Lecture: HEPATITIS C: Clinical and Treatment Update

Anthony Ognjan, DO FACP
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Please check where applicable and sign below. Provide additional pages as necessary.

Name of CME Activity: ACOFP 52nd Annual Convention and Scientific Seminars

Dates and Location of CME Activity: March 12-15, 2015, The Cosmopolitan Las Vegas, Nevada
Lecture: HEPATITIS C: Clinical and Treatment Update
Saturday, March 14, 2015 10:30-Noon

Name of Faculty/Moderator: Anthony Ognjan, DO FACP

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Please indicate the name(s) of the organization(s) with which you have a financial relationship or interest, and the specific clinical area(s) that correspond to the relationship(s). If more than four relationships, please list on separate piece of paper:

<table>
<thead>
<tr>
<th>Organization With Which Relationship Exists</th>
<th>Clinical Area Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>1.</td>
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<tr>
<td>2.</td>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
<td>4.</td>
</tr>
</tbody>
</table>

*If you checked “Speakers' Bureau” in item B, please continue:

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* Did you travel to participate in this training?  Yes: No
* Did the company provide you with slides of the presentation in which you were trained as a speaker?  Yes: No
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Signature: [Signature]
Date: 1/10/15

Anthony Ognjan, DO FACP

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Deadline: Monday, January 12, 2015
“Hepatitis” is a general term that refers to severe swelling or inflammation of the liver in response to certain drugs, toxins, excessive alcohol or infections—whether from bacteria or viruses.

Hepatitis C

Lecture Objectives

1. Appreciate the Global epidemiological scope and impact of Hepatitis C
2. Understand Patients at risk, and short term and long term complications of infection
3. Overview of Clinical complication: Hepatic and Extra hepatic clinical concerns
4. Appreciate new diagnostic and treatment recommendations and guidelines
5. Introduction to Hepatitis C Virology; and new and evolving anti-viral Treatment strategies
Hepatitis C

Lecture Outline

• Viral History
• Epidemiology
  Statistics
  Transmission risk
  Vertical Transmission
  Health Care worker Risk
• Virus
  Virus
  Quasispecies
• Clinical
  Infection outcomes (Chronic Disease)
  Pathophysiology
  Predictive Factors for Progressive Disease
  Persons at risk
  Extra Hepatic Disease Manifestations
• Diagnosis
  Serology
  Liver Biopsy
  Diagnostic Studies
• Treatment
  Interferon / Ribavirin (combination)
  Ribavirin
  Interferon
  History
  Definition
  Biologic Activity
  Pegylated Interferons
  Interferon Uses
  Interferon Side Effects
  Genotypic variability
  Who to treat / Who not to
  Therapeutic Monitoring
  Genotypic Response Variations
  Protease Inhibitors
• Summary

History
Epidemic:

The term epidemic (Greek "epi" [on] plus "demos" [people]), first used by Homer, took its medical meaning when Hippocrates* used it as the title of one of his famous treatises. At that time, epidemic was the name given to a collection of clinical syndromes, such as coughs or diarrheas, occurring and propagating in a given period at a given location....

*5th century BC, Hippocrates’ Corpus Hippocraticum contains 7 books, titled Epidemics Hippocrates used the adjective epidemios (on the people) to mean “which circulates or propagates in a country”

Hepatitis C

Hepatitis/Jaundice History in time

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>430 BC</td>
<td>Hippocrates: Epidemic Jaundice</td>
</tr>
<tr>
<td>3,000 BC</td>
<td>China (Outbreaks of Jaundice)</td>
</tr>
<tr>
<td>500 BC</td>
<td>Babylon (Outbreaks of Jaundice)</td>
</tr>
<tr>
<td>17th - 18th Century</td>
<td>Military out breaks: 1629 Germany - Jaundice 1743 British army - “Flanders” 1899-1902 Boer war 1894 Japanese/Russian War 1870 Franco Prussian war</td>
</tr>
<tr>
<td>1861-1865</td>
<td>American Civil War 40,000 “Jaundice” cases among Union Troops</td>
</tr>
<tr>
<td>1883</td>
<td>15% (191/1289). Dock workers, Bremen Shipyards (Germany) : Small Pox Vaccination ▶ (First recognized out break of “Serum Hepatitis” – B)</td>
</tr>
<tr>
<td>1885</td>
<td>▶ Recognized Transmittable through Blood transfusions and Syringes</td>
</tr>
<tr>
<td>1937</td>
<td>▶ Recognized Transmitted from Vaccine administration (Equipment)</td>
</tr>
<tr>
<td>1900-1950</td>
<td>Epidemics of Jaundice recognized: Patients in VD (salvarsan therapy); Diabetic, TB clinics Vaccines, Serum therapy; Blood transfusions etc ▶ Use of large syringes and long needles</td>
</tr>
<tr>
<td>1908</td>
<td>McDonald postulates Infectious Hepatitis (A) is caused by a Virus</td>
</tr>
<tr>
<td>1942</td>
<td>(1939-45) WWII ▶ 28,585 Soldiers (Yellow Fever vaccine) : “Serum Hepatitis Epidemic of 1942” ▶ ~16 Million cases (Jaundice) Hepatitis A or B (C?)</td>
</tr>
<tr>
<td>1947</td>
<td>*FO MacCallum classifies viral hepatitis: Viral A “Infectious” Viral B “Serum”</td>
</tr>
</tbody>
</table>

Hepatitis C

Hepatitis History

*Paleovirology Analysis:

**Hepatitis B virus:**
- Originally infected birds back when the dinosaurs roamed the earth

**Hepatitis C Virus (HCV):**
- In the absence of historical and archaeological records of infection…. the evolution of HCV and other human hepatitis viruses can only be inferred indirectly from their epidemiology and by genetic analysis of contemporary virus populations.

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### Hepatitis C History

#### Evolution linage

<table>
<thead>
<tr>
<th>Years*</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 million years ago</td>
<td>❖ Ancestors of Hepatitis C</td>
</tr>
<tr>
<td>400 years ago</td>
<td>❖ Different Subtypes arise</td>
</tr>
<tr>
<td>200 years ago</td>
<td>❖ Six main genotypes of HCV arise</td>
</tr>
</tbody>
</table>

*Given the nature of the Evolution of Viruses, Hepatitis C has probably been around for hundreds of thousands of years or more before evolving into the current strains

---

*Difficult to appreciate the origin of HCV. Such a short period of human history and the virus is found even in remote areas all over the world.

Hepatitis C:
- Mainly spread by direct blood to blood contact, making it difficult to spread and evolve rapidly
- Especially considering that the main transmission routes (Blood product use and needle use) have only been in existence for a short period of time

Franciscus A. A Brief History of Hepatitis C. hcpp FACT sheet• Hepatitis C Support Project • www.hcvadvocate.org
Hepatitis C

History

Discovery Time Line

<table>
<thead>
<tr>
<th>Year</th>
<th>Factoid</th>
</tr>
</thead>
</table>
| Mid 1970's | ❖ Harvey J. Alter MD*, leading a research team, demonstrated that most post-transfusion hepatitis cases were not due to hepatitis A or B viruses.  
❖ Despite this discovery, international research effort to identify the virus, (Non-A,Non-B hepatitis) failed for the next decade. |
| 1987   | Joint collaboration of Chiron Corporation (Michael Houghton, George Kuo, Qui-Lim Choo) and CDC (Dr. D.W. Bradley) identify the Hepatitis C virus.                                                        |
| 1988   | Clinical Hepatitis C was independently confirmed by Dr. Alter by verifying its presence in a panel of Non A - Non B Blood specimens.                                                                         |
| 1989   | Discovery of "Hepatitis C virus" (HCV), published in two articles in the journal "Science".                                                                                                             |

*Chief of the Clinical Studies and Associate Director of Research in the Department of Transfusion Medicine at the NIH Clinical Center.
Hepatitis C
Epidemiology / Statistics

KEY: “Baby Boomers”

The Baby Boomer Generation
• Born: 1946 to 1964
• Age in 2015: 51-69

2012 Life expectancy for
Females: 81.2 years
Males: 76.4 years

HEPATITIS C
Epidemiology Statistics
World Wide

- 170 MILLION INFECTED WORLD WIDE
- 230,000 NEW CASES YEARLY
- New cases: PRIMARILY: 30 - 49 YEAR OLD
- Mortality Annually: World wide 350,000: 15,000 US

NORTHERN EGYPT 38%
USA (3.9 MILLION) 1.8%
SCANDANAVIA 0.15%

Wagner J. We Now Have the Cure for Hepatitis C, but Can We Afford It? Health- Scientific American Volume 331, #3 August 15, 2014 http://www.scientificamerican.com/article/we-now-have-the-cure-for-hepatitis-c-but-can-we-afford-it/ (Accessed 1/15/2015)
Hepatitis C

Epidemiology Statistics
United States

- **FACTOID**
  - **US:** >3 million chronically infected with hepatitis C virus (HCV). [1,2]
  - Number of new infections have been declining for decades: However: HCV-related morbidity/mortality is projected to continue rising another 20 years. [3]
  - 50-75% HCV infected, have not received a diagnosis (Are untreated)
  - Many will have disease progression to decompensated cirrhosis, hepatocellular carcinoma, and other liver complications. [3,4]

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HEPATITIS C
Disease Transmission

**UNDEFINED (MOST COMMON)**

- TRANSFUSIONS*
- SHARING NEEDLES (IVDU)
- INTRA FAMILY SPREAD (???)
- NEEDLE STICKS
- SEXUAL TRANSMISSION
- PERINATAL SPREAD
- NO INSECTS

<table>
<thead>
<tr>
<th>Transfusion Associated Cases*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE - SEROLOGY SCREENING</td>
<td>(1980) 15 - 20%</td>
</tr>
<tr>
<td>POST - SEROLOGY SCREENING</td>
<td>(1994) 0.01%</td>
</tr>
</tbody>
</table>

Presently blood transfusion risk : 1 : 2,000,000 (Blood Screening)

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4 Rein DB, Wittenborn JS, Weinbaum CM, Sabin M, Smith BD, Lessere SB. Forecasting the morbidity and mortality associated with prevalent cases of pre-cirrhotic chronic hepatitis C in the United States. Dig Liver Dis 2011;43:66-72

HEPATITIS C

*TRANSMISSION

Infection sources

**Sources of infection for Persons with Hepatitis C**

- IVDA 60%
- Transfusions 10%
- Sexual 15%
- Unknown 10%
- **Other** 5%

**Unknowingly infected by poorly sterilized medical equipment. Some may also have been infected through tattoos and piercings with contaminated needles.**

* Adapted from CDC

Hepatitis C

History

Diagnostic Milestones: Protected Blood supply

**Chronological Breakdown***

<table>
<thead>
<tr>
<th>Year</th>
<th>Blood Supply: Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950's</td>
<td>Test developed to detect ALT, (Occurs at higher levels in people with hepatitis).</td>
</tr>
<tr>
<td>1960's</td>
<td>Still Working: No agent of Hepatitis Identified</td>
</tr>
<tr>
<td>1981-83</td>
<td>Debate in medical journals and among health officials over use of ALT test to detect Hepatitis C.</td>
</tr>
<tr>
<td>1986</td>
<td>All blood banks are using ALT test and other indirect Hepatitis C test routinely.</td>
</tr>
<tr>
<td>1990</td>
<td>HCV EIA screening of all Blood donations by 1st Generation EIA Test</td>
</tr>
<tr>
<td>1992</td>
<td>Second Generation HCV Antibody Screening Tests</td>
</tr>
<tr>
<td>1999</td>
<td>HCV (“PCR”): Quantitative Analysis Nucleic Acid available (“NAT”)</td>
</tr>
</tbody>
</table>


Hepatitis C

Vertical transmission*

*Transmission of a communicable disease from an infected mother to her child during the birth process*.

Mother-to-child transmission occurs relatively infrequently.

<table>
<thead>
<tr>
<th>Mother’s Sero-status</th>
<th>INFANT: Transmission risk of HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV (+AB and +RNA)</td>
<td>1.4 - 5.8% [1,2]</td>
</tr>
<tr>
<td>Co-infection</td>
<td>10.8 - 19.4% [1,2]</td>
</tr>
<tr>
<td>HCV and HIV Positive</td>
<td></td>
</tr>
</tbody>
</table>

- Not clear when transmission occurs during pregnancy, may occur both during gestation and at delivery
- There is no evidence that breast-feeding spreads HCV [3,4]


Hepatitis C

Comparative Risk of Health care worker Infection Risk

<table>
<thead>
<tr>
<th>Virus</th>
<th>Acquiring from Positive Blood Exposure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>30%</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>3% **</td>
</tr>
<tr>
<td>HIV</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

* These numbers are most likely influenced by the size of the inoculums, the size of the needle, and the depth of inoculation.
** After a needle-stick injury involving blood known to be infected ranged from 0 to 10 percent in various studies [1,2]

<table>
<thead>
<tr>
<th>Risk activity</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casual household contact</td>
<td>Casual contact, and contact with saliva appear very low risk for infection [2]</td>
</tr>
<tr>
<td>Nosocomial transmission</td>
<td>Documented (Patient to Patient):</td>
</tr>
<tr>
<td></td>
<td>Colonoscopy</td>
</tr>
<tr>
<td></td>
<td>Hemodialysis</td>
</tr>
<tr>
<td></td>
<td>Surgery</td>
</tr>
</tbody>
</table>

**Virus**

Quasispecies

---

**Hepatitis C**

**Virology**

**Flaviviridae**

- Family of viruses that are primarily spread through arthropod vectors (Mainly ticks and mosquitoes).
- The family gets its name from Yellow Fever virus, a type virus of Flaviviridae
- Flavus means yellow in Latin.

<table>
<thead>
<tr>
<th>Genus</th>
<th>Members</th>
</tr>
</thead>
</table>
| I. Flavivirus | ❖ Yellow fever virus  
               ❖ West Nile virus  
               ❖ Dengue Fever  
               ❖ 67 identified human and animal viruses |
| II. Hepacivirus | ❖ Hepatitis C virus  
                     - Single member |
| III. Pestivirus | ❖ Bovine diarrhea |

**Major diseases caused by the Flaviviridae family include:**

- Dengue fever
- Japanese encephalitis
- Kyasanur Forest disease
- Murray Valley encephalitis
- St. Louis encephalitis
- Tick-borne encephalitis
- West Nile encephalitis
- Yellow fever
- Hepatitis C Virus Infection

Flaviviridae

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<th>Genus</th>
<th></th>
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<tr>
<td>I.</td>
<td>Flavivirus</td>
</tr>
<tr>
<td>II.</td>
<td>Hepacivirus</td>
</tr>
<tr>
<td>III.</td>
<td>Pestivirus</td>
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- Dengue fever
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- Kyasanur Forest disease
- Murray Valley encephalitis
- St. Louis encephalitis
- Tick-borne encephalitis
- West Nile encephalitis
- Yellow fever
- Hepatitis C Virus Infection

HEPATITIS C VIROLOGY
Genotype / Quasispecies

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1*</td>
<td>75%</td>
</tr>
<tr>
<td>Genotype 2 or 3</td>
<td>20-25%</td>
</tr>
<tr>
<td>Genotype 4</td>
<td></td>
</tr>
<tr>
<td>Genotype 5</td>
<td></td>
</tr>
<tr>
<td>Genotype 6</td>
<td></td>
</tr>
</tbody>
</table>

Patients with genotypes 2 & 3 are more than twice as likely as patients with genotype 1 to achieve a sustained virological response to Interferon Based therapy.
HEPATITIS C Virology
Phenotype

Flavavirus (1989) RNA:
HEPATITIS C SIX “MAJOR” GENOTYPES
➢ 9,400 NUCLEOTIDES coding : 3,000 amino acids
➢ “HIGH” REPLICATIVE CAPACITY leads to:

GENOTYPIC “QUASISPECIES” * **

➢ SERUM VIRAL LOADS ( >500,000 viral copies /cc common)

* Cluster (cloud or swarm) of variant viruses arising from mutations within a viral isolate. Particularly RNA viruses, secondary to the inherently high mutation rate, caused by copy errors occurring during replication by RNA-dependent RNA polymerase (in the absence of genome proof-reading that occurs with RNA - RNA replication).

**Hepatitis C Genotypes and Quasispecies. Viral Hepatitis US Department of Veteran Affairs http://www.hepatitis.va.gov/provider/reviews/genotypes.asp

HEPATITIS C Virology
GENOTYPIC “QUASISPECIES”

Resistant Virus variants are present before Treatment*

In every Patient, HCV exists as a population Mixture of Genetically Distinct but closely related virions : “Quasispecies” [1]

Factoid:
➢ ~10¹⁷ virus produced per day
➢ ~1 nucleotide Mutation Virus Produced
➢ All possible single and double Nucleotide mutants precede treatment [2]

Most resistant variants are relatively “unfit”; and may not be detectable prior to therapy with current technology [3,4]

1. Pawlotsky JM. Clin Liver Dis. 2003; 7; 45-66

Clinical

Infection out comes (Chronic Disease)
Pathophysiology
Predictive Factors for Progressive Disease
Persons at risk
Extra Hepatic Disease Manifestations

*Chronic hepatitis C is defined as infection with the hepatitis C virus ....
 .... persisting for more than six months.*

HEPATITIS C VIRUS

CLINICAL

VIROLOGICAL OUTCOMES (Acute and Chronic Infection)

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Characteristics</th>
<th>Modifying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute*: Infection</td>
<td>Detectable Viremia : 1 - 3 weeks</td>
<td>*Most (70-80%) are Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Detectable Antibody : 3 - 12 weeks</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure: ~15-25%</td>
<td>Spontaneous viral “Clearance”</td>
</tr>
<tr>
<td></td>
<td>❖ Normalization liver function tests</td>
</tr>
<tr>
<td></td>
<td>❖ Plasma clearance of HCV-RNA</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Characteristics</th>
<th>Modifying</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic: Infection~ 60-85%</td>
<td>Active infection: &gt; Six Months</td>
<td>+ Hepatitis C Antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ Detectable RNA Virus: PCR</td>
</tr>
</tbody>
</table>

*Associated Acute symptoms:
Exposure to symptom onset is 4–12 weeks (range: 2–24 weeks):
Fever Anorexia Fatigue Nausea Dark urine Vomiting Clay-colored stool Arthralgias Abdominal pain Jaundice
Hepatitis C

CLINICAL
History of Chronic Hepatitis C

<table>
<thead>
<tr>
<th>Clinical Issue</th>
<th>Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Chronic Infection* (&gt;6mos : Active)</td>
<td>75-85% “Life long” with Quasispecies</td>
</tr>
<tr>
<td>❖ Chronic Infection with liver Disease</td>
<td>~70% Over Decades</td>
</tr>
<tr>
<td>❖ Hepatic Cirrhosis</td>
<td>5-20% Period of 20-25 years</td>
</tr>
<tr>
<td>❖ Related Mortality (ESLD)</td>
<td>Variable Period of 25-30 years</td>
</tr>
<tr>
<td>❖ Hepatocellular Cancer (HCC)</td>
<td>1-4% ❖ 5th Most common cancer</td>
</tr>
<tr>
<td></td>
<td>❖ 3rd Most common cause cancer death (world wide)</td>
</tr>
<tr>
<td></td>
<td>❖ HCV : 1 million deaths/year</td>
</tr>
</tbody>
</table>

* “Spontaneous” resolution of Chronic infection occurs (0.5 - 0.74% per year)


HEPATITIS C

Chronic Infection
Predictive factors for “Chronic Infection”

- Older than 40 years at time of diagnosis
- Longer duration of infection
- Males
- “Weakened” immune status
- Co-infection with other Hepatotropic virus (Hepatitis B Genotype I and its “Quasispecies” (1a)
- Iron “Overload” states, and Alcoholics
- HIV co-infection

Alcoholic beverage consumption
Accelerates HCV associated fibrosis and cirrhosis, and makes liver cancer more likely
Hepatitis C

**Extra Hepatic Manifestations**

First recognized in the 1990s, several syndromes and conditions have now been linked to hepatitis C.

High index of suspicion and a knowledge of the extrahepatic manifestations of HCV in order to not only treat the manifestation but also initiate timely therapies for the underlying HCV.

### Extrahepatic tissues can serve as a reservoir for HCV with special tropism for the Lymphoid tissues

<table>
<thead>
<tr>
<th>Observation</th>
<th>Consequence</th>
</tr>
</thead>
</table>
| Extrahepatic tissues can serve as a reservoir for HCV with special tropism for the Lymphoid tissues \(^{(1,2)}\) | • Chronic inflammation  
• Tissue damage  
• Immune-complex aggregation  
• Activation autoimmune phenomena  
• Neoplasia  
• Cryoglobulinaemia                                                   |

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Since 1990s several clinical syndromes have been linked to hepatitis C, while others are still emerging. In some patients, Extra hepatic manifestations can be the dominant feature (While hepatic disease is "mild").


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### Extra Hepatic Manifestations of Hepatitis C

<table>
<thead>
<tr>
<th>Status</th>
<th>Associated Clinical</th>
</tr>
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</table>
| Primary Vasculitis (High Viral Loads) | - Essential Mixed Cryoglobulinemia  
- Purpura  
- Arthritis / Arthralgia  
- Cerebritis  
- Neuiritis (Vasonervorum)  
- Glomerulonephritis        |
| Dermal Manifestations         | - Porphyria Cutanea tarda  
- Lichen planus               |
| Rare                          | - Aplastic anemia or  
- Non-Hodgkin's lymphoma       |

---

For example, a patient with a dominant vasculitis may present with cryoglobulinaemia, purpura, arthritis, cerebritis, neuroitis, and glomerulonephritis.
DIAGNOSIS

Diagnostic Serology
- HCV Genotyping

Liver Staging:
- Liver Biopsy
- Elastography
- Serum Fibrotic Markers

HEPATITIS C
Persons at Risk

WHO TO SCREEN:
IVDUs / Intra-Nasal Drug User
Blood product transfusion (Before 1992)
Organ transplants (Before 1992)
Clotting factors (Before 1987)
All hemodialysis patients
Unexplained “ALT” elevations
Health care workers with percutaneous or mucous membrane exposure
Children born to HCV infected women
ALL “BABY BOOMERS”

Epidemiology
Hepatitis C Testing*
New Testing Guidelines: BABY BOOMERS

CDC Recommendations for the Identification of Chronic Hepatitis C Virus Infection among Persons Born During 1945–1965

**RATIONAL:**

<table>
<thead>
<tr>
<th>TESTING ALL BABY BOOMERS:</th>
</tr>
</thead>
</table>
| • Increasing HCV-Associated Morbidity and Mortality | • Leading cause of liver transplants and liver cancer.  
• Annual HCV-associated US mortality increased >50% from 1999 to 2007.  
• Born during 1945-1965 account for 73% of all HCV-associated deaths |
| • Benefits of HCV Treatment | • New therapies, including interferon-free regimens, can halt disease progression and provide a virologic cure in most HCV-infected persons.  
• "New" agents Less Toxic, Shorter treatment times, Highly effective |
| • Resource Implications | • One-time birth year testing estimated to identify 800,000 infections  
• With linkage to care and treatment: avert >120,000 HCV-related deaths.  
• Estimated to save $1.5-$7.1 billion in liver disease-related costs. |

---

**Hepatitis C**

Diagnosis
Testing Overview

![Hepatitis C Serum Antibody Detection After Exposure](chart)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTA Elevation</td>
<td>Variable</td>
</tr>
<tr>
<td>LTA Elevation Correlation to disease</td>
<td>None</td>
</tr>
<tr>
<td>Viral Load Correlation to Liver injury</td>
<td>None</td>
</tr>
<tr>
<td>Radiographic (CT, MRI, US)</td>
<td>Not until Advanced disease</td>
</tr>
<tr>
<td>Liver Biopsy (Gold Standard)</td>
<td>Best : Scarring / Inflammation</td>
</tr>
</tbody>
</table>
Hepatitis C
Diagnosis

Diagnostic Serology

<table>
<thead>
<tr>
<th>Test</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elisa Screening</td>
<td>Third Generation</td>
</tr>
<tr>
<td>RIBA confirmation (Not necessary)</td>
<td>With “low” pre-test suspicion</td>
</tr>
<tr>
<td>Viral quantation (PCR or bChain DNA)</td>
<td>Disease Activity: Response to treatment</td>
</tr>
<tr>
<td>Viral genotype</td>
<td>• 70 - 80% of USA strains are type I, Ia</td>
</tr>
<tr>
<td></td>
<td>• Selecting Treatment regimens and the length of treatment;</td>
</tr>
<tr>
<td></td>
<td>• HCV genotype also helps to predict the likelihood of curing HCV.</td>
</tr>
<tr>
<td>*NS3 Q80K polymorphism (Protease)</td>
<td>• G1 genotypes (+40%)</td>
</tr>
</tbody>
</table>

Advanced cirrhosis with mixed Macronodular and Macronodular Patterns and Moderate cholestasis

Hepatitis C
Diagnostic Hepatic Disease Staging

Liver Biopsy: "Gold Standard"
• Useful information about the degree of fibrosis in HCV-infected patients.
• Histology is important for making decisions in the management of HCV infection.
• Liver Health: Urgency to begin treatment

Transient Elastography: (2013)
• Ultrasound (low frequency elastic waves) to measure liver elasticity
• Increase accuracy, when combined with blood markers
• Predicting mild fibrosis, severe fibrosis and cirrhosis.

Serum Fibrotic Markers:
Can be useful for distinguishing liver cirrhosis from chronic hepatitis
### Hepatitis C

#### Hepatic Disease Staging I

<table>
<thead>
<tr>
<th>Study</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Biopsy</td>
<td>❖ Gold standard to stage Liver fibrosis</td>
<td>❖ Invasive test</td>
</tr>
<tr>
<td></td>
<td>❖ Stage Cirrhosis</td>
<td>❖ Hospitalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>❖ Expensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>❖ Risks : Pain and Bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Small Sample size:</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>❖ Sampling error</td>
</tr>
</tbody>
</table>
|                               |                                         | ❖ Pathologist’s Variation                        | **Liver Biopsy**
|                               |                                         | **Pros**                                       |
|                               | ❖ Invasive test                         | ❖ Hospitalized                                  |
|                               | ❖ Stage Cirrhosis                       | ❖ Expensive                                     |
|                               | ❖ No pain, or sedation required         | ❖ Risks : Pain and Bleeding                     |
|                               | ❖ 5—7 minutes to perform                | **Cons**                                       |
|                               | ❖ Less expensive than liver biopsy      | ❖ Small Sample size:                           |
|                               | ❖ No side effects.                      | ❖ Sampling error                                 |
|                               |                                         | ❖ Pathologist’s Variation                        |
| Hepatic Elastography (Fibroscan™) | ❖ Non-invasive test                     | Technical limitations:                         |
| (Liver Stiffness)             | ❖ Performed at the point of care        | ❖ Ascites                                       |
|                               | ❖ No pain, or sedation required         | ❖ Morbidly obese                                |
|                               | ❖ 5—7 minutes to perform                | ❖ Limits in diagnosing low-to-moderate fibrosis  |
|                               | ❖ Less expensive than liver biopsy      | ❖ Inferior to that for serum                    |
|                               | ❖ No side effects.                      | fibrosis markers (??)                          |

Afdhal FH. *Fibroscan (Transient Elastography) for the Measurement of Liver Fibrosis.* Gastroenterol Hepatol (N Y). Sep 2012; 8(9): 605–607

#### Hepatic Disease Staging II

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Fibrotic Markers*</td>
<td>❖ Blood sample can be readily collected in</td>
<td>❖ Assays Must Be performed in validated</td>
</tr>
<tr>
<td></td>
<td>minutes</td>
<td>laboratories.</td>
</tr>
<tr>
<td></td>
<td>❖ Quick Turn around</td>
<td>❖ Cannot be used without algorithms that</td>
</tr>
<tr>
<td></td>
<td>❖ Alternative to a liver biopsy</td>
<td>detects false positives and false negatives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>❖ Equation alone is not a diagnosis tool.</td>
</tr>
</tbody>
</table>

*Increasing understanding of the pathogenesis of hepatic fibrosis has suggested several markers which could be useful indicators of hepatic fibrogenesis and fibrosis. Markers include serum markers of liver function, ECM synthesis, fibrolytic processes, ECM degradation and fibrogenesis related cytokines.*

Afdhal FH. *Fibroscan (Transient Elastography) for the Measurement of Liver Fibrosis.* Gastroenterol Hepatol (N Y). Sep 2012; 8(9): 605–607
Hepatitis C
Diagnosis: Liver Biopsy

Metavir (Pathology grading)

METAVIR:
Designed for patients with hepatitis C.
- Scoring: grading and a staging system.
- GRADE: activity or amount of inflammation
- STAGE: Amount of fibrosis or scarring.
- Grade is assigned a number based on the degree of inflammation, which is usually scored from 0-4
  0 = No activity
  3 or 4 = Considered Severe Disease

<table>
<thead>
<tr>
<th>Score</th>
<th>Pathologic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Fibrosis (no scarring) : Stellate enlargement of portal tract</td>
</tr>
<tr>
<td>1</td>
<td>No septa formation (Minimal scarring)</td>
</tr>
<tr>
<td>2</td>
<td>Rare Septa Formation</td>
</tr>
<tr>
<td>3</td>
<td>Numerous septa without Cirrhosis (spreading bridging fibrosis)</td>
</tr>
<tr>
<td>4</td>
<td>Cirrhosis or advanced scarring of the liver</td>
</tr>
</tbody>
</table>

http://www.hepatitiscentral.com/hcv/biopsy/charts/metavir.html

Hepatitis C
Disease Staging
Fibroscan™ (Elastography)

- Elastography is a medical imaging modality that maps the elastic properties of soft tissue.
- High degree of accuracy for predicting mild fibrosis, severe fibrosis and cirrhosis.

<table>
<thead>
<tr>
<th>Fibroscan™</th>
<th>FDA approved April 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utilization</td>
<td>Europe, South America, Canada, Asia, China and Japan</td>
</tr>
</tbody>
</table>
| Technical limitations | Ascites
Morbidly obese
Large amounts of chest wall fat
Less likely to distinguish the difference between no or minimal fibrosis. |
| Fibroscan and Serum Biomarker testing* | Combination to exclude patients with cirrhosis:
- To avoid biopsy
- Cirrhotics would require appropriate screening with endoscopy and ultrasound for liver cancer,
- Non-Cirrhotics could proceed with treatment. |

* Fibrometer—a blood test that measures hyaluronate, prothrombin time, platelets, AST, a2 macroglobulin, urea, and age—in combination can provide an 87% accuracy rate.

"It's an outpatient procedure taking less than 15 minutes"
Stuart Gordon, M.D.,
Director of Hepatology at Henry Ford Hospital.
Detroit Michigan
Hepatitis C

Relative Financial Impact

<table>
<thead>
<tr>
<th>Procedure/Study</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver Biopsy [1,2]</td>
<td>$2,000-7,000*</td>
</tr>
<tr>
<td>Serum Markers [4]</td>
<td>$300-400</td>
</tr>
</tbody>
</table>

*For patients not covered by health insurance


<table>
<thead>
<tr>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procurement</td>
<td>$71,000</td>
</tr>
<tr>
<td>Hospital Transplant Adm</td>
<td>$316,900</td>
</tr>
<tr>
<td>Physician During Transplant</td>
<td>$46,600</td>
</tr>
<tr>
<td>180 days Post Transplant</td>
<td>$93,900</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>$23,300</td>
</tr>
<tr>
<td></td>
<td>$557,100</td>
</tr>
</tbody>
</table>

2 Liver Biopsy HCSP Fact sheet
4 Noninvasive assessment of liver disease and Biopsy. NATAP

Clinical Benefits
Who to treat
Who Not to treat
Patient Priorities
Agent time line

Hepatitis C

Treatment

Goal of treatment:

- Reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma,
- By the achievement of virologic cure as evidenced by an SVR*.

*Sustained Virologic Response
Hepatitis C
Treatment

VIROLOGIC CURE*: STANDARDS AND CONSIDERATIONS

*Requires use of US Food and Drug Administration (FDA)-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of 25 IU/mL or lower

GOAL:
Virologic cure*: Sustained Virologic Response (“SVR”):
Continued absence of detectable HCV RNA
>12 weeks [3 months] after completion of therapy

<table>
<thead>
<tr>
<th>VIROLOGIC “CURE”</th>
<th>FACTOID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable:</td>
<td>SVR Large prospective studies: &gt;99% of patients followed &gt;5 years)</td>
</tr>
<tr>
<td>+ Detectable HCV Serum antibodies</td>
<td>No detectable HCV RNA</td>
</tr>
<tr>
<td>No Detectable HCV RNA:</td>
<td>Serum, Liver tissue, Mononuclear cells</td>
</tr>
</tbody>
</table>


Hepatitis C
Treatment
WHO to treat?

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

- American Association for The study of Liver Disease / Infectious Disease Society of America.

Hepatitis C

Treatment

Who to treat: General Clinical Factoids

**WHO TO TREAT:**

- Evidence clearly supports treatment in all HCV-infected persons:
  - Except
  - Those with limited life expectancy (<12 months) due to non-liver-related comorbid conditions
  - "Urgent" initiation of treatment is recommended for some patients, such as those with advanced fibrosis or compensated cirrhosis


Hepatitis C

Treatment

Patient Clinical Benefits from Hepatitis C: "Cure (SVR)

**CLINICAL LIVER DISEASE IMPACT**

- Decrease in liver inflammation improved (Decrease Aminotransferase levels)
- Reduction in the rate of progression of liver Fibrosis, Necrosis, Cirrhosis
- Improvement: Portal hypertension, Splenomegaly (Other clinical manifestations of advanced liver disease) also improved.
- 70% Reduction in the risk of liver cancer (Hepatocellular carcinoma)
- 90% Reduction in the risk of liver-related mortality and liver transplantation

Reduces Morbidity and Mortality from severe Extra-Hepatic manifestations*:

- Cryoglobulinemic vasculitis (Affecting ~10% to 15% of HCV-infected patients)
- HCV-infected associated lymphoproliferative disorders (Including Non-Hodgkin Lymphoma): Achieve complete or partial remission in up to 75% of cases
- Patients achieving SVR have substantially improved quality of life, which includes physical, emotional, and social health.

### Hepatitis C

#### Relative Financial Impact

Estimated U.S. Average 2011 Billed Charges Per Transplant*

<table>
<thead>
<tr>
<th>Organ</th>
<th>30 days pre transplant</th>
<th>Procurement</th>
<th>Hospital Transplant Admission</th>
<th>Physician During Transplant</th>
<th>180 days Post Transplant</th>
<th>Immuno-suppressants</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart only</td>
<td>$47,200</td>
<td>$80,400</td>
<td>$634,300</td>
<td>$67,700</td>
<td>$137,800</td>
<td>$30,300</td>
<td>$997,700</td>
</tr>
<tr>
<td>Single Lung</td>
<td>$10,300</td>
<td>$73,100</td>
<td>$302,900</td>
<td>$33,500</td>
<td>$117,700</td>
<td>$23,700</td>
<td>$561,200</td>
</tr>
<tr>
<td>Double Lung</td>
<td>$21,400</td>
<td>$90,300</td>
<td>$458,500</td>
<td>$56,300</td>
<td>$142,600</td>
<td>$28,200</td>
<td>$797,300</td>
</tr>
<tr>
<td>Heart-lung</td>
<td>$56,800</td>
<td>$130,500</td>
<td>$777,700</td>
<td>$81,000</td>
<td>$169,000</td>
<td>$33,000</td>
<td>$1,148,400</td>
</tr>
<tr>
<td><strong>LIVER</strong></td>
<td>$25,400</td>
<td>$71,000</td>
<td>$316,900</td>
<td>$46,600</td>
<td>$93,900</td>
<td>$23,300</td>
<td>$557,100</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>$17,000</td>
<td>$67,200</td>
<td>$91,200</td>
<td>$18,500</td>
<td>$50,800</td>
<td>$18,200</td>
<td>$262,900</td>
</tr>
<tr>
<td>Pancreas</td>
<td>$17,000</td>
<td>$65,000</td>
<td>$108,900</td>
<td>$17,800</td>
<td>$61,400</td>
<td>$19,300</td>
<td>$289,400</td>
</tr>
<tr>
<td>Intestine</td>
<td>$55,100</td>
<td>$78,500</td>
<td>$787,900</td>
<td>$104,100</td>
<td>$146,600</td>
<td>$34,600</td>
<td>$2,206,800</td>
</tr>
</tbody>
</table>


---

### Hepatitis C

#### Treatment Priority

**Highest Priority** for Treatment Owing to Highest Risk for Severe Complications
- Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
- Organ Transplantation
- Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)
- Proteinuria, Nephrotic syndrome, or Membranoproliferative Glomerulonephritis

**High Priority** for Treatment Owing to High Risk for Complications
- Hepatic Fibrosis
- HIV Co-infection
- Hepatitis B Co-infection
- Other Co-existing Liver Diseases
- Debilitating Fatigue
- Type II Diabetes Mellitus (Insulin Resistant)
- Porphyria Cutanea Tarda

**ELEVATED RISK:**
- Men who have sex with men (MSM) with high-risk sexual practices
- Active injection drug users
- Incarcerated persons
- Persons on long-term hemodialysis
- HCV-infected women of child-bearing potential wishing to get pregnant

HCV-Target*
Populations of Special Interest

N=2063

- Cirrhotics 49%
- Age > 65 19%
- Black 12%
- Liver Transplant 11%
- Hispanic 7%
- HIV Co-infected 2%

*HCV TARGET: Hepatitis C Therapeutic Registry and Research Network.
http://www.hcvtarget.org

* An ongoing longitudinal observational study at 43 academic and 13 community centers in North America and Europe.

Treatment

Therapeutic Advances
“Time-line”
Hepatitis C Treatment
Therapeutic Advances: Time line

<table>
<thead>
<tr>
<th>Year</th>
<th>Therapy</th>
<th>Response (SVR): 12 weeks</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990's</td>
<td>Interferon</td>
<td>14-20%</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>Interferon / Ribavirin</td>
<td>43% GT1</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>* peg-INF Ribavirin</td>
<td>70-80% GT2/GT3 Other GT</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>PROTEASE INHIBITORS ** Telapirivir peg-INF Ribavirin Boceprevir peg-INF Ribavirin</td>
<td>51-53% 40-60%</td>
<td>24 - 48 wk 24 - 48 wk</td>
</tr>
<tr>
<td>2013</td>
<td>Simeprevir ** peg-INF Ribavirin</td>
<td>80-95% (GT1 Only)</td>
<td>12 - 24 wk</td>
</tr>
<tr>
<td>2014</td>
<td>Paritaprevir / Ritonavir / Ombitasivir / Dasabuvir Ribavirin</td>
<td>93-97%</td>
<td>12-24 wk</td>
</tr>
<tr>
<td>2013</td>
<td>NUCLEOTIDE ANALOGUE INHIBITOR** Sofosbuvir peg-INF Ribavirin</td>
<td>80-95%</td>
<td>12-24 wk</td>
</tr>
</tbody>
</table>

* peg-INF: "Pegylated Interferon"  GT= "Genotype"
** Referred to as "Direct acting agents"
1 Efficacy of simeprevir is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism, screening for this mutation is strongly recommended by the manufacturer.
Hepatitis C Treatment

THEN...

Ribavirin / Interferon

Ribavirin
Rebetrol ®

Nucleoside anti-metabolite
(Interfere with duplication of viral genetic material)

Anti-viral drug which is active against a number of DNA and RNA viruses.

ACTIVITIES:
- Influenza
- Flavivirus (Hepatitis C)
- Viral hemorrhagic fevers:
  - Lasa fever
  - Crimean-Congo hemorrhagic fever
  - Hantavirus
- Smallpox
- Hepatitis B
- Polio
- Measles
- West Nile virus
- Dengue fever

Nucleoside drug resemble adenosine or guanosine,

- First synthesized in 1970
- Large Volume of distribution
  - CSF / Brain
- Toxic Side effects
  - Teratogenic
  - Severe Anemia:
**Interferon**

- 1954  Yasu-ichi Nagano, Yasuhiko Kojima  
- 1957  Alick Isaacs, Jean Lindemann:  Coined “Interferon”  
- 1980  Recombinant DNA allows mass production

---

**Hepatitis C**

**Treatment**

Interferon Functional Definition

**Interferons**

<table>
<thead>
<tr>
<th>Family of naturally-occurring proteins produced by cells of the immune system.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three classes of Interferons have been identified:</td>
</tr>
<tr>
<td>- Alpha, Beta and Gamma.</td>
</tr>
<tr>
<td>Each class has different overlapping biological and physiological</td>
</tr>
</tbody>
</table>

- Together, Interferons “Modulate” the immune system’s attack on Viruses, Bacteria, Tumors and other foreign agents.  
- Interferons effects slow, Block, or Change the Biologic growth or function of the agent (Organism).
Hepatitis C
Treatment
Interferons Biologic activity

Interferons
- Produced by a wide variety of cells in response to the presence of double-stranded RNA. (Key indicator of viral infection).
- Interferons assist the immune response:
  - Inhibiting viral replication
  - Activating natural killer cells/macrophages
  - Increasing antigen presentation to lymphocytes
  - Inducing the resistance of host cells to viral infection.
- When the antigen is presented to matching T and B cells, those cells multiply and strategically and specifically wipe out the foreign substance.


Hepatitis C
Treatment
Interferons: Pegylated interferon

Pegylated interferon
alfa-2b (Peg-Intron®) and alfa-2a (Pegasys®)

Polyethylene Glycol (PEG) attached to interferon molecules.

PEG causes the interferon to remain in the body longer, prolonging Half life and drug effectiveness.
Hepatitis C

TREATMENT

Pegylated Interferon: Advantage Administered by subcutaneous or intramuscular injection

<table>
<thead>
<tr>
<th>Interferon Comparison</th>
<th>Interferon</th>
<th>Pegylated Interferon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longer Drug Half life</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Consistent Blood Levels</td>
<td>Variable</td>
<td>Yes</td>
</tr>
<tr>
<td>Dosage Interval</td>
<td>3X week</td>
<td>Once Week</td>
</tr>
<tr>
<td>Side effects:</td>
<td>With Injection</td>
<td>With Injection</td>
</tr>
</tbody>
</table>


Interferon

Side effects

- Flu-like symptoms following each injection (Fever, Chills, Headache, Muscle aches and pains, Malaise); Alopecia
- These symptoms vary from mild to severe and occur in up to half of all patients.
- The symptoms tend to diminish with repeated injections
  Management
  - Analgesics: Acetaminophen - Tylenol®
  - Antihistamines: Diphenhydramine - Benadryl®
- Interferon therapy causes ("Bone marrow") Immunosuppression:
  Neutropenia, Anemia, Thrombocytopenia

All known adverse effects are usually reversible and disappear a few days after the therapy has been finished.
Interferon
Side effects Depression and suicide

<table>
<thead>
<tr>
<th>Psychiatric Side effects</th>
<th>Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>5</td>
<td>16.6%</td>
</tr>
<tr>
<td>Major Depression disorder</td>
<td>3</td>
<td>10%</td>
</tr>
<tr>
<td>Brief psychotic disorder</td>
<td>1</td>
<td>3.3%</td>
</tr>
<tr>
<td>Panic attacks</td>
<td>1</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

- Reported among patients receiving Interferons
- Unclear whether depression and suicidal thoughts are caused by the diseases being treated or the Interferons themselves.....

Therefore, all patients receiving treatment with an interferon should be observed for the development of depression and suicidal thoughts.

* Incidence of Psychiatric Side Effects During Pegylated Interferon- Alpha Retreatment in Non responder Hepatitis C Virus-Infected Patients

Hepatitis C

Interferon Uses

- Hairy cell leukemia
- AIDS-related Kaposi’s Sarcoma
- Chronic Myelogenous Leukemia
- Malignant Melanoma
- Condylomata Acuminata
- Chronic Hepatitis C
- Chronic Hepatitis B

### Hepatitis C

#### Genotypic Response Variations

**Historically** : Interferon Ribavirin :

<table>
<thead>
<tr>
<th>Genotype *</th>
<th>Agents</th>
<th>Duration</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1</td>
<td>75% US</td>
<td>Pegylated interferon alpha Ribavirin</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Genotype 2</td>
<td>20-25% US</td>
<td>Pegylated interferon alpha Ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 3</td>
<td></td>
<td>Pegylated interferon alpha Ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>Genotype 4</td>
<td></td>
<td>Pegylated interferon alpha Ribavirin</td>
<td>48 weeks</td>
</tr>
</tbody>
</table>

- **Control Chronic Carriers**
  - Spontaneous resolution (0.5 - 0.74% per year)

---

- * IL28B designates single-nucleotide polymorphisms (SNPs) in the interferon λ gene region in chromosome 19, and it is related to interferon responsiveness. [1]
- * Other factors such as High Viral Load, Older age, Black race and Advanced Fibrosis or Cirrhosis negatively influence SVR rates. To Interferon [2,3]

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### Hepatitis C Treatment

**NOW...**

**Direct Acting Agents “DAA”**

**Interferon “Free”...**
Hepatitis C

Treatment
Interferon / Ribavirin Regimens

As the currently available interferon alpha-based treatments for chronic hepatitis C are associated with many side effects....

And effective in only about half of patients, more research is needed to develop safer, more effective and cheaper drugs......

Hepatitis C

Direct Acting Agents

Rapid breakthroughs in the treatment of hepatitis C virus (HCV) infection have dramatically altered the treatment landscape for this chronic disease.
Hepatitis C

Treatment Issues and Observations

Then: Interferon Based Vs. Now: Direct Acting Agents*

<table>
<thead>
<tr>
<th>Interferon Base regimens</th>
<th>Direct Acting Agent regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Several Factors:</td>
<td></td>
</tr>
<tr>
<td>- Racial or ethnic background</td>
<td></td>
</tr>
<tr>
<td>- L28B genotype</td>
<td></td>
</tr>
<tr>
<td>- Baseline HCV RNA level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Studies with Sofosbuvir and Ledipasvir, these factors do not play a prominent role in determining treatment response</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Side effects associated with Interferon therapy:
Prevented many patients from undergoing treatment are a major reason for treatment failure...

Significant achievement of interferon-free drug regimens is the lower rate; and decreased severity of side effects.

<table>
<thead>
<tr>
<th>Direct acting agents*</th>
<th>Issues to be addressed:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The regimens: tested predominantly in middle-aged: white men without cirrhosis</td>
<td></td>
</tr>
<tr>
<td>- More-difficult-to-treat patients with cirrhosis, HIV/HCV co-infection, Renal failure, remain a challenging</td>
<td></td>
</tr>
<tr>
<td>- Not clear if these regimens will be effective in HCV genotypes 4, 5, 6, common World wide</td>
<td></td>
</tr>
</tbody>
</table>


Virologic Principles

Direct Acting Agents
Hepatitis C
Life Cycle Of HIV, HBV, HCV: Pro-viral Reservoir
HCV is curable

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Cell Genome</td>
<td>PROVIRUS (DNA)</td>
<td>cccDNA</td>
<td>NONE</td>
</tr>
<tr>
<td>Viron RNA Polymerase</td>
<td>&quot;Viral / Host&quot;</td>
<td>Viral / Host / Viral</td>
<td>HCV NS5B</td>
</tr>
<tr>
<td>Error Prone Replication</td>
<td>Viral / Host factors</td>
<td>Viral / Host factors</td>
<td>Viral / Host Factors</td>
</tr>
<tr>
<td>&quot;Plasticity of Genome&quot;</td>
<td>High</td>
<td>Constrained</td>
<td>Very High: Quasispecies</td>
</tr>
<tr>
<td>Recombination</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
</tbody>
</table>


Hepatitis C
Treatment
HBV HIV and HCV have targeted drugs approved or in development

HIV
- Protease
- Co-Receptor
- Integrase

HBV
- RT (Nucleoside/Nucleotide)

HCV
- NS3-4A Protease
- NS4B
- NS5A
- NS5B (Nucleos(t)ide)
- Non-nucleoside: Multiple classes
- Cyclophilin
- mir-122
- Entry

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Hepatitis C

Treatment

Unlike HIV and HBV; HCV is curable

<table>
<thead>
<tr>
<th>Virus</th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Mutation Rate</td>
<td>Very High</td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Virions Produced Daily</td>
<td>(10^{10})</td>
<td>(10^{13})</td>
<td>(10^{12})</td>
</tr>
<tr>
<td>Long-lived proviral reservoir</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Viral Targets of Therapy</td>
<td>Multiple</td>
<td>One</td>
<td>Multiple</td>
</tr>
<tr>
<td>Cure With Current Therapy</td>
<td>No Integrated Viral DNA</td>
<td>NO (cccDNA)</td>
<td>YES</td>
</tr>
<tr>
<td>Current Therapeutic Goals</td>
<td>Lifelong suppression</td>
<td>Lifelong suppression</td>
<td>Cure or eradication of HCV Infection</td>
</tr>
</tbody>
</table>

Adapted from sorano V. JAC 2008;62(1):1-4 www.hivforum.org

http://www.idsociety.org/uploadedFiles/IDSA/Hepatitis_C/For_IDSA_Members/HCV%20drug%20resist%202012%20Forum%20for%20Collab%20HIV.pdf

Hepatitis C

Treatment

Genomic Organization Of Hepatitis C polyprotein / Anti-viral targets

Upon infection and Within the Infected Hepatic Cell:
The HCV genome (~9,000 nucleotides) is translated in a single polypeptide of 3,000 amino acids. Then the polypeptide is cleaved to produce ten proteins:

- **Capsid**
  - Core
  - E1
  - E2
  - p7

- **Envelope**
  - NS2
  - NS3
  - NS4A
  - NS4B

- **Protease**
  - NS5A
  - NS5B

**NS3/4A Protease Inhibitors**
- High Potency

**NS5A Inhibitors**
- High Potency
- "Direct"

- **Non-NUC NS5B Inhibitors**
  - NUC NS5B Inhibitors
  - Intermediate Potency
  - "Direct"

*Phosphoprotein plays a key role in Hepatitis C virus RNA replication*

*HCV structure* by Graham Colm at en.wikipedia.
Hepatitis C

Treatment

HCV Drug Classification and Development Phase

<table>
<thead>
<tr>
<th>NS5B Inhibitors (Nucleos/tides)</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sofosbuvir</td>
<td>3</td>
</tr>
<tr>
<td>Maritabine (RG-7128)</td>
<td>2</td>
</tr>
<tr>
<td>VX-135</td>
<td>2</td>
</tr>
<tr>
<td>IDX184</td>
<td>2 (Hold)</td>
</tr>
<tr>
<td>GS-5938</td>
<td>2 (Hold)</td>
</tr>
<tr>
<td>GS-8620</td>
<td>1</td>
</tr>
<tr>
<td>TMC-649128</td>
<td>1</td>
</tr>
<tr>
<td>NS5B Inhibitors (Non Nuc) Phase</td>
<td></td>
</tr>
<tr>
<td>Deleobuvir (BI207127)</td>
<td>3</td>
</tr>
<tr>
<td>Aft-333</td>
<td>3</td>
</tr>
<tr>
<td>Cetrobuvir (ANA598)</td>
<td>2b</td>
</tr>
<tr>
<td>Telaprevir (GS-5190)</td>
<td>2</td>
</tr>
<tr>
<td>Filobuvir (PF688554)</td>
<td>2</td>
</tr>
<tr>
<td>Aft-672</td>
<td>2</td>
</tr>
<tr>
<td>VX-222</td>
<td>2</td>
</tr>
<tr>
<td>BMS-791325</td>
<td>2a</td>
</tr>
<tr>
<td>TMC647065</td>
<td>2</td>
</tr>
<tr>
<td>VCH-759</td>
<td>2</td>
</tr>
<tr>
<td>GS-9669</td>
<td>3</td>
</tr>
<tr>
<td><strong>NS3/4A Protease Inhibitors</strong></td>
<td>Phase</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Approved</td>
</tr>
<tr>
<td>Bosaprevir</td>
<td>Approved</td>
</tr>
<tr>
<td>Simeprevir (TMC435)</td>
<td>3</td>
</tr>
<tr>
<td>Faldaprevir</td>
<td>3</td>
</tr>
<tr>
<td>Asunaprevir (BMS-650032)</td>
<td>3</td>
</tr>
<tr>
<td>Vaniprevir (MK-7909)</td>
<td>3</td>
</tr>
<tr>
<td>Abt-455/rv</td>
<td>3</td>
</tr>
<tr>
<td>GS-9256</td>
<td>2b</td>
</tr>
<tr>
<td>GS-9461</td>
<td>2</td>
</tr>
<tr>
<td>Danoprevir (RG7227)</td>
<td>2</td>
</tr>
<tr>
<td>Sovaprevir (ACH-1625)</td>
<td>2</td>
</tr>
<tr>
<td>MK-5172</td>
<td>2</td>
</tr>
<tr>
<td>ACH-2684</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Non-NUC NS5B Inhibitors</strong></td>
<td>Phase</td>
</tr>
<tr>
<td>Daclatasvir (BMS-790052)</td>
<td>3</td>
</tr>
<tr>
<td>ABT-450/rv</td>
<td>3</td>
</tr>
<tr>
<td>Ledipasvir (GS-5885)</td>
<td>3</td>
</tr>
<tr>
<td>GS-2366805</td>
<td>2</td>
</tr>
<tr>
<td>ACH-3102</td>
<td>2a</td>
</tr>
<tr>
<td>ACH-2928</td>
<td>1b</td>
</tr>
<tr>
<td>PPL-461</td>
<td>1b</td>
</tr>
<tr>
<td><strong>Host-targeting antivirals</strong></td>
<td>Phase</td>
</tr>
<tr>
<td>AK-542</td>
<td>3 (Hold)</td>
</tr>
<tr>
<td>SCY-646 (Cyclophilin)</td>
<td>2</td>
</tr>
<tr>
<td>ANA773 (TLR-7)</td>
<td>1</td>
</tr>
</tbody>
</table>

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Hepatitis C Treatment

Introduction

Direct acting agents Issues and factors

- Lack of data in the “so-called” more difficult to treat “real-life patients”
- Previous non-response to IFN-based therapies and cirrhosis.
- Comorbidities: Renal impairment.
  - Liver Transplant
  - Co-infection: HIV and or Hepatitis B
  - Compensated vs. Non-compensated Liver disease
- Future role of ribavirin and or Interferon
- How short could HCV treatment duration possibly become?
Hepatitis C

Treatment

Classes of Direct Acting Agents ("DAAs")

Four classes of DAAs, which are defined by their mechanism of action and therapeutic target

<table>
<thead>
<tr>
<th>Class of Direct Acting Agent</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Non-structural Proteins</td>
<td>3/4A (NS3/4A)</td>
</tr>
<tr>
<td>❖ Protease Inhibitors (&quot;PI&quot;)</td>
<td>NS3 NS4A</td>
</tr>
<tr>
<td>❖ RNA Polymerase Inhibitors:</td>
<td></td>
</tr>
<tr>
<td>❖ Nucleoside Polymerase Inhibitors (NPI)</td>
<td></td>
</tr>
<tr>
<td>❖ Non-Nucleoside Polymerase Inhibitors (NNPI)</td>
<td>NS5B</td>
</tr>
<tr>
<td>❖ NS5A Inhibitors</td>
<td>Phosphoprotein plays a key role in Hepatitis C virus RNA replication</td>
</tr>
</tbody>
</table>


Hepatitis C

Treatment

Direct Acting Agents Initial treatment Genotype 1a

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ledipasvir (90 mg)</td>
<td>HARVONI ®</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Sofosbuvir (400 mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paritaprevir (150 mg)</td>
<td>VIEKIRA PAK ®</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Ritonavir (100mg mg)</td>
<td></td>
<td>No Cirrhosis</td>
</tr>
<tr>
<td>Ombitasvir (25 mg)</td>
<td></td>
<td>24 weeks</td>
</tr>
<tr>
<td>Dasabuvir (250 mg)</td>
<td></td>
<td>+ Cirrhosis</td>
</tr>
<tr>
<td>+ RIBIVIRIN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir (400 mg)</td>
<td>Sovaldi ®</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Simeprevir (150 mg)</td>
<td>Olysio ®</td>
<td>No Cirrhosis</td>
</tr>
<tr>
<td>+ RIBIVIRIN</td>
<td></td>
<td>24 weeks + Cirrhosis</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Protease Inhibitors</td>
<td>Victris ®</td>
<td>28 weeks*</td>
</tr>
<tr>
<td>Boceprevir (800mg TID)</td>
<td>Incivek ®</td>
<td>24-36 weeks*</td>
</tr>
<tr>
<td>Teleprevir (1125mg BID)</td>
<td></td>
<td>* Cycled with peg-INF and Ribivirin: See prescribing information</td>
</tr>
<tr>
<td>With : peg-INF and Ribivirin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HEPATITIS Treatment
Phase 3 Trials of **Interferon-free regimens** for the Treatment of Hepatitis C

### Trial Name | Drug | Patient Status HEC C: | Number | SVR Overall: Response | SVR 1 Genotype |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ION-1</td>
<td></td>
<td>LDV-SOF (12-24 wks)</td>
<td>Untreated</td>
<td>865 (99%)</td>
<td>1a: 97-99% 1b: 97-100%</td>
</tr>
<tr>
<td>ION 2</td>
<td></td>
<td>LDV-SOF (12-24 wks)</td>
<td>Treated</td>
<td>440 (94-99%)</td>
<td>1a: 94-99% 1b: 87-100%</td>
</tr>
<tr>
<td>ION-3</td>
<td></td>
<td>LDV-SOF (8-12 wks)</td>
<td>Untreated</td>
<td>647 (93-95%)</td>
<td>1a: 93-95% 1b: 95-98%</td>
</tr>
<tr>
<td>SAPPHIRE I</td>
<td></td>
<td></td>
<td>AOD (12 wks)</td>
<td>394 (96%)</td>
<td>1a: 95% 1b: 98%*</td>
</tr>
<tr>
<td>SAPPHIRE II</td>
<td></td>
<td></td>
<td>AOD (12 wks)</td>
<td>384 (96%)</td>
<td>1a: 96% 1b: 97%</td>
</tr>
<tr>
<td>PEARL III</td>
<td></td>
<td>AOD</td>
<td>Treated</td>
<td>319</td>
<td>1b: 100%</td>
</tr>
<tr>
<td>PEARL IV</td>
<td></td>
<td>AOD</td>
<td>Untreated</td>
<td>305</td>
<td>1a: 99%</td>
</tr>
<tr>
<td>Turquoise II</td>
<td></td>
<td></td>
<td>AOD</td>
<td>390 (92-96%)</td>
<td>1a: 12wk 92% 1b: 24wk 96%</td>
</tr>
<tr>
<td>HALLMARK DUAL</td>
<td></td>
<td>DCV and ACV</td>
<td>Treated</td>
<td>737</td>
<td>1b: 82-90%</td>
</tr>
</tbody>
</table>

LDV- SOF : Ledopasvir – Sofosbuvir  
“AOD” : ABT 450/ritonavir Ombitasvir I Dasabuvir  
DCV and ASV : Daclatasvir Asunaprevir  
SRV= Sustained Viral Response  

---

HEPATITIS Treatment
Phase 3 Trials of **Interferon-free regimens** for the Treatment of Hepatitis C

### HEPATITIS GENOTYPES 2 & 3

### Trial Name | Drug | Patient Status HEC C: | Number | SVR Overall: Response | SVR 1 Genotype |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FISSION</td>
<td></td>
<td>SOF- RBV 12 wk PEG-RBV 24 wk</td>
<td>Untreated</td>
<td>256: 67% 243: 67 %</td>
<td>G2 : 97% G3 : 56%</td>
</tr>
<tr>
<td>POSITRON</td>
<td></td>
<td>SOF-RBV 12 Wk Placebo</td>
<td>Untreated</td>
<td>207: 78% 71: 0</td>
<td>G2 : 93% G3 : 61%</td>
</tr>
<tr>
<td>FUSION</td>
<td></td>
<td>SOF-RBV 12 wk SOF-RBV 16 wk</td>
<td>TREATED</td>
<td>103: 50% 96: 73%</td>
<td>G2: 86% G3: 30% G2: 94% G3: 62%</td>
</tr>
<tr>
<td>VALENCE</td>
<td></td>
<td>SOF-RBV 12 wk SOF-RBV 24 wk</td>
<td>TREATED Untreated</td>
<td>84 250</td>
<td>85%</td>
</tr>
</tbody>
</table>

SOF-RBV : Sofosbuvir - Ribavirin  
SRV= Sustained Viral Response  
DEFINING TREATMENT

Direct Acting No Peg Vs. Direct Acting - PEG regimens

Special Considerations
- Age greater than 65 years
- Racial Difference
- Treatment Experienced Cirrhotic patients
- Decompensated Liver Disease
- Shortest Treatment Duration

Hepatitis C

HCV-TARGET Data*: Genotype 1
AGE > 65 years


*Crude SVR data
Non-Randomized/Non Comparable
Hepatitis C

HCV-TARGET Data*: (Response Race Difference)

Genotype 1  Black

Hepatitis C: Cirrhosis Vs Non-Cirrhosis
SVR12 for Treatment Experienced, Genotypes1, Cirrhotic Status

SOF = sofosbuvir
SMV = simeprevir


*Crude SVR data
Non-Randomized/Non-Comparable

Dieterich D, Bacon B, Flamm S, Kowdley K et al Evaluation of sofosbuvir and simeprevir-based regimens in the TRIO network - Academic and community treatment of a real-world, heterogeneous population. Annual Meeting of the American Association for the Study of Liver Diseases Boston, MA Nov 7-11 2014
Hepatitis C Treatment

Decompensated Liver Disease

SVR 12 By CTP Class

Child-Turcotte-Pugh

<table>
<thead>
<tr>
<th>CTP</th>
<th>One year Survival</th>
<th>Two year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>B</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>C</td>
<td>45%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Patient Factoids
- 28 patients Baseline MELD score > 15.
- 28 patients (26%) treatment-emergent serious adverse events (SAEs)
  - 96% CTP C: Ascites
  - 88% CTP C: Encephalopathy
- 3 Patients CTP B: liver transplantation (1 Died)
- 7 patients CTP C:
  - 2 Underwent liver transplantation,
  - 3 Discontinued due to adverse events,
  - 2 Died.

Hepatitis C Treatment in Compensated Cirrhosis

Study Meta-analyses in compensated cirrhosis (LONESTAR, ELECTRON, ELECTRON-2, ION-1, ION-2, SIRIUS).

<table>
<thead>
<tr>
<th>Clinical Factoid</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis diagnosed by biopsy of fibroscan*</td>
<td>91%</td>
</tr>
<tr>
<td>Treatment experienced (Majority)</td>
<td>69%</td>
</tr>
<tr>
<td>Males</td>
<td>67%</td>
</tr>
<tr>
<td>Genotype 1a</td>
<td>60%</td>
</tr>
<tr>
<td>IL28B non-CC</td>
<td>79%</td>
</tr>
<tr>
<td>(Experienced) Previous protease inhibitor</td>
<td>67%</td>
</tr>
<tr>
<td>Platelet &lt;90,000/uL</td>
<td>18%</td>
</tr>
<tr>
<td>Albumin &lt;3.5g/dL</td>
<td>11%</td>
</tr>
</tbody>
</table>

LDV= Ledipasvir
SOF= Sofosbuvir
RBV= Ribavirin

Six studies

12 WEEKS Vs. 24 Weeks

Bourliere M et al.: An Integrated Safety and Efficacy Analysis of >500 Patients with Compensated Cirrhosis Treated with Ledipasvir/Sofosbuvir with or without Ribavirin. 65th Annual Meeting of the American Association for the Study of Liver diseases, November 7-11, 2014, Boston, USA; abstract 82.
ION-3
Ledispavir + Sofosbuvir + Ribavirin
HCV G1 Treatment Naïve
Non-cirrhotic: 8 weeks Vs 12 weeks

SOF = Sofosbuvir
LDV = Ledispavir

SVR12 (%)

<table>
<thead>
<tr>
<th></th>
<th>8 WEEKS</th>
<th>12 WEEKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOF / LDV</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>202/205</td>
<td>206/216</td>
<td></td>
</tr>
<tr>
<td>SOF / LDV + RBV</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>201/216</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Symposium during the 65th American Association for the Study of Liver Diseases (AASLD) Annual Meeting on November 10, 2014, in Boston, Massachusetts.

“In summary, IFN-free combination therapy in real-life cohorts has demonstrated high HCV cure rates and good safety. However, ribavirin and longer treatment durations still seem to play a role at least in the more challenging cirrhotic previous treatment non-responders”.

- Jurgen K. Rockstroh M.D

Feedback from the real-world: do HCV cure rates in real-life patient cohorts hold what clinical trials promised? Summary from AASLD 2014 for Hepatitis C Boston 7-11 November 2014 Jurgen K. Rockstroh M.D., Professor of Medicine University of Bonn, German
http://www.natap.org/2014/AASLD/AASLD_93.htm
Conclusions

- No more Interferon for Genotype 1 (Still a selected role for Ribavirin)
- Possible role for INF as "placeholder" for Genotype 3:
  (Pending New DAAs to place into combination regimens
- Full disclosure to patients: (Risk of resistance)

- Important Considerations for treatment:
  - Correct regimen for patients genotype or subtype
  - Appropriate duration of therapy (or unnecessarily prolonged)
  - Need to assess degree of Hepatic fibrosis pre-treatment
  - Education: Re: importance of medication compliance
  - Attention to drug-drug interactions
  - Monitoring during and after treatment (Especially patients with advanced fibrosis)

Recommendations

(AASLD HCV Treatment Recommendations for Treatment-
Naive Patients)
### AASLD HCV Treatment Recommendations for Treatment-Naive Patients

#### Genotype 1a
- **AGENT**: Harvoni®
- **Duration**: 12 Weeks
- **Olysio® + Solvaldi®**
  - 12 Weeks: No Cirrhosis
  - 24 Weeks: + Cirrhosis
- **Viekira Pak® + Ribavirin**
  - 12 Weeks: No Cirrhosis
  - 24 Weeks: No Cirrhosis

#### Genotype 1b
- **AGENT**: Harvoni
- **Duration**: 12 Weeks
- **Olysio® + Solvaldi®**
  - 12 Weeks: No Cirrhosis
  - 24 Weeks: + Cirrhosis
- **Viekira Pak® + Ribavirin**
  - 12 Weeks: No Cirrhosis
  - 24 Weeks: No Cirrhosis

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8 weeks may be considered in patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.

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http://www.hepmag.com/articles/2512_18756.shtml
## Hepatitis C

### Treatment

Controversies.....

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### Hepatitis C

**Treatment: Protease Inhibitors**

#### Treatment costs

<table>
<thead>
<tr>
<th>Drug combination</th>
<th>Estimated cost</th>
<th>Factoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peg Interferon/Ribavirin</td>
<td>$18,000 – $36,000</td>
<td>$500 Peg interferon /week $100 Ribavirin /week</td>
</tr>
<tr>
<td>Peg Interferon / Ribavirin</td>
<td>$48,000 - $85,000</td>
<td>$1,100 /week more</td>
</tr>
<tr>
<td>With either: Telaprevir or Boceprevir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver transplant</td>
<td>Estimated First-Year Charge: $314,600</td>
<td>Annual Follow-up Charge: $21,900</td>
</tr>
</tbody>
</table>

---

# Hepatitis C

## Drugs and Costs

Prescription medication approved by the FDA and their estimated non-generic **WEEKLY COST**

<table>
<thead>
<tr>
<th>Drug (Brand Name)</th>
<th>Class</th>
<th>Manufacturer</th>
<th>Cost (week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boceprevir (Victrelis®)</td>
<td>Protease</td>
<td>Merck</td>
<td>$1,100 *</td>
</tr>
<tr>
<td>Ledipasvir-Sofosbuvir (Harvoni®)</td>
<td>Direct acting</td>
<td>Gilead Sciences</td>
<td>$7,875</td>
</tr>
<tr>
<td>Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (Viekira Pak)</td>
<td>Direct Acting</td>
<td>AbbVie</td>
<td>$6,943</td>
</tr>
<tr>
<td>Peginterferon alfa-2a (Pegasys®)</td>
<td>Immune mod</td>
<td>Genentech (Roche)</td>
<td>$770</td>
</tr>
<tr>
<td>Peginterferon alfa-2b (PegIntron®)</td>
<td>Immune Mod</td>
<td>Schering (Merck)</td>
<td>$700</td>
</tr>
<tr>
<td>Ribavirin (Copegus®, Rebetol®, Ribasphere®)</td>
<td>Neucleoside</td>
<td>Various Companies</td>
<td>Varies **</td>
</tr>
<tr>
<td>Simeprevir (Olysio®)</td>
<td>Protease</td>
<td>Janssen (Johnson &amp; Johnson)</td>
<td>$5,530</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi®)</td>
<td>Direct acting</td>
<td>Gilead Science</td>
<td>$7,000</td>
</tr>
</tbody>
</table>

* Boceprevir cost does not include drugs needed to take in combination;
**Ribavirin prices varied based on dosing but generics can range from $45 to $70 per week.


## Hepatitis C

### Drugs and Treatment:

....“it will contain two drugs, one of which is already available at $1,000 per dose, or $84,000 for a complete 12-week course. The dual-drug combination will likely cost even more”....

....“if every patient in California with advanced liver damage (Hepatitis C) were treated, the cost would be $6.3 billion”....

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### Hepatitis C Drugs and Treatment

**Issues:**

<table>
<thead>
<tr>
<th>Experts nearly all agreed that for cost and medical reasons, not every patient with hepatitis C needs to be immediately treated with the new drugs. (~3 million Americans Infected)</th>
<th>“I can’t imagine how that would be feasible without bankrupting our system,” - Rena K. Fox, professor of medicine at the University of California, San Francisco</th>
</tr>
</thead>
<tbody>
<tr>
<td>We don’t have the ability to change the (Drug) price, we have to decide which patients are the most urgent.</td>
<td>Drug makers defend the prices citing research costs and saying the pills are curative for many patients, thus avoiding costly complications like transplants.</td>
</tr>
<tr>
<td>Waiting might be a better answer for some patients – particularly those with little or no liver damage</td>
<td>Additional treatments are expected Patients with more advanced liver damage from the virus would be treated first.</td>
</tr>
</tbody>
</table>

**Consideration/Debate:**

- **But patients may not want to wait**
  - Ryan Clary, Executive director of the National Viral Hepatitis Roundtable, (a consumer group partially funded by the drug industry).
  - Televisio
den advertisements sponsored by Gilead are encouraging people to be screened for hepatitis and to talk with their doctors about new treatment options.
Treatment

References and organizations

HCV - TARGET: Hepatitis C Therapeutic Registry and Research Network.
http://www.hcvtarget.org
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http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm

• American Association For the Study of Liver Disease / Infectious Disease Society of America. Recommendations for Testing, Managing, and Treating Hepatitis C http://hcvguidelines.org/
Hepatitis C

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Direct Acting Agents- “DAA”- (Antiviral agents)


Hepatitis C

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- Wapner J. We Now Have the Cure for Hepatitis C, but Can We Afford It? Health- Scientific American Volume 331,#3 August 14, 2014 http://www.scientificamerican.com/article/we-now-have-the-cure-for-hepatitis-c-but-can-we-afford-it/ (Accessed 1/15/2015)