CCHCS Care Guide: Hepatitis C

SUMMARY | **DECISION SUPPORT** | **PATIENT EDUCATION/SELF MANAGEMENT**

GOALS

- Identify Hepatitis C (HCV) infected patients
- Monitor all HCV patients for signs of cirrhosis
- Use most appropriate HCV treatment regimen based on AASLD/IDSA* guidelines
- Monitor patients on treatment and stop treatment when indicated (futility rules)
- Goal of HCV antiviral treatment is to achieve a sustained virologic response (SVR) - cure

ALERTS

HCV TREATMENT

- HCV treatment requires referral to the Headquarters (HQ) CCHCS HCV warmline: CDCR_CPHCS_HCV_Questions@cdcr.ca.gov for appropriate regimen selection
- Do not initiate HCV treatment without appropriate regimen selection from the HCV Central Treatment Team at HQ

CIRRHOTICS

- Screen for hepatocellular carcinoma and varices – **patients require continued screening even after HCV treatment**
- Identify and manage decompensated cirrhosis

TREATMENT

PATIENT SELECTION

- AASLD/IDSA* recommends treatment for all patients with chronic HCV infection, except those with life expectancies < 12 months that cannot be remediated by treating HCV, by liver transplantation, or by other directed therapy.
  - Unless there is a medical contraindication, all patients with chronic HCV are treatment candidates if they desire treatment and are willing to adhere to a medication and monitoring plan.
- AASLD/IDSA* notes that there are factors that impact the access to HCV medications and the ability to deliver HCV treatment to patients. Strategies for prioritizing HCV treatment based on AASLD/IDSA* guidance are discussed on page 5.
- HCV evaluation and treatment is generally not initiated in reception centers. When indicated, HCV treatment will begin after the patient has transferred to a mainline institution.

TREATMENT

- The recommended medication regimen depends on genotype and many clinical factors including the presence or absence of cirrhosis, co-infection with Human Immunodeficiency Virus (HIV) or Hepatitis B Virus (HBV), other comorbidities and any history of prior treatment.
- The FDA is approving new medications frequently and treatment regimens are changing rapidly as the new agents are being released. For this reason, all patients should be referred to the HCV Central Treatment Team at HQ for selection of most appropriate treatment regimen (see page 7).

MONITORING

ALL CHRONIC HCV INFECTED PATIENTS:

- Annual clinical assessment: Consider labs including CBC, CMP, PT/INR every 12 months to assess progression of liver disease. Determine FIB4 (see page 4) annually. Calculate Child-Pugh score (see page 6) as indicated.
- Vaccines: Offer and document Hepatitis A Virus (HAV), HBV, and pneumococcal (PPSV23 once; after age 65, PCV13 followed by second PPSV23 1 year later). Encourage annual influenza vaccination.

HCV PATIENTS RECEIVING ANTIVIRAL THERAPY:

- See page 6 regarding intervals for CBC, CMP, HCV viral load.
- Assess for side effects at each visit.
- Follow up as clinically indicated, typically every 4 weeks during active treatment, more frequently if needed.

CHRONIC HCV INFECTED PATIENTS WITH CIRRHOSIS

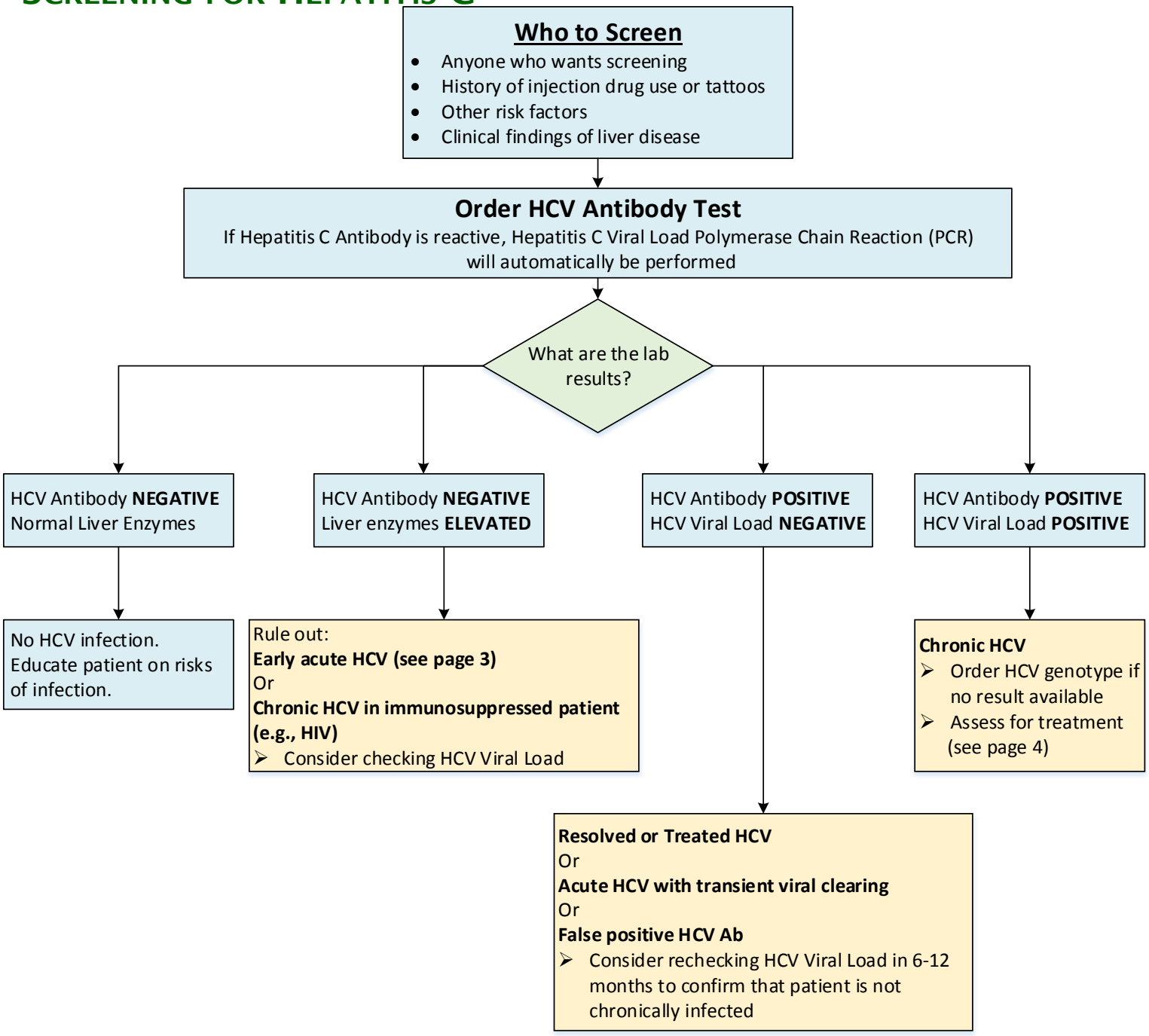
- Ultrasound every 6 months to screen for hepatocellular carcinoma. **Continue Hepatocellular carcinoma (HCC) screening after HCV treatment.**
- See CCHCS ESLD Care Guide.

TABLE OF CONTENTS

*American Association for the Study of Liver Diseases, Infectious Diseases Society of America

Information contained in the Care Guide is not a substitute for a health care professional's clinical judgment. Evaluation and treatment should be tailored to the individual patient and the clinical circumstances. Furthermore, using this information will not guarantee a specific outcome for each patient.
Refer to "Disclaimer Regarding Care Guides" for further clarification.

SCREENING FOR HEPATITIS C



ACUTE HCV: DIAGNOSIS, EVALUATION, AND TREATMENT

DEFINITION

- Positive HCV viral load with negative HCV antibody, OR
- Documented change in HCV antibody from negative to positive within a 6 month time period, OR
- A new (within the last 3 months) positive HCV antibody accompanied by:
  - A new elevation of ALT (defined as at least 5 times prior baseline level obtained within the last 24 months), or
  - An increase of ALT to more than 5 times > normal ALT levels if no baseline labs in last 24 months, and
  - No other concomitant conditions to explain the rise in liver enzymes.

EVALUATION

- The majority of patients are asymptomatic. Clinical presentation may include jaundice, dark urine, fatigue, and/or right upper quadrant abdominal pain.
- "Time Zero" is date of first signs and symptoms of acute hepatitis or first lab abnormalities. If none of these are present, the most recent date of IV drug use or tattooing can be used to determine the interval for HCV lab surveillance.

LAB EVALUATION of Acute HCV

	CBC	CMP	PT/INR	HCV viral load	HIV test
Baseline: week zero	✓	✓	✓	✓	✓
Week 8 to 12		✓		✓	
Week 16		✓		✓*	

**If HCV viral load at week 8 to 12 is negative, order additional HCV viral load to confirm that the patient cleared the acute infection. Repeat HCV viral load every 4-6 weeks until 2 negative HCV viral loads are obtained.*

INTERPRETATION of Diagnostic Studies

HCV antibody	HCV antibody signal: cut off	HCV viral load	Alanine aminotransferase (ALT)	Interpretation
Negative	Low	Negative	Normal	HCV negative
		Positive	High	Acute HCV
Positive	Low	Negative	Normal	False positive HCV Antibody
		Negative	High	Early acute HCV
		Positive	High	Acute HCV
Positive	High	(New) Positive	High	Acute re-infection
		Positive	Normal	Chronic HCV
		Negative	Any	Treated or cleared HCV

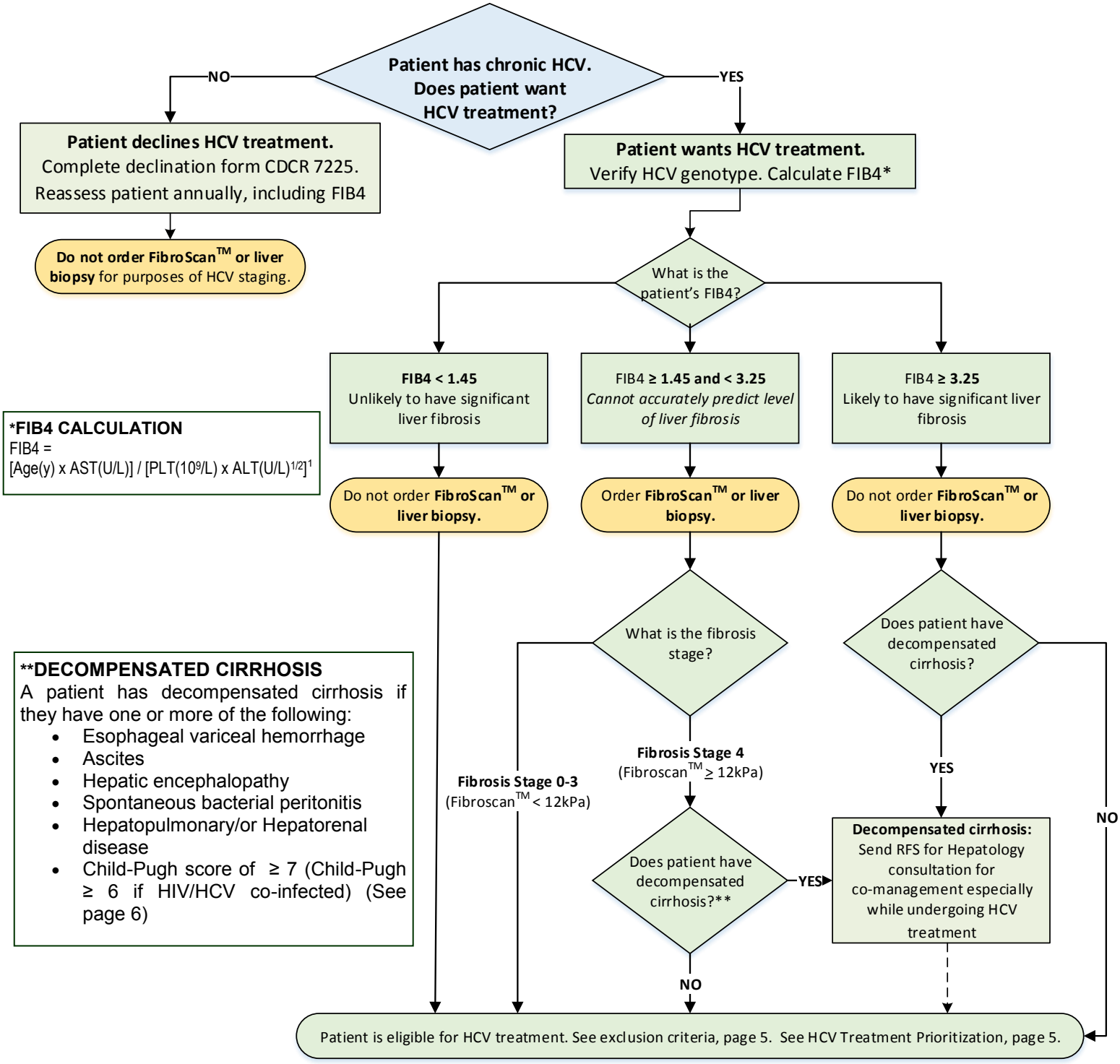
- Consult the HCV warmline: CDCR CPHCS HCV Questions@cdcr.ca.gov if the diagnosis (acute or chronic) is uncertain.
- Counsel patient regarding risk reduction.

TREATMENT

- 20-50% of patients with acute HCV will clear their infection without treatment within 6 months of initial exposure. Due to these high clearance rates, AASLD/IDSA* guidelines do not currently recommend treatment during the acute HCV phase. Instead, interval surveillance is recommended as noted above. If the patient does not spontaneously clear the HCV, the same treatment work up and decision management is advised as for the chronically infected patient.
- Rare cases of fulminant hepatic failure may benefit from acute HCV treatment; contact the HCV warmline: CDCR CPHCS HCV Questions@cdcr.ca.gov for urgent consultation regarding these cases.
- Provide patient education to patients who spontaneously clear HCV to include the risk of reinfection with high risk exposures.

*American Association for the Study of Liver Diseases, Infectious Diseases Society of America

CHRONIC HCV: PATIENT SELECTION FOR TREATMENT



***FIB4 CALCULATION**

FIB4 =
[Age(y) x AST(U/L)] / [PLT(10^9/L) x ALT(U/L)$^{1/2}$][1]

****DECOMPENSATED CIRRHOSIS**

A patient has decompensated cirrhosis if they have one or more of the following:

- Esophageal variceal hemorrhage
- Ascites
- Hepatic encephalopathy
- Spontaneous bacterial peritonitis
- Hepatopulmonary/or Hepatorenal disease
- Child-Pugh score of ≥ 7 (Child-Pugh ≥ 6 if HIV/HCV co-infected) (See page 6)

FIBROSCAN™ uses transient elastography to measure liver stiffness.[2] The shear wave velocity has been correlated with stages of fibrosis in HCV patients in the following manner:

FibroScan result (kpa)	≤ 7.0	> 7.0	≥ 9.5	≥ 12.0
Equivalent stage of fibrosis (HCV)	F0-F1	F2	F3	F4

LIVER BIOPSY

- Used infrequently due to non-invasive alternatives and some issues with sampling and observer variability.
- If done, adequate biopsy defined as 15 mm in length with a minimum of 6-8 portal tracts seen.
- Biopsy not required for patients with FIB4 <1.45 or ≥3.25 unless clinical condition is unclear.

[1]Vallet-Pichard, A et al, FIB-4: an Inexpensive and Accurate Marker of Fibrosis in HCV Infection. Comparison with Liver Biopsy and FibroTest. Hepatology 2007;46:32-36.

[2]Ziol, M et al, Noninvasive Assessment of Liver Fibrosis by Measurement of Stiffness in Patients With Chronic Hepatitis C. Hepatology 2005; 48-54.

HCV TREATMENT PRIORITIZATION

Due to the significant number of patients eligible for treatment, patients at highest risk for complication or death if they remain untreated will be prioritized to receive HCV treatment first. Priority groups are listed below.

Risk Group	Clinical Examples
1 (Highest)	• Any previous Fibroscan or liver biopsy demonstrating stage 3 or 4 fibrosis (≥ 9.5 kPa) • Cirrhosis otherwise diagnosed • Diagnosis of decompensated cirrhosis (see page 4) • Diagnosis of hepatocellular carcinoma (see exclusion criteria below) • HIV co-infection and any previous Fibroscan or liver biopsy demonstrating greater than stage 1 fibrosis (> 7.0 kPa) • Liver Transplantation (consult with transplant and HCV specialists required) • Women of childbearing age who wish to get pregnant in the next 12 months • Serious extra-hepatic manifestations of HCV (e.g., leukocytoclastic vasculitis, membranoproliferative glomerulonephritis, or symptomatic cryoglobulinemia)
2 (Medium)	• Does not qualify for risk group 1 and: • Any previous Fibroscan or liver biopsy demonstrating stage 2 fibrosis (> 7.0 kPa) • Age > 50 years old • HIV or HBV co-infection • Patients with diabetes • HCV genotype 3 • Body mass index > 30 kg/m^2 • GFR < 30 • Does not meet any priority group 1 criteria
3 (Lowest)	• Any previous Fibroscan or liver biopsy demonstrating stage 0-1 fibrosis (≤ 7.0 kPa) • Does not meet any priority group 1 or 2 criteria

HCV TREATMENT EXCLUSION CRITERIA

TREATMENT EXCLUSION CRITERIA

Release Date Exclusion

Clinical History	Minimum # of Months*
Not cirrhotic	5
Decompensated cirrhotic and/or previous Direct Acting Agents (DAA) treatment failure	8

*Patients will be excluded from treatment consideration in CCHCS if they will be released before the evaluation and course of treatment can be completed. The minimum # of months noted above shows the minimum number of months of incarceration needed to complete HCV therapy based on patient factors.
More time may be required in some cases.

Exclusion Criteria: HCV Treatment (all)

- Life expectancy < 12 months that cannot be remediated by treating HCV, by transplantation, or by other directed therapy
- Inability to cooperate with treatment
- Inability to give informed consent
- Pregnancy or inability to practice contraception

Exclusion Criteria: DAA

- On a medication contraindicated for use with DAA and unable to substitute
- Allergy to DAA
- Allergy to Ribavirin (if regimen requires RBV)

Exclusion Criteria: Ribavirin

- Poorly controlled or unstable cardiopulmonary disease
- Anemia; hemoglobin < 11 g/dl or hematocrit < 33%
- Allergy to Ribavirin
- Inability to practice contraception during and for 6 months after treatment completion (teratogen)

ADVANCED LIVER DISEASE/CIRRHOSIS:

For persons with advanced liver disease (Metavir stage F3 or F4), the severity of liver dysfunction can be estimated using the Child Turcotte Pugh scoring system (CTP). Variations in the timing and subjectivity inherent in the scoring (e.g., in grading ascites or encephalopathy) are the major limitations of CTP scoring.

CHILD-PUGH (CTP) POINTS			
Number of points	**1**	**2**	**3**
Encephalopathy *	None	Grade 1-2	Grade 3-4 (or chronic)
Ascites	None	Mild/Moderate (diuretic-responsive)	Severe (diuretic-refractory)
Bilirubin (mg/dl)§	< 2	2-3	> 3
Modified total bilirubin§	< 4	4-7	> 7
Albumin (g/dl)	> 3.5	2.8-3.5	< 2.8
INR	< 1.7	1.7-2.3	> 2.3

CHILD-PUGH CIRRHOSIS SCORING[1,2,3]

Class	Points	One year survival (%)	Two year survival (%)
A	5-6	95	90
B	7-9	80	70
C	10-15	45	38

***ENCEPHALOPATHY GRADING**

Grade 1	mild confusion, anxiety, restlessness, fine tremor, slowed coordination
Grade 2	drowsiness, disorientation, asterixis
Grade 3	somnolent but arousable, marked confusion, incomprehensible speech, incontinence, hyperventilation
Grade 4	coma, decerebrate posturing, flaccidity

§Modified total bilirubin used to score patients who have Gilbert's syndrome or who are taking atazanavir or indinavir

[1] Child CG, Turcotte JG. The Liver and Portal Hypertension. *Philadelphia, WB Saunders Co*. 1964.
[2] Pugh RN, Murray-Lyon IM, Dawson JL, et. al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973; 60:646.
[3] Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. *NEJM*. 1966; 274:473.

SPECIAL POPULATIONS

Hepatitis B virus (HBV) co-infection (requires co-management by CCHCS HCV specialist)

- Persons with HBV/HCV co-infection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC.
- During HCV treatment, cases of HBV reactivation have been reported, in some cases resulting in fulminant hepatitis, hepatic failure, and death.
- Screening for HBV infection and viremia is required prior to starting HCV treatment. If HBV infection is noted, treatment for HBV viremia may be recommended; otherwise, monthly HBV viral loads are recommended during HCV treatment.

HIV co-infection (requires co-management by CCHCS HIV specialist)

- Note multiple interactions exist with HCV and HIV medications. Do not adjust HIV medications without HIV specialist input.

Renal Impairment

- No dosage adjustment is required for GFR ≥ 30 mL/min. Specific HCV treatment recommendations exist for patients on dialysis or with GFR < 30 mL/min.

Pregnancy

- Ribavirin is a known teratogen and cannot be used in pregnancy. Also, extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of therapy in both female patients and in female partners of male patients who are, or have recently taken Ribavirin therapy.

Transplant (requires co-management by CCHCS HCV specialist)

- Specific HCV treatment recommendations exist for patients with a kidney or liver transplant.

SELECTION OF HCV TREATMENT REGIMEN

Chronic HCV treatment is advancing more rapidly than CCHCS Care Guide revision cycles. In order to avoid the publication of outdated HCV treatment regimens in this Hepatitis C Care Guide, the provider is referred to *HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C*; www.hcvguidelines.org (American Association for the Study of Liver Diseases/Infectious Diseases Society of America) for information regarding the most up to date specific recommended treatment regimens. Treatment protocol selection depends on HCV genotype, whether the patient is treatment naïve or treatment experienced, and additional clinical factors.

All patients requesting treatment should be referred to the HQ CCHCS HCV warmline: CDCR_CPHCS_HCV_Questions@cdcr.ca.gov for selection of the most appropriate treatment regimen by the HCV Central-Treatment Team at HQ.

LAB STUDIES		βHCG	CBC	CMP	PT/ INR	HCV viral load	HIV test	HBV serology[5]
Pre-treatment	Within past 12 months					✓	✓	✓
	Within past 3 months		✓	✓	✓			
	Within past 1 month	✓[1]						
During Treatment	Week 2			✓[2]				
	Week 4		✓[3]	✓		✓		
	Week 8		✓[3]	✓[4]				
	Week 12		✓[3]	✓[4]		✓		
End of treatment			✓[3]	✓[4]		✓		
After treatment	3 months after treatment ends					✓		

[1] Recommended for women of child bearing age in whom ribavirin is being considered.
[2] Obtain CMP at treatment week 2 if cirrhosis and taking ombitasvir/paritaprevir/ritonavir with or without dasabuvir.
[3] Obtain CBC at treatment week 8, 12, 16 (if applicable) if taking ribavirin.
[4] Obtain CMP at treatment week 8, 12, 16 (if applicable) if taking elbasvir/grazoprevir.
[5] HBV serology includes HBV surface antigen, HBV surface antibody, HBV core antibody total (not IgM). If HBV surface antibody is negative, obtain HBV viral load.

INTERPRETATION OF HCV TREATMENT LAB RESULTS– DURING TREATMENT

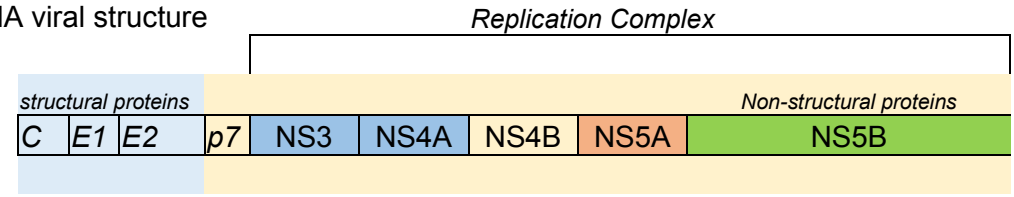
Rx week	Result	Action/Interpretation
Any week	ALT: > 10 fold increase	**Stop treatment,** clinical evaluation recommended
	ALT increase but < 10 fold; with increased bilirubin, alkaline phosphatase or INR and/or symptomatic (weakness, nausea, vomiting, jaundice)	
	ALT increase but < 10 fold and asymptomatic	Recheck ALT in 2 weeks
Week 4	HCV VL*: Detectable	Check HCV VL at week 6
Week 6	HCV VL: 1 log increase from week 4	**Stop treatment**
	HCV VL: < 1 log increase from week 4	Continue treatment
12 weeks post Rx	HCV VL: Detectable	Treatment failure. Refer for retreatment
	HCV VL: Undetectable	SVR=Cure. Further VL testing not indicated

VL*= viral load

RESISTANCE TO DIRECT ACTING ORAL AGENTS

HCV is an approximately 9.5 kilobase RNA virus that replicates at a rate of billions of copies daily. Many of these viral copies are not functional due to errors during replication. However, the rate of replication allows for drug-resistant virus to develop when a patient is taking a HCV combination that is suboptimal or if patient is not adherent with medication.

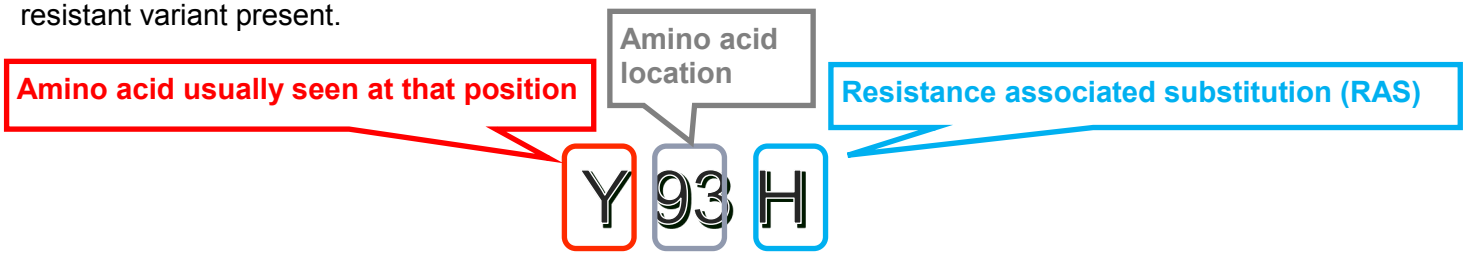
HCV RNA viral structure



HCV Medication Class	NS3/4A Protease Inhibitors	NS5A Inhibitors	NS5B Polymerase Inhibitors Nucleotide	NS5B Polymerase Inhibitors Non-nucleotide
Medications	Boceprevir,* Grazoprevir, Paritaprevir, Simeprevir*, Telaprevir*	Daclastavir, Elbasvir, Ledipasvir, Ombitasvir, Velpatasvir	Sofosbuvir	Dasabuvir

*No longer available in the U.S.
Adapted from: Schaefer EA, Chung RT. Anti-hepatitis C virus drugs in development. Gastroenterology 2012; 142:1340. Graphic 93884 Version 1.0

An area of the HCV virus conferring resistance to a particular medication is called a resistance associated substitution (RAS). An RAS' name identifies the amino acid position where the substitution took place, the amino acid that is normally coded for (preceding the amino acid position), and the amino acid that is now being coded for. Multiple letters following the amino acid position indicate a mixed virus with more than one resistant variant present.



The presence of RAS impacts HCV treatment depending on the patient genotype, the level of liver fibrosis, and if the patient is treatment experienced or naïve. RAS can remain present for weeks to months. Some RAS confer cross class resistance, while others only affect specific members of a medication class. Resistance can be overcome in some cases with the addition of ribavirin or additional agents and/or the extension of treatment duration.

Testing for resistance

The most common drug resistant virus develops as a result of NS3 or NS5A failures; NS5B failures are rarely seen in clinical settings. There are commercially available assays to detect RAS in genotype 1 NS3/4a, NS5A and NS5B and in genotype 3 NS5A regions. RAS testing is to be ordered in only specific instances; see hcvguidelines.org for more information. Baseline RAS testing is not recommended for treatment naïve patients. RAS testing is not recommended prior to retreatment of DAA failures. Do not order RAS testing without prior consultation with CCHCS HCV warmline at: **CDCR CPHCS HCV Questions@cdcr.ca.gov**

MEDICATIONS

DIRECT ACTING ORAL AGENTS

- **WARNING: Risk of Hepatitis B virus reactivation in patients co-infected with HCV and HBV.** Test all patients for evidence of current or prior HBV infection before initiating HCV treatment.
- If treatment interruption occurs or is anticipated, contact the HCV warmline ASAP.
- Multiple drug-drug interactions may occur. Consult pharmacy or HCV warmline prior to initiating new medications during HCV treatment course (see page 12).

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
Daclatasvir [Daklinza®] Tablet: 30 mg, 60 mg, 90 mg NS5A inhibitor	*Activity in genotype 1, 2, 3, 4* Dose: • 60 mg daily in combination with sofosbuvir • 30 mg daily with strong CYP3A inhibitors • 90 mg daily with moderate CYP3A inducers Renal dosing: No dose adjustment required	• Bradycardia when administered with sofosbuvir and amiodarone (not recommended) • Headache • Fatigue • **Monotherapy is contraindicated**: Do not use daclatasvir alone as HCV resistance will develop • Strong CYP3A inducers contraindicated (e.g., phenytoin, rifampin, carbamazepine, oxcarbazepine)
Dasabuvir & Ombitasvir/ paritapravir/ritonavir (PrOD) Tablets [Viekira Pak®]: 250 mg & 12.5/75/50 mg Tablet [Viekira XR®]: 200/8.33/50/33.33 mg Dasabuvir: NS5B polymerase inhibitor Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor	*Activity in genotype 1* Dose: • Viekira Pak: Combination of 2 ombitasvir/paritapravir/ritonavir tablets once daily with 1 dasabuvir tablet twice daily • Viekira XR: 3 tablets once daily with a meal Renal dosing: • No dose adjustment required • Limited data in hemodialysis patients Hepatic impairment: • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C)	• ALT elevations > 5x upper limit of normal (ULN) within first 4 weeks of treatment ➢ D/c if ALT persistently > 10x ULN; ➢ Consider d/c if ALT elevation is accompanied by signs/symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR • Contains ritonavir; HIV patients must be on suppressive HIV regimen to prevent development of HIV resistant mutations • Fatigue • Nausea • Pruritis and skin reactions including rash • Insomnia • Increased risk of hepatic decompensation and hepatic failure in patients with cirrhosis • Many drug interactions. See prescribing information
Elbasvir/grazoprevir [Zepatier®] Tablet: 50/100 mg Elbasvir NS59 inhibitor Grazoprevir NS3 149 protease inhibitor	*Activity in genotype 1 and 4* Dose: One tablet once daily with or without food Renal dosing • No dose adjustment required including hemodialysis patients Hepatic impairment • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B or C)	• ALT elevations > 5x upper limit of normal (ULN) at or after 8 weeks of treatment ➢ Perform hepatic lab testing prior to therapy, at treatment week 8, and as clinically indicated. Perform additional hepatic lab testing at week 12 if on 16 weeks of therapy ➢ D/c if ALT persistently > 10x ULN; ➢ Consider d/c if ALT elevation is accompanied by signs/symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR • Fatigue • Headache • Nausea • Contraindicated with nafcillin, oral ketoconazole, bosentan, rifampin, tacrolimus, etravirine, cobicistat, modafinil, carbamazepine, oxcarbazepine • Caution with statins: not to exceed 20mg atorvastatin or 10mg rosuvastatin

MEDICATIONS

DIRECT ACTING ORAL AGENTS CONTINUED

- **WARNING: Risk of Hepatitis B virus reactivation in patients co-infected with HCV and HBV.** Test all patients for evidence of current or prior HBV infection before initiating HCV treatment.
- If treatment interruption occurs or is anticipated, contact the HCV warmline ASAP.
- Multiple drug-drug interactions may occur. Consult pharmacy or HCV warmline prior to initiating new medications during HCV treatment course (see page 12).

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
Glecaprevir/Pibrentasvir [Mavyret®] Tablet: 100/40 mg Glecaprevir NS3149 protease inhibitor Pibrentasvir NS59 inhibitor	*Activity in all genotypes* Dose: Three tablets orally once daily with food Renal dosing: • No adjustments needed Hepatic impairment: • Not recommended in patients with moderate hepatic impairment (Child-Pugh B) • Contraindicated in patients with severe hepatic impairment (Child-Pugh C)	• Fatigue • Headache • Contraindicated with atazanavir, rifampin, carbamazepine, efavirenz, ethinyl estradiol, darunavir, lopinavir/ritonavir, atorvastatin, lovastatin, simvastatin • Caution with digoxin, dabigatran, cyclosporine, pravastatin (↓pravastatin dose 50%), rosuvastatin (not to exceed rosuvastatin 10mg)
Ledipasvir/sofosbuvi (HAR) [Harvoni®] Tablet: 90/400 mg Ledipasvir NS59 inhibitor Sofosbuvir NS5B inhibitor	*Activity in genotype 1, 4, 5, 6* Dose: One tablet once daily with or without food Renal dosing: • eGFR<30 or HD: safety and efficacy has not been established	• Fatigue • Headache • Nausea • Significant drug-drug interaction with acid lowering agents • Bradycardia when administered with amiodarone (not recommended) • Contraindicated with P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazpine, rifampin, rifabutin, rifapentine), tipranavir • Caution with digoxin, statins, tenofovir DF
Ombitasvir/paritapravir/ ritonavir (PrO) [Technivie®] Tablet:12.5/75/50 mg Ombitasvir: NS5A inhibitor Paritaprevir: NS3/4A protease inhibitor Ritonavir: CYP3A inhibitor	*Activity in genotype 4* Dose: Two ombitasvir/ paritapravir/ritonavir tablets twice daily (typically paired with ribavirin) Renal dosing: • No dose adjustment required • Limited data in hemodialysis patients Hepatic impairment: • Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C)	• ALT elevations > 5x upper limit of normal (ULN) within first 4 weeks of treatment ➢ D/c if ALT persistently > 10x ULN; ➢ Consider d/c if ALT elevation is accompanied by signs/symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR • Contains ritonavir; HIV patients must be on suppressive HIV regimen to prevent development of HIV resistant mutations • Fatigue • Nausea • Pruritis and skin reactions including rash • Insomnia • Increased risk of hepatic decompensation and hepatic failure in patients with cirrhosis • Many drug interactions. See prescribing information

MEDICATIONS

DIRECT ACTING ORAL AGENTS CONTINUED

- **WARNING: Risk of Hepatitis B virus reactivation in patients co-infected with HCV and HBV.** Test all patients for evidence of current or prior HBV infection before initiating HCV treatment.
- If treatment interruption occurs or is anticipated, contact the HCV warmline ASAP.
- Multiple drug-drug interactions may occur. Consult pharmacy or HCV warmline prior to initiating new medications during HCV treatment course (see page 12).

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
Sofosbuvir (SOF) [SOVALDI®] Tablet: 400 mg NS5B Polymerase Inhibitor	*Activity in all genotypes* Dose: One tablet once daily with or without food Renal dosing: • CrCl < 30 ml/min and HD: Limited data available	• Fatigue • Headache • **Monotherapy is contraindicated:** Do not use SOF alone as HCV resistance will develop • Bradycardia when administered with amiodarone (not recommended) • Contraindicated with P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine)
Sofosbuvir/Velpatasvir [Epclusa®] Tablet: 400/100 mg Sofosbuvir NS5B inhibitor Velpatasvir NS5A inhibitor	*Activity in all genotypes* Dose: One tablet once daily with or without food Renal dosing: • CrCl < 30 ml/min and HD: Limited data available	• Fatigue • Headache • Significant drug-drug interaction with acid lowering agents. • Bradycardia when administered with amiodarone (not recommended) • Contraindicated with P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine), efavirenz, tipranavir, tapotecan • Caution with digoxin, statins, tenofovir DF

Bold = Formulary *See prescribing information for complete description of adverse effects and drug interactions.

MEDICATIONS

DIRECT ACTING ORAL AGENTS CONTINUED

- **WARNING: Risk of Hepatitis B virus reactivation in patients co-infected with HCV and HBV.** Test all patients for evidence of current or prior HBV infection before initiating HCV treatment.
- If treatment interruption occurs or is anticipated, contact the HCV warmline ASAP.
- Multiple drug-drug interactions may occur. Consult pharmacy or HCV warmline prior to initiating new medications during HCV treatment course (see page 12).

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
Sofosbuvir/Velpatasvir/ Voxilaprevir **[Vosevi®]** Tablet: 400/100/100 mg Sofosbuvir NS5B inhibitor Velpatasvir NS5A inhibitor Voxilaprevir NS3/4A protease inhibitor	*Activity in all genotypes* Dose: One tablet once daily with food Renal dosing: • CrCl < 30 ml/min and HD: Limited data available Hepatic impairment: • Not recommended for patients with moderate to severe hepatic impairment (Child-Pugh B and C)	• Fatigue • Headache • Diarrhea • Nausea • Significant drug-drug interaction with acid lowering agents • Bradycardia when administered with amiodarone (not recommended) • Contraindicated with P-gp inducers (e.g., carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifampin, rifabutin, rifapentine), atazanavir, lopinavir, tipranavir, efavirenz • Caution with statins, cyclosporine, digoxin

Bold = Formulary *See prescribing information for complete description of adverse effects and drug interactions.

DRUG-DRUG INTERACTIONS

Multiple drug-drug interactions exist between the direct acting HCV medications and other medication classes including, but not limited to, certain antimicrobials, analgesics, antiarrhythmics, oral contraceptives, anxiolytics, lipid lowering agents, acid lowering agents, antiretrovirals, herbal preparations, corticosteroids, and anticonvulsants and specific medications such as rifampin, salmeterol, and warfarin.

The HCV Central Treatment Team at HQ will use the patient's current medication list when choosing the appropriate HCV treatment regimen for that patient. If the patient requires addition of any medication during his/her HCV treatment course the prescribing provider will need to address possible drug-drug interactions prior to prescribing.

For more information on drug-drug interactions:

- **Contact the HCV warmline at CDCR CPHCS HCV Questions@cdcr.ca.gov**
- **http://www.hep-druginteractions.org**

Using the Drug-Drug Interaction Tool on LifeLine:

1. Go to Lifeline (http://lifeline/Pages/Home.aspx).
2. Under Divisions/Programs, select Quality Management.
3. Under External Links, select Quality Management Portal.
4. Under Care Team Tools, select All Care Team Tools.
5. Under Pharmacy/Medication Management, select Drug-Drug Interaction Checker.

Or select the hyperlink below:
http://cphcspfdccdww01/Reports/Pages/Report.aspx?ItemPath=/QM/Tools/DrugDrugInterationSearch

MEDICATIONS

HCV AGENTS—OTHER

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
RIBAVIRIN (RBV) **Tablet**/capsule: 200 mg	*Activity in all genotypes* Dose: Based on body weight (total daily dose, divided two times a day) <75 kg: 1000 mg >75 kg: 1200 mg Renal dosing: CrCl 30-50 ml/min: Alternating doses, 200 mg and 400 mg every other day CrCl < 30 ml/min: 200 mg daily HD: 200 mg daily	Anemia: • The primary clinical toxicity of ribavirin is hemolytic anemia (See anemia management, page 14). • After about 2 weeks of ribavirin treatment, approximately 10% develop severe anemia; this may result in worsening of cardiac disease and has led to fatal and nonfatal myocardial infarctions. Teratogenicity (Pregnancy): • Due to the risk of fetal malformations and fetal death with ribavirin, a negative pregnancy test is required before treatment consideration. • Women of childbearing potential must use 2 forms of effective contraception during treatment and for 6 months after treatment. • Men whose female partners are pregnant or may become pregnant must use barrier contraception during treatment and for 6 months after treatment. • Histamine-like side effects: nasal stuffiness, itching, skin irritation, asthma-like syndrome.

COLONY STIMULATING FACTORS (EPOETIN ALFA)

MEDICATION	DOSING	ADVERSE EFFECTS/INTERACTIONS*
EPOETIN ALFA 10,000 units/ml, 20,000 units/ml, 40,000 units/ml, 4,000 units/ml, 3,000 units/ml, 2,000 units/ml	Usual Dose: • 50-100 units/kg subQ, (IV preferred if dialysis) three times weekly or • 150-300 units/kg subQ once weekly (maximum 40,000 units weekly) Titrate to maintain Hgb 10-12 g/dl • Frequent Hgb monitoring is required • Avoid increase of Hgb > 1g/dl over a two week period	• Epoetin alfa does not have a U.S. Food and Drug Administration (FDA) indication for the treatment of ribavirin associated anemia although it is commonly used for this complication of treatment. • Epoetin alfa is associated with significant toxicities, including pure red cell aplasia and cardiovascular risks such as thromboembolic events and strokes. • Use with caution in patients with malignancies, HTN, cardiovascular disease, hypercoagulable conditions, sickle cell disorders and seizures. • "FDA Drug Safety Communication: Erythropoiesis-Stimulating Agents (ESAs): Epogen® states: • Health care professionals who prescribe epoetin alfa to patients with anemia from causes other than cancer chemotherapy are required to provide a copy of the Medication Guide to each patient. Please see http://www.fda.gov/downloads/Drugs/Drugsafety/ucm088988.pdf for a copy of this medication guide. • Patients need to know about increase risks of CV related conditions, stroke, death. • Prior to the initiation of epoetin for the correction of anemia in the patient receiving HCV treatment, a consultation with the CCHCS HCV warmline is *strongly recommended at:* CDCR CPHCS HCV Questions@cdcr.ca.gov

Bold = Formulary *See prescribing information for complete description of adverse effects and drug interactions.

MANAGEMENT OF SIDE EFFECTS OF HCV TREATMENT WITH RIBAVIRIN

ANEMIA - *CONSIDER CONSULTATION WITH HCV WARMLINE AT CDCR CPHCS HCV QUESTIONS@CDCR.CA.GOV*

HEMOGLOBIN g/dl	ACTION
< 10 g/dl in patients with no history of cardiac disease	• Decrease ribavirin (RBV) to 600 mg/day* • Recheck Hgb weekly
≥ 2 g/dl decrease during any 4 week period and history of stable cardiovascular disease	• Decrease RBV to 600 mg/day* • Recheck Hgb weekly
Hgb 8.6-9.0 g/dl	• RBV dose reduction to 600 mg/day if not already done • Weekly Hgb monitoring • Consider epoetin alfa if the dose has been reduced to 600 mg/day for at least two weeks with continued drop in Hgb ◦ Careful review with patient of risks/benefits of epoetin alfa versus stopping HCV treatment.** § Provide the epoetin alfa medication guide (see page 13) • Symptomatic anemia: discontinue HCV treatment** §
Hgb 8.0-8.5 g/dl	• RBV dose reduction to 600 mg/day if not already done • Weekly Hgb monitoring • Careful review with patient of risks/benefits of epoetin alfa vs. stopping HCV treatment** § • If considered clinically stable to continue HCV treatment and if the patient agrees, provide epoetin alfa medication guide (see page 13) • Symptomatic anemia: Consider inpatient management and RBC transfusion and consider discontinuing HCV treatment** §
Hgb 7.5-7.9 g/dl	• Review with patient the risks of anemia and stopping HCV treatment vs. the risk of continuing HCV treatment and epoetin alfa.** § Provide epoetin alfa medication guide to patients starting epoetin alfa (see page 13). • Stop RBV (If on DAA, discontinue medication and contact the HCV warmline) • Weekly CBC monitoring • Symptomatic anemia: Discontinue HCV treatment** § and consider inpatient management and RBC transfusion
Hgb < 7.5 g/dl or symptomatic anemia	• Terminate HCV treatment§

*If RBV dose is reduced for anemia:
- Once Hgb has increased to > 10.0 g/dl, increase the ribavirin dose by 200 mg/day at two week intervals until the initial dose is reached

**If RBV is temporarily stopped due to anemia:
- Recheck Hgb within two weeks and at two week intervals until stable
- If Hgb is > 10.0 g/dl, restart RBV at a dose of 600 mg/day if patient's weight < 75 kg; 800 mg/day if patient's weight ≥ 75 kg
- If hemoglobin remains > 10.0 g/dl, increase dose by 200 mg/day at two week intervals until the initial dose is reached

§ **Consultation with the CCHCS HCV warmline is *strongly* recommended prior to stopping HCV Treatment CDCR CPHCS HCV Questions@cdcr.ca.gov.**

PATIENT EDUCATION/SELF MANAGEMENT

WHAT YOU SHOULD KNOW: HEPATITIS C VIRUS

WHAT IS HEPATITIS C?

- Hepatitis C is a virus that causes swelling and irritation of the liver.
- The liver helps with digestion and filters waste products out of the blood.
- Hepatitis C can cause serious damage to the liver.
- Hepatitis C has no vaccine, but you can be vaccinated for hepatitis A and B to prevent more damage to your liver.

HOW DO YOU GET HEPATITIS C?

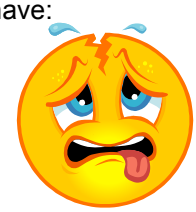
You can get hepatitis C from:

- Dirty needles (tattoos or piercing)
- Snorting drugs with infected equipment
- Sharing needles to inject drugs
- Unprotected sex (rarely)
- A blood transfusion if you got one in the USA before 1992 (All blood now tested for hepatitis C before transfusion)

HOW DO YOU KNOW IF YOU HAVE HEPATITIS C?

- Most people who have hepatitis C look and feel fine.
- You can have hepatitis C for a long time and not know it.
- Usually hepatitis C is found by doing blood tests.
- If hepatitis C damages the liver, it can cause scarring. This is called cirrhosis (sir-oh-sis).
- Your health care provider may order more tests to see how much liver damage you have.

- Some people with hepatitis C can have:
  - Fatigue
  - Stomach pain
  - Joint pain
  - Night sweats
  - Loss of appetite or nausea



WHAT CAN YOU DO TO TAKE CARE OF YOURSELF?

- Get vaccinated for hepatitis A and B. Get yearly vaccinations for pneumonia and the flu.
- Do not drink alcohol or use illegal drugs - these will damage your liver more.
- Do not take a lot of medications like acetaminophen (Tylenol®) and ibuprofen (Motrin®). Talk to your health care provider about all medications, including over-the-counter medications, vitamins, and herbs to be sure they will not damage your liver. Ask your health care provider before you take any pain medicine.
- Do not get tattoos in prison because of the risk of new infection with hepatitis C, hepatitis B, or HIV.
- Do not share your toothbrush, razor, or other personal items.
- Eat a healthy diet and try to lose weight if you are overweight.
- Drink plenty of water.
- Get plenty of rest and regular exercise.
- Quit smoking cigarettes.
- Follow your health care provider's instructions about medications for hepatitis C treatment.
- See your health care provider regularly.

CAN HEPATITIS C BE CURED?

- For many years hepatitis C treatment was difficult and took up to 12 months– the treatment is better now and many patients can be cured of hepatitis C (but if they continue to inject drugs or do other risky things they can get it again).
- Hepatitis C treatment is not an emergency. The liver damage/scar tissue happens over many years, and some people never get much damage or scarring.
- What specific hepatitis C treatment to use, how long the treatment needs to be given, and how soon a person should be treated all depend on many things which are different for each person. You should discuss your case with your health care provider.
- You can get re-infected if you are exposed to HCV virus again. Successful treatment does not provide protection from repeat HCV infections.

EDUCACIÓN PARA EL PACIENTE/CONTROL PERSONAL DEL CASO

LO QUÉ DEBE SABER: HEPATITIS C

¿QUÉ ES LA HEPATITIS C?

- La hepatitis C es un virus que produce inflamación e irritación del hígado.
- El hígado ayuda a la digestion y filtra los productos de desecho fuera de la sangre.
- La hepatitis C puede causar daños serios al hígado.
- No existe vacuna para prevenir la hepatitis C, pero usted puede vacunarse contra la hepatitis A y B para evitar dañar más su hígado.

¿CÓMO SE PUEDE CONTRAER LA HEPATITIS C?

La hepatitis C se puede contraer de las siguientes maneras:

- Agujas contaminadas (tatuajes o perforaciones).
- Inhalar drogas usando un equipo infectado.
- Compartir agujas para inyectarse drogas.
- Practicar sexo sin protección (raras veces).
- Mediante transfusion de sangre si se realizó en EE.UU. antes de 1992. (Actualmente, toda transfusion de sangre es sometida a la prueba de la hepatitis C antes de realizarse.)

¿CÓMO SABER SI USTED SUFRE DE LA HEPATITIS C?

- La mayoría de las personas enfermas lucen y se sienten sanas.
- Se puede sufrir de la hepatitis C por un tiempo largo y no saberlo.
- Usualmente se puede detectar la hepatitis C mediante un examen de sangre.
- Si la hepatitis C daña el hígado, puede producer cicatrices. Esto se conoce como cirrosis.
- Su medico puede indicarle otros exámenes para verificar el daño que tiene su hígado.
- Algunas personas que sufren de la hepatitis C presetan:
  - Fatiga
  - Dolor estomacal
  - Dolor en las articulaciones
  - Sudoración nocturna
  - Pérdida del apetito o náuseas

¿QUÉ PUEDE HACER USTED PARA CUIDARSE?

- Hágase vacunar contra la hepatitis A y B. Vacúnese anualmente contra la neumonía y la gripe.
- No consuma alcohol ni use drogas ilícitas - estas producirán más daño al hígado.
- No ingiera gran cantidad de medicamentos como el acetaminofén (Tylenol®) y Motrin®. Consulte con su medico acerca de todos los medicamentos, incluyendo los medicamentos de venta sin prescripción, vitaminas y hierbas para evitar dañar el hígado. Consulte con su médico antes de ingerir cualquier medicamento analgésico.
- No se realice tatuajes en la prisión para evitar enfermedades de transmisión sanguínea.
- No comparta su cepillo de dientes, rasuradora u otros objetos personales.
- Trate de adelgazar si tiene sobrepeso.
- Mantenga una dieta sana.
- Ingiera abundante cantidad de agua.
- Tenga mucho descanso y realice ejercicio con regularidad.
- Abandone el hábito de fumar cigarrillos.
- Siga las instrucciones de su médico acerca de los medicamentos para tratar la hepatitis C.
- Consulte con regularidad con su médico.

¿TODA PERSONA QUE SUFRE DE LA HEPATITIS C NECESITA TRATAMIENTO?

- Durante muchos años el tratamiento de la hepatitis C era muy difícil y tomaba hasta 12 meses – el tratamiento es mejor ahora y muchos pacientes pueden ser curados de la hepatitis C (pero si continúan inyectándose drogas o haciendo otras cosas riesgosas, pueden volver a contagiarse).
- El tratamiento de la hepatitis C no es una emergencia. El daño al hígado o los tejidos de cicatriz que se forman toman muchos años para realizarse, y algunas personas nunca tienen mucho daño o muchas cicatrices
- El tratamiento específico que debe ser usado contra la hepatitis C, cuánto tiempo debe durar el tratamiento y qué tan pronto una persona debe tratarse depende de muchos factores y estos varían en cada persona. Discuta su caso con su médico.
- Puede volver a infectarse si vuelve a estar expuesto al virus del VHC. Un tratamiento que tiene éxito no protege contra las infecciones recurrentes del VHC.