

Treatment of HCV Genotype 5 or 6

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Module 5: [Treatment of Chronic Hepatitis C Infection](#)

Lesson 5: [Treatment of HCV Genotype 5 or 6](#)

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Introduction

Background: In the United States, fewer than 2% of hepatitis C infections involve genotype 5 or 6 infection. Genotype 5 hepatitis C infection (HCV) is endemic to South Africa where up to 40% of individuals with chronic hepatitis C from that geographic region have genotype 5 infection. Scattered pockets of genotype 5 HCV have also been isolated among regions in Europe. Genotype 6 hepatitis C infection has been found primarily in China, Korea, Taiwan, and Southeast Asia, including Thailand, Vietnam, Singapore, and Malaysia. Almost all the cases of genotype 6 in the United States occur in immigrants from Asia and Southeast Asia. Available data suggest that patients with genotype 6 infection have a similar natural history as those with genotype 1. The following discussion regarding initial treatment and retreatment of patients with genotype 5 or 6 chronic hepatitis C assumes the patient and their clinician have already made the decision to initiate hepatitis C therapy. Because of the low prevalence of genotype 5 and 6 in the United States, relatively little is known about the optimal treatment of genotype 5 or 6 infection. The estimated cost for the recommended regimens in the 2016 American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) guidance for genotype 5 or 6 infection ranges from approximately \$75,000 to \$95,000 ([Figure 1](#)).

Medications used to Treat Hepatitis C: The [HCV Medications](#) section on this web site provides detailed information for each of the FDA-approved medications listed in the treatment recommendations, including links to the full prescribing information and to patient assistance programs. Adherence with the treatment regimen is extremely important. Thus, patients should receive detailed counseling regarding the importance of adherence prior to starting therapy, as well as intensive monitoring and follow-up during therapy.

Genotype 5 or 6: Initial Treatment

Background: There are relatively few studies related to the optimal treatment regimen for patients with genotype 5 or 6 chronic HCV infection, particularly for direct-acting antiviral agents with these genotypes. Older studies in treatment-naïve patients with genotype 5 infection that have examined the combination of interferon (either standard or pegylated) with ribavirin for 48 weeks have reported sustained virologic response (SVR) rates of approximately 60 to 70%. Most studies that have addressed initial treatment of patients with genotype 6 are observational and with small sample sizes, reporting sustained virologic response rates of 70 to 80% with peginterferon plus ribavirin when given for 48 weeks (and only slightly lower when given for 24 weeks). Limited data with a 12 week course of either velpatasvir-sofosbuvir or ledipasvir-sofosbuvir suggest high SVR rates for initial therapy of genotype 5 or 6.

Factors to Consider Prior to Choosing Treatment Regimen: For patients chronically infected with genotype 5 or 6 hepatitis C, little is known regarding baseline factors that may predict response to therapy. The management of genotype 5 or 6 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA Guidance (see [Initial Treatment of HCV Infection](#)): The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for patients with hepatitis C genotype 5 or 6 infection who will receive initial treatment. Note that acid suppressing medications may significantly decrease the absorption of ledipasvir-sofosbuvir, thereby potentially causing lower drug levels.

Genotype 5 or 6: Initial Treatment Table 1. Treatment-Naïve Patients

Recommended for Genotype 5 or 6 Patients with and without Cirrhosis

Sofosbuvir- Velpatasvir

*Fixed-dose
combination of
sofosbuvir (400
mg)/velpatasvir (100
mg) one tablet once
daily for 12 weeks*

Rating: [Class I](#), [Level A](#)

Recommended for Genotype 5 or 6 Patients with and without Cirrhosis

Ledipasvir- Sofosbuvir

*Fixed-dose
combination of
ledipasvir (90
mg)/sofosbuvir (400
mg) one tablet once
daily for 12 weeks*

Rating: [Class IIa](#), [Level B](#)

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial

treatment of HCV infection. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.

Key Studies to Support Recommendations: The following key studies support the recommendations for treatment of patients with chronic hepatitis C and genotype 5 or 6 infection who are treatment naive or who have previously received treatment and had virologic relapse with a regimen that included peginterferon and ribavirin. Click on the study name (blue) to see more details and to view a PowerPoint slide summary.

- [ASTRAL-1](#): In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naive and treatment-experienced patients with chronic hepatitis C genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo. The study included 34 patients with genotype 5 and 41 with genotype 6. Among the treatment-naive patients treated with sofosbuvir-velpatasvir, 23 (96%) of 24 with genotype 5 infection achieved an SVR12 and 38 (100%) of 38 with genotype 6 achieved an SVR12.
- [NEUTRINO](#): In this large phase 3 trial, treatment-naive patients with genotype 1, 4, 5, or 6 chronic hepatitis C received a 12-week course of sofosbuvir plus weight-based ribavirin plus peginterferon. Among the 327 patients enrolled, 1 had genotype 5, and 6 had genotype 6. All 7 of the patients with genotype 5 or 6 achieved an SVR12.
- [ATOMIC](#): This phase 2 study enrolled 316 treatment-naive patients with chronic hepatitis C genotype 1, 4, 5, or 6 and examined the efficacy of 12 versus 24 weeks of therapy with peginterferon, weight-based ribavirin, and sofosbuvir. Of the 316 patients enrolled, none had genotype 5 and a total of 5 patients had genotype 6 infection. All of the patients with genotype 6 were assigned to 24 weeks of therapy and 5 (100%) of 5 achieved an SVR12.
- **New Zealand Genotype 3 and 6 Study**: In this open-label, phase 2 study performed at two centers in New Zealand, investigators enrolled treatment-naive and treatment-experienced patients with genotypes 3 or 6 HCV infection. One arm of this study enrolled 25 patients with genotype 6 HCV to receive a 12-week course of ledipasvir-sofosbuvir. Overall, 24 (96%) of the 25 patients with genotype 6 HCV achieved an SVR12; the one patient in this cohort who did not achieve an SRV12 dropped out of the study at week 8 and thus did not complete the full 12 weeks of ledipasvir-sofosbuvir therapy. Only two of the treatment-naive patients with genotype 6 had cirrhosis.
- **Ledipasvir-Sofosbuvir for Genotype 5 Infection**: In a phase 2, open-label study conducted in France, investigators enrolled 21 treatment-naive and 20 treatment experienced patients with HCV genotype 5 infection to receive a 12-week course of ledipasvir-sofosbuvir. For the treatment-naive patients with genotype 5 infection, 20 (95%) of 21 achieved an SVR12. The results for patients with genotype 5 infection were similar regardless of cirrhosis status.

Genotype 5 or 6: Retreating Persons who Failed Prior Therapy

Background: Given the very low prevalence of genotypes 5 and 6 in the United States, limited data and experience exists with retreatment of patients with genotype 5 or 6. Recommendations are primarily based on limited data in treatment-naïve and treatment-experienced patients with genotype 5 or 6, and by extrapolating from experience with other HCV genotypes.

Factors to Consider Prior to Choosing Treatment Regimen: For patients chronically infected with genotype 5 or 6 hepatitis C, insufficient data exist regarding the impact of cirrhosis on the optimal retreatment regimen or duration of therapy. The retreatment of genotype 5 or 6 patients with decompensated cirrhosis, renal impairment, HIV coinfection, acute hepatitis C infection, or post-liver transplantation is not addressed in this lesson.

AASLD/IDSA Guidance (see [Retreatment of Persons in Whom Prior Therapy has Failed](#)): The following is a summary of joint recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA). The recommendations listed below are for patients with hepatitis C genotype 5 or 6 infection who are treatment experienced and in whom prior therapy failed. Of note, the recommended and alternative regimens for retreatment of genotype 5 or 6 are the same as those listed for initial treatment of genotype 5 or 6.

Genotype 5 or 6: Retreatment

Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended for Retreatment of patients with Genotype 5 or 6 regardless of cirrhosis status

Sofosbuvir-Velpatasvir

Fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) one tablet once daily for 12 weeks

Rating: [Class IIa](#), [Level B](#)

Recommended for Retreatment of patients with Genotype 5 or 6 regardless of cirrhosis status

Ledipasvir-Sofosbuvir

Fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) one tablet once daily for 12 weeks

Rating: [Class IIa](#), [Level C](#)

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.

Key Studies to Support Recommendations: There are limited data from studies that adequately address the retreatment of patients with genotype 5 or 6 hepatitis C infection who failed prior therapy.

- [ASTRAL-1](#): In the phase 3 ASTRAL-1 trial, investigators randomized treatment-naive and treatment-experienced patients with chronic hepatitis C genotype 1, 2, 4, 5, or 6 infection in a 5:1 ratio to receive a 12-week course of either sofosbuvir-velpatasvir or placebo. The study included 34 patients with genotype 5 and 41 with genotype 6. Among the treatment-experienced patients treated with sofosbuvir-velpatasvir, 11 (100%) of 11 with genotype 5 infection achieved an SVR12 and 3 (100%) of 3 with genotype 6 achieved an SVR12.
- **Ledipasvir-Sofosbuvir for Genotype 5 Infection:** In a small, open-label study conducted in France, investigators enrolled 21 treatment-naive and 20 treatment experienced patients with HCV genotype 5 infection to receive a 12-week course of ledipasvir-sofosbuvir. For the treatment-experienced patients with genotype 5 infection, 19 (95%) of 20 achieved an SVR12. The results in patients with genotype 5 were similar regardless of cirrhosis status.

Genotype 5 or 6: Future Treatment Options

Future Direct-Acting Antiviral Agents: In vitro data have shown that several investigational agents have established antiviral activity against genotype 5 and/or 6, including grazoprevir and elbasvir. Since most phase 2 and 3 hepatitis C clinical trials are performed in the United States, which has a low HCV genotype 5 and 6 prevalence, limited data are likely to be generated in the near future for direct-acting antiviral agents and their clinical efficacy in treating patients with genotype 5 or 6.

- **Elbasvir-Grazoprevir:** The 3 studies, C-EDGE Treatment-Naive and C-EDGE Treatment-Experienced) allowed enrollment of patients with genotypes 6, but the number of treated patients is small. Elbasvir-grazoprevir is not FDA approved for the treatment of patients with genotype 5 or 6 infection.

Summary Points

- Genotype 5 hepatitis C virus infection is uncommon in the United States, but endemic in South Africa.
- Genotype 6 hepatitis C virus infection is also infrequently seen in the United States and primarily is found in China, Korea, Taiwan, and Southeast Asia.
- Experience with treatment of genotype 5 or 6 in the United States is limited. Recommendations for initial treatment or retreatment are based on in vitro data and limited experience in clinical trials.
- The recommended regimen for initial treatment or retreatment of patients with genotype 5 or 6 is a 12-week course of either (1) sofosbuvir-velpatasvir or (2) ledipasvir-sofosbuvir; these recommendations are the same for patients without cirrhosis and for those with compensated cirrhosis.

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Figures

Figure 1 Cost of Medication Regimens used to Treat Genotypes 5 or 6 Chronic HCV

This figure shows the approximate cost of different regimens used for treatment-naive and/or treatment-experienced patients with genotypes 5 and 6 chronic HCV. This chart does not show the cost of regimens not recommended for treatment. Cost based on available wholesale acquisition price data.

Estimated Medication Cost* for Treatment of Genotype 5 and 6 Chronic HCV	
Regimen and Duration	Cost of Regimen*
Sofosbuvir-Velpatasvir x 12 weeks	\$74,760
Ledipasvir-Sofosbuvir x 12 weeks	\$94,500

*Cost estimates based on Wholesale Acquisition Cost (WAC)

Genotype 5 or 6: Initial Treatment

Table 1. Treatment-Naive Patients

Recommended for Genotype 5 or 6 Patients with and without Cirrhosis

Sofosbuvir- Velpatasvir

*Fixed-dose
combination of
sofosbuvir (400
mg)/velpatasvir (100
mg) one tablet once
daily for 12 weeks*

Rating: [Class I](#), [Level A](#)

Recommended for Genotype 5 or 6 Patients with and without Cirrhosis

Ledipasvir- Sofosbuvir

*Fixed-dose
combination of
ledipasvir (90
mg)/sofosbuvir (400
mg) one tablet once
daily for 12 weeks*

Rating: [Class IIa](#), [Level B](#)

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Initial treatment of HCV infection. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.

Genotype 5 or 6: Retreatment

Table 2. Peginterferon plus Ribavirin Treatment-Experienced Patients

Recommended for Retreatment of patients with Genotype 5 or 6 regardless of cirrhosis status

Sofosbuvir- Velpatasvir

*Fixed-dose
combination of
sofosbuvir (400
mg)/velpatasvir (100
mg) one tablet once
daily for 12 weeks*

Rating: [Class IIa](#), [Level B](#)

Recommended for Retreatment of patients with Genotype 5 or 6 regardless of cirrhosis status

Ledipasvir- Sofosbuvir

*Fixed-dose
combination of
ledipasvir (90
mg)/sofosbuvir (400
mg) one tablet once
daily for 12 weeks*

Rating: [Class IIa](#), [Level C](#)

Source: AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Retreatment of persons in whom prior therapy has failed. [[AASLD/IDSA Hepatitis C Guidance](#)] - Accessed March 10, 2017.

