

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.

[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](#)).

- [Simplified Pangenotypic HCV Treatment for Treatment-Naive Adults Without Cirrhosis](#)
- [Simplified Pangenotypic HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis](#)

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.

Recommended and alternative regimens are listed by pan-genotypic activity and 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 by genotype (although most patients will fall into the simplified treatment algorithms above).

- [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 ([Chiu, 2020](#)). 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 Adults Without Cirrhosis

Who Is **NOT** Eligible for Simplified Treatment (Without Cirrhosis)

Patients who have any of the following characteristics:

- Prior hepatitis C treatment
- Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis)
- 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 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 $<150,000/\text{mm}^3$, 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](#).
 - Drug-drug interactions are particularly important in HIV co-infection
 - In those with HIV, the simplified treatment approach should not be used in those on TDF containing

regimens with eGFR <60 ml/min because of the need of additional monitoring.

- **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)
 - *Any time 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.
- Until retreatment occurs, 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](#).

^a FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated by: $(\text{age [years]} \times \text{AST [U/L]}) \div (\text{platelet count [10}^9\text{/L]} \times \text{ALT}^{1/2} \text{ [U/L]})$.

^b A patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or if they have any of the following from a previously performed test: (1) transient elastography indicating cirrhosis (ie, liver stiffness >12.5 kPa); (2) noninvasive serologic tests above the proprietary cutoff indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test); (3) clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count $<150,000/\text{mm}^3$); or (4) prior liver biopsy showing cirrhosis.

^c Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements.

^d Drug-drug interaction assessment should be performed using the [table](#) in the monitoring section of the HCV guidance or the University of Liverpool drug interaction [checker](#).

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Simplified HCV Treatment Algorithm for Treatment-Naive Adults With Compensated Cirrhosis

Who Is *NOT* Eligible for Simplified Treatment (With Cirrhosis)

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)
- 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/mm³, 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](#).
 - Drug-drug interactions are particularly important in HIV co-infection
 - In those with HIV, the simplified treatment approach should not be used in those on TDF containing regimens with eGFR <60 ml/min because of the need of additional monitoring.
- **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)
 - *Any time 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.

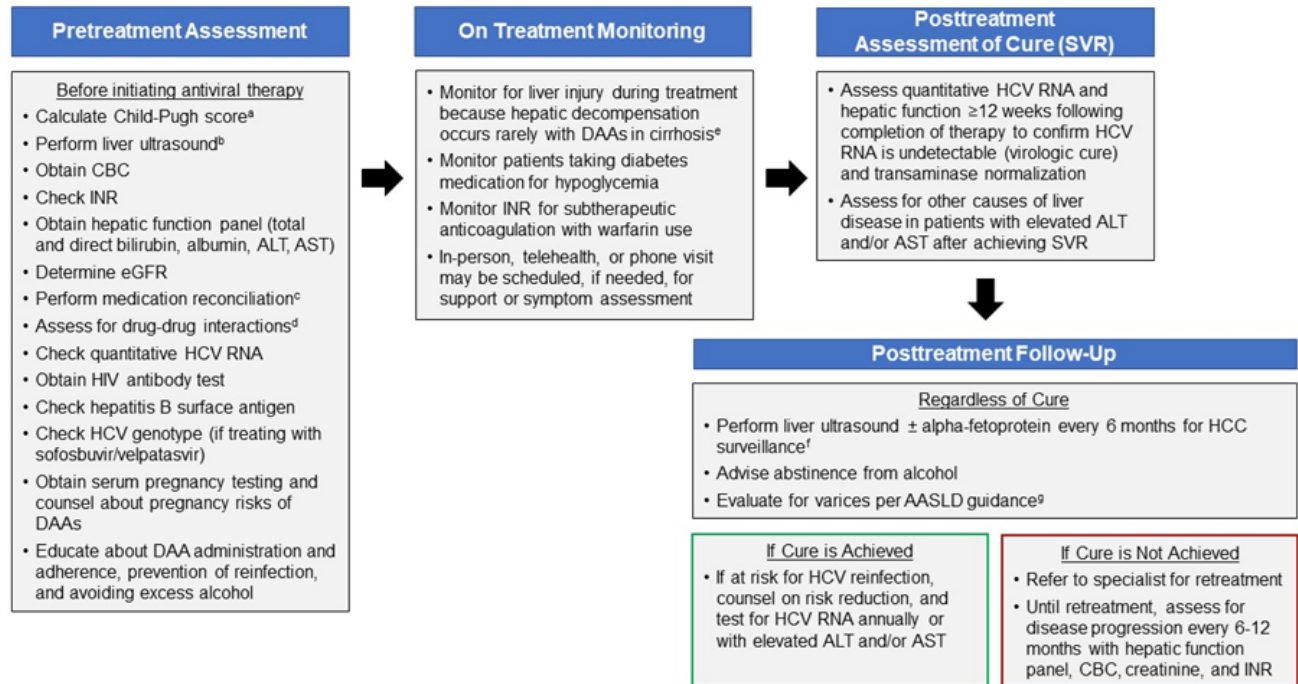
Follow-Up After Achieving Virologic Cure (SVR)

- 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, creatinine, 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](#).



^a Child-Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, ≥1.7. Patients with a Child-Pugh score ≥7 (ie, Child-Pugh B or C) have decompensated cirrhosis; this simplified treatment approach is not recommended for patients with decompensated cirrhosis.

^b Obtain liver ultrasound within 6 months prior to initiating antiviral treatment to exclude hepatocellular carcinoma and ascites. This simplified treatment approach is not recommended for patients with hepatocellular carcinoma and/or decompensated cirrhosis.

^c Medication reconciliation should record currently prescribed medications, over-the-counter drugs, and herbal/dietary supplements.

^d Drug-drug interaction assessment should be performed using the [table](#) in the monitoring section of the HCV guidance or the University of Liverpool drug interaction [checker](#).

^e Development of jaundice, ascites, spontaneous bacterial peritonitis, variceal hemorrhage, or hepatic encephalopathy may suggest hepatic decompensation. Patients should be referred to a specialist if they develop worsening liver blood tests (ie, bilirubin, AST, ALT, INR), jaundice, ascites, encephalopathy, or new liver-related symptoms).

^f 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.

^g See [AASLD guidance](#) for recommendations regarding the evaluation and management of varices.

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Treatment-Naive Genotype 1

Three 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 Adults Without Cirrhosis](#)

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Treatment-Naive Genotype 1a Without Cirrhosis

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

Treatment-Naive Genotype 1a 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)	12 weeks	I, A
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
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (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

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, 2018](#)). 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 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 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.

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. A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 99.1% (1599/1613) among participants with genotype 1, with or without compensated cirrhosis ([Mangia, 2020](#)).

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](#)); ([Ioannou, 2016](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)). 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.

Alternative Regimen

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 >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).

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Treatment-Naive Genotype 1a With Compensated Cirrhosis

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

Treatment-Naive Genotype 1a 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	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING 
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, 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.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 3 recommended regimens with comparable efficacy.

Recommended Regimens

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. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 98.3% (349/355) among adults with genotype 1 and

compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

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%).

Alternative Regimen

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 ([Zeuzem, 2017](#)); ([Lawitz, 2015c](#)).

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 >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.

Last update: October 24, 2022

Treatment-Naive Genotype 1b Without Cirrhosis

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

Treatment-Naive Patients Genotype 1b 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
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks ^b	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
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

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

^b For HIV/HCV coinfecting patients, a treatment duration of 12 weeks is recommended.

^c An 8-week regimen can be considered in those with genotype 1b infection and mild fibrosis (see text for details).

Recommended Regimens

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, 2018](#)). 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.

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.

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 (genotype 1, 4, or 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 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.

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.

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, 2017](#)); ([Ioannou, 2016](#)); ([Wilder, 2016](#)); ([O'Brien, 2014](#)). 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).

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Treatment-Naive Genotype 1b With Compensated Cirrhosis

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

Treatment-Naive Genotype 1b 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	I, B
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

^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.

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

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). Among 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 (100 mg) or 12 weeks of sofosbuvir/velpatasvir ([Jacobson, 2017](#)). Of participants treated with sofosbuvir/velpatasvir, 99% (170/172) with genotype 1a and 97% (57/59) with genotype 1b achieved SVR with a single relapse observed with each subtype.

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](#)). A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated SVR12 rates of 99.6% (n=848) and 98.2% (n=60) among participants with genotype 1 infection without or with compensated cirrhosis, respectively, with 8 weeks of treatment ([Lampertico, 2020](#)).

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 ([Zeuzem, 2017](#)); ([Lawitz, 2015c](#)).

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%).

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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 Adults Without Cirrhosis](#)

Last update: October 24, 2022

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, 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](#)). A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated SVR12 rates of 99.0% (n=274) and 98.0% (n=29) among participants with genotype 2 infection without or with compensated cirrhosis, respectively, with 8 weeks of treatment ([Lampertico, 2020](#)).

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 (100 mg) 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. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 99.3% (1535/1546) among adults with genotype 2 infection (with or without compensated cirrhosis) who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

Last update: October 24, 2022

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, 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	I, B

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

Treatment-Naive Genotype 2 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.

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](#)). A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 98.5% (266/270) among adults with genotype 2 infection and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

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](#)). Real-world data support the use of 8 weeks in cirrhotic patients ([Flamm, 2020](#)).

Last update: October 24, 2022

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 Adults Without Cirrhosis](#)

Last update: October 24, 2022

Treatment-Naive Genotype 3 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and 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 ([Drysdale, 2019](#)); ([Sterling, 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. A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated an SVR12 of 99.2% (n=320) among noncirrhotic participants with genotype 3 infection with 8 weeks of treatment ([Lampertico, 2020](#)).

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 ([Drysdale, 2019](#)); ([Mangia, 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. Another study among 90 noncirrhotic treatment-naive patients—most receiving opioid agonist therapy—treated with only 8 weeks of sofosbuvir/velpatasvir demonstrated an SVR rate of 96% (86/90) ([Boyle, 2020](#)). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 98.3% (1649/1677) among participants with genotype 3, with or without compensated cirrhosis ([Mangia, 2020](#)).

Last update: October 24, 2022

Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, evidence level and alphabetically for: Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis^a 		
RECOMMENDED	DURATION	RATING 
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for patients without baseline NS5A RAS Y93H	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) ^b	8 weeks	I, B
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	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	12 weeks	IIa, B
<p>^a For decompensated cirrhosis, please refer to the appropriate section.</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

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, 16% (n=43) 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. A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 96.9% (314/324) among adults with genotype 3 infection and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

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.

If NS5A resistance testing is unavailable, glecaprevir/pibrentasvir should be used. If drug drug interactions or other considerations preclude the use of glecaprevir/pibrentasvir then a referral to a specialist in HCV treatment should be considered.

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](#)).

Alternative Regimen

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 Adults Without Cirrhosis](#)

Last update: October 24, 2022

Treatment-Naive Genotype 4 Without Cirrhosis

Recommended and alternative regimens listed by pangenotypic, 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 sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
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) ^b	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.

^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, 93% (43/46) of patients with genotype 4, 100% (2/2) with genotype 5, and 90% (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 100% (16/16) with genotype 4, 100% (2/2) with genotype 5, and 100% (7/7) 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. A meta-analysis of real-world cohorts that examined glecaprevir/pibrentasvir treatment response among adults demonstrated an SVR12 of 98.3% (n=55) among noncirrhotic participants with genotype 4 infection with 8 weeks of treatment ([Lampertico, 2020](#)).

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](#)). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 99.6% (238/239) among participants with genotype 4, with or without compensated cirrhosis ([Mangia, 2020](#)).

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-coinfected 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. In a study among treatment-naive participants with genotype 4 infection that compared 8 weeks versus 12 weeks of elbasvir/grazoprevir treatment for those with F0 to F2 fibrosis (all with F3 to F4 fibrosis received 12 weeks of treatment), SVR rates were 94% (50/53) in the 8-week arm and 96% (26/27) in the 12-week arm ([Asselah, 2020](#)).

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 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.

Last update: October 24, 2022

Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended and alternative regimens listed by pangenotypic, 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](#)). A real-world, pooled analysis of 12 cohort studies demonstrated an SVR of 100% (38/38) among adults with genotype 4 infection and compensated cirrhosis who were treated with 12 weeks of sofosbuvir/velpatasvir ([Mangia, 2020](#)).

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, 99% (145/146) 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. Another open-label, single-arm study evaluating 12 weeks of ledipasvir/sofosbuvir that included 22 genotype 4, treatment-naive patients (one with cirrhosis) reported an SVR12 of 95% (21/22) in this patient population ([Abergel, 2016](#)).

Last update: October 24, 2022

Treatment-Naive Genotype 5 or 6

Recommended and alternative regimens listed by pangenotypic, 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	I, A ^c
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) ^d	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 compensated cirrhosis, rating is I, B.

^d 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 100% (2/2) with genotype 5 and 100% (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 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.

An integrated analysis of the 181 participants with genotype 5 or 6 from phase 2/3 studies including those above showed comparable response rates between 8 weeks and 12 weeks of treatment with no signal of poorer performance among cirrhotic patients with an 8-week regimen ([Yao, 2020](#)).

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, 96% (23/24) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12. 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% in a cohort of patients (n=23) from Southwest China, none of whom had clinical cirrhosis ([Wu, 2019](#)). SVR was also 100% in a cohort of predominantly Vietnamese patients (n=43) residing in the United States, 12% of whom had cirrhosis ([Nguyen, 2019](#)). A real-world, pooled analysis of 12 cohorts that evaluated adults treated with 12 weeks of sofosbuvir/velpatasvir demonstrated an SVR of 98.5% (67/68) among participants with genotype 5 or 6 infection; all 13 participants with compensated cirrhosis achieved SVR ([Mangia, 2020](#)).

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. An open-label, single-arm study that included 41 genotype 5-infected patients demonstrated an overall SVR12 rate of 95% (39/41) ([Abergel, 2016](#)). The SVR12 rate was also 95% specifically among 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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Related References

Abergel A, Asselah T, Metivier S, Loustaud-Ratti V. [Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study](#). *Lancet Infect Dis*. 2016;16(4):459-464.

Abergel A, Metivier S, Samuel D, et al. [Ledipasvir plus sofosbuvir for 12 weeks in patients with hepatitis C genotype 4 infection](#). *Hepatology*. 2016;64(4):1049-1056.

Abergel A, Hezode C, Asselah T, et al. [A phase 3, global, multicenter, open-label study to investigate the efficacy of elbasvir/grazoprevir fixed-dose combination for 8 weeks in treatment-naïve, HCV GT1b-infected patients, with non-severe fibrosis: STREAGER](#). The International Liver Congress. Paris, France; 2018.

Afdhal NH, Zeuzem S, Kwo PY, Chojkier M, Gitlin N, Puoti M, et al. [Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection](#). *N Engl J Med*. 2014;370(20):1889-1898.

Asselah T, Bourgeois S, Pianko S, Zeuzem S, Sulkowski M, Foster GR, et al. [Sofosbuvir/velpatasvir in patients with hepatitis C virus genotypes 1-6 and compensated cirrhosis or advanced fibrosis](#). *Liver Int*. 2018;38(3):443-450.

Asselah T, Kowdley KV, Zadeikis N, Wang S, Hassanein T, Horsmans Y, et al. [Efficacy of glecaprevir/pibrentasvir for 8 or 12 weeks in patients with hepatitis C virus genotype 2, 4, 5, or 6 infection without cirrhosis](#). *Clin Gastroenterol Hepatol*. 2018;16(3):417-426.

Asselah T, Reesink H, Gerstoft J, et al. [Efficacy of elbasvir and grazoprevir in participants with hepatitis C virus genotype](#)

[4 infection: a pooled analysis](#). Liver Int. 2018;38(9):1583-1591.

Asselah T, Lee SS, Yao BB, et al. [Efficacy and safety of glecaprevir/pibrentasvir in patients with chronic hepatitis C virus genotype 5 or 6 infection \(ENDURANCE-5.6\): an open-label, multicentre, phase 3b trial](#). Lancet Gastroenterol Hepatol. 2019;4(1):45-51.

Asselah T, Pol S, Hezode C, et al. [Efficacy and safety of elbasvir/grazoprevir for 8 or 12 weeks for hepatitis C virus genotype 4 infection: a randomized study](#). Liver Int. 2020;40(5):1042-1051.

Babatin MA, AlGhamdi AS, Assiri AM, et al. [Treatment efficacy of ledipasvir/sofosbuvir for 8 weeks in non-cirrhotic chronic hepatitis C genotype 4 patients](#). Saudi J Gastroenterol. 2019;25(1):55-60.

Backus LI, Belperio PS, Shahoumian TA, Loomis TP, Mole LA. [Real-world effectiveness and predictors of sustained virological response with all-oral therapy in 21,242 hepatitis C genotype-1 patients](#). Antivir Ther. 2017;22(6):481-493.

Berg T, Naumann U, Stoehr A, et al. [Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry](#). Aliment Pharmacol Ther. 2019;49(8):1052-1059.

Boerekamps A, Vanwolleghem T, Van Der Valk M, et al. [8 weeks of sofosbuvir/ledipasvir is effective in DAA-naive non-cirrhotic HCV genotype 4 infected patients \(HEPNED-001 study\)](#). J Hepatol. 2019;70(3):554-557.

Boyle A, Marra F, Peters E, et al. [Eight weeks of sofosbuvir/velpatasvir for genotype 3 hepatitis C in previously untreated patients with significant \(F2/3\) fibrosis](#). J Viral Hepat. 2020;27(4):371-375.

Brown RS, Hezode C, Wang S, et al. [Preliminary efficacy and safety of 8-week glecaprevir/pibrentasvir in patients with HCV genotype 1-6 infection and compensated cirrhosis: the EXPEDITION-8 study \[Abstract LB-7\]](#). The Liver Meeting. San Francisco, CA; 2018.

Brown RS, Buti M, Rodrigues L, et al. [Efficacy and safety of 8-week glecaprevir/pibrentasvir in treatment-naive patients with chronic hepatitis c virus genotype 1, 2, 3, 4, 5, or 6 infection and compensated cirrhosis: EXPEDITION-8 complete results \[abstract LP9\]](#). Presented at Liver Meeting, 2019; November 8-12. Boston, Massachusetts; 2019.

Chayama K, Suzuki F, Karino Y, et al. [Efficacy and safety of glecaprevir/pibrentasvir in Japanese patients with chronic genotype 1 hepatitis C virus infection with and without cirrhosis](#). J Gastroenterol. 2018;53(4):557-565.

Chiu WN, Hung CH, Lu SN, et al. [Real-world effectiveness of glecaprevir/pibrentasvir and ledipasvir/sofosbuvir for mixed genotype hepatitis C infection: a multicenter pooled analysis in Taiwan](#). J Viral Hepat. 2020;27(9):866-872.

D'Ambrosio R, Pasulo L, Puoti M, et al. [Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C](#). J Hepatol. 2019;70(3):379-387.

Drysdale K, Townley C, Mahomed F, Foster G. [Effectiveness of therapy in 16,567 directly-acting antiviral treated people in England: High response rates in genotype 3 hepatitis C infection regardless of degree of fibrosis, but ribavirin improves response in cirrhosis](#). International Liver Congress. Vienna, Austria; 2019.

Esteban R, Pineda JA, Calleja JL, et al. [Efficacy of sofosbuvir and velpatasvir, with and without ribavirin, in patients with hepatitis C virus genotype 3 infection and cirrhosis](#). Gastroenterology. 2018;155(4):1120-1127.e4.

Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, et al. [Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection](#). N Engl J Med. 2015;373(27):2599-2607.

Flamm SL, Kort J, Marx SE, et al. [Effectiveness of 8-week glecaprevir/pibrentasvir for treatment-naive, compensated cirrhotic patients with chronic hepatitis C infection](#). Adv Ther. 2020;37(5):2267-2274.

- Forns X, Lee SS, Valdes J, Lens S, Ghalib R, Aguilar H, et al. [Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis \(EXPEDITION-1\): a single-arm, open-label, multicentre phase 3 trial](#). *Lancet Infect Dis*. 2017;17(10):1062-1068.
- Foster GR, Afdhal NH, Roberts SK. [Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection](#). *N Engl J Med*. 2015;373(27):2608-2617.
- Foster GR, Gane E, Asatryan A, Asselah T, Ruane PJ, Pol S, et al. [ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naive HCV genotype 3-infected patients without cirrhosis](#). *J Hepatol [Internet]*. 2017;66(1):S33. [http://dx.doi.org/10.1016/S0168-8278\(17\)30326-4](http://dx.doi.org/10.1016/S0168-8278(17)30326-4)
- Gane EJ, Hyland RH, An D, Svarovskaia ES, Pang PS, Brainard D, et al. [Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection](#). *Gastroenterology*. 2015;149(6):1454-1461.
- Gupta N, Mbituyumuremyi A, Kabahizi J, et al. [Treatment of chronic hepatitis C virus infection in Rwanda with ledipasvir-sofosbuvir \(SHARED\): a single-arm trial](#). *Lancet Gastroenterol Hepatol*. 2019;4(2):119-126.
- Hezode C, Reau N, Svarovskaia ES, Doehle BP, Shanmugam R, Dvory-Sobol H, et al. [Resistance analysis in patients with genotype 1-6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies](#). *J Hepatol*. 2018;68(5):895-903.
- Ingiliz P, Christensen S, Kimhofer T, Hueppe D, Lutz T, Schewe K, et al. [Sofosbuvir and ledipasvir for 8 weeks for the treatment of chronic hepatitis C virus \(HCV\) infection in HCV-monoinfected and HIV-HCV-coinfected individuals: results from the German hepatitis C cohort \(GECCO-01\)](#). *Clin Infect Dis*. 2016;63(10):1320-1324.
- Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI, et al. [Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs national health care system](#). *Gastroenterology*. 2016;151(3):457-471.e5.
- Isakov V, Chulanov V, Abdurakhmanov D, et al. [Sofosbuvir/velpatasvir for the treatment of HCV: excellent results from a phase-3, open-label study in Russia and Sweden](#). *Infect Dis (Lond)*. 2019;51(2):131-139.
- Jacobson IM, Asante-Appiah E, Wong P, Black T, Howe A, Wahl J, et al. [Prevalence and impact of baseline NSA resistance associated variants \(RAVs\) on the efficacy of elbasvir/grazoprevir \(EBR/GZR\) against GT1a infection \[abstract LB-22\]](#). The Liver Meeting. San Francisco, CA; 2015.
- Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. [Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials](#). *Gastroenterology*. 2017;153(1):113-122.
- Kohler JJ, Nettles JH, Amblard F, Hurwitz SJ, Bassit L, Stanton RA, et al. [Approaches to hepatitis C treatment and cure using NS5A inhibitors](#). *Infect Drug Resist*. 2014;7:41-56.
- Kohli A, Kapoor R, Sims Z, Nelson A, Sidharthan S, Lam B, et al. [Ledipasvir and sofosbuvir for hepatitis C genotype 4: a proof-of-concept, single-centre, open-label phase 2a cohort study](#). *Lancet Infect Dis*. 2015;15(9):1049-1054.
- Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz EJ, et al. [Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis](#). *N Engl J Med*. 2014;370(20):1879-1888.
- Kowdley KV, Sundaram V, Jeon CY, Qureshi K, Latt NL, Sahota A, et al. [Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 hepatitis C virus infection](#). *Hepatology*. 2016;65(4):1094-1103.
- Krishnan P, Pilot-Matias T, Schnell G, Tripathi R, Ng TI, Reisch T, et al. [Pooled resistance analysis in HCV genotype 1-6 infected patients treated with glecaprevir/pibrentasvir in phase 2 and 3 clinical trials](#). *Antimicrob Agents Chemother*. 2018;62(10):pii: e01249-18.

Kwo PY, Wyles DL, Wang S, Poordad F, Gane E, Maliakkal B, et al. [100% SVR4 with ABT-493 and ABT-530 with or without ribavirin in treatment-naive HCV genotype 3-infected patients with cirrhosis](#). J Hepatol. 2016;64(2):S208.

Kwo PY, Gane EJ, Peng CY, Pearlman B, Vierling JM, Serfaty L, et al. [Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection](#). Gastroenterology. 2017;152(1):164-175.e4.

Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, et al. [Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis](#). J Hepatol. 2017;67(2):263-271.

Lampertico P, Carrión JA, Curry M, et al. [Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis](#). J Hepatol. 2020;72(6):1112-1121.

Lawitz EJ, Gane EJ, Pearlman B, et al. [Efficacy and safety of 12 wks vs 18 wks of treatment w/ GRZ and ELB w/ or without RBV for HCV GT1 infection in previously untreated pts w/ cirrhosis and pts w/ previous null response w/ or without cirrhosis \(C-WORTHY\), randomised, open-label phase 2 trial](#). Lancet. 2015;385(9973):1075-1086.

Mangia A, Milligan S, Khalili M, et al. [Global real-world evidence of sofosbuvir/velpatasvir as a simple, effective regimen for the treatment of chronic hepatitis C patients: Integrated analysis of 12 clinical practice cohorts](#). International Liver Congress. Vienna, Austria; 2019.

Mangia A, Milligan S, Khalili M, et al. [Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts](#). Liver Int. 2020;40(8):1841-1852.

Marcus JL, Hurley LB, Chamberland S. [No difference in effectiveness of 8 vs 12 weeks of ledipasvir and sofosbuvir for treatment of hepatitis C in black patients](#). Clin Gastroenterol Hepatol. 2018;16(6):927-935.

Mettikanont P, Bunchorntavakul C, Reddy KR. [Systematic review: epidemiology and response to direct-acting antiviral therapy in genotype 6 chronic hepatitis C virus infection](#). Aliment Pharmacol Ther. 2019;49(5):492-505.

Naganuma A, Chayama K, Notsumata K, et al. [Integrated analysis of 8-week glecaprevir/pibrentasvir in Japanese and overseas patients without cirrhosis and with hepatitis C virus genotype 1 or 2 infection](#). J Gastroenterol. 2019;54(8):752-761.

[National Academies of Sciences, committee on a national strategy for the elimination of hepatitis B and C, board on population health and public health practice: a national strategy for the elimination of hepatitis B and C: phase two report](#). Washington, DC: National Academies Press; 2017.

Nguyen MH, Trinh H, Do S, Nguyen T, Nguyen P, Henry L. [Open label study of 8 vs. 12 weeks of ledipasvir/sofosbuvir in genotype 6 treatment naïve or experienced patients](#). Am J Gastroenterol. 2017;112(12):1824-1831.

Nguyen E, Trinh S, Trinh H, et al. [Sustained virologic response rates in patients with chronic hepatitis C genotype 6 treated with ledipasvir+sofosbuvir or sofosbuvir+velpatasvir](#). Aliment Pharmacol Ther. 2019;49(1):99-106.

O'Brien TR, Lang Kuhs KA, Pfeiffer RM. [Subgroup differences in response to 8 weeks of ledipasvir/sofosbuvir for chronic hepatitis C](#). Open Forum Infect Dis. 2014;1(3):ofu110.

Rockstroh JK, Nelson M, Katlama C, et al. [Efficacy and safety of grazoprevir \(MK-5172\) and elbasvir \(MK- 8742\) in patients with hepatitis C virus and HIV co-infection \(C-EDGE CO-INFECTION\): a non-randomised, open-label trial](#). Lancet HIV. 2015;2(8):e319-327.

Rockstroh J, Lacombe K, Viani RM, Orkin C, Wyles D, Luetkemeyer A, et al. [Efficacy and safety of Glecaprevir/Pibrentasvir in patients co-infected with hepatitis C virus and human immunodeficiency virus-1: the EXPEDITION-2 Study \[Abstract LBP-522\]](#). In The International Liver Congress. EASL [Internet]. 2017.

[http://dx.doi.org/10.1016/S0168-8278\(17\)30467-1](http://dx.doi.org/10.1016/S0168-8278(17)30467-1)

Rockstroh JK, Lacombe K, Viani RM, et al. [Efficacy and safety of glecaprevir/pibrentasvir in patients coinfecting with hepatitis C virus and human immunodeficiency virus type 1: the EXPEDITION-2 study](#). Clin Infect Dis. 2018;67(7):1010-1017.

Sterling RK, Zeuzem S, Wetzel T, et al. [Safety and efficacy of glecaprevir/pibrentasvir for the treatment of HCV genotype 1-6: results from the HCV-TARGET study](#). International Liver Congress. Vienna, Austria; 2019.

Su F, Green PK, Ioannou GN. [The Association association between race/ethnicity and the effectiveness of direct antiviral agents for hepatitis C virus infection](#). Hepatology. 2017;65(2):426-438.

Sulkowski MS, Hézode C, Gerstoft J, et al. [Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir \(MK-5172\) and elbasvir \(MK-8742\) with or without ribavirin in patients with HCV GT1 mono-infection and HIV/HCV coinfection \(C-WORTHY\): a randomised, open-label phase 2 trial](#). Vierling JM, Mallolas J, Pol S, Kugelmas M, Murillo A, Weis N, et al. Lancet. 2015;285(9973):1087-1097.

Tang L, Parker A, Flores Y, et al. [Treatment of hepatitis C with 8 weeks of ledipasvir/sofosbuvir: highly effective in a predominantly black male patient population](#). J Viral Hepat. 2018;25(2):205-208.

Terrault NA, Zeuzem S, Di Bisceglie AM, Lim JK, Pockros PJ, Frazier LM, et al. [HCV-TARGET study group. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response](#). Gastroenterology. 2016;151(6):1131-1140.e5.

Thompson A, Zeuzem S, Rockstroh JK, Kwo PY, Roth D, Lawitz EJ, et al. [The combination of grazoprevir and elbasvir +RBV is highly effective for the treatment of GT1a-infected patients](#). The Liver Meeting 2015. San Francisco, CA; 2015.

vonFelden J, Vermehren J, Ingiliz P, et al. [High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection](#). Aliment Pharmacol Ther. 2018;47(9):1288-1295.

Wei L, Lim SG, Xie Q, et al. [Sofosbuvir-velpatasvir for treatment of chronic hepatitis C virus infection in Asia: a single-arm, open-label, phase 3 trial](#). Lancet Gastroenterol Hepatol. 2019;4(2):127-134.

Wilder JM, Jeffers LJ, Ravendhran N, et al. [Safety and efficacy of ledipasvir-sofosbuvir in black patients with hepatitis C virus infection: a retrospective analysis of phase 3 data](#). Hepatology. 2016;63(2):437-444.

Wong KA, Worth A, Martin R, Svarovskaia ES, Brainard DM, Lawitz EJ, et al. [Characterization of Hepatitis C virus resistance from a multiple-dose clinical trial of the novel NS5A inhibitor GS-5885](#). Antimicrob Agents Chemother. 2013;57(12):6333-6340.

Wu DB, Jiang W, Wang YH, et al. [Safety and efficacy of sofosbuvir-based direct-acting antiviral regimens for hepatitis C virus genotype 6 in Southwest China: Real-world experience of a retrospective study](#). J Viral Hepat. 2019;26(3):316-322.

Yao BB, Fredrick LM, Schnell G, et al. [Efficacy and safety of glecaprevir/pibrentasvir in patients with HCV genotype 5/6: an integrated analysis of phase 2/3 studies](#). Liver Int. 2020;.

Zeuzem S, Ghalib R, K. Reddy R, Pockros PJ, Ben Ari, iv Z, Zhao Y, et al. [Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial](#). Ann Intern Med. 2015;163(1):1-13.

Zeuzem S, Rockstroh JK, Kwo PY, et al. [Predictors of response to grazoprevir/elbasvir among HCV genotype 1 \(GT1\)-infected patients: integrated analysis of phase 2-3 trials \[abstract 700\]](#). In Liver Meeting 2015. San Francisco, CA; 2015.

Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ari ZB, Zhao Y, et al. [Grazoprevir-Elbasvir Combination Therapy for](#)

[Treatment-Naive Cirrhotic and Noncirrhotic Patients With Chronic Hepatitis C Virus Genotype 1, 4, or 6 Infection: A Randomized Trial](#). *Ann Intern Med*. 2015;163(1):1-13.

Zeuzem S, Mizokami M, Pianko S, Mangia A, Han KH, Martin R, et al. [NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: prevalence and effect on treatment outcome](#). *J Hepatol*. 2017;66(5):910-918.

Zeuzem S, Foster GR, Wang S, et al. [Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 Infection](#). *N Engl J Med* [Internet]. 2018;378(4):354-369. <https://doi.org/10.1056/nejmoa1702417>
