

Initial Treatment of Adults with HCV Infection

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with interferon, peginterferon, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether investigational, or US Food and Drug Administration (FDA) approved.

The level of evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different genotypes). Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient or clinical setting. Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte- Pugh [CTP] class B or C), HCV infection post liver transplant, and severe renal impairment, end-stage renal disease (ESRD), or post kidney transplant are addressed in other sections of the guidance.

[Simplification of the treatment regimen](#) may expand the number of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. This would align with the National Academies of Science, Engineering, and Medicine strategy to reduce cases of chronic HCV infection by 90% by 2030 ([NAS, 2017](#)).

Recommended and alternative regimens are listed in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug-drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response or regimen selection. All patients should have access to an HCV care provider during treatment, although preset clinic visits and/or blood tests depend on the treatment regimen and may not be required for all regimens/patients. Patients receiving ribavirin require additional monitoring for anemia during treatment (see [Monitoring](#) section).

The following pages include guidance for management of treatment-naive patients.

- [Simplified HCV Treatment for Treatment-Naive Patients Without Cirrhosis](#)
- [Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis](#)
- [Genotype 1](#)
- [Genotype 2](#)
- [Genotype 3](#)
- [Genotype 4](#)
- [Genotype 5 or 6](#)

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen is recommended in this circumstance. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

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Simplified HCV Treatment* for Treatment-Naive Patients Without Cirrhosis

Who Is **NOT** Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- End-stage renal disease (ie, eGFR <30 mL/min/m²) (see [Patients with Renal Impairment](#) section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who do not have cirrhosis and have not previously received hepatitis C treatment

Pretreatment Assessment*

- [Calculate FIB-4 score.](#)
- **Cirrhosis assessment:** Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.
 - Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
 - Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
 - Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm³, etc)
 - Prior liver biopsy showing cirrhosis
- **Medication reconciliation:** Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment:** Drug-drug interactions can be assessed using the [AASLD/IDSA guidance](#) or the University of Liverpool [drug interaction checker](#).
- **Education:** Educate the patient about proper administration of medications, adherence, and prevention of reinfection.
- **Pretreatment laboratory testing:**
 - *Within 6 months of initiating treatment:*
 - Complete blood count (CBC)
 - Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
 - Calculated glomerular filtration rate (eGFR)
 - *Anytime prior to starting antiviral therapy:*
 - Quantitative HCV RNA (HCV viral load)
 - HIV antigen/antibody test
 - Hepatitis B surface antigen
 - *Before initiating antiviral therapy:*

- Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

Recommended Regimens*

- Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks

On-Treatment Monitoring

- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- No laboratory monitoring is required for other patients.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

Post-Treatment Assessment of Cure (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

Follow-Up After Achieving Virologic Cure (SVR)

- No liver-related follow-up is recommended for noncirrhotic patients who achieve SVR.
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated ALT, AST, or bilirubin.
- Advise patients to avoid excess alcohol use.

Follow-Up for Patients Who Do *Not* Achieve a Virologic Cure

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- For patients unable to be retreated, assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended.
- Advise patients to avoid excess alcohol use.

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment, including the treatment of patients with cirrhosis, can be found [here](#).

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Simplified HCV Treatment Algorithm for Treatment-Naive Adults

With Compensated Cirrhosis

Who Is **NOT** Eligible for Simplified Treatment

Patients who have any of the following characteristics:

- Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score ≥ 7 (ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤ 3.5 g/dL, or INR ≥ 1.7)
- Prior hepatitis C treatment
- End-stage renal disease (ie, eGFR <30 mL/min/m²) (see [Patients with Renal Impairment](#) section)
- HIV or HBsAg positive
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

(see [HCV guidance](#) for treatment recommendations for these patients)

Who Is Eligible for Simplified Treatment

Adults with chronic hepatitis C (any genotype) who have compensated cirrhosis (Child-Pugh A) and have not previously received hepatitis C treatment

Liver biopsy is not required. For the purpose of this guidance, a patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 **or** any of the following findings from a previously performed test.

- Transient elastography indicating cirrhosis (eg, FibroScan stiffness >12.5 kPa)
- Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test, etc)
- Clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count $<150,000/\text{mm}^3$, etc)
- Prior liver biopsy showing cirrhosis

Pretreatment Assessment*

- [Calculate FIB-4 score](#).
- [Calculate CTP score](#): Patients with a CTP score ≥ 7 (ie, CTP B or C) have decompensated cirrhosis and this simplified treatment approach is not recommended.
- **Ultrasound of the liver** (conducted within the prior 6 months): Evaluate to exclude HCC and subclinical ascites.
- **Medication reconciliation**: Record current medications, including over-the-counter drugs and herbal/dietary supplements.
- **Potential drug-drug interaction assessment**: Drug-drug interactions can be assessed using the [AASLD/IDSA guidance](#) or the University of Liverpool [drug interaction checker](#).
- **Education**: Educate the patient about proper administration of medications, adherence, and prevention of reinfection.
- **Pretreatment laboratory testing**:
 - *Within 3 months of initiating treatment*:
 - Complete blood count (CBC)
 - International normalized ratio (INR)

- Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST])
- Calculated glomerular filtration rate (eGFR)
- *Anytime prior to starting antiviral therapy:*
 - Quantitative HCV RNA (HCV viral load)
 - HIV antigen/antibody test
 - Hepatitis B surface antigen
 - HCV genotype (if treating with sofosbuvir/velpatasvir)
- *Before initiating antiviral therapy:*
 - Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age.

Recommended Regimens*

- **Genotype 1-6:**
Glecaprevir (300 mg) / pibrentasvir (120 mg) to be taken with food for a duration of 8 weeks
- **Genotype 1, 2, 4, 5, or 6**
Sofosbuvir (400 mg) / velpatasvir (100 mg) for a duration of 12 weeks
NOTE: Patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, see HCV guidance for treatment recommendations.

On-Treatment Monitoring

- Providers may order blood tests to monitor for liver injury during treatment because hepatic decompensation (eg, jaundice, etc) occurs rarely among patients with cirrhosis receiving HCV antiviral treatment.
- Patients should see a specialist if they develop worsening liver blood tests (eg, bilirubin, AST, ALT, etc); jaundice, ascites, or encephalopathy; or new liver-related symptoms.
- Inform patients taking diabetes medication of the potential for symptomatic hypoglycemia. Monitoring for hypoglycemia is recommended.
- Inform patients taking warfarin of the potential for changes in their anticoagulation status. Monitoring INR for subtherapeutic anticoagulation is recommended.
- An in-person or telehealth/phone visit may be scheduled, if needed, for patient support, assessment of symptoms, and/or new medications.

Post-Treatment Assessment of Cure (SVR)

- Assessment of quantitative HCV RNA and a hepatic function panel are recommended 12 weeks or later following completion of therapy to confirm HCV RNA is undetectable (virologic cure) and transaminase normalization.
- Assessment for other causes of liver disease is recommended for patients with elevated transaminase levels after achieving SVR.

Follow-Up After Achieving Virologic Cure (SVR)

- Ultrasound surveillance for HCC (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis in accordance with [AASLD guidance](#).
- Upper endoscopic surveillance for esophageal varices is recommended in accordance with AASLD guidance on [portal hypertensive bleeding in cirrhosis](#).
- Patients with ongoing risk for HCV infection (eg, intravenous drug use or MSM engaging in unprotected sex) should be counseled about risk reduction, and tested for HCV RNA annually and whenever they develop elevated

ALT, AST, or bilirubin.

- Patients should abstain from alcohol to avoid progression of liver disease.

Follow-Up for Patients Who Do *Not* Achieve a Virologic Cure

- Patients in whom initial HCV treatment fails to achieve cure (SVR) should be evaluated for retreatment by a specialist, in accordance with AASLD/IDSA guidance.
- Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with [AASLD guidance](#).
- Assessment for disease progression every 6 to 12 months with a hepatic function panel, CBC, and INR is recommended.
- Patients should abstain from alcohol to avoid progression of liver disease.

*More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found [here](#).

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Treatment-Naive Genotype 1

Four highly potent DAA combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of compensated cirrhosis.

With certain regimens, patients with genotype 1a may have higher virologic failure rates than those with genotype 1b. Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens ([Zeuzem, 2017](#)); ([Jacobson, 2015b](#)). These RASs are found by population sequencing in roughly 5% to 10% of patients and relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic response with certain regimens in those with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations ([Zeuzem, 2015c](#)). In clinical settings where RAS testing is unavailable, regimens for which the presence of specific RAS(s) factor into treatment selection should be avoided. For further guidance, please see the [HCV Resistance Primer](#) section.

Compared to interferon-based therapy, DAAs are associated with a higher rate of drug-drug interactions with concomitant medications. Thus, attention to drug interactions is an important treatment consideration (see [Drug Interactions](#) table). The product prescribing information and other resources (eg, <http://www.hep-druginteractions.org>) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all the regimens discussed.

The following pages include guidance for management of treatment-naive patients with genotype 1 infection.


- [Treatment-Naive Genotype 1a Without Cirrhosis](#)
- [Treatment-Naive Genotype 1b Without Cirrhosis](#)
- [Treatment-Naive Genotype 1a With Compensated Cirrhosis](#)
- [Treatment-Naive Genotype 1b With Compensated Cirrhosis](#)
- [Simplified HCV Treatment for Treatment-Naive Patients Without Cirrhosis](#)

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Treatment-Naive Genotype 1a Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs for elbasvir ^a	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
<p>^a Includes genotype 1a resistance-associated substitutions (RASs) at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.</p> <p>^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.</p>		

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) ([Zeuzem, 2015f](#)). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin ([Sulkowski, 2015b](#)). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir in genotype 1a-infected patients ([Zeuzem, 2017](#)). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir ([Zeuzem, 2017](#)). Among treatment-naive patients, the presence of baseline NS5A RASs with greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

In the phase 3 open-label C-EDGE TE trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, 58 genotype 1a-infected patients received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, and there were no virologic failures ([Kwo, 2017](#)). Subsequent integrated analysis of the elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir plus ribavirin for 16 or 18 weeks ([Jacobson, 2015b](#)); ([Thompson, 2015](#)).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used (additional information is available in the [RAS](#) section).

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) ([Kwo, 2017b](#)), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 or 12 weeks of glecaprevir/pibrentasvir ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either study arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR for genotype 1a was 98% (47/48) ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotypes 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2017](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

In an integrated analysis of 602 DAA-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 99.2% (597/602) ([Naganuma, 2019](#)). Real-world cohorts from Germany (63% genotype 1a) and Italy (32% genotype 1a) show similarly high efficacy in treatment-naive, noncirrhotic patients with genotype 1 infection treated with 8 weeks of glecaprevir/pibrentasvir. Using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up), SVR was 100% in both the German (228/228) ([Berg, 2019](#)) and the Italian (307/307) ([D'Ambrosio, 2019](#)) cohorts.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on two registration trials: ION-1 (865 treatment-naive patients;

those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin ([Afdhal, 2014a](#)). SVR12 was 97% to 99% across all study arms with no difference in SVR12 based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) ([Kowdley, 2014](#)). SVR12 rates were 93% to 95% across all study arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients who received 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis ([Backus, 2016](#)); ([Ingiliz, 2016](#)); ([Ioannou, 2016](#)); ([Kowdley, 2016](#)); ([Terrault, 2016](#)). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% ([Su, 2017](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)); ([Ioannou, 2016](#)). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found similar SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) ([Marcus, 2018](#)). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively ([Tang, 2018](#)). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see [HIV/HCV Coinfection](#) section). For others with potential negative prognostic factors, shortening treatment duration should be done at the discretion of the practitioner.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6 infection—with or without compensated cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir for 12 weeks, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR12 with a single relapse observed with each subtype.


In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) ([Wei, 2019](#)). Of the 129 participants with genotype 1 infection (17% genotype 1a), 100% achieved SVR.

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Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs ^b for elbasvir	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^c	8 weeks	I, B

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Includes genotype 1a RASs at amino acid position 28, 30, 31, or 93 known to confer antiviral resistance. If 1 or more RASs are present, another recommended regimen should be used.

^c Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information. For patients with HIV/HCV coinfection, a treatment duration of 12 weeks is recommended.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease ([Zeuzem, 2015f](#)). SVR12 was 97% in this subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients ([Lawitz, 2015c](#)). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen ([Lawitz, 2015c](#)); ([Zeuzem, 2017](#)).

Presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients ([Zeuzem, 2017](#)). Baseline NS5A RASs were identified in

12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to 99% (133/135) in patients without these RASs ([Zeuzem, 2017](#)). Among treatment-naive patients, the presence of baseline NS5A RASs with a greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs are based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures ([Kwo, 2017](#)). Subsequent integrated analysis of elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir for 16 or 18 weeks plus ribavirin ([Jacobson, 2015b](#)); ([Thompson, 2015](#)).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid position 28, 30, 31, or 93), another recommended regimen should be selected.

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated the use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR12 among these patients was 98% (47/48) ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2018](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1 (n=95, genotype 1a), 2, 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures ([Brown, 2018](#)).

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on two registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin ([Afdhal, 2014a](#)). SVR12 rates were 97% to 99% across all study arms with no difference in SVR12 based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR12 with no difference in SVR12


observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%).

The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6—19% of whom had cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Last update: November 6, 2019

Treatment-Naive Genotype 1b Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:		
Treatment-Naive Patients Genotype 1b Without Cirrhosis		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks ^a	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
<hr/>		
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are HIV-uninfected and whose HCV RNA level is <6 million IU/mL	8 weeks ^c	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

^a An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).
^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
^c For HIV/HCV coinfecting patients, a treatment duration of 12 weeks is recommended.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) ([Zeuzem, 2015f](#)). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The SVR12 was 92% (144/157) in treatment-naive patients with genotype 1a and 99% (129/131) in those with genotype 1b. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive non-cirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin ([Sulkowski, 2015b](#)). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

A phase 3, global STREAGER trial of 89 treatment-naive patients with genotype 1b infection and low fibrosis stage (defined as a transient elastography score <9.5 or a Fibrotest® score <0.59 [F0 to F2]) evaluated the efficacy of 8 weeks of elbasvir/grazoprevir and found an SVR rate of 98% (87/89), supporting the option of using a shorter treatment duration for genotype 1b patients with low scores using these fibrosis staging modalities ([Abergel, 2018](#)).

In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs.

Glecaprevir/Pibrentasvir

Based on favorable data for 8 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) ([Kwo, 2017b](#)), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills ([Zeuzem, 2016](#)). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. All genotype 1b patients achieved SVR ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected persons with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2017](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

CERTAIN-1 evaluated 8 weeks of glecaprevir/pibrentasvir among 129 Japanese DAA-naive noncirrhotic patients (97% genotype 1b); SVR12 was of 99% (128/129) ([Chayama, 2018](#)). Real-world cohorts from Germany (34% genotype 1a) and Italy (67% genotype 1a) demonstrate similarly high efficacy among treatment-naive, noncirrhotic genotype 1 patients treated with 8 weeks of glecaprevir/pibrentasvir using a modified intention-to-treat analysis (excluding those not completing treatment or lost to follow-up). SVR rates were 100% in both the German (228/228) ([Berg, 2019](#)) and the Italian (307/307) ([D'Ambrosio, 2019](#)) cohorts.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1

investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin ([Afdhal, 2014a](#)). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening ledipasvir/sofosbuvir therapy from 12 weeks to 8 weeks (with or without ribavirin) ([Kowdley, 2014](#)). SVR12 rates were 93% to 95% across all study arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2%; 2/123). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2%; 2/131). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Real-world cohort studies of ledipasvir/sofosbuvir for treatment-naive, noncirrhotic black patients reported lower SVR12 rates with shorter duration therapy compared to white patients, although the absolute difference in SVR12 rates was <5% ([Su, 2016](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)); ([Ioannou, 2016](#)). A subsequent real-world study among a Northern California Kaiser Permanente cohort of 436 black patients—most of whom were treated with an 8-week regimen—found comparable SVR12 rates with 8 and 12 weeks of therapy (95.6% and 95.8%, respectively) ([Marcus, 2018](#)). Similarly, a Maryland Veterans Health Administration real-world cohort of black patients with predominantly genotype 1 infection found SVR12 rates of 93.7% (131/140) and 91.4% (332/363) with 8- and 12-week regimens, respectively ([Tang, 2018](#)). These data coupled with the availability of excellent rescue therapies for patients in whom initial DAA therapy fails support the use of 8 weeks of ledipasvir/sofosbuvir for black patients without cirrhosis and HCV RNA <6 million IU/mL.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see [HIV/HCV Coinfection](#) section).

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 infection who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR12 with no difference observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.


The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed in each subtype.

Last update: November 6, 2019

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 1b Patients With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks ^c	I, B

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^c For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

For genotype 1b-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease ([Zeuzem, 2015f](#)). SVR12 was 97% in the subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients ([Lawitz, 2015c](#)). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen ([Lawitz, 2015c](#)); ([Zeuzem, 2017](#)).

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12; all genotype 1b patients achieved SVR ([Forns, 2017](#)).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection ([Rockstroh, 2017](#)). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1 (n=136, genotype 1b), 2, 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures ([Brown, 2018](#)).

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin ([Afdhal, 2014a](#)). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as cirrhotic. There was no difference in SVR12 rate in cirrhotic (97%) versus noncirrhotic patients (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); ([Feld, 2015](#)). Of the 328 genotype 1 patients included, 323 achieved SVR12 with no difference in SVR12 observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR12 (99%). Baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR12 rate for genotype 1 ([Hézode, 2018](#)). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6 infection—19% of whom had compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Last update: November 6, 2019

Treatment-Naive Genotype 2

The following pages include guidance for management of treatment-naive patients with genotype 2 infection.


- [Treatment-Naive Genotype 2 Without Cirrhosis](#)
- [Treatment-Naive Genotype 2 With Compensated Cirrhosis](#)
- [Simplified HCV Treatment for Treatment-Naive Patients Without Cirrhosis](#)

Last update: November 6, 2019

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 2 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

^a Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-2 was a randomized, double-blind, placebo-controlled trial of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks among 302 genotype 2-infected treatment-naive or -experienced participants. Treatment-experienced patients included those previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon. Patients randomized to placebo later received open-label treatment with glecaprevir/pibrentasvir for 12 weeks. Among 202 patients randomized to active treatment, 70% (141/202) were treatment naive and none had cirrhosis. The SVR12 rates were 99% and 100% by intention-to-treat and modified intention-to-treat analysis, respectively. There were no virologic failures. One participant who achieved SVR4 was lost to follow-up before the SVR12 evaluation. There was no effect of baseline RASs on SVR12 rate. Overall, therapy was well tolerated and the adverse event profile was not different compared to placebo ([Asselah, 2018b](#)).

A shorter duration of glecaprevir/pibrentasvir for 8 weeks was evaluated in the SURVEYOR-II, part 4 study. This was a single-arm, phase 2 study that evaluated glecaprevir/pibrentasvir for 8 weeks among 203 treatment-naive or -experienced patients (previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 2, 4, 5, or 6 infection without cirrhosis. Of the 142 genotype 2-infected patients, 137 (96%) were treatment naive. Among the treatment-naive, genotype 2-infected participants, 135/137 (99%) achieved SVR12. The presence of baseline RASs had minimal effect on SVR12 rates. Fifty-three of 126 (42%) treatment-naive and -experienced participants with genotype 2 had the L31M RAS within the NS5A gene at baseline. Fifty-one of 53 (96%) of these participants achieved SVR12 ([Asselah, 2018b](#)).

While not a head-to-head comparison, the results of ENDURANCE-2 and SURVEYOR-II, part 4 indicate that glecaprevir/pibrentasvir administered for 8 or 12 weeks is highly efficacious among genotype 2-infected, treatment-naive patients without cirrhosis. In an integrated analysis of 297 DAA-naive, noncirrhotic patients with genotype 2 infection treated with 8 weeks of glecaprevir/pibrentasvir in 6 phase 2 or 3 clinical trials, SVR12 was 98% (252/257) ([Naganuma, 2019](#)). Additionally, a real-world cohort of treatment-naive, noncirrhotic genotype 2 patients from Italy treated with glecaprevir/pibrentasvir for 8 weeks achieved an SVR rate of 98% (173/175) ([D'Ambrosio, 2019](#)).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%); ([Foster, 2015a](#)). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced participants without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 ([Feld, 2015](#)). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in participants with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure ([Asselah, 2018](#)).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection ([Jacobson, 2017](#)).


In a single-arm, phase 3 study from Asia that included 375 treatment-naive and -experienced patients with genotype 1, 2, 3, 4, 5, or 6 infection (18% with cirrhosis) treated with 12 weeks of sofosbuvir/velpatasvir, SVR was achieved in 95% (362/375) ([Wei, 2019](#)). Of the 62 patients with genotype 2 infection, 100% achieved SVR.

Last update: November 6, 2019

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg) ^b	8 weeks ^c	I, B

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^c For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir compared to sofosbuvir plus ribavirin (SVR12 99% vs 94%); ([Foster, 2015a](#)). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 ([Feld, 2015](#)). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in those with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure ([Asselah, 2018](#)).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection ([Jacobson, 2017](#)).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Participants were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 ([Forns, 2017](#)). EXPEDITION-1 included 31 treatment-naive and -experienced persons with genotype 2 infection and compensated cirrhosis; all achieved SVR12. Baseline NS5A RASs were detected (by next-generation sequencing using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced patients with genotype 2 infection.

EXPEDITION-8 evaluated glecaprevir/pibrentasvir for a reduced duration of 8 weeks in 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2 (n=26), 4, 5 or 6 infection. Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. SVR12 was 99% with no virologic failures ([Brown, 2018](#)).

Last update: November 6, 2019

Treatment-Naive Genotype 3

The following pages include guidance for management of treatment-naive patients with genotype 3 infection.


- [Treatment-Naive Genotype 3 Without Cirrhosis](#)
- [Treatment-Naive Genotype 3 With Compensated Cirrhosis](#)
- [Simplified HCV Treatment for Treatment-Naive Patients Without Cirrhosis](#)

Last update: November 6, 2019

Treatment-Naive Genotype 3 Without Cirrhosis

Recommended regimens listed alphabetically for:

Treatment-Naive Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A

^a Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) ([Foster, 2017](#)). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K achieved SVR with an 8 week duration vs 161/163 without A30K) ([Krishnan, 2018](#)). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12-week duration of glecaprevir/pibrentasvir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence at this time to recommend testing for RASs or extension of therapy in the setting of an A30K substitution.

In addition, data from real-world cohorts support the effectiveness of an 8-week regimen of glecaprevir/pibrentasvir therapy for treatment-naive, noncirrhotic patients with genotype 3 infection ([Sterling, 2019](#)); ([Drysdale, 2019](#)). Among treatment-naive patients with genotype 3, 99% (162/164) of patients in a German cohort ([Berg, 2019](#)) and 96% (46/48) of patients in an Italian cohort ([D'Ambrosio, 2019](#)) treated with 8 weeks of glecaprevir/pibrentasvir achieved SVR12.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and

-experienced patients without cirrhosis or with compensated cirrhosis ([Foster, 2015a](#)). Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin.




The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) ([Jacobson, 2017](#)). There were no virologic failures.

A subsequent open-label study conducted in Russia and Sweden demonstrated similar response rates in noncirrhotic genotype 3 patients ([Isakov, 2019](#)). Additionally, an observational cohort study from Germany supports the effectiveness of 12 weeks of sofosbuvir/velpatasvir among treatment-naive patients with genotype 3 infection ([von Felden, 2018](#)). Of 167 treatment-naive genotype 3 patients (25% cirrhosis in overall cohort), 162 were cured and there were no virologic failures. Other real-world data from cohorts across North America, Canada, and the United Kingdom also demonstrate high SVR rates with 12 weeks of sofosbuvir/velpatasvir among genotype 3, treatment-naive, noncirrhotic patients ([Mangia, 2019](#)); ([Drysedale, 2019](#)).

Another recent study provided information about the use of sofosbuvir/velpatasvir in patients with genotype 3b, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial of patients enrolled from Asia treated with sofosbuvir/velpatasvir reported an overall SVR of 86% among 84 patients with genotype 3 infection, with or without cirrhosis ([Wei, 2019](#)). Among patients with genotype 3a, 95% (40/42) achieved SVR12. In the subgroup of noncirrhotic patients with genotype 3b, 89% (25/28) achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir. All patients with genotype 3b enrolled in this trial had NS5A RASs at A30K or L31M, or both.

Last update: November 6, 2019

Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:		
Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis ^a 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks ^c	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H for velpatasvir	12 weeks	I, A
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for patients with baseline NS5A RAS Y93H for velpatasvir	12 weeks	IIa, B

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis^a

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^c For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Recommended Regimens

Glecaprevir/Pibrentasvir

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 ([Kwo, 2016b](#)).

A recent real-world cohort of 723 Italian treatment-naive and -experienced patients with or without cirrhosis were treated with glecaprevir/pibrentasvir according to the manufacturer's prescribing information. One hundred percent (21/21) of patients with genotype 3 infection who received 12 or 16 weeks of glecaprevir/pibrentasvir (likely indicative of more advanced liver disease or treatment experience) achieved SVR12, compared to 95.8% (46/48) who received an 8-week regimen ([D'Ambrosio 2019](#)). Comparably high SVR12 rates were reported with 12 weeks of glecaprevir/pibrentasvir among cirrhotic persons with genotype 3 infection in other real-world cohorts ([Drysdale, 2019](#)); ([Sterling, 2019](#)).

EXPEDITION-8 included an evaluation of glecaprevir/pibrentasvir for a reduced duration of 8 weeks in treatment-naive patients with compensated cirrhosis including genotype 3 (n=63). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from this study. Among the participants with genotype 3, 95% (60/63) achieved SVR12 with a single participant experiencing virologic failure (relapse) and 2 participants lost to follow-up ([Brown, 2019](#)).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized 552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin ([Foster, 2015a](#)). Among those with compensated cirrhosis, the SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12 compared to 97% (242/249) in those without this RAS ([Foster, 2015a](#)). Ribavirin use was not evaluated in this study.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis ([Jacobson, 2017](#)). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

To explore whether ribavirin is required for patients with genotype 3 infection and cirrhosis, a randomized, open-label study of 204 genotype 3 patients with compensated cirrhosis (including participants with NS3/4 protease inhibitor and NS5B inhibitor treatment experience) was conducted at 29 sites in Spain. SVR12 was achieved in 91% without ribavirin (5% relapse rate) and 96% with ribavirin (2% relapse rate). Baseline NS5A RASs affected response rates. Among patients with Y93H RAS, 50% (2/4) treated with sofosbuvir/velpatasvir without ribavirin achieved SVR12 compared to 89% (8/9) among those receiving ribavirin as part of their treatment regimen ([Esteban, 2018](#)). In 293 patients with genotype 3 infection (25% with cirrhosis and 4% with DAA experience) enrolled in a multicenter cohort study from Germany in which patients received 12 weeks of sofosbuvir/velpatasvir with or without ribavirin, there was only 1 virologic failure in a patient with DAA treatment experience ([von Felden, 2018](#)). All 5 genotype 3 cirrhotic patients with RASs were prescribed ribavirin along with sofosbuvir/velpatasvir and achieved SVR. Pending further data on optimal therapy in the setting of a baseline Y93H substitution, patients with compensated cirrhosis should have ribavirin added to the regimen of sofosbuvir/velpatasvir or another regimen should be considered.

Another recent study provided information about use of sofosbuvir/velpatasvir therapy in patients with genotype 3b infection, a subtype rarely encountered in the United States. The single-arm, open-label, phase 3 trial enrolled patients from Asia (predominantly China) and treated them with 12 weeks of sofosbuvir/velpatasvir. Ninety percent (60/67) of patients with cirrhosis achieved SVR12 ([Wei, 2019](#)). In the subset of 14 patients with genotype 3b infection and cirrhosis, however, only 50% (7/14) achieved SVR12. All patients with genotype 3b enrolled in this trial had NS5A RASs at either A30K or L31M, or both. The influence of subtype and RASs on SVR rates warrants consideration in the use of sofosbuvir/velpatasvir among cirrhotic patients with genotype 3 infection, although genotype 3b is rare in non-Asian populations.

Alternative Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis ([Jacobson, 2017](#)). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2 virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12.

Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

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Treatment-Naive Genotype 4

The following pages include guidance for management of treatment-naive patients with genotype 4 infection.

- [Treatment-Naive Genotype 4 Without Cirrhosis](#)
- [Treatment-Naive Genotype 4 With Compensated Cirrhosis](#)


- [Simplified HCV Treatment for Treatment-Naive Patients Without Cirrhosis](#)

Last update: November 6, 2019

Treatment-Naive Genotype 4 Without Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^a	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) ^b	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, B

^a Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^b An 8-week regimen can be considered in patients with favorable baseline characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in part 4 of the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) ([Kwo, 2017b](#)), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills ([Asselah, 2018b](#)). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week versus 12-week course of glecaprevir/pibrentasvir for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis ([Asselah, 2018b](#)). In the intention-to-treat analysis, 43/46 patients with genotype 4, 2/2 with genotype 5, and 9/10 with genotype 6 achieved SVR12; there were no known virologic failures.

EXPEDITION-1 investigated use of glecaprevir/pibrentasvir in treatment-naive (75%) or -experienced (interferon or

peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 16/16 (100%) with genotype 4, 2/2 (100%) with genotype 5, and 7/7 (100%) with genotype 6 ([Forns, 2017](#)). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.

Ledipasvir/Sofosbuvir

In the HEPNED-001 study from the Netherlands, 40 treatment-naive, noncirrhotic patients with (n=30) and without (n=10) HIV coinfection were treated with ledipasvir/sofosbuvir for 8 weeks; 93% (28/30) of HIV/HCV-coinfected patients and 100% (10/10) of HCV-monoinfected patients achieved SVR12 ([Boerekamps, 2019](#)). Patients were predominantly infected with genotypes 4a and 4d; 2.5% each were infected with 4c and 4t. In another study that evaluated 8 weeks of ledipasvir/sofosbuvir among treatment-naive, noncirrhotic patients from Saudi Arabia with genotype 4 infection, SVR12 was 98% ([Babatin, 2019](#)). Notably, 91% of patients had a baseline HCV RNA level <6 million IU/mL. These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection, with 8-weeks therapy a consideration for those with favorable characteristics (ie, no cirrhosis, HCV RNA <6 million IU/mL, and absence of genotype 4r).

In a study of from Rwanda, 300 treatment-naive patients with genotype 4 infection were treated with ledipasvir/sofosbuvir for 12 weeks. The major subtypes among participants were 4k (n=134), 4r (n=48), 4q (n=42), and 4v (n=24). Overall SVR was 87% with subtype differences evident; SVR for 4r infection was 56% compared to 93% for other subtypes ([Gupta, 2019](#)). The influence of subtype on SVR warrants consideration of the use of ledipasvir, although 4r is rare in non-African populations.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) ([Feld, 2015](#)).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) versus 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse ([Jacobson, 2017](#)).

Elbasvir/Grazoprevir

The phase 3 C-EDGE treatment-naive trial of elbasvir/grazoprevir included 18 patients with genotype 4 infection. With 12 weeks of therapy, SVR was 100% (18/18) ([Zeuzem, 2015](#)). A similar SVR12 of 96% (54/56) was seen in treatment-naive patients with genotype 4 infection from the combined phase 2/3 elbasvir/grazoprevir database of HIV/HCV coinfecting patients treated for 12 weeks ([Rockstroh, 2015](#)).


An integrated analysis of a phase 2/3 trial evaluated elbasvir/grazoprevir with or without ribavirin among 111 treatment-naive patients with genotype 4 infection (predominantly subtype 4a and 4d); 26% of participants had HIV/HCV coinfection and 13% had cirrhosis. Elbasvir/grazoprevir without ribavirin for 12 weeks resulted in an SVR12 of 96% (97/101) ([Asselah, 2018c](#)). Baseline RASs and subtype did not appear to impact SVR12 rates.

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Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 4 Patients With Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks ^c	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^c For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) ([Feld, 2015](#)).

The POLARIS-2 phase 3 study randomized DAA-naive patients (19% with compensated cirrhosis, overall) to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse ([Jacobson, 2017](#)).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients received the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 ([Forns, 2017](#)). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR12 rates among treatment-naive and -experienced participants with genotype 4. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for genotype 4-infected, treatment-naive patients with compensated cirrhosis.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2, 4 (n=13), 5 or 6 infection. SVR12 was 99% with no virologic failures ([Brown, 2018](#)). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the

study.

Elbasvir/Grazoprevir

In an integrated analysis of phase 2/3 trials, 15 treatment-naive patients with genotype 4 infection and cirrhosis were treated with 12 weeks of elbasvir/grazoprevir with or without ribavirin, resulting in an SVR of 96% ([Asselah, 2018c](#)).

Ledipasvir/Sofosbuvir


The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4 patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) ([Kohli, 2015](#)). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4, treatment-naive patients (1 with cirrhosis) with a SVR12 of 95% (21/22) ([Abergel, 2016](#)).

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Treatment-Naive Genotype 5 or 6

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis^a

RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks ^c	I, A ^d
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) ^e	12 weeks	Ila, B

^a For [decompensated cirrhosis](#), please refer to the appropriate section.

^b Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

^c For HIV/HCV-coinfected patients, a treatment duration of 12 weeks is recommended.

^d For compensated cirrhosis, rating is I, B.

^e Not recommended for genotype 6e if subtype is known.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100%

SVR12 in 34 patients with genotype 4, 5, or 6) ([Kwo, 2017b](#)), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills ([Asselah, 2018b](#)). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis ([Asselah, 2018b](#)). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR12; there were no known virologic failures. Further, ENDURANCE-5,6 was a phase 3b, single-arm, open-label, multicenter study of the efficacy of glecaprevir/pibrentasvir among DAA-naive patients with genotype 5 (n=23) or 6 (n=61) infection. Participants without cirrhosis received an 8-week regimen; those with cirrhosis (11% of patients) received 12 weeks of treatment ([Asselah, 2019](#)). Overall SVR was 98% with 2 virologic failures; treatment failed in a patient with genotype 6f and cirrhosis, and in another noncirrhotic participant with genotype 5a.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 2/2 with genotype 5 and 7/7 with genotype 6 ([Forns, 2017](#)). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5 or genotype 6 infection.

EXPEDITION-8 evaluated 8 weeks of glecaprevir/pibrentasvir among 280 treatment-naive patients with compensated cirrhosis and genotype 1, 2, 4, 5 (n=1) or 6 (n=9) infection. SVR12 was 99% with no virologic failures ([Brown, 2018](#)). Patients with a prior history of decompensation, hepatocellular carcinoma, and HIV or HBV coinfection were excluded from the study.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 5 and 6 infection in patients with and without cirrhosis ([Feld, 2015](#)). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 23 (96%) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12 (100%). An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR ([Jacobson, 2017](#)).

Two real-world cohort studies evaluated 12 weeks of sofosbuvir /velpatasvir among predominantly treatment-naive patients with genotype 6 infection. SVR was 100% (n=23) in a cohort of patients from Southwest China, none of whom had clinical cirrhosis ([Wu, 2019](#)). SVR was also 100% (n=43) in a cohort of predominantly Vietnamese patients residing in the United States, 12% of whom had cirrhosis ([Nguyen, 2019](#)).

Ledipasvir/Sofosbuvir

Although there are limited data on patients with genotype 5 infection, the in-vitro activity of sofosbuvir and ledipasvir are quite good with EC50 of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single-arm study that included 41 genotype 5-infected patients with an overall SVR12 rate of 95% (39/41) ([Abergel, 2016](#)). The SVR12 rate was also 95% specifically in treatment-naive patients (20/21), of whom only 3 had cirrhosis but all achieved SVR12.

Ledipasvir has in-vitro activity against most genotype 6 subtypes, except for 6e ([Wong, 2013](#)); ([Kohler, 2014](#)). A small, 2-center, open-label study (NCT01826981) investigated the safety and in-vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% treatment-

naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6l; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events ([Gane, 2015](#)).

In the largest US study, 60 patients with genotype 6 infection were randomized to 8 weeks (treatment-naive, no cirrhosis) or 12 weeks (treatment-naive or -experienced, with or without cirrhosis) of ledipasvir/sofosbuvir; SVR rates were 95% in both treatment groups ([Nguyen, 2017](#)). A real-world cohort of 92 treatment-naive patients with genotype 6 infection (predominantly Vietnamese patients residing in the United States, 51% with cirrhosis) was treated with 12 weeks of ledipasvir/sofosbuvir; SVR12 was 96.6% ([Nguyen, 2019](#)). Subtype data were not available.

A recent systematic review that examined the response to DAA therapy among persons with genotype 6 infection highlighted the heterogeneity of SVR rates in response to ledipasvir/sofosbuvir treatment across Asian countries (64% in Myanmar versus 100% in Vietnam) ([Mettikanont, 2019](#)). The reasons for this difference are likely multiple; the variable distribution of subtypes within the populations is a potential explanation. Pending more data, a conservative approach is recommended, with subtype 6e patients best treated with an alternative regimen.

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