


**9:45 – 10:45 am**

**Advances in Chronic Hepatitis C Infection**

**SPEAKER**  
Michael Curry, MD



**Presenter Disclosure Information**

The following relationships exist related to this presentation:

- ▶ Michael Curry, MD: Consultant for Abbvie Inc.; Bristol-Myers Squibb Company; and Gilead Sciences, Inc.

**Off-Label/Investigational Discussion**

- ▶ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

**Objectives**

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- Outline epidemiology and risk factors for chronic hepatitis C
- Review the natural history and clinical impact of chronic hepatitis C infection
- Discuss the current treatment options for chronic hepatitis C infection

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**Case Study**

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**Laura**

- 72 years old
- HCV genotype 1
- Treatment-naïve
- HCV RNA level >1,000,000 IU/mL
- Liver biopsy: cirrhosis
- No features of decompensated liver disease
- Normal PTT, bilirubin, and platelet count

**Case Study 1 ~ Continued**

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**Laura**

- Patient wants to know prognosis and treatment options
- Afraid of adverse effects described with interferon therapy

**Case Study 2**

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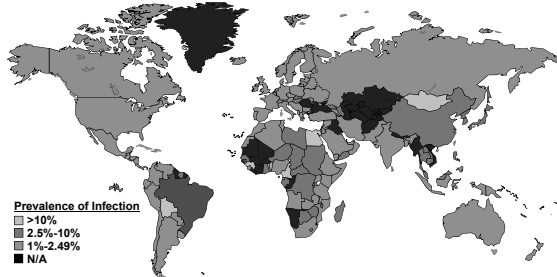
**Joanne**

- 50 years old
- Hypertension and diabetes
- HCV, genotype 1, diagnosed 10 years ago
- Results of elastography suggest cirrhosis
- Did not respond to prior course of pegylated interferon and ribavirin

Should we treat Joanne again? Can she be cured of her hepatitis C?

## Hepatitis C Worldwide Prevalence

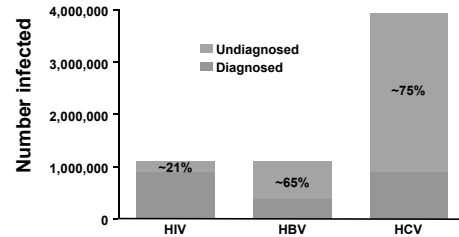
~180 Million With Hepatitis C Infection



<http://www.who.int/csr/disease/hepatitis/Hcpc.pdf>

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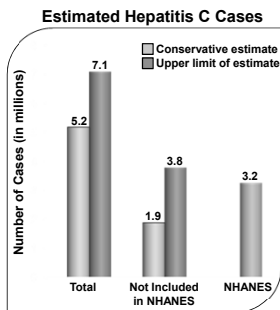
## Hepatitis C: Under Diagnosed in the United States



HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus.  
Institute of Medicine. *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*, 2010.

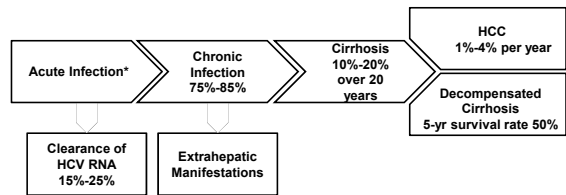
## Chronic Hepatitis C Infection in the United States

- ≥5.2 million living with chronic HCV in US
  - Prevalence: 2%
- Chronic HCV cases not included in NHANES estimate
  - Homeless (n=142,761-337,6100)
  - Incarcerated (n=372,754-664,826)
  - Veterans (n=1,237,461-2,452,006)
  - Active military (n=6805)
  - Healthcare workers (n=64,809-259,234)
  - Nursing home residents (n=63,609)
  - Chronic hemodialysis (n=20,578)
  - Hemophiliacs (n=12,971-17,000)



Chak E, et al. *Liver Int*. 2011; 31:1090-1101.  
<http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section2>.

## Natural History of Hepatitis C Infection



\*20%-30% of individuals are symptomatic.  
HCC=hepatocellular carcinoma.

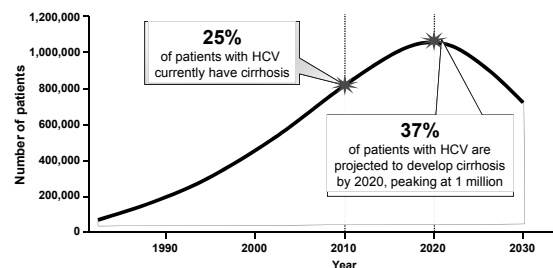
Chen SL, Morgan TR. *Int J Med Sci*. 2006.

## Factors Associated with Hepatitis C Disease Progression

- Alcohol consumption
  - 30 g/day in men
  - 20 g/day in women } ~ 2 drinks per day
- Disease acquisition at >40 years
- Male gender
- HIV coinfection
- Hepatitis B virus coinfection
- Immunosuppression

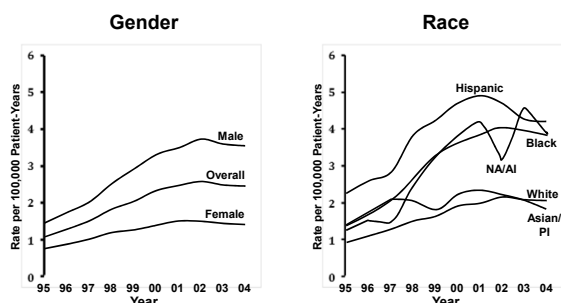
NIH Consensus Development Conference Statement. 2002.  
Poynard et al. *Lancet*. 1997;349:825-832.

## Hepatitis C-Related Cirrhosis is Projected to Peak Over the Next 10 Years



Davis GL, et al. *Gastroenterology* 2010

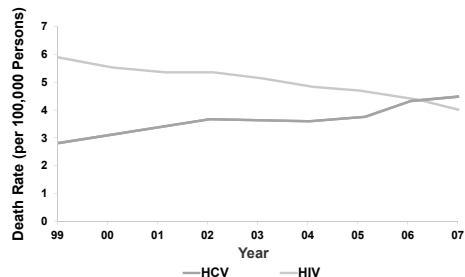
## Annual Adjusted Hepatitis C Mortality Rates in the United States



Wise M, et al. *Hepatology*. 2008

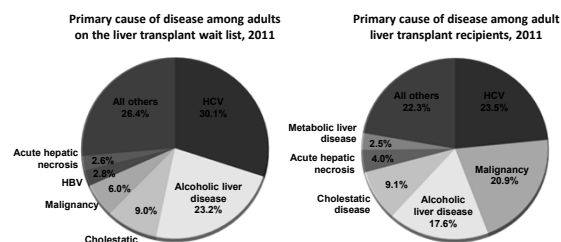
## Increasing Number of Deaths Among HCV-Infected Persons, Surpassing HIV

National Center for Health Statistics 1999-2007



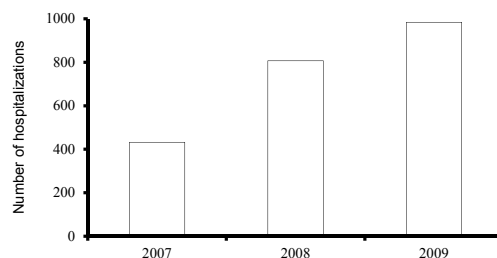
Ly KN, et al. *Ann Intern Med*. 2012

## Hepatitis C Is Leading Indication of Liver Transplants in the US



Available at: [http://srr.transplant.hrsa.gov/annual\\_reports/2011/pdf/03\\_20liver\\_12.pdf](http://srr.transplant.hrsa.gov/annual_reports/2011/pdf/03_20liver_12.pdf).

## Increasing Number of Hospitalizations related to Hepatitis C Infection in Los Angeles County, 2007-2009



Sie et al. *J Viral Hepat* 2013

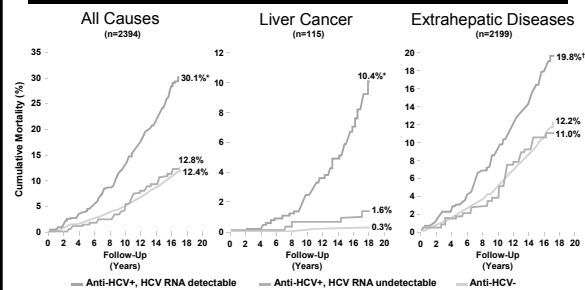
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## Extrahepatic Manifestations of Chronic Hepatitis C

- Hematologic/Oncologic:
  - Mixed cryoglobulinemia
  - Lymphoma
- Renal: Glomerulonephritis
- Dermatologic:
  - Porphyria cutanea tarda
  - Cutaneous necrotizing vasculitis
  - Lichen planus
- Diabetes
- Fatigue
- Depression

Source of Images: <http://hepatitisnewdrugs.blogspot.com/2010/12/hepatitis-c-virus-infection-simple-and.html>; <http://hepatitisnewdrugresearch.com/lichen-planus-and-the-hepatitis-c-virus.html>; <http://hepatitisnewdrugs.blogspot.com/2010/10/hepatitis-c-rash-porphyria-cutanea.html>

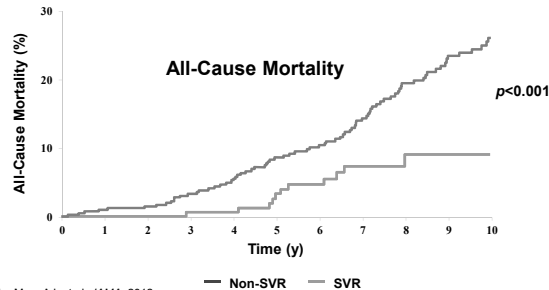
## Chronic HCV Infection Increases Mortality from Both Hepatic and Extrahepatic Diseases



\* $p < 0.001$  for comparison among all 3 groups and  $p < 0.001$  for HCV RNA detectable versus undetectable.  
 \* $p < 0.001$  for comparison among all 3 groups and  $p = 0.002$  for HCV RNA detectable versus undetectable.  
 Community-based, long-term, prospective study in Taiwan (REVEAL-HCV, Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer, 1991-2008).  
 Lee M-H, et al. *J Infect Dis*. 2012

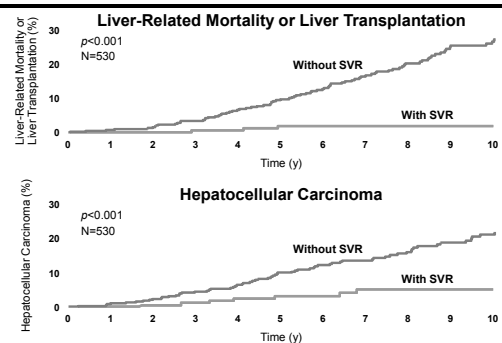
## Sustained Virologic Response is Associated with Reduction in All-Cause Mortality

An international, multicenter, long-term follow-up study from 5 tertiary care hospitals in Europe and Canada of 530 advanced fibrosis/cirrhotic HCV patients treated with IFN-based regimen between 1990-2003



van der Meer AJ, et al. JAMA. 2012

## Sustained Virologic Response is Associated with a Reduction in Liver-Related Mortality and HCC



van der Meer AJ, et al. JAMA. 2012;

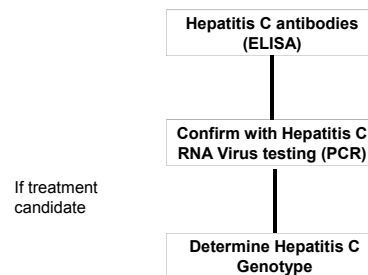
## 2013 Updated USPSTF HCV Screening Recommendations

### Risk Assessment:\*

- Those at high risk for HCV infection:
  - Most important risk factor is past or current injection drug use
  - Additional risk factors include:
    - Receiving a blood transfusion before 1992
    - Long-term hemodialysis
    - Being born to an HCV-infected mother
    - Incarceration
    - Intranasal drug use
    - Getting an unregulated tattoo, and other percutaneous exposures
- Adults born between 1945 and 1965 ("Baby Boomers")

\*Grade B recommendation for persons at high risk for infection and adults born between 1945 and 1965. Moyer VA, on behalf of the USPSTF. Ann Intern Med. 2013

## Screening for Chronic Hepatitis C



## Serological Tests Hepatitis C Antibodies

- Serologic test is the enzyme-linked immunosorbent assay (ELISA)
- Rare false positives with autoimmune hepatitis
- Rare false negatives in immunocompromised or recently exposed patients
- Molecular testing required to confirm active/ongoing infection

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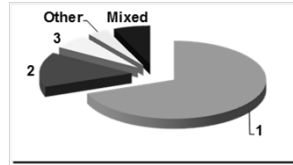
## Molecular Tests Hepatitis C RNA

- Viral load expressed as IU/ml:
  - Ranges from non-detected to near a hundred million IUs
  - Mean viral load is at 1 Million IU/ml
- Different ways of testing
  - PCR (RNA), TMA, etc
- No correlation with disease severity

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## Molecular Tests Genotype

- 6 genotypes
- Significance
  - Treatment response
  - Duration of treatment
  - Not severity of disease



## Goals of therapy

### Primary Goal

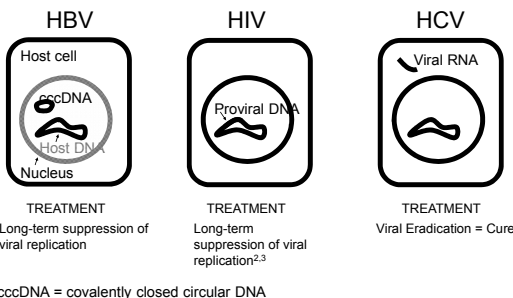
⇒ Clearance of virus

### Secondary Goal

- Decrease rate of decompensation
- Decrease risk of hepatocellular carcinoma
- Improved histology

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## Hepatitis C Differs from HIV and HBV No long-term or Latent Reservoir



1. Pawlotsky JM. *J Hepatol* 200. 2. Siliciano JD, Siliciano RF. *J Antimicrob Chemother* 2004. 3. Lucas GM. *J Antimicrob Chemother* 2005.

## Options for Liver Fibrosis Assessment

Liver Biopsy      Serum Biomarkers      Elastography      Ultrasound

## Liver Biopsy and Histology

- Gold standard for defining status of liver injury
- Identifies features useful in decision to embark on therapy
- May reveal advanced fibrosis or cirrhosis that necessitates surveillance for HCC or screening for varices
- Helps identify concurrent liver disease

## Laboratory Assessment of Fibrosis

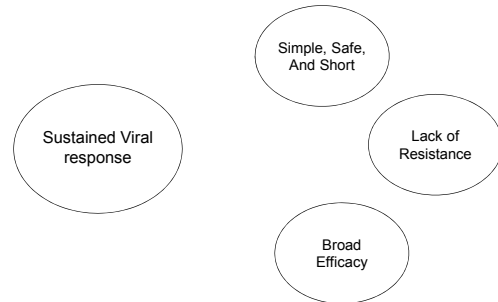
Test	Sensitivity (%)	Specificity (%)	AUC	Comment
APRI	48	94	0.84	AST/platelet count
FIB-4	74	80	0.85	Platelet count, AST, ALT, α-fetoprotein level
Fibrotect	77	82	0.89	Haptoglobin, α2-macroglobulin, apolipoprotein A1, γGT, bilirubin, gender
Fibrospect II	76	73	0.82	Hyaluronan, TIMP-1, α2-macroglobulin

1. Chou R, Wasson N. *Ann Intern Med* 2013.
2. Wai CT, Greenson JK, Fontana RJ, Kalishchik JD, Marrero JA, Conjeevaram HS, Lok AS. *Hepatology* 2003.
3. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, Fontaine H, Pol S. *Hepatology* 2007.
4. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M. *Hepatology* 2006.
5. Ibert-Bilmeu F, Ratzu V, Pieroni L, Charlotte F, Benhamou Y, Poynard T. *Lancet* 2001.
6. Patel K, Gordon SC, Jacobson I, Hézode C, Oh E, Smith KM, Pawlotsky JM, McHutchison JG. *J Hepatol* 2004.

## Abdominal Ultrasound

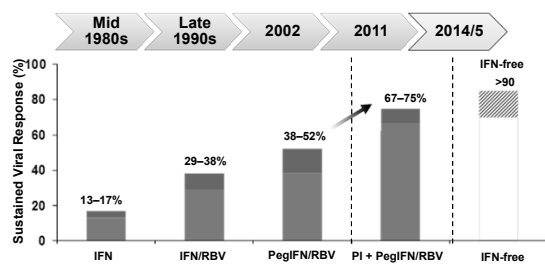
- Pros
  - Readily available
  - Noninvasive
  - Assess for liver disease complications
- Cons
  - Operator dependent
  - Cannot assess for fibrosis stage
  - Insensitive for early cirrhosis

## Hepatitis C: Achieving a Cure

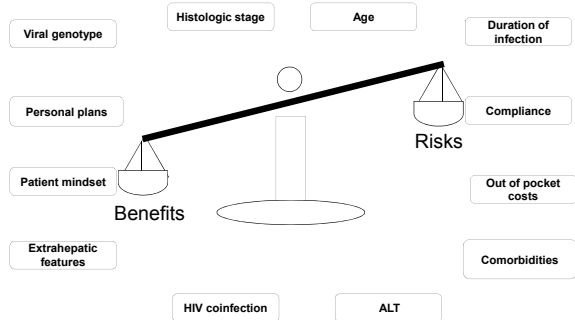


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## Evolution of Hepatitis C Therapy Genotype 1



## To Treat or Not to Treat: Previous Constellation of Considerations



## Properties of Direct Acting Agents

Class of Drug	Mode of Action	Potency/Genotypic Activity	Barrier to Resistance	Drug-Drug Interaction Potential	Dosing	Agents
Protease Inhibitor	Inhibits assembly and packaging of HCV	High Variable GT activity	Low (1a<1b)	High	qd to tid	Boceprevir Telaprevir Simeprevir Paritaprevir
NS5B nucleoside/nucleotide polymerase inhibitors	Directly inhibits HCV RNA chain elongation	High Pan-genotypic activity	High	Low	qd	Sofosbuvir
NS5B Non-nucleoside polymerase inhibitors	Indirectly inhibits HCV RNA chain elongation	Variable, based on GT subtype	Very low (1a<1b)	Variable	qd to bid	Dasabuvir
NS5A inhibitors	Regulates HCV replication	High Pan-genotypic activity	High (GT 1b) Low (GT 1a)	Low to moderate	qd	Ledipasvir Ombitasvir

Adapted from Stedman CAM. J Gastroenterol Hepatol 2013

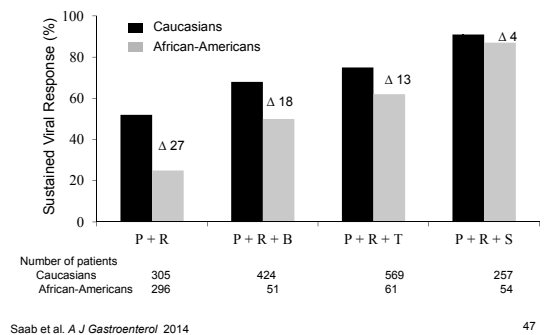
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## First Generation Direct Acting Agents

- Telaprevir and boceprevir previously used in HCV genotype 1 with Pegylated interferon (PEG)/Ribavirin (RBV)
- Markedly improved SVR rates and shorter duration versus PEG/RBV only
- Poor tolerability and increased severity of adverse effects

Adapted from Moradpour et al. Nat Rev Microbiol. 2007

### Differences in Sustained Viral Responses between African Americans and Caucasians Treated with Interferon-based Therapy



### Treatment of Genotype 1 Patients Sustained Viral Response Rates

Regiment*	Cohort	Non cirrhotic	Cirrhotic
SOF/LED (duration)	Treatment naïve	96-99% (8-12 wks)	94% (12 wks)
	Treatment experienced	95% (12 wks)	100% (24 wks)
SOF/SIM (duration)	Treatment naïve	95% (12 wks)	100% (24 wks)
	Treatment experienced	95% (12 wks)	100% (24 wks)
3-D ± R (duration)	Genotype 1a	96% (12wks)	89-95% (12-24wks)
	Genotype 1b	100% (12 wks)	99% (12 wks)

\*All FDA-approved Regiments : Regiments and Rates obtained from Package Inserts  
Abbreviations: SOF – sofosbuvir; LED – ledipasvir; SIM – simeprevir; 3-D – ombitasvir, paritaprevir +ritonavir, dasabuvir ; R-ribavirin  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/205834s000tbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205834s000tbl.pdf)  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/205123s001tbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001tbl.pdf)  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/206619tbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619tbl.pdf)

### Treatment of Genotype 2 Patients Sustained Viral Response Rates

Regiment	Non cirrhotic		Cirrhrotic		FDA Approved
	Naïve	Experienced	Naïve	Experienced	
SOF/R x 12 weeks	97%	91%	100%	88%	Yes

Abbreviations: SOF – sofosbuvir; R-ribavirin  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204671s000tbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000tbl.pdf)

### Treatment of Genotype 3 Patients Sustained Viral Response Rates

Regiment	Non cirrhotic		Cirrhrotic		FDA Approved
	Naïve	Experienced	Naïve	Experienced	
SOF/R x 24 weeks	93%	85%	92%	60%	Yes
SOF/LED/R x 12 weeks	100%	89%		73%	No

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; R-ribavirin  
[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/204671s000tbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000tbl.pdf)

### Treatment Prioritization by AASLD/IDSA

#### Highest Priority for Treatment Owing to Highest Risk for Severe Complications

- patients with advanced fibrosis (Metavir F3)
- patient with cirrhosis (Metavir F4)
- liver transplant recipients
- patients with severe extrahepatic hepatitis C

#### High Priority for Treatment Owing to High Risk for Complications

- Fibrosis (Metavir F2)
- HIV-1 coinfection
- HBV coinfection
- Other coexistent liver disease (eg, NASH)
- Debilitating fatigue
- Type 2 Diabetes mellitus (insulin resistant)
- Porphyria cutanea tarda

<http://hcvguidelines.org/full-report/when-and-whom-initiatehcv-therapy>

### Treatment Prioritization by AASLD/IDSA (continued)

#### High HCV Transmission Risk

- MSM with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis

<http://hcvguidelines.org/full-report/when-and-whom-initiatehcv-therapy>

## Recommended assessments prior to starting antiviral therapy

Assessment of potential drug-drug interactions

Following laboratory tests recommended within **6 weeks** prior to starting antiviral therapy:

- CBC, INR
- Hepatic panel
- TSH; if IFN is used
- Calculated glomerular filtration rate (GFR)

Following laboratory test recommended within **12 weeks** of starting antiviral therapy:

- HCV genotype and quantitative HCV viral load

<http://hcvguidelines.org>

## Recommended monitoring during antiviral therapy

- Every 4 weeks:
  - CBC, creatinine level, calculated GFR, and hepatic function panel
- Every 12 weeks:
  - TSH if on IFN.
  - More frequent assessment for drug-related toxic effects (eg, CBC for patients receiving RBV) is recommended as clinically indicated.
- Quantitative HCV viral load testing:
  - After 4 weeks of therapy
  - End of treatment,
  - 12 weeks following completion of therapy.

<http://hcvguidelines.org>

## Recommended monitoring for patients in whom treatment failed to achieve an SVR

- Disease progression assessment every 6 to 12 months with hepatic panel, CBC, and INR.
- Hepatocellular carcinoma surveillance with ultrasound every 6 months for patients with advanced fibrosis (F3 or F4).
- Endoscopic surveillance for esophageal varices is recommended with cirrhosis.
- Evaluation for retreatment is recommended as effective alternative treatments become available.

<http://hcvguidelines.org>

## Recommended follow-up for patients who achieve an SVR

- For patients without advanced fibrosis (F0 - F2), follow-up same as if never infected with HCV.
- Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or unexplained hepatic dysfunction develops.
- Hepatocellular carcinoma surveillance with twice yearly ultrasound for patients with advanced fibrosis (F3 or F4).
- Endoscopy to screen for varices if cirrhosis present. Patients with varices should be treated and followed up as indicated.

<http://hcvguidelines.org>

## Decision to Start Oral Antiviral Therapy for Chronic Hepatitis C

### Pros

- Safe
- Effective
- Tolerable
- Short duration

### Con

- Adverse effects  
Nausea, headache, rash, fatigue
- Costs
- Drug-Drug interactions

## Approximate Costs of Antiviral Therapy

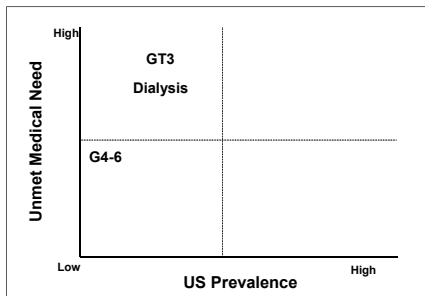
	<u>SOF/R</u> <u>x 12-24 weeks</u>	<u>SOF/LED</u> <u>x 8-24 weeks</u>	<u>SOF/SIM</u> <u>x 12-24 weeks</u>	<u>3-D ± R</u> <u>x 12-24 weeks</u>
List price	93-186k	66-198k	165-330k	90-180k
Patient Assistant Program	Available	Available	Available	Available
Co-Payment Cards	Available	Available	Available	Available

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; SIM – simeprevir; 3-D – ombitasvir, paritaprevir +ritonavir, dasabuvir; R-ribavirin; PAP – Patient Assistant Program



## Drug Development Goals

*Not all needs being met*



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## Keeping your liver healthy

- Minimize alcohol consumption
- Exercise regularly and eat healthy
- Low salt diet
- Hepatitis A and B immunization if naive

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## Summary

- Most individuals do not know they are infected with hepatitis C
  - Appropriate screening is essential
- Patients with hepatitis C are at risk of hepatic and extra-hepatic manifestations.
  - Hepatitis C currently the leading indication for liver transplantation in the United States
- Currently available therapy is effective, safe, and tolerable

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