MEDICATION COVERAGE POLICY

PHARMACY AND THERAPEUTICS ADVISORY COMMITTEE

Health Plan of San Joaquin

POLICY:	Hepatitis C	**P&T DATE:**	5/11/2021
CLASS:	Infectious Diseases	**REVIEW HISTORY:** (*month/year*)	5/21, 2/20, 9/19, 12/18, 9/18, 2/18, 12/17, 9/17, 5/17, 2/17, 12/16, 9/16, 5/16, 2/16, 11/15, 9/15, 2/15, 9/14, 5/14, 2/14, 2/12
LOB:	Medi-Cal		

Background

There is an estimated 2.2 to 3.2 million persons who are chronically infected with the hepatitis C virus (HCV) in the United States.[1] However, about 50% are unaware that they are infected.[2] The first step towards improving health outcomes among persons with HCV infection and preventing transmission is to identify those with active infections.[3] The next step would be to treat those identified patients and reduce all-cause mortality and liver-related health adverse consequences, as evidenced by an SVR (sustained virologic response) that translates to achievement of a virologic cure. Obtaining SVR is associated with more than a 70% reduction in the risk of hepatocellular carcinoma, as well as a 90% reduction in the risk of liver-related mortality and liver transplantation.[4]

Although there are current regimens available that show evidence of high SVR rates, they are complicated by the variable price of therapy (treatment of genotype 1 HCV infection based on HPSJ prices can range from $56,000 to $300,000 regardless of cirrhosis status). The California Department of Health Care Services (DHCS) assists with these high costs by providing a set payment per week of treatment that follows their policies on the management and treatment of chronic Hepatitis C. However, as a managed care organization, we want to ensure that regimens being used are not only safe and recommended by guidelines, but cost effective as well.

Objectives

- Summarize DHCS policy for Hepatitis C treatment (refer to appendix 1 for full policy)
- Define commonly used terminology (e.g. level of evidence, IFN ineligible, treatment experienced)
- Review history of Hepatitis C agents, their corresponding serious adverse events, and specific criteria necessary for erythropoietin use in Hepatitis C treatment related anemia
- Summarize American Association for the Study of Liver Diseases (AASLD) combination regimens with genotypes they can or cannot be used in
- Summarize AASLD recommendations for renal dosing adjustments and patients with concomitant HIV infections
- Summarize criteria that must be met for initial and continued coverage of Hepatitis C agents
- Analyze utilization of Hepatitis C agents
- Compare and analyze safety, efficacy, costs, and levels of evidence for agents recommended by AASLD guidelines for Hepatitis C per genotype, treatment experience, cirrhosis presence/type, and liver transplant status
- Review HPSJ preferred treatment regimens for Hepatitis C per genotype, treatment experience, and cirrhosis presence/type, and liver transplant status

CA Department of Health Care Services Hepatitis C Policy Key Points[5]

- Treatment considerations, choice of regimen, and monitoring for hepatitis C virus infected patients will be based off of AASLD guidelines.
- Guidelines apply to all new FDA approved drugs and AASLD approved regimens.
- If a regimen is more cost effective and has either equivalent or better levels of evidence in the specific patient population, then we can ask the provider to substitute to that regimen.

Definitions

A. Level of Evidence[6]

Classification	Description
Class I	Conditions for which there is evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment
Class IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy
Class IIb	Usefulness and efficacy are less well established by evidence and/or opinion
Class III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful
Level of Evidence	**Description**
Level A*	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent
Level B*	Data derived from a single randomized trial, nonrandomized studies, or equivalent
Level C	Consensus opinion of experts, case studies, or standard of care

*Due to it not being ethical or practical to test IFN-sparing HCV treatments in some situations, hence when those instances arise, the panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B if a single pre-determined, FDA-approved equivalency was established.

B. Serious Adverse Event (SAE)[7]

Per the FDA Safety Information and Adverse Event Reporting Program, a serious adverse event (SAE) is labeled as such when the patient outcomes can lead to the following:

- Death
- Life-threatening
- Hospitalization
- Disability or permanent damage
- Congenital anomalies or birth defects
- Intervention to prevent permanent impairment or damage
- Any other important medical events such as allergic bronchospasm or serious blood dyscrasias

C. Peginterferon alfa ineligible (IFN ineligible)[8]

- Intolerance to IFN
- Autoimmune hepatitis and other autoimmune disorders
- Hypersensitivity to PEG or any of its components
- Decompensated hepatic disease
- Major uncontrolled depressive illness
- A baseline neutrophil count below 1500/μL, a baseline platelet count below 90,000 μL or baseline hemoglobin below 10 g/dL
- A history of preexisting cardiac disease

D. Child Turcotte Pugh (CTP) Classification of Severity of Cirrhosis[8]

	Class A	Class B	Class C
Total points	5–6	7–9	10–15
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (µmol/L)	<34	34–50	>50
Serum albumin (g/L)	>35	28–35	<28
Prothrombin time/international normalized ratio	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I–II (or suppressed with medication)	Grade III–IV (or refractory)

E. Other commonly used terms[8]

Terminology	Definition
IFN eligible	Persons who do not meet criteria to be IFN ineligible
Treatment Naïve	Persons who have not received any prior treatment for Hepatitis C
Treatment Experienced	Persons who have received prior treatment for Hepatitis C. Specific treatments they have been exposed to are with the correlating recommended regimens in Appendix 2.
Sustained Virologic Response (SVR)	Continued absence of detectable HCV RNA at least 12 weeks after completion of therapy
Direct-acting antiviral	Equivalent to protease inhibitors: Boceprevir, Telaprevir, Simeprevir, Paritaprevir, Grazoprevir, Elbasvir, etc.
Decompensated cirrhosis	Persons with moderate or severe hepatic impairment as shown by Child Turcotte Pugh (CTP) class B or C, and who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma

Medications for Hepatitis C

Approval	Brand	Generic	Route (#)	Serious Adverse Events
2002[9]	Copegus, Ribasphere	Ribavirin	Oral (4-6)	• Birth defects/fetal death, avoid use in pregnancy • Anemia with fatal or nonfatal MI • Hepatic failure and death • Severe hypersensitivity reactions • Pulmonary disorders • Severe depression and suicidal ideations • Autoimmune and infectious disorders • Bone marrow suppression with azathioprine • Growth impairment in pediatrics
2002[10]	Pegasys*	Peginterferon alfa-2a	IM (1)	• Neuropsychiatric reactions • Cardiovascular disorders • Bone marrow suppression • Autoimmune and endocrine disorders • Ophthalmologic disorders • Hepatic decompensation in cirrhotic patients, exacerbation in hepatitis B • Pulmonary disorders • Infections (bacterial, viral, fungal)

				• Colitis and pancreatitis • Hypersensitivity and serious skin reactions • Growth impairment in pediatrics • Peripheral neuropathy with telbivudine
2011[11]	Incivek*	Telaprevir	Oral (6)	• Anemia • Serious skin reactions • Rash
2011[12]	Victrelis*	Boceprevir	Oral (12)	• Anemia • Neutropenia
2013[13]	Olysio†	Simeprevir	Oral (1)	• Bradycardia with Sovaldi, amiodarone • Hepatic decompensation/hepatic failure • Photosensitivity • Rash
2013[14]	Sovaldi	Sofosbuvir	Oral (1)	• Bradycardia with amiodarone
2014[15]	Viekira Pak†	Paritaprevir/Ritonavir /Ombitasvir + Dasabuvir	Oral (4)	• Increased risk of ALT elevation • Hepatic decompensation/ hepatic failure in patients with cirrhosis
2014[16]	Harvoni	Sofosbuvir/Ledipasvir	Oral (1)	• Bradycardia with amiodarone
2015[17]	Technivie†	Paritaprevir/Ritonavir /Ombitasvir	Oral (2)	• Increased risk of ALT elevation • Hepatic decompensation/ hepatic failure in patients with cirrhosis
2015[18]	Daklinza	Daclatasvir	Oral (1)	• Bradycardia with Sovaldi, amiodarone
2016[27]	Zepatier	Elbatasvir/Grazoprevir	Oral (1)	• Increased risk of ALT elevation • Contraindicated with CTP Class B or C
2016[28]	Epclusa	Sofosbuvir/Velpatasvir	Oral (1)	• Bradycardia with amiodarone
2016[29]	Viekira XR†	Paritaprevir/Ritonavir /Ombitasvir + Dasabuvir	Oral (3)	• Increased risk of ALT elevation • Hepatic decompensation/ hepatic failure in patients with cirrhosis
2017[33]	Vosevi	Sofosbuvir/Velpatasvir /Voxilaprevir	Oral (1)	• Contraindicated in patients taking Rifampin • Risk of Hepatitis B Reactivation • Bradycardia with amiodarone
2017[34]	Mavyret	Glecaprevir/ Pibrentasvir	Oral (3)	• Contraindicated in patients with severe hepatic impairment (CTP Class C), not recommended for use in CTP Class B • Coadministration with Atazanivr and Rifampin • Risk of Hepatitis B Reactivation
***No longer recommended for use in Hepatitis C treatment by AASLD guidelines** **†Product discontinued by manufacturer, no longer available on the market**				

Pipeline Medications for Hepatitis C[30]

Proposed Release Date/Status	Drug	Company	MOA	Possible Indication	Frequency of Dosing
No current pipeline drugs for Hepatitis C. Merck and Janssen have discontinued drug development for the listed combinations.					
PoI = polymerase inhibitor; PI = protease inhibitor; GT = genotype					

Medications for Hepatitis C by Mechanism of Action

NS5B RNA Polymerase Inhibitor		NS5A Protein Inhibitor	
• ALS-335 • Dasabuvir	• MK-3682 • Sofosbuvir	• Velpatasvir • Odalasvir • Elbasvir • Ombitasvir	• MK-8408 • Pibrentasvir • Ledipasvir • Daclatasvir
NS3/4A Protease Inhibitor		**Interferons**	**RNA/DNA replication inhibitor**
• Voxilaprevir • Sovaprevir • Grazoprevir • Paritaprevir	• Glecaprevir • Boceprevir • Simeprevir • Telaprevir	• Peginterferon Alfa-2a • Peginterferon Alfa-2b	• Ribavirin

Erythropoietin Stimulating Agents (ESA) in Hepatitis C Treatment Related Anemia

According to the 2016 AASLD Guidelines, for patients taking Ribavirin and have a history of cardiovascular disease and a hemoglobin (Hgb) level below 10 g/dL, a dose reduction to 600 mg/day of Ribavirin is recommended in symptomatic or clinically indicated patients.[8] Discontinuation of Ribavirin is recommended for those with hemoglobin levels below 8.5 g/dL.[8] Reductions of Ribavirin dosing in 200 mg decrements towards a 600 mg/day dose did not appear to affect or compromise SVR rates.[19, 20]

In the case that a dose reduction or discontinuation of Ribavirin does not help raise the hemoglobin levels back to 10 g/dL at the 2 week re-assessment, the addition of erythropoietin or darbepoetin at the lowest ESA dose sufficient to alleviate symptoms is suggested.[21, 22] There is no optimal hemoglobin level for patients with hepatitis C, but reducing or interrupting the ESA dose once hemoglobin levels exceed 10 g/dL is recommended to prevent the increased risks of death and other serious cardiovascular adverse events.[9, 23, 24] Also, if the hemoglobin rises too rapidly (e.g. more than 1g/dL in any 2-week period), then a reduction of the ESA dose is suggested to reduce the rapid response.[9, 23, 24]

- **Coverage Criteria for ESA in Hepatitis C Treatment Related Anemia**
  - Initial approval:
    - Patient must meet all of the following criteria:
      - [1] Treatment regimen that includes Ribavirin, with or without peg-interferon
      - [2] Documentation of a Hgb level <8.5 g/dL OR of a Hgb level <10 g/dL two weeks after dose reduction of ribavirin to 600 mg/day
    - Approvals will be for a one-time fill, two weeks at a time.
  - Continuation:
    - Patient must meet all of the following criteria:
      - [1] Documentation of a Hgb level <10 g/dL after two weeks of prior ESA use
      - [2] Rise in hemoglobin is no more than 1 g/dL from the level two weeks prior

Different Drug Combination Regimens by AASLD[8]

RECOMMENDED REGIMENS				
Abbreviation	**Generic Name(s)**	**Brand Name(s)**	**Genotypes**	**Monthly Cost**
DCV + SOF	Daclatasvir + Sofosbuvir	Daklinza + Sovaldi	1a, 1b, 2, 3	$48,392.40
LDV-SOF	Sofosbuvir/Ledipasvir	Harvoni	1a, 1b, 4, 5, 6	$32,130.00
~~**PrO**~~	~~Paritaprevir/Ritonavir/Ombitasvir~~	~~Technivie~~	~~4~~	~~$25,234.17~~
~~**PrOD**~~	~~Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir~~	~~Viekira Pak~~	~~1a, 1b~~	~~$27,428.61~~
~~**PrOD**~~	~~Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir~~	~~Viekira XR~~	~~1a, 1b~~	~~$28,328.44~~
SOF	Sofosbuvir	Sovaldi	2, 3, 4	$27,652.80
~~**SMV + SOF**~~	~~Simeprevir + Sofosbuvir~~	~~Olysio + Sovaldi~~	~~1a, 1b~~	~~$49,498.51~~
ELB-GRZ	Elbasvir/Grazoprevir	Zepatier	1a, 1b, 4	$18,564.00
SOF-VEL	Sofosbuvir/Velpatasvir	Epclusa	Pangenotype	$25,418.40
ELB-GRZ + SOF	Elbasvir/Grazoprevir + Sofosbuvir	Zepatier + Sovaldi	3	$46,218.80
SOF-VEL-VOX	Sofosbuvir/Velpatasvir/Voxilaprevir	Vosevi	2, 3	$29,904.00
GLE-PIB	Glecaprevir/Pibrentasvir	Mavyret	1a, 1b, 2, 3, 4, 5, 6	$15,839.99
RBV can be added onto any of the above regimens, varies per treatment regimen needed				
RBV	Ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg)	Copegus, Ribasphere, Ribapak	All	$311.78

NOT RECOMMENDED REGIMENS	
Generic Name(s)	**Genotypes**
Sofosbuvir + Ribavirin	1
Peginterferon alfa + Ribavirin	ALL
Peginterferon alfa alone	ALL
Ribavirin alone	ALL
DAA alone	ALL
Peginterferon alfa + Ribavirin + only one DAA	1, 2, 3
Peginterferon alfa + Ribavirin + Simeprevir	4, 5, 6
Telaprevir or Boceprevir based	2, 3, 4, 5, 6
Ledipasvir based	2
Simeprevir based (no IFN)	1, 3
Peginterferon alfa + Ribavirin + Sofosbuvir	2, 3, 4, 5, 6
DAA = direct-acting antiviral	

Summary of Recommendations for Renal Dose Adjustments

Agents	CrCl 50-80 mL/min	CrCl 30-50 mL/min	CrCl <30 mL/min, without cirrhosis, urgency to treat/retreat is high, renal transplant is not an immediate option				
			Genotype 1a	Genotype 1b	Genotype 4	Genotype 2, 3, 5 or 6	RBV intolerant or ineligible
DCV	Standard	Standard					
LDV-SOF	Standard	Standard					
~~PrO~~	~~Standard~~	~~Standard~~					
~~PrOD~~	~~Standard~~	~~Standard~~	~~Preferred w/RBV~~	~~Preferred~~			
SOF	Standard	Standard					
~~SMV~~	~~Standard~~	~~Standard~~					
ELB-GRZ	Standard	Standard	Preferred	Preferred	Preferred		
SOF/VEL	Standard	Standard					
GLE-PIB	Standard	Standard	Preferred	Preferred	Preferred	Preferred	N/A
Peg-IFN*	180 µg/day	180 µg/day	N/A	N/A	N/A	Preferred	N/A
RBV	Standard	Alternate 200 mg, 400 mg	200 mg TIW or QD			Dose Adjust	

*CrCl <30 mL/min: 135 µg/day, ESRD with HD: 135 µg/week

Co-infection with HIV

Please refer to the Hepatitis C treatment guidelines (www.hcvguidelines.org) as well as the HIV/AIDS practice guidelines (www.aidsinfo.nih.gov) for recommendations in dose adjustments for patients with HIV/HCV co-infection. Any recommendations or changes shall be done in collaboration with the HIV practitioner.

Treatment of Adolescents – Ages 12 to 17 years[32]

As of April 7, 2017 Harvoni and Sovaldi were FDA approved for hepatitis C treatment in children ages 12 to 17.

- Harvoni is indicated for Genotype 1, 4, 5, 6 without cirrhosis or mild cirrhosis, aged 12 or older, weighing at least 77 pounds (35 kg)
- Sovaldi with Ribavirin is indicated for Genotype 2 or 3 without cirrhosis or mild cirrhosis, aged 12 or older, weighing at least 77 pounds (35 kg)

Documentation Requirements Prior to, During, and After Therapy[8]

- **Pre-Treatment Initiation Criteria**
  - Meets at least one of the identification requirements per the latest DHCS Hepatitis C Treatment Policy (refer to Appendix 1)
  - Is 18 years of age or older
  - Has been evaluated for readiness to initiate treatment and will adhere to the treatment
  - Does not have a life expectancy less than 12 months
  - Laboratory testing
    - Any time prior to initiating therapy (required)
      - Documentation of baseline hepatitis C virus-RNA level

- Serum pregnancy test in woman of childbearing age if RBV is also being initiated
- Screening at baseline and continuously throughout treatment for evidence of current or prior Hepatitis B infection is required.[31]
    - This is due to cases of hepatitis B reactivation occurring within 4 to 8 weeks of treatment resulting in serious liver problems or death.[31]

- Within 12 weeks prior to starting antiviral therapy
    - Complete blood count
    - Baseline hepatic function panel (albumin, total and direct bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase levels)
    - Glomerular filtration rate
- If requested regimen contains any HCV NS3 protease inhibitor (e.g. paritaprevir, simeprevir, grazoprevir), patient has history of decompensated liver disease or current CTP score of 7 or greater, then patient should NOT receive treatment due to lack of safety data. Also, if the CTP score is 5 or 6 and the person receiving treatment cannot be closely monitored for laboratory or clinical symptoms during treatment, then treatment with the requested regimen will be modified to an alternative preferred regimen.
- If requested regimen is for Zepatier, ensure that the patient is CTP class A and that close monitoring of total and direct bilirubin and transaminase levels occur every 1 to 2 weeks for the first 4 weeks is possible. If drug-induced liver injury is present then discontinuation is recommended, but if patient is tolerating and there are not signs/symptoms of liver injury, then continuous lab monitoring without discontinuation is recommended.
- Genotype 1a infected individuals:
    - If requesting for Zepatier, NS5A Resistance Genetic Testing MUST be performed and results provided. If no test is performed then an alternative preferred regimen will be recommended.
    - If requesting for Daklinza and patient has cirrhosis, NS5A Resistance Testing is recommended.
    - Due to baseline NS5A resistance-associated variants (RAV - positions M28, Q30, L31, and Y93 in genotype 1a) being strong pre-treatment predictors of treatment outcome for certain regimens, testing for these RAVs before deciding the treatment regimen is recommended.
- Genotype 3 infected individuals requesting Epclusa:
    - RAV testing for Y93H (NS5A testing) is recommended in treatment naïve/cirrhotic and treatment experienced/non-cirrhotic patients
    - Ribavirin should be included if test returns positive.
        - In comparing SVR12, rates went from 97% without baseline polymorphisms to 88% with Y93H polymorphism.
    - If patient is treatment experienced with SOF+RBV and do not require urgent treatment, recommended to defer treatment pending new future regimens. If retreatment is urgent, Epclusa x 24 weeks may be considered.

- Any additional information that would support the use of an alternate regimen from HPSJ preferred regimens
    - Examples
        - Patient meets criteria for being IFN ineligible
        - Contraindications to preferred regimens per individual package inserts
- If requesting for retreatment, provide all above information as well as past treatment history.
- Initial approval will last 6 weeks with a quantity limit up to 28 days of therapy per fill.

- **<u>After Treatment Criteria for Follow-up</u>**
  Quantitative HCV viral load 12 weeks after the completion of treatment is required and must be provided.

HPSJ Preferred Hepatitis C Treatment Regimens[a]

[a]Refer to Appendix 2 and 3 for further details on each regimen

Note: *Viekira Pak, Viekira XR, and Technivie are currently no longer commercially available as of January 2019.*

Genotype 1a, Treatment Naive, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	98%	12	$28,799.97	I	A
	Mavyret	99%	8	$31,679.98	I	A
2	Zepatier	92%	12†	$26,208.00	I	A
3	Harvoni	94-98%	12	$43,199.97	I	A
4	Harvoni	95%	8	$145,177.20	I	B
5	Daklinza & Sovaldi	96%	12	$34,944.00	I	B
6	Zepatier	100%	16	$31,679.98	IIa	B
†NS5A Resistance Testing must be ***negative*** to be approved for this regimen						
Justification: All agents have comparable efficacy. As there is no specific preferred regimen among the class I, level A recommended regimens, Epclusa and Mavyret will be 1st preferred due to overall safety, efficacy, cost, and duration of treatment. Zepatier notes a risk of liver injury. The package inserts also clearly state that Zepatier is contraindicated for use in CTP class B or C. Patients in this specific treatment group are non-cirrhotic, hence this adverse event does not affect the order of the regimens as much. If an alternate regimen from the preferred is requested then it will be considered on a case by case basis. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin. Harvoni x 8 weeks is only a viable option if patient meets the following criteria: Genotype 1, treatment naïve, non-cirrhotic, non-black, HIV-uninfected, and baseline HCV RNA below 6 million IU/mL(Class I, Level B) AND patient must not be able to receive either 1st, 2nd, 3rd, 4th, 5th, preferred therapies due to a level B evidence rating.						

Genotype 1a, Treatment Naive, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Zepatier	97%	12†	$26,208.00	I	A
	Epclusa	99%	12	$28,799.97	I	A
2	Harvoni	97-99%	12	$43,199.97	I	A
3	Mavyret	98%	12	$47,519.97	I	A
4	Zepatier	100%	16	$34,944.00	IIa	B
†NS5A Resistance Testing must be ***negative*** to be approved for this regimen						
Justification: For this treatment group, Zepatier and Epclusa are the most cost effective regimens. It shows comparable efficacy to the Harvoni and Mavyret. The 1st to 4th preferred regimens show shorter duration of treatment, lower overall cost, less risk of adverse events, and a high level of evidence. Zepatier is contraindicated in CTP Class B or C and is also known to have a risk of liver injury. Regimens containing Olysio and Sovaldi or Daklinza and Sovaldi are no longer recommended. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin. If the addition of Ribavirin is needed, Zepatier will become the last preferred regimen for this treatment group.						

Genotype 1a, Treatment Experienced with PEG/RBV, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	100%	12	$28,799.97	I	A
	Mavyret	99%	8	$31,679.98	I	A

2	Zepatier	93-94%	12†	$26,208.00	I	A
3	Harvoni	94%	12	$43,199.97	I	A
4	Daklinza & Sovaldi	83%	12	$145,177.20	I	B
5	Zepatier & Ribavirin	96-100%	16	$34,944.00	IIa	B

†NS5A Resistance Testing must be *negative* to be approved for this regimen

Justification:

All recommended regimens were preferred based on SVR-12, treatment duration, and levels of evidence. Overall the first 3 preferred regimens have greater sample sizes in the trials used to obtain SVR-12 as compared to trials with Harvoni and Daklinza with Sovaldi. Zepatier notes a risk of liver injury. The package inserts also clearly state that Zepatier is contraindicated for use in CTP class B or C. Patients in this specific treatment group are non-cirrhotic, hence this adverse event does not affect the order of the regimens as much. If an alternate regimen from the preferred is requested then it will be considered on a case by case basis. Recommendations for the use of Daklinza were derived from a trial that was performed for 24 weeks and had a sample size of 21 patients. Also, the trial was for patient's treatment experienced with PI + PEG + RBV. But in patients with just treatment experience with PEG + RBV for 12 weeks, there is an even lower SVR-12 rate of just 83% which suggests that further direct studies are needed before its cost effectiveness can truly be discerned. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin.

Genotype 1a, Treatment Experienced with PEG/RBV, Compensated Cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Zepatier	93-95%	12†	$26,208.00	I	A
	Epclusa	100%	12	$28,799.97	I	A
2	Harvoni & Ribavirin	96%	12	$43,199.97	I	A
3	Mavyret	98.9%	12	$47,519.97	I	B
4	Zepatier & Ribavirin	96-100%	16	$34,944.00	I	B

†NS5A Resistance Testing must be *negative* to be approved for this regimen

Justification:

Regimens with a Class I, Level A evidence are not specifically tiered in any order per AASLD guidelines. These regimens share similar efficacy as well. Overall, the final order of preferred regimens is based on overall cost and treatment duration. It is important to note that Zepatier is contraindicated in CTP class B/C and are known to have an increased risk of liver injury within the initial month of treatment initiation. Although Harvoni does not have as significant a risk, it is the next preferred regimen after Epclusa and Zepatier due the addition of Ribavirin. Mavyret is third preferred due to decreased duration and high SVR-12 compared to Zepatier with Ribavirin. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin.

Genotype 1b, Treatment Naive, Non-cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Epclusa	99%	12	$28,799.97	I	A
	Mavyret	99%	8	$31,679.98	I	A
2	Zepatier	95-99%	12	$26,208.00	I	A
3	Harvoni	97-99%	12	$43,199.97	I	A
4	Harvoni	95%	8	$28,799.98	I	B
5	Daklinza & Sovaldi	100%	12	$145,177.20	I	B

Justification:

The resulting preference in regimens were based on overall level of evidence, cost, similar efficacy, and treatment duration. Note that NS5A resistance testing is not necessary for Genotype 1b treatment regimens.

Harvoni x 8 weeks is only a viable option if patient meets the following criteria: Genotype 1, treatment naïve, non-cirrhotic, non-black, HIV-uninfected, and baseline HCV RNA below 6 million IU/mL(Class I, Level B) AND patient must not be able to receive either 1st, 2nd, 3rd, 4th, 5th, 6th preferred therapies due to a level IB evidence rating.

Genotype 1b, Treatment Naive, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Zepatier	99%	12	$26,208.00	I	A
	Epclusa	99%	12	$28,799.97	I	A
2	Harvoni	97-99%	12	$43,199.97	I	A
3	Mavyret	100%	12	$47,519.97	I	A

Justification:
Overall preferences were based on levels of evidence, SVR-12, safety, and overall cost. Note that NS5A resistance testing is not necessary for Genotype 1b treatment regimens.

Genotype 1b, Treatment Experienced with PEG/RBV, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	98%	12	$28,799.97	I	A
	Mavyret	99%	8	$31,679.98	I	A
2	Zepatier	93-94%	12	$26,208.00	I	A
3	Harvoni	94%	12	$43,199.97	I	A
4	Daklinza & Sovaldi	83%	12	$145,177.20	I	B

Justification:
Mavyret and Epclusa are the most cost effective regimens, showing a high efficacy and lower treatment duration for patients who have failed prior treatment with PEG + RBV. Overall preferences were based on levels of evidence, SVR-12, safety, and overall cost. Zepatier has an increased risk of liver injury, but these outcomes were reported mainly in patients with evidence of advanced cirrhosis prior to beginning treatment. The package insert also clearly states that Zepatier is contraindicated for use in CTP class B or C. Patients in this treatment group are non-cirrhotic, hence the updated adverse event does not affect this treatment regimen.

Genotype 1b, Treatment Experienced with PEG/RBV, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Zepatier	93-95%	12	$26,208.00	I	A
	Epclusa	98%	12	$28,799.97	I	A
2	Harvoni & Ribavirin	96%	12	$43,199.97	I	A
3	Mavyret	99%	12	$26,208.00	I	B

Justification:
Overall preferences were based on levels of evidence, SVR-12, safety, and overall cost. Zepatier has the possibility of a serious adverse event of liver injury within the first month of initiation, especially in patients with advanced cirrhosis. Zepatier is contraindicated in CTP class B or C and can only be initiated if the patient is CTP class A. Due to the cost effectiveness and lower pill burden of Zepatier and Epclusa, it is the preferred regimen over Harvoni with Ribavirin. Mavyret has a level of evidence of 1B making it the least preferred regimen in this treatment group.

Genotype 1a or 1b, Treatment Experienced with Protease Inhibitor + PEG/RBV, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	100%	12	$28,799.97	I	A
2	Harvoni	94%	12	$43,199.97	I	A

3	Zepatier & Ribavirin	93-96%	12†	$26,208.00	IIa	B
4	Zepatier & Ribavirin	96-100%	16	$34,944.00	IIa	B
5	Mavyret	92%	12	$47,519.97	IIa	B

†NS5A Resistance Testing must be *negative* to be approved for this regimen in genotype 1A patients, or must be Genotype 1b

Justification:
All recommended regimens were preferred based on SVR-12, levels of evidence, and lastly cost. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin.

Genotype 1a or 1b, Treatment Experienced with Protease Inhibitor + PEG/RBV, Compensated Cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Epclusa	100%	12	$28,799.97	I	A
2	Harvoni with Ribavirin	94%	12	$43,199.97	I	A
3	Zepatier & Ribavirin	93-96%	12†	$26,208.00	IIa	B
4	Zepatier & Ribavirin	96-100%	16	$34,944.00	IIa	B
5	Mavyret	92%	12	$47,519.97	IIa	B

†NS5A Resistance Testing must be *negative* to be approved for this regimen in genotype 1A patients, or must be Genotype 1b

Justification:
All recommended regimens were preferred based on SVR-12, levels of evidence, and lastly cost. Zepatier in genotype 1a patients has been noted to have a significantly reduced SVR-12 if NS5A resistance is present at baseline and would require prolonged treatment for 16 weeks along with the addition of Ribavirin.

Genotype 1a or 1b, Treatment Experienced with Sovaldi (Non-NS5A), Non-cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Vosevi†	97%	12	$89,712.00	I	A
2	Epclusa*	95%	12	$28,799.97	IIa	B
3	Mavyret	98%	12	$47,519.97	IIa	B
4	Harvoni & Ribavirin	100%	12	$43,199.97	IIa	B

†For Genotype 1a patients only
*For Genotype 1b patients only

Justification:
Vosevi is the solely level 1A recommended regimen and will be first preferred for genotype 1A patients that meet this treatment group. For genotype 1B patients, Epclusa will be preferred over Mavyret due to lower overall pill burden and similar SVR-12. Mavyret and Epclusa had overall low sample sizes hence the lower level of evidence. Harvoni and Ribavirin has 100% SVR-12 but requires use of Ribavirin and has more risks of adverse effects, hence it is least preferred.

Genotype 1a or 1b, Treatment Experienced with Sovaldi (Non-NS5A), Compensated Cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Vosevi†	97%	12	$89,712.00	I	A
2	Epclusa*	95%	12	$28,799.97	IIa	B
3	Mavyret	98%	12	$47,519.97	IIa	B

†For Genotype 1a patients only
*For Genotype 1b patients only

Justification:

Vosevi is the solely level 1A recommended regimen and will be first preferred for genotype 1A patients that meet this treatment group. For genotype 1B patients, Epclusa will be preferred over Mavyret due to lower overall pill burden, similar SVR-12 and lower cost. Mavyret and Epclusa had overall low sample sizes hence the lower level of evidence.

Genotype 1a or 1b, Treatment Experienced with NS5A-Inhibitor, Regardless of Cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Vosevi	96-100%	12	$89,712.00	I	A
2	Mavyret	94%	16	$63,359.84	IIa	B
Justification: Vosevi is the solely level 1A recommended regimen and will be first preferred for genotype 1A patients that meet this treatment group.						

Genotype 2, Treatment Naive, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	99-100%	12	$28,799.97	I	A
	Mavyret	99%	8	$31,679.98	I	A
2	Daklinza & Sovaldi	100%	12	$145,177.20	IIa	B
Justification: Preferred regimens are based on levels of evidence and treatment duration in order to comply with DHCS policy.						

Genotype 2, Treatment Naive, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	99-100%	12	$28,799.97	I	A
2	Mavyret	100%	12	$47,519.88	I	B
3	Daklinza & Sovaldi	100%	12	$145,177.20	IIa	B
Justification: Preferred regimens are based on levels of evidence to comply with DHCS policy. Also noted that Mavyret clinical trials had a sample size that was low hence the lower level of evidence.						

Genotype 2, Treatment Experienced with PEG/RBV, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	99-100%	12	$28,799.97	I	A
	Mavyret	98%	8	$31,679.98	I	A
2	Daklinza & Sovaldi	100%	12	$145,177.20	IIa	B
Justification: Preferred regimens are based on levels of evidence and duration of therapy.						

Genotype 2, Treatment Experienced with PEG/RBV, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	99-100%	12	$28,799.97	I	A
2	Mavyret	100%	12	$47,519.88	I	B
3	Daklinza & Sovaldi	100%	12	$145,177.20	IIa	B
Justification:						

Preferred regimens are based on levels of evidence to comply with DHCS policy.

Genotype 2, Treatment Experienced with Sovaldi, Regardless of Cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	97%	12	$28,799.97	I	B
2	Mavyret	99-100%	12	$47,519.97	IIb	B
[a]Corresponds to persons treatment experienced with SOF + RBV + IFN eligible						
Justification: Preferred regimens are based on levels of evidence to comply with DHCS policy. Note that although Mavyret has a high SVR-12, the population specific to this treatment group within the trials was unclear, hence the lower level of evidence.						

Genotype 3, Treatment Naive, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	98%	12	$28,799.97	I	A
	Mavyret	95%	8	$31,679.98	I	A
2	Daklinza & Sovaldi	67-97%	12	$145,177.20	I	A
Justification: Preferred regimens are based on levels of evidence to comply with DHCS policy as well as treatment duration, safety, and cost. Also, the 67% in SVR-12 for Daklinza with Sovaldi was found in non-cirrhotic genotype 3 patients with a NS5A Y93H polymorphism. For Daklinza regimens in genotype 3, it is suggested that a negative NS5A Y93H polymorphism would be required before further consideration of either regimen can occur.						

Genotype 3, Treatment Naive, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa†	93%	12	$28,799.97	I	A
2	Mavyret	100%	12	$47,519.97	I	A
3	Vosevi*	100%	12	$89,712.00	IIa	B
4	Daklinza & Sovaldi	58-88%	24	$290,354.40	IIa	B
5	Daklinza & Sovaldi & Ribavirin	58-88%	24	$290,354.40	IIa	B
†Y93H polymorphism Testing must be ***negative*** to be approved for this regimen, if positive, addition of Ribavirin is necessary *Only if Y93H polymorphism is present						
Justification: Preferred regimens are based on levels of evidence to comply with DHCS policy. For both Epclusa and Daklinza regimens in genotype 3, it is suggested that a negative NS5A Y93H polymorphism would be required before further consideration of either regimen can occur. In cirrhotic patients with Y93H polymorphism, Epclusa regimens are recommended to have Ribavirin added or Vosevi can be used instead (note trial only involved 6 patients that would meet this treatment group).						

Genotype 3, Treatment Experienced with PEG/RBV, Non-cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa†	95%	12	$28,799.97	I	A
2	Daklinza & Sovaldi	92-98%	12	$145,177.20	I	A
3	Mavyret	96%	16	$63,359.96	IIa	B

4	Vosevi	84%	12	$89,712.00	IIa	B

† Y93H polymorphism Testing must be *negative* to be approved for this regimen, if positive, addition of Ribavirin is necessary

Justification:
Preferences were based on level of evidence to comply with DHCS policy, as well as SVR-12, and total cost. For both Epclusa and Daklinza regimens in genotype 3, it is suggested that a negative NS5A Y93H polymorphism would be required before further consideration of either regimen can occur. In cirrhotic patients with Y93H polymorphism, Epclusa regimens are recommended to have Ribavirin added. Also noted that the true appropriate length of therapy is still unclear for Mavyret treatment in this patient group, hence 16 weeks was deemed appropriate as an alternative regimen.

Genotype 3, Treatment Experienced with PEG/RBV, Compensated Cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Epclusa & Ribavirin	89%	12	$28,799.97	I	B
2	Zepatier & Sovaldi	100%	12	$127,008.00	I	B
3	Mavyret	96%	16	$63,359.96	IIa	B
4	Vosevi	84%	12	$89,712.00	IIb	B

Justification:
Preferences were based on level of evidence to comply with DHCS policy, SVR-12, and total cost. Please note that Zepatier with Sovaldi for 12 weeks is placed as the second preferred regimen in this treatment group due to a smaller sample size (half the size) used during trials in comparison to the study for Epclusa with Ribavirin.

Genotype 3, Treatment Experienced with DAA, Regardless of Cirrhosis

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Vosevi	96%	12	$89,712.00	I	A
2	Vosevi with Ribavirin	-	12	$89,712.00	IIa	C

Justification:
Preferences were based on level of evidence to comply with DHCS policy. Note that Vosevi with Ribavirin is only intended for patients with treatment failure to NS5A inhibitor and cirrhosis.

Genotype 4, Treatment Naive, Non-Cirrhotic

Preference	Regimens	SVR-12	Duration (weeks)	Total Cost	Class	Level
1	Epclusa	100%	12	$28,799.97	I	A
	Mavyret	100%	8	$31,679.98	I	A
2	Zepatier	93-95%	12	$26,208.00	IIa	B
3	Harvoni	95-100%	12	$43,199.97	IIa	B

Justification:
Preferences were based on level of evidence to comply with DHCS policy, as well as SVR-12, safety, total duration, and total cost. Zepatier has increased risk of liver injury, but these outcomes were reported mainly in patients with evidence of advanced cirrhosis prior to beginning treatment. The package inserts also clearly state that Zepatier is contraindicated for use in CTP class B or C, hence in this treatment group it can be initiated if the patient is non-cirrhotic/CTP class A. Vigilance in evaluating contraindications for each individual agent is necessary in ensuring the safety of patients taking HCV regimens. Zepatier is preferred over Harvoni due to cost effectiveness.

Genotype 4, Treatment Naive, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	100%	12	$28,799.97	I	A
2	Mavyret	100%	12	$47,519.97	I	B
3	Zepatier	100%	12	$26,208.00	IIa	B
4	Harvoni	95-100%	12	$43,199.97	IIa	B

Justification:
Preferences were based on level of evidence to comply with DHCS policy, SVR-12, and total cost. Zepatier has increased risk of liver injury, but these outcomes were reported mainly in patients with evidence of advanced cirrhosis prior to beginning treatment. The package insert also clearly states that Zepatier are contraindicated for use in CTP class B or C, hence use in this treatment group can be initiated if the patient is non-cirrhotic/CTP class A. Vigilance in evaluating contraindications for each individual agent is necessary in ensuring the safety of patients taking HCV regimens. Note that the Mavyret regimen has a lower level of evidence due to the SVR-12 results are from a mixed sample size of 16 treatment naïve- and -experienced genotype 4 patients with compensated cirrhosis. Zepatier is preferred over Harvoni due to cost effectiveness.

Genotype 4, Treatment Experienced with PEG/RBV, Non-Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	100%	12	$28,799.97	I	A
2	Mavyret	93%	8	$31,679.98	I	B
3	Harvoni	95%	12	$43,199.97	IIa	B
4	Zepatier	87%	12	$26,208.00	IIa	B
5	Zepatier & Ribavirin	87%	16	$34,944.00	IIa	B

Justification:
Preferences were based on level of evidence to comply with DHCS policy, SVR-12, pill burden, cost, and adverse effects. Zepatier has increased risk of liver injury, but these outcomes were reported mainly in patients with evidence of advanced cirrhosis prior to beginning treatment. The package insert also clearly states that Zepatier is contraindicated for use in CTP class B or C, hence use in this treatment group can be initiated if the patient is non-cirrhotic/CTP class A. Vigilance in evaluating contraindications for each individual agent is necessary in ensuring the safety of patients taking HCV regimens.

Genotype 4, Treatment Experienced with PEG/RBV, Compensated Cirrhotic						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa	100%	12	$28,799.97	I	A
2	Mavyret	100%	12	$47,519.97	IIa	B
3	Harvoni & Ribavirin	94%	12	$43,199.97	IIa	B
4	Zepatier	87%	12	$26,208.00	IIa	B
5	Zepatier	87%	16	$34,944.00	IIa	B

Justification:
Preferences were based on level of evidence to comply with DHCS policy, SVR-12, and overall cost. Zepatier has increased risk of liver injury, but these outcomes were reported mainly in patients with evidence of advanced cirrhosis prior to beginning treatment. The package insert also clearly states that Zepatier is contraindicated for use in CTP class B or C, hence use in this treatment group can be initiated if the patient is non-cirrhotic/CTP class A. Vigilance in evaluating contraindications for each individual agent is necessary in ensuring the safety of patients taking HCV regimens.

Genotype 4, Treatment Experienced with NS5A Inhibitor, Regardless of Cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Vosevi	96%	12	$89,712.00	I	A
Justification: There is currently only one option available for this treatment group.						

Genotype 5 or 6, Treatment Naïve, Regardless of cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Mavyret	100%	8* or 12†	$31,679.98 or $47,519.97	I	A
	Epclusa	96-100%	12	$28,799.97	I	B
2	Harvoni	95-96%	12	$43,199.97	IIa	B
Genotype 5 or 6, Treatment Experienced with PEG/RBV, Regardless of cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Mavyret	100%	12†	$47,519.97	I	B
	Mavyret	100%	8*	$31,679.98	IIa	B
	Epclusa	100%	12	$28,799.97	IIa	B
2	Harvoni	100%	12	$43,199.97	IIa	B
Genotype 5 or 6, DAA Treatment Experienced (Includes NS5A inhibitor), Regardless of cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Vosevi	100%	12	$89,712.00	IIa	B
†For patient's that have cirrhosis *For patient's without cirrhosis						
Justification for Genotypes 5 & 6, regardless of treatment history and cirrhosis status: There is very limited data on both regimens in either genotype 5 or 6. Preferences were based on level of evidence to comply with DHCS policy, SVR-12, and overall cost.						

Decompensated Cirrhosis, Genotype 1, 4, 5, or 6, Regardless of Treatment History						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa & Ribavirin	94-96%	12	$28,799.97	I	A
2	Harvoni & Ribavirin	87%	12	$43,199.97	I	A
3[b]	Epclusa	86-92%	24	$57,599.94	I	A
4[b]	Harvoni	89%	24	$86,399.94	I	A
5	Daklinza & Sovaldi & Ribavirin	83%	12	$145,177.20	I	B
6[a]	Epclusa & Ribavirin	97%	24	$57,599.94	II	C
7[a]	Harvoni & Ribavirin	89%	24	$86,399.94	II	C
8[b]	Daklinza & Sovaldi	89%	24	$290,354.40	II	C
Decompensated Cirrhosis, Genotype 2 or 3, Regardless of Treatment History						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Epclusa & Ribavirin	85-100%	12	$28,799.97	I	A
2[b]	Epclusa	85-100%	24	$57,599.94	I	A
3	Daklinza & Sovaldi & Ribavirin	83%	12	$145,177.20	II	B

4[b]	Daklinza & Sovaldi	83%	24	$290,354.40	II	C
5[a]	Epclusa & Ribavirin	-	24	$57,599.94	II	C

[a]Corresponds to persons treatment experienced with Sovaldi
[b]Ribavirin ineligible

Justification:
Treatment regimens for decompensated cirrhotic patients were first arranged based on the corresponding level of evidence to comply with DHCS Policy, then by SVR-12 and overall cost. Note that Sovaldi with Ribavirin in Genotype 2 or 3 decompensated cirrhotic patients is no longer recommended. There is no outcome data for decompensated patients with history of Sofosbuvir failure. The recommended regimen is based off compensated cirrhotic patients.

Post-Liver Transplantation, Genotype 1, 4, 5, or 6, Regardless of Treatment History, Infection in Allograft, Includes those with Compensated Cirrhosis						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1†	Mavyret	98%	12	$47,519.97	I	A
2	Harvoni & Ribavirin	96%	12	$43,199.97	I	A
3	Daklinza & Sovaldi & Ribavirin	87-94%	12	$145,177.20	I	B
Post-Liver Transplantation, Genotype 2 or 3, Regardless of Treatment History, Infection in Allograft, Includes those with Compensated Cirrhosis						
1†	Mavyret	98%	12	$47,519.97	I	A
2	Daklinza & Sovaldi & Ribavirin	87-94%	12	$145,177.20	II	A
3	Epclusa & Ribavirin	-	12	$28,799.97	II	C
4	Mavyret	-	12	$47,519.97	II	C

*SVR-4 based on a retrospective multicenter analysis
†For patient's without cirrhosis

Justification:
Treatment regimens for decompensated cirrhotic patients were first arranged based on the corresponding level of evidence to comply with DHCS Policy, then by SVR-12, pill burden, and overall cost.

Post-Liver Transplantation/Decompensated Cirrhosis, Genotype 1, 4, 5 or 6, Regardless of Treatment History						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Harvoni & Ribavirin	60-85%	12	$43,199.97	I	B
Post-Liver Transplantation/Decompensated Cirrhosis, Genotype 2or 3, Regardless of Treatment History						
Preference	**Regimens**	**SVR-12**	**Duration (weeks)**	**Total Cost**	**Class**	**Level**
1	Daklinza & Sovaldi & Ribavirin	83-91%	12	$145,177.20	II	A
2	Epclusa & Ribavirin	-	12	$28,799.97	II	C

Justification:
There is very little evidence overall for patients within these treatment groups. As these are the only currently listed recommendations per AASLD, any other treatment regimens will be considered investigational and evaluated on a case-by-case basis per the criteria for coverage of Investigational Services (Title 22 § 51303).

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REVIEW & EDIT HISTORY

Document Changes	Reference	P&T Date	P&T Chairman
Creation of Policy	Role of PI's in Hep C 2-21-12.doc	2/2012	Allen Shek PharmD BCPS
Update to Policy	HCV update (Sovaldi) 2014-02-18.doc	2/2014	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HCV (Sovaldi) Criteria Update 2014-05-29.doc	5/2014	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HCV Treatment Update 2014-09-16.doc	9/2014	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HCV Update 2-17-15.doc	2/2015	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2015-09.docx	9/2015	Jonathan Szkotak, PharmD, BCACP
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2015-11.docx	11/2015	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2016-02.docx	2/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2016-05.docx	5/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2016-09.docx	9/2016	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2016-12.docx	12/2016	Johnathan Yeh, PharmD
Review of Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2017-02.docx	2/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2017-05.docx	5/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2017-09.docx	9/2017	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2017-12.docx	12/2017	Johnathan Yeh, PharmD
Review of Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2018-02.docx	2/2018	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2018-09.docx	9/2018	Johnathan Yeh, PharmD
Update to Policy	HPSJ Coverage Policy – Infectious Disease – Hepatitis C 2018-12.docx	12/2018	Matthew Garrett, PharmD
Update to Policy	Hepatitis C	9/2019	Matthew Garrett, PharmD
Review of Policy	Hepatitis C	2/2020	Matthew Garrett, PharmD
Update to Policy	Hepatitis C	5/2020	Matthew Garrett, PharmD
Review of Policy	Hepatitis C	5/2021	Matthew Garrett, PharmD

Appendix 1. California Department of Health Care Services Treatment Policy for the Management of Chronic Hepatitis C Effective March 30, 2020

This policy was developed by the California Department of Health Care Services (DHCS) based upon a review of the medical literature, the most recent guidelines, and reports published by the American Association for the Study of Liver Diseases (AASLD)/ Infectious Diseases Society of America (IDSA). This policy may be revised as new information becomes available.

1. Treatment considerations and choice of regimen for hepatitis C virus (HCV)-infected patients:
    a. Please refer to AASLD guidelines (hcvguidelines.org) for recommended treatment regimens and durations.

2. Identifying treatment candidates:
    a. Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy who cannot be remediated by HCV therapy, liver transplantation, or another directed therapy.

    b. Patient readiness and adherence:
        i. Patients shall be evaluated for readiness to initiate treatment.
        ii. Patients selected for treatment shall be able and willing to strictly adhere to treatment protocols prescribed by their provider.
        iii. Caution shall be exercised with patients who have a history of treatment failure with prior HCV treatment due to non-adherence with treatment regimen and appointments.
        iv. Patients shall be educated regarding the potential risks and benefits of HCV therapy, as well as the potential for resistance and failed therapy if medication is not taken as prescribed.

3. Other considerations
    a. Quantity limits:
        i. Prescription of HCV therapy will be dispensed in quantities up to 28 days at a time.
    b. Criteria for reauthorization/continuation of therapy:
        i. Initial authorization criteria have been met.
        ii. Evidence of lack of adherence may result in denial of treatment reauthorization.
        iii. Missed medical appointments related to HCV may result in the denial of treatment authorization.
    c. Laboratory testing:
        i. Documentation of baseline HCV-RNA level.
        ii. Laboratory testing and monitoring should be consistent with current AASLD/IDSA guidelines.
    d. Populations unlikely to benefit from HCV Treatment:

According to AASLD/IDSA HCV guidelines, “patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation or another directed therapy do not require antiviral treatment. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.” Please refer to AASLD guidelines for more information on populations unlikely to benefit from HCV treatment (hcvguidelines.org).

e. Retreatment:

Retreatment will be considered where there is evidence that such retreatment will improve patient outcomes. Please refer to AASLD guidelines for recommended retreatment regimens (hcvguidelines.org).

f. Criteria for coverage of investigational services (Title 22 § 51303):
    i. Investigational services are not covered except when it is clearly documented that all of the following apply.
    ii. Conventional therapy will not adequately treat the intended patient's condition.
    iii. Conventional therapy will not prevent progressive disability or premature death.
    iv. The provider of the proposed service has a record of safety and success with it equivalent or superior to that of other providers of the investigational service.
    v. The investigational service is the lowest cost item or service that meets the patient's medical needs and is less costly than all conventional alternatives.
    vi. The service is not being performed as a part of a research study protocol.
    vii. There is a reasonable expectation that the investigational service will significantly prolong the intended patient's life or will maintain or restore a range of physical and social function suited to activities of daily living.
    viii. All investigational services require prior authorization. Payment will not be authorized for investigational services that do not meet the above criteria or for associated inpatient care when a beneficiary needs to be in the hospital primarily because she/he is receiving such non-approved investigational services.

g. Unlabeled use of medication:

Authorization for unlabeled use of drugs shall not be granted unless the requested unlabeled use represents reasonable and current prescribing practices. The determination of reasonable and current prescribing practices shall be based upon:
    i. Reference to current medical literature.
    ii. Consultation with provider organizations and academic and professional specialists.

Appendix 2. Preference of AASLD Recommendations per Genotype[1]

For regimens with Ribavirin, the daily pill total is based off a dose of 1000 mg using Ribavirin (RBV) 200 mg capsules, also add a minimum additional cost per week of $77.94.

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes/Past Treatment	Trial
Genotype 1a, Treatment Naive, Non-cirrhotic												
1	GLE-PIB	No	99%	3	$3,959.99	8	$31,679.98	1	A	3		SURVEYOR-1 ENDURANCE-1
1	SOF-VEL	No	98%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	ELB-GRZ	No	92%	1	$2,184.00	12	$26,208.00	I	A	2	No baseline NS5A RAVs	C-EDGE C-WORTHY
3	LDV-SOF	No	94-98%	1	$3,600.00	12	$43,199.97	I	A	1		ION-1, ION-3
4	LDV-SOF	No	95%	1	$3,600.00	8	$28,799.98	I	B	1	<6 million IU/mL	ION-3
5	(Alt) DCV + SOF	No	96%	2	$12,098.10	12	$145,177.20	I	B	2		ALLY-2
6	(Alt) ELB-GRZ	No	100%	6	$2,184.00	16	$34,944.00	IIa	B	10	Baseline NS5A RAVs present	C-EDGE TE, Zeuzem, 2015[55] Kwo, 2015[56]
Genotype 1a, Treatment Naive, Compensated Cirrhotic												
1	ELB-GRZ	No	97%	1	$2,184.00	12	$26,208.00	I	A	2	No baseline NS5A RAVs	C-EDGE C-WORTHY
1	SOF-VEL	No	99%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	LDV-SOF	No	97-99%	1	$3,600.00	12	$43,199.97	I	A	1		ION-1, ION-3
3	GLE-PIB	No	98%	3	$3,959.99	12	$47,519.97	1	A	3		EXPEDITION-1
4	(Alt) ELB-GRZ	Yes	100%	6	$2,184.00	16	$34,944.00	IIa	B	10	Baseline NS5A RAVs present	C-EDGE TE Zeuzem, 2015[55] Kwo, 2015[56]

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes	Trial
Genotype 1a, Treatment Experienced with PEG/RBV, Non-cirrhotic												
1	GLE-PIB	No	99%	3	$3,959.99	8	$31,679.98	1	A	3		ENDURANCE-1
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	ELB-GRZ	No	93-94%	1	$2,184.00	12	$26,208.00	I	A	2	No baseline NS5a RAVs present	C-EDGE TE Zeuzem, 2015[55]
3	LDV-SOF	No	94%	1	$3,600.00	12	$43,199.97	I	A	1		ION-2
4	(Alt) DCV + SOF	No	83%	2	$12,098.10	12	$145,177.20	I	B	2		Pol, 2015[16] Welzel, 2015[12]
5	(Alt) ELB-GRZ	Yes	96-100%	6	$2,184.00	16	$34,944.00	IIa	B	10		C-EDGE TE, Zeuzem 2015[55], Jacobsen, 2015[57]
Genotype 1a, Treatment Experienced with PEG/RBV, Compensated Cirrhotic												
1	ELB-GRZ	No	93-95%	1	$2,184.00	12	$26,208.00	I	A	2	No baseline NS5A RAVs present	C-EDGE TE, Zeuzem, 2015[55]
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	(Alt) LDV-SOF	Yes	96%	6	$3,600.00	12	$43,199.97	I	A	9		SIRIUS Bourliere, 2014a[21]/b[22]
3	GLE-PIB	No	98.9%	3	$3,959.99	12	$47,519.97	I	B	3		EXPEDITION-1
4	(Alt) ELB-GRZ	Yes	96-100%	6	$2,184.00	16	$34,944.00	I	B	10	Baseline NS5A RAVs present	C-EDGE TE, Zeuzem 2015[55], Jacobsen, 2015[57]

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Past Treatment	Trial
Genotype 1b, Treatment Naive, Non-cirrhotic												
1	GLE-PIB	No	99%	3	$3,959.99	8	$31,679.98	1	A	3		SURVEYOR-1 ENDURANCE-1
1	SOF-VEL	No	99%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	ELB-GRZ	No	95-99%	1	$2,184.00	12	$26,208.00	I	A	2		C-EDGE C-WORTHY
3	LDV-SOF	No	97-99%	1	$3,600.00	12	$43,199.97	I	A	1		ION-1, ION-3
4	LDV-SOF	No	95%	1	$3,600.00	8	$28,799.98	I	B	1	<6 million IU/mL	ION-3
5	DCV + SOF	No	100%	2	$12,098.10	12	$145,177.20	I	B	2		ALLY-2
Genotype 1b, Treatment Naive, Compensated Cirrhotic												
1	ELB-GRZ	No	99%	1	$2,184.00	12	$26,208.00	I	A	2		C-EDGE
1	SOF-VEL	No	99%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	LDV-SOF	No	97-99%	1	$3,600.00	12	$43,199.97	I	A	1		ION-1, ION-3
3	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	1	A	3		EXPEDITION-1
Genotype 1b, Treatment Experienced with PEG/RBV, Non-cirrhotic												
1	GLE-PIB	No	99%	3	$3,959.99	8	$31,679.98	I	A	3		ENDURANCE-1
1	SOF-VEL	No	98%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	ELB-GRZ	No	93-94%	1	$2,184.00	12	$26,208.00	I	A	2		C-EDGE TE, Zeuzem, 2015[55]
3	LDV-SOF	No	94%	1	$3,600.00	12	$43,199.97	I	A	1		ION-2
4	(Alt) DCV + SOF	No	83%	2	$12,098.10	12	$145,177.20	I	B	2		Pol, 2015[16] Welzel, 2015[12]

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes	Trial
Genotype 1b, Treatment Experienced with PEG/RBV, Compensated Cirrhotic												
1	ELB-GRZ	No	93-95%	1	$2,184.00	12	$26,208.00	I	A	2		C-EDGE TE, Zeuzem 2015[55]
1	SOF-VEL	No	98%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	(Alt) LDV-SOF	Yes	96%	6	$3,600.00	12	$43,199.97	I	A	9		SIRIUS Bourliere, 2014a[21]/b[22]
3	GLE-PIB	No	99%	3	$3,959.99	12	$47,519.97	I	B	3		EXPEDITION-1
Genotype 1a or 1b, Treatment Experienced with Protease Inhibitor + PEG/RBV, Non-Cirrhotic												
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	LDV-SOF	No	94%	1	$3,600.00	12	$43,199.97	I	A	1		Afdhal, 2014
3	(Alt) ELB-GRZ	Yes	93-96%	1	$2,184.00	12	$26,208.00	IIa	B	10	All Genotype 1b or Genotype 1a and no baseline NS5a RAVs present	Summa, 2012[58] Howe, 2014[59] Forns, 2015[60]
4	(Alt) ELB-GRZ	Yes	96-100%	6	$2,184.00	16	$34,944.00	IIa	B	10	Baseline NS5a RAVs present	C-EDGE TE, Zeuzem 2015[55], Jacobsen, 2015[57]
5	GLE-PIB	No	92%	3	$3,959.99	12	$47,519.97	IIa	B	3		MAGELLAN-1
Genotype 1a or 1b, Treatment Experienced with Protease Inhibitor and PEG/RBV, Compensated Cirrhotic												
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	(Alt) LDV-SOF	Yes	96%	6	$3,600.00	12	$43,199.97	I	A	9		SIRIUS Bourliere, 2014a[21]/b[22]
3	(Alt) ELB-GRZ	Yes	93-96%	1	$2,184.00	12	$26,208.00	IIa	B	10	All Genotype 1b or Genotype 1a and no baseline NS5a RAVs present	Summa, 2012[58] Howe, 2014[59] Forns, 2015[60]

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes	Trial
Genotype 1a or 1b, Treatment Experienced with Protease Inhibitor and PEG/RBV, Compensated Cirrhotic (Cont.)												
4	(Alt) ELB-GRZ	Yes	96-100%	6	$2,184.00	16	$34,944.00	IIa	B	10	Baseline NS5a RAVs present	C-EDGE TE, Zeuzem 2015[55], Jacobsen, 2015[57]
5	GLE-PIB	No	92%	3	$3,959.99	12	$47,519.97	IIa	B	3		MAGELLAN-1
Genotype 1a or 1b, Treatment Experienced with Sovaldi (Non-NS5A), Non-Cirrhotic												
1	SOF-VEL-VOX	No	97%	1	$7,476.00	12	$89,712.00	I	A	1	Genotype 1A only	POLARIS-4
2	SOF-VEL	No	95%	1	$2,400.00	12	$28,799.97	IIa	B	2	Genotype 1B only	POLARIS-4
3	GLE-PIB	No	98%	3	$3,959.99	12	$47,519.97	IIa	B	3		ENDURANCE-1 EXPEDITION-1 MAGELLAN-1
4	(Alt) LDV-SOF	Yes	100%	6	$3,600.00	12	$43,199.97	IIa	B	9	Excludes Simeprevir history	Osinusi, 2014[17] Wyles, 2015b[18] Reddy, 2015[19]
Genotype 1a or 1b, Treatment Experienced with Sovaldi (Non-NS5A), Compensated Cirrhotic												
1	SOF-VEL-VOX	No	97%	1	$7,476.00	12	$89,712.00	I	A	1	Genotype 1A only	POLARIS-4
2	SOF-VEL	No	95%	1	$2,400.00	12	$28,799.97	IIa	B	2	Genotype 1B only	POLARIS-4
3	GLE-PIB	No	99%	3	$3,959.99	12	$47,519.97	IIa	B	3		EXPEDITION-1 MAGELLAN-1
Genotype 1a or 1b, Treatment Experienced with NS5A inhibitor, Regardless of Cirrhosis												
1	SOF-VEL-VOX	No	96-100%	1	$7,476.00	12	$89,712.00	I	A	1		POLARIS-1
2	(Alt) GLE-PIB	No	94%	3	$3,959.99	16	$63,359.96	IIa	B	3	Excludes NS3/4 PI inclusive DAA regimens	MAGELLAN-1

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes	Trial
Genotype 2, Treatment Naïve, Non-cirrhotic												
1	GLE-PIB	No	99%	3	$3,959.99	8	$31,679.98	I	A	3		SURVEYOR-2 ENDURANCE-2
1	SOF-VEL	No	99-100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	DCV + SOF	No	100%	2	$12,098.10	12	$145,177.20	IIa	B	2		Wang, 2014[28] ALLY-2 Sulkowski, 2014b[29]
Genotype 2, Treatment Naïve, Compensated Cirrhotic												
1	SOF-VEL	No	99-100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	B	3		EXPEDITION-1
3	(Alt) DCV + SOF	No	100%	2	$12,098.10	16 to 24	$193,569.60 to $290,354.40	IIa	B	2		Wang, 2014[28] ALLY-2 Sulkowski, 2014b[29]
Genotype 2, Treatment Experienced with PEG/RBV, Non-cirrhotic												
1	GLE-PIB	No	98%	3	$3,959.99	8	$31,679.98	I	A	3		SURVEYOR-2
1	SOF-VEL	No	99-100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1 ASTRAL-2 POLARIS-2
2	(Alt) DCV + SOV	No	100%	2	$12,098.10	12	$145,177.20	IIa	B	2		Wang, 2014[28] ALLY-2 Sulkowski, 2014b[29]
Genotype 2, Treatment Experienced with PEG/RBV, Compensated Cirrhotic												
1	SOF-VEL	No	99%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1 ASTRAL-2 POLARIS-2
2	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	B	3		EXPEDITION-1
3	(Alt) DCV + SOF	No	100%	2	$12,098.10	16 to 24	$193,569.60 to $290,354.40	IIa	B	2		Wang, 2014[28] ALLY-2

												Sulkowski, 2014b[29]
Preference	**Drug(s)**	**RBV**	**SVR-12**	**Pills**	**Weekly Cost**	**Duration (weeks)**	**Treatment Cost**	**Class**	**Level**	**SAE**	**Notes**	**Trial**
Genotype 2, Treatment Experienced with Sovaldi, Regardless of Cirrhosis												
1	SOF-VEL	No	97%	1	$2,400.00	12	$28,799.97	I	B	2		POLARIS-4
2	GLE-PIB	No	99-100%	3	$3,959.99	12	$47,519.97	IIb	B	3		ENDURANCE-2 EXPEDITION-1
Genotype 3, Treatment Naïve, Non-cirrhotic												
1	GLE-PIB	No	95%	3	$3,959.99	8	$31,679.98	I	A	3		ENDURANCE-3
1	SOF-VEL	No	98%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1 ASTRAL-3
2	DCV + SOF	No	67-97%	2	$12,098.10	12	$145,177.20	I	A	2		ALLY-3 ENDURANCE-3
Genotype 3, Treatment Naïve, Compensated Cirrhotic												
1	SOF-VEL	No	93%	1	$2,400.00	12	$28,799.97	I	A	2	Add RBV if Y93H polymorphism present = 3rd line	ASTRAL-1 ASTRAL-3
2	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	A	3		SURVEYOR-2
3	SOF-VEL-VOX	No	100%	1	$7,476.00	12	$89,712.00	IIa	B	1	If Y93H polymorphism present	POLARIS-3
4	DCV + SOF	No	58-88%	2	$12,098.10	24	$290,354.40	IIa	B	2		ALLY-2 ALLY-3
5	DCV + SOF	Yes	58-88%	7	$12,098.10	24	$290,354.40	IIa	B	10		ALLY-2 ALLY-3
Genotype 3, Treatment Experienced with PEG/RBV, Non-cirrhotic												
1	SOF-VEL	No	95%	1	$2,400.00	12	$28,799.97	I	A	2	Add RBV if Y93H polymorphism present = 2nd line	ASTRAL-3 POLARIS-2 Planko, 2015[67]
2	(Alt) DCV + SOF	No	92-98%	2	$12,098.10	12	$145,177.20	I	A	2		ALLY-3
3	(Alt) GLE-PIB	No	96%	3	$3,959.99	16	$63,359.96	IIa	B	3	Especially if A30K	SURVEYOR-2

											substitution present	
4	(Alt) SOF-VEL-VOX	No	84%	1	$7,476.00	12	$89,712.00	IIa	B	1	Only if Y93H polymorphism present	POLARIS-3 ASTRAL-3
Preference	**Drug(s)**	**RBV**	**SVR-12**	**Pills**	**Weekly Cost**	**Duration (weeks)**	**Treatment Cost**	**Class**	**Level**	**SAE**	**Notes**	**Trial**
Genotype 3, Treatment Experienced with PEG/RBV, Compensated Cirrhotic												
1	(Alt) SOF-VEL	Yes	89%	6	$2,400.00	12	$28,799.97	I	B	9		ASTRAL-3 POLARIS-3 Planko, 2015[67]
2	ELB-GRZ + SOF	No	100%	2	$10,584.20	12	$127,008.00	I	B	3		C-ISLE
3	(Alt) GLE-PIB	No	96%	3	$3,959.99	16	$63,359.96	IIa	B	3		SURVEYOR-2
4	SOF-VEL-VOX	No	84%	1	$7,476.00	12	$89,712.00	IIb	B	1	Only if Y93H polymorphism present	POLARIS-3 ASTRAL-3
Genotype 3, DAA Treatment Experienced (including NS5A inhibitors), Regardless of Cirrhosis												
1	SOF-VEL-VOX	No	96%	1	$7,476.00	12	$89,712.00	I	A	1		POLARIS-1 POLARIS-4
2	SOF-VEL-VOX	Yes	-	6	$7,476.00	12	$89,712.00	IIa	C	9	For NS5A inhibitor failure and cirrhotic	POLARIS-1 POLARIS-4
Genotype 4, Treatment Naive, Non-Cirrhotic												
1	GLE-PIB	No	100%	3	$3,959.99	8	$31,679.98	I	A	3		SURVEYOR-2
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	ELB-GRZ	No	97-98%	1	$2,184.00	12	$26,208.00	IIa	B	2		Asselah, 2015[64]
3	LDV-SOF	No	95-100%	1	$3,600.00	12	$43,199.97	IIa	B	1		Abergel, 2015[36] Kohli, 2015[37]
Genotype 4, Treatment Naive, Compensated Cirrhotic												
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	B	3		EXPEDITION-1
3	ELB-GRZ	No	100%	1	$2,184.00	12	$26,208.00	IIa	B	2		Asselah, 2015[64]

												Zeuzem, 2015[55]
4	LDV-SOF	No	95-100%	1	$3,600.00	12	$43,199.97	IIa	B	1		Abergel, 2015[36] Kohli, 2015[37]
Preference	**Drug(s)**	**RBV**	**SVR-12**	**Pills**	**Weekly Cost**	**Duration (weeks)**	**Treatment Cost**	**Class**	**Level**	**SAE**	**Notes**	**Trial**
Genotype 4, Treatment Experienced with PEG/RBV, Non-cirrhotic												
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	GLE-PIB	No	93%	3	$3,959.99	8	$31,679.98	I	B	3		SURVEYOR-2
3	LDV-SOF	No	95%	1	$3,600.00	12	$43,199.97	IIa	B	1		SYNERGY
4	ELB-GRZ	No	87%	1	$2,184.00	12	$26,208.00	IIa	B	2	Treatment relapse	Asselah, 2015[64]
5	ELB-GRZ	Yes	87%	1	$2,184.00	16	$34,944.00	IIa	B	10	Virologic Failure	Asselah, 2015[64]
Genotype 4, Treatment Experienced with PEG/RBV, Compensated Cirrhotic												
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	I	A	2		ASTRAL-1
2	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	IIa	B	3		EXPEDITION-1
3	LDV-SOF	Yes	94%	1	$3,600.00	12	$43,199.97	IIa	B	9		SYNERGY
4	ELB-GRZ	No	87%	1	$2,184.00	12	$26,208.00	IIa	B	2	Treatment relapse	Asselah, 2015[64]
5	ELB-GRZ	No	87%	1	$2,184.00	16	$34,944.00	IIa	B	10	Virologic Failure	Asselah, 2015[64]
Genotype 4, DAA Treatment Experienced (including NS5A inhibitors), Regardless of Cirrhosis												
1	SOF-VEL-VOX	No	96%	1	$7,476.00	12	$89,712.00	I	A	1		POLARIS-1 POLARIS-4
Genotype 5 or 6, Treatment Naïve, Regardless of Cirrhosis												
1	GLE-PIB	No	100%	3	$3,959.99	8	$31,679.98	I	A	3	Non-cirrhotic	ENDURANCE-4 SURVEYOR-2
1	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	A	3	Cirrhotic	EXPEDITION-1
1	SOF-VEL	No	96-100%	1	$2,400.00	12	$28,799.97	I	B	2		ASTRAL-1

2	LDV-SOF	No	95-96%	1	$3,600.00	12	$43,199.97	IIa	B	1		Abergel, 2015[36] Wong, 2013[40] Kohler, 2014[41]

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes	Trial
Genotype 5 or 6, Treatment Experienced with PEG/RBV, Regardless of Cirrhosis												
1	GLE-PIB	No	100%	3	$3,959.99	12	$47,519.97	I	B	3	Cirrhotic	EXPEDITION-1
1	GLE-PIB	No	100%	3	$3,959.99	8	$31,679.98	IIa	B	3	Non-cirrhotic	ENDURANCE-4 SURVEYOR-2
1	SOF-VEL	No	100%	1	$2,400.00	12	$28,799.97	IIa	B	2		ASTRAL-1
2	LDV-SOF	No	100%	1	$3,600.00	12	$43,199.97	IIa	B	1		Abergel, 2015[36]
Genotype 5 or 6, DAA Treatment Experienced (including NS5A inhibitors), Regardless of Cirrhosis												
1	SOF-VEL-VOX	No	100%	1	$7,476.00	12	$89,712.00	IIa	B	1		POLARIS-1

Appendix 3. Preference of AASLD Recommendations per Unique Population[1]

Costs are based off contracted rates. For regimens with Ribavirin, the daily pill total is based off a low initial dose of 600 mg using Ribavirin (RBV) 200 mg capsules, also add a minimum additional cost per week of $46.76.

Preference	Drug(s)	RBV	SVR-12	Pills	Weekly Cost	Duration (weeks)	Treatment Cost	Class	Level	SAE	Notes/Past Treatment	Trial
Decompensated Cirrhosis: Genotype 1, 4, 5, 6 Regardless of Treatment History												
1	SOF-VEL	Yes	94-96%	4	$2,400.00	12	$28,799.97	I	A	9		ASTRAL-4
2	LDV-SOF	Yes	87%	4	$3,600.00	12	$43,199.97	I	A	9		SOLAR-1 SOLAR-2
3	SOF-VEL	No	86-92%	1	$2,400.00	24	$57,599.94	I	A	9	RBV ineligible	ASTRAL-4
4	LDV-SOF	No	89%	1	$3,600.00	24	$86,399.94	I	A	9	RBV ineligible	SOLAR-1 SOLAR-2
5	DCV + SOF	Yes	83%	5	$12,098.10	12	$145,177.20	I	B	10	Only GT 1, 4	ALLY-1 UNITY-2
6	SOF-VEL	Yes	97%	4	$2,400.00	24	$57,599.94	II	C	9	SOF or NS5A	Gane, 2016[69]
7	LDV-SOF	Yes	89%	4	$3,600.00	24	$86,399.94	II	C	9	SOF	SOLAR-2 Osinusi, 2014[17] Wyles, 2015b[18]
8	DCV + SOF	No	89%	2	$12,098.10	24	$290,354.40	II	C	2	RBV ineligible, Only GT 1, 4	ALLY-1 UNITY-2
Decompensated Cirrhosis: Genotype 2 or 3, Regardless of Treatment History												
1	SOF-VEL	Yes	85-100%	4	$2,400.00	12	$28,799.97	I	A	9		ASTRAL-4
2	SOF-VEL	No	-	4	$2,400.00	24	$57,599.94	I	A	1	RBV ineligible	-
3	DCV + SOF	Yes	85-100%	5	$12,098.10	12	$145,177.20	II	B	10		ALLY-1 Welzel, 2015b

4	DCV + SOF	No	94%	5	$12,098.10	24	$290,354.40	II	C	2	RBV ineligible	ALLY-1 Welzel, 2015b
5	SOF-VEL	Yes	-	4	$2,400.00	24	$57,599.94	II	C	9	Failed Sofosbuvir	-
Preference	**Drug(s)**	**RBV**	**SVR-12**	**Pills**	**Weekly Cost**	**Duration (weeks)**	**Treatment Cost**	**Class**	**Level**	**SAE**	**Notes**	**Trial**
Post-Liver Transplantation: Genotype 1, 4, 5, or 6, Regardless of Treatment History, Infection in Allograft, Includes those with Compensated Cirrhosis												
1	GLE-PIB	No	98%	3	$3,959.99	12	$47,519.97	I	A	3	Non-cirrhotic	MAGELLAN-2
2	LDV-SOF	Yes	96%	4	$3,600.00	12	$43,199.97	I	A	9		SOLAR-1
3	(Alt) DCV + SOF	Yes	87-94%	5	$12,098.10	12	$145,177.20	I	B	10		ALLY-1 Fontana, 2015[46] Herzer, 2015[47]
Post-Liver Transplantation: Genotype 2 or 3, Regardless of Treatment History, Infection in Allograft, Includes those with Compensated Cirrhosis												
1	GLE-PIB	No	98%	3	$3,959.99	12	$47,519.97	I	A	3	Non-cirrhotic	MAGELLAN-2
2	DCV + SOF	Yes	87-94%	5	$12,098.10	12	$145,177.20	II	A	10		ALLY-1 Fontana, 2015[46] Herzer, 2015[47]
3	SOF-VEL	Yes	-	4	$2,400.00	12	$28,799.97	II	C	9		-
4	GLE-PIB	No	-	3	$3,959.99	12	$47,519.97	II	C	3	Cirrhotic	-
Post-Liver Transplantation/Decompensated Cirrhosis: Genotype 1, 4, 5, or 6, Regardless of Treatment History												
1	LDV-SOF	Yes	60-85%	4	$3,600.00	12	$43,199.97	I	B	9		SOLAR-1
Post-Liver Transplantation/Decompensated Cirrhosis: Genotype 2 or 3, Regardless of Treatment History												
1	DCV + SOF	Yes	83-91%	5	$12,098.10	12	$145,177.20	II	A	10		ALLY-1 Fontana, 2015[46] Herzer, 2015[47]
2	SOF-VEL	Yes	-	4	$2,400.00	12	$28,799.97	II	C	9		-

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