

Hepatitis C Introduction and Overview

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Learning Objectives

After attending this presentation, learners will be able to:

- List the genotypes of HCV and how they relate to treatment effects
- Stage HCV infection and describe why it is important to accurately stage
- Recall the clinical presentation of advanced liver disease (cirrhosis)
- Describe emerging treatments of HCV and how the changing landscape will impact treatment decisions in the near future
- List the new changes to the HCV Guidelines (Sept 2018)

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ARS Question #1: Which test most accurately stage liver fibrosis?

1. Fibroscan
2. Fibrosure
3. APRI
4. Liver biopsy
5. Liver percussion

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ARS Question #2: What percent of persons with chronic HCV infection develop cirrhosis over 30 years?

1. 0 – 5%
2. 5% – 20%
3. 20% – 50%
4. 50% – 75%
5. >75%

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ARS Question #3: What is the most common genotype of HCV in the United States?

1. Genotype 1
2. Genotype 2
3. Genotype 3
4. Genotype 4
5. Genotype 5–6

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Objectives

- Epidemiology
- Natural History
- Staging
- Genome and Drug Targets
- Viral Kinetics With Therapy
- Current Treatments
- What Does SVR Really Mean?

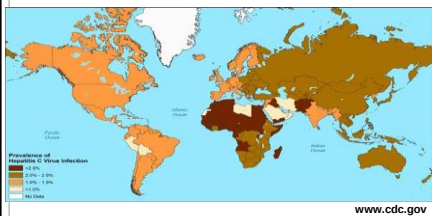
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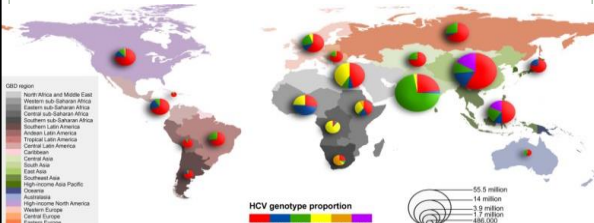
HCV Worldwide



- 170 million infected
- Highest Asia & Africa
- Egypt > 15%
- USA 1.6%
 - 3-4 million infected

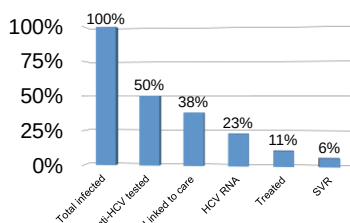
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Worldwide prevalence of each HCV genotype by GBD



HCV genotype 1 (83.4 million cases; 46.2%) - one-third of which are in East Asia.
 Genotype 3 (54.3 million; 30.1%); genotypes 2, 4, and 6 (22.8%); genotype 5 <1%.
 While genotypes 1 and 3 dominate in most countries irrespective of economic
 status, largest proportions of genotypes 4 and 5 are in lower-income countries.

The Treatment Cascade of HCV infection in the US: ~3 – 4 million persons infected

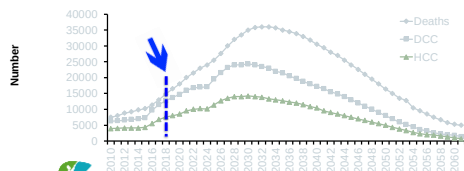


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Adapted from Holmberg et al. NEJM 2013

Future Burden of Hepatitis C Related Morbidity and Mortality in the US

- Markov model of health outcomes
 - Of 2.7 M HCV infected persons in primary care
 - 1.47 M will develop cirrhosis
 - 350,000 will develop liver cancer
 - 897,000 will die from HCV-related complications



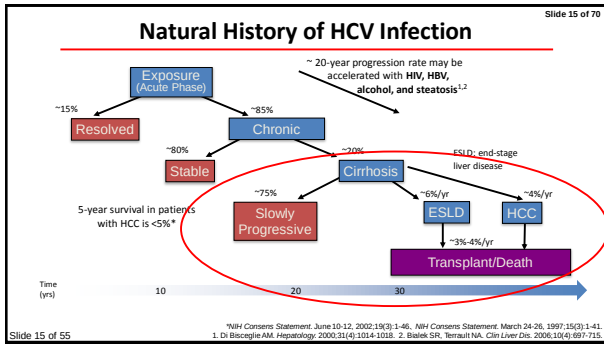
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Rain D., et al. Dig Liver Dis 2010

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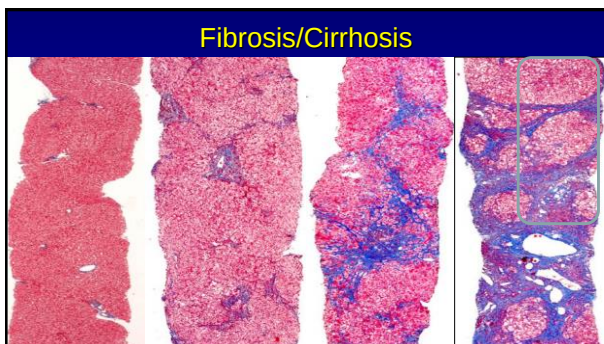
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FIB-4

- Uses easily acquired information
 - Age
 - Platelet Count
 - AST
 - ALT
- Formula

$$\frac{\text{AGE} \times \text{AST}}{\text{PLT} \times \sqrt{\text{ALT}}}$$
- Interpretation: <1.45 is F0/1 or >3.25 is F3/4 with 65% Positive Predictive value

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Sterling RK et al. HEPATOLOGY 2006

APRI

- Uses easily acquired information
 - Platelet Count / AST
- Formula

$$\frac{\frac{\text{AST (IU/L)}}{\text{AST (ULN) (IU/L)}}}{\text{Platelet Count (10}^9\text{/L)}}$$
- Interpretation:
 - < 0.5 ~ F0/1
 - >1.05 ~ F3/4

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Transient Elastography (Fibroscan)

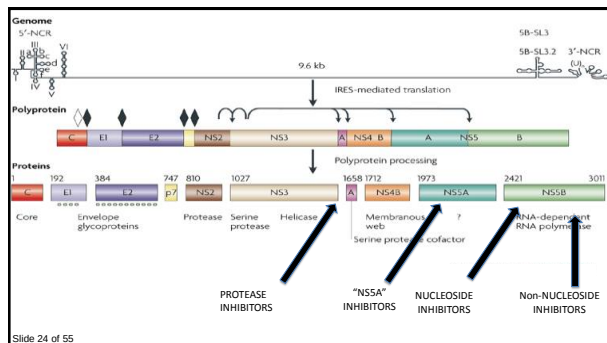


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Suffixes Matter!

- --- PREVIR (Protease / NS3-4a)
- --- ASVIR (NS5a)
- --- BUVIR (NS5b)

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Agents and Regimens: Fall 2017

	Antiviral			
	NS3	N5SA	Non-Nuc NS5B	Nuc NS5B
Ledipasvir/sofosbuvir FDC		○		○
Paritaprevir/r/ombitasvir FDC + dasabuvir	○	○	○	
Simeprevir + sofosbuvir	○			○
Glecaprevir / pibrentasvir FDC	○	○		
Sofosbuvir + daclatasvir		○		○
Elbasvir/grazoprevir FDC	○	○		
Velpatasvir/sofosbuvir FDC		○		○
Velpat/ Sof / voxilaprevir FDC	○	○		○

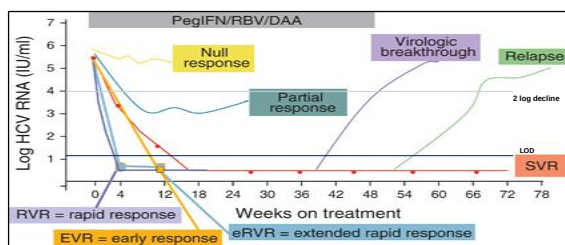
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On Treatment Viral Kinetics



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Antiviral HCV treatments (FDA-approved as of September, 2017)

Monotherapies

IFN-2a
IFN-2b
PEG-IFN 2a
PEG-IFN 2b

IFN-2a + Ribavirin
IFN-2b + Ribavirin
PEG-IFN 2a + Ribavirin*
PEG-IFN 2b + Ribavirin

PEG-IFN + ribavirin plus either:
Boceprevir (GT1)
Telaprevir (GT1)
Simeprevir (GT1)

In combination with other agents:
Sofosbuvir

Combination Therapies

Elbasvir + Grazoprevir
(GT 1, 4)

Ledipasvir + Sofosbuvir
(FDC, GT1,4,5,6)

Daclatasvir + Sofosbuvir
(GT1,3)^{4b}

Simeprevir + Sofosbuvir (GT1)

Paritaprevir / ritonavir / ombitasvir
(FDC) + dasabuvir (GT1)

Paritaprevir / ritonavir / ombitasvir
(FDC) (GT4)

Pangenotypic Regimens (GT 1 – 6)

Velpatasvir / Sofosbuvir FDC

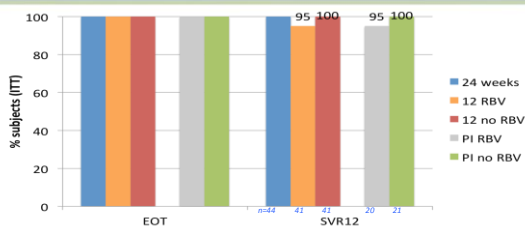
Voxilaprevir / Velpatasvir /

Sofosbuvir FDC

Glecaprevir / Pibrentasvir FDC

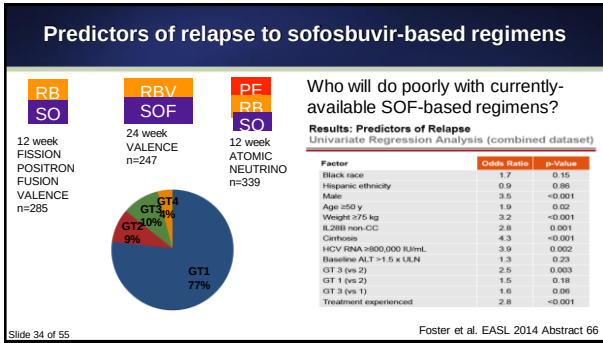
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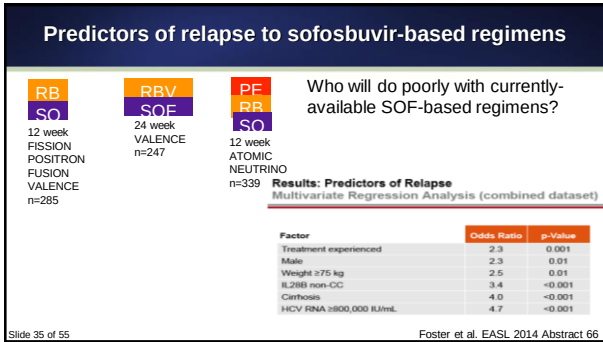
Sofosbuvir plus Daclatasvir for GT1



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Predictors of relapse to sofosbuvir-based regimens

**RB
SO**

12 week
FISION
POSITRON
FUSION
VALENCE
n=285

**RRV
SOF**

24 week
VALENCE
n=247

**PF
RR
SO**

12 week
ATOMIC
NEUTRINO
n=339

Who will do poorly with currently-available SOF-based regimens?

Six factors associated with relapse:
 Treatment-experienced
 IL28B non-CC
 Male sex
 Weight > 75 kg
 Cirrhosis
 High viral load >800,000 IU/mL

SVR12 Rates by Number of Negative Predictors
 Derived From Multivariate Analysis (combined dataset)

Number of Negative Predictors	SVR12 (%)
0	100
1	100
2	99
3	94
4	88
5	68
6	57

Foster et al. EASL 2014 Abstract 66

Updated Guidelines

<https://www.hcvguidelines.org>

AASLD HCV Guidance Recommendations for Testing, Managing, and Treating Hepatitis C

Start Here: Choose a patient profile from the menu above.

Welcome to HCVGuidelines.org

The AASLD and EASL in partnership with the panel have created an updated web experience to facilitate easier and faster access to this important resource. Please select a patient profile from the menu above, click on a Guidance section below, or use the search box to begin.

- Contents and Introduction - Select a Page
- Testing, Evaluation, and Monitoring of Hepatitis C - Review Topics
- Initial Treatment of HCV Infection - Choose Patient Genotype
- Retreatment of Persons in Whom Prior Therapy Has Failed - Choose Patient Genotype
- Management of Unique Populations - Review Recommendations

Recent Announcements

21 What's New, Updates, and Changes to the Guidance

This version of the guidance has been updated to reflect several important developments.

ARS Question #4:

Which of the following statements is true of FDA approval of glecaprevir/pibrentasvir?

1. It is an 8 week regimen only in patients without cirrhosis
2. It is a 12 week regimen regardless of presence of cirrhosis
3. It is an 8 week regimen only in treatment naïve patients
4. It is a 16 week regimen in patients with prior treatment experience to DAA
5. It is a single daily dosed pill

ARS Question #5:

Which of the following statements is true of FDA approval of sofosbuvir/velpatasvir/voxilaprevir?

1. It is an 8 week regimen only in patients without cirrhosis
2. It is a 12 week regimen regardless of presence of cirrhosis
3. It is an 8 week regimen regardless of prior treatment experience to DAA
4. It is approved for all genotypes across all DAA failures

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Does Failure = Resistance?

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Broad Cross-Resistance With "Early Generation" NS5As

Fold Change	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V	Y93H/N
Ledipasvir	20x	> 100x	> 100x/ > 100x	> 1000x/ > 10,000		> 100x/—
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x/ > 10,000x	< 10x	20x/50x
Daclatasvir	> 100x	> 1000x	> 100x/ > 1000x	> 1000x/ > 10,000x	< 10x	20x/50x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x/ > 1000x	< 10x	> 100x/—
Velpatasvir	< 10x	< 3x	20x/50x	> 100x/ > 1000x	< 3x	< 3x/—
Pibrentasvir	< 3x	< 3x	< 3x	< 10x/< 10x	< 3x	< 3x/< 3x
Ruzasvir	< 10x	< 10x	< 10x	< 10x	< 10x	< 10x

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Question-and-Answer

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