobson I, et al. AASLD 2015; San Francisco, CA. Abstract LB-22.

EBR/GZR Efficacy in HCV GT1a: Resistance Is the Key Predictor of Response

Multivariable Logistic Regression Model	eOR (95% CI)	*P* Value
Baseline HCV > 800,000 IU/mL (ref = ≤ 800,000)	0.091 (0.012-0.695)	.0208
With baseline NS5A RAVs (ref = no baseline NS5A RAVs)	0.111 (0.040-0.309)	< .0001
RBV use (ref = no RBV use)	0.709 (0.218-2.300)	.5663
Cirrhotic (ref = noncirrhotic)	1.659 (0.518-5.315)	.3942
HCV/HIV coinfected (ref = HCV monoinfected)	1.113 (0.441-2.809)	.8205



Zeuzem S, et al. AASLD 2015; San Francisco, CA. Abstract 700.

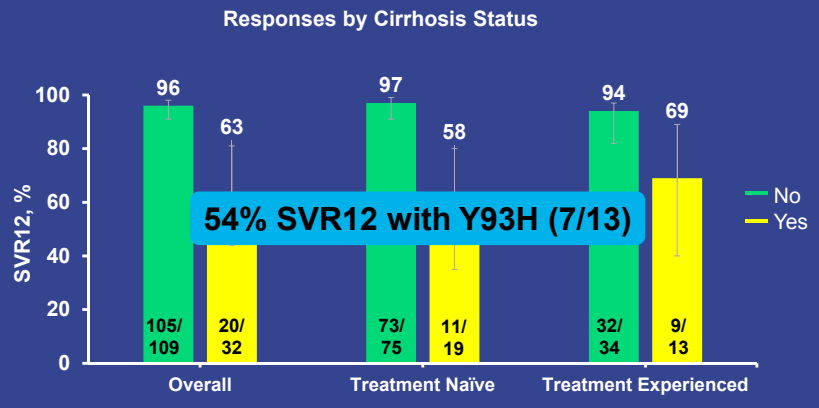
Treatment-Naïve Patients With GT2/3: Recommended vs Alternative

Treatment Naïve		SOF/VEL	DCV + SOF	SOF + RBV
2	Noncirrhotic	12 wks	12 wks	–
	Cirrhotic	12 wks	16-24 wks	–
Adverse events (occurring in ≥ 10% of patients)		Fatigue, headache, nausea, anemia	Fatigue, headache, nausea, rash, diarrhea	
3	Noncirrhotic	12 wks	12 wks	–
	Cirrhotic	12 wks[a,b]	24 wks ± R[a,b]	–
Adverse events (occurring in ≥ 10% of patients)		Fatigue, headache, nausea, anemia	Fatigue, headache, nausea, rash, diarrhea	

R = weight-based RBV.
[a]Consider RAV testing.
[b]Add RBV if Y93H.

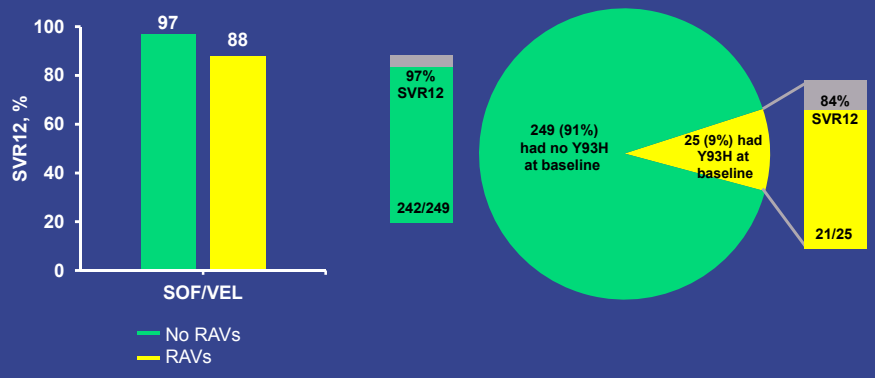
AASLD/IDSA. http://hcvguidelines.org.

Effect of Cirrhosis and Y93H in GT3



Nelson DR, et al. *Hepatology*. 2015;61:1127-35.

NS5A RAVs and Responses to SOF/VEL



Foster GR, et al. *N Engl J Med*. 2015;373:2608-17.

Treatment-Naïve Patients With GT4-6: Recommended vs Alternative

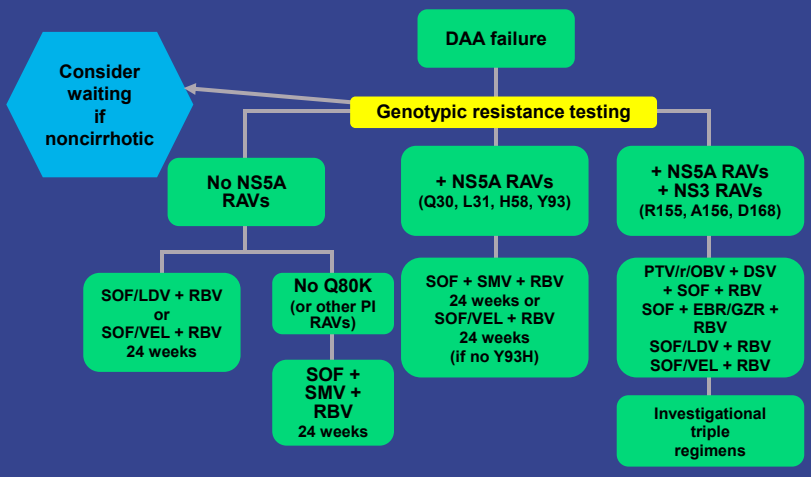
Treatment Naïve		LDV/SOF	PTV/r/OBV + DSV	EBR/GZR	SOF/VEL
4	Noncirrhotic	12 wks	12 wks + R	12 wks	12 wks
	Cirrhotic	12 wks	12 wks + R	12 wks	12 wks
Adverse events (occurring in ≥ 10% of patients)		Fatigue, headache, nausea	Fatigue, headache, nausea, pruritus, insomnia	Fatigue, headache, nausea	Fatigue, headache, nausea, anemia
5-6	Noncirrhotic	12 wks	–	–	12 wks
	Cirrhotic	12 wks	–	–	12 wks
Adverse events (occurring in ≥ 10% of patients)		Fatigue, headache, nausea			Fatigue, headache, nausea, anemia

R = weight-based RBV.

AASLD/IDSA. http://hcvguidelines.org.

Retreatment of HCV

Resistance Testing in Treatment-Experienced Patients



Wyles D. 2016.

Treatment-Experienced Patients With GT1: Recommended vs Alternative

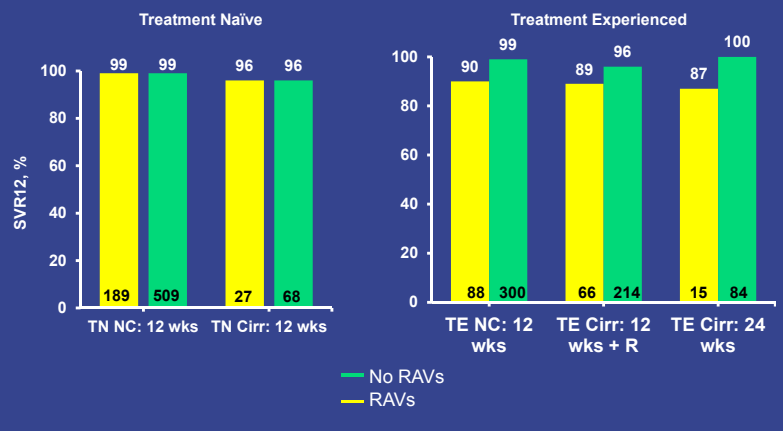
	IFN + RBV	LDV/SOF	DCV + SOF	SMV + SOF	PTV/r/OBV + DSV	EBR/GZR	SOF/VEL
1a	Noncirrhotic	12 wks	12 wks	12 wks	12 wks + R	No RAVs: 12 wks RAVs: 16 wks + R	12 wks
	Cirrhotic	12 wks + R[a] 24 wks[a]	24 wks ± R	24 wks ± R	24 wks + R	No RAVs: 12 wks RAVs: 16 wks + R	12 wks
1b	Noncirrhotic	12 wks	12 wks	12 wks	12 wks	12 wks	12 wks
	Cirrhotic	12 wks + R 24 wks	24 wks ± R	24 wks ± R	12 wks	12 wks	12 wks

[a]Consider RAV testing.

AASLD/IDSA. http://hcvguidelines.org.

Effect of Baseline NS5A RAVs With LDV/SOF

- SVR12 to guideline-recommended regimens of LDV/SOF by LDV RAV[a] status



[a]LDV RAVs at 24, 28, 30, 31, 32, 58, and 93 at 1% cutoff.

Zeuzem S, et al. AASLD 2015; San Francisco, CA. Abstract 91.

Treatment-Experienced Patients With GT1: Recommended vs Alternative

	PI + PEG + RBV	LDV/SOF	DCV + SOF	EBR/GZR	SOF/VEL
1	Noncirrhotic	12 wks	12 wks	No RAVs: 12 wks + R RAVs: 16 wks + R	12 wks
	Cirrhotic	12 wks + R[a] 24 wks[a]	24 wks ± R	No RAVs: 12 wks + R RAVs: 16 wks + R	12 wks

	SOF + RBV ± IFN	LDV/SOF
1	Noncirrhotic	12 wks + R
	Cirrhotic	24 wks + R

[a]Consider RAV testing.

AASLD/IDSA. http://hcvguidelines.org.

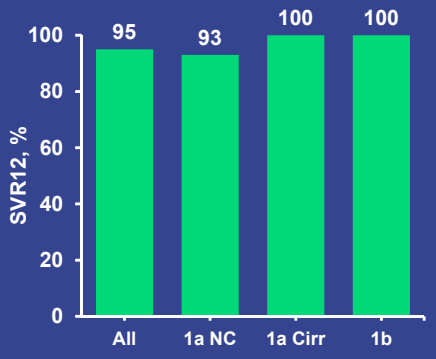
DAA-Experienced Patients: SOF + SMV or NS5A

- Consider deferral
- RAV testing if planning to proceed with therapy
- Nucleotide-based therapy—additional agents based on RAV testing
  - Extend therapy to 24 weeks
  - Use RBV if possible
- Consider nucleotide-based triple or quad regimens

AASLD/IDSA. http://hcvguidelines.org.

Retreatment With SOF + PTV/r/OBV + DSV

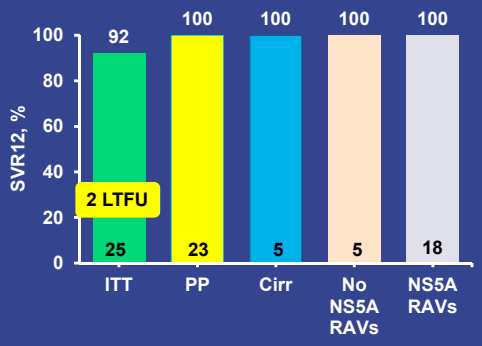
- 22 DAA-treated patients
  - 20 GT1a, 2 GT1b
    - 6/22 with cirrhosis
  - 14/20 GT1a failed 3D regimen
  - No LDV/SOF failures
- RAVs
  - 5 with D168E/V
  - 4 with Y93C/F/H
  - 12 with Q30E/H/R
- SOF + PTV/r/OBV + DSV
  - RBV for all GT1a
  - 24 weeks for GT1a with cirrhosis



Poordad F, et al. EASL 2016; Barcelona, Spain. Abstract SAT-156.

Retreatment of SOF + EBR/GZR Failures

- 25 patients who failed short-course SOF + EBR/GZR (4-8 weeks)
- 22 GT1a, 3 GT1b
  - 20 failed 4 weeks
- 5 (20%) with cirrhosis
- 80% with NS5A RAVs
- 52% with NS3 RAVs
  - 44% with NS3/NS5A RAVs
- SOF + EBR/GZR + RBV for 12 weeks



- 100% SVR12 (9/9) in patients with dual RAVs

Lawitz E, et al. EASL 2016; Barcelona, Spain. Abstract SAT-148.

Treatment-Experienced Patients With GT2/3: Recommended vs Alternative

	IFN + RBV	SOF/VEL	DCV + SOF
2	Noncirrhotic	12 wks	12 wks
	Cirrhotic	12 wks	16-24 wks
3	Noncirrhotic	12 wks[a,b]	12 wks[a,b]
	Cirrhotic	12 wks + R	24 wks + R

	SOF + RBV	DCV + SOF	SOF/VEL
2	ANY	24 wks ± R[a,b]	12 wks
3	ANY	24 wks + R	12 wks + R

R = weight-based RBV.
[a]Consider RAV testing.
[b]Add RBV if Y93H.

AASLD/IDSA. http://hcvguidelines.org.

Treatment-Experienced Patients With GT4-6: Recommended vs Alternative

	PEG/RBV	LDV/SOF	PTV/r/OBV	EBR/GZR	SOF/VEL
4	Noncirrhotic	12 wks	12 wks + R	REL:12 wks NR: 16 wks + R	12 wks
	Cirrhotic	12 wks + R 24 wks	12 wks + R	REL:12 wks NR: 16 wks + R	12 wks
5-6	Noncirrhotic	12 wks	--	--	12 wks
	Cirrhotic	12 wks	--	--	12 wks

R = weight-based RBV; REL = relapsed; NR = non-responsive.

AASLD/IDSA. http://hcvguidelines.org.

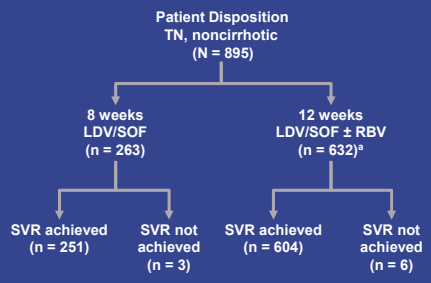
On-Treatment Monitoring

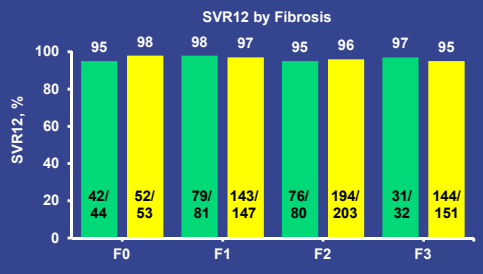
- Week 2
  - LFTs with PTV/r/OBV + DSV
- Week 4
  - CBC, Cr, LFTs
  - HCV RNA—repeat at week 6 if detectable
    - Stop if > 1 log increase in HCV RNA after week 4
    - No recommendation to stop or extend based on detectable but < LLOQ
- Week 8
  - LFTs with EBR/GZR (also at week 12 if 16 weeks total)
- Stop therapy for ALT > 10 × baseline
  - Stop for < 10 × baseline if symptoms also present (or elevated bilirubin/INR)

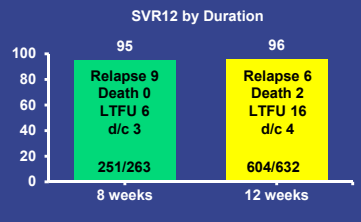
ALT = alanine aminotransferase; CBC = complete blood count;
Cr = creatinine; INR = international normalized ratio;
LFTs = liver function tests; LLOQ = lower limit of quantification.

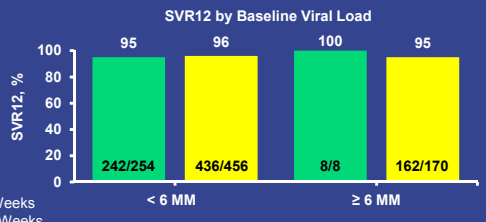
AASLD/IDSA. http://hcvguidelines.org.

Real-World Experience From the TRIO Network:
Effectiveness of 8- or 12-Week LDV/SOF in Treatment-Naive, Noncirrhotic GT1 Patients









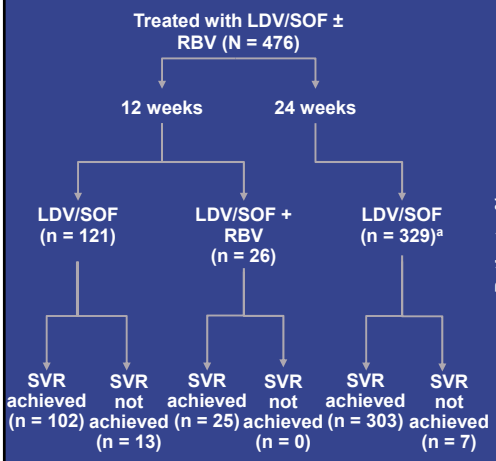
8 Weeks
12 Weeks

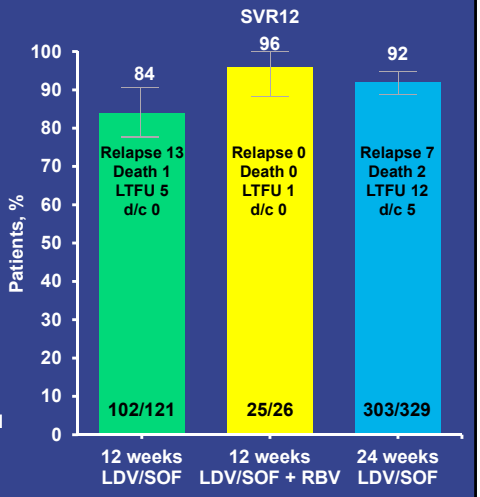
[a]21 patients were on 12 weeks of LDV/SOF + RBV.

Curry M, et al. AASLD 2015; San Francisco, CA. Abstract 1046.

Real-World Experience From the TRIO Network:

Effectiveness of 12- or 24-Week LDV/SOF and 12-Week LDV/SOF + RBV in Treatment-Experienced, Cirrhotic GT1 Patients



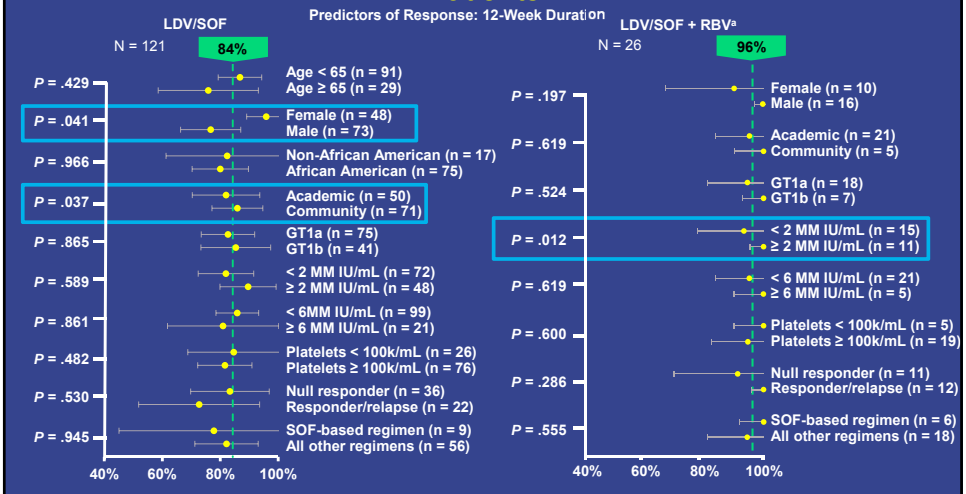


[a]8 of 329 were treated with 24 weeks of LDV/SOF + RBV.

Curry M, et al. AASLD 2015; San Francisco, CA. Abstract 1108.

Real-World Experience From the TRIO Network:

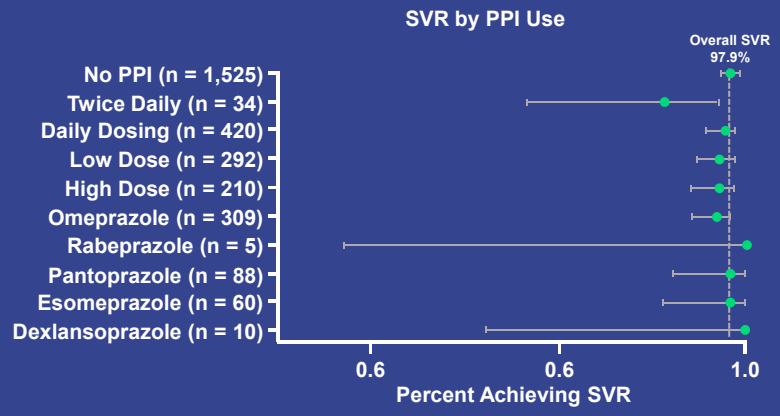
Effectiveness of 12- or 24-Week LDV/SOF and 12-Week LDV/SOF + RBV in Treatment-Experienced, Cirrhotic GT1 Patients



Closed circles = SVR12; whiskers = 95% confidence interval.
[a]Age excluded from LDV/SOF + RBV plot due to n < 5 in 65+ group.
Ethnicity excluded from LDV/SOF + RBV plot due to n < 5 in African American group.

Curry M, et al. AASLD 2015; San Francisco, CA. Abstract 1108.

Predictors of Response By PPI Usage: HCV-TRIO Real-Life Data



PPI = proton pump inhibitor.
Closed circles = proportions; whiskers = 95% confidence interval.

Tapper EB, et al. *Hepatology.* 2016. [epub ahead of print].

Real-World Experience From the TRIO Network: All Patients

- Observed SVR12 rates similar to those in clinical trials
  - LDV/SOF: 94.1%
  - LDV/SOF + RBV: 97.4%
- No differences in SVR rates by:
  - Age
  - Sex
  - Ethnicity
  - Prior treatment experience
  - HIV coinfection
  - Liver transplant
- Two significant predictors of lower SVR rates:
  - Treatment in an academic center (92.4% vs 96.0%; $P < .0001$)
  - Treatment not in alignment with FDA labeling (85.2% vs 95.1%; $P < .0001$)

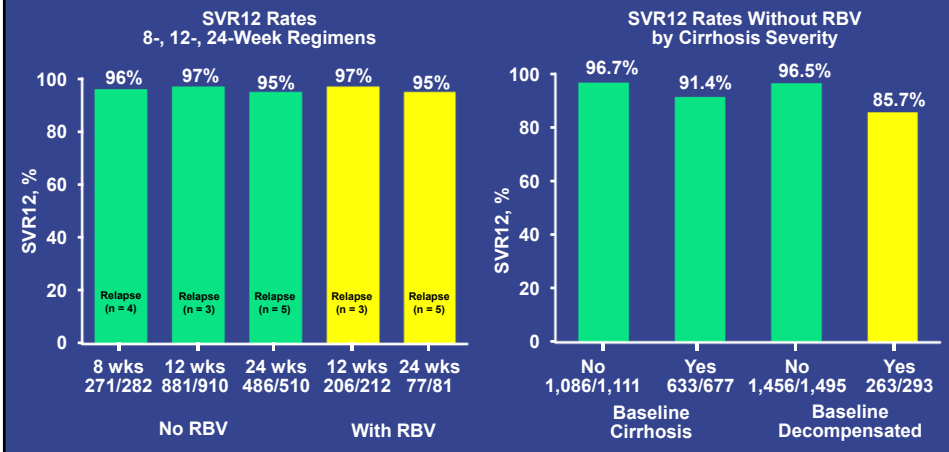
Tapper EB, et al. *J Viral Hepatol.* 2016. [epub ahead of print].

Treatment Outcomes With 8-, 12-, and 24-Week Regimens of LDV/SOF: Analysis of a Multicenter, Prospective, Observational Study

- Patients treated according to local standards of care at academic (n = 44) and community medical centers (n = 17) in North America and Europe
- N = 2,389 started treatment, virologic outcome known for 2,099
  - 60% male, median age 60 years, 25% black, 66% GT1a, 27% GT1b, 50% TN
  - 41% cirrhotics (18% decomp), 4% HIV coinfection, 13% had received LT
- Patients who received RBV more likely to:
  - Be treatment experienced (67% vs 47%)
  - Have cirrhosis (58% vs 38%)
  - Have lower baseline platelet counts (median 133 vs 176 x 10^3/μL)
  - Have a history of hepatic decompensation (29% vs 17%)
  - Have received liver transplant (48%)
- 586 patients qualified for 8-week treatment duration, of these 255 (44%) received 8 weeks
  - SVR rates were similar for those who qualified and received 8 weeks vs those who qualified for 8 weeks but received 12 weeks (96% vs 98%)
- Adverse events reported in 66% of patients (headache, 21.5%; fatigue, 24.7%; infections and infestations, 9.0%; nausea, 8.8%; diarrhea, 7.1%; insomnia, 6.5%)
  - Serious adverse events reported in 5% of all patients who started therapy

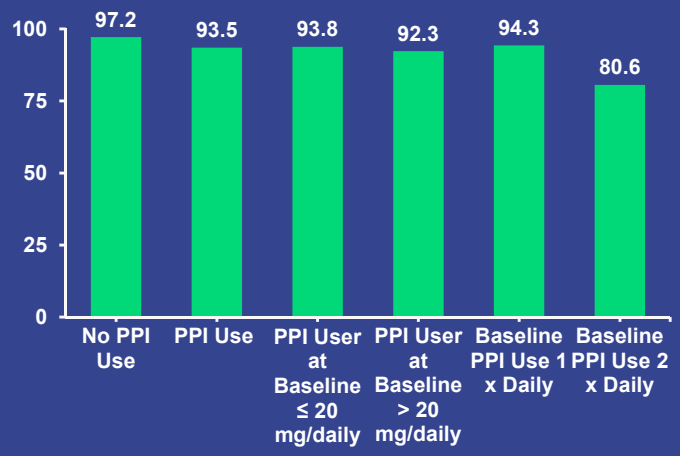
Terrault N, et al. *Gastroenterology*. 2016. [epub ahead of print].

HCV TARGET: SVR12 Rates With LDV/SOF ± RBV in HCV GT1



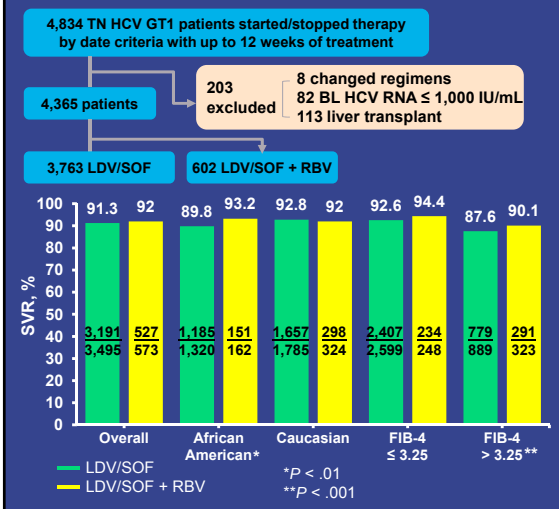
Terrault N, et al. *Gastroenterology*. 2016. [epub ahead of print].

HCV TARGET: Real-World Data for PPIs and SVR



Terrault N, et al. *Gastroenterology*. 2016. [epub ahead of print].

Effectiveness of LDV/SOF in Treatment-Naive GT1 Patients Treated in Routine Medical Practice: VA



- No significant differences in unadjusted SVR based on age, sex, decompensated liver disease, DM, HIV coinfection, BMI, baseline HCV RNA, subtype, and IL28B polymorphism.

SVR by LDV/SOF Tx Duration in TN GT1

	LDV/SOF	
	8 weeks	12 weeks
Overall	92.1% (1,169/1,269)	94.3% (1,924/2,040)
Undetectable Wk 4 on Tx HCV RNA	94.7% (880/929)	96.0% (1,268/1,321)
Detectable < 15 IU/mL Wk 4 on Tx HCV RNA	92.3% (84/91)	94.4% (169/179)
Detectable ≥ 15 IU/mL Wk 4 on Tx HCV RNA	87.2% (75/86)	89.6% (301/336)

- SVR rates nearly matched those in clinical trials
- African American, FIB-4 > 3.25, and 8-week treatment duration were predictors associated with decreased SVR

Backus L, et al. *Hepatology*. 2016;64:405-14.

HCV Treatment Considerations Among PWIDs

- Treatment is recommended for PWIDs with chronic HCV infection
- History of injection drug use and recent drug use at treatment initiation are not associated with reduced SVR
- The decision to initiate therapy should be based on the availability of agents and disease characteristics
- DAA therapy does not require specific methadone and buprenorphine dose adjustment; monitor for signs of opioid toxicity or withdrawal
- PWIDs with ongoing social issues, history of psychiatric disease, and those with more frequent drug use during therapy are at risk of lower adherence; counsel on the importance of adherence
- Clinical management should include harm-reduction programs, social work, and social support services

PWIDs = persons who inject drugs.

Grebely J, et al. *Int J Drug Policy*. 2015;26:1028-38.

HCV Reinfection Following SVR: Considerations Among PWIDs

- Do not exclude HCV treatment based on perceived risk of reinfection
- After SVR, monitor for HCV reinfection annually among PWIDs with ongoing risk behaviors
- Provide harm-reduction education and counseling to prevent HCV reinfection

Grebely J, et al. *Int J Drug Policy*. 2015;26:1028-38.

Treatment as Prevention: Can We Get in Front of This Epidemic?

- Extrapolation from HIV treatment and theoretical evidence point to its potential
- Treating contacts of an HCV-infected individual or treating high-risk injection drug users may have a greater positive effect than random treatment of all injection drug users
- Efficacy of these strategies has not been proven in clinical studies

Hickman M, et al. *Curr Opin Infect Dis.* 2015;28:576-82.

Faculty Discussion

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Contact Information

Call (toll-free) 866 858 7434
E-mail info@med-iq.com

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