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Hepatitis C Guidance 2018 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection

AASLD-IDSA HCV Guidance Panel^a

(See the Commentary by Jhaveri et al on pages 1493–7.)

Recognizing the importance of timely guidance regarding the rapidly evolving field of hepatitis C management, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) developed a web-based process for the expeditious formulation and dissemination of evidence-based recommendations. Launched in 2014, the hepatitis C virus (HCV) guidance website undergoes periodic updates as necessitated by availability of new therapeutic agents and/or research data. A major update was released electronically in September 2017, prompted primarily by approval of new direct-acting antiviral agents and expansion of the guidance's scope. This update summarizes the latest release of the HCV guidance and focuses on new or amended recommendations since the previous September 2015 print publication. The recommendations herein were developed by volunteer hepatology and infectious disease experts representing AASLD and IDSA and have been peer reviewed and approved by each society's governing board.

Keywords. hepatitis C; direct-acting antiviral treatment; HCV guidance; chronic HCV treatment.

The landscape of hepatitis C virus (HCV) treatment has evolved substantially since the US Food and Drug Administration approved the first direct-acting antiviral agents (DAAs) in 2011. The 11 single-drug or coformulated DAA pharmaceuticals currently available collectively provide most persons with chronic HCV infection the opportunity for cure. DAA therapy is generally simpler, better tolerated, of shorter duration, and more effective than interferon-based treatment. The rapid expansion of available regimens and their respective indications and caveats, however, occasion complex therapeutic decisions. Given the myriad hepatic [1–5] and extrahepatic [4, 6–19] benefits associated with viral clearance, treatment is strongly recommended for all persons with chronic HCV infection (except those with a short life expectancy who cannot be remediated). Restricting access to DAAs based on criteria such as fibrosis stage or recent drug use based on rationing cost to payors is neither evidence based nor patient centered.

The HCV guidance provides peer-reviewed, unbiased, evidence-based recommendations to aid clinicians with decisions throughout the course of HCV management. This summary focuses on updated recommendations related to antiviral therapy as of 1 May 2018. Since the last published

document [20], certain previously recommended regimens have been downgraded to alternative status due to considerations such as pill burden, use of ribavirin, and/or longer duration. New recommendations regarding universal testing of pregnant women and testing and care of key populations at elevated risk are also highlighted. Recommendations that address testing, when and in whom to initiate HCV therapy, and monitoring have been largely unchanged since the previous publication and are provided in the [Supplementary Materials](#). Readers are encouraged to consult the online guidance (www.HCVGuidelines.org) for updated recommendations subsequent to this report, related evidence reviews, and information that addresses other aspects of HCV testing and management.

PROCESS

The guidance was developed and is updated by a panel of hepatology and infectious diseases HCV experts using an evidence-based review of available information. Based on scientific evidence and expert opinion, recommendations are rated by the level of evidence (I, II, or III) and strength of the recommendation (A, B, or C) using a system adapted from the American College of Cardiology and the American Heart Association (see [Supplementary Materials](#)) [21, 22]. Use of this well-established approach accommodates expert assessment of the quality of the evidence and efficiently provides consistent measures of the strength of the recommendations, given the rapid pace of approvals. See the guidance website for additional details about the processes and methods used.

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The panel classifies therapeutic regimens as recommended, alternative, or not recommended based on patient factors (treatment naive vs experienced, cirrhosis status, comorbidities) and viral characteristics (genotype [GT], subtype, resistance-associated substitutions [RASs]). Recommended regimens are considered equivalent. Alternative regimens are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data. This condensed update primarily discusses recommended regimens; see the guidance website for information about alternative regimens, which may be optimal in certain situations.

INITIAL TREATMENT

Genotype 1

Four regimens are recommended for treatment-naive GT1 patients (see Table 1). Because patients with GT1a tend to experience higher relapse rates than those with GT1b with certain regimens, GT1 infection that cannot be subtyped should be treated as GT1a.

With GT1a, baseline RASs that cause a significant reduction in nonstructural protein 5A (NS5A) inhibitor activity adversely impact response to some NS5A inhibitor-containing regimens [23, 24]. Nonetheless, pretreatment RAS testing is recommended in the setting of GT1a infection prior to selecting a therapeutic regimen only when using elbasvir/grazoprevir [25].

Twelve weeks of elbasvir/grazoprevir is recommended for treatment-naive patients (with or without compensated cirrhosis) with GT1b infection or GT1a without NS5A RAS(s) for elbasvir. (I, A)

C-EDGE assessed the efficacy of this regimen in treatment-naive adults (GT1, GT4, and GT6); 91% had GT1 [23]. Sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) and 99% (129/131) in patients with GT1a and GT1b, respectively. In C-WORTHY, SVR12 rates with this regimen were 92% (48/52) and 95% (21/22) among GT1a and GT1b treatment-naive noncirrhotic patients, respectively [26, 27]. Compensated cirrhosis did not alter efficacy in either trial.

With GT1a, certain baseline NS5A RASs significantly reduce SVR12 with a 12-week elbasvir/grazoprevir regimen [23]. Treatment extension to 16 weeks plus ribavirin for GT1a with baseline NS5A RASs is categorized as an alternative regimen based on extrapolation of C-EDGE treatment-experienced data. No virologic failures occurred among 58 GT1a, treatment-experienced patients treated with elbasvir/grazoprevir plus ribavirin for 16 weeks [24, 28, 29]. When encountering these NS5A RASs, choosing another option rather than 16 weeks of elbasvir/grazoprevir plus ribavirin is recommended.

Eight weeks of glecaprevir/pibrentasvir is recommended for treatment-naive GT1 patients without cirrhosis; 12 weeks is recommended for those with compensated cirrhosis. (I, A)

In SURVEYOR-I, 97% (33/34) of GT1 noncirrhotic patients treated with an 8-week regimen achieved SVR [30]. ENDURANCE-1 randomized 703 noncirrhotic, GT1 patients (treatment naive or experienced with interferon/peginterferon ± ribavirin or sofosbuvir plus ribavirin ± peginterferon) to 8 or 12 weeks of glecaprevir/pibrentasvir [31]. SVR12 rates were 99% (348/351) and 99.7% (351/352) in the 8- and 12-week arms, respectively. EXPEDITION-1 investigated a 12-week regimen among treatment-naive or -experienced (interferon/peginterferon ± ribavirin or sofosbuvir plus ribavirin ± peginterferon) patients with GT1, GT2, GT4, GT5, or GT6 and compensated cirrhosis; SVR12 was 99% (145/146) [32]. EXPEDITION-2 examined glecaprevir/pibrentasvir (8 weeks noncirrhotic; 12 weeks cirrhotic) among 153 human immunodeficiency virus (HIV)/HCV-coinfected adults with GT1-6 [33]. Overall SVR12 was 98%; no virologic failures occurred in the 94 GT1 patients. Neither subtype nor baseline RASs impacted SVR12 results in DAA-naive GT1 patients in these trials.

Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive GT1 patients, with or without compensated cirrhosis. (I, A) Eight weeks is recommended for non-black, HIV-negative noncirrhotic patients whose HCV RNA level is <6 million IU/mL. (I, B)

ION-1 investigated ledipasvir/sofosbuvir treatment duration (12 vs 24 weeks) and the need for ribavirin among 865 GT1 patients with (16%) or without compensated cirrhosis [34]. SVR12 was 97% to 99% across all study arms, with no difference based on treatment duration, ribavirin use, or subtype. SVR12 rates were comparable in cirrhotic (97%) and noncirrhotic (98%) patients. ION-3 investigated an 8-week regimen (± ribavirin) in 647 GT1 noncirrhotic patients [35]. SVR12 was 93% to 95% across all study arms. Relapse rate was higher in the 8-week vs 12-week arm (20/431, 4.6% vs 3/216, 1.4%) regardless of ribavirin use. Post hoc analysis of the ribavirin-free, 8-week arm identified lower relapse rates in patients with baseline HCV RNA <6 million IU/mL [36].

Real-world cohort data generally show comparable effectiveness of 8- and 12-week courses of ledipasvir/sofosbuvir in noncirrhotic, treatment-naive patients [37–41]. However, methodologic issues might limit generalizability of these data.

Twelve weeks of sofosbuvir/velpatasvir is recommended for treatment-naive GT1 patients, with or without compensated cirrhosis. (I, A)

ASTRAL-1 evaluated this regimen among 624 treatment-naive or interferon-experienced (± ribavirin or a protease inhibitor [n = 201]) participants with GT1, GT2, GT4, GT5, or GT6 infection [42]. SVR12 was 98.5% (323/328) in those with GT1 with no subtype difference. SVR12 was 99% (120/121) among all cirrhotic participants. Baseline NS5A RASs did not influence SVR for GT1 [43]. POLARIS-2 randomized 941 DAA-naive patients

Table 1. Summary of Recommended Regimens for Initial and Retreatment of Hepatitis C Virus Genotype 1–6 Infection

Regimen	Patient Population	Duration (Weeks)	Caveats and Other Considerations
Genotype 1			
Daclatasvir + sofosbuvir	Decompensated cirrhosis regardless of subtype	12	Add dose-escalating RBV ^a
	HIV/HCV coinfection when antiretroviral regimen cannot be made to accommodate recommended regimens	12	
Elbasvir/grazoprevir	Treatment naïve or PEG/RBV experienced regardless of cirrhosis	12	For GT1a, check RASs to NS5A; use a different recommended regimen if high-fold variants detected
	Severe renal impairment (CKD stage 4/5) <i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>	12	
Glecaprevir/pibrentasvir	Treatment naïve or PEG/RBV experienced without cirrhosis	8	
	Treatment naïve or PEG/RBV experienced with cirrhosis, and non-NS5A failures (including NS3) regardless of cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Ledipasvir/sofosbuvir	Treatment naïve regardless of cirrhosis	12	
	Treatment naïve, no cirrhosis, non-black, HIV negative, and HCV RNA <10 ⁶ IU/mL	8	
	PEG/RBV (± NS3 protease inhibitor) experienced without cirrhosis	12	
	Decompensated cirrhosis, treatment naïve or PEG/RBV (± NS3 protease inhibitor) experienced	12	Add dose-escalating RBV ^a
	Decompensated cirrhosis, prior sofosbuvir failure only	24	Add RBV
	Post liver transplant regardless of cirrhosis or decompensation	12	Add dose-escalating RBV ^a
	Post kidney transplant regardless of cirrhosis	12	
Sofosbuvir/velpatasvir	Treatment naïve or PEG/RBV ± NS3 protease inhibitor experienced regardless of cirrhosis	12	Same for GT1a and GT1b
	GT1b, non-NS5A DAA experienced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naïve or PEG/RBV (± NS3 protease inhibitor) experienced	12	Add dose-escalating RBV ^a
	Decompensated cirrhosis, DAA failure (including NS5A) ^b	24	Add RBV
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitor) regardless of cirrhosis	12	Same for GT1a and GT1b
	GT1a, non-NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Genotype 2			
Daclatasvir + sofosbuvir	Decompensated cirrhosis ^b	12	Add dose-escalating RBV ^a
	Post liver transplant regardless of cirrhosis or decompensation ^b	12	Add dose-escalating RBV ^a
Glecaprevir/pibrentasvir	Treatment naïve or PEG/RBV experienced without cirrhosis	8	
	Treatment naïve or PEG/RBV experienced with cirrhosis, and sofosbuvir failures regardless of cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis <i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>	12	

Table 1. Continued

Regimen	Patient Population	Duration (Weeks)	Caveats and Other Considerations
Sofosbuvir/velpatasvir	Treatment naïve, or PEG/RBV or non-NS5A experienced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naïve or PEG/RBV or non-NS5A experienced	12	Add weight-based RBV
	Decompensated cirrhosis, DAA failure (including sofosbuvir ± NS5A) ^b	24	Add dose-escalating RBV ^a
	Post liver transplant with decompensated cirrhosis	12	Add weight-based RBV
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Genotype 3			
Daclatasvir + sofosbuvir	Decompensated cirrhosis	12	Add dose-escalating RBV ^a
	Post liver transplant regardless of cirrhosis or decompensation	12	Add dose-escalating RBV
Glecaprevir/pibrentasvir	Treatment naïve without cirrhosis	8	
	Treatment naïve with compensated cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis	12	
<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>			
Sofosbuvir + elbasvir/grazoprevir	PEG/RBV experienced with compensated cirrhosis ^b	12	
<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>			
Sofosbuvir/velpatasvir	Treatment naïve without cirrhosis	12	
	Treatment naïve with cirrhosis or PEG/RBV experienced without cirrhosis	12	Check for Y93H RAS; if present, use a different recommended regimen when available or 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (an alternative regimen) ^b
	Decompensated cirrhosis, treatment naïve or PEG/RBV experienced	12	Add weight-based RBV ^a
	Decompensated cirrhosis, previously exposed to DAA (including sofosbuvir ± NS5A) ^b	24	Add weight-based RBV
	Post liver transplant with decompensated cirrhosis	12	Add weight-based RBV
Sofosbuvir/velpatasvir/voxilaprevir	PEG/RBV experienced with cirrhosis, or DAA failure (including NS5A inhibitors) regardless of cirrhosis	12	Add RBV for prior NS5A inhibitor failure and cirrhosis ^b
<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>			
Genotype 4			
Daclatasvir + sofosbuvir	Decompensated cirrhosis ^b	12	Add dose-escalating RBV ^a
	HIV/HCV coinfection when antiretroviral regimen cannot be made to accommodate recommended regimens	12	
Elbasvir/grazoprevir	Treatment naïve or PEG/RBV experienced with prior relapse, regardless of cirrhosis	12	Not recommended for other treatment failures
	Severe renal impairment (CKD stage 4/5)	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Glecaprevir/pibrentasvir	Treatment naïve or PEG/RBV experienced without cirrhosis	8	
	Treatment naïve or PEG/RBV experienced with cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis	12	
<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>			

Table 1. Continued

Regimen	Patient Population	Duration (Weeks)	Caveats and Other Considerations
Ledipasvir/sofosbuvir	Treatment naive regardless of cirrhosis or PEG/RBV experienced without cirrhosis	12	
	Decompensated cirrhosis, treatment naive or PEG/RBV experienced	12	Add dose-escalating RBV ^a
	Decompensated cirrhosis, sofosbuvir failure ^b	24	Add weight-based RBV
	Post liver transplant regardless of cirrhosis or decompensation	12	Add dose-escalating RBV ^a
	Post kidney transplant regardless of cirrhosis	12	
Sofosbuvir/velpatasvir	Treatment naive or PEG/RBV experienced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naive or PEG/RBV (± NS3 protease inhibitor) experienced	12	Add weight-based RBV ^a
	Decompensated cirrhosis, DAA failure (including NS5A) ^b	24	Add weight-based RBV
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Genotype 5 or 6			
Glecaprevir/pibrentasvir	Treatment naive or PEG/RBV experienced without cirrhosis	8	
	Treatment naive or PEG/RBV experienced with cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		
Ledipasvir/sofosbuvir	Treatment naive or PEG/RBV experienced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naive or PEG/RBV experienced	12	Add dose-escalating RBV ^a
	Decompensated cirrhosis, sofosbuvir failure ^b	24	Add dose-escalating RBV ^a
	Post liver transplant regardless of cirrhosis or decompensation	12	Add weight-based RBV ^a ; use dose-escalating RBV if decompensated
	Post kidney transplant regardless of cirrhosis	12	
Sofosbuvir/velpatasvir	Treatment naive or PEG/RBV experienced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naive or PEG/RBV (± NS3 protease inhibitor) experienced	12	Add weight-based RBV ^a
	Decompensated cirrhosis, DAA failure (including NS5A) ^b	24	Add weight-based RBV
Sofosbuvir/velpatasvir/voxilaprevir	NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12	
	<i>Not for decompensated cirrhosis or post liver transplant with cirrhosis</i>		

Cirrhosis refers to compensated cirrhosis unless otherwise specified.

Abbreviations: CKD, chronic kidney disease; DAA, direct-acting antiviral agent; GT, genotype; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NS5A, nonstructural protein 5A; PEG, peginterferon; RAS, resistance-associated substitution; RBV, ribavirin.

^aExtend treatment duration to 24 weeks if RBV ineligible.

^bRepresents off-label use.

(all genotypes; with or without compensated cirrhosis) to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir [44]. Ninety-nine percent (170/172) and 97% (57/59) of patients with GT1a and GT1b achieved SVR, respectively.

Genotype 2

Two regimens are recommended for treatment-naive GT2 patients (see Table 1).

Eight weeks of glecaprevir/pibrentasvir is recommended for treatment-naive GT2 patients without cirrhosis; 12 weeks is recommended for those with compensated cirrhosis. (I, A)

ENDURANCE-2 evaluated 12 weeks of glecaprevir/pibrentasvir among 302 noncirrhotic, GT2 treatment-naive or -experienced (interferon/peginterferon ± ribavirin or sofosbuvir plus ribavirin ± peginterferon) participants [45]. SVR12 was 99%; no virologic

failures occurred. In SURVEYOR-II part 4, 99% (135/137) of treatment-naïve persons with GT2 infection achieved SVR12 following 8 weeks of glecaprevir/pibrentasvir [45]. In EXPEDITION-1, which was a study of treatment-naïve or -experienced patients with compensated cirrhosis, SVR12 with 12 weeks of glecaprevir/pibrentasvir was 100% among the 31 GT2 patients [32].

Twelve weeks of sofosbuvir/velpatasvir is recommended for treatment-naïve GT2 patients, with or without compensated cirrhosis. (I, A)

ASTRAL-2 evaluated 12 weeks of sofosbuvir/velpatasvir vs sofosbuvir plus ribavirin among 266 treatment-naïve or interferon-experienced GT2 patients (with or without compensated cirrhosis) and demonstrated superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%) [46]. ASTRAL-1 included 104 GT2 treatment-naïve or -experienced participants (with or without compensated cirrhosis); all achieved SVR12 [42]. Pooled analysis of GT2 patients in ASTRAL-1 and ASTRAL-2 demonstrated SVR12 rates of 100% (29/29) in those with compensated cirrhosis and 99% (194/195) in treatment-naïve participants [47]. POLARIS-2 randomized DAA-naïve patients (with or without cirrhosis) to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir [44]. All 53 GT2 patients in the sofosbuvir/velpatasvir arm achieved SVR12.

Genotype 3

Two regimens are recommended for treatment-naïve GT3 patients (see Table 1).

Eight weeks of glecaprevir/pibrentasvir is recommended for treatment-naïve GT3 patients without cirrhosis; 12 weeks is recommended for those with compensated cirrhosis. (I, A)

ENDURANCE-3 randomized 348 treatment-naïve, noncirrhotic GT3 participants to 12 weeks of glecaprevir/pibrentasvir or sofosbuvir and daclatasvir [48]. An open-label arm evaluated 8 weeks of glecaprevir/pibrentasvir in 157 additional participants. SVR12 was 95% in those who received 8 or 12 weeks of glecaprevir/pibrentasvir; both regimens met noninferiority criteria compared to sofosbuvir/daclatasvir. Among treatment-naïve GT3 patients with compensated cirrhosis in SURVEYOR-II parts 3 and 2, SVR12 rates were 98% (39/40) and 100% (48/48) with 12 weeks of glecaprevir/pibrentasvir alone and ± ribavirin, respectively [49, 50].

In a pooled analysis, a baseline A30K substitution was associated with reduced SVR12 with 8 weeks of glecaprevir/pibrentasvir, whereas a Y93H substitution was not [51]. Seventy-eight percent (14/18) of treatment-naïve, noncirrhotic GT3 patients with baseline A30K achieved SVR12. Baseline RASs did not influence SVR among patients with compensated cirrhosis, although the analysis was limited due to the low prevalence of NS5A RASs. Pending further real-world data, RAS testing or

extension of therapy in the setting of A30K is not currently recommended due to insufficient evidence.

Twelve weeks of sofosbuvir/velpatasvir is recommended for treatment-naïve GT3 patients, with or without compensated cirrhosis. (I, A)

ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir vs 24 weeks of sofosbuvir plus ribavirin in 552 treatment-naïve or -experienced GT3 patients [46]. Among treatment-naïve participants receiving sofosbuvir/velpatasvir, SVR12 rates were 98% (160/163) and 93% (40/43) in those without and with compensated cirrhosis, respectively. In the sofosbuvir/velpatasvir arm, 16% (43/250) had baseline NS5A RASs; 88% achieved SVR12 compared to 97% without baseline RASs. SVR12 was realized in 84% (21/25) of those with the Y93H substitution. Pending further data on therapy in the setting of a baseline Y93H substitution and cirrhosis, addition of RBV or use of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is recommended. In POLARIS-3, a study of DAA-naïve, cirrhotic GT3 patients, all 6 participants in the sofosbuvir/velpatasvir/voxilaprevir arm who had the Y93H substitution achieved SVR12 [44].

Genotype 4

Four regimens are recommended for treatment-naïve GT4 patients (see Table 1).

Eight weeks of glecaprevir/pibrentasvir is recommended for treatment-naïve GT4 patients without cirrhosis (I, A); 12 weeks is recommended for those with compensated cirrhosis. (I, B)

ENDURANCE-4 enrolled 121 noncirrhotic, DAA-naïve (68%) or -experienced (sofosbuvir plus ribavirin ± peginterferon) patients with GT4, GT5, or GT6 to receive 12 weeks of glecaprevir/pibrentasvir [45]. SVR12 was 99% (75/76) for GT4 patients. SURVEYOR-II part 4 investigated an 8-week course in noncirrhotic, DAA-naïve patients; SVR12 was 93% (43/46) among GT4 participants [45]. EXPEDITION-1 included 16 treatment-naïve or -experienced GT4 participants with compensated cirrhosis; all achieved SVR12 [32].

Twelve weeks of sofosbuvir/velpatasvir is recommended for treatment-naïve GT4 patients, with or without compensated cirrhosis. (I, A)

ASTRAL-1 included 64 GT4 treatment-naïve patients (with or without compensated cirrhosis) who were treated with this regimen; all achieved SVR12 [42]. Of the 57 GT4 patients treated with sofosbuvir/velpatasvir in POLARIS-2, 98% achieved SVR [44]. Overall, 19% of participants had compensated cirrhosis.

Twelve weeks of elbasvir/grazoprevir is recommended for treatment-naïve GT4 patients, with or without compensated cirrhosis. (IIa, B)

A pooled analysis evaluated 66 treatment-naive GT4 patients treated with this regimen; 10 participants received weight-based ribavirin and 9.1% were cirrhotic; SVR12 was 97% (64/66) [52]. Addition of ribavirin numerically increased SVR12 in treatment-experienced participants but could not be definitively assessed.

Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive GT4 patients, with or without compensated cirrhosis. (IIa, B)

SYNERGY evaluated this regimen in 21 GT4 patients; 60% were treatment naive and 43% had advanced fibrosis [53]. All 20 patients who completed treatment achieved SVR12. A second single-arm study including 22 GT4 treatment-naive patients (1 cirrhotic) reported 95% SVR12 [54].

Genotype 5 or 6

Three regimens are recommended for treatment-naive patients with GT5 or GT6 infection (see Table 1).

Eight weeks of glecaprevir/pibrentasvir is recommended for treatment-naive GT5 or GT6 patients without cirrhosis; 12 weeks is recommended for those with compensated cirrhosis. (I, A)

In SURVEYOR-II, SVR12 was 100% with a 12-week glecaprevir/pibrentasvir regimen in 34 noncirrhotic patients with GT4, GT5, or GT6 [30]. In SURVEYOR-II part 4, 2/2 noncirrhotic patients with GT5 and 9/10 with GT6 achieved SVR12 with an 8-week regimen [45]. Among the DAA-naive or -experienced noncirrhotic patients with GT5 (n = 26) or GT6 (n = 19) enrolled in ENDURANCE-4, SVR12 rates were 100% with a 12-week regimen [45]. In EXPEDITION-1, 2/2 participants with compensated cirrhosis and GT5 and 7/7 with GT6 achieved SVR12 with a 12-week regimen [32].

Twelve weeks of sofosbuvir/velpatasvir is recommended for treatment-naive GT5 or GT6 patients, with or without compensated cirrhosis. (I, B)

ASTRAL-1 included 24 GT5 and 38 GT6 treatment-naive participants (with or without cirrhosis) who were treated with this regimen. SVR12 rates were 96% and 100%, respectively [42]. An additional 9 GT6 patients received sofosbuvir/velpatasvir in POLARIS-2; all achieved SVR [44].

Twelve weeks of ledipasvir/sofosbuvir is recommended for treatment-naive GT5 or GT6 patients, with or without compensated cirrhosis. (IIa, B)

Although data are limited for GT5 patients, in vitro activity of sofosbuvir and ledipasvir are favorable. A single-arm study involving 41 GT5 patients reported 95% overall SVR12, including 100% (3/3) of those with cirrhosis [54].

Ledipasvir has in vitro activity against most GT6 subtypes, except GT6e [55, 56]. A small study that investigated 12 weeks

of ledipasvir/sofosbuvir in treatment-naive or -experienced patients included 25 with GT6 (23 treatment naive; 2 with cirrhosis) with an SVR12 of 96% (24/25) [57].

Mixed Genotypes

DAA treatment data for mixed genotype infections are sparse, but utilization of a pangenotypic regimen (eg, glecaprevir/pibrentasvir or sofosbuvir/velpatasvir) should be considered. When the optimal regimen or duration is unclear, expert consultation should be sought.

RETREATMENT

Regimen choice for retreatment of persons in whom prior therapy failed depends on which agent(s) the individual has been exposed to and clinical and viral factors. Treatment recommendations for peginterferon/ribavirin-experienced patients of all genotypes largely mirror those for treatment-naive persons (see Table 1) with a few exceptions, which are addressed in the online guidance.

Genotype 1

Prior Treatment With an NS3 Protease Inhibitor Plus Peginterferon/Ribavirin

Twelve weeks of sofosbuvir/velpatasvir is recommended for GT1 NS3 protease inhibitor plus peginterferon/ribavirin-experienced patients, with or without compensated cirrhosis. (I, A)

ASTRAL-1 trial evaluated this regimen in treatment-naive or -experienced patients (with or without compensated cirrhosis) with GT1, GT2, GT4, GT5, or GT6 [42]. SVR12 was 100% (48/48) among participants with a prior protease inhibitor plus peginterferon/ribavirin failure. Similarly high SVR rates were seen in a phase 2 trial wherein 100% (27/27) of patients with a comparable treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir [58].

Twelve weeks of glecaprevir/pibrentasvir is recommended for GT1 NS3 protease inhibitor plus peginterferon/ribavirin-experienced patients, with or without compensated cirrhosis. (IIa, B)

Parts 1 and 2 of MAGELLAN-1 included 42 GT1 patients previously treated with a DAA; 24% had cirrhosis. Among those previously treated with protease inhibitor-based therapy who were retreated with glecaprevir/pibrentasvir for 12 weeks, 92% (23/25) achieved SVR12 [59, 60]. Neither patient who failed to achieve SVR experienced virologic failure.

Prior Treatment With a DAA Regimen Containing Sofosbuvir but Not an NS5A Inhibitor

Practically speaking, this population includes patients who received sofosbuvir plus ribavirin, sofosbuvir plus peginterferon/ribavirin, or sofosbuvir plus simeprevir.

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT1a patients previously treated with a sofosbuvir-based regimen not containing an NS5A inhibitor, with or without compensated cirrhosis. (I, A)

POLARIS-4 compared this regimen to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients [61]. Sixty-nine percent of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon; 11% were exposed to sofosbuvir plus simeprevir. Forty-six percent of participants in each study arm had cirrhosis. SVR12 rates for GT1a patients were 98% (53/54) and 89% (39/44) for sofosbuvir/velpatasvir/voxilaprevir and sofosbuvir/velpatasvir, respectively. One relapse occurred in the sofosbuvir/velpatasvir/voxilaprevir arm, but it was not due to treatment-emergent RASs.

Twelve weeks of glecaprevir/pibrentasvir is recommended for GT1 patients previously treated with a sofosbuvir-based regimen not containing an NS5A inhibitor, with or without compensated cirrhosis. (IIa, B)

There are limited data to guide recommendations for glecaprevir/pibrentasvir in GT1 patients who failed a prior sofosbuvir regimen not containing an NS5A inhibitor. ENDURANCE-1 had only 1 patient in the 8-week arm and 2 in the 12-week arm with a prior sofosbuvir-containing regimen failure [31]. In EXPEDITION-1, only 11 participants had a previous sofosbuvir-containing regimen failure, and none had a prior simeprevir plus sofosbuvir failure [32]. Twelve weeks of glecaprevir/pibrentasvir, however, was evaluated in prior NS3/4A treatment failures in MAGELLAN-1, which included patients with a prior simeprevir plus sofosbuvir failure [59, 60]. Pending further clinical trial or real-world data, 12 weeks of treatment is recommended for these patients.

Twelve weeks of sofosbuvir/velpatasvir is recommended for GT1b patients previously treated with a sofosbuvir-based regimen not containing an NS5A inhibitor, with or without compensated cirrhosis. (IIa, B)

POLARIS-4 included a 12-week arm of sofosbuvir/velpatasvir in non-NS5A inhibitor-DAA experienced patients [61]. While only sofosbuvir/velpatasvir did not meet the prespecified efficacy threshold, this was primarily driven by failures in patients with GT1a or GT3. Although this study was not powered to assess efficacy differences by genotype/subtype, SVR12 rates in GT1b patients were 95% (21/22) and 96% (23/24) for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively.

Prior Treatment With a Regimen Containing an NS5A Inhibitor

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT1 NS5A inhibitor-experienced patients, with or without compensated cirrhosis. (I, A)

POLARIS-1 evaluated this regimen in patients with a prior NS5A inhibitor-containing DAA failure [61]. Sixty-one percent of the

cohort experienced treatment failure with a combination NS5B inhibitor/NS5A inhibitor regimen (eg, sofosbuvir/ledipasvir), while 32% were previously treated with an NS5A inhibitor plus an NS3 inhibitor, with or without an NS5B inhibitor. SVR12 in GT1 patients was 97% (146/150). Baseline RASs and/or cirrhosis were not significant predictors of virologic failure. Therefore, baseline RAS testing is not recommended prior to using this regimen.

Genotype 2

Prior Treatment With Sofosbuvir Plus Ribavirin

Twelve weeks of sofosbuvir/velpatasvir is recommended for GT2 sofosbuvir plus ribavirin-experienced patients, with or without compensated cirrhosis. (I, B)

POLARIS-4 included a 12-week arm of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients [61]. Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon and 46% had cirrhosis. SVR12 for GT2 was 97% (32/33) in the sofosbuvir/velpatasvir arm.

Twelve weeks of glecaprevir/pibrentasvir is recommended for GT2 sofosbuvir plus ribavirin-experienced patients, with or without compensated cirrhosis. (IIb, B)

ENDURANCE-2 enrolled treatment-naïve or -experienced GT2 patients without cirrhosis to evaluate 12 weeks of glecaprevir/pibrentasvir [45]. Among 202 participants in the active-treatment arm, 30% (61/202) were treatment experienced; 6 were sofosbuvir plus ribavirin-experienced, all of whom achieved SVR12. EXPEDITION-1 evaluated this regimen in treatment-naïve or -experienced patients (interferon/peginterferon ± ribavirin or sofosbuvir plus ribavirin ± peginterferon) with compensated cirrhosis [32]. Overall, 25% (n = 36) of patients were treatment experienced; 11 had a history of sofosbuvir failure (unclear how many had GT2). SVR12 in GT2 patients was 100% (31/31).

Prior Treatment With Sofosbuvir Plus an NS5A Inhibitor (Velpatasvir or Daclatasvir)

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT2 sofosbuvir plus an NS5A inhibitor-experienced patients, with or without compensated cirrhosis. (I, B)

POLARIS-1 evaluated 12 weeks of sofosbuvir/velpatasvir/voxilaprevir compared to placebo among patients with all genotypes who were previously treated with an NS5A inhibitor-containing regimen. There were 5 GT2 patients, and all achieved SVR12 [61].

Genotype 3

Prior Treatment With a DAA Regimen (Including NS5A Inhibitors)

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT3 DAA-experienced patients, with or without

compensated cirrhosis. (I, A) Addition of weight-based ribavirin is recommended for those with cirrhosis. (IIa, C)

POLARIS-1 and POLARIS-4 included GT3 patients (with or without compensated cirrhosis) who had previously received a DAA regimen (\pm NS5A inhibitor) [61]. POLARIS-4 excluded NS5A inhibitor failures; SVR was 96% (52/54) for GT3 patients treated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. In POLARIS-1, which included patients with a prior NS5A inhibitor failure, SVR12 was 95% (74/78) for GT3 patients randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir; the 4 patients who experienced a relapse had cirrhosis. Until further real-world data are available, addition of weight-based ribavirin

is recommended to reduce relapse risk in NS5A inhibitor-experienced GT3 patients with cirrhosis.

Genotype 4

Prior Treatment With a DAA Regimen (Including NS5A Inhibitors)

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT4 DAA-experienced patients, with or without compensated cirrhosis. (I, A)

POLARIS-1 and POLARIS-4 evaluated sofosbuvir/velpatasvir/voxilaprevir; participants included 22 GT4 patients with a prior NS5A inhibitor-containing DAA regimen failure and 19 with a

Table 2. Drug Interactions Between Direct-acting Antivirals and Antiretroviral Drugs—Preferred Regimens

	Ledipasvir/Sofosbuvir (LDV/SOF)	Sofosbuvir/Velpatasvir (SOF/VEL)	Elbasvir/Grazoprevir (ELB/GRZ)	Glecaprevir/Pibrentasvir (GLE/PIB)	Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX)
Ritonavir-boosted atazanavir (ATZ)	▲ LDV ▲ ATZ ^a	▲ VEL ▲ ATZ ^a	▲ ELB ▲ GRZ ▲ ATZ	▲ GLE ▲ PIB ▲ ATZ	▲ VOX ▲ ATZ
Ritonavir-boosted darunavir (DRV)	▲ LDV ◄► DRV ^a	◄► VEL ◄► DRV ^a	▲ ELB ▲ GRZ ◄► DRV	▲ GLE ◄► PIB ▲ DRV	▲ VOX ▼ DRV
Ritonavir-boosted lopinavir (LPV)	ND ^a	◄► VEL ◄► LPV ^a	▲ ELB ▲ GRZ ◄► LPV	▲ GLE ▲ PIB ▲ LPV	ND
Ritonavir-boosted tipranavir (TPV/r)	ND	ND	ND	ND	ND
Efavirenz (EFV)	▼ LDV ▼ EFV ^a	▼ VEL ▼ EFV	▼ ELB ▼ GRZ ▼ EFV	ND	ND
Rilpivirine (RPV)	◄► LDV ◄► RPV	◄► VEL ◄► RPV	◄► ELB ◄► GRZ ◄► RPV	◄► GLE ◄► PIB ▲ RPV	◄► VOX ▼ RPV
Etravirine (ETV)	ND	ND	ND	ND	ND
Raltegravir (RAL)	◄► LDV ◄► RAL	◄► VEL ◄► RAL	◄► ELB ◄► GRZ ▲ RAL	◄► GLE ◄► PIB ▲ RAL	ND
Cobicistat-boosted elvitegravir (COB)	▲ LDV ▲ COB ^a	▲ VEL ▲ COB ^a	▲ ELB ▲ GRZ ▲ COB	▲ GLE ▲ PIB ▲ COB	▲ VOX ▲ COB ^a
Dolutegravir (DTG)	◄► LDV ◄► DTG	◄► VEL ◄► DTG	◄► ELB ◄► GRZ ▲ DTG	▼ GLE ▼ PIB ▲ DTG	ND
Tenofovir alafenamide (TAF)/emtricitabine (FTC)/bictegravir (BIC)	▼ LDV ◄► BIC	ND	ND	ND	◄► VOX ▲ BIC
Maraviroc (MVC)	ND	ND	ND	ND	ND
Tenofovir (TFV) disoproxil fumarate	◄► LDV ▲ TFV ^c	◄► VEL ▲ TFV ^b	◄► ELB ◄► GRZ ▲ TFV	▲ TFV	▲ TFV ^b
Tenofovir (TFV) alafenamide	◄► LDV ▲ TFV ^d	◄► VEL ▲ TFV ^d	ND	◄► TFV	▲ TFV ^b

Green indicates coadministration is safe; yellow indicates a dose change or additional monitoring is warranted; and pink indicates the combination should be avoided.

Abbreviation: ND, no data.

^aCaution only with tenofovir disoproxil fumarate.

^bIncrease in tenofovir depends on which additional concomitant antiretroviral agents are administered.

^cAvoid tenofovir disoproxil fumarate in patients with an estimated glomerular filtration rate <60 mL/min; tenofovir concentrations may exceed those with established renal safety data in individuals on ritonavir- or cobicistat-containing regimens.

^dStudied as part of fixed-dose combinations with ledipasvir/sofosbuvir or sofosbuvir/velpatasvir plus TAF, emtricitabine, elvitegravir, and cobicistat.

Table 3. Recommended Regimens for Patients With Chronic Kidney Disease

Recommendation	Genotype	Duration (Weeks)	Rating
CKD stage 1, 2, and 3 ^a	Follow standard direct-acting antiviral agents; treatment guidance		
CKD stage 4 and 5 ^b			
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) ^c	1a, 1b, 4	12	I, B
Daily coformulated 3-tablet combination of glecaprevir (300 mg)/pibrentasvir (120 mg)	1, 2, 3, 4, 5, 6	12	I, B

Abbreviations: CKD, chronic kidney disease; NS5A, nonstructural protein 5A.

^aCKD stages: 1 normal (estimated glomerular filtration rate [eGFR] >90 mL/min); 2 mild CKD (eGFR 60–89 mL/min); 3 moderate CKD (eGFR 30–59 mL/min).

^bCKD stages: 4 severe CKD (eGFR 15–29 mL/min); 5 end-stage CKD (eGFR <15 mL/min).

^cBaseline NS5A resistance-associated substitution (RAS) testing is recommended for genotype 1a prior to elbasvir/grazoprevir therapy; if NS5A RASs at positions 28, 30, 31, and/or 93 are identified, glecaprevir/pibrentasvir is recommended.

prior non-NS5A inhibitor DAA regimen failure [61]. Overall, 46% of patients in these trials had compensated cirrhosis (number with GT4 not provided). Among the 22 patients with a prior NS5A inhibitor-containing regimen failure, 91% (20/22) achieved SVR12. All patients with a prior non-NS5A inhibitor DAA regimen failure achieved SVR12 (19/19).

Genotype 5 or 6

Prior Treatment With a DAA Regimen (Including NS5A Inhibitors)

Twelve weeks of sofosbuvir/velpatasvir/voxilaprevir is recommended for GT5 or GT6 DAA-experienced patients, with or without compensated cirrhosis. (IIa, B)

Minimal phase 3 data are available addressing sofosbuvir/velpatasvir/voxilaprevir efficacy in this patient population. All 7 patients with GT5 (n = 1) or GT6 (n = 6) in POLARIS-1 achieved SVR12; all had prior treatment failure with an NS5A inhibitor-containing regimen [61]. Overall, 46% of participants had compensated cirrhosis (percentage with GT5 or GT6 not provided).

UNIQUE POPULATIONS

Decompensated Cirrhosis and Recurrent HCV Infection Post Liver Transplantation

DAA therapy offers significant potential benefits for patients with decompensated cirrhosis and those who develop recurrent HCV infection after liver transplantation [62–68]. Liver transplant center consultation should be strongly considered for

these vulnerable patients. For those with decompensation, use of protease inhibitor-containing regimens should be considered with extreme caution due to potential toxicity. Treatment deferral to the post liver transplant period may be considered if organ availability might increase for a patient willing to consider an organ procured from an HCV-infected donor. See Table 1 for recommended regimens and the online guidance for additional information addressing the specialized care these patients require.

Acute Hepatitis C

Acute hepatitis C refers to the first 6 months after initial infection. As there is a 20% to 50% chance of spontaneous resolution of the infection during this period [69, 70], monitoring HCV RNA for at least 12 to 16 weeks before starting treatment is recommended. If initiating treatment during the acute infection period to minimize onward transmission or loss to follow-up, the same regimens are recommended as for chronic HCV (see Table 1). See Supplementary Materials for additional recommendations regarding testing, monitoring, and management of acute HCV infection.

HIV/HCV Coinfection, HBV/HCV Coinfection, or Prior HBV Infection

HIV infection remains independently associated with advanced fibrosis and cirrhosis in patients with active HCV [71–74]. As HCV clearance can ameliorate these risks [75–77], HCV therapy in HIV-infected patients is a priority. Efficacy and adverse event rates associated with current DAA regimens are similar in those with HIV/HCV coinfection vs HCV mono-infection [78–88].

Table 4. Recommendations for Whom and When to Treat Among Hepatitis C Virus-infected Children

Recommendation	Rating
If direct-acting antiviral regimens are available for a child's age group, treatment is recommended for all hepatitis C virus-infected children aged >3 years as they will benefit from antiviral therapy, independent of disease severity.	I, B
Treatment of children aged 3 to 12 years with chronic hepatitis C should be deferred until interferon-free regimens are available.	II, C
The presence of extrahepatic manifestations, such as cryoglobulinemia, rashes, and glomerulonephritis, as well as advanced fibrosis should lead to early antiviral therapy to minimize future morbidity and mortality.	I, C

Table 5. Recommended Regimens for Adolescents Aged ≥12 Years or Weighing ≥35 kg Without Cirrhosis or With Compensated Cirrhosis

Recommendation	Duration (Weeks)	Rating
Daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with GT1 who are treatment naive without cirrhosis or with compensated cirrhosis ^a or treatment experienced ^b without cirrhosis	12	I, B
Daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with GT1 who are treatment experienced ^b with compensated cirrhosis ^a	24	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin ^c for patients with GT2 who are treatment naive or treatment experienced ^b without cirrhosis or with compensated cirrhosis ^a	12	I, B
Daily sofosbuvir (400 mg) plus weight-based ribavirin ^c for patients with GT3 who are treatment naive or treatment experienced ^b without cirrhosis or with compensated cirrhosis ^a	24	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients with GT4, GT5, or GT6 who are treatment naive or treatment experienced ^b without cirrhosis or with compensated cirrhosis ^a	12	I, B

Abbreviation: GT, genotype.

^aChild-Pugh A.

^bInterferon-based regimen, with or without ribavirin.

^cSee ribavirin dosing table in [Supplementary Materials](#) for recommended weight-based dosages.

Thus, HCV treatment recommendations for HIV/HCV coinfection mirror those for HCV mono-infection (see [Table 1](#)), with consideration of the complex drug interactions that can occur between DAAs and antiretroviral medications (see [Table 2](#)).

All patients who initiate HCV DAA therapy should be assessed for hepatitis B virus (HBV) coinfection with hepatitis B surface antigen (HBsAg) testing and for evidence of prior infection with anti-HBs and anti-HBc testing. [Supplementary Table 9](#) addresses how to monitor patients with coinfection or prior infection during HCV treatment. HBsAg-positive, HIV/HCV-coinfected patients should be on antiretroviral agents with activity against HBV, preferably tenofovir disoproxil fumarate or tenofovir alafenamide. For HIV-infected patients who are only anti-HBc positive and not on tenofovir-based antiretroviral therapy, monitoring for HBV reactivation is recommended (see [Supplementary Materials](#)).

Renal Impairment

HCV infection is independently associated with development of chronic kidney disease (CKD) [89, 90] and an increased risk of progression to end-stage renal disease (ESRD) in persons with chronic HCV and CKD [91]. Current DAA regimens can be safely dosed in persons with mild to moderate renal impairment (ie, estimated glomerular filtration rate ≥30 mL/min; see [Tables 1](#) and [3](#)). Elbasvir/grazoprevir and glecaprevir/

pibrentasvir are recommended regimens for patients with severe renal impairment or ESRD (see [Table 3](#)) based on C-SURFER [92] and EXPEDITION-4 [93] data, respectively. Exceptions to using elbasvir/grazoprevir are similar to the treatment-naive GT1 population. When relevant, renal transplant evaluation should be conducted before HCV treatment as wait-list time is reduced when both the donor and recipient are HCV positive [94]. See online guidance for recommendations regarding HCV treatment in kidney transplant recipients.

Children and Adolescents

Approximately 132 000 US children and adolescents have active HCV [95]. HCV-related liver disease generally progresses slowly in children, and cirrhosis and liver cancer occur infrequently [96–98]. Comorbidities such as obesity and HIV or HBV coinfection, however, may accelerate progression. Extrahepatic manifestations of HCV infection, transmission risk, and stigmatization also remain concerns. Antiviral therapy for children and adolescents affords benefits akin to those realized in adults. Ledipasvir/sofosbuvir and sofosbuvir plus ribavirin [99, 100] are recommended in certain circumstances for adolescents (see [Tables 4](#) and [5](#)); approval of interferon-free regimens for younger children is expected in the near future. [Tables 6](#) and [7](#) address HCV testing recommendations for perinatally exposed children and siblings of HCV-infected children,

Table 6. Recommendations for Hepatitis C Virus (HCV) Testing of Perinatally Exposed Children and Siblings of HCV-infected Children

Recommendation	Rating
All children born to HCV-infected women should be tested for HCV infection. Testing is recommended using an antibody-based test at or after 18 months of age.	I, A
Testing with an HCV RNA assay can be considered in the first year of life, but the optimal timing of such a test is unknown.	Ila, C
Repetitive testing by HCV RNA is not recommended.	III, A
Children who are anti-HCV positive after 18 months of age should be tested with an HCV RNA assay after age 3 years to confirm chronic hepatitis C infection.	I, A
The siblings of children with vertically acquired HCV should be tested for HCV infection if born from the same infected mother.	I, C

Abbreviation: HCV, hepatitis C virus.

Table 7. Recommendations for Counseling Parents Regarding Transmission and Prevention in Hepatitis C Virus-infected Children

Recommendation	Rating
Parents should be informed that hepatitis C is not transmitted by casual contact and, as such, HCV-infected children do not pose a risk to other children and can participate in school, sports, and athletic activities and can engage in all other regular childhood activities without restrictions.	I, B
Parents should be informed that universal precautions should be followed at school and in the home of children with HCV infection. Educate family members and children about the risk and routes of HCV transmission and the techniques for avoiding blood exposure, such as avoiding the sharing of toothbrushes, razors, and nail clippers and the use of gloves and dilute bleach to clean up blood.	I, B

Abbreviation: HCV, hepatitis C virus.

and transmission and prevention counseling recommendations. See the [Supplementary Materials](#) for recommendations regarding monitoring and medical management of HCV-infected children.

Pregnancy

As risk factor–based screening has not been shown to be effective [101–103], screening with an HCV antibody assay (with confirmatory nucleic acid testing for a positive result) is newly recommended for pregnant women. Without increased testing of pregnant women, exposed children are unlikely to receive appropriate testing. Recent increases in HCV infection among young women of reproductive age have resulted in at least 29 000 HCV-infected women giving birth each year [104–107]. Testing pregnant women at the initiation of prenatal care is recommended. Those known to be anti-HCV positive in the past can be checked for active infection with HCV RNA testing.

DAA therapy is not recommended for pregnant women due to lack of safety and efficacy data. Women of reproductive age with HCV should be counseled about the benefits of antiviral treatment prior to pregnancy in order to improve maternal health and eliminate the risk of mother-to-child transmission. Care of HCV-infected pregnant women should be coordinated between the obstetrician and the HCV provider. Cesarean delivery is not

recommended for the prevention of perinatal transmission. See [Table 8](#) for recommendations addressing screening, treatment, and monitoring of pregnant HCV-infected women and postpartum issues and [Supplementary Table 11](#) for recommendations regarding ribavirin and pregnancy.

Key Populations

People who inject drugs (PWID), men who have sex with men (MSM), and individuals in jails and prisons bear a particularly high burden of chronic HCV infection. Injection drug use accounts for the majority of new HCV infections, and the rising use of opioids has become an important driver in the perpetuation of the epidemic. Acute HCV infection is also increasingly being reported among HIV-infected and uninfected MSM due to a variety of risk factors. Finally, HCV infection disproportionately affects individuals in correctional institutions, where the prevalence of infection ranges from 17% to 23% [108, 109], far exceeding the 1.0% prevalence [95] in the general population. More than 90% of these individuals are ultimately released and reenter the general population, where they can transmit HCV and develop liver-related and extrahepatic complications [110, 111].

Achieving the goal of HCV elimination will depend on diagnosing and treating HCV infection in these groups and

Table 8. Recommendations Addressing Screening, Treatment, and Monitoring of Pregnant Hepatitis C Virus-infected Women and Postpartum Issues

Recommendation	Rating
All pregnant women should be tested for HCV infection (see recommendations for initial HCV testing and follow-up), ideally at the initiation of prenatal care.	IIb, C
For women of reproductive age with known HCV infection, antiviral therapy is recommended before considering pregnancy, whenever practical and feasible, to reduce the risk of HCV transmission to future offspring.	I, B
Treatment during pregnancy is not recommended due to the lack of safety and efficacy data.	IIb, C
HCV RNA and routine liver function tests are recommended at initiation of prenatal care for HCV-antibody–positive pregnant women to assess the risk of MTCT and degree of liver disease.	I, B
All pregnant women with HCV infection should receive prenatal and intrapartum care that is appropriate for their individual obstetric risk(s) as there is no currently known intervention to reduce MTCT.	I, B
In HCV-infected pregnant women with pruritus or jaundice, there should be a high index of suspicion for intrahepatic cholestasis of pregnancy with subsequent assessment of alanine aminotransferase ALT, aspartate aminotransferase AST, and serum bile acids.	I, B
HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. Antenatal and perinatal care should be coordinated with a maternal–fetal medicine (ie, high-risk pregnancy) obstetrician.	I, B
Breastfeeding is not contraindicated in women with HCV infection, except when the mother has cracked, damaged, or bleeding nipples or in the context of human immunodeficiency virus coinfection.	I, B
Women with HCV infection should have their HCV RNA reevaluated after delivery to assess for spontaneous clearance.	I, B

Abbreviations: HCV, hepatitis C virus; MTCT, mother-to-child transmission.

Table 9. Recommendations for Hepatitis C Virus (HCV) Testing, Treatment, and Harm Reduction Among People Who Inject Drugs; Testing, Treatment, and Prevention of HCV Infection Among Men Who Have Sex With Men; and Testing and Treatment of HCV Infection in Jail and Prison Settings

Management Area	Recommendation	Rating
Management of HCV infection in PWID		
Screening and treatment	Annual HCV testing is recommended for PWID with no prior testing or past negative testing and subsequent injection drug use. Depending on level of risk, more frequent testing may be indicated.	Ila, C
	Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV antibody testing with reflexive or immediate confirmatory RNA testing with linkage to care for those who are infected.	Ila, C
	PWID should be counseled on measures to reduce risk of HCV transmission to others.	I, C
	PWID should be offered linkage to harm reduction services when available, including needle/syringe service programs and substance use disorder treatment programs.	I, B
Contraindications to treatment	Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment.	Ila, B
Testing and prevention of reinfection	At least annual testing with HCV RNA is recommended for PWID with recent injection drug use after they have spontaneously cleared HCV infection or have been successfully treated.	Ila, C
Management of HCV infection in MSM		
Testing and prevention	Annual HCV testing is recommended for sexually active HIV-infected adolescent and adult MSM. Depending on the presence of high-risk sexual or drug use practices, more frequent testing may be warranted.	Ila, C
	HCV testing at HIV PreP initiation and at least annually thereafter (while on PreP) is recommended in HIV-uninfected MSM. Depending on sexual or drug use risk practices, more frequent testing may be warranted.	Ila, C
	All MSM should be counseled about the risk of sexual HCV transmission with high-risk sexual and drug use practices and be educated about measures to prevent HCV infection and transmission.	Ila, C
Treatment	Antiviral treatment for HCV-infected MSM should be coupled with ongoing counseling about the risk of HCV reinfection and be educated on methods to reduce the risk of HCV reinfection after cure.	I, B
Testing and prevention of reinfection	At least annual (and risk-based, if indicated) HCV testing with HCV RNA is recommended for sexually active MSM after successfully treated or spontaneously cleared HCV infection.	Ila, C
Management of HCV infection in correctional settings		
Screening and treatment in jail settings	Jails should implement opt-out HCV testing, encompassed by HCV antibody testing followed by confirmatory HCV RNA if antibody positive. <ul style="list-style-type: none"> Chronically infected individuals should receive counseling about HCV infection and be provided linkage to follow-up community healthcare for evaluation of liver disease and treatment upon release. Chronically infected individuals whose jail sentence is sufficiently long enough to complete the total number of pills required for a course of antiviral therapy should receive treatment for chronic HCV infection according to AASLD/IDSA guidelines while incarcerated. Upon release, patients should be provided linkage to community healthcare for surveillance for HCV-related complications. 	Ila, C
	Testing and treatment in prison settings	Prisons should implement opt-out HCV testing. Chronically infected individuals should receive antiviral therapy according to AASLD/IDSA guidelines while incarcerated. Upon release, patients should be provided linkage to community healthcare for surveillance for HCV-related complications.
Continuation of treatment in jail and prison settings	To prevent HCV reinfection and reduce the risk of progression of HCV-associated liver disease, prisons should provide harm reduction and evidence-based treatment for underlying substance use disorders.	Ila, C
	Jails and prisons should facilitate continuation of HCV therapy for individuals on treatment at the time of incarceration.	Ila, C

Abbreviations: AASLD, American Association for the Study of Liver Diseases; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDSA, Infectious Diseases Society of America; MSM, men who have sex with men; PreP, preexposure prophylaxis; PWID, people who inject drugs.

implementing harm-reduction strategies to prevent future infections. As a result, the panel has chosen to focus attention on HCV management among these key populations to reduce HCV transmission and decrease HCV-related morbidity and mortality. Table 9 includes recommendations for HCV testing, treatment, and harm reduction among PWID; testing, treatment, and prevention of HCV infection among MSM; and testing and treatment of HCV infection in jail and prison settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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