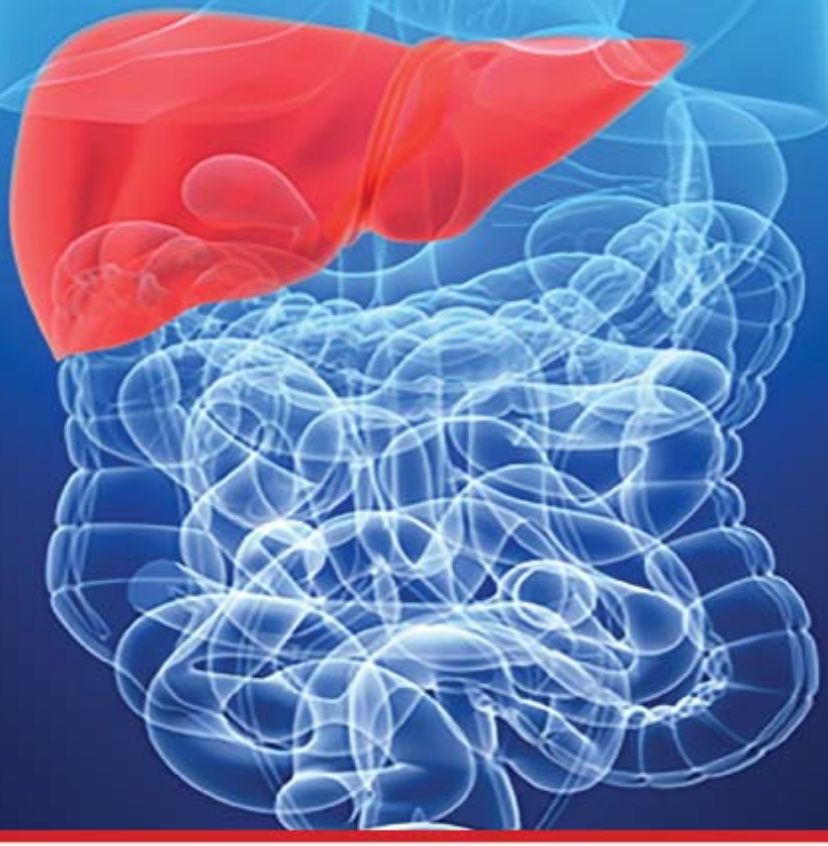
HEPATITIS C:

Balancing Cost and Cure Rates in a Managed Care Environment



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Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Vanita K. Pindolia, PharmD, BCPS

  - *No financial interest/relationship relating to the topic of this activity*

Agenda

6:20 AM – 6:55 AM	The Evolving Treatment Guidelines: Therapeutic Recommendations for Various Hepatitis C Virus Patient Types *Paul Kwo, MD*
6:55 AM – 7:30 AM	The Unprecedented Evolution of the Hepatitis C Treatment Armamentarium: Challenges for Payers *Vanita K. Pindolia, PharmD, BCPS*
7:30 AM – 7:45 AM	Faculty Discussion/Question & Answer Session

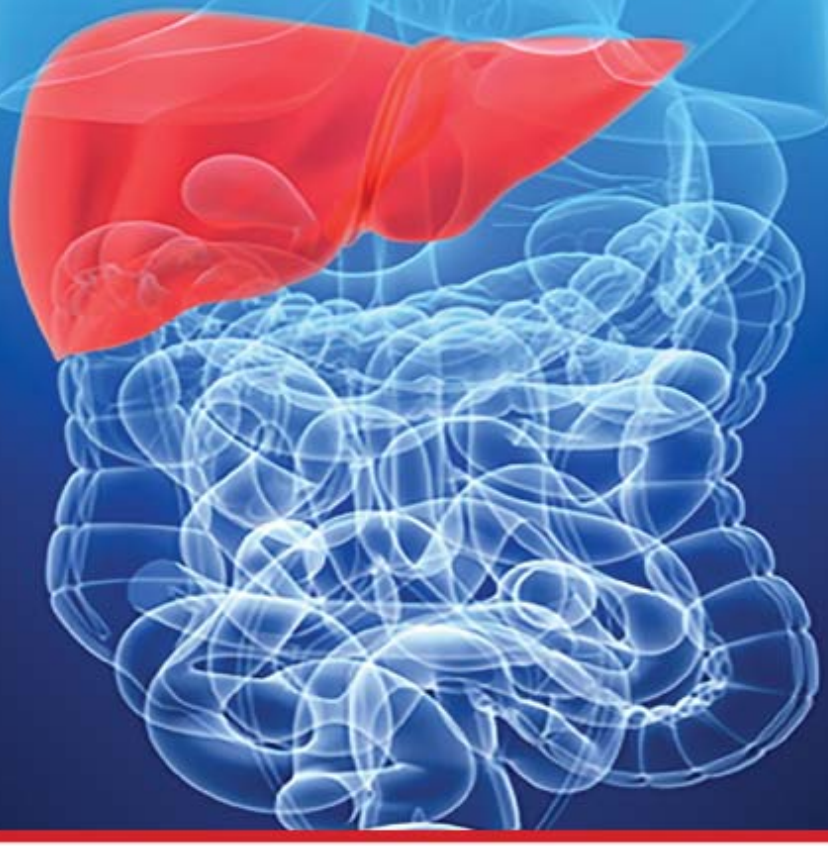
Educational Objectives

After completing this activity, the participant should be better able to:

- Apply evidence-based treatment strategies to optimize outcomes for patients with HCV within a managed care setting
- Explain recently updated AASLD, IDSA, and ACG treatment guidelines on current and emerging treatment options for HCV, including efficacy, safety, and tolerability
- Develop benefit design to address the economic challenges presented to payers with the introduction of new HCV treatment options
- Evaluate pharmacy management strategies, including specialty pharmacy services and disease management, that MCOs can implement to improve overall patient outcomes for HCV patients
- Provide accurate and appropriate counsel as part of the managed care treatment team

HEPATITIS C:

Balancing Cost and Cure Rates in a Managed Care Environment



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The Evolving Treatment Guidelines: Therapeutic Recommendations for Various Hepatitis C Virus Patient Types

Paul Kwo, MD
Professor of Medicine
Division of Gastroenterology and Hepatology
Indiana University

Faculty Disclosure

- The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:

Paul Kwo, MD

  - *Consulting Fees:* AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, and Merck & Co., Inc.
  - *Research Grant Funding*: AbbVie, Inc., Bristol-Myers Squibb, Gilead Sciences, Inc., Janssen Pharmaceuticals, and Merck & Co., Inc.

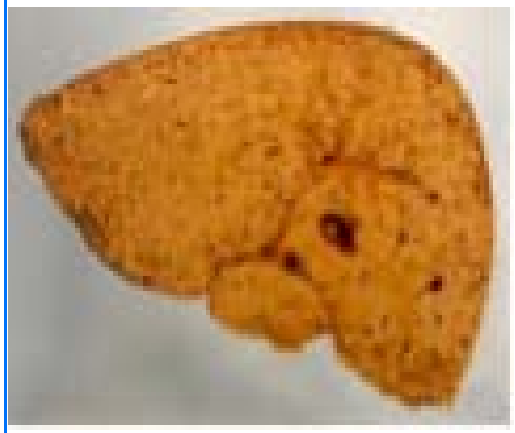
Agenda

- Hepatitis C virus (HCV) infection and associated complications
- HCV treatment guidelines
- Emerging therapies
- Summary

HCV Infection and Associated Complications

Risk Factors Associated with Faster Fibrosis Progression in Chronic HCV

Disease state factors

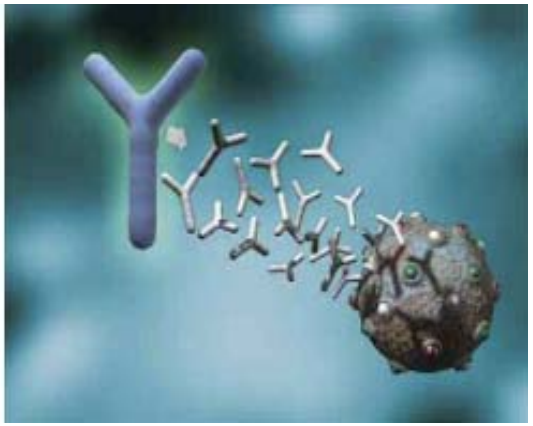


- Fibrosis stage
- HCV onset after 40 years of age
- Persistently elevated ALT

Host factors

- Male gender
- Age >45 years
- Obesity/steatosis
- Diabetes
- HIV, HBV co-infection
- Immune system compromise
- Iron overload
- Life style (ETOH, smoking)

Viral factors

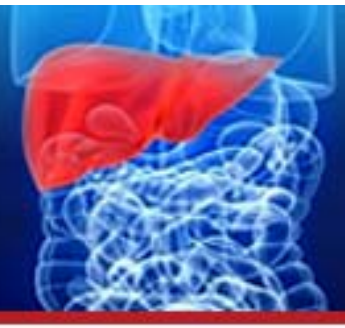


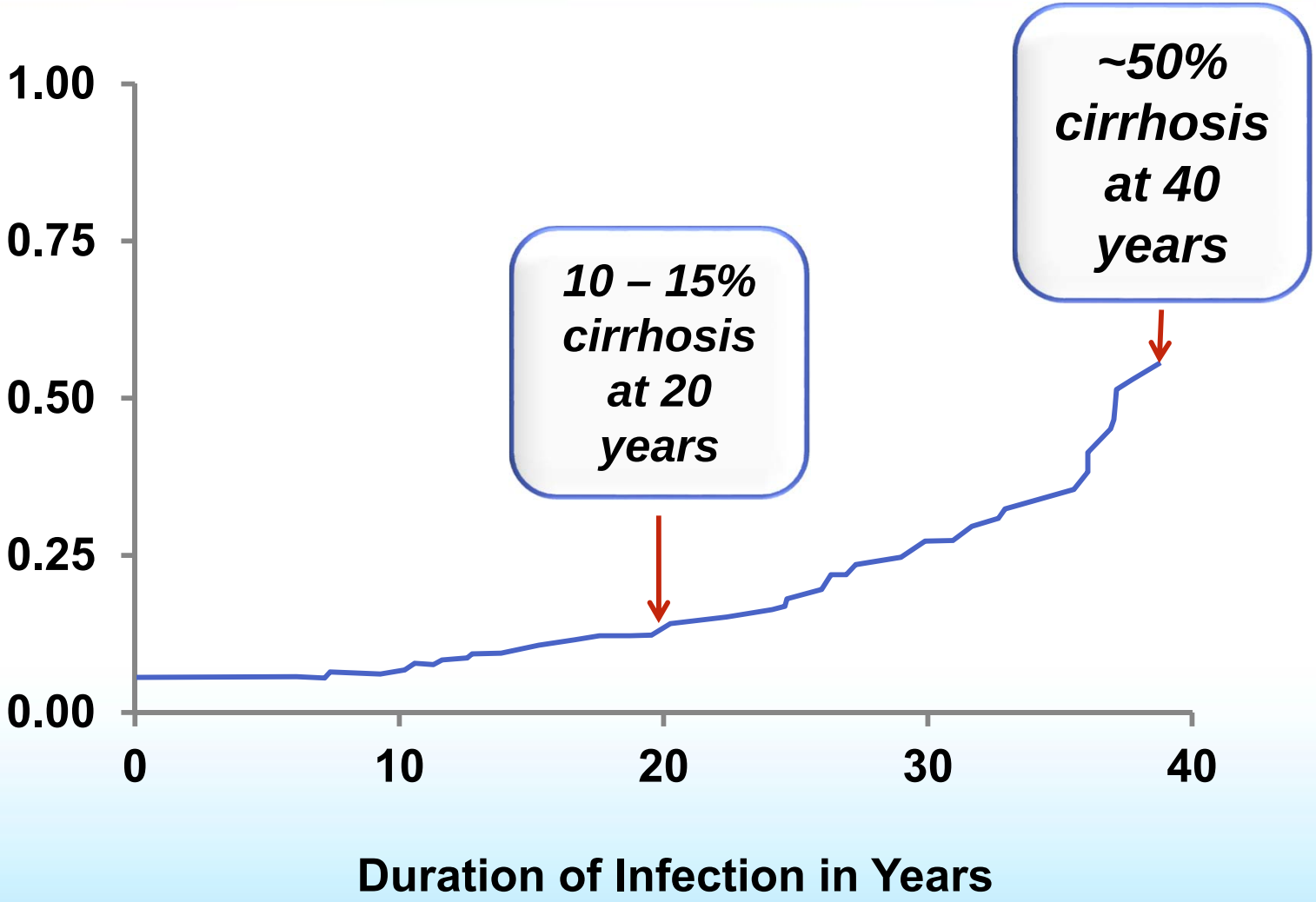
- Genotype 3

Poynard T, Afdhal NH. *Antivir Ther.* 2010;15:281-291.
Poynard T, et al. *Lancet.* 1997;349:825-832.

ALT=alanine transaminase

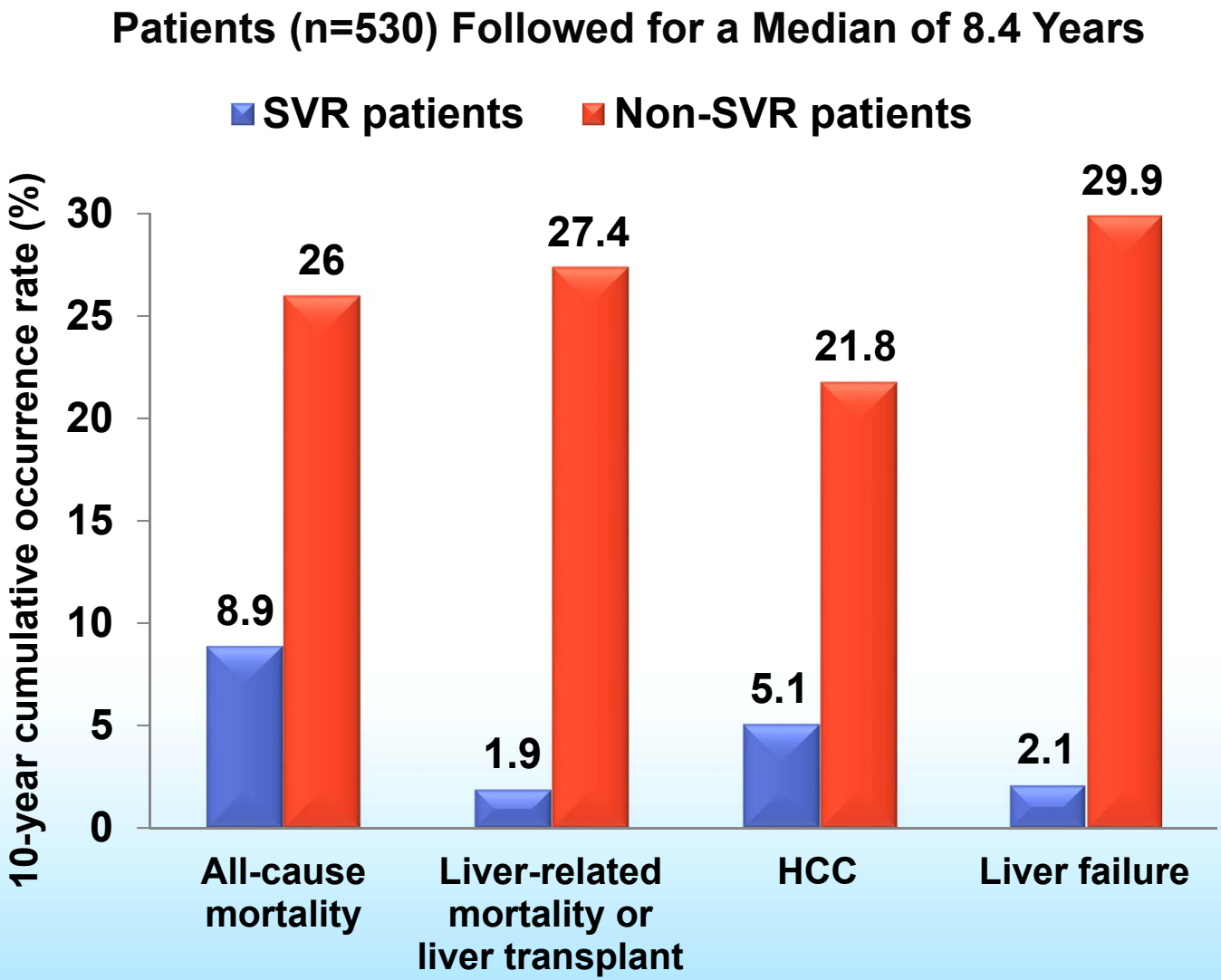
Disease Progression in HCV is Not Linear: Importance of Early Treatment





Poynard T, et al. *J Hepatol*. 2001;34:730-739.

SVR and All-Cause Mortality in Chronic HCV Patients with Advanced Fibrosis



- Baseline factors significantly associated with all-cause mortality
  - Older age
  - Diabetes
  - Genotype 3 (2-fold increase in mortality and HCC)
  - Higher fibrosis score
  - Severe alcohol use

Van der Meer A, et al. *JAMA.* 2012; 308:2584–2593.

SVR=sustained virologic response; HCC=heptocellular carcinoma.

HCV Genotype 3 Associated with Significantly Higher Risk of Cirrhosis and HCC vs. GT 1

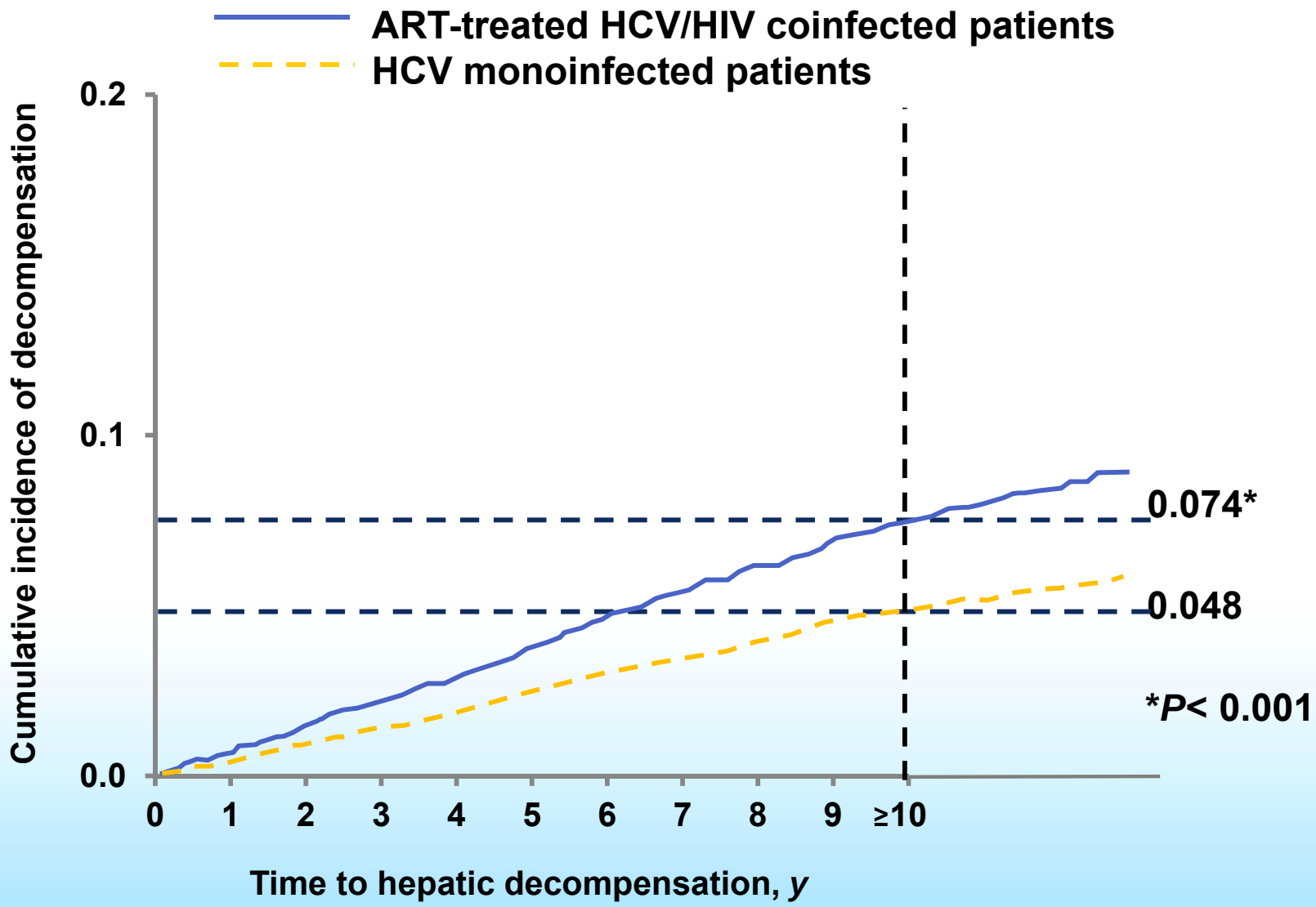
- Analysis of the VA Clinical Case Registry of patients with active HCV viremia (n=110,484)
  - GT 1: n=88,348 (80%)
  - GT2: n=13,077 (12%)
  - GT3: n=8,337 (7.5%)
- Mean follow-up: 5.4 years
- 31% higher risk of cirrhosis and HCC in patients with GT 3 vs. GT1 independent of age, diabetes, BMI, and antiviral treatment

	Hazard Ratio	Confidence Interval
Cirrhosis	1.31	1.22-1.39
HCC	1.80	1.61-2.03

Kanwal F, et al. *Hepatology.* 2014;60:98-105.

HCC=heptocellular carcinoma; GT=genotype.

HCV/HIV Coinfected Patients Have Higher Rates of Hepatic Decompensation Despite ART



Lo Re V 3rd, et al. *Ann Intern Med*. 2014:160:369-379.

ART=antiretroviral therapy.

HCV Infection Associated with Significantly Higher Prevalence of Comorbidities

	Incidence of Comorbidities (%)	
	Employees w/ HCV (n=1329)	Employees w/out HCV (n=26,580)
Neoplasm	19*	13
Metabolic abnormality (eg, diabetes)	34*	27
Mental disorder	20*	10
Systemic Disorders		
Nervous	31*	24
Circulatory	36*	28
Digestive	42*	18
Genitourinary	35*	28

***P*<0.0001 vs. employees without HCV infection**

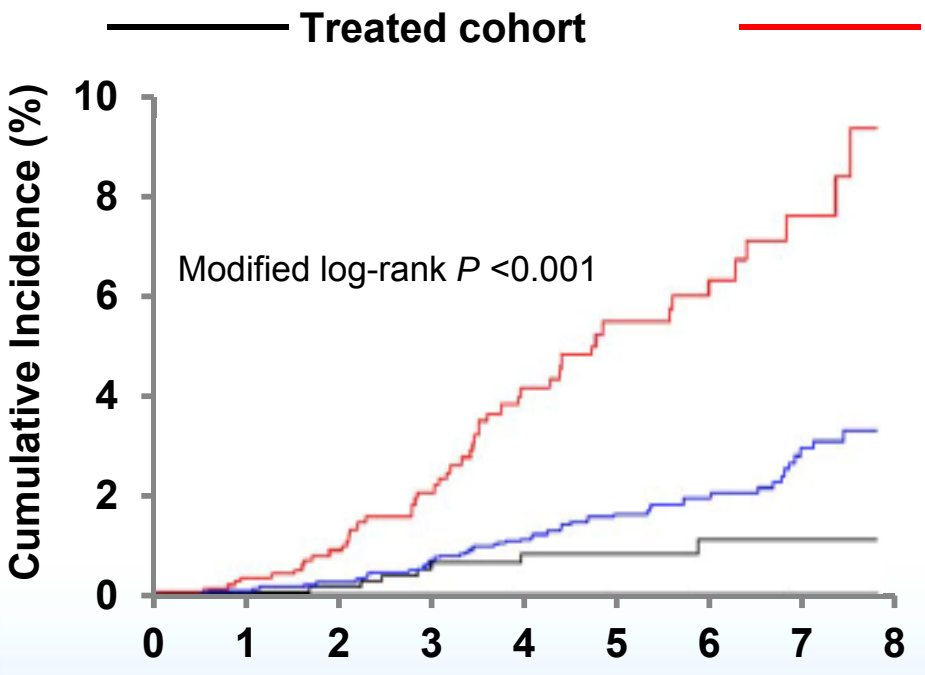
- Significantly higher prevalence of comorbidities in the HCV-infected vs. non-infected cohort

Retrospective claims data from Human Capital Management Services Research Reference Database (2001-2007). HCV status by ICD-9 codes. Controls matched on demographic characteristics.

Su J, et al. *Hepatology*. 2010;52:436-442.

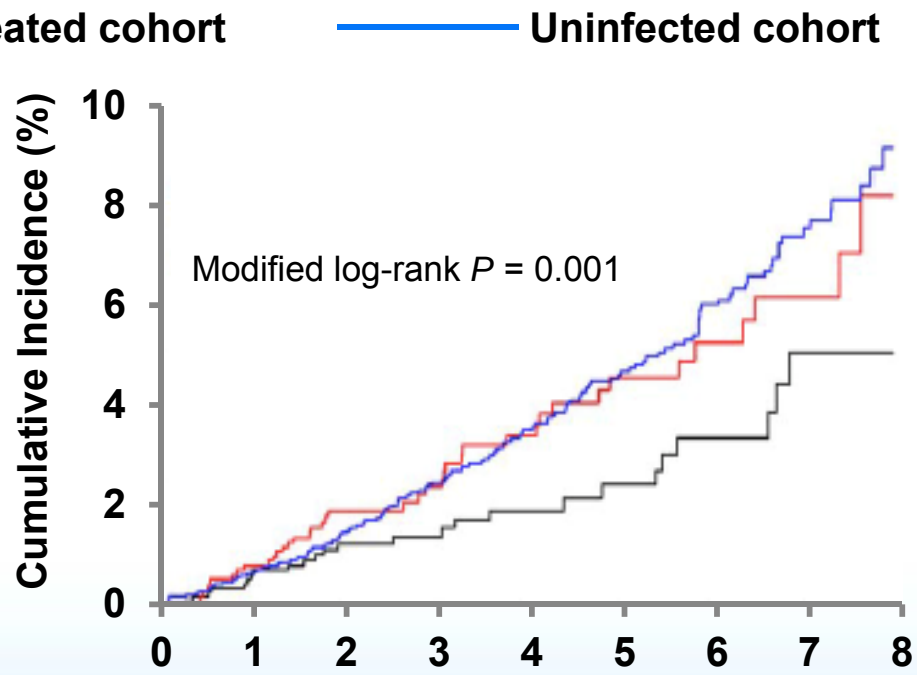
Achievement of SVR Decreases Complications Associated with HCV Management

Cumulative incidence of ESRD in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event



Number at risk									
Treated	1411	1400	987	755	586	418	303	168	47
Untreated	1411	1388	962	711	530	362	262	152	43
Uninfected	5644	5591	3928	2980	2322	1624	1194	684	201

Cumulative incidence of acute coronary event in three study cohorts, analyzed by the modified log rank test with death adjusted as a competing risk event



Number at risk									
Treated	1411	1394	983	751	580	411	296	161	46
Untreated	1411	1383	955	717	538	367	263	151	42
Uninfected	5644	5566	3889	2935	2276	1590	1157	653	191

Hsu YC, et al. *Hepatology*. 2014;59:1293-1302.

ESRD=end stage renal disease.

HCV Screening and Engagement in Care

Who Should Be Tested For HCV?

One-time HCV testing is recommended for persons born between 1945 and 1965*, without prior ascertainment of risk. **Rating: Class I, Level B**	**Birth cohort screening**

Other persons should be screened for risk factors for HCV infection, and 1-time testing should be performed for all persons with behaviors, exposures, and conditions associated with an increased risk of HCV infection.

Risk Behaviors	Risk Exposures	Other

• Injection-drug use (current or ever, including those who injected once)
• Intranasal illicit drug use
	• Long-term hemodialysis (ever)
	• Getting a tattoo in an unregulated setting
	• Health care, emergency medical, and public safety workers after needlesticks, sharps, or mucosal exposures to HCV-infected blood
	• Children born to HCV-infected women
	• Prior recipients of transfusions or organ transplants, including persons who:
	  o were notified that they received blood from a donor who later tested positive for HCV infection
	  o received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
	  o received clotting factor concentrates produced before 1987
	• Persons who were ever incarcerated
		• HIV infection
		• Unexplained chronic liver disease and chronic hepatitis including elevated alanine aminotransferase levels
		• Solid organ donors (deceased and living)

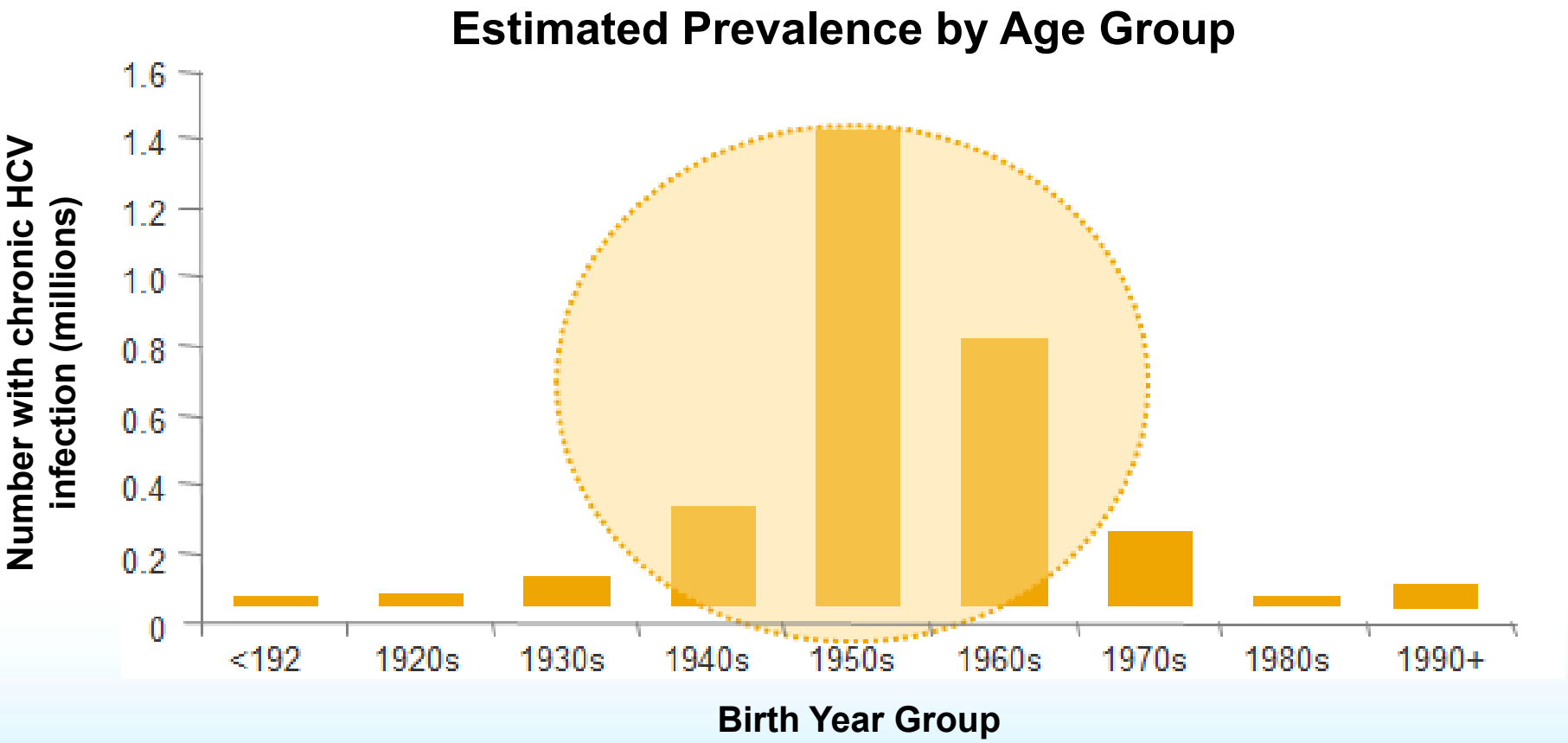
Rating: Class I, Level B

Risk-based screening

***Regardless of country of birth**

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

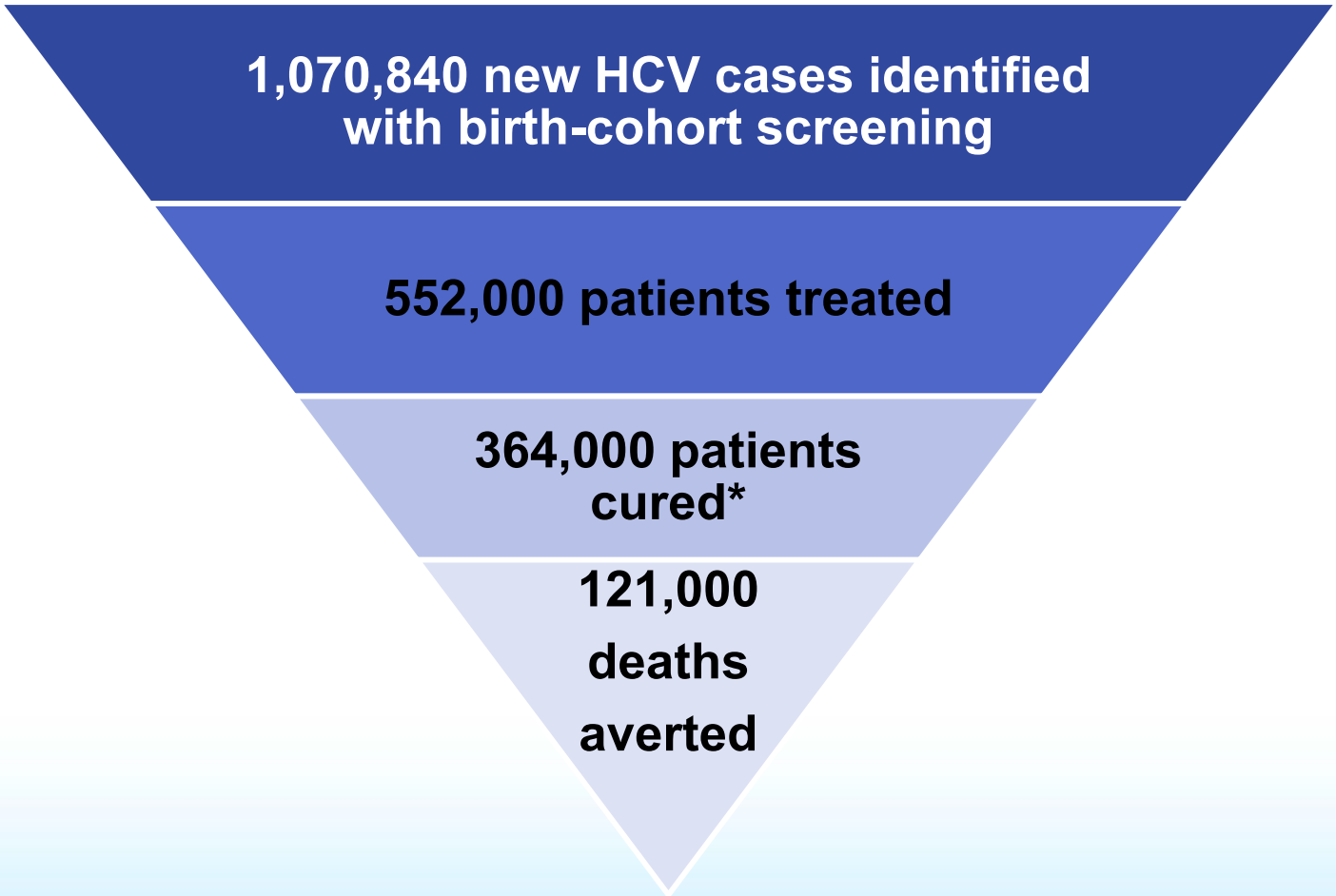
Baby Boomers Account for 76.5% of HCV in the US



- Up to 75% of people with HCV in the US are undiagnosed
- An estimated 35% of undiagnosed baby boomers with HCV currently have advanced fibrosis (F3-F4, bridging fibrosis to cirrhosis)

Smith BD, et al. *MMWR*. August 17, 2012;61;1-18.
McGarry LJ et al. *Hepatology*. 2012;55:1344-1 355.

Screening by Birth Cohort May Prevent >120,000 Deaths Due to HCV Infection



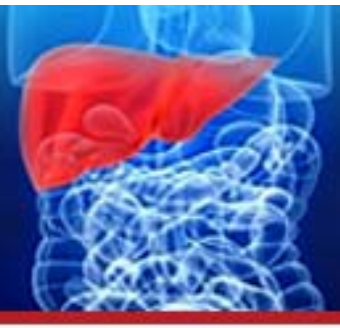
*With pegylated interferon and ribavirin plus DAA treatment.

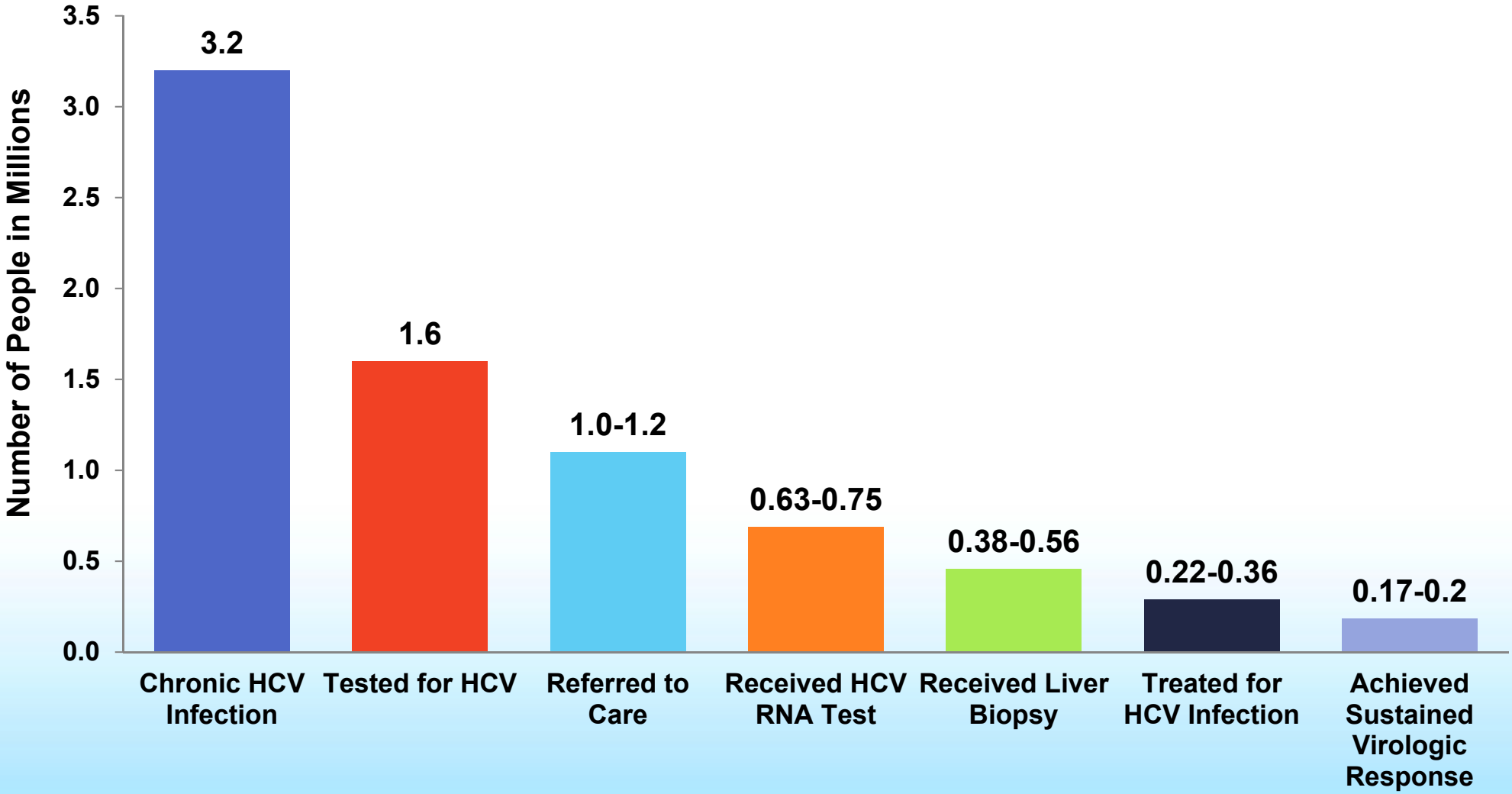
†Deaths due to decompensated cirrhosis or hepatocellular carcinoma within 1945-1965 birth cohort. 470,000 deaths under birth cohort screening vs 592,000 deaths under risk-based screening.

1. Rein D, et al. *Ann Intern Med.* 2012;156:263-270.
2. McGarry LJ, et al. *Hepatology*. 2012;55:1344-1355.

DAA=direct-acting antiviral agents against the NS3/4A serine protease.

Patient Engagement in HCV Care

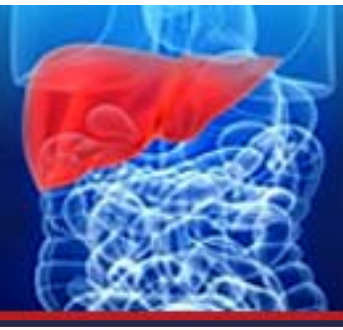


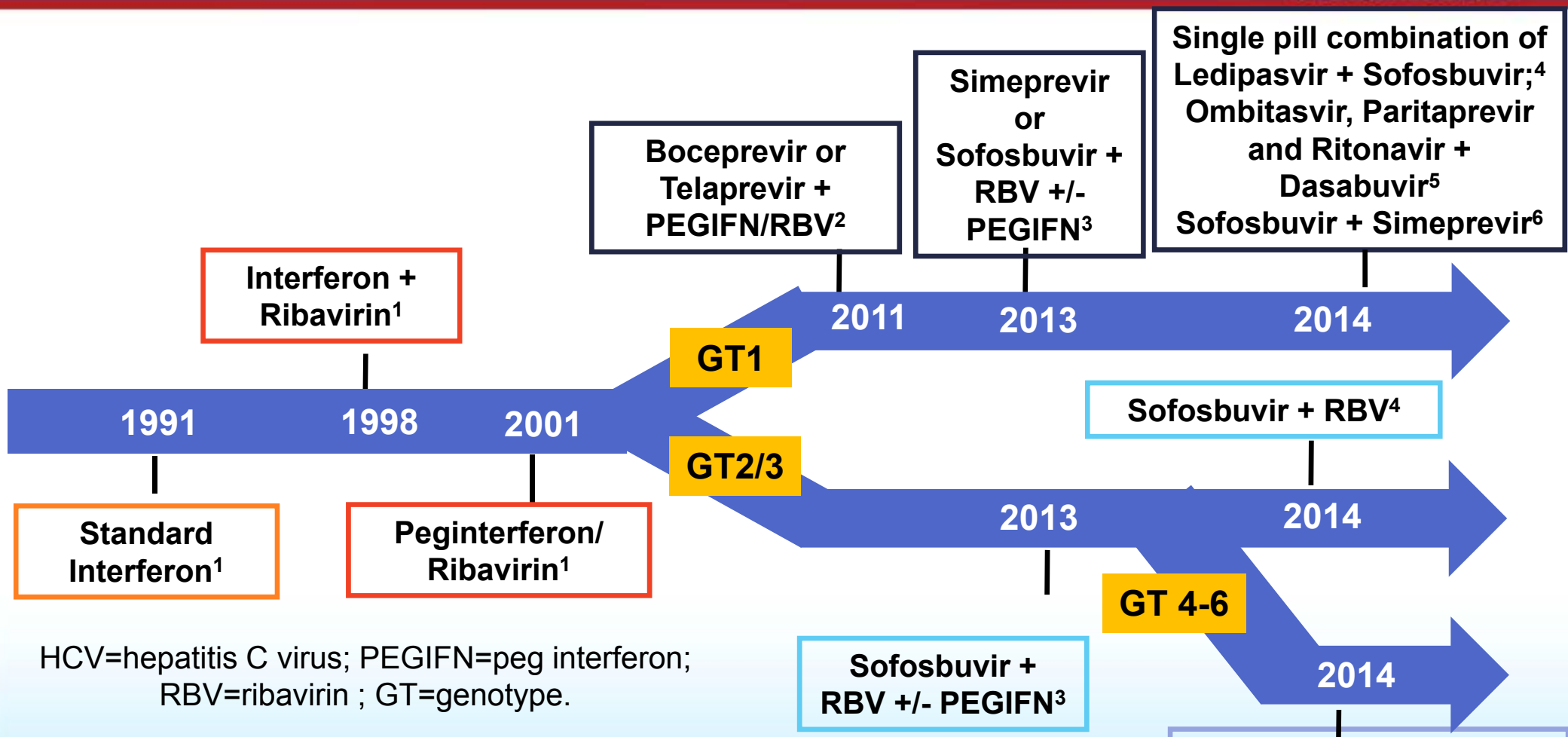


Holmberg SD, et al. *N Engl J Med*. 2013;368:1859-1861.

HCV Treatment Guidelines

Rapidly Evolving HCV Treatment Landscape





HCV=hepatitis C virus; PEGIFN=peg interferon; RBV=ribavirin ; GT=genotype.

1. Ghany MG, et al. *Hepatology*. 2009;49:1335-1374; 2. Tungol A, et al. *Am J Manag Care Pharm*. 2011;17:685-694; 3. Young CA. *Pharmacy Today*. January 1, 2014. http://www.pharmacist.com/simeprevir-and-sofosbuvir-two-new-drugs-chronic-hcv-infection. Accessed March 19, 2015; 4. Harvoni® [package insert]. Foster City, CA: Gilead Sciences, Inc.; October 2014; 5. VIEKIRA PAK® [package insert]. North Chicago, IL: AbbVie Inc.; February 2015; 6. Olysio® [package insert]. Titusville, NJ: Janssen Products, LP, Inc.; November 2014.

AASLD/IDSA Treatment Guidelines: Recommendations for Initiation of Treatment

Recommendations for when and in whom to initiate treatment

Treatment is recommended for patients with chronic HCV infection

Rating: Class I, Level A

Immediate treatment is assigned the highest priority for those patients with advanced fibrosis (Metavir F3), those with compensated cirrhosis (Metavir F4), liver transplant recipients, and patients with severe extrahepatic hepatitis C.

Based on available resources, **immediate** treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority.

Ratings: See tables

AASLD/IDSA=American Association for the Study of Liver Diseases; IDSA=International Antiviral Society.
AASLD/IDSA. http://www.hcvguidelines.org/full-report/when-and-whom-initiate-hcv-therapy. Accessed March 3, 2015.

HCV Treatment Benefits All Patients

- Evidence clearly supports treatment in all HCV-infected persons*
  - Successful hepatitis C treatment results in SVR and is expected to benefit nearly all chronically infected persons
- Urgent treatment initiation recommended for
  - Advanced fibrosis (Metavir F3)
  - Compensated cirrhosis (Metavir F4)
  - Liver transplantation
  - Severe extrahepatic HCV
- Reduced HCV transmission expected with treatment of:
  - Women wishing to become pregnant
  - Long-term hemodialysis pts
  - MSM with high-risk sexual practices
  - Injection drug users
  - Incarcerated persons

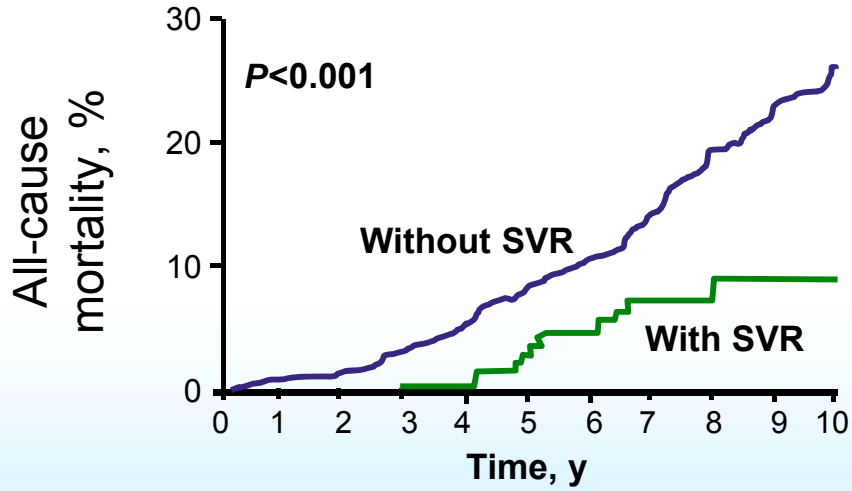
*except those with limited life expectancy due to non-liver related comorbidities

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

Achievement of SVR Associated with Reduced Mortality

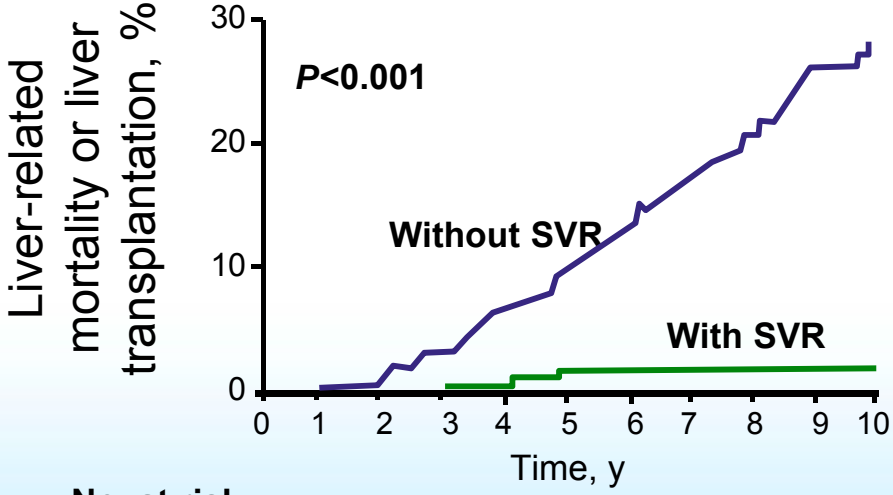
- 530 adults with advanced fibrosis prospectively followed for median 8.4 years after HCV treatment
- 192 (36%) achieved SVR

All-cause mortality



No. at risk											
Without SVR	405	393	382	363	344	317	295	250	207	164	135
With SVR	192	181	168	162	156	144	125	88	56	40	28

Liver-related mortality or liver transplantation



No. at risk											
Without SVR	405	392	380	358	334	305	277	229	187	146	119
With SVR	192	181	168	162	156	144	125	88	56	40	28

Van der Meer AJ, et al. *JAMA.* 2012:308:2584-2593.

Recommended Regimens for Treatment-Naïve HCV Genotype 1 Patients

Subtype	Non-Cirrhotic		Compensated Cirrhosis	
	Regimen	Duration (wks)	Regimen	Duration (wks)
GT 1a or 1b	LDV/SOF	12*	LDV/SOF	12
GT 1a	OMV/PTV/RTV + DSV + RBV	12	OMV/PTV/RTV + DSV + RBV	24
GT 1b	OMV/PTV/RTV + DSV	12	OMV/PTV/RTV + DSV + RBV	12
GT 1a	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
GT 1b	SMV + SOF	12	SMV + SOF	24

*Shorter course can be considered in patients with pretreatment HCV RNA < 6 million IU/mL at provider's discretion but should be done with caution.

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; SMV=simeprevir.

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

Recommended Regimens for Treatment-Experienced HCV Genotype 1 Patients

Subtype/ Prior Therapy	Non-Cirrhotic		Compensated Cirrhosis	
	Regimen	Duration (wks)	Regimen	Duration (wks)
Prior Pegylated Interferon/Ribavirin				
• GT 1a or 1b • GT 1a or 1b	LDV/SOF	12	LDV/SOF LDV/SOF + RBV	24 12
• GT 1a • GT 1b	OMV/PTV/RTV + DSV + RBV OMV/PTV/RTV + DSV	12 12	OMV/PTV/RTV + DSV + RBV OMV/PTV/RTV + DSV + RBV	24 12
• GT 1a or 1b	SMV + SOF ± RBV	12	SMV + SOF ± RBV	24
Prior SOF				
• GT 1a or 1b	Defer therapy*		LDV/SOF + RBV	24
Prior PI				
• GT 1b or 1b • GT 1a or 1b	LDV/SOF	12	LDV/SOF LDV/SOF + RBV	24 12

***Based on limited available data, pts without advanced fibrosis and without an urgent need for HCV treatment should defer antiviral therapy pending additional data or consider clinical trial.12 weeks of retreatment with LDV/SOF/RBV achieved 100% SVR**

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; SMV=simeprevir

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

All Oral Regimens for Other Populations

Population	Regimen	Duration (wks)
GT 2	SOF + RBV	12
GT 3	SOF + RBV	24
GT 4	OMV/PTV/RTV + DSV + RBV LDV/SOF	12
GT 6	LDV/SOF	12
GT 1/2/3/4 HCC pre-OLT	SOF + RBV	48*
GT 1, post-OLT (Metavir ≤F2; including compensated cirrhosis)	OMV/PTV/RTV + DSV + RBV LDV/SOF + RBV	24 12
GT 1/4 decompensated cirrhosis (CTP B or C)	LDV/SOF + RBV‡	12†
GT 2/3 decompensated cirrhosis (CTP B or C)	SOF + RBV	Up to 48 weeks

***Up to 48 weeks or until transplantation, whichever occurs first.**
‡Not FDA approved but recommended in AASLD/IDSA guidance.
†24 weeks of SOF/LDV if anemia or RBV intolerance; 24 weeks of SOF/LDV + RBV (600 mg/day with increasing dose if tolerated) if prior SOF failure.

LDV=ledipasvir; SOF=sofosbuvir; OMV=ombitasvir; PTV=paritaprevir; RTV=ritonovir; DSV=dasabuvir; RBV=ribavirin; HCC=hepatocellular carcinoma; OLP=orthotopic liver transplantation; CTP=Child-Turcotte-Pugh

1. Sovaldi® [package insert]. Foster City, CA: Gilead Sciences, Inc.; November 2014;. 2. VIEKIRA PAK®[package insert]. North Chicago, IL: AbbVie Inc.; February 2015; 3. AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

AASLD/IDSA Guidance for Patients with HCV/HIV Coinfection

- Same recommendations as in HCV-monoinfected patients
- Drug–drug interactions must be assessed
  - Need to adjust or withhold RTV if receiving a boosted PI with OMV/PTV/RTV + DSV
  - Potential for LDV-mediated increase in tenofovir levels, especially if tenofovir used with RTV
    - Avoid LDV if CrCl <60 mL/min or if receiving tenofovir with RTV-boosted PI
  - Do not interrupt antiretroviral therapy
- Do not use OMV/PTV/RTV ± DSV in coinfected patients not taking antiretroviral therapy

RTV=ritonavir; PI=protease inhibitor; OMV=ombitasvir; PTV=paritaprevir; DSV=dasabuvir; LDV=ledipasvir; CrCl=creatinine clearance

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

Summary of Current Treatment Recommendations

- PegIFN no longer recommended for first-line therapy of any patient
- 3 FDA-approved pegIFN-free regimens for genotype 1
- No differences in treatment recommendations for HCV mono-infected vs HCV/HIV-co-infected patients
  - Drug–drug interactions must be assessed

PegIFN=pegylated interferon

AASLD/IDSA Recommendations for Testing, Managing, and Treating Hepatitis C. 2015. http://www.hcvguidelines.org/full-report-view. Accessed March 2, 2015.

Emerging Therapies

HCV Therapies in Development

On Market

IFN & PEG IFN
Ribavirin
Boceprevir
Simeprevir
Sofosbuvir
Ombitasvir
Ledipasvir
Paritaprevir
Dasabuvir

Phase III

Asunaprevir
Daclatasvir†
Beclabuvir
Elbasvir
Grazoprevir
GS-5816

Phase II

Sovaprevir
Samatasvir
VX-135
ABT-493
ABT-530
ACH-3102
TMC647055

Phase I

TT-034
VGX-6150

Research/ Preclinical

Many others, including immune stimulants and gene therapy

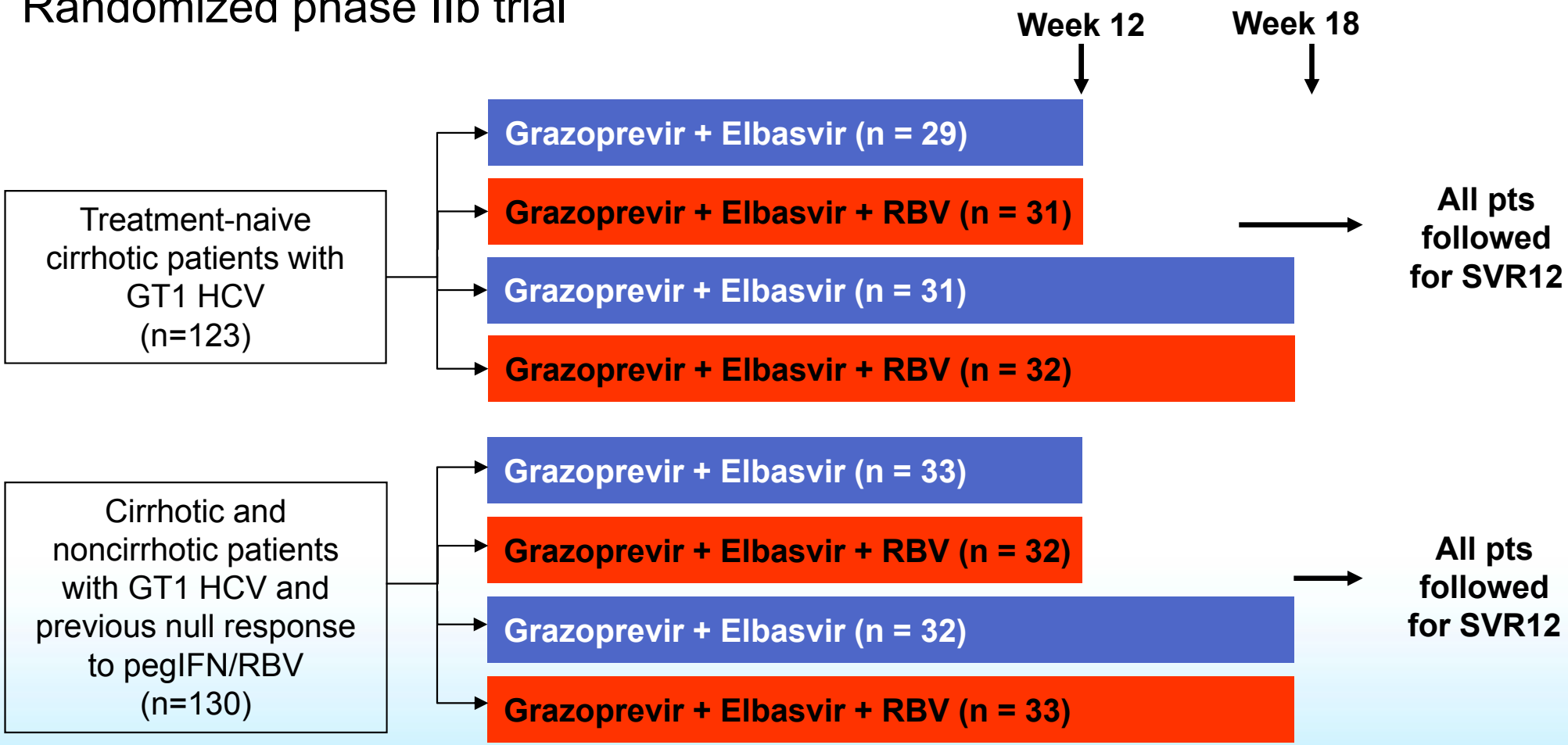
- Interferons
- Ribavirins
- Protease inhibitors
- Polymerase inhibitors
- NS5A inhibitors
- Other

*Sample, not an exhaustive list.
†NDA submitted March 2015.

Hepatitis C Drugs. http://hcvdrugs.com/detailed_ref.html. Updated February 24, 2015. Accessed March 19, 2015.

C-WORTHY: Grazoprevir + Elbasvir ± RBV x 12 or 18 Weeks in GT1 HCV Patients

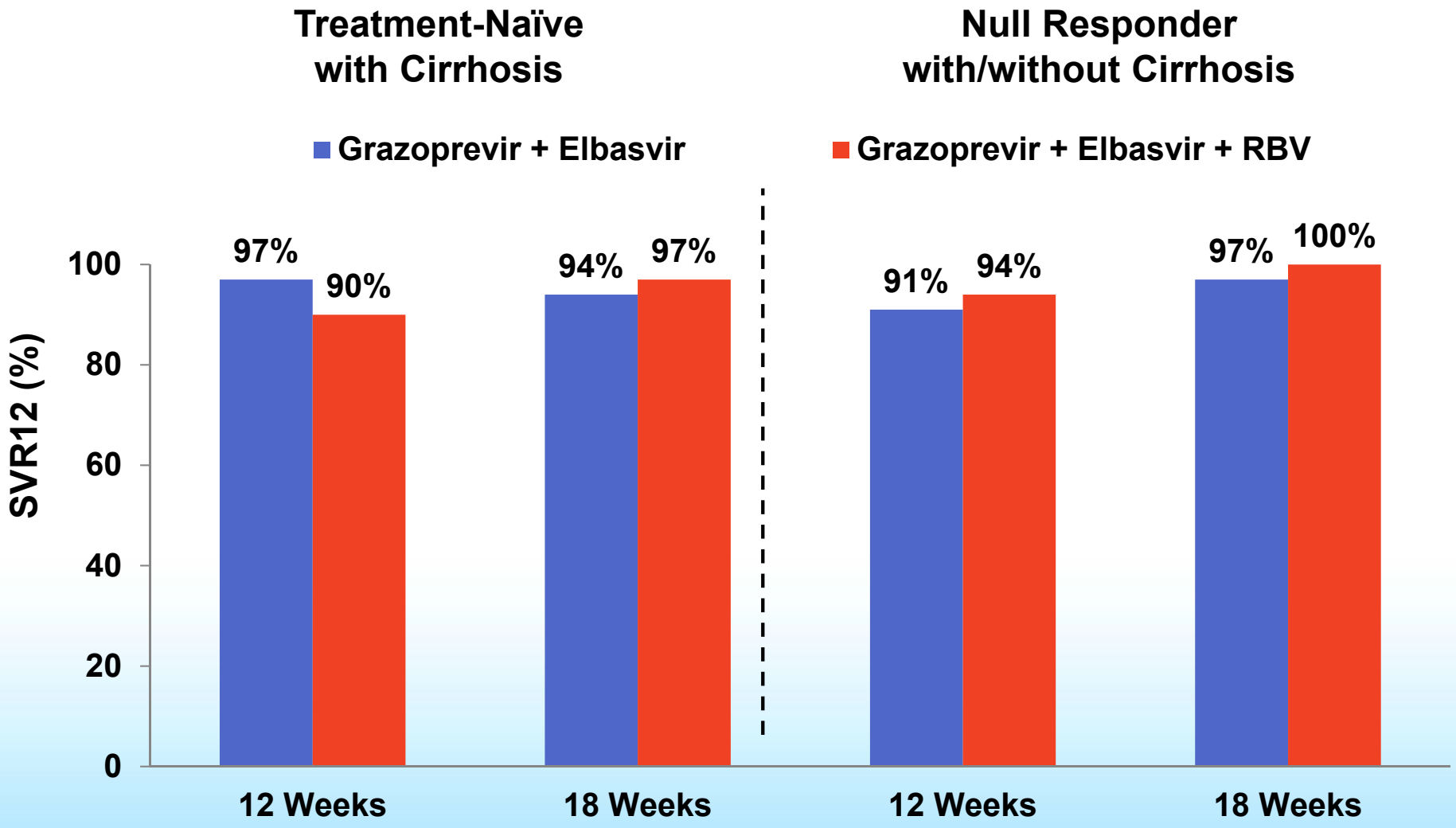
Randomized phase IIb trial



Grazoprevir 100 mg once daily; elbasvir 50 mg once daily; weight-based RBV 800, 1200, or 1400 mg daily.

Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract 196.

C-WORTHY: SVR12 Rates of Grazoprevir + Elbasvir ± RBV x 12 or 18 Weeks



Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract 196.

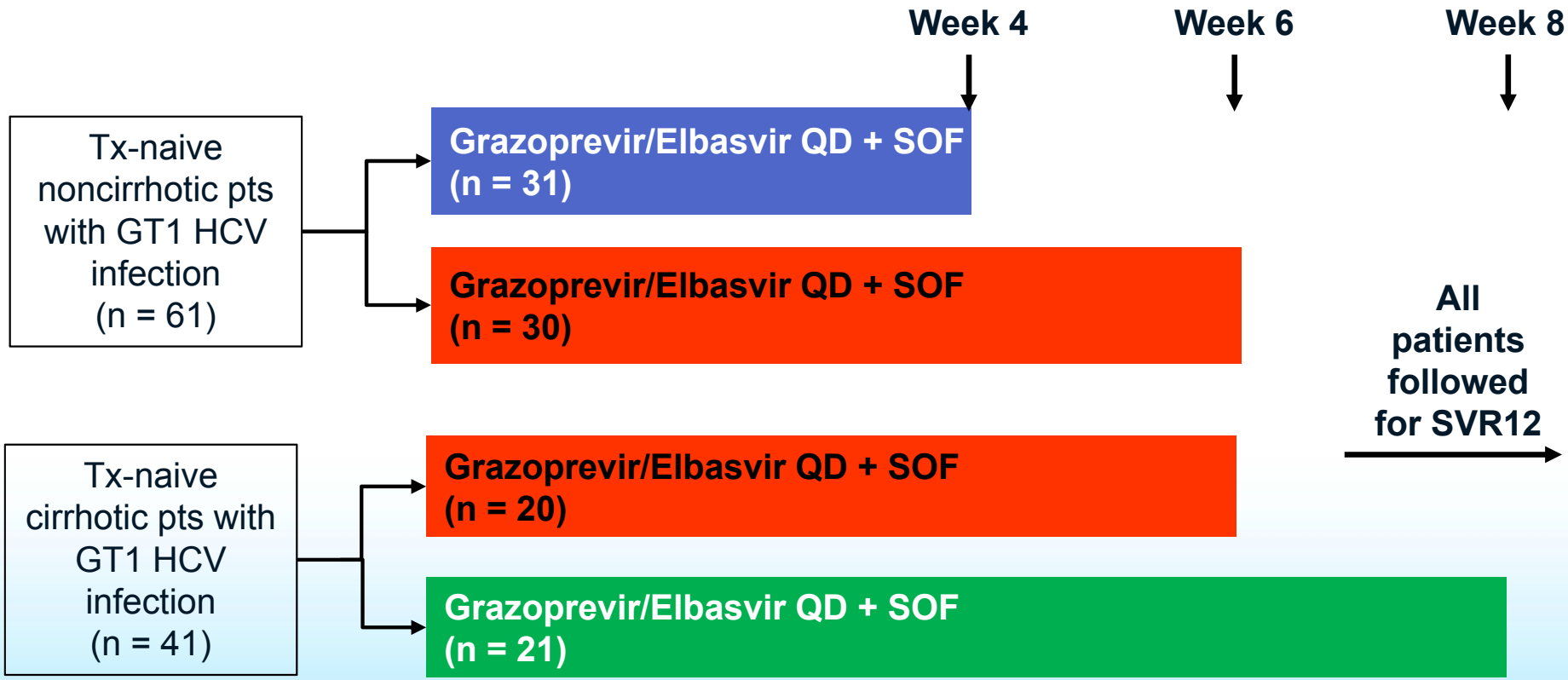
C-WORTHY: Summary

- SVR12 was 92% in null responders with cirrhosis treated fro 12 weeks with grazopevir + elbasvir ± RBV
- High efficacy without RBV and with only 12 weeks of treatment
- Grazopevir + elbasvir were generally safe and well-tolerated

Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract 196.

C-SWIFT: Grazoprevir/Elbasvir + SOF x 4, 6, or 8 Weeks in Treatment-Naive GT1 HCV

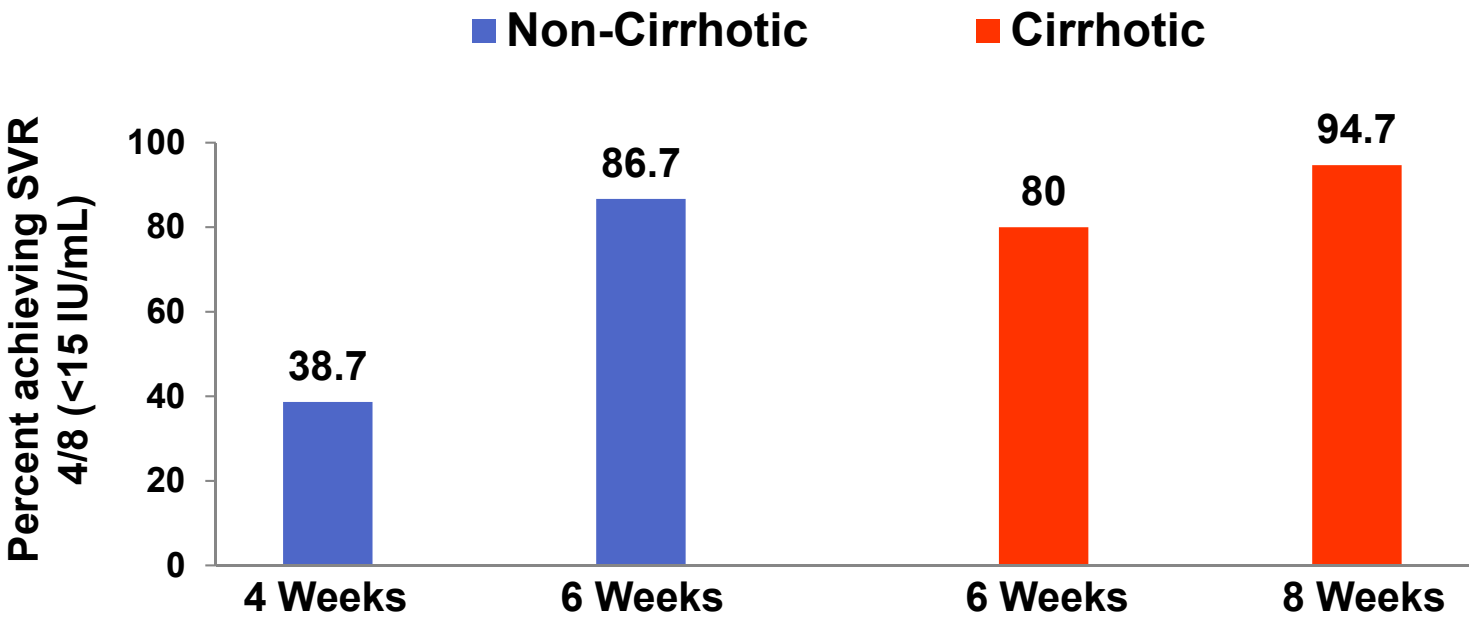
- Randomized, open-label phase II trial
- Primary endpoint: SVR12



Grazoprevir/elbasvir 100/50 mg QD FDC; sofosbuvir (SOF) 400 mg QD

Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-33.

C-SWIFT Interim Results: Modified ITT SVR4/8 With Grazoprevir/Elbasvir + SOF



SVR4/8 by HCV Subtype, % (n/N)	No Cirrhosis		Cirrhosis	
	4 Weeks (n = 31)	6 Weeks (n = 30)	6 Weeks (n = 20)	8 Weeks (n = 21)
GT1a	35 (9/26)	85 (22/26)	81 (13/16)	93 (14/15)
GT1b	60 (3/5)	100 (4/4)	75 (3/4)	100 (4/4)

Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-33.

C-SWIFT: Summary

- Combined regimen of grazoprevir/elbasvir + SOF may be able to shorten treatment duration to 6-8 weeks among cirrhotic and noncirrhotic treatment-naïve GT1 patients
- Factors that may have impacted likelihood of SVR in the 4 and 6 week arms include
  - Genotype (GT 1a vs. 1b)
  - Baseline viral load
  - IL28B status
  - PK of component medicines in the regimens

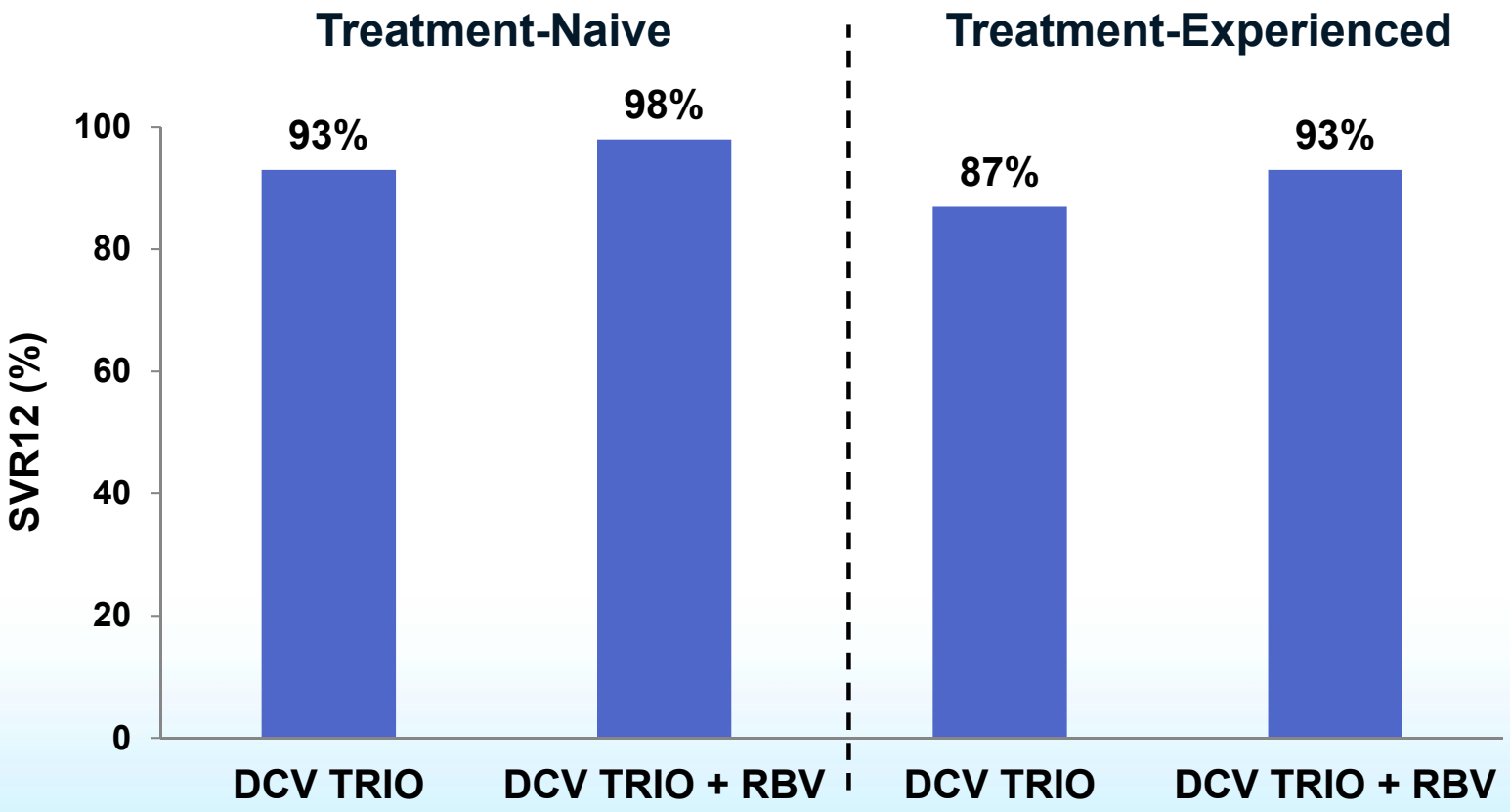
Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-33.

UNITY-2: Daclatasvir/Asunaprevir/Beclabuvir ± RBV in Patients with GT 1 Infection and Compensated Cirrhosis

- All-oral daclatasvir-based regimen (DCV TRIO)
  - Daclatasvir (NS5A inhibitor)
  - Asunaprevir (NS3 protease inhibitor)
  - Beclanabuvir (non-nucleoside NS5B polymerase inhibitor)
- UNITY-2 study
  - Fixed dose combination of DCV TRIO twice daily ± RBV in GT 1 treatment-naïve and treatment experienced compensated cirrhotics

Muir A, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-2.

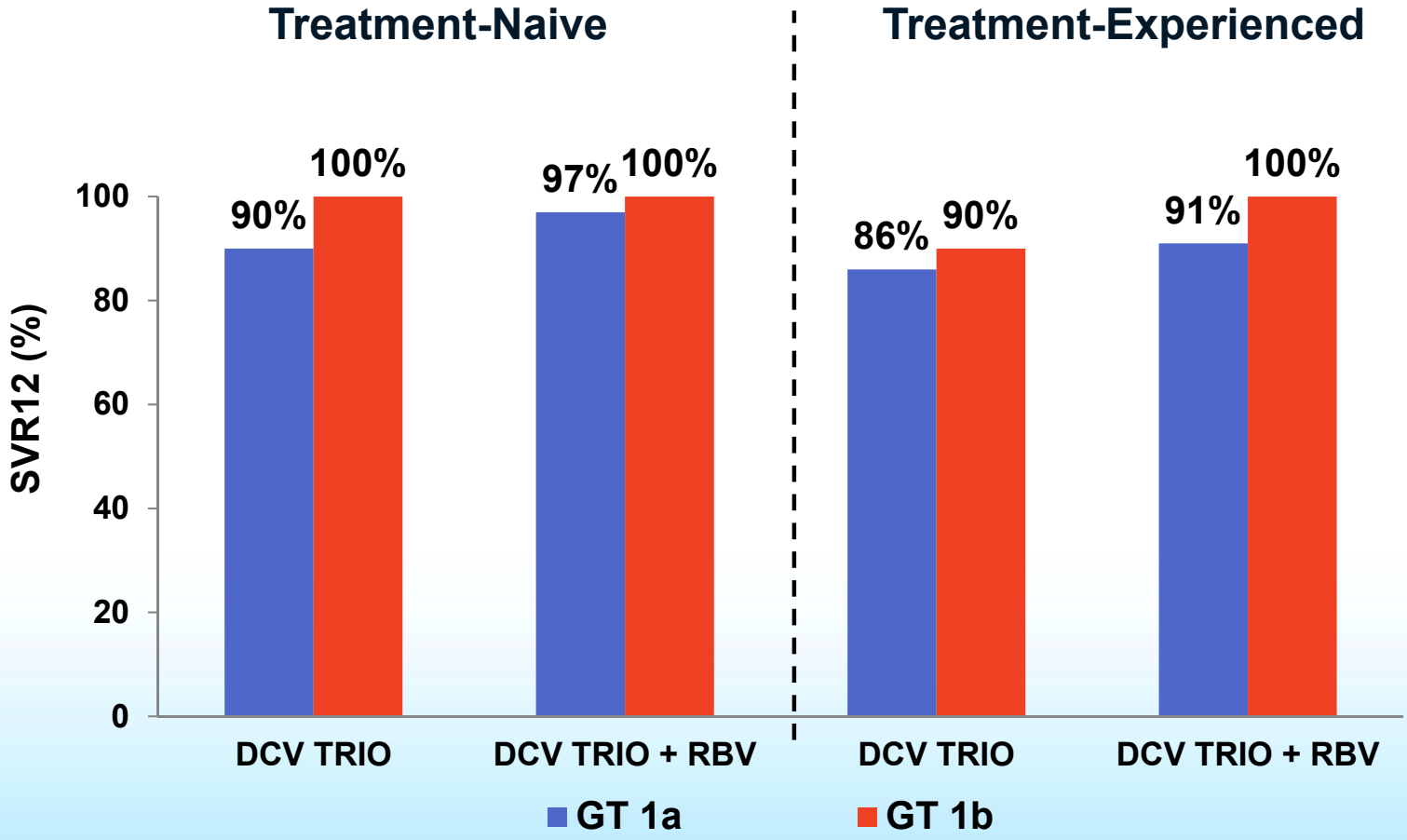
UNITY-2: SVR12 in GT1 Treatment-Naïve and Treatment-Experienced Cirrhotic Patients



DCV=Daclatasvir+Asunaprevir+Beclanabuvir

Muir A, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-2.

UNITY-2: SVR12 in GT 1 vs. GT 1b



DCV=Daclatasvir+Asunaprevir+Beclanabuvir

Muir A, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-2.

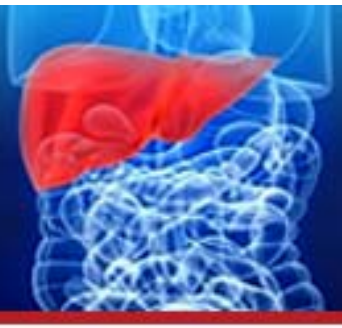
UNITY-2: Summary

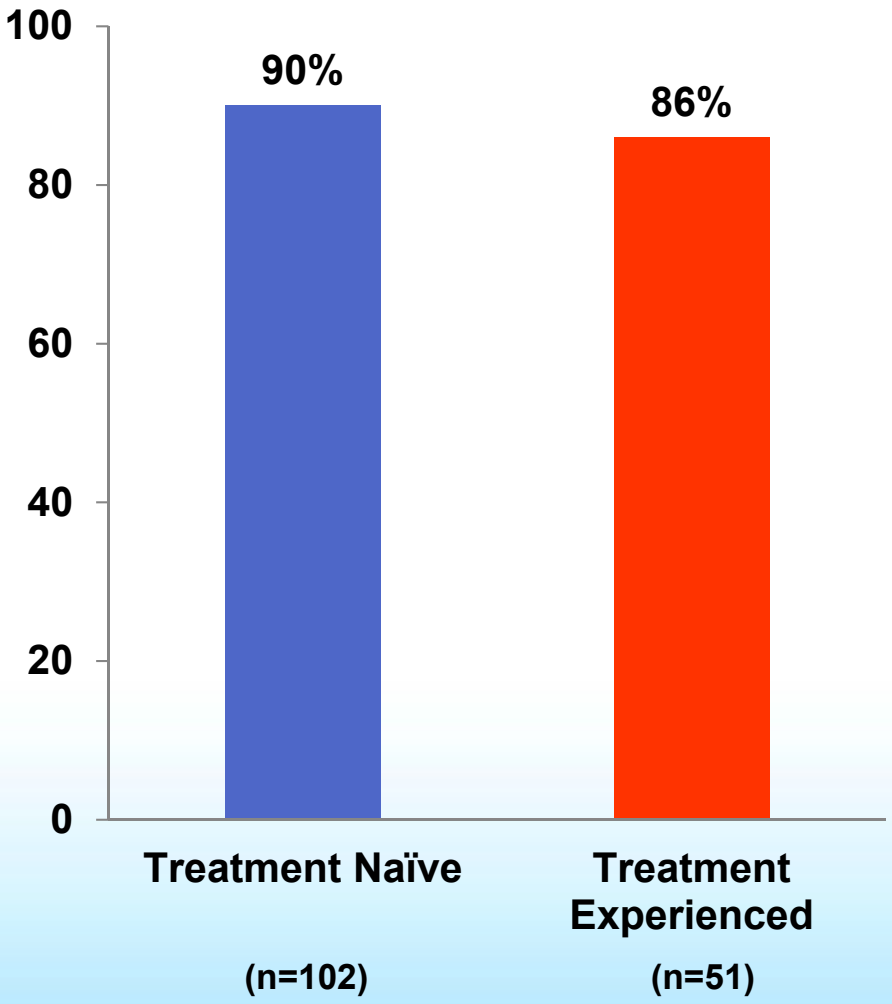
- DCV TRIO ± RBV was safe and well-tolerated with low rates of serious adverse events and discontinuation due to adverse events
- Most common adverse events (AEs) with DCV TRIO were headache, nausea, diarrhea, and fatigue

DCV=Daclatasvir+Asunaprevir+Beclanabuvir

Lawitz E, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-33.

ALLY-3: SVR12 in GT 3 Patients Treated with Daclatasvir + Sofosbuvir





- ALLY-3: Phase 3 open-label trial
- Once daily 60 mg daclatasvir + 400 mg sofosbuvir for 12 weeks without ribavirin
- Baseline characteristics:
  - Median age: 55 years
  - Baseline VL: >800,000 IU/ml
  - Unfavorable IL28B gene variants: 60%
  - Cirrhosis was present in 19% of TN and 25% of TE
- Patients with cirrhosis were less likely to achieve SVR12
- Combination was generally safe and well-tolerated

Nelson D, et al. Presented at AASLD. Boston, MA. November 7-11, 2014. Abstract LB-3.

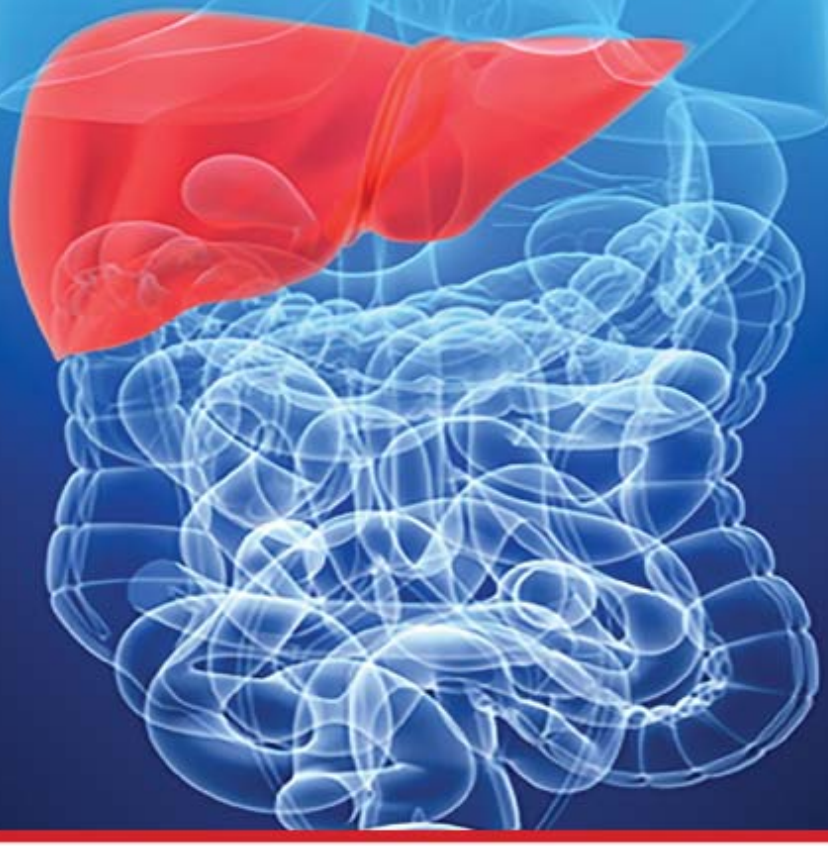
Summary

Summary

- >4.5 million Americans are infected with HCV
- One time HCV testing is recommended for persons born between 1945-1965; other persons should be screened for risk factors for HCV infection
- Birth cohort screening increases the potential number of patient eligible for treatment, but treatment engagement and achievement of SVR is low
- Treatment is recommended for patients with chronic HCV infection; the evidence clearly supports treatment in all HCV-infected persons
  - PegIFN no longer recommended for first-line therapy of any patient
- Several additional therapies are in late phase development

HEPATITIS C:

Balancing Cost and Cure Rates in a Managed Care Environment



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The Unprecedented Evolution of the Hepatitis C Treatment Armamentarium: Challenges for Payers

Vanita K. Pindolia, PharmD, BCPS
VP, Ambulatory Clinical Pharmacy Programs
Henry Ford Health System/Health Alliance Plan

Overview

- Economic Overview: Challenges for Payers and Healthcare Purchasers
- HCV Treatment: Ethical Dilemmas
- HCV Drug Management Strategies
- HCV Drug Contracting Strategies
- Role of Specialty Pharmacies

Economic Overview of the Challenges Presented to Payers and Healthcare Purchasers

Sens. Ron Wyden (D-Ore.), Chairman of the Senate Finance Committee, and Chuck Grassley (R-Iowa), the Judiciary Committee's ranking member asked drug makers how they justify the high price of HCV therapy:

> *"The large patient population HCV patients combined with the high price of each individual treatment creates a question as to whether payors of health care, including Medicare and Medicaid, can carry such a load."*

> *"HCV drug cost also could dramatically increase the government's spending on other programs, including …prisoners with HCV. Over 1.8 million people with HCV are incarcerated (32.8% of total cases of HCV in US). Even with 44% discount for treating prison populations, American taxpayers could end up paying billons of dollars …"*

Economic Overview of the Challenges Presented to Payers and Healthcare Purchasers (cont'd)

Analysis of HCV drug therapy impact on 2015 Medicare Part D spending:

> *"We estimate that the cost of HCV drug therapies … will increase 2015 federal spending on the individual Medicare Part D program by approximately $2.9 billion to $5.8 billion."*

> *"We estimate that the cost of HCV drug therapies will increase total annual individual Medicare Part D beneficiary premiums by $481 million to $965 million in 2015."*

Millimen, Inc. The impact of new hepatitis C drug therapy on individual Medicare Part D spending. http://www.natap.org/2014/HCV/partdpremiumstudymilliman.pdfnsight/2013/convergence-of-risk-and-opportunity.pdf. Accessed March 4, 2015.

Economic Overview of the Challenges Presented to Payers and Healthcare Purchasers (cont'd)

CMS data on Hep C drug spend in 2014 to ProPublica:

> *"Medicare spent more than $4.7 billion on Hep C drugs in 2014 – more than 15 times what it spent on Hep C drugs in 2013."*
>
> *"The federal government spent $65 billion on all Part D drugs in 2013."*
>
> Although the newer drugs have a higher SVR12 rate and *"curing Hep C will likely prevent liver cancer, prevent liver transplantation and save other health care dollars down the road … still, the drugs may not save money for Medicare, even in the long run."*
>
> A recent cost-effectiveness study published in *Annals of Internal Medicine* found that only 25% of the Hep C drug cost would be offset by avoiding hospitalizations and other treatment costs.

The Cost of a Cure: Medicare Spent $4.5 Billion on New Hepatitis C Drugs Last Year. http://www.propublica.org/article/cost-of-a-cure-medicare-spent-4.5-billion-on-hepatitis-c-drugs-last-year. Accessed April 2, 2015.
Chhatwal, J, et al. *Ann Intern Med*. 2015;162(6):397-406.

Economic Overview of the Challenges Presented to Payers and Healthcare Purchasers (cont'd)

Southeastern Pennsylvania Transportation Authority filed class action suit in US District Court on December 9, 2014 due to high cost associated with HCV drug therapy ($2.4 million for HCV drugs for its employees in 2014)

California Technology Assessment Forum (CTAF) Report:

> *"Because chronic infection with HCV is relatively common, the cost of hepatitis c drugs translates into an enormous potential budget impact for federal, state, and private health insurers."*

Institute for Clinical and Economic Review.
http://www.ctaf.org/sites/default/files/assessments/CTAF_HCV2_Final_Report_013015.pdf. November 17, 2014.
Accessed March 16, 2015.

Treatment of HCV: Uncertainties and Ethical Quandaries

- Determining the population that will need treatment HCV…not a simple answer
  - Acute HCV: 15% of HCV infections
    - 849 confirmed cases of acute HCV in US (2007)
    - CDC estimates ~17,000 cases of new HCV infections in US after adjusting for asymptomatic infections and underreporting (2007)
    - No treatment needed
  - Chronic HCV: 85% of HCV infections
    - ~3.2 million Americans
    - Most prevalent among those born from 1945 to 1965
    - An estimated 50% of population is unaware they have chronic HCV
- CDC estimates that one time testing for HCV for those born between 1945-1965 could identify an estimated 800,000 undiagnosed cases

Centers for Disease Control. Hepatitis C information for professionals. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed March 4, 2015. Centers for Disease Control. Hepatitis C testing for anyone born during 1945-1965: new CDC recommendations. http://www.cdc.gov/Features/HepatitisCTesting/index.html. Accessed March 4, 2015.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Could widespread screening for HCV lead to unnecessary treatment or overtreatment?
- Course of HCV progression
  - Retrospective studies of natural course of HCV suggests that end stage liver disease is common; cirrhosis develops within 20 years and liver cancer with 30 years
    - These studies were usually composed of sicker people with multiple medical problems (ie, referral bias)
    - Of this sicker HCV population (symptomatic population found to have HCV), 80-85% will die from non-hepatic causes
  - Based upon CDC 2011 data, 2.7 million people are infected with HCV in US
  - ~16,000 people die or have liver transplantation each year due to HCV
    - Equates to ~<0.6% of infected HCV patients

Koretz RL, et al. *BMJ.* 2015;350:g7809. Kyosawa K, et al. *Hepatology*. 1990;12:671-675. Tong MJ, et al. *West J Med*. 1996;164:399-404. Seeff LB. *Liver Int*. 2009;29 (Suppl 1):89-99. McCombs J, et al. *JAMA Intern Med*. 2014;174:204-212.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- HCV treatment efficacy
  - Impact on clinical outcomes (morbidity and mortality) is most compelling data to assure treatment effectiveness
    - Such trials for HCV limited to interferon-based therapy
  - HCV clinical trials: surrogate markers are used as outcome measures (eg, SVR12 or SVR24)
    - Few patients develop end stage liver disease
    - Often takes years to manifest end stage liver disease
    - SVR does not equate to cure
      - Simeprevir PILLAR study: undetectable HCV RNA declined from 336 pts at end of treatment to 303 (SVR12), 300 (SVR24) and 293 (SVR72)
      - Long-term data for newer HCV drug regimens are not yet available

Koretz RL, et al. *BMJ.* 2015;350:g7809; Fried MW, et al. *Hepatology*. 2013;58:1918-1929.

SVR=sustained virologic response

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Correlation of SVR into long-term clinical benefit
  - Patients who develop a SVR…
    - Usually do not show evidence of viral RNA in other body tissues
    - Exhibit less liver-related morbidity and mortality vs. patients with no SVR
  - Studies suggest that patients who achieved SVR were less likely to have risk factors associated with disease progression
    - Selection bias: Those less likely to progress to liver failure respond to treatment; few patients progress to liver failure

Koretz RL, et al. *BMJ.* 2015. 350:g7809; Fried MW, et al. *Hepatology*. 2013;58:1918-1929.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Harm in treating all patients found to be HCV-positive?
  - Actual AEs and their severity are found during post-marketing when larger populations are exposed to the drug
  - Harvoni® and Sovaldi® - Recent new serious and life-threatening drug warning added to drug labels (March 20, 2015)
    - Serious and Life-threatening cases of symptomatic bradycardia as well as one case of fatal cardiac arrest with coadministration of Amiodarone
  - Negative experience with telaprevir
    - Based upon clinical trials evaluated for telaprevir approval in 2011, serious AEs occurred in 3% of patients
    - December 2012 black box warning added to the label due to severe and fatal skin reactions
- Could we be exposing a large population to drug therapy that may not need it?
  - Large, randomized, long-term studies can provide insight on disease progression with/without HCV treatment, correlation of SVR12 with cure rates, and true clinical outcomes
  - Observational study of 3.5 years of follow up for 2800 participants who received HCV treatment is expected to be completed in 2016

Koretz RL, et al. *BMJ.* 2015;350:g7809.; Sovaldi® [package insert]. Foster City, CA: Gilead Sciences, Inc.; November 2014; Harvoni® [package insert]. Foster City, CA: Gilead Sciences, Inc.; October 2014; Viekira Pak® [package insert]. North Chicago, IL: AbbVie, Inc.; February 2015; Incivek® [package insert]. Cambridge, MA: Vertex Pharmaceuticals, Inc.; October 2013; Clinical Trials.gov/. https://clinicaltrials.gov/ct2/show/NCT00689390. Accessing March 20, 2015.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Economic analyses conducted to inform California Medicaid of the financial gain/loss of treating its HCV population with newer HCV drug therapies
- Health system value analysis based on clinical trial data for Harvoni® and available statistics on HCV-related complications
  - Per 1,000 patients treated with any stage of liver involvement, Harvoni® prevents
    - 6 cases of cirrhosis and 2 HCV-related deaths in the first year alone
    - 44 cases of cirrhosis, 5 of HCC and 17 HCV-related deaths at five years
      - 7% of incremental treatment costs would be offset by these reductions
    - 6-fold reduction in cirrhosis, 50% reduction in HCC and 140 HCV-related deaths at 20 years
      - 25% of treatment costs would be offset by these reductions

HCC=hepatocellular carcinoma

Institute for Clinical and Economic Review. http://www.ctaf.org/sites/default/files/assessments/CTAF_HCV2_Final_Report_013015.pdf. November 17, 2014. Accessed March 16, 2015.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Health System Value Analysis for 33,000 Medi-Cal and Department of Corrections' patients with chronic HCV
  - Treatment of HCV at any stage of liver involvement increases costs by $3 billion or $33 PMPM
    - Costs offsets after 5 years: Total $254 million (net expenditure of $2.8 billion)
    - Cost offsets after 20 years: Total $1.2 billion (net expenditures of $1.8 billion
    - This represents a 5% increase in $PMPM for Medi-Cal
      - 0.5% to 1% increase in $PMPM is considered manageable increase in expenditure
  - If treatment with chronic HCV was restricted to those with patients with fibrosis levels of F3 or F4
    - Initial expenditures for new therapies would be $800 million (1.4% increase in $PMPM)
    - Total net expenditures after 20 years would be $475 million (<1% increase in $PMPM)

Institute for Clinical and Economic Review. http://www.ctaf.org/sites/default/files/assessments/CTAF_HCV2_Final_Report_013015.pdf. November 17, 2014. Accessed March 16, 2015.

Treatment of HCV: Uncertainties and Ethical Quandaries (cont'd)

- Care Value Analysis
  - "While treating patients at all fibrosis stages was more expensive in comparison to waiting to treat until patients reached F3 or F4, it was also more effective."
- Dilemma of using Care Value Analysis demonstrating cost-effectiveness with Health System Value Analysis demonstrating unmanageable costs
  - If the one-year PMPM increase were to be < 1%, only16,500 of the Medi-Cal/Department of Corrections could be treated
  - Not enough funds to treat entire population of patients at all stages of fibrosis

Institute for Clinical and Economic Review.
http://www.ctaf.org/sites/default/files/assessments/CTAF_HCV2_Final_Report_013015.pdf. November 17, 2014.
Accessed March 16, 2015.

Effect of High Prescription Drug Costs on Patient's Out-of-Pocket Costs

- Healthcare Purchasers have had to increase patient out-of-pocket expenses for medications (eg premiums/deductibles/copayment) to help offset the high cost of drugs
- Increased out-of-pocket costs are not limited to new medications such as those for HCV
  - Many patients must now pay substantially higher co-pays for generic drugs that their insurers have recently designated "non-preferred" or "higher cost generics"
  - Drugs placed into this category includes many recommended as first-line treatment in evidence-based guidelines for highly prevalent chronic conditions such as hypertension, diabetes, epilepsy, schizophrenia, migraine headache, osteoporosis, Parkinson's disease, and HIV
  - 5-tier drug plans or high deductible plans

Oster G, Fendrick AM. *Am J Manag Care*. 2014;20:693-695.

HCV Drug Management Strategies

- Utilize prior authorization
  - Ensures appropriate genotype, drug selection, and duration
  - Utilize fibrosis staging to prioritize the need for therapy
    - Accurate assessment of fibrosis is vital in assessing the urgency for treatment
    - Degree of hepatic fibrosis is a robust predictor of disease progression and clinical outcomes
    - Metavir scores versus liver biopsy
      - Metavir score is a standardized measure of fibrosis and inflammation seen on a liver biopsy
- Identify and encourage use of preferred agents
  - May be different per line of business
- Encourage collaborative and coordinated care

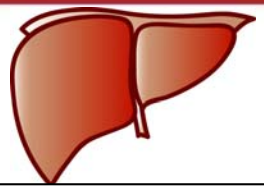
AASLD/IDSA. Recommendations for testing, managing and treating hepatitis C. http://www.hcvguidelines.org/full-report-view. Accessed March 16, 2015.

HCV Drug Management Strategies

- Contracts with pharmaceutical manufacturer
  - Value-based contracts
    - Coordination with specialty pharmacy providers
    - Including disease education and adherence programs
    - Monitoring HCV RNA response to therapy (SVR 12 or SVR 24)
  - Single vs. multiple formulary HCV drugs
    - Gilead: Harvoni® and Sovaldi® as ‘single’ HCV drug
    - Abbvie: Viekira Pak® as single HCV drug
    - Combination of pharmaceutical industries’ drug products

AASLD/IDSA. Recommendations for testing, managing and treating hepatitis C. http://www.hcvguidelines.org/full-report-view. Accessed March 16, 2015.

HCV Drug Contracting Strategies



METAVIR FIBROSIS SCORE
(n=1000 Chronic Genotype 1 HCV patients)

F0 (17%)

50% tx naïve + baseline HCV RNA < 6 million IU/ml

8 wk H = 85 12 wk H = 85
or
12 wk V+R = 170

F1 (35%)

50% tx naïve + baseline HCV RNA < 6 million IU/ml

8 wk H = 175 12 wk H = 175
or
12 wk V+R = 350

F2 (22%)

25% tx naïve + baseline HCV RNA < 6 million IU/ml

8 wk H = 55 12 wk H = 165
or
12 wk V+R = 220

F3 (14%)

2% tx naïve + baseline HCV RNA < 6 million IU/ml

8 wk H = 3 12 wk H = 137
or
12 wk V+R = 140

F4
(Compensated Cirrhosis; 12%)

100% tx experienced with cirrhosis

12 wk H + R = 114 24 wk H = 6
or
24 wk H = 120
or
24 wk V + R = 120

H=Harvoni®; V=Viekira Pak®; R=Ribavirin

Thein HH, et al. *Hepatology*. 2008;48:418-431.

HCV Drug Contracting Demo

HCV Drug Contracting Strategies

HARVONI ($31,500/4-wk at WAC) for n=1000					
			Option A	Option B	
	8-wk H	12 wk H	12 wk HR/24 wk H	24 wk H	Total Cost (Option A /Option B)
	$63,000/pt (n=318)	$94,500/pt (n=562)	$99,000/pt/$189,000 pt (n=114/n=6)	$189,000 (n=120)	
0% Rebate	$20. M	$53.1 M	$12.4 M	$22.7 M	$85.6 M/$95.8 M
20% Rebate	$16. M	$42.5 M	$9.9 M	$18.1 M	$68.5 M/$76.7 M
25% Rebate	$15. M	$39.8 M	$9.3 M	$17. M	$64.2 M/$71.9 M
30% Rebate	$14. M	$37.2 M	$8.7 M	$15.9 M	$59.9 M/$67.1 M
40% Rebate	$12. M	$31.9 M	$7.5 M	$13.6 M	$51.3 M/$57.5 M

VIEKIRA ($27,773/4-wk at WAC) for n=1000			
	12 wk V + R (n = 880)	24 wk V + R (n = 120)	Total Cost
	$87,819/pt	$175,638	
0% Rebate	$77.3 M	$21.1 M	$98.4 M
20% Rebate	$61.8 M	$16.9 M	$78.7 M
25% Rebate	$58. M	$15.8 M	$73.8 M
30% Rebate	$54.1 M	$14.8 M	$68.9 M
40% Rebate	$46.4 M	$12.6 M	$59. M

H=Harvoni®;
V=Viekira Pak®;
R=Ribavirin

HCV Pharmacy Management Strategies

- Coordinate with specialty pharmacy providers
  - Including disease education and adherence programs
  - Monitoring response to therapy
- Partial prescription fills to decrease waste
  - Limit fills to 2-week supply
    - Real world drug discontinuation rates are typically higher then within clinical trials
    - CVS/Caremark data
      - In real world,10.2% of 738 patients (sofosbuvir + PEG-RBV) discontinued therapy vs 2% in clinical trial
      - In real world, 9% of 680 patients (sofosbuvir + RBV) discontinued therapy vs 0-2% in the pivotal clinical trials
  - Coordinate next fill with timely HCV RNA test results

AASLD/IDSA. Recommendations for testing, managing and treating hepatitis C. http://www.hcvguidelines.org/full-report-view. Accessed March 16, 2015.
CVS Health. September 2014. http://www.cvshealth.com/sites/default/files/hepatitisCutilization.pdf. Accessed March 16, 2015.

Opportunities for Specialty Pharmacies

- Specialty pharmacy services can achieve evidence-based and patient-centered approaches to evaluating and managing HCV therapies to both improve patient outcomes and facilitate cost savings
  - Specialty pharmacy services that view HCV patients holistically are important because of the potential for comorbid conditions
- A multifaceted approach is needed to support the patient, including direct education, clinical outreach, ongoing adherence messaging and reminders, and technology-based tools to create a sense of patient connection
  - Trained HCV care teams of clinical pharmacists, pharmacy technicians, nurses, and call center personnel are needed to deliver focused services for patients with HCV

Partnership Between Specialty Pharmacy and Health Plans Can Improve Outcomes

- As many as three-quarters of plans now mandate specialty pharmacy use to access HCV products
  - Specialty pharmacists are uniquely positioned close to HCV patients providing plans an ally in their attempts to manage HCV product use and ensure patient adherence to their treatment
- One-on-one counseling by pharmacists with expertise specifically in managing HCV patients will enhance collaboration that is needed to continually monitor adherence, side effects and drug interactions, and communicate with the treating physician when adjustments are needed

Specialty Pharmacy Journal. June 2014. http://www.healthstrategies.com/blog/impact-patients-and-specialty-pharmacies-evolving-payer-interventions-manage-hepatitis-c-agents. Accessed March 16, 2015.

Adherence Counseling for Patients with HCV

Initial	Ongoing	Follow Up
Therapy and disease state overview including • Disease state education • Drug administration • Treatment-related averse events (AEs) • Importance of adherence • Depression screening	• Discuss diagnosis and treatment • Review dose, administration, duration of therapy • Depression screening • Address barriers to adherence • Provide guidance for missed doses and AE management • Laboratory reminders and importance of follow up testing	• Adherence assessment including medication possession and refills • Address barriers to adherence • Enact dispensing and/or prescriber engagement to support adherence

Dorholt M. Specialty Pharmacy Times. August 20, 2014. http://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2014/august-2014/Managing-Hepatitis-C-Costs-Improving-Patient-Outcomes. Accessed March 16, 2015.

Utilizing Technology to Improve Adherence

Medication Reminders	Reminders pop up when it's time to take a medication; user can mark as taken, snooze, or mark as skipped
Adherence graph	Users can view a graph that charts their adherence through the course of therapy
Viral load graph	Users can enter viral load following lab work and app graphs their data over time
E-mail	Medication regimen, adherence graph, and viral load graph can all be emailed to the doctor/nurse/caregiver
Online tracking	Users document their viral load, doctor visits, symptoms using an app or web-based system

Dorholt M. Specialty Pharmacy Times. August 20, 2014. http://www.specialtypharmacytimes.com/publications/specialty-pharmacy-times/2014/august-2014/Managing-Hepatitis-C-Costs-Improving-Patient-Outcomes. Accessed March 16, 2015.

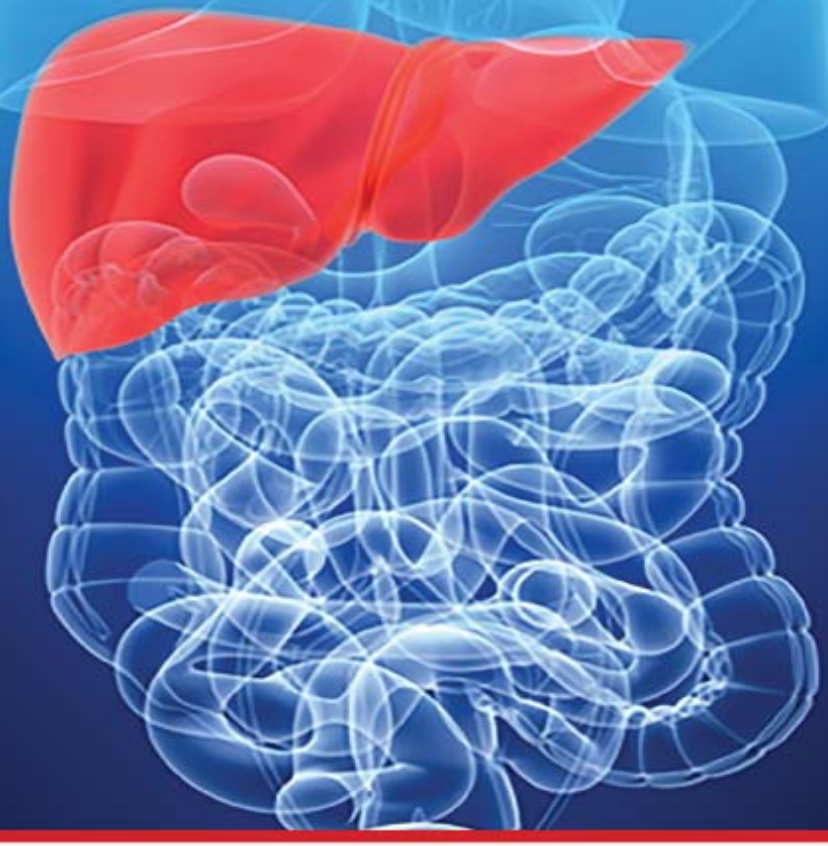
HCV Management Plan

Intervention	Timing	Description
HCV Baseline Assessment	Week 0	Collect/verify labs (eg, weight, viral load, biopsy, Hb) and previous HCV therapy, duration, and outcome
Pharmacist Verification	New RXs	Evaluate therapy by genotype, treatment history, effectiveness, and safety; resolve actual or potential drug-related problems
Care Plan	Week 0, PRN	Identify treatment goals and document care plan
Medical Assessment	Week 0, Monthly	Collect/verify allergies, comorbidities, concomitant medications; clinician triage
Patient Education and Training	Week 0, PRN	Clinician initial consult (drug, disease, expectations, AE management; adherence); HCV educational packet; injection training
Support Program Referral	Week 0, PRN	Facilitate enrollment in manufacturer programs and other supportive organizations
Side Effect Management	Week 0, PRN	HCV Care Kits, side effect management guides, and clinician counseling
Adherence and Distribution Calls	At Least Monthly	Outbound call by patient care coordinator to arrange refills, evaluate side effects, education needs, and administration
Futility Rules and Treatment Outcomes	Varies by Regimen	Collect VL and provide recommendations for treatment plan; outreach to obtain SVR results

Fairview Hospital Specialty Pharmacyhttp://www.fairview.org/Pharmacy/Specialtypharmacy/index.htm. Accessed March 16, 2015.

HEPATITIS C:

Balancing Cost and Cure Rates in a Managed Care Environment



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Audience Question and Answer Session

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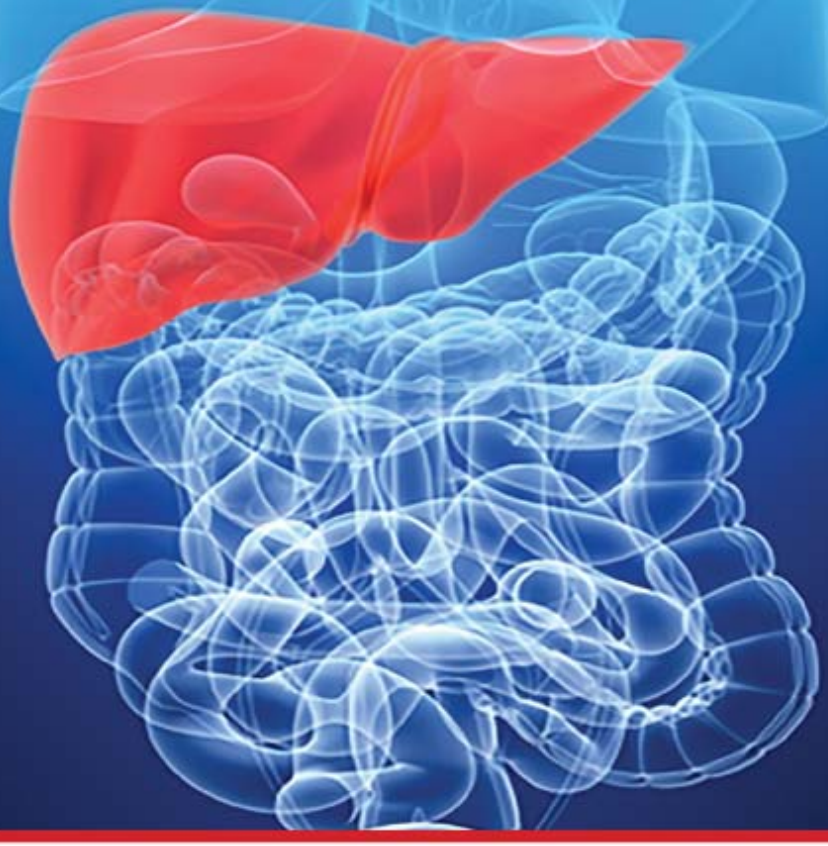

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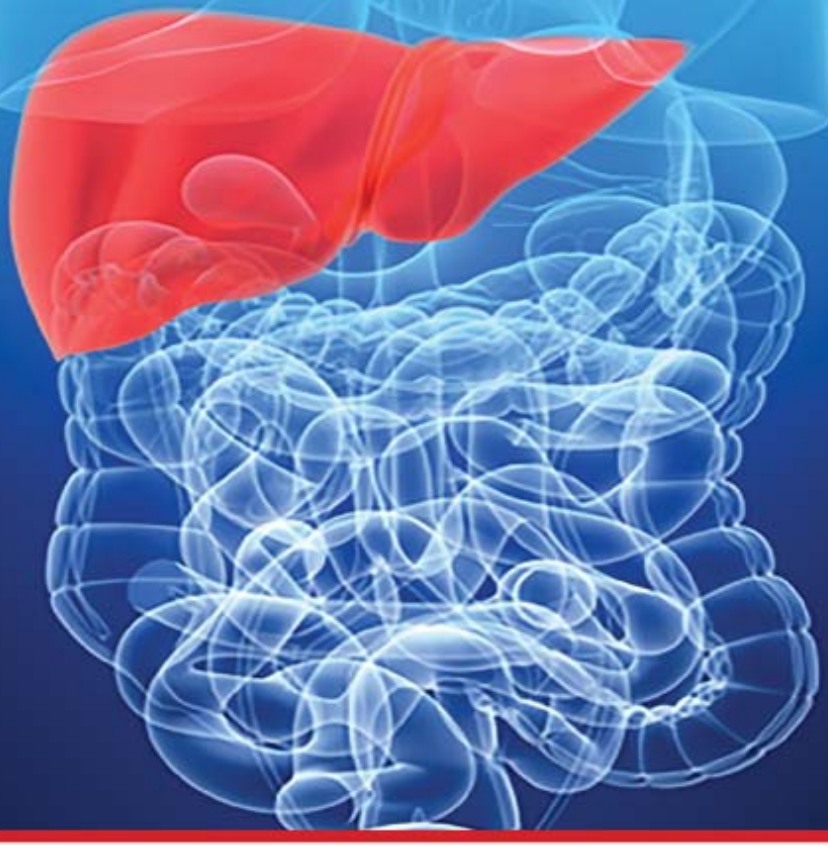
Key Takeaways and Closing Comments

HEPATITIS C:

Balancing Cost and Cure Rates in a Managed Care Environment



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