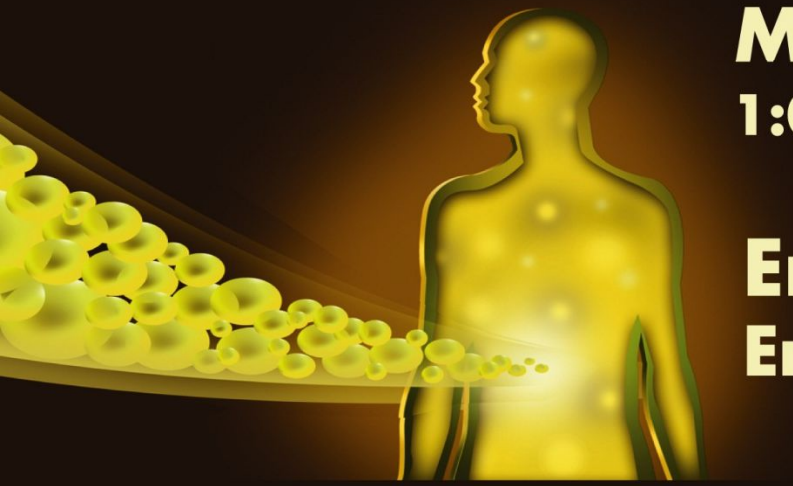
INTERACTIVE CPE SYMPOSIUM

INDIVIDUALIZING TREATMENT REGIMENS FOR HEPATITIS C:

A 2016 Update for Specialty Pharmacists



Monday, May 2, 2016
1:00 – 2:30 PM • Interactive CPE Activity

Encore at Wynn Las Vegas
Encore Ballroom 1-3

This symposium will provide live credit (L) for those states requiring it.

Supported by an educational grant from Merck & Co Inc.

Presented by The University of Tennessee College of Pharmacy

University of Tennessee College of Pharmacy

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Disclaimer

The following presentation was recorded in May 2016. Since then the following changes have occurred:

- Sofosbuvir/velpatasvir was approved in June 2016
- It is the first FDA approved pan-genotypic Hepatitis C therapy and is recommended by the AASLD guidelines as a treatment option for all HCV genotypes

Participating Faculty

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Disclosures

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Pamela S. Belperio, PharmD, BCPS, AAHIVE, reports having no relevant financial or advisory relationships with corporate organizations related to this activity.

Brittany Mills, PharmD, MBA, BCACP, AAHIVP, reports having no relevant financial or advisory relationships with corporate organizations related to this activity.

Agenda

1:00–1:05 PM	**Welcome and Conference Goals** *Pamela S. Belperio, PharmD, BCPS, AAHIVE*
1:05–1:15 PM	**Current Status of HCV Therapy** *Brittany Mills, PharmD, MBA, BCACP, AAHIVP*
1:15–1:25 PM	**Considerations for Individualized Treatment** *Brittany Mills, PharmD, MBA, BCACP, AAHIVP*
1:25–1:40 PM	**Latest Guideline-Based Therapy Recommendations** *Pamela S. Belperio, PharmD, BCPS, AAHIVE*
1:40–1:55 PM	**Emerging Treatment Options and Trends** *Pamela S. Belperio, PharmD, BCPS, AAHIVE*
1:55–2:15 PM	**Pharmacist-Led Education Strategies** *Brittany Mills, PharmD, MBA, BCACP, AAHIVP*
2:15–2:25 PM	**Q&A Session** *Pamela S. Belperio, PharmD, BCPS, AAHIVE, and Brittany Mills, PharmD, MBA, BCACP, AAHIVP*
2:25–2:30 PM	**Closing Remarks and Educational Outcomes Activity** *Pamela S. Belperio, PharmD, BCPS, AAHIVE*

Learning Objectives

- **ASSESS** individualized treatment plans for HCV treatment and associated monitoring parameters.
- **RECOGNIZE** patient-specific disease state complications relevant to drug therapy selection and modifications.
- **EVALUATE** benefits, risk, and characteristics of drugs in the HCV pipeline.
- **RECOMMEND** strategies to cope with social challenges and increase patient adherence with therapy.

HCV = hepatitis C virus.

CPE Information

INTENDED AUDIENCE – This activity is designed for specialty pharmacists in attendance at the 2016 Armada Specialty Pharmacy Summit. No prerequisites required.

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DISCLAIMER – The opinions and recommendations by faculty and other experts whose input is included in this educational activity are their own. Please review the complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects, before administering pharmacologic therapy to patients.

Educational Grant

The University of Tennessee
College of Pharmacy
would like to acknowledge an
educational grant from
Merck & Co.,
which helped to make this activity possible.

Current Status of HCV Therapy

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Clinical Pharmacist, Pharmacy Manager
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Chicago, Illinois

Hepatitis C Virus (HCV) in the US

- Most common blood-borne infection
  - Estimated 2.5 to 4.7 million infected in the United States
- Chronic, slow disease progression
  - Most patients remain undiagnosed.
  - Prevalence estimated to be as high as 11% in 1945–1965 cohort.
- Leading cause of:
  - Liver disease: cirrhosis, liver cancer
  - Liver transplantation
  - Liver-related mortality
- High financial burden

Edlin BR, et al. *Hepatology*. 2015;62:1353-1363; Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis – United States, 2013. Updated October 19, 2015; Spradling PR, et al. *Clin Infect Dis.* 2012;55:1047-1055.

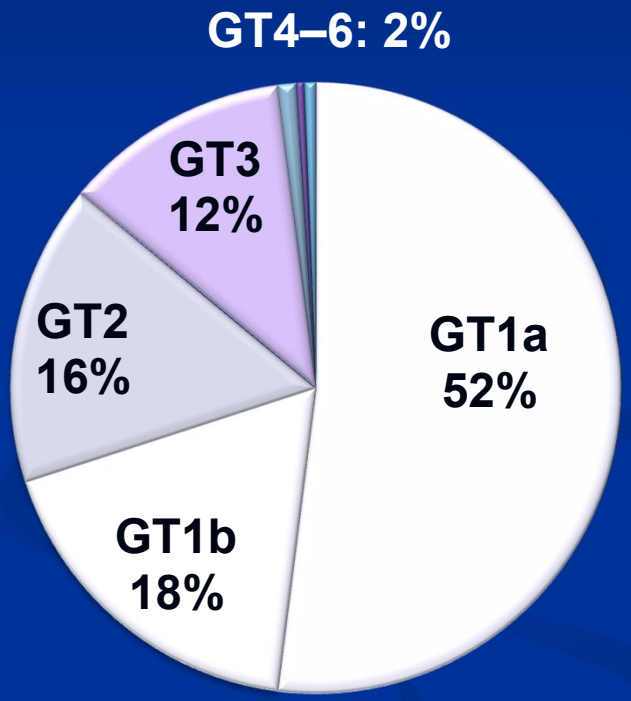
Goal of HCV Treatment

Sustained virologic response (SVR) = Viral Cure

Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis – United States, 2013. Updated October 19, 2015.

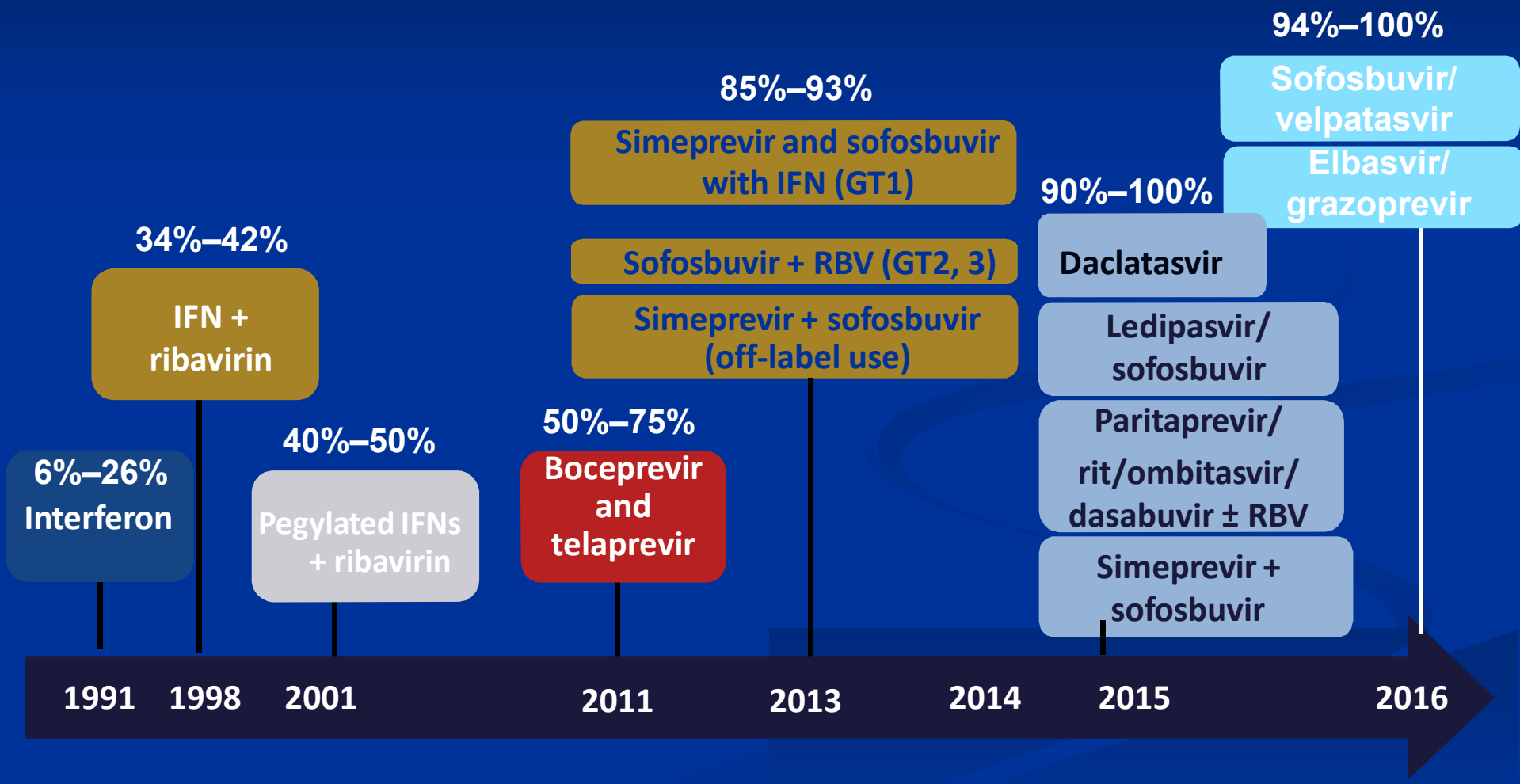
HCV Genotypes

- Six genotypes: GT1–6
  - Subtypes (a, b, c)
- GT1a and GT1b: most common
- GT1–3: broad geographic representation
- GT4–6: cluster geographically
- Treatment regimen differs based on genotype.



Manos MM, et al. *J Med Virol.* 2012;84:1744-1750.

HCV Therapy: Past, Present, and Future



GT = genotype; IFN = interferon; RBV = ribavirin.

HCV Treatment: Paradigm Shift

1 DAA + Peg-IFN/RBV (Triple Therapy)

2011–2014

- Boceprevir
- Telaprevir
- Simeprevir
- Sofosbuvir

IFN-Free Oral Regimens

Late 2014–2015

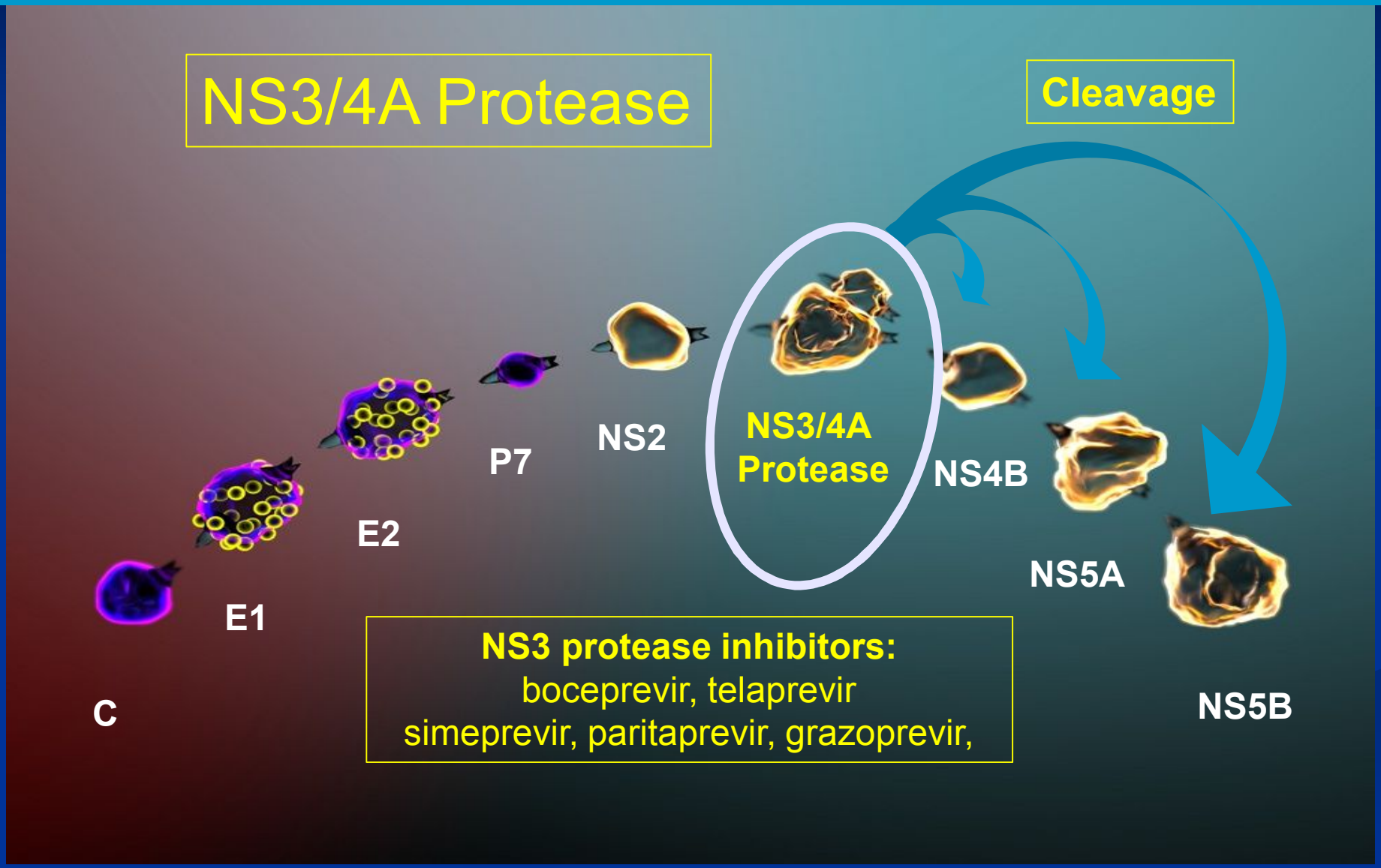
- SOF + simeprevir ± RBV
- SOF/LDV (fixed-dose combination) ± RBV
- Ombitasvir/paritaprevir/ritonavir and dasabuvir ± RBV

DAA = direct-acting antiviral; LDV = ledipasvir; SOF = sofosbuvir.

HCV Therapy Continues to Evolve into 2016

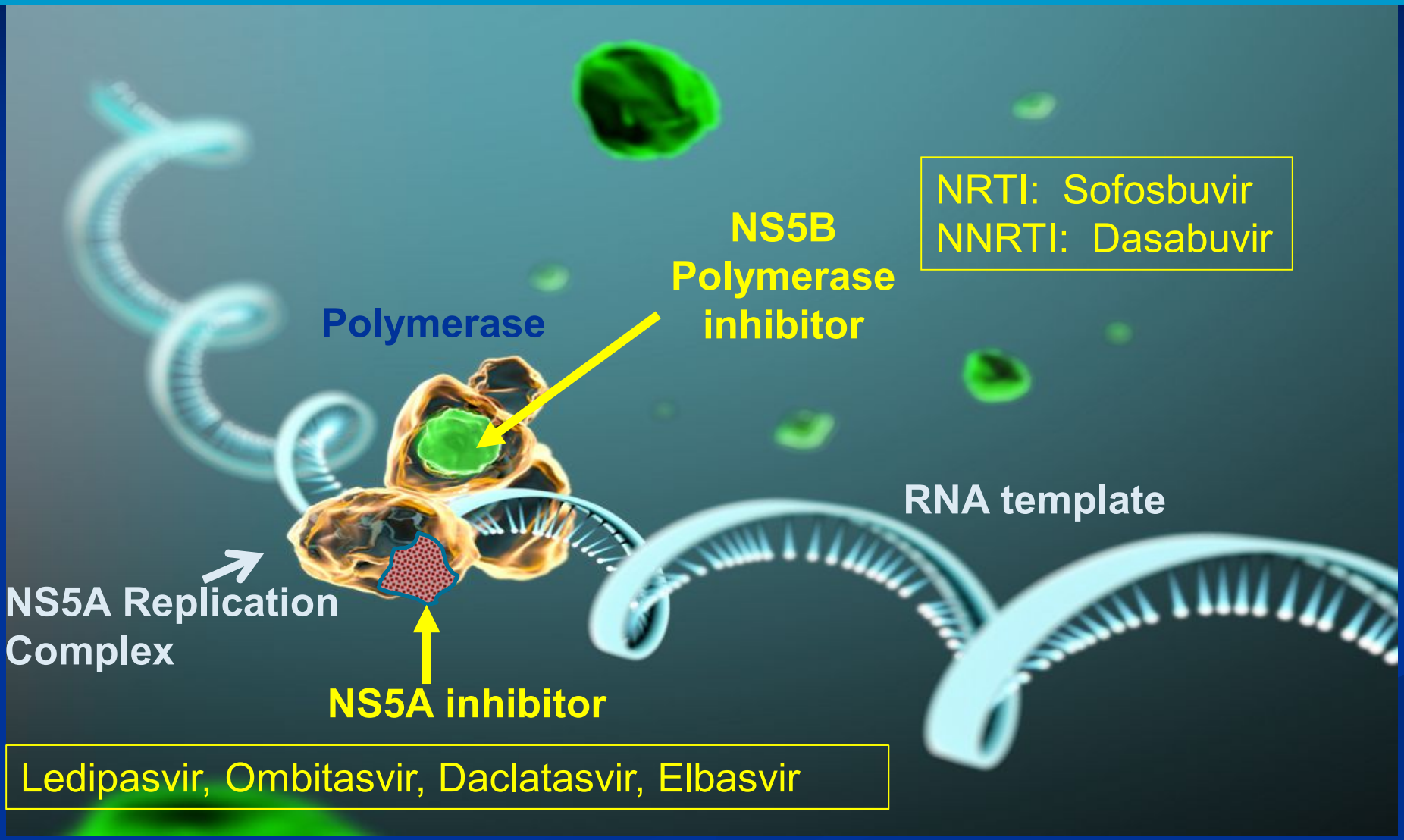
- Daclatasvir
  - August 2015: GT3, must be used with sofosbuvir
  - February 2016: GT1, must be used with sofosbuvir
- Elbasvir/grazoprevir
  - January 2016: GT1 and GT4

NS3/4A Protease Cleaves the HCV Polyprotein



Kwong A, et al. *Drug Discov Today*. 2006;3:211-220. For educational purposes only.

Inhibition of the NS5B Polymerase or NS5A Halts HCV Replication



NNRTI = non-nucleoside reverse transcription inhibitor; NRTI = nucleoside reverse transcription inhibitor.

Kwong A, et al. *Drug Discov Today*. 2006;3:211-220.

Classes of DAAs in Available Products

	NS3/4A (protease inhibitor)	NS5A	NS5B (polymerase inhibitor)
LDV/SOF		Ledipasvir	Sofosbuvir (NRTI)
OPrD	Paritaprevir	Ombitasvir	Dasabuvir (NNRTI)
EBR/GZR	Grazoprevir	Elbasvir	
Daclatasvir		Daclatasvir	
Genetic barriers to resistance	**Low**	**Lowest**	**High (uncommon)**

EBR/GZR = elbasvir/grazoprevir; OPrD = ombitasvir, paritaprevir, ritonavir, and dasabuvir.

AASLD/IDSA HCV Guidelines; FDA package labeling.

Considerations for Individualized Treatment

Brittany Mills, PharmD, MBA, BCACP, AAHIVP
Clinical Pharmacist, Pharmacy Manager
Walgreens at Howard Brown Health Center
Chicago, Illinois

Baseline Factors That May Influence Response

Viral Factors	• **HCV RNA level** • **HCV genotype (GT1, 2, 3, 4, 5, 6)** • **Genotype subtype (GT1a vs 1b)**
Host Factors	• **Race/ethnicity** • **Gender** • **IL28B (CC, CT, TT)** • **BMI**
Stage of Liver Disease	• **Compensated vs decompensated**

BMI = body mass index.

AASLD/IDSA HCV Guidelines.

Patient Considerations for Selecting HCV Treatment

- Treatment history
  - Peg-IFN/RBV, HCV protease inhibitor, SOF
- Comorbidities
  - Potential for drug-drug interactions
- Ability to adhere to treatment goals and monitoring
- Active substance use disorders
- Insurance

AASLD/IDSA HCV Guidelines.

Drug Characteristics: Availability of All-Oral Regimens by Genotype

Regimen	GT1	GT2	GT3	GT4	GT5/6
Sofosbuvir + RBV	√	√	√	√	
Simeprevir + sofosbuvir	√				
Ledipasvir/ sofosbuvir	√			√	√
Ombitasvir/ paritaprevir/ritonavir and dasabuvir	√			√ No dasabuvir	
Daclatasvir + sofosbuvir	√		√		
Elbasvir/grazoprevir	√			√	

AASLD/IDSA HCV Guidelines; FDA package labeling.

Comparison of Drug Profiles

	NS3/4A PIs, 1st Generation	NS3/4A PIs 2nd Generation	NS5A Inhibitor	Nucleoside NS5B Inhibitor	Nonnucleo-side NS5B Inhibitor
Efficacy					
Pan-genotypic efficacy					
Resistance profile					
Adverse events					
Drug-drug interactions					
Dosing	tid	qd-bid	qd	qd	bid

 Good  Moderate  Less favorable

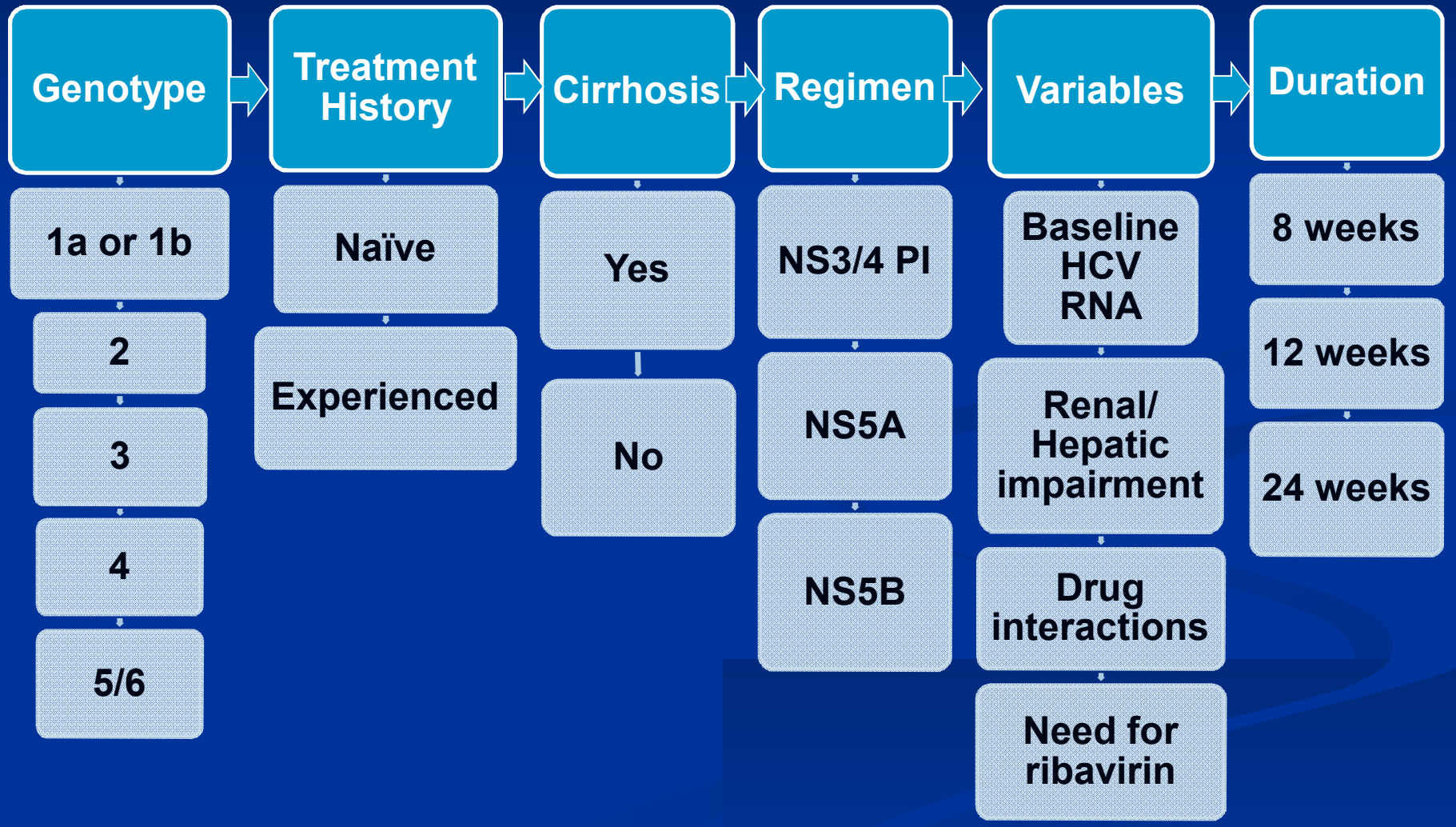
bid = twice a day; PI = protease inhibitor; qd = every day; tid = 3 times a day.

Farnik H, et al. *Antivir Ther*. 2012;17:771-783; Schinazi R, et al. *Liver Int*. 2014;34:69-78.

Multiple Factors

HCV Genotype	Fibrosis Stage	Extrahepatic Manifestations
Comorbidities	Contraindications Drug Interactions	Treatment History
Occupation	Social and Behavioral Support	Personal Plans

Individualized Treatment Strategy



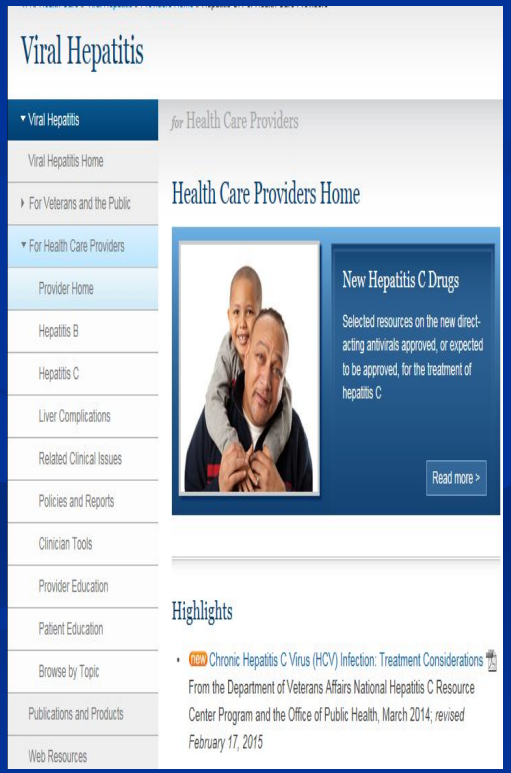
Latest Guideline-Based Therapy Recommendations

Pamela S. Belperio, PharmD, BCPS, AAHIVE
National Public Health Clinical Pharmacist
VA Office of Public Health/Population Health
Department of Veterans Affairs
Los Angeles, California

Guideline-Based Therapy Recommendations

- **AASLD-IDSA guidelines**
  http://www.hcvguidelines.org/

- **Department of Veterans Affairs Treatment Considerations**
  http://www.hepatitis.va.gov/provider/index.asp



AASLD = American Association for the Study of Liver Diseases; IDSA = Infectious Diseases Society of America.

Highlights

- Testing and Linkage to Care
- When and In Whom to Initiate Therapy
- Overview of Cost, Reimbursement, and Cost-effectiveness Considerations for Hepatitis C Treatment Regimens
- Initial Treatment and Retreatment
- Unique Patient Populations
  - HIV/HCV Coinfection
  - Decompensated Cirrhosis
  - Post-Liver Transplant
  - Renal Impairment
- Acute HCV Infection

AASLD/IDSA HCV Guidelines.

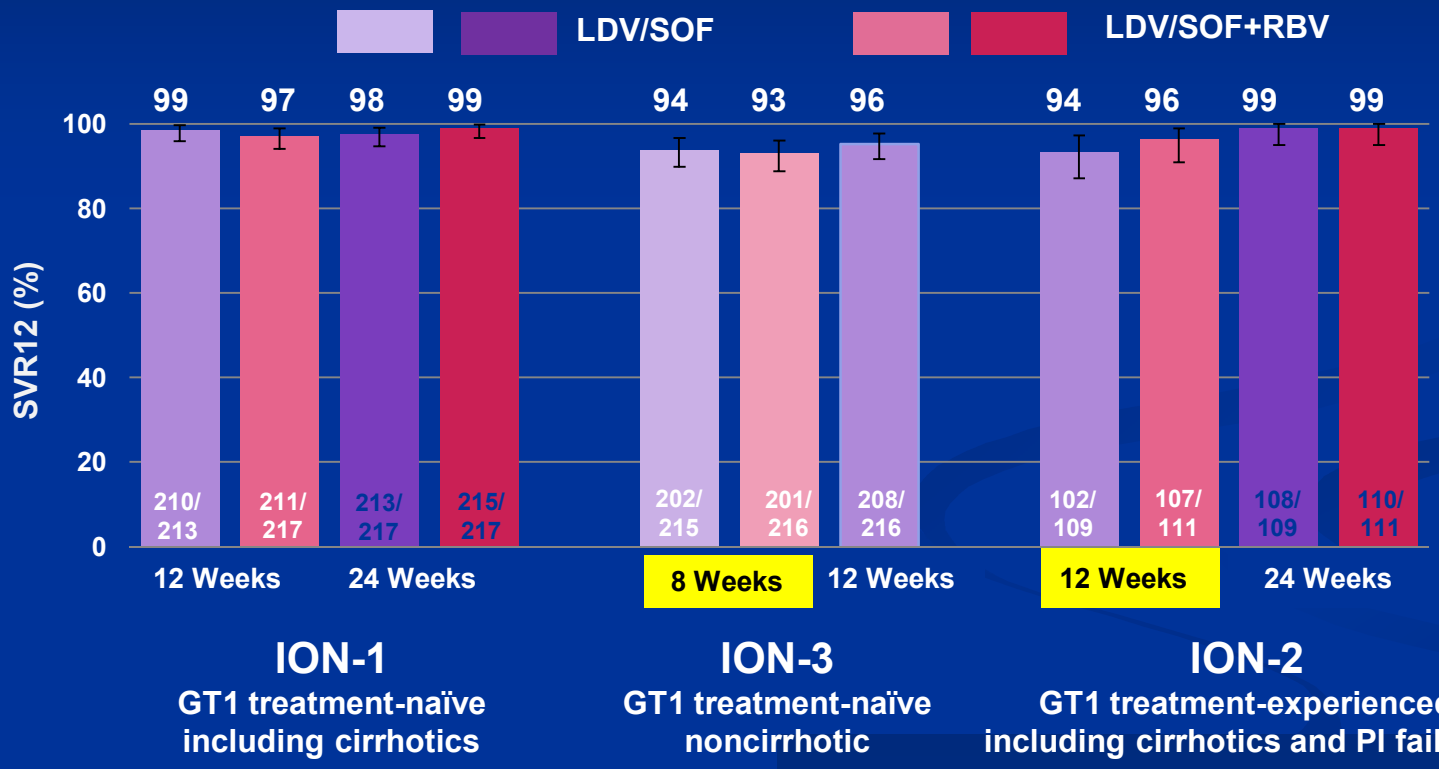
Approach to Treatment

- All patients are candidates for treatment unless limited life expectancy.
- Treatment urgency
  - Advanced liver disease
  - Post-liver transplant
  - HIV/HCV coinfection
    - Same treatment for HCV and HIV/HCV coinfection
  - Extrahepatic manifestations
- Non-FDA–indicated recommendations

FDA = US Food and Drug Administration; HIV = human immunodeficiency virus.

AASLD/IDSA HCV Guidelines.

Efficacy of LDV/SOF in GT1

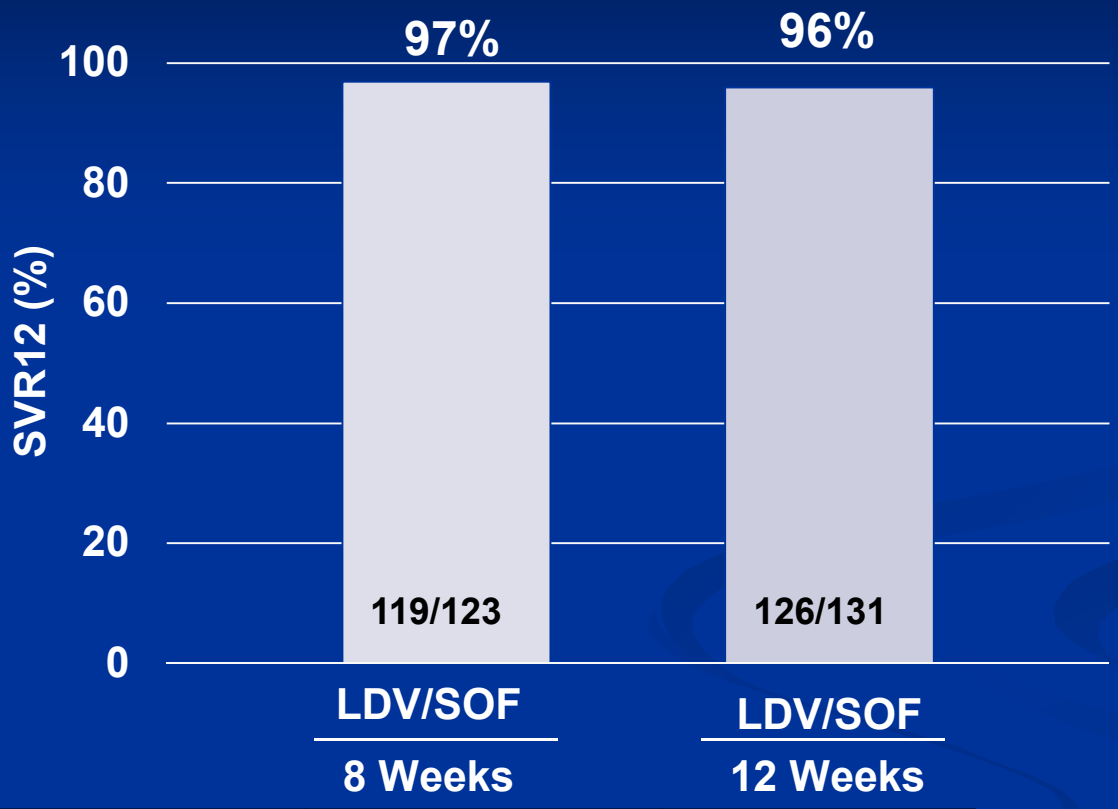


Excluding 1 subject with GT4 infection; error bars represent 95% confidence intervals.

SVR12 = sustained virologic response at 12 weeks.

Afdhal N, et al. *N Engl J Med.* 2014;370:1889-1898; Afdhal N, et al. *N Engl J Med.* 2014;370:1483-1493; Kowdley K, et al. *N Engl J Med.* 2014;370:1879-1888.

ION-3: GT1, Treatment-Naïve, Noncirrhotic SVR12 in Patients with HCV RNA <6 Million IU/mL



Relapse Rates by Baseline Viral Load	LDV/SOF 8 weeks	LDV/SOF 12 weeks
HCV RNA <6M IU/mL	2% (2/123)	2% (2/131)

Eight weeks of LDV/SOF was noninferior to 12 weeks for patients with HCV RNA <6M IU/mL and in the overall population.

Kowdley KV, et al. *N Engl J Med*. 2014;370:1879-1888; FDA analysis of SVR by baseline viral load.

Genotype 1: Ombitasvir/Paritaprevir/Ritonavir + Dasabuvir Efficacy

Study	Population	Regimen	SVR12
SAPPHIRE-1	Treatment (Tx)-naïve HCV GT1 patients without cirrhosis	OPrD + RBV x 12 weeks	GT1a: 96% (308/322)
SAPPHIRE-II	Tx-experienced HCV GT1 patients without cirrhosis	OPrD + RBV x 12 weeks	GT1a: 96% (166/173)
PEARL-II	Tx-experienced HCV GT1b patients without cirrhosis	OPrD x 12 weeks	GT1b: 100% (91/91)
PEARL-III	Tx-naïve HCV GT1b patients without cirrhosis	OPrD for 12 weeks	GT1b: 100% (209/209)
PEARL-IV	Tx-naïve HCV GT1a patients without cirrhosis	OPrD + RBV for 12 weeks	GT1a: 97% (97/100)
TURQUOISE-II	Tx-naïve and Tx-experienced HCV GT1 patients with cirrhosis	OPrD + RBV x 12 weeks OPrD + RBV x 24 weeks	GT1a: 89% (124/140) GT1b: 99% (67/68) GT1a: 95% (115/121)

Feld JJ, et al. *N Engl J Med*. 2014;370:1594-1603; Zeuzem S, et al. *N Engl J Med*. 2014;370:1604-1614; Andreone P, et al. *Gastroenterology*. 2014;147:359-365; Ferenci P, et al. *N Engl J Med*. 2014;370:1983-1992; Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982

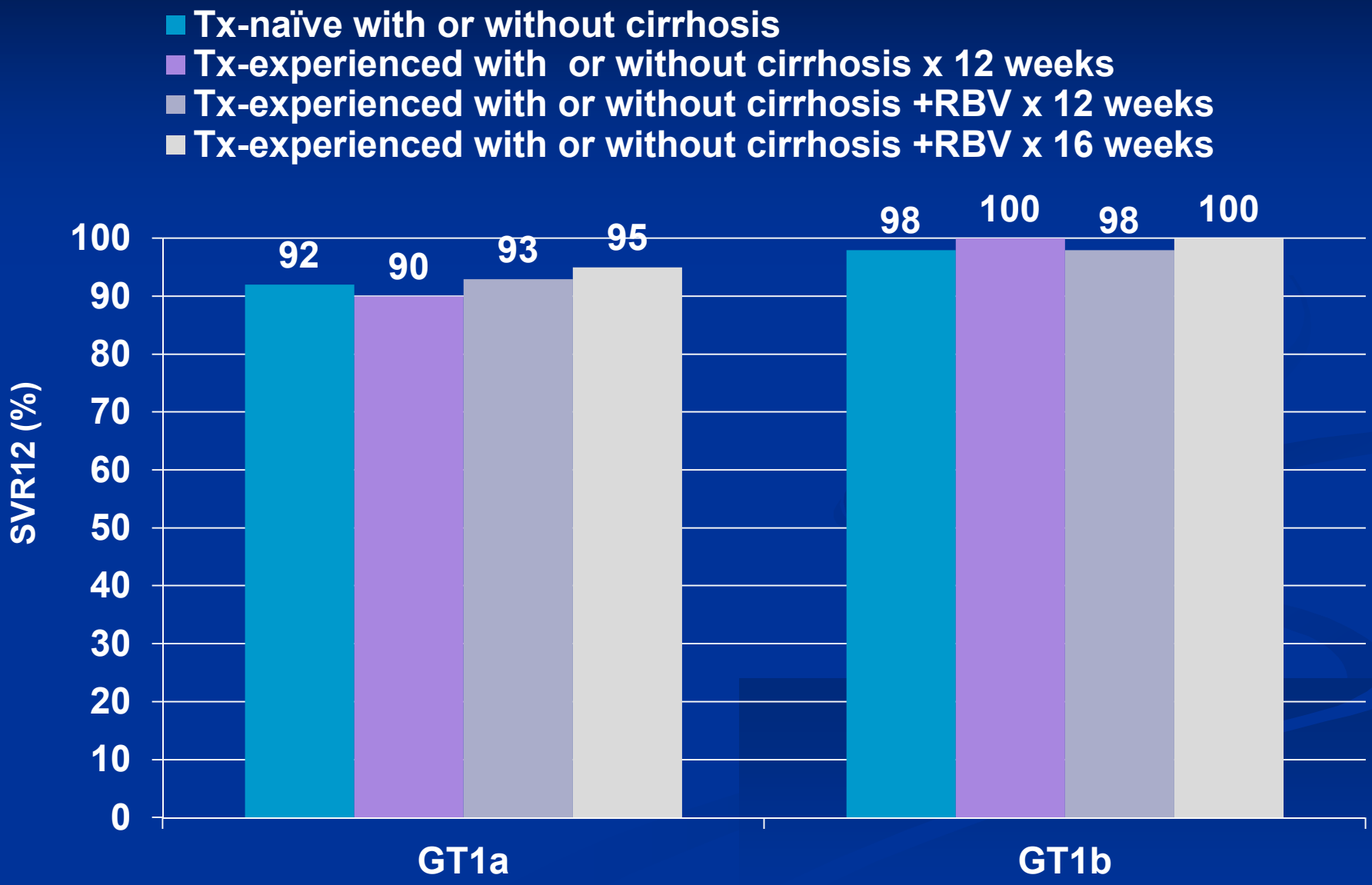
Genotype 1 and 4: Elbasvir/Grazoprevir Efficacy

Study	Population	Regimen	SVR12
C-EDGE-TN	Tx-naïve HCV GT1 patients with or without cirrhosis	EBR/GZR x 12 weeks	273/288 (95%) 1a: 92%;1b: 98%
C-EDGE-Coinfection	Tx-naive HCV/HIV GT1 patients with or without cirrhosis	EBR/GZR x 12 weeks	179/189 (95%)
C-EDGE-TE	Prior peginterferon/ribavirin Tx-experienced HCV GT1 patients with or without cirrhosis	EBR/GZR x 12 weeks EBR/GZR +RBV x 16 weeks	90/96 (94%) 1a: 90%;1b:100% 93/96 (97%) 1a: 95%; 1b: 100%
C-SALVAGE	Prior peg/ribavirin + HCV protease inhibitor Tx-experienced HCV GT1 patients with or without cirrhosis	EBR/GZR + RBV x 12 weeks	76/79 (96%) 1a: 93%;1b: 98%
C-SURFER	Tx-naive and prior peginterferon/ribavirin Tx-experienced GT1 patients with severe renal impairment, including hemodialysis	EBR/GZR x 12 weeks	115/122 (94%)
Pooled*	Tx-naïve HCV mono- and coinfected GT4 patients with or without cirrhosis	EBR/GZR x 12 weeks	64/66 (97%)
C-EDGE-TE	Prior peginterferon/ribavirin Tx-experienced HCV GT4 patients	EBR/GZR +RBV x 16 weeks	8/8 (100%)

*C-EDGE-TN, C-EDGE-Coinfection, C-SCAPE.

Zeuzem S, et al. *Ann Intern Med*. 2015;163:1-13; Rockstroh JK, et al. *Lancet HIV*. 2015;2:e319-327; Kwo P, et al. EASL 2015. Abstract P0886; Buti M, et al. *Clin Infect Dis*. 2016;62:32-36; Roth D, et al. *Lancet*. 2015;386:1537-1545; Brown A, et al. EASL 2015. Abstract P0771.

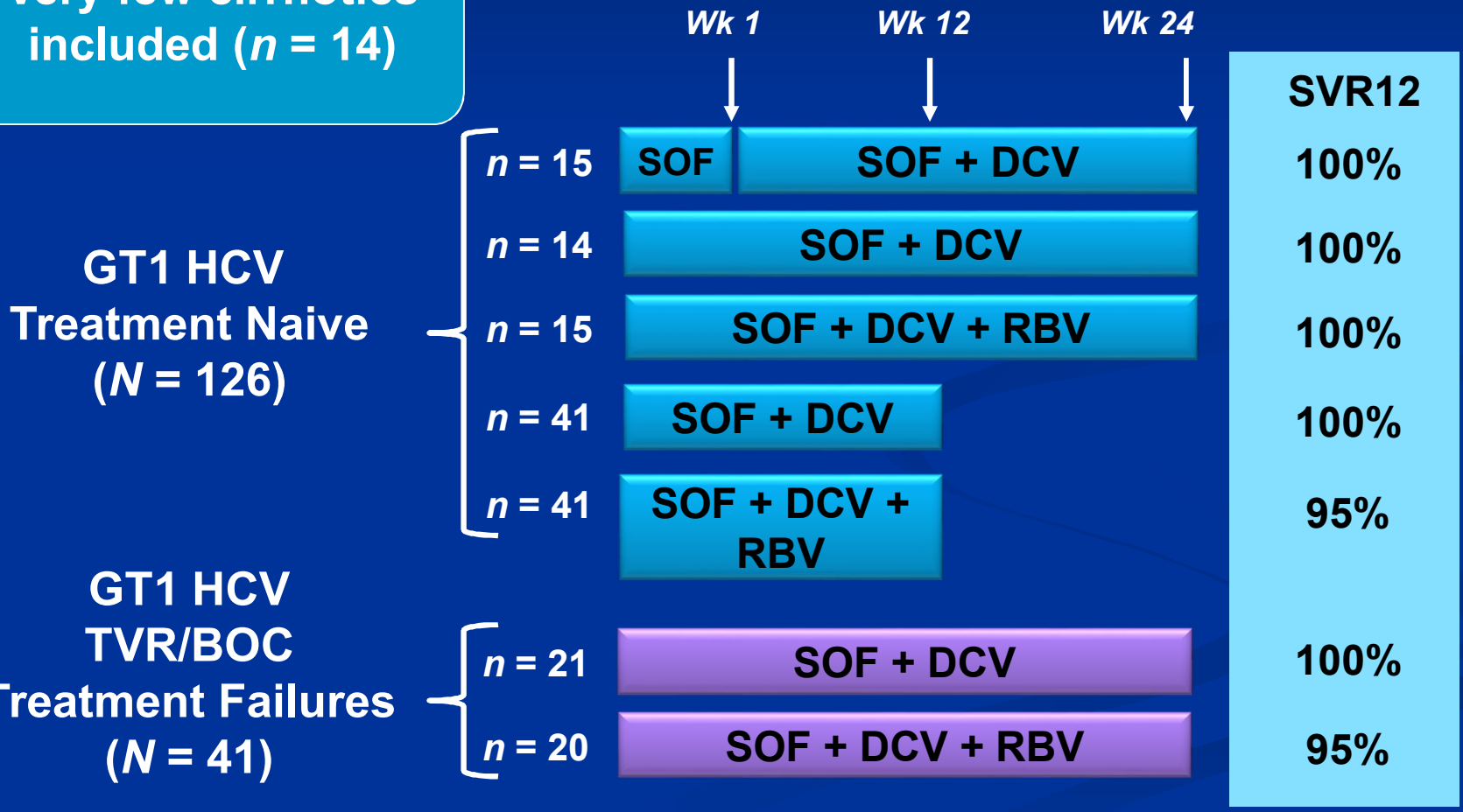
Elbasvir/Grazoprevir Efficacy for GT1



Zeuzem S, et al. *Ann Intern Med*. 2015;163:1-13; Kwo P, et al. EASL 2015. Abstract P0886; Buti M, et al. *Clin Infect Dis*. 2016;62:32-36.

Daclatasvir + Sofosbuvir in Treatment-Naive and Experienced GT1 HCV Infection

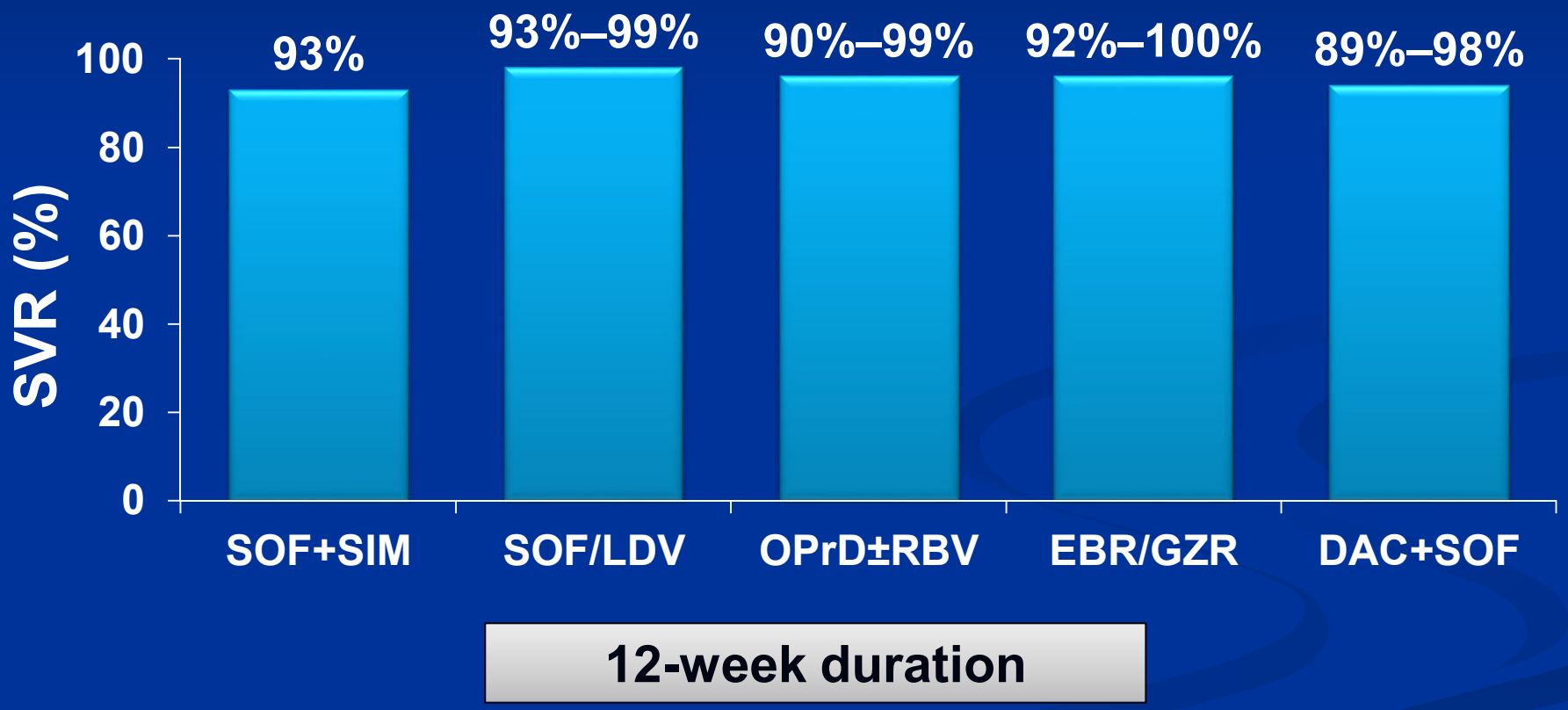
Very few cirrhotics included (*n* = 14)



BOC = boceprevir; DCV = daclatasvir; TVR = telaprevir.

Sulkowski MS, et al. *N Engl J Med*. 2014;370:211-221.

Summary of Trials for GT1



DAC = daclatasvir; SIM = simeprevir.

Jacobson IM, et al. AASLD 2013. Abstract 1379; Afdhal N, et al. *N Engl J Med.* 2014;370:1889-1898; Afdhal N, et al. *N Engl J Med.* 2014;370:1483-1493; Kowdley K, et al. *N Engl J Med.* 2014;370:1879-1888; Feld JJ, et al. *N Engl J Med*. 2014;370:1594-1603; Zeuzem S, et al. *N Engl J Med*. 2014;370:1604-1614; Andreone P, et al. *Gastroenterology*. 2014;147:359-365; Ferenci P, et al. *N Engl J Med*. 2014;370:1983-1992; Poordad F, et al. *N Engl J Med*. 2014;370:1973-1982; Zeuzem S, et al. *Ann Intern Med*. 2015;163:1-13; Kwo P, et al. EASL 2015. Abstract P0886; Buti M, et al. *Clin Infect Dis*. 2016;62:32-36; Sulkowski MS, et al. *N Engl J Med*. 2014;370:211-221.

Recommendations for Genotype 1

	DAC+SOF	LDV/SOF	OPrD	EBR/GZR	SOF+SIM
Genotype 1a (TN or TE) noncirrhotic	12 weeks	12 weeks; 8 weeks if TN and low VL	12 weeks + RBV	Test for NS5A RAV; (-)RAV, then 12 weeks; (+)RAV, then 16 weeks +RBV	12 weeks
Genotype 1b (TN or TE) noncirrhotic	12 weeks	12 weeks; 8 weeks if TN and low VL	12 weeks	12 weeks	12 weeks
Cirrhosis, CTP A	24 weeks	+RBV 12 weeks; -RBV 24 weeks	1b: 12 weeks; 1a: 24 weeks +RBV	12 weeks (1a: if NS5A RAV, then 16 weeks + RBV)	24 weeks
Cirrhosis, CTP B or C	12 weeks +RBV	12 weeks + RBV			
Renal insufficiency (eGFR <30 mL/min)				12 weeks (1a: if NS5A RAV, then 16W + RBV)	

In CTP B or C initiate RBV at 600 mg/day. CTP = Child Turcotte Pugh; eGFR = estimated glomerular filtration rate; RAV = resistance-associated variant; TE = treatment experienced; TN = treatment naïve; VL = viral load.

AASLD/IDSA HCV Guidelines.

Impact of Baseline NS5A Resistance-Associated Polymorphisms

SVR in HCV GT1a patients with or without baseline NS5A polymorphisms (RAPs)

	EBR/GZR for 12 Weeks SVR12	EBR/GZR + RBV for 16 Weeks SVR12	DAC+SOF ±RBV SVR12
No baseline NS5A polymorphisms (M28, Q30, L31, or Y93)	98% 441/450	100% 49/49	95% 142/149
Presence of baseline NS5A polymorphism (M28, Q30, L31, or Y93)	70% 39/56	100% 6/6	76% 13/17

FDA label recommends baseline testing for NS5A RAPs
(For DAC, "consider" only in patients with cirrhosis)

FDA package labeling.

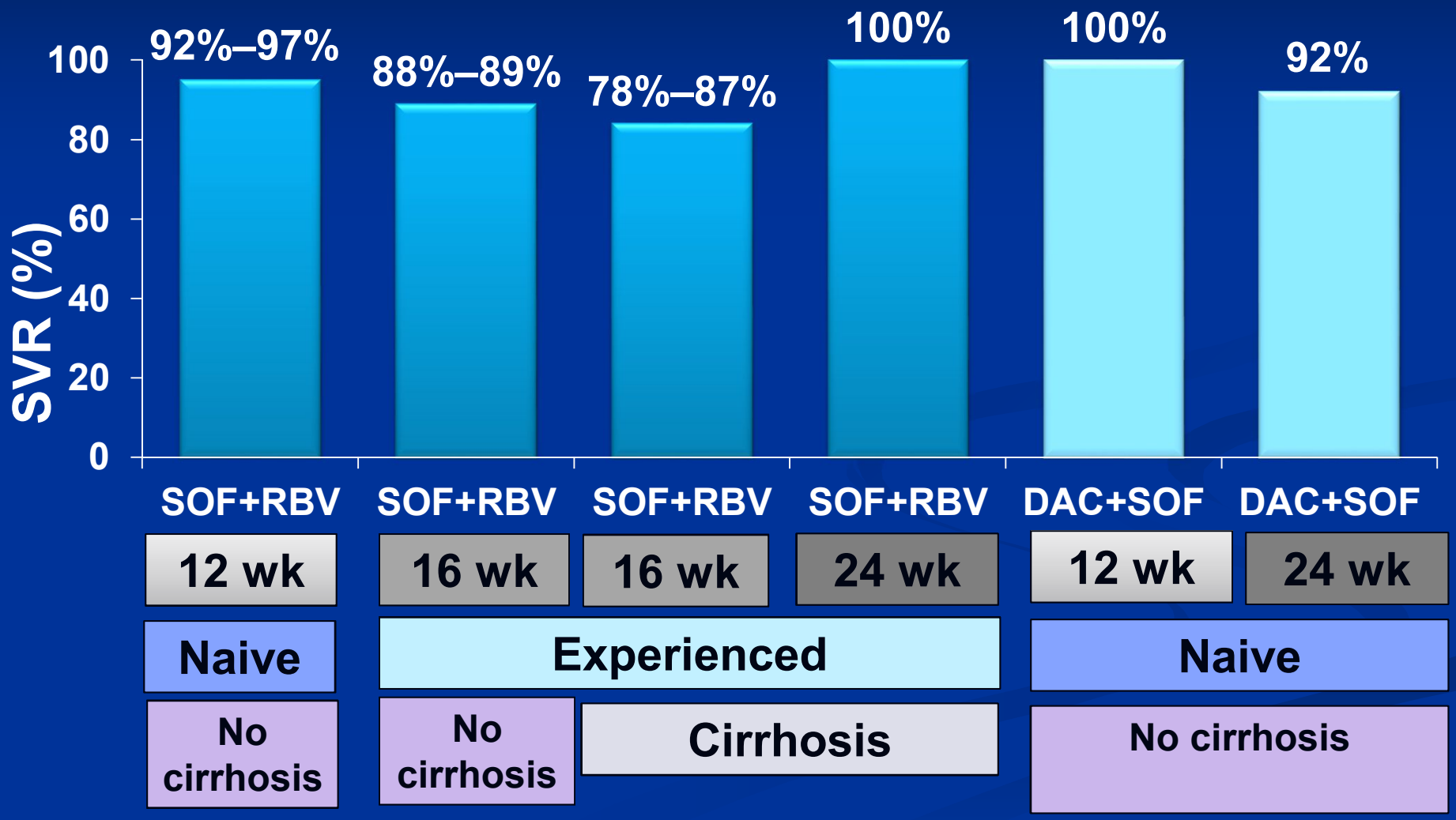
RAP: Definition and How to Test (VA)

- RAP = resistance-associated polymorphism
  - Changes in amino acids that have been shown to emerge during treatment or that have been tested in vitro (replicon) and show a change in susceptibility (EC_{50}) of >2.5-fold
  - Sometimes referred to as RAV (resistance-associated variant)
- When to test
  - GT1a: for NS5A, before starting EBR/GZR
  - GT3: for NS5A, before starting daclatasvir
  - Retreatment of all-oral DAA failures: test for RAV to all drugs used in the proposed treatment regimen
- How to interpret
  - GT1a: if NS5A RAV present at position 28, 30, 31, or 93 and using EBR/GZR, then add RBV and Tx for 16 weeks
  - GT3: if NS5A RAV present at Y93, then add ribavirin to DCV+SOF or wait for next generation of DAAs

EC_{50} = 50% effective concentration.

VA Guidelines. Chronic HCV infection. Available at: www.hepatitis.va.gov. Updated March 28, 2016.

Summary of Trials for GT2



Jacobson IM, et al. *N Engl J Med*. 2013;368:1867-1877; VALENCE: Zeuzem S, et al. *N Engl J Med*. 2014;370:1993-2001; Foster GR, et al. *Gastroenterology*. 2015;149:1462-1470.

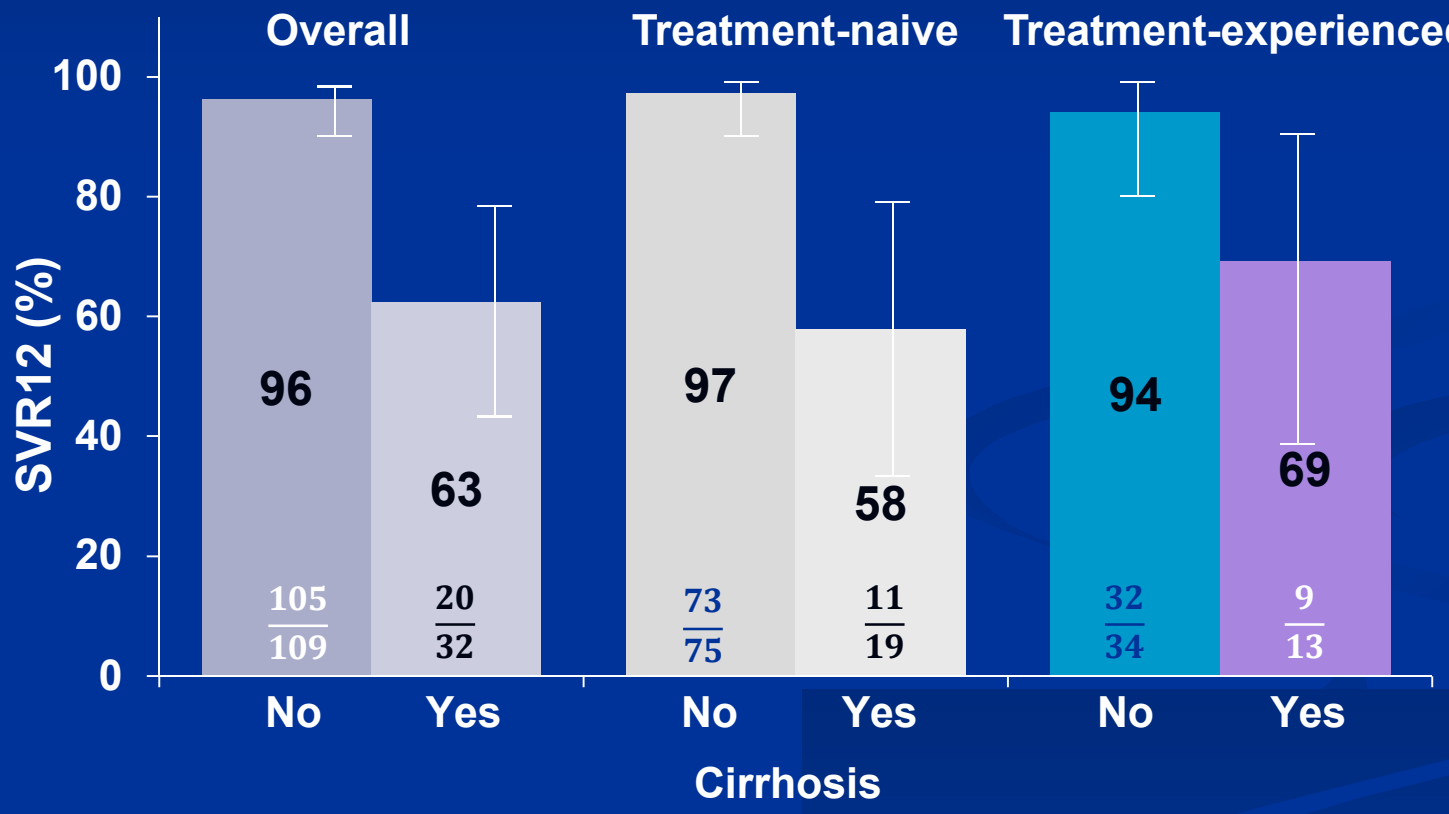
Recommendations for Genotype 2

	Sofosbuvir + Ribavirin	Daclatasvir + Sofosbuvir* *Not FDA-approved.
Naïve Noncirrhotic	12 weeks	Use if ribavirin intolerant 12 weeks
Cirrhosis	16 weeks (no data)	Use if ribavirin intolerant 16–24 weeks
Experienced Noncirrhotic	16 weeks	Use if ribavirin intolerant 12 weeks
Cirrhotic	16–24 weeks	Use if ribavirin intolerant 16–24 weeks (VA: add RBV)
Sofosbuvir failures		Use with ribavirin 24 weeks

SVRs: 87%–100%

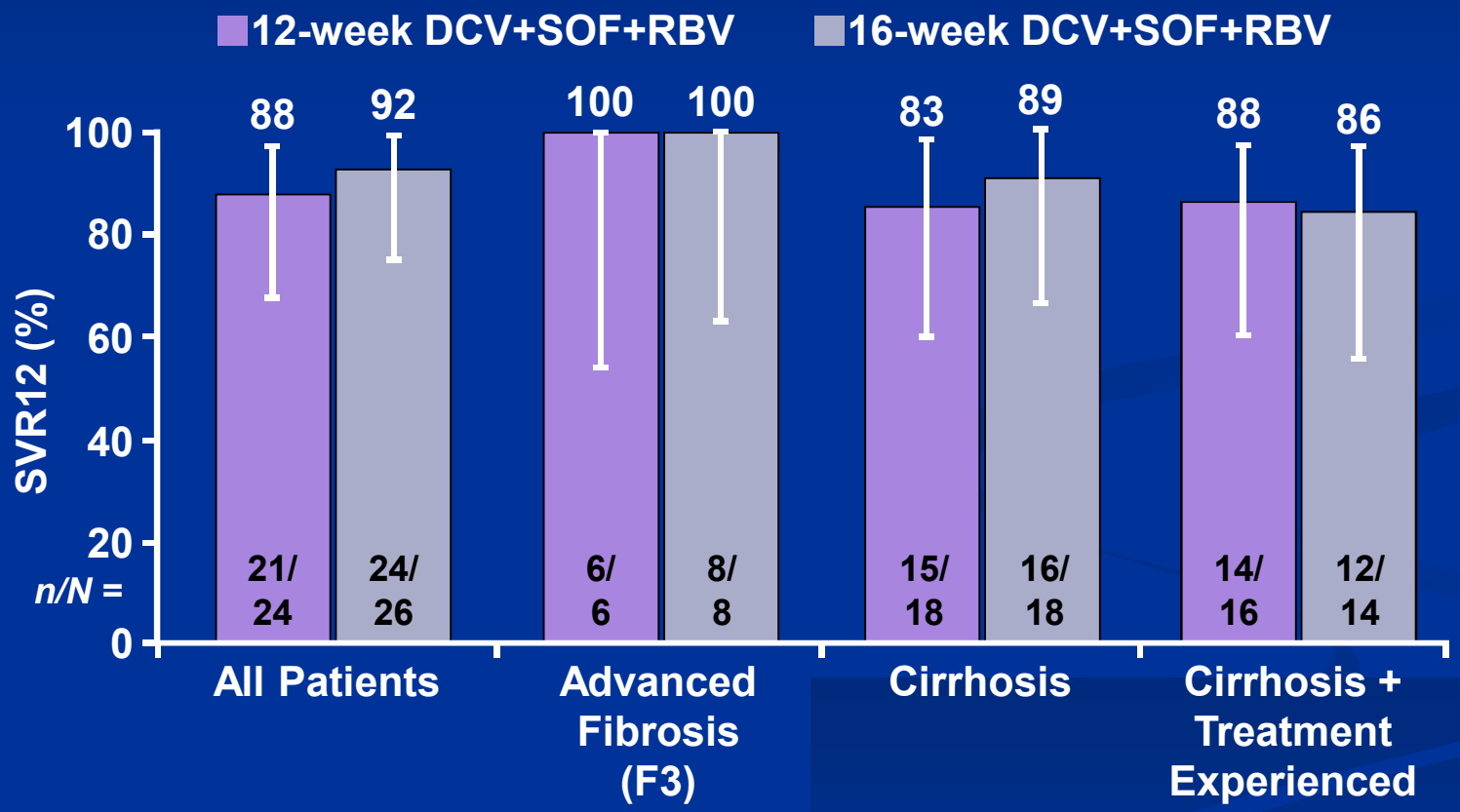
AASLD/IDSA HCV Guidelines.

Genotype 3: DCV + SOF for 12 Weeks in TN and TE, with and Without Cirrhosis



Pianko S, et al. AASLD 2014. Abstract 197.

ALLY-3+: DCV + SOF + RBV in Patients With GT3 HCV and Advanced Liver Disease



Leroy V, et al. AASLD 2015. Abstract LB-3.

Recommendations for Genotype 3

Population	SOF/PEG/RBV	DCV+SOF
Naive, no cirrhosis	12 weeks	12 weeks
Naive, cirrhosis	12 weeks	24 weeks, ± RBV (VA: 12 weeks with RBV)
Experienced Peg/RBV failure, no cirrhosis	12 weeks	12 weeks
Experienced Peg/RBV failure, cirrhosis	12 weeks	24 weeks, with RBV
Experienced, prior SOF failure		24 weeks, with RBV

AASLD/IDSA HCV Guidelines.

Genotype 4

	Paritaprevir/ Ritonavir/ Ombitasvir	Ledipasvir/ Sofosbuvir	EBR/GZR
Treatment-naïve with or without cirrhosis	12 weeks with RBV	12 weeks	12 weeks
Treatment-experienced with or without cirrhosis CTP A	12 weeks with RBV	12 weeks with RBV for cirrhosis	12 weeks (relapser) 16 weeks with RBV (all others)
Cirrhosis, CTP B/C*	Do not use	12 weeks with RBV or 24 weeks without RBV	Do not use

*DAC+SOF +RBV x 12 weeks may by used for CTP B/C; if RBV intolerant DAC+SOF x 24 weeks may be used.

AASLD/IDSA HCV Guidelines.

Guidance for HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected patients
- Do not use OPrD in coinfected patients not taking antiretroviral therapy
- Consider drug–drug interactions
  - Need to adjust or withhold ritonavir if receiving a boosted PI with OPrD
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Use cautiously in those with any CKD
  - Other interactions at aidsinfo.nih.gov/guidelines, hiv-druginteractions.org

CKD = chronic kidney disease.

AASLD/IDSA HCV Guidelines.

Guidance for Renal Impairment

- If CrCl >30 mL/min, no dosage adjustment needed with:
  - Elbasvir/grazoprevir
  - LDV/SOF
  - OPrD
  - SMV
  - SOF
- If CrCl <30 mL/min
  - Elbasvir/Grazoprevir

CrCl = creatinine clearance.

AASLD/IDSA HCV Guidelines.

Key Monitoring Guidance

- Before and during treatment
  - HCV RNA before treatment and at Week 4
    - If detectable at Week 4, assess again at Week 6
  - ALT
    - OPrD: before treatment and at Week 4; if elevated at Week 4, assess again at Week 6 and Week 8
    - EBR/GZR: before treatment and at Week 8; if elevated at Week 8, assess again at Week 12 and as needed while treatment continues
- After treatment
  - If pretreatment Metavir ≥ F3, ultrasound for HCC every 6 months

ALT = alanine aminotransferase; HCC = hepatocellular carcinoma.

AASLD/IDSA HCV Guidelines; FDA package labeling.

Emerging Treatment Options and Trends

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All-Oral DAAs: What's Coming in 2016 and Beyond?

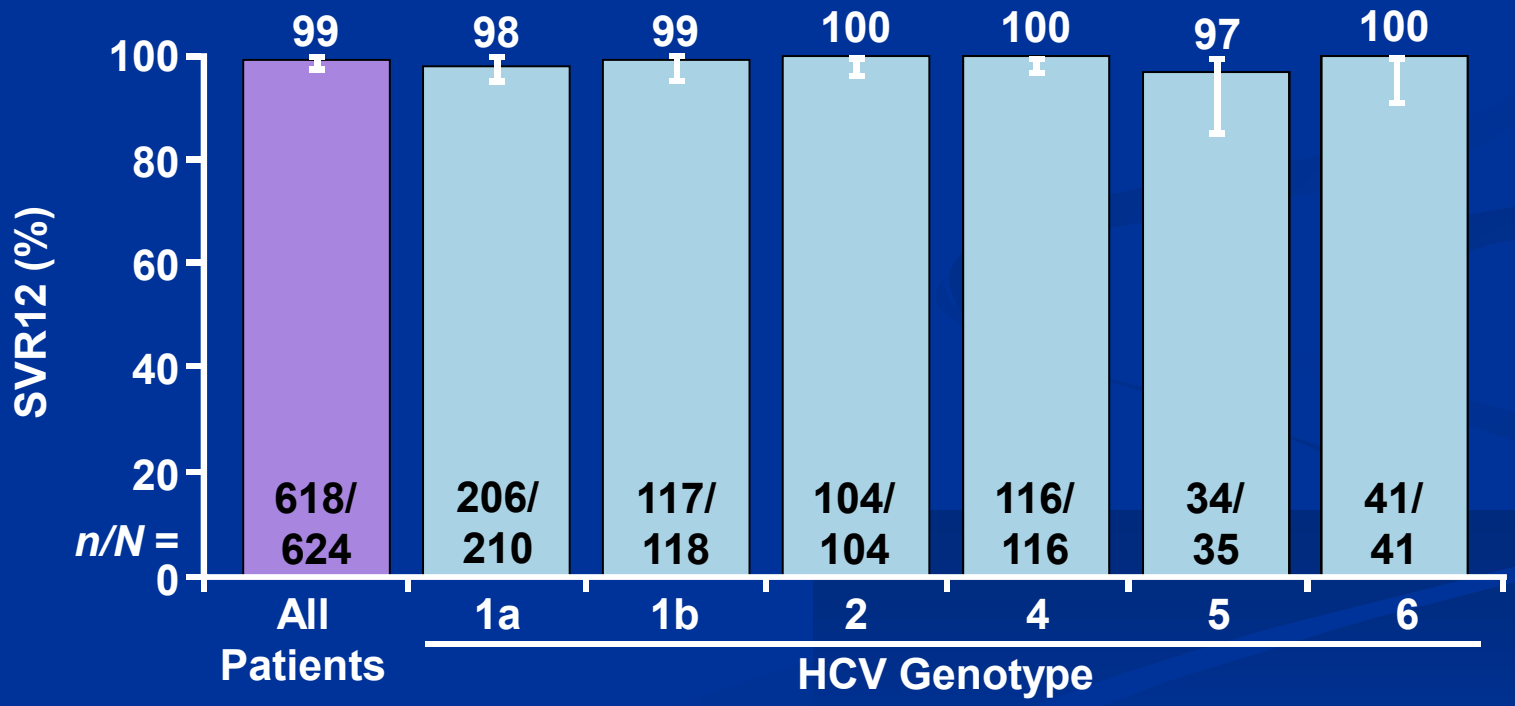
	Protease Inhibitors	Polymerase Inhibitors		NS5A Inhibitors	Other
		Nucleotide	Non-nucleotide		
Currently available	Simeprevir	SOF		LDV	RBV
	Paritaprevir/ ritonavir		Dasabuvir	Ombitasvir	
				Daclatasvir*	
	Grazoprevir			Elbasvir	
Expected in 2016		SOF		Velpatasvir	

*Used with sofosbuvir.

All genotypes, prior PI failures, shorter treatment duration for some

ASTRAL-1: SVR12 with Sofosbuvir/Velpatasvir in GT1, 2, 4, 5, 6 HCV

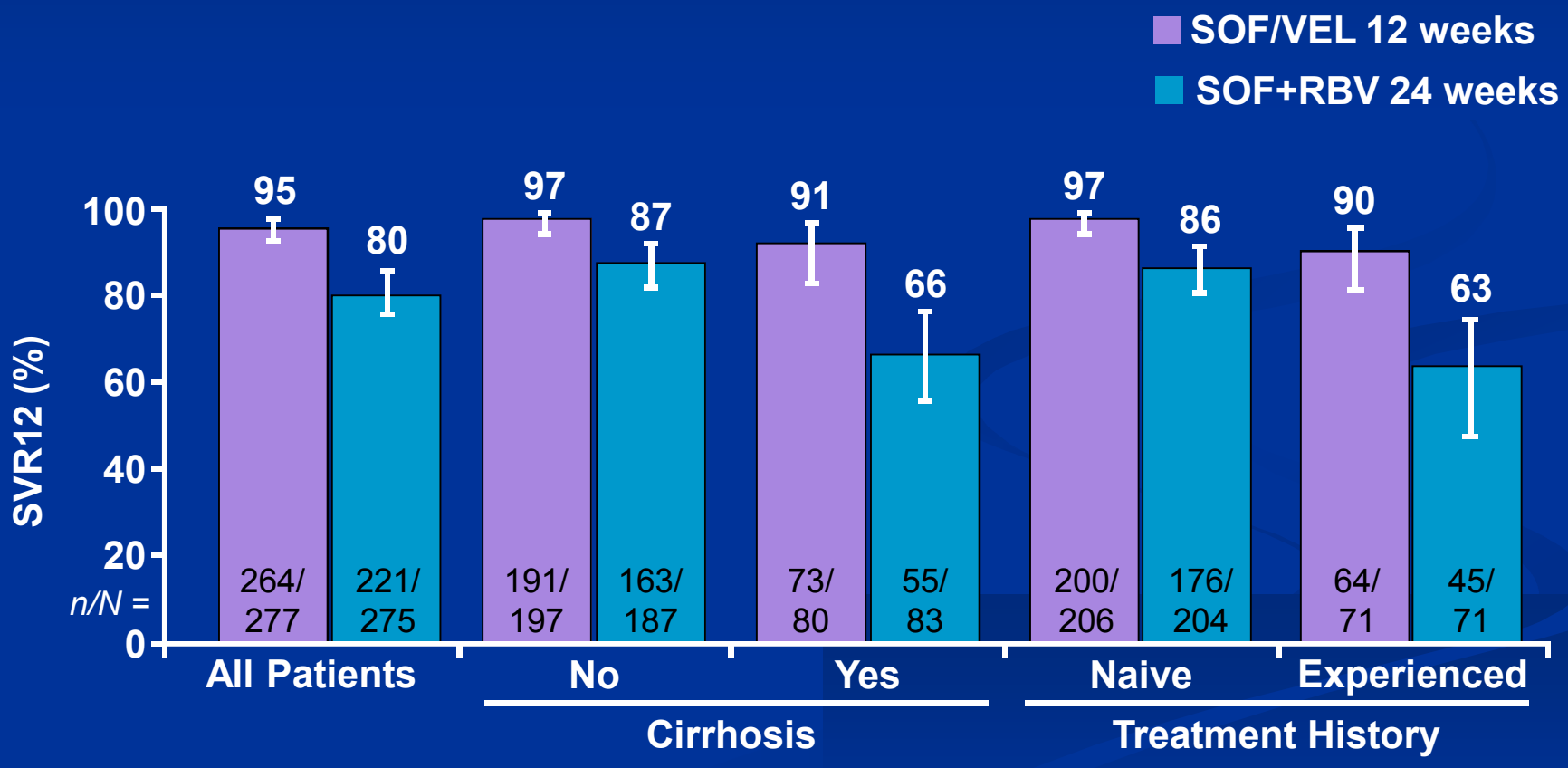
- Key baseline characteristics: cirrhosis 19%; Tx-experienced 32%; baseline (BL) NS5A RAVs 42%
- No impact of cirrhosis, Tx-experience, BL NS5A RAVs on SVR rates



Feld JJ, et al. AASLD 2015. Abstract LB-2; Feld JJ, et al. *N Engl J Med*. 2015;373:2599-2607.

ASTRAL-3, Sofosbuvir/Velpatasvir in GT3

- SVR rate numerically lower with vs without BL NS5A RAPs (88% vs 97%)



VEL = velpatasvir.

Mangia A, et al. AASLD 2015. Abstract 249; Foster GR, et al. *N Engl J Med*. 2015;373:2608-2617.

Combination Regimens for Treatment Failures

General principles: Resistance testing, add ribavirin, use longer duration

Failed Regimen	Potential Regimen	Duration	SVR
NS3/4A Protease Inhibitors	LDV/SOF (+RBV if cirrhosis)	12 weeks	94%–98%
		12 weeks no cirrhosis; 24 weeks with cirrhosis	98%
	DAC+SOF (+RBV if cirrhosis)		96%
	EBV/GZR ± RBV	12–16 weeks based on RAPs	
SOF+SIM	LDV/SOF +RBV or DAC+SOF+RBV	24 weeks	85%–91%
NS5A Inhibitor or SOF+SIM	SOF+EBV/GZR+RBV	12 weeks	100% (23/23)
	SOF+OPrD ± RBV	GT1b: 12 weeks GT1a: 24 weeks	93% (14/15)

AASLD/IDSA HCV Guidelines.

Unanswered Questions

- "Real-world" results
  - Efficacy vs effectiveness
  - Comparative effectiveness
  - Retreatment of those who fail
- Resistance
  - Future implications
- Cost of treatments
  - Market competition
  - Disparities

Pharmacist-Led Education Strategies

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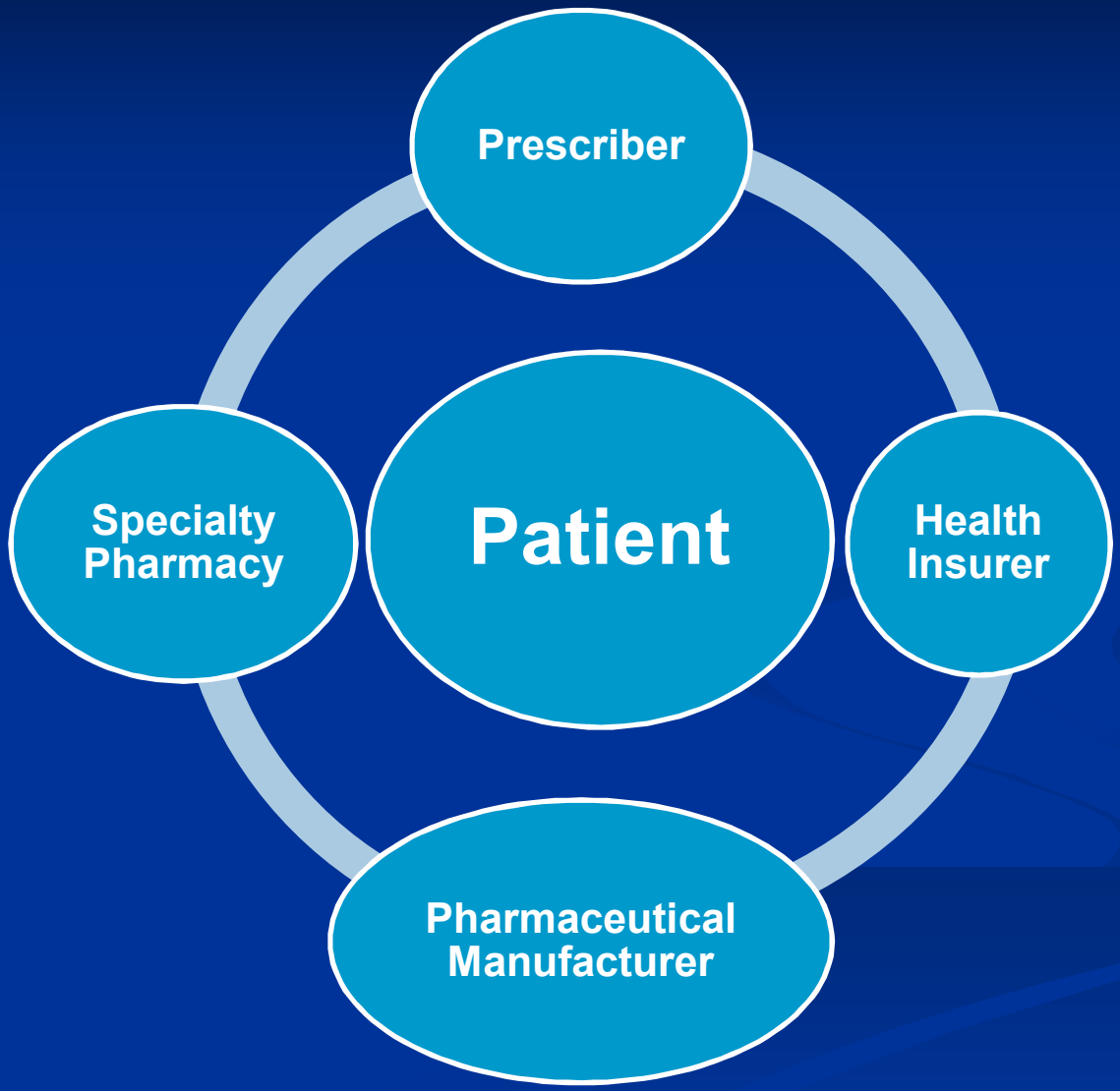
HCV Drug Management Challenges

- High cost of therapy
- Over 3.2 million people chronically infected
- Treatment regimens vary in duration, pill burden, need for ribavirin, baseline resistance testing, and cost.
- Less than optimal medication adherence may lead to treatment failure and drug resistance.
- Medication waste if patient does not start or complete treatment
- Transient patients – lose or gain patients in the middle of treatment due to changing health plan

Collaborative Approach to Treatment



Role of the Clinical Pharmacist in HCV Management

- HCV screening
- HCV medication selection
- Treatment plan and monitoring
- HCV med management (ie, initiate treatment, adjust dose, discontinue under pharmacist scope of practice)
- Management of adverse drug events related to therapy

Role of the Clinical Pharmacist in HCV Management (cont'd)

- Patient adherence assessment
- E-consult services
- Telemedicine services to outlying clinics (ie, Clinical Video Telehealth [CVT])
- Population management to identify patients requiring treatment

Role of the Specialty Pharmacist in HCV Management

- Medication reconciliation
- Verify regimen selection against guidelines
- Advise HCV provider of existing drug-drug interactions
- Advise patient of potential OTC drug-drug interactions
- Patient adherence assessment
- Support for medication acquisition (ie, co-pay assistance, foundation assistance)
- Connect patient with local support (ie, case management, support group)
- HAV/HBV vaccination recommendations
- End of treatment education (SVR, HCC monitoring when applicable, reinfection risk, antibody positivity)

HAV = hepatitis A virus; HBV = hepatitis B virus; OTC = over the counter.

Critical to Success…

- Pretreatment assessment
  - Patient understanding of treatment goals
  - Provision of education on adherence and follow-up
- Well-established therapeutic relationship between practitioner and patient
- Ensure accessibility to treatment for duration

Sample Pharmacist Clinical Interventions

Pharmacist Intervention	Description
Baseline assessment	• Patient demographic and clinical laboratory data collection (eg, HCV genotype/subtype, prior Tx history and outcome, baseline VL, liver fibrosis stage, hemoglobin, CrCl) • Comorbidities, allergies, concomitant medications • Evaluation of HCV regimen appropriateness (safety, efficacy, drug interactions, contraindications)
Initial and ongoing patient education, treatment monitoring, adherence support	• Pharmacist counseling (disease, drug regimen, adverse event management, adherence) • Educational brochures
Referral to patient assistance programs	• Manufacturer financial assistance programs or supportive organizations (eg, substance abuse counseling)
Adherence and distribution outreach	• Arrange timely refills based on Tx start date • Assess Tx tolerance, administration technique
On-treatment monitoring	• Obtain VL at Week 4 (and as required, if applicable) for response and adherence • Gather SVR12 data

Factors Affecting Adherence

- Patient characteristics
  - Lack of understanding of the disease, complications, low motivation, forgetfulness
- Antiviral treatment
  - Regimen complexity, treatment duration, prior treatment failure, side effects
- Social and economic conditions
  - Unstable living conditions, lack of familial support, cultural beliefs, medication cost, substance abuse
- Health care system
  - Poor patient-provider relationship, medication distribution systems, adherence support

Drug-Specific Treatment Considerations

	LDV/SOF	OPrD	EBR/GZR	DAC
Pill burden	1 pill	4 pills	1 pill	1 pill*
Dosing frequency	qd	bid (with food)	qd	qd
Duration	8–12 wks	12–24 wks	12–16 wks	12–24 wks
Drug interaction potential	Low (PPIs/H2RA)	High	Moderate	Moderate†
Special monitoring	None	LFTs including bilirubin	LFTs	None
Use in decompensated cirrhosis	OK	Do not use in CPT B or C	Do not use in CPT B or C	OK
Adverse effects	Fatigue, headache, nausea	Nausea, pruritus, insomnia	Fatigue, headache, nausea	Headache, fatigue, nausea, diarrhea

*Must be used with sofosbuvir; †Dose adjustments of DAC required with strong CYP3A inducers and inhibitors.
H2RA = H2-receptor antagonist; LFT = liver function test; PPI = proton pump inhibitor.
VA Guidelines. Chronic HCV infection. Available at: www.hepatitis.va.gov. Updated March 28, 2016.

All Oral: Pill Burden

LDV/SOF:
1 tablet once a day

OPrD:
2 tablets AM and 1 tablet twice daily

WITH or WITHOUT

RBV:
Up to 3 tablets twice daily

EBR/GZR:
1 tablet once a day

DAC + SOF:
2 tablets once a day

FDA package labeling.

Ledipasvir/Sofosbuvir

- Ledipasvir 90 mg/sofosbuvir 400 mg
  - One pill once a day for most patients
  - Some patients will require ribavirin
  - 8-week regimen can be considered for naïve, noncirrhotic, low viral load patients
  - Special administration with PPIs and H2RAs

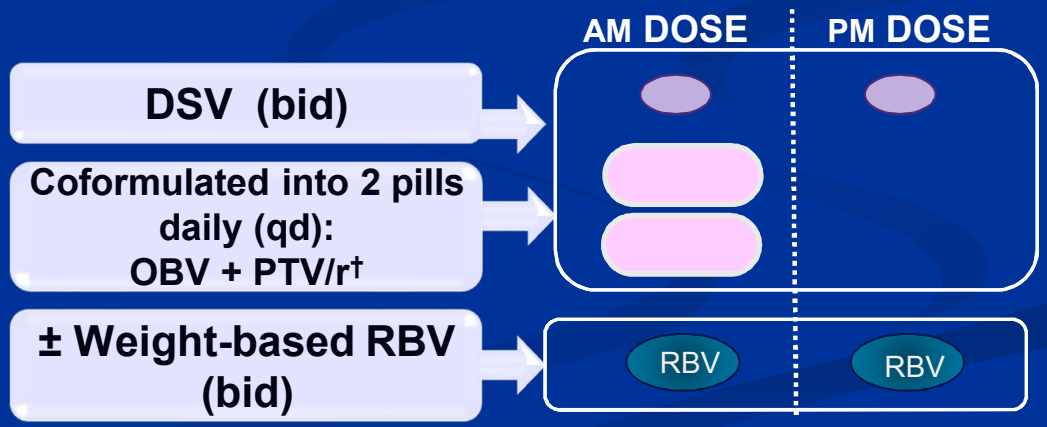
FDA package labeling.

Ombitasvir, Paritaprevir/Ritonavir + Dasabuvir

	Ombitasvir (OBV)	Paritaprevir/r (PTV/r)*	Dasabuvir (DSV)
Mechanism of action	NS5A inhibitor	NS3/4A protease inhibitor (ritonavir: prolongs half-life)	Non-nucleos(t)ide NS5B-palm polymerase inhibitor
Dosing	25 mg qd	150 mg qd	250 mg **bid**

*r = ritonavir, a CYP3A inhibitor; †Each OBV/PTV/r tablet contains 12.5/75/50 mg of each component, respectively.

- **LFT monitoring required (cirrhosis)**
- **High drug-interaction potential**



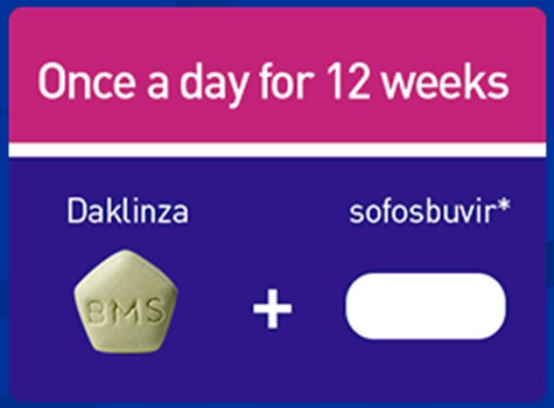
To maximize absorption, should be taken with a meal without regard to fat or calorie content.

FDA package labeling.

Daclatasvir

- Daclatasvir 60 mg
  - NS5A inhibitor
  - GT1 and GT3
  - MUST be used with sofosbuvir
  - Two pills (daclatasvir + sofosbuvir) once a day for 12 weeks (for most patients)
  - NS5A baseline resistance testing for GT1a with cirrhosis
  - ? 16 weeks + ribavirin for those with baseline NS5A RAVs
  - Dose adjust daclatasvir with CYP3A inhibitors and inducers

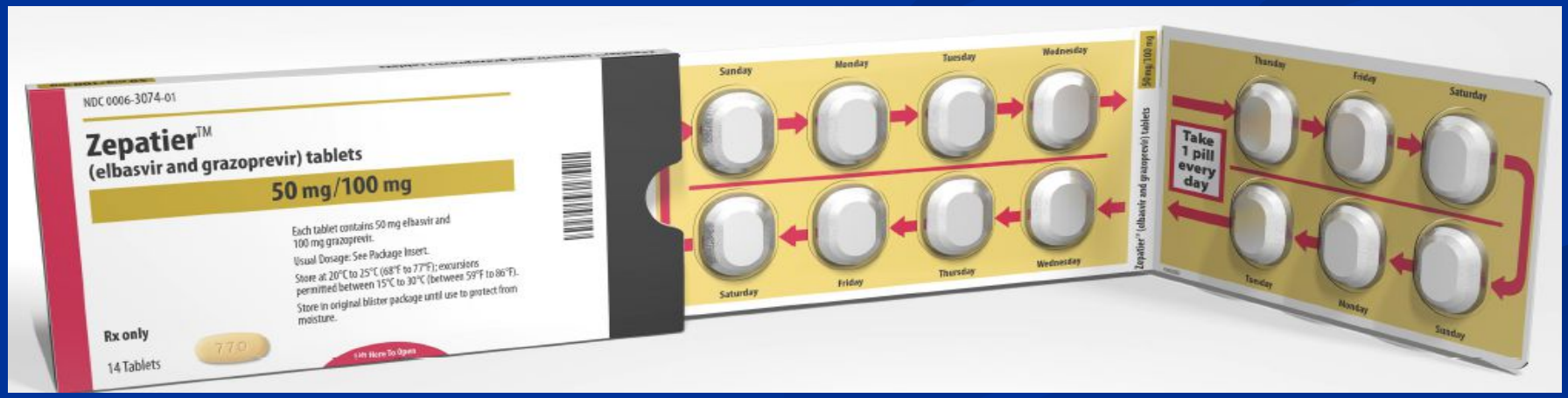
Strong CYP3A inhibitors	30 mg daily
Moderate CYP3A inducers	90 mg daily (3 x 30 mg or 30 mg +60 mg)
Strong CYP3A inducers	Contraindicated



FDA package labeling.

Elbasvir/Grazoprevir

- Elbasvir 50 mg/grazoprevir 100 mg
  - NS5A inhibitor/NS3 protease inhibitor
  - One pill once a day (for most patients)
  - 12 weeks for most patients
  - 16 weeks + ribavirin for some GT1a and GT4 patients
  - Moderate drug interaction potential



FDA package labeling.

Elbasvir/Grazoprevir

- Benefits
  - Can be used in renal failure and dialysis
  - Same regimen/duration with and without cirrhosis
- Issues
  - GT1a: test for RAV before prescribing
    - Positions 28, 30, 31, and 93
    - Ribavirin needed in ~6%–12% of patients with GT1a
  - Do not use in CPT B or C (decompensated; CTP ≥7)
  - Monitor LFTs at Week 8 (and Week 12 for 16-week regimen)
    - Elevated ALT in ~1% (2% Asian or >65 years of age or CTP A)
    - Stop if ALT >10x, symptoms, increase in bilirubin or INR

INR = international normalized ratio.
FDA package labeling.

Drug Interaction Assessment

- http://www.hep-druginteractions.org/
- Drug-drug interactions must be considered when selecting a treatment regimen.
- Providers should consult a knowledgeable clinical pharmacist for specific questions regarding drug-drug interactions.

Common Side Effects

Effect	DAC+SOF	EBR/GZR	LDV/SOF	OPrD	SOF+SIM
Headache	√	√	√		√
Fatigue	√	√	√	√	√
Nausea	√	√	√	√	√
Diarrhea	√				
Insomnia			√	√	√
ALT ↑		√		√	
Other	Lipase ↑		Lipase ↑ Bili ↑	Skin reactions; pruritus	Bili ↑; pruritus; photo-sensitivity

Bili = bilirubin.

VA Guidelines. Chronic HCV infection. Available at: www.hepatitis.va.gov. Updated March 28, 2016.

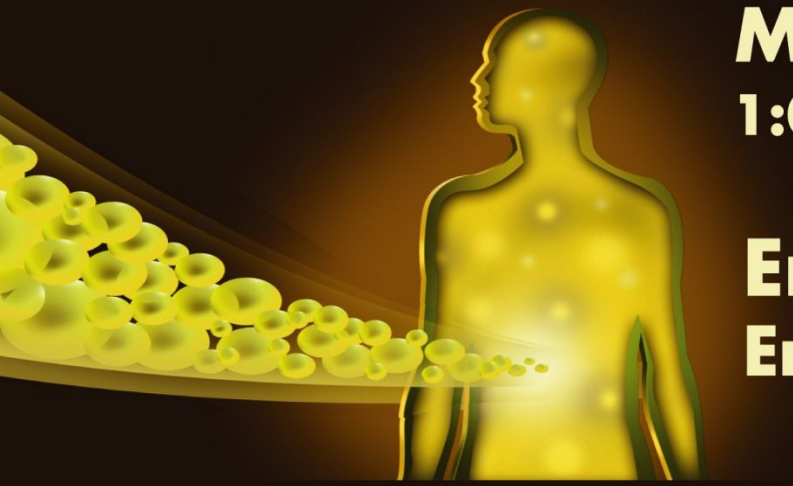
Summary

- Rapidly evolving treatment landscape
  - IFN-free cure rates >90%
  - More tailored approach in the near future
- Rising demand for treatment anticipated
  - Increased screening
  - Accessibility of oral regimens
- Pharmacist interventions play a key role in promoting the use of cost-effective regimens and improving treatment outcomes.

INTERACTIVE CPE SYMPOSIUM

INDIVIDUALIZING TREATMENT REGIMENS FOR HEPATITIS C:

A 2016 Update for Specialty Pharmacists



Monday, May 2, 2016
1:00 – 2:30 PM • Interactive CPE Activity

Encore at Wynn Las Vegas
Encore Ballroom 1-3

This symposium will provide live credit (L) for those states requiring it.

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