4 – 5 pm

Advances in Chronic Hepatitis C Infection

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Michael P. 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

- 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

Case Study

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

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

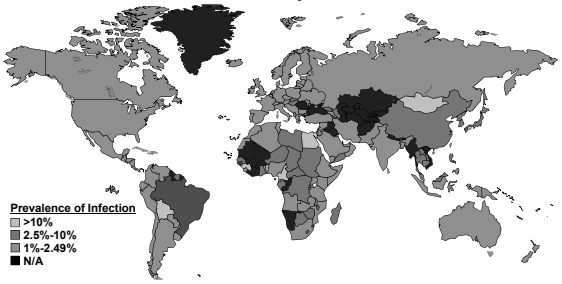
Case Study 2

Joanne
- 50 years old
- Hypertension and diabetes
- HCV, genotype 1, diagnosed10 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?

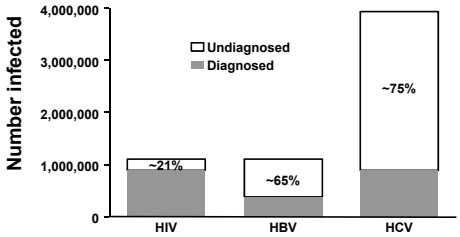
Hepatitis C Worldwide Prevalence

~180 Million With Hepatitis C Infection



http://www.who.int/csr/disease/hepatitis/Hepc.pdf.

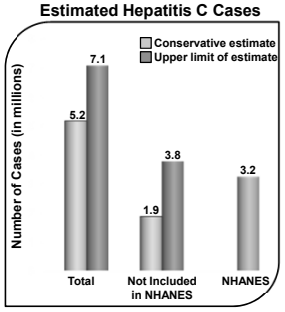
Hepatitis C: Under Diagnosed in the United States



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.

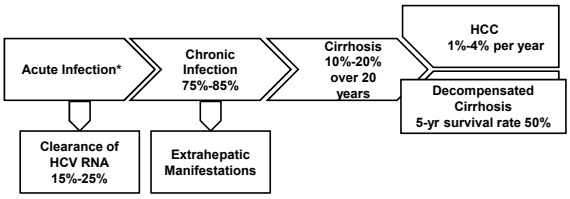
Chronic Hepatitis C Infection in the United States

- ≥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.

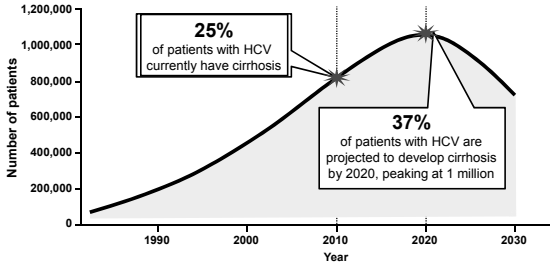
Factors Associated with Hepatitis C Disease Progression

- 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

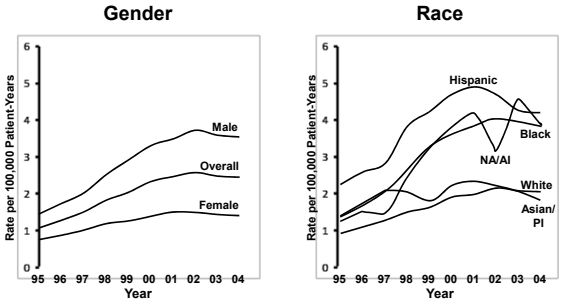
NIH Consensus Development Conference Statement. 2002.
Poynard et al. *Lancet.* 1997;349:825-832.

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



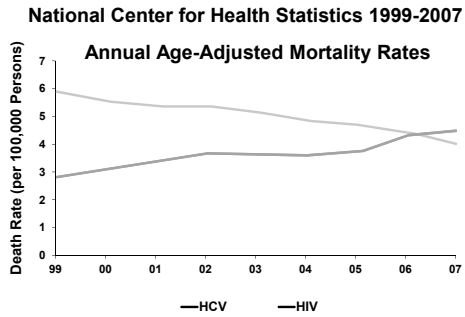
Davis GL, et al. *Gastroenterology* 2010

Annual Adjusted Hepatitis C Mortality Rates in the United States



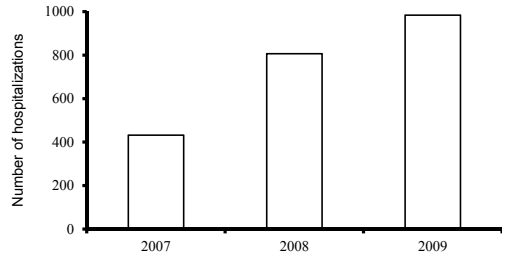
Wise M, et al. *Hepatology.* 2008

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



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

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



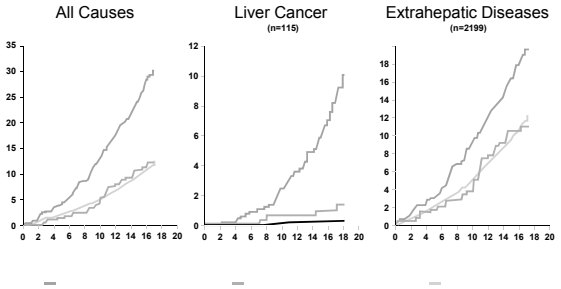
Sie et al. *J Viral Hepat* 2013

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://hepatitiscnewdrugs.blogspot.com/2010/12/hepatitis-c-virus-infection-simple-and.html; http://hepatitiscnewdrugresearch.com/lichen-planus-and-the-hepatitis-c-virus.html; http://hepatitiscnewdrugs.blogspot.com/2010/10/hepatitis-c-rash-porphyria-cutanea.html

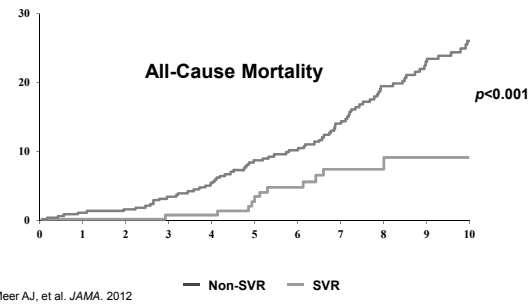
Chronic HCV Infection Increases Mortality from Both Hepatic and Extrahepatic Diseases



**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

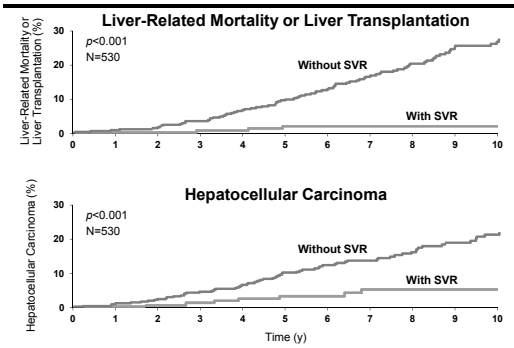
Sustained Virologic Response is Associated with Reduction in All-Cause Mortality

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

Hepatitis C antibodies (ELISA)

↓

Confirm with Hepatitis C RNA Virus testing (PCR)

If treatment candidate

↓

Determine Hepatitis C Genotype

Serological Tests
Hepatitis C Antibodies

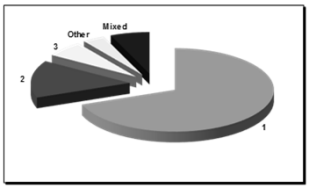
- Serologic test is the enzyme-linked immunosorbent assay (ELISA)
- Rare false positives with autoimmune hepatitis
- Rare false negatives in immunocompromised or recently exposed patients
- Molecular testing required to confirm active/ongoing infection

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

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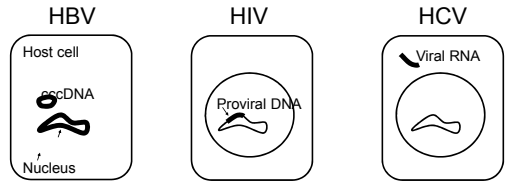
Hepatitis C Differs from HIV and HBV No long-term or Latent Reservoir



HBV	HIV	HCV
TREATMENT	TREATMENT	TREATMENT
Long-term suppression of viral replication	Long-term suppression of viral replication[2,3]	Viral Eradication = Cure

cccDNA = covalently closed circular DNA

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

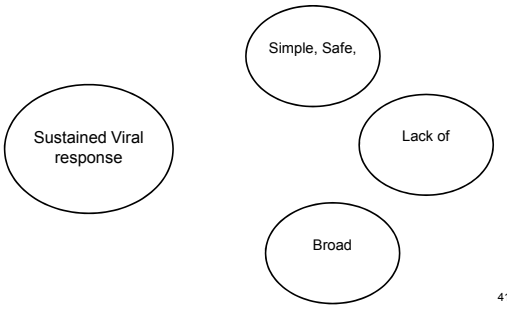
Test	Sensitivity (%)	Specificity (%)	AUC	Comment
APRI	48	94	0.84	AST/platelet count
FIB-4	74	80	0.85	Platelet count, AST, ALT, α-fetoprotein level
Fibrotest	77	82	0.89	Haptoglobin, α2-macroglobulin, apolipoprotein A1, γGT, bilirubin, gender
Fibrospect II	76	73	0.82	Hyaluronan, TIMP-1, α2-macroglobulin

1. Chou R, Wasson N. *Ann Intern Med* 2013
2. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. *Hepatology* 2003.
3. Vallet-Prichard 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, S Sulkowski M, Torriani FJ, Dieterich DT, Thomas DL, Messinger D, Nelson M. *Hepatology* 2006.
5. Ibert-Bismut F, Ratziu 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.

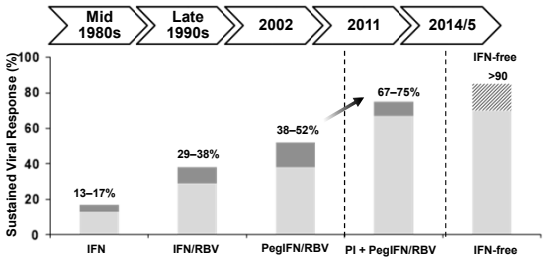
Abdominal Ultrasound

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

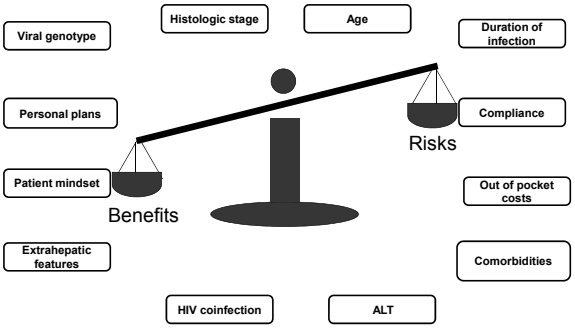
Hepatitis C: Achieving a Cure



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

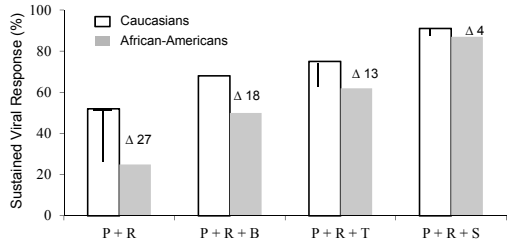
Adapted from Stedman CAM. *J Gastroenterol Hepatol* 2013

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 a;. *Nat Rev Microbiol.* 2007

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



Number of patients				
Caucasians	305	424	569	257
African-Americans	296	51	61	54

Saab et al. *A J Gastroenterol* 2014

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)		95% (12 wks)	100% (24 wks)
3-D ± R (duration)	Genotype 1a	96% (12wks)	89-95% (12-24wks)
	Genotype1b	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/2014/205834s000lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/205123s001lbl.pdf
http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206619lbl.pdf

Treatment of Genotype 2 Patients
Sustained Viral Response Rates

Regiment	Non cirrhotic		Cirrhotic		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/2013/204671s000lbl.pdf

Treatment of Genotype 3 Patients
Sustained Viral Response Rates

Regiment	Non cirrhotic		Cirrhotic		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
SOF/DCV	90%	63%			Yes

Abbreviations: SOF – sofosbuvir; LED – ledipasvir; R-ribavirin

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204671s000lbl.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 (F 0 - 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

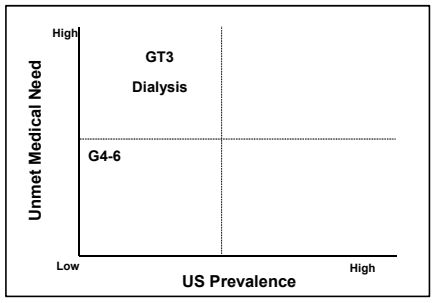
Approximate Costs of Antiviral Therapy

	SOF/R x 12-24 weeks	SOF/LED x 8-24 weeks	SOF/SIM x 12-24 weeks	3-D ± R x 12-24 weeks
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



Keeping your liver healthy

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

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