Hepatitis C Treatment in 2016

Amanda Noska, MD, MPH
Providence VAMC & The Miriam Hospital & Immunology Center
Brown University

Disclosures

- I have no financial disclosures.

Learning Objectives

- Discuss the epidemiology and immunology of hepatitis C in the United States.
- Discuss the importance of prior treatment history and liver staging in determining a HCV treatment regimen.
- Discuss current available hepatitis C treatment options.
- Describe common side effects and drug-drug interactions of directly-acting antiviral medications for HCV.
- Describe immunizations related to various types of hepatitis.

Multiple Choice

1. What is the most common barrier to patients accessing hepatitis C treatment currently?
   a) Unstable mental health disorders
   b) Insurance coverage
   c) Drug-drug interactions
   d) A life-expectancy of <1 year

Multiple Choice

2. Which of the following drugs interacts with Ledipasvir/sofosbuvir to decrease serum levels of ledipasvir?
   a) Methadone
   b) Levothyroxine
   c) Levetiracetam
   d) Omeprazole

Multiple Choice

3. Based on the ION trials, which of the following patients might be a candidate for 8 weeks of ledipasvir/sofosbuvir?
   a) GT 1a, treatment naïve, non-cirrhotic, HCV viral load 4 million
   b) GT 3, treatment naïve, non-cirrhotic, HCV viral load 3 million
   c) GT 1b, treatment naive, cirrhotic, HCV VL 2 million
   d) GT 4, treatment naïve, non-cirrhotic, HCV viral load 6 million

Multiple Choice

4. Which of the following is among the most common noted side effect of daclatasvir?

a) Nausea
b) Fatigue
c) Skin rash
d) diarrhea

Multiple Choice

5. Which of the following measures are important to preventing morbidity associated with chronic hepatitis C?

a) Weekly lab monitoring
b) Vaccination against hepatitis B alone
c) Vaccination against hepatitis A and B
d) Avoidance of all medications metabolized by the liver

Hepatitis C

First described in 1989, Blood screening began in 1990.

Peak prevalence occurs in those born 1945-1965.

Worldwide 350,000-500,000 people die annually from HCV related causes.

Cirrhosis develops in 10-20% of patients with chronic HCV infection over 20-30 years on average, although rates vary widely (from 2% to 51%).

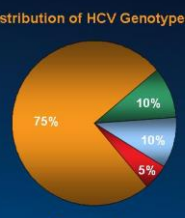
After cirrhosis due to HCV has developed, the *annual* risk of developing HCC is 1-5%.

AASLD. 2015.
Westbrook R, J of Hepatology. 2014;61:558-68.
Grebely J et al. Hepatology.2014;59:109-120.
Alric L. Hepatology. 2014;60(6):Epub.

HCV Strains

- Hepatitis C virus
  - RNA virus–high mutation rates
  - Evolved different genotypes
- 6 known genotypes
  - Genotype 1 (75%)
  - Genotype 2 (10%)
  - Genotype 3 (10%)
- The above 3 are the most common in the United States
- Little difference in mode of transmission or natural history of infection among different genotypes

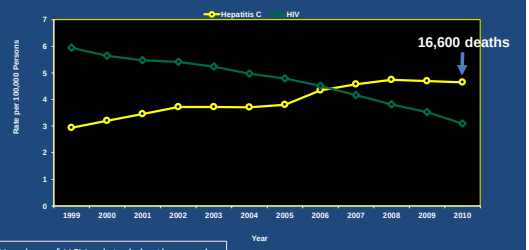
variable geographic distribution



Flamm SL. *JAMA*. 2003;289:2413-2417.

Slide courtesy of Dr. Lynn Taylor

Deaths Due to HCV Infections Now Exceed Those Due to HIV Infection



Number of HCV-related deaths may be over 60,000 because of under-reporting on death certificates

Ly KN, Xing J, Klevens RM, Jiles RB, Holmberg SD. Causes of death and characteristics of decedents with viral hepatitis, United States, 2010. *Clin Infect Dis.* 2014 Jan;58(1):40-9. Mahajan, IDSA 2013

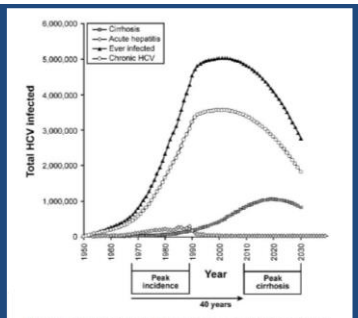
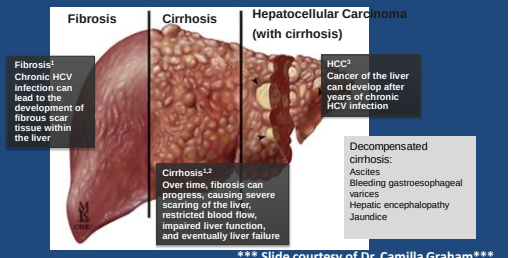


Figure 1. Estimates by year of prevalent cases ever infected (*top line*), with chronic hepatitis C (*open circles*), and cirrhosis (*solid squares*). Acute infections (*solid gray line*) peaked between 1970 and 1990. The peak of chronic hepatitis prevalence was 2001, while the highest prevalence of cirrhosis is projected to be between 2010 and 2030, about 40 years after the peak of acute infections.

Davis G. Gastroenterology. 2010;138:513–521

Chronic HCV Infection May Lead to Chronic Liver Disease and Liver Cancer



*** Slide courtesy of Dr. Camilla Graham***

Chronic liver disease includes fibrosis, cirrhosis, and hepatic decompensation; HCC=hepatocellular carcinoma.
1. Highleyman L. Hepatitis C Support Project. http://www.hcvadvocate.org/hepatitis/factsheets_pdf/Fibrosis.pdf. Accessed August 18, 2011.
2. Bataller R et al. *J Clin Invest.* 2005;115:209-218.
3. Medline Plus. http://www.nlm.nih.gov/medlineplus/ency.article/000280.htm. Accessed August 28, 2012; 4. Centers for Disease Control and Prevention. http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm. Accessed May 8, 2012.

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Distribution of Fibrosis Scores

- F0 = 15%
- F1 = 25%
- F2 = 20%
- F3 = 15%
- F4 = 25%

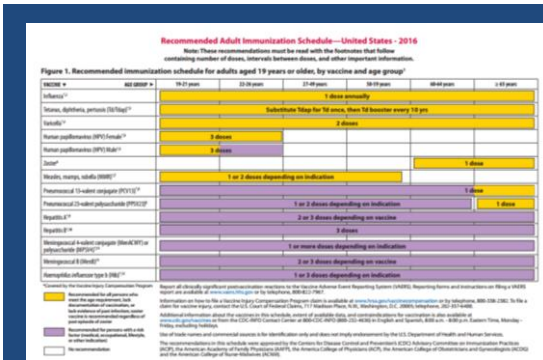
Recently infected and slow progressors

"Advanced fibrosis

- Limits of fibrosis tests:
  - Liver biopsies are +/- 1 fibrosis stage
  - Noninvasive tests are best at determining a high versus low probability of advanced fibrosis

*** Slide courtesy of Dr. Camilla Graham***

Immunizations


Recommended Adult Immunization Schedule—United States - 2016

Note: These recommendations must be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

Figure 1. Recommended immunization schedule for adults aged 19 years or older, by vaccine and age group[1]

VACCINE ▼ / AGE GROUP ▶	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥ 65 years
Influenza[2,3]	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap)[4]	Substitute Tdap for Td once, then Td booster every 10 yrs					
Varicella[5,6]	2 doses					
Human papillomavirus (HPV) Female[7,8]	3 doses					
Human papillomavirus (HPV) Male[7,8]	3 doses					
Zoster[9]					1 dose	
Measles, mumps, rubella (MMR)[10,11]	1 or 2 doses depending on indication					
Pneumococcal 13-valent conjugate (PCV13)[12]	1 dose					
Pneumococcal 23-valent polysaccharide (PPSV23)[13]	1 or 2 doses depending on indication					1 dose
Hepatitis A[14,15]	2 or 3 doses depending on vaccine					
Hepatitis B[16,17]	3 doses					
Meningococcal 4-valent conjugate (MenACWY) or polysaccharide (MPSV4)[18,19]	1 or more doses depending on indication					
Meningococcal B (MenB)[20,21]	2 or 3 doses depending on vaccine					
Haemophilus influenzae type b (Hib)[22,23]	1 or 3 doses depending on indication					

*Covered by the Vaccine Injury Compensation Program

Recommended for all persons who meet the age requirement, lack documentation of vaccination, or lack evidence of past infection, unless vaccine is recommended regardless of past episode of cancer

Recommended for persons with a risk factor (medical, occupational, lifestyle, or other indication)

No recommendation

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.

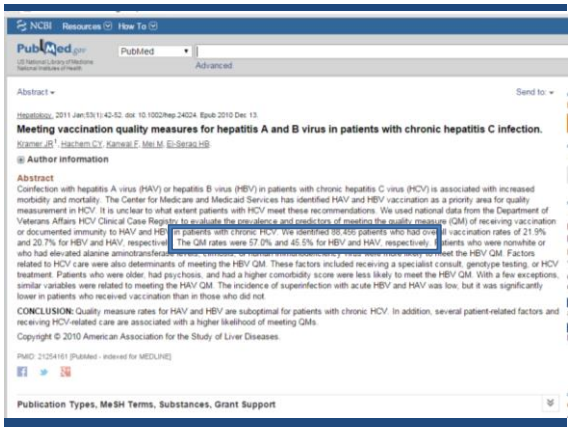
Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C., 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 8:00 a.m.–8:00 p.m. Eastern Time, Monday–Friday, excluding holidays.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the America College of Physicians (ACP), the American College of Obstetricians and Gynecologists (ACOG) and the American College of Nurse-Midwives (ACNM).

CDC and ACIP Vaccine Schedule: http://www.cdc.gov/vaccines/schedules/downloads/adult/adult-schedule.pdf


NCBI Resources How To

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Abstract
Send to:

Hepatology. 2011 Jan;53(1):42-52. doi: 10.1002/hep.24024. Epub 2010 Dec 13.

Meeting vaccination quality measures for hepatitis A and B virus in patients with chronic hepatitis C infection.

Kramer JR[1], Hachem CY, Kanwal F, Mei M, El-Serag HB

Author information

Abstract

Coinfection with hepatitis A virus (HAV) or hepatitis B virus (HBV) in patients with chronic hepatitis C virus (HCV) is associated with increased morbidity and mortality. The Center for Medicare and Medicaid Services has identified HAV and HBV vaccination as a priority area for quality measurement in HCV. It is unclear to what extent patients with HCV meet these recommendations. We used national data from the Department of Veterans Affairs HCV Clinical Case Registry to evaluate the prevalence and predictors of meeting the quality measure (QM) of receiving vaccination or documented immunity to HAV and HBV in patients with chronic HCV. We identified 88,456 patients who had overall vaccination rates of 21.9% and 20.7% for HBV and HAV, respectively. The QM rates were 57.0% and 45.5% for HBV and HAV, respectively. Patients who were nonwhite or who had elevated alanine aminotransferase levels, cirrhosis, or human immunodeficiency virus were more likely to meet the HBV QM. Factors related to HCV care were also determinants of meeting the HBV QM. These factors included receiving a specialist consult, genotype testing, or HCV treatment. Patients who were older, had psychosis, and had a higher comorbidity score were less likely to meet the HBV QM. With a few exceptions, similar variables were related to meeting the HAV QM. The incidence of superinfection with acute HBV and HAV was low, but it was significantly lower in patients who received vaccination than in those who did not.

CONCLUSION: Quality measure rates for HAV and HBV are suboptimal for patients with chronic HCV. In addition, several patient-related factors and receiving HCV-related care are associated with a higher likelihood of meeting QMs.

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PMID: 21254161 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances, Grant Support

Gyarmathy et al.

- Evaluated 186 from Hungary, PWIDs between 2005-2006
  - Co-infection with HAV/HCV was 12%
  - HBV/HCV 9%
  - HAV/HBV 7%, and
  - HAV/HBV/HCV 4%

Gyarmathy VA, Neaigus A, Ujhelyi. The European Journal of Public Health Jun 2009, 19 (3) 260-265.

HAV/HCV Coinfection

Acute hepatitis A infection in patients with chronic hepatitis C virus (HCV) infection can be devastating.

In a prospective study by Vento, 432 patients with chronic hepatitis C (183 with cirrhosis) were observed over a 7-year period.

- Of the 17 patients with concurrent HAV infection, seven (41.4%) developed fulminant hepatitis and six died (35.3%).

Vento S. *J of Viral Hepatitis*. 2002; 7(51):7-8.

Hepatitis A Vaccination

Two doses required

Havrix©:1440 ELISA Units (1 ml) IM with a booster dose (1440 units) at 6+ months after the primary immunization

VAQTA ©: 50 units (1 ml) IM with a booster dose (50 units) given at 6-18 months after primary immunization.

www.uptodate.com

HBV/HCV Coinfection

An estimated 7-20 million people worldwide are living with both chronic hepatitis B and hepatitis C infections.

Patients with HBV/HCV coinfection have an increased risk for cirrhosis, hepatocellular carcinoma (HCC) and even death.

Potthoff A, Manns MP, Wiedemeyer H. Expert Opin on Pharmacotherapy. 2010;11(6):919-28.

Hepatitis B Immunization

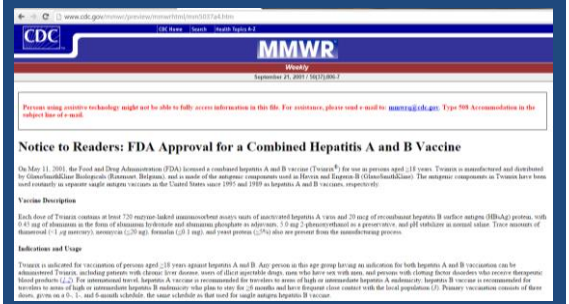
Energix-B©:

- Immunocompetent hosts:
  - 1 ml/dose for 3 total doses administered at 0, 1, and 6 months.
- Immunocompromised hosts:
  - 20 mcg/ml: administer 2 ml per dose at 0, 1, 2 and 6 months.

Recombivax HB©:

- Immunocompromised hosts:
  - 40 mcg/ml: administer 1 ml per dose at 0, 1, and 6 months

www.uptodate.com



CDC

MMWR

Weekly

September 21, 2001 / 50(37);806-7

Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation in the subject line of e-mail.

Notice to Readers: FDA Approval for a Combined Hepatitis A and B Vaccine

On May 11, 2001, the Food and Drug Administration (FDA) licensed a combined hepatitis A and B vaccine (Twinrix®) for use in persons aged ≥18 years. Twinrix is manufactured and distributed by GlaxoSmithKline Biologicals (Rixensart, Belgium), and is made of the antigenic components used in Havrix and Engerix-B (GlaxoSmithKline). The antigenic components in Twinrix have been used routinely in separate single antigen vaccines in the United States since 1995 and 1989 as hepatitis A and B vaccines, respectively.

Vaccine Description

Each dose of Twinrix contains at least 720 enzyme-linked immunosorbent assays units of inactivated hepatitis A virus and 20 mcg of recombinant hepatitis B surface antigen (HBsAg) protein, with 0.45 mg of aluminum in the form of aluminum hydroxide and aluminum phosphate as adjuvants, 1.0 mg 2-phenoxyethanol as a preservative, and pH stabilizer as neutral saline. Trace amounts of thiomersal (<1 µg mercury), neomycin (≤20 ng), formaldehyde (≤5.1 mg), and yeast protein (≤5%) also are present from the manufacturing process.

Indications and Usage

Twinrix is indicated for vaccination of persons aged ≥18 years against hepatitis A and B. Any person in this age group having an indication for both hepatitis A and B vaccination can be administered Twinrix, including patients with chronic liver disease, users of illicit injectable drugs, men who have sex with men, and persons with clotting factor disorders who receive therapeutic blood products (2,3). For international travel, hepatitis A vaccine is recommended for travelers to areas of high or intermediate hepatitis A endemicity; hepatitis B vaccine is recommended for travelers to areas of high or intermediate hepatitis B endemicity who plan to stay for ≥6 months and have frequent close contact with the local populations (3). Primary vaccination consists of three doses, given on a 0-, 1-, and 6-month schedule; the same schedule as that used for single antigen hepatitis B vaccine.

Twinrix©: Hepatitis A and B vaccine

Hepatitis A and recominant hepatitis B inactivated vaccine

- Hepatitis A virus antigen 720 ELISA units and hepatitis B surface ag 20 mcg/mL (1 ml)
- Contains aluminum, trace amounts of neomycin, and some yeast protein

Given as 1 mL intramuscular injections at 0, 1, and 6 months (3 doses total)

- Hep A component is ½ that of the Hep A vaccine alone, so it may be less immunogenic after 1 dose.
- Hep B component is likewise ½ that of the Hep B vaccine alone, so it may be less immunogenic after a single dose.
- Should not be used as post-exposure prophylaxis.

Developing a HCV Vaccine: The Challenges

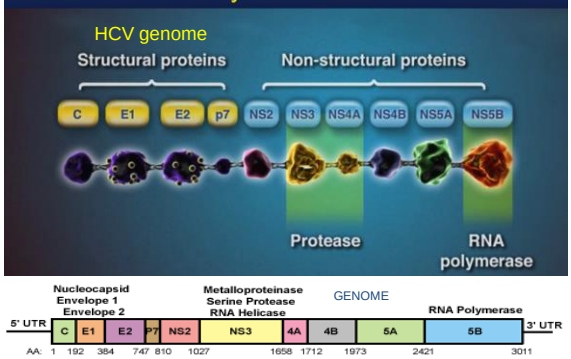
Hepatitis C is highly variable even among strains

HCV mutates quickly

The vaccine likely needs to be specific to only one genotype

Utilization of the T cell response is critical to viral clearance

Specific Targets for HCV Treatment: Protease and Polymerase Inhibition



RESEARCH ARTICLE | HEPATITIS C VIRUS

A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory

Leo Swadling[1,*], Stefania Capone[2,*], Richard D. Antrobus[1,3,*], Anthony Brown[1], Rachel Richardson[1], Evan W. Newell[4,5], John Halliday[2,6], Christabel Kelly[2,6], Dan Bowen[1], Joannah Fergusson[1], Ayako Kurioka[1], Virginia Ammendola[7], Mariarosaria Del Sorbo[7], Fabiana Grazioli[7], Maria Luisa Esposito[7], Loredana Siani[7], Cinzia Traboni[7], Adrian Hill[1,3], Stefano Colloca[7], Mark Davis[4], Alfredo Nicosia[2,7,8], Riccardo Cortese[8,†], Antonella Folgori[2], Paul Klenerman[1,9] and Eleanor Barnes[1,3,9,†]

[1]Nuffield Department of Medicine, University of Oxford, Oxford OX3 7BY, UK.
[2]ReiThera Srl (ex Okairos), Viale Città d'Europa 679, 00144 Rome, Italy.
[3]The Jenner Institute, University of Oxford, Oxford OX3 7DQ, UK.
[4]Department of Microbiology and Immunology, Stanford University, Stanford, CA 94305, USA.
[5]Singapore Immunology Network, Singapore 138648, Singapore.
[6]National Institute for Health Research Oxford Biomedical Research Centre, and Translational Gastroenterology Unit, Oxford OX3 7LE, UK.
[7]CEINGE, via Gaetano Salvatore 486, 80145 Naples, Italy.
[8]Department of Molecular Medicine and Medical Biotechnology, University of Naples Federico II, Via S. Pansini 5, 80131 Naples, Italy.
[9]Okairos AG, 4052 Basel, Switzerland.
*Corresponding author. E-mail: ellie.barnes@ndm.ox.ac.uk
*† These authors contributed equally to this work.
†‡ Present address: Kenes AG, Elisabethenstrasse 15, 4051 Basel, Switzerland.

Science Translational Medicine 05 Nov 2014:
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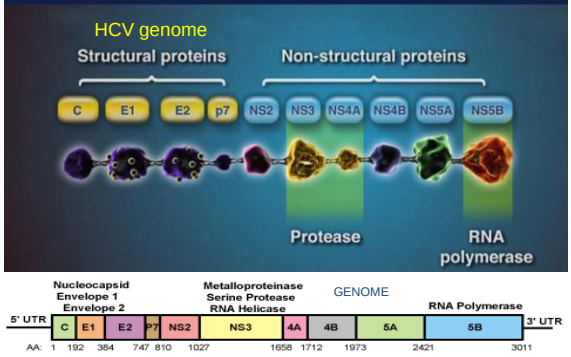
DOI: 10.1126/scitranslmed.3009985

Abstract

A protective vaccine against hepatitis C virus (HCV) remains an unmet clinical need. HCV infects millions of people worldwide and is a leading cause of liver cirrhosis and hepatocellular cancer. Animal challenge experiments, immunogenetics studies, and assessment of host immunity during acute infection highlight the critical role that effective T cell immunity plays in viral control. In this first-in-man study, we have induced antiviral immunity with functional characteristics analogous to those associated with viral control in natural infection, and improved upon a vaccine based on adenoviral vectors alone. We assessed a heterologous prime-boost vaccination strategy based on a replicative defective simian adenoviral vector (ChAd3) and modified vaccinia Ankara (MVA) vector encoding the NS3, NS4, NS5A, and NS5B proteins of HCV genotype 1b. Analysis used single-cell mass cytometry and human leukocyte antigen class I peptide tetramer technology in healthy human volunteers. We show that HCV-specific T cells induced by ChAd3 are optimally boosted with MVA, and generate very high levels of both CD8⁺ and CD4⁺ HCV-specific T cells targeting multiple HCV antigens. Sustained memory and effector T cell populations are generated, and T cell memory evolved over time with improvement of quality (proliferation and polyfunctionality) after heterologous MVA boost. We have developed an HCV vaccine strategy, with durable, broad, sustained, and balanced T cell responses, characteristic of those associated with viral control, paving the way for the first efficacy studies of a prophylactic HCV vaccine.

Treatment

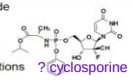
Specific Targets for HCV Treatment: Protease and Polymerase Inhibition



December 2013
FIRST IFN-Free Therapy FDA-approved

Sofosbuvir — Nucleotide Analogue Inhibitor of HCV NS5B polymerase enzyme

- Potent HCV-specific nucleotide analog (chain terminator)
- Safe and well tolerated
  - Once daily, no food effect
  - No significant drug interactions
  - No safety signals in preclinical/clinical studies
- High barrier to resistance
  - No virologic breakthrough to date
- Pangenotypic antiviral effect



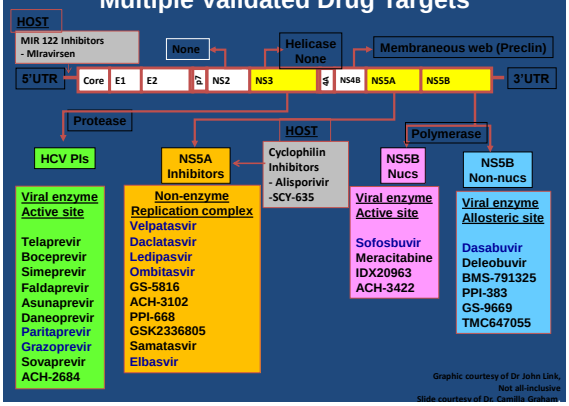
?cyclosporine

"historic"
"game-changer"
"miracle drug"

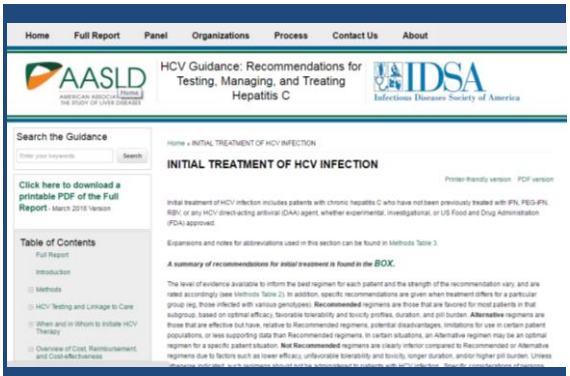
Effective for treatment-naives + pts who failed prior IFN treatment, cirrhotics, decompensated cirrhotics

Slide courtesy of Dr. Lynn Taylor

Multiple Validated Drug Targets



Graphic courtesy of Dr John Link, Not all-inclusive
Slide courtesy of Dr. Camilla Graham



Website: http://www.hcvguidelines.org

Case #1

A 56 yo M with diabetes mellitus, peptic ulcer disease due to NSAIDS with prior upper GI bleed, opioid use disorder in remission, tobacco dependence, and chronic hepatitis C genotype 1a, fibrosis stage 2, HCV viral load 2.6 million, presents for evaluation to your office.

Pt's EGD last month shows no active upper GI bleeding and well-healed peptic ulcers. He has never been treated for chronic hepatitis C before, presents today to discuss his treatment options. Pt has no known mental health disorders, is stably housed, and hasn't used injection drugs in over 10 years, stable on methadone. Pt is found to have early stage (F1) disease.

Provided the patient has no drug-drug interactions…

1. Which of the following directly-acting antivirals are options for treatment?
   a) Ledipasvir 90 mg/sofosbuvir 400 mg x 8 weeks
   b) Sofobuvir 400 mg + weight-based ribavirin x 12 weeks
   c) Pariteprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg + dasabavir 250 mg BID (PrOD) + weight-based ribavirin x 8 weeks
   e) Daclatasvir 60 mg + Sofosbuvir 400 mg x 24 weeks

Case #1

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   e) Daclatasvir 60 mg + Sofosbuvir 400 mg x 24 weeks

Case #1

This patient's med list includes 40 mg omeprazole, levothyroxine 125 mcg, levetiracetam 1000 mg BID, and methadone 90 mg daily.

3. What changes would you suggest to the patient's gastoenterologist regarding this pt's medications prior to treatment initiation?
   a) Suggest an alternate anti-convulsant
   b) Reduce omeprazole to 20 mg daily if clinically feasible and advise the patient to take the drug at the same time as Ledipasvir/Sofosbuvir
   c) Increase the levothyroxine
   d) Reduce the pt's methadone dose
   e) No changes needed here

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   c) Increase the levothyroxine
   d) Reduce the pt's methadone dose
   e) No changes needed here

A. Genotype 1a

Genotype 1a Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who do not have cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based RBV for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who do not have cirrhosis.**
  Rating: Class I, Level B

§ Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.
*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1a Treatment-naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who have compensated cirrhosis and in whom no baseline high fold-change NS5A RAVs[§] for elbasvir are detected.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1a infection who have compensated cirrhosis.**
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
§ Includes G1a polymorphisms at amino acid positions 28, 30, 31, or 93. Amino acid substitutions that confer resistance.

Genotype 1b Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily simeprevir (150 mg) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who do not have cirrhosis.**
  Rating: Class I, Level B

*The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 1b Treatment-naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of grazoprevir (100 mg)/elbasvir (50 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who have compensated cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 1b infection who have compensated cirrhosis.[†]**
  Rating: Class I, Level A

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 1 Trials

Genotype 1: C-EDGE

382 patients received 12 weeks of elbasvir 50 mg + grazoprevir 100 mg for genotype 1 HCV.

- 50% genotype 1a
- 41% genotype 1b

SVR12 was 92% in treatment-naïve patients with HCV genotype 1a infection (144/157) without cirrhosis.

SVR12 was 99% in genotype 1b (129/131) without cirrhosis.

Genotype 1: C-WORTHY

74 patients, treatment-naïve, non-cirrhotic, included both HCV mono-infected and HIV/HCV co-infected patients who received 12 weeks of elbasvir/grazoprevir without ribavirin.

SVR 12 was 92% (48/52) for GT 1a treatment-naïve, non-cirrhotic patients.

SVR-12 was 95% (21/22) for GT 1b treatment-naïve non-cirrhotic patients.

Genotype 1: C-EDGE, Cirrhotic pts

92 (22%) patients in the trial had Metavir F4 disease consistent with cirrhosis.

SVR 12 was 97% (90/92) in the subgroup of cirrhotic patients with GT 1 disease.

Presence or absence of compensated cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen.

Genotype 1: RAVs

Baseline NS5A Resistance-associated variants (RAVs) significantly reduce rates of SVR12 with a 12-week course of the elbasvir/grazoprevir regimen in GT 1a patients.

NS5A RAVs were identified at baseline in 12% (19/154) of GT 1a patients enrolled in the C-EDGE study.

- 58% (11/19) achieved SVR12 compared to
- 99% (133/135) SVR12 in patients without RAVs
- Both groups got 12 weeks of elbasvir/grazoprevir

Recommendation: Patients should be tested for RAVS to NS5A inhibitors before beginning treatment.

Genotype 1: ION Trials

ION-1: Ledipasvir 90 mg/sofosbuvir 400 mg

865 treatment-naïve patients, including pts with cirrhosis.

- SVR12 with LED/SOF was 97% to 99%
- There was no significant difference in SVR12 based on:
  - Use of RBV
  - HCV genotype 1 subtype
  - Length of treatment (12 vs. 24 week regimens)
- 16% of subjects had cirrhosis
  - SVR12 was 97% with cirrhosis
  - SVR12 was 98% for those without cirrhosis

Genotype 1: ION Trials

ION-3: Ledipasvir 90 mg/sofosbuvir 400 mg

647 treatment-naïve patients, non-cirrhotic only

- SVR12 was 93%-95% across all treatment groups
- There was no significant difference between 12 and 8 week regimens with or without ribavirin
- There were lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels below 6 million IU/mL (2%; 2 of 123)

Genotype 1: PEARL-IV, SAPPHIRE-1, TURQUOISE-II

SAPPHIRE-I: Paritaprevir 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg + Dasabavir 25 mg BID x 12 wks (PrOD) + weight-based ribavirin

322 treatment-naïve, non-cirrhotic patients with genotype 1a

- SVR12 was 95% with 12 weeks of PrOD and ribavirin
- Virologic failure was higher in GT1a (7 of the 8 failures were GT 1a)

PEARL-IV:

305 treatment-naïve, non-cirrhotic patients with genotype 1a

- SVR12 was lower in ribavirin-free arm
  - 90% for PrOD alone x 12 weeks
  - 97% for PrOD + weight-based ribavirin x 12 weeks
- This trial provided the rationale for recommendation to use ribavirin with all GT1a disease if using PrOD

Genotype 1: PEARL-IV, SAPPHIRE-1, TURQUOISE-II

TURQUOISE-II: PrOD + weight-based ribavirin

261 treatment-naïve and -experienced patients with genotype 1a and cirrhosis.

- 12 versus 24 weeks of PrOD + ribavirin
- SVR12 rates were 89% in the 12-week arm
- SVR12 was 95% in the 24-week arm
  - Treatment failures driven by null responders to PEG-IFN/RBV among treatment-experienced group

Due to at least 2 cases of CTP class A compensated cirrhotic patients dying or requiring liver transplant after receipt of PrOD or PrO, this regimen is now contraindicated in patients with Child Turcotte Pugh (CTP) class B or C hepatic impairment (decompensated liver disease).

Genotype 1: OPTIMIST-1 and -2

Simeprevir 150 mg and sofosbuvir 400 mg in chronically infected patients with HCV genotype 1

OPTIMIST-1:

310 treatment-naïve and -experienced patients without cirrhosis

- SVR12 was 97% (150/155) for 12 weeks of SIM/SOF
- SVR12 was 83% (128/155) for 8 weeks of SIM/SOF
- SVR 12 in treatment naïve was 97% for the 12 week regimen
- SVR 12 in treatment experienced was 95% for the 12 week regimen

OPTIMIST-2:

103 treatment-naïve and -experienced patients with cirrhosis

- Overall SVR12 rate was 83% (86/103)
- SVR12 was 88% (44/50) among treatment-naïve
- SVR12 was 79% (42/53) among treatment-experienced

Genotype 1: ALLY-2

ALLY-2: Daclatasvir + Sofosbuvir x 12 weeks in Co-infected pts with HIV/HCV (genotypes 1-4)

- 123 pts had genotype 1 HCV, 83 (54%) treatment-naïve
- SVR12 was 96% in treatment-naïve patients (n=71)with GT1a including 9 pts with cirrhosis

- Of the 88 treatment-naïve patients:
  - 21 patients with GT 1a were treated for 24 weeks (including 11 also with ribavirin)
  - 67 were treated for 12 weeks (33 with RBV)
  - There were no virologic relapses in either group
  - Only 14 cirrhotic patients were included, so recommendations for 12 vs. 24 weeks remain unclear.

Genotype 1: ALLY-1

ALLY-1: Daclatasvir + sofosbuvir + weight-based RBV in 60 patients with advanced cirrhosis

- SVR12 was only 76% in patients with GT1a (n=34) who received 12 weeks of therapy
- SVR12 was 100% in patients with GT1b ((n=11) who received 12 weeks of therapy
- Therefore 24 weeks of treatment is recommended for GT1a with cirrhosis, although the SVR12 remains unclear in this group

Genotype 2

Case #2

A 65 yo M with history of anemia of chronic disease, GERD, asthma, CAD and chronic hepatitis C genotype 2, fibrosis stage 3, HCV viral load 4 million, presents for evaluation. Pt presents to your office for initial evaluation of hepatitis C. He is interested in treatment. Pt's anemia has been thoroughly evaluated and appears to be anemia of chronic disease. His last hemoglobin was 9.5. He denies having ever had any bleeding, melena, BRBPR, hematemesis, epistaxis or hemoptysis. Patient uses an albuterol inhaler as needed, omeprazole 20 mg daily, and take metoprolol tartrate 100 mg daily, lisinopril 10 mg daily, aspirin 325 mg daily, and simvastatin 10 mg daily for CAD.

1. Which of the following is a contraindication to the use of ribavirin in this patient?
   a) Drug-drug interaction with omeprazole
   b) Hemoglobin baseline < 11.0
   c) Coronary artery disease history
   d) Patient's HCV genotype (2)

Case #2

A 65 yo M with history of anemia of chronic disease, GERD, asthma, CAD and chronic hepatitis C genotype 2, fibrosis stage 3, HCV viral load 4 million, presents for evaluation. Pt presents to your office for initial evaluation of hepatitis C. He is interested in treatment. Pt's anemia has been thoroughly evaluated and appears to be anemia of chronic disease. His last hemoglobin was 9.5. He denies having ever had any bleeding, melena, BRBPR, hematemesis, epistaxis or hemoptysis. Patient uses an albuterol inhaler as needed, omeprazole 20 mg daily, and take metoprolol tartrate 100 mg daily, lisinopril 10 mg daily, aspirin 325 mg daily, and simvastatin 10 mg daily for CAD.

1. Which of the following is a contraindication to the use of ribavirin in this patient?
   a) Drug-drug interaction with omeprazole
   b) Hemoglobin baseline < 11.0
   c) Coronary artery disease history
   d) The patient's HCV genotype

Genotype 2 Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who do not have cirrhosis and who are not eligible to receive RBV.**
  Rating: Class IIa, Level B

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 Treatment-naïve Patients with Compensated Cirrhosis‡ - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 16 weeks to 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis and who are not eligible to receive RBV.**
  Rating: Class IIa, Level B
- **Daily sofosbuvir (400 mg) and weight-based RBV for 16 weeks to 24 weeks is a Recommended regimen for treatment-naïve patients with HCV genotype 2 infection who have compensated cirrhosis.**
  Rating: Class IIa, Level C

‡ For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 2 Trials

Genotype 2: FISSION, VALENCE, POSITRON Trials

Sofosbuvir 400 mg daily and weight-based ribavirin

FISSION: 499 treatment-naïve pts with GT 2 or 3, randomized to daily PEG-IFN/RBV x 24 wks vs. Sofosbuvir + RBV x 12 weeks
- SVR12 was 97% (68/70) in patients in the SOF/RBV GT 2 group
- SVR12 was 78% in the PEG-IFN/RBV arm

POSITRON: 278 interferon-ineligible or unwilling, treatment-naïve and treatment-experienced GT2 and GT3 pts randomized to 12 weeks Sofosbuvir + RBV vs. placebo x 12 weeks.
- SVR12 was 93% (101/109) among GT2s

Genotype 2: FISSION, VALENCE, POSITRON Trials

VALENCE: 419 treatment-naïve and treatment-experienced patients with HCV genotype 2 or 3. GT 2 patients received 12 weeks of SOF + RBV versus placebo.
- SVR12 for GT2 was 97% (31/32) for SOF + RBV x 12 weeks

The overall SVR12 was 94% in a pooled analysis of all 3 trials with SOF/RBV x 12 weeks (for GT 2)
- Patients with cirrhosis tended to do worse in all 3 trials
- Thus therapy was extended to 16 weeks in pts with cirrhosis (despite limited data)

Genotype 3

Case #3

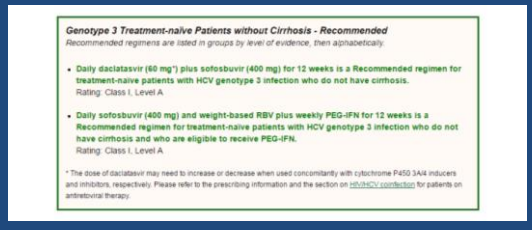
A 45 yo M w/ a seizure disorder, hypothyroidism, and treatment-experienced hepatitis C genotype 3 without cirrhosis (null response to PEG-IFN + RBV after 12 weeks), presents for treatment. His provider decides to treat this patient with 12 weeks of daclatasvir + sofosbuvir. Which of the following drug-drug interactions are you most concerned about?

a) Carbamazepine
b) Pantoprazole
c) Levothyroxine
d) Levetiracetam
e) Omeprazole

Case #3

A 45 yo M w/ a seizure disorder, hypothyroidism, and treatment-experienced hepatitis C genotype 3 without cirrhosis (null response to PEG-IFN + RBV after 12 weeks), presents for treatment. His provider decides to treat this patient with 12 weeks of daclatasvir + sofosbuvir. Which of the following drug-drug interactions are you most concerned about?

a) Carbamazepine
b) Pantoprazole
c) Levothyroxine
d) Levetiracetam
e) Omeprazole



Genotype 3 Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 3 infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 3 infection who do not have cirrhosis and who are eligible to receive PEG-IFN.**
  Rating: Class I, Level A

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 Treatment-naive Patients with Compensated Cirrhosis[1]- Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily sofosbuvir (400 mg) and weight-based RBV plus weekly PEG-IFN for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 3 infection who have compensated cirrhosis and who are eligible to receive PEG-IFN.**
  Rating: Class I, Level A
- **Daily daclatasvir (60 mg*) plus sofosbuvir (400 mg) for 24 weeks with or without weight-based RBV is a Recommended regimen for treatment-naive patients with HCV genotype 3 infection who have compensated cirrhosis.**
  Rating: Class IIa, Level B

[1] For decompensated cirrhosis, please refer to the appropriate section.

* The dose of daclatasvir may need to increase or decrease when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Genotype 3 Trials

Genotype 3: ALLY-3 Trial

ALLY-3: 101 treatment-naïve patients with and without cirrhosis, daclatasvir 60 mg daily + sofosbuvir 400 mg daily x 12 weeks (no ribavirin)

- Overall SVR12 rate of 90%
- SVR12 was 97% among treatment-naïve non-cirrhotic pts
- SVR12 was 58% among treatment-naïve cirrhotic pts,
- This data suggests that cirrhotic patients might benefit from extension of therapy to 24 weeks.

DAC + SOF+ RBV x 12 vs. 16 weeks in those with cirrhosis:

- SVR12 rates were 88% (15/17) for those in the 12 week arm versus
- SVR12 of 89% (16/18) in the 16 week arm

Genotype 3: BOSON Trial

592 patients total, both treatment-naïve and treatment-experienced (IFN-eligible ONLY)

196 received sofosbuvir and RBV for 16 weeks
199 received Sofosbuvir and RBV for 24 weeks
197 received sofosbuvir plus PEG-IFN/RBV for 12 weeks

SVR12 rates among treatment-naïve patients with GT3:

- 77% (70/91) for SOF + RBV x 16 weeks
- 57% for those with cirrhosis in SOF + RBV arm x 16 weeks arm
- 88% (83/94) for SOF+ RBV x 24 weeks
- 82% for those with cirrhosis in SOF + RBV x 24 weeks arm
- 95% (89/94) for SOF + PEG-IFN/RBV x 12 weeks
- 91% for those with cirrhosis in SOF + RBV x 12 weeks arm

Genotype 3: VALENCE Trial

250 treatment-naïve (42%) and -experienced (58%) subjects with genotype 3 (cirrhotic (n=45) and non-cirrhotic (n=100)) received sofosbuvir (400 mg daily) plus weight-based RBV x 24 weeks.

- Overall SVR12 rate was 84%
- SVR12 was 93% in treatment-naïve
- SVR12 was 77% in treatment-experienced
- Cirrhosis didn't impact results significantly.

Genotype 3: C-SWIFT Trial

40 patients with GT 3, treatment-naïve, with and without cirrhosis, randomized to 8 versus 12 weeks of triple therapy with elbasvir/grazoprevir + sofosbuvir (400 mg) daily.

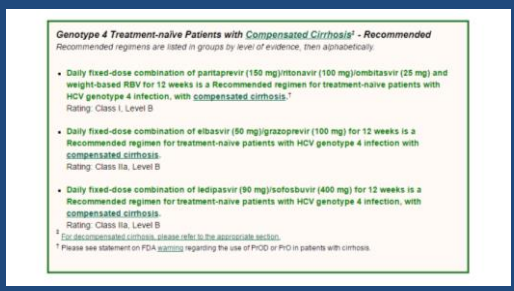
- SVR12 was 93% (14/15) for 8 weeks (non-cirrhotic)
- SVR12 was 100% (14/14) for 12 weeks of therapy (non-cirrhotic)
- SVR12 was 91% (10/11) for cirrhotics x 12 weeks

Genotype 4

Genotype 4 Treatment-naïve Patients without Cirrhosis - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class I, Level A
- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class IIa, Level B
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection who do not have cirrhosis.**
  Rating: Class IIa, Level B



Genotype 4 Treatment-naïve Patients with Compensated Cirrhosis[‡] - Recommended

Recommended regimens are listed in groups by level of evidence, then alphabetically.

- **Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based RBV for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection, with compensated cirrhosis.[†]**
  Rating: Class I, Level B
- **Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection with compensated cirrhosis.**
  Rating: Class IIa, Level B
- **Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is a Recommended regimen for treatment-naive patients with HCV genotype 4 infection, with compensated cirrhosis.**
  Rating: Class IIa, Level B

‡ For decompensated cirrhosis, please refer to the appropriate section.
† Please see statement on FDA warning regarding the use of PrOD or PrO in patients with cirrhosis.

Genotype 4 Trials

Genotype 4: SYNERGY Trial

21 patients with GT4, both treatment-naïve and –experienced, both cirrhotic and non-cirrhotic, randomized to 12 weeks of ledipasvir/sofosbuvir

- 60% were treatment-naïve
- 43% had advanced fibrosis (F3 or F4)

Overall SVR12 was 100% for all 20 patients

Genotype 4: PEARL-1 Trial

PEARL-I:

86 treatment-naïve GT4 patients, non-cirrhotic received 12 weeks of the daily fixed-dose combination of paritaprevir/ritonavir/ombitasvir (PrO) +/- RBV

- SVR12 was 100% (42/42) in the PrO + RBV group
- SVR12 was 91% (40/44) in the PrO arm

Genotype 4: AGATE-I and –II Trials

AGATE-1:
120 treatment-naïve and -experienced patients with GT4 + cirrhosis
- 12 versus 16 weeks of paritaprevir/ritonavir/ombitasvir (PrO) + RBV
- SVR12 was 96% in the 12 week PrO + RBV
- SVR12 was 100% in the 16 week PrO + RBV arm

AGATE-II:
100 treatment-naïve and -experienced non-cirrhotic GT4 patients received 12 weeks of PrO + RBV
- Overall SVR12 was 94% for 12 weeks of PrO + RBV

AGATE-II:
60 treatment-naïve and -experienced GT4 patients with cirrhosis
- 12 versus 24 weeks of PrO + RBV
  - SVR12 was 97% for 12 weeks of PrO + RBV in cirrhotic pts

Genotype 4: C-EDGE Trial

66 treatment-naïve GT4 patients, with and without cirrhosis, received elbasvir (50 mg)/grazoprevir (100 mg) x 12 weeks
- 6 were cirrhotic (9.1%)
- 28 were co-infected with HIV (42.4%)
- 10 also received RBV
- 56 did not receive RBV

- Overall SVR12 was 97% (64/66) regardless of status of cirrhosis or coinfection
- 1 treatment failure
- Baseline RAVs did not impact SVR12 rates

Genotype 4: NEUTRINO Trial

28 treatment-naïve patients with GT4 with and without cirrhosis received 12 weeks of sofosbuvir 400 mg daily + PEG-IFN 2a + RBV

- SVR12 was 96% (27/28)
- The one treatment failure was in a cirrhotic pt

Ribavirin

Important to carefully consider the patient's baseline comorbidities.
- **If you have to stop RBV, you have to stop *treatment*.**
- Pts with prior CVA, CAD, COPD, etc… may be risky candidates due to anemia and low oxygen carrying capacity that can result

Avoid ribavirin in pts w/ anemia or thalassemia
- Anyone with hemoglobin <11.0 should not receive RBV
- Particularly problematic in women (Pregnancy category X); 2 forms of contraception needed

Ribavirin needs to be dosed according to renal function.
CrCl >50, no dose adjustment
CrCl 30-50: Alternate 200 mg and 400 mg every other day
CrCl <30: 200 mg once daily
ESRD: 200 mg once daily

Ribavirin's half-life is very long.
Capsule, single dose; 44 hours in HCV pts
Tablet: 120-170 hours

www.rxlistinfo.com, Ribavirin Drug Information, 2015.

Beware: Drug-Drug Interactions

Common:
- **Antacids**
- **H2 blockers**
- **PPIs**
- **Herbal medications**
- **HAART (PIs, NNRTIs)**
- **Many others**

Double check for these, with patient, online, and with pharmacy

Be sure to ask patients about herbal remedies, antacids, OTC meds, etc.

Ledipasvir Solubility Decreases as pH Increases: Products that Increase Gastric pH are Expected to Decrease Concentration of Ledipasvir

- Caltrate (all forms)
- Os-Cal (all forms)
- Tums (all forms)
- Viactiv
- Wellesse calcium/vitamin D
- Citracal (all forms)
- Alka-Mints®
- Calel-D®
- Calcid®
- Chooz®
- Miralac®
- Rolaids®
- Gas-X® with Maalox® (containing Calcium Carbonate, Simethicone)
- Rolaids® Plus Gas Relief (containing Calcium Carbonate, Simethicone)
- Titralac® Plus (containing Calcium Carbonate, Simethicone)
- Alamag®
- Alumina and Magnesia®
- Gen-Alox®
- Kudrox®
- M.A.H.®
- Maalox (all forms)
- Magagel®
- Magnalox®
- Maldroxal®
- Mylanta®
- Ri-Mox®
- Rulox®
- Mag-Ox®
- Maox®
- Uro-Mag®

Separate these OTC products and Harvoni administration by **at least 4 hours**

***** Slide courtesy of Dr. Camilla Graham*****

H2 Blockers and Proton Pump Inhibitors with Harvoni

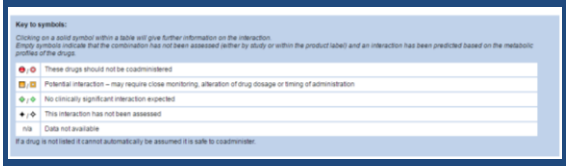
H2 blockers **Famotidine 40mg BID** **Ranitidine 150mg BID** **Tagamet 800mg BID**	**H2 blocker may be administered at the same time with LED/SOF OR 12 hours apart from LED/SOF at a dose that does not exceed doses comparable to famotidine 40mg BID**
Proton Pump Inhibitors **Omeprazole 20mg daily** **Prevacid 30mg daily** **Aciphex 20mg daily** **Protonix 40mg daily** **Nexium 20 to 40mg daily (try to stay with lower dose if possible)**	PPI doses comparable to omeprazole 20mg or lower can be administered at the same time with LED/SOF under fasted conditions.

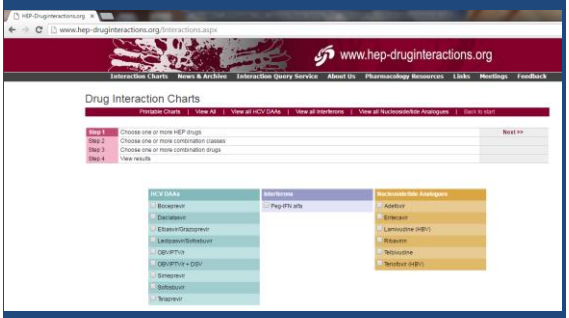
https://www.medicines.org.uk/emc/medicine/29471

***** Slide courtesy of Dr. Camilla Graham*****

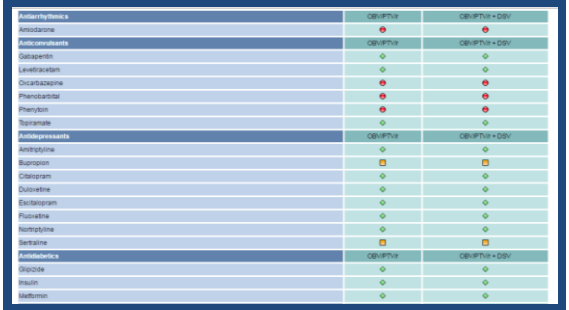
Drug-Drug Interactions

www.hep-druginteractions.org/interactions.asp

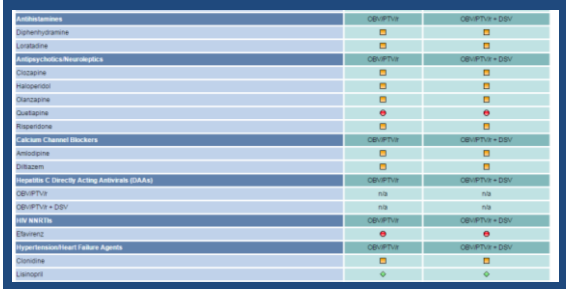




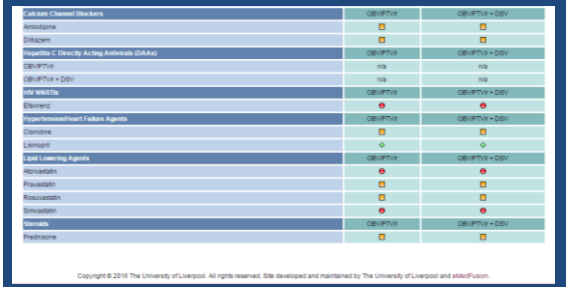
Ritonavir: Drug-Drug Interactions



Ritonavir: Drug-Drug Interactions



Ritonavir: Drug-Drug Interactions



5 Pre/Post Multiple Choice Questions

1. What is the most common barrier to patients accessing hepatitis C treatment currently?
   a) Unstable mental health disorders
   b) Insurance coverage
   c) Drug-drug interactions
   d) A life-expectancy of <1 year

5 Pre/Post Multiple Choice Questions

2. Which of the following drugs interacts with Ledipasvir/sofosbuvir to decrease serum levels of ledipasvir?
   a) Methadone
   b) Levothyroxine
   c) Levetiracetam
   d) Omeprazole

5 Pre/Post Multiple Choice Questions

3. Based on the ION trials, which of the following patients might be a candidate for 8 weeks of ledipasvir/sofosbuvir?
   a) GT 1a, treatment naïve, non-cirrhotic, HCV viral load 4 million
   b) GT 3, treatment naïve, non-cirrhotic, HCV viral load 3 million
   c) GT 1b, treatment naive, cirrhotic, HCV VL 2 million
   d) GT 4, treatment naïve, non-cirrhotic, HCV viral load 6 million

5 Pre/Post Multiple Choice Questions

4. Which of the following is among the most common noted side effect of daclatasvir?
   a) Nausea
   b) Fatigue
   c) Skin rash
   d) diarrhea

Multiple Choice

5. Which of the following measures are important to preventing morbidity associated with chronic hepatitis C?
   a) Weekly lab monitoring
   b) Vaccination against hepatitis B alone
   c) Vaccination against hepatitis A and B
   d) Avoidance of all medications metabolized by the liver

Thank you for your attention.

Questions/Comments?

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