IDSA FEATURES







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

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.

document [20], certain previously recommended regimens

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 (\pm 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 naive 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)	12	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
Glecaprevir/pibrentasvir	Treatment naive or PEG/RBV experienced without cirrhosis	8	
	Treatment naive 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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
Ledipasvir/sofosbuvir	Treatment naive regardless of cirrhosis	12	
	Treatment naive, 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 naive 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 naive 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 naive 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) regard- less of cirrhosis	12	Same for GT1a and GT1b
	GT1a, non-NS5A failures (including NS3 protease inhibitors) regardless of cirrhosis	12	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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 naive or PEG/RBV experienced without cirrhosis	8	
	Treatment naive or PEG/RBV experienced with cir- rhosis, 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	12	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		

Table 1. Continued

Regimen	Patient Population	Duration (Weeks)	Caveats and Other Considerations
Sofosbuvir/velpatasvir	Treatment naive, or PEG/RBV or non-NS5A experi- enced regardless of cirrhosis	12	
	Decompensated cirrhosis, treatment naive or PEG/ RBV or non-NS5A experienced	12	Add weight-based RBV
	Decompensated cirrhosis, DAA failure (including sofos- buvir ± 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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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 naive without cirrhosis	8	
	Treatment naive with compensated cirrhosis	12	
	Post liver transplant without cirrhosis	12	
	Severe renal impairment (CKD stage 4 or 5)	8–12 12	Treatment duration depends on presence of cirrhosis
	Post kidney transplant regardless of cirrhosis Not for decompensated cirrhosis or post liver transplant with cirrhosis	IZ	
Sofosbuvir + elbasvir/grazoprevir	PEG/RBV experienced with compensated cirrhosis ^b	12	
ooloobavii i olooovii/grazopievii	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis	12	
Sofosbuvir/velpatasvir	Treatment naive without cirrhosis	12	
	Treatment naive 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 naive 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
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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 naive 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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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 Not for decompensated cirrhosis or post liver trans-	12	

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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		
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
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	
	Not for decompensated cirrhosis or post liver trans- plant with cirrhosis		

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.

(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

^aExtend treatment duration to 24 weeks if RBV ineligible.

^bRepresents off-label use.

failures occurred. In SURVEYOR-II part 4, 99% (135/137) of treatment-naive persons with GT2 infection achieved SVR12 following 8 weeks of glecaprevir/pibrentasvir [45]. In EXPEDITION-1, which was a study of treatment-naive 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-naive GT2 patients, with or without compensated cirrhosis. (I, A)

ASTRAL-2 evaluated 12 weeks of sofosbuvir/velpatasvir vs sofosbuvir plus ribavirin among 266 treatment-naive 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-naive 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-naive participants [47]. POLARIS-2 randomized DAA-naive 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-naive GT3 patients (see Table 1).

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

ENDURANCE-3 randomized 348 treatment-naive, 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-naive 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-naive, 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-naive 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-naive or -experienced GT3 patients [46]. Among treatment-naive 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-naive, 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-naive GT4 patients (see Table 1).

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

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

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

ASTRAL-1 included 64 GT4 treatment-naive 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-naive 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 peginter-feron/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 \pm 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-naive 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-naive or -experienced patients (interferon/peginterferon \pm ribavirin or sofosbuvir plus ribavirin \pm 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 (± 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 Iopinavir (LPV)	NDª	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 alafenam- ide (TAF)/emtric- itabine (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

blncrease 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°	Follow standard direct-	acting antiviral agents; treatment guidance	
CKD stage 4 and 5 ^b			
Daily fixed-dose combination of elbasvir (50 mg)/grazo- previr (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.

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/vel-patasvir/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 monoinfection [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

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).

Baseline 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.

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.

Thus, HCV treatment recommendations for HIV/HCV coinfection mirror those for HCV monoinfection (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 132000 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

^aChild-Pugh A.

^bInterferon-based regimen, with or without ribavirin.

^cSee ribavirin dosing table in Supplementary Materials for recommended weight-based dosages

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.	Ilb, 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.	Ilb, 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 PW	ID	
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.	lla, 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 MS	M	
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 corr	rectional 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. 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.	lla, 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.	IIa, C
	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
Continuation of treatment in jail and prison settings	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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References

1. Marcellin P, Boyer N, Gervais A, et al. Long-term histologic improvement and loss of detectable intrahepatic HCV RNA in patients with chronic hepatitis

- C and sustained response to interferon-alpha therapy. Ann Intern Med 1997;
- Poynard T, McHutchison J, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002; 122:1303-13.
- Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013; 158:329–37.
- van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012; 308:2584–93.
- Veldt BJ, Heathcote EJ, Wedemeyer H, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med 2007; 147:677–84.
- Fabrizi F, Dixit V, Messa P. Antiviral therapy of symptomatic HCV-associated mixed cryoglobulinemia: meta-analysis of clinical studies. J Med Virol 2013; 85:1019–27.
- Sise ME, Bloom AK, Wisocky J, et al. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. Hepatology 2016; 63:408-17
- Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for hepatitis C infection. Aliment Pharmacol Ther 2005: 21:653–62.
- Takahashi K, Nishida N, Kawabata H, Haga H, Chiba T. Regression of Hodgkin lymphoma in response to antiviral therapy for hepatitis C virus infection. Intern Med 2012; 51:2745–7.
- Svoboda J, Andreadis C, Downs LH, Miller WT Jr, Tsai DE, Schuster SJ. Regression of advanced non-splenic marginal zone lymphoma after treatment of hepatitis C virus infection. Leuk Lymphoma 2005; 46:1365–8.
- Mazzaro C, Little D, Pozzato G. Regression of splenic lymphoma after treatment of hepatitis C virus infection. N Engl J Med 2002; 347:2168–70; author reply 2168–70.
- Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011; 9:509–516.e1.
- Younossi ZM, Jiang Y, Smith NJ, Stepanova M, Beckerman R. Ledipasvir/sofosbuvir regimens for chronic hepatitis C infection: insights from a work productivity economic model from the United States. Hepatology 2015; 61:1471–8.
- Younossi ZM, Stepanova M, Afdhal N, et al. Improvement of health-related quality of life and work productivity in chronic hepatitis C patients with early and advanced fibrosis treated with ledipasvir and sofosbuvir. J Hepatol 2015; 63:337-45.
- Younossi ZM, Stepanova M, Feld J, et al. Sofosbuvir/velpatasvir improves patient-reported outcomes in HCV patients: results from ASTRAL-1 placebo-controlled trial. J Hepatol 2016; 65:33–9.
- Younossi ZM, Stepanova M, Henry L, et al. Effects of sofosbuvir-based treatment, with and without interferon, on outcome and productivity of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2014; 12:1349–59.e13.
- Younossi ZM, Stepanova M, Henry L, Nader F, Hunt S. An in-depth analysis of patient-reported outcomes in patients with chronic hepatitis C treated with different anti-viral regimens. Am J Gastroenterol 2016; 111:808–16.
- Younossi ZM, Stepanova M, Nader F, et al. Patient-reported outcomes in chronic hepatitis C patients with cirrhosis treated with sofosbuvir-containing regimens. Hepatology 2014; 59:2161–9.
- Jezequel C, Bardou-Jacquet E, Desille Y, et al. Survival of patients infected by chronic hepatitis C and F0-F1 fibrosis at baseline after a 15 years follow-up. J Hepatol 2015; 62(2 Supplement):S589.
- Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology 2015; 62:932–54.
- Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM.
 Standardized reporting of clinical practice guidelines: a proposal from the Conference on Guideline Standardization. Ann Intern Med 2003; 139:493–8.
- Methodology manual and policies from the ACCF/AHA task force on practice guidelines. Dallas, TX: American College of Cardiology Foundation and American Heart Association, Inc., 2010.
- Zeuzem S, Mizokami M, Pianko S, et al. NS5A resistance-associated substitutions in patients with genotype 1 hepatitis C virus: prevalence and effect on treatment outcome. I Hepatol 2017: 66:910–8.
- 24. Jacobson IM, Asante-Appiah E, Wong P, et al. Prevalence and impact of baseline NSA resistance associated variants (RAVs) on the efficacy of elbasvir/grazoprevir (EBR/GZR) against GT1a infection. In: 66th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco. CA. 2015.
- Zeuzem S, Rockstroh JK, Kwo P, et al. Predictors of response to grazoprevir/elbasvir among HCV genotype 1 (GT1)-infected patients: integrated analysis of phase

- 2–3 trials. In: 66th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, CA, 2015.
- 26. Sulkowski M, Hezode 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 hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015; 385:1087–97.
- 27. Lawitz E, Gane E, Pearlman B, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet 2015; 385:1075–86.
- Kwo P, Gane EJ, Peng CY, et al. Effectiveness of elbasvir and grazoprevir combination, with or without ribavirin, for treatment-experienced patients with chronic hepatitis C infection. Gastroenterology 2017; 152:164–75.e4.
- Thompson A, Zeuzem S, Rockstroh J, et al. The combination of grazoprevir and elbasvir +RBV is highly effective for the treatment of GT1a-infected patients. In: 66th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, CA, 2015.
- Kwo PY, Poordad F, Asatryan A, et al. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. J Hepatol 2017: 67:263–71.
- 31. Zeuzem S, Feld J, Wang S, et al. ENDURANCE-1: efficacy and safety of 8- versus 12-week treatment with ABT-493/ABT-530 in patients with chronic HCV genotype 1 infection. In: 67th Annual Meeting of the American Association for the Study of Liver Diseases. Boston, MA, 2016.
- 32. Forns X, Lee SS, Valdes J, 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; 17:1062–8.
- 33. Rockstroh J, Lacombe K, Viani RM, 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: International Liver Congress 2017. Amsterdam, Netherlands, 2017.
- Afdhal N, Zeuzem S, Kwo P, et al; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370:1889-98.
- Kowdley KV, Gordon SC, Reddy KR, et al; ION-3 Investigators. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370:1879–88.
- Kowdley KV, An D, Pang PS, Wyles D. Analysis of subgroup differences in the ION-3 trial of ledipasvir-sofosbuvir in chronic hepatitis C infection. Open Forum Infect Dis 2015; 2:ofv056.
- 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; 22:481–93.
- 38. Ingiliz P, Christensen S, Kimhofer T, 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; 63:1320–4.
- Ioannou GN, Beste LA, Chang MF, 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; 151:457–71.e5.
- Kowdley KV, Sundaram V, Jeon CY, et al. Eight weeks of ledipasvir/sofosbuvir is effective for selected patients with genotype 1 hepatitis C virus infection. Hepatology 2017; 65:1094–103.
- 41. Terrault NA, Zeuzem S, Di Bisceglie AM, 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; 151:1131–1140.e5.
- Feld JJ, Jacobson IM, Hézode C, et al; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med 2015; 373-2599-607
- Hezode C, Reau N, Svarovskaia ES, et al. Resistance analysis in patients with genotype 1–6 HCV infection treated with sofosbuvir/velpatasvir in the phase III studies. J Hepatol 2018; 68:895–903.
- Jacobson IM, Lawitz E, Gane EJ, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017; 153:113–22.
- Asselah T, Kowdley KV, Zadeikis N, 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; 16:417–26.

- Foster GR, Afdhal N, Roberts SK, et al; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. N Engl J Med 2015; 373:2608–17.
- Asselah T, Bourgeois S, Pianko S et al. Sofosbuvir/velpatasvir in patients with hepatitis C virus genotypes 1–6 and compensated cirrhosis or advanced fibrosis. Liver Int 2018; 38:443–50.
- Foster GR, Gane E, Asatryan A, et al. ENDURANCE-3: safety and efficacy of glecaprevir/pibrentasvir compared to sofosbuvir plus daclatasvir in treatment-naïve HCV genotype 3-infected patients without cirrhosis. J Hepatol 2017; 66(1 Supplement):S33.
- Wyles D, Poordad F, Wang S, et al. Glecaprevir/pibrentasvir for HCV genotype 3
 patients with cirrhosis and/or prior treatment experience: a partially randomized
 phase III clinical trial. Hepatology 2018; 67:514–23.
- Kwo PY, Wyles DL, Wang S, 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 Supplement):S208.
- 51. Krishnan P, Pilot-Matias T, Schnell G. 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; Epub ahead of print.
- 52. Asselah T, Reesink H, Gerstoft J, et al. High efficacy of elbasvir and grazoprevir with or without ribavirin in 103 treatment-naive and experienced patients with HCV genotype 4 infection: a pooled analysis. Liver Int 2018; Epub ahead of print.
- Kohli A, Kapoor R, Sims Z, 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: 15:1049–54.
- Abergel A, Asselah T, Metivier S, et al. Ledipasvir-sofosbuvir in patients with hepatitis C virus genotype 5 infection: an open-label, multicentre, single-arm, phase 2 study. Lancet Infect Dis 2016; 16:459–64.
- 55. Wong KA, Worth A, Martin R, 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; 57:6333–40.
- Kohler JJ, Nettles JH, Amblard F, et al. Approaches to hepatitis C treatment and cure using NS5A inhibitors. Infect Drug Resist 2014; 7:41–56.
- Gane EJ, Hyland RH, An 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; 149:1454–61.e1.
- Pianko S, Flamm SL, Shiffman ML, et al. Sofosbuvir plus velpatasvir combination therapy for treatment-experienced patients with genotype 1 or 3 hepatitis C virus infection: a randomized trial. Ann Intern Med 2015: 163:809–17.
- Poordad F, Felizarta F, Asatryan A, et al. Glecaprevir and pibrentasvir for 12 weeks for hepatitis C virus genotype 1 infection and prior direct-acting antiviral treatment. Hepatology 2017; 66:389–97.
- Poordad F, Pol S, Asatryan A, et al. MAGELLAN-1, part 2: glecaprevir and pibrentasvir for 12 or 16 weeks in patients with chronic HCV genotype 1 or 4 and prior direct-acting antiviral treatment failure. Gastroenterology 2017; 152:S1057.
- Bourlière M, Gordon SC, Flamm SL, et al; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med 2017; 376:2134–46.
- 62. Manns M, Samuel D, Gane EJ, et al; SOLAR-2 Investigators. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis 2016: 16:685–97.
- Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. Gastroenterology 2015; 148:100–7.e1.
- 64. Curry MP, O'Leary JG, Bzowej N, et al; ASTRAL-4 Investigators. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. N Engl J Med 2015; 373-2618-28
- Charlton M, Everson GT, Flamm SL, et al; SOLAR-1 Investigators. Ledipasvir and sofosbuvir plus ribavirin for treatment of HCV infection in patients with advanced liver disease. Gastroenterology 2015; 149:649–59.
- Charlton M, Gane E, Manns MP, et al. Sofosbuvir and ribavirin for treatment of compensated recurrent hepatitis C virus infection after liver transplantation. Gastroenterology 2015; 148:108–17.
- 67. Welzel TM, Petersen J, Ferenci P, et al. Safety and efficacy of daclatasvir plus sofosbuvir with or without ribavirin for the treatment of chronic HCV genotype 3 infection: interim results of a multicenter European compassionate use program. In: 66th Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco. CA. 2016.
- Welzel TM, Petersen J, Herzer K, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. Gut 2016; 65:1861–70.
- Kamal SM. Acute hepatitis C: a systematic review. Am J Gastroenterol 2008; 103:1283–97.

- Grebely J, Page K, Sacks-Davis R, et al; InC3 Study Group. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology 2014; 59:109–20.
- Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. AIDS 2008; 22:1979–91.
- de Lédinghen V, Barreiro P, Foucher J, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. J Viral Hepat 2008; 15:427–33.
- Fierer DS, Dieterich DT, Fiel MI, et al. Rapid progression to decompensated cirrhosis, liver transplant, and death in HIV-infected men after primary hepatitis C virus infection. Clin Infect Dis 2013; 56:1038–43.
- Kirk GD, Mehta SH, Astemborski J, et al. HIV, age, and the severity of hepatitis C virus-related liver disease: a cohort study. Ann Intern Med 2013; 158:658–66.
- Berenguer J, Alvarez-Pellicer J, Martín PM, et al; GESIDA3603/5607 Study Group. Sustained virological response to interferon plus ribavirin reduces liver-related complications and mortality in patients coinfected with human immunodeficiency virus and hepatitis C virus. Hepatology 2009; 50:407–13.
- Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. JAMA 2012; 308:370–8.
- 77. Mira JA, Rivero-Juárez A, López-Cortés LF, et al; Grupo Andaluz para el Estudio de las Hepatitis Víricas de la Sociedad Andaluza de Enfermedades Infecciosas. Benefits from sustained virologic response to pegylated interferon plus ribavirin in HIV/hepatitis C virus-coinfected patients with compensated cirrhosis. Clin Infect Dis 2013; 56:1646–53.
- Bhattacharya D, Belperio PS, Shahoumian TA, et al. Effectiveness of all-oral antiviral regimens in 996 human immunodeficiency virus/hepatitis C virus genotype 1-coinfected patients treated in routine practice. Clin Infect Dis 2017; 64:1711–20.
- Naggie S, Cooper C, Saag M, et al; ION-4 Investigators. Ledipasvir and sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015; 373:705–13.
- Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. JAMA 2015; 313:1223–31.
- 81. Wyles D, Bräu N, Kottilil S, et al; ASTRAL-5 Investigators. Sofosbuvir and velpatasvir for the treatment of hepatitis C virus in patients coinfected with human immunode-ficiency virus type 1: an open-label, phase 3 study. Clin Infect Dis 2017; 65:6–12.
- Dieterich D, Rockstroh JK, Orkin C, et al. Simeprevir (TMC435) with pegylated interferon/ribavirin in patients coinfected with HCV genotype 1 and HIV-1: a phase 3 study. Clin Infect Dis 2014; 59:1579–87.
- Sulkowski MS, Naggie S, Lalezari J, et al; PHOTON-1 Investigators. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. JAMA 2014; 312:353–61.
- 84. Sulkowski MS, Sherman KE, Dieterich DT, et al. Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomized trial. Ann Intern Med 2013; 159:86–96.
- Rodriguez-Torres M, Gaggar A, Shen G, et al. Sofosbuvir for chronic hepatitis C virus infection genotype 1-4 in patients coinfected with HIV. J Acquir Immune Defic Syndr 2015: 68:543-9.
- Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection, JAMA 2015: 313:1232–9.
- Dieterich D, Nelson M, Soriano V, et al; STARTVerso4 Study Group. Faldaprevir and pegylated interferon α-2a/ribavirin in individuals co-infected with hepatitis C virus genotype-1 and HIV. AIDS 2015; 29:571–81.
- Wyles DL, Ruane PJ, Sulkowski MS, et al; ALLY-2 Investigators. Daclatasvir plus sofosbuvir for HCV in patients coinfected with HIV-1. N Engl J Med 2015; 373:714–25.
- Rogal SS, Yan P, Rimland D, et al; Electronically Retrieved Cohort of HCV Infected Veterans Study Group. Incidence and progression of chronic kidney disease after hepatitis C seroconversion: results from ERCHIVES. Dig Dis Sci 2016; 61:930–6.
- Fabrizi F, Verdesca S, Messa P, Martin P. Hepatitis C virus infection increases the risk of developing chronic kidney disease: a systematic review and meta-analysis. Dig Dis Sci 2015; 60:3801–13.
- Lee JJ, Lin MY, Chang JS, et al. Hepatitis C virus infection increases risk of developing end-stage renal disease using competing risk analysis. PLoS One 2014; 9:e100790.
- Roth D, Nelson DR, Bruchfeld A, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet 2015; 386:1537–45.
- Gane E, Lawitz E, Pugatch D. Glecaprevir and pibrentasvir in patients with HCV and severe renal impairment. N Engl J Med 2017; 377:1448–55.
- Kucirka LM, Singer AL, Ros RL, Montgomery RA, Dagher NN, Segev DL. Underutilization of hepatitis C-positive kidneys for hepatitis C-positive recipients. Am J Transplant 2010; 10:1238–46.

- Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med 2014; 160:293–300.
- Jhaveri R. Diagnosis and management of hepatitis C virus-infected children. Pediatr Infect Dis J 2011; 30:983–5.
- Goodman ZD, Makhlouf HR, Liu L, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C Trial. Hepatology 2008; 47:836–43.
- Minola E, Prati D, Suter F, et al. Age at infection affects the long-term outcome of transfusion-associated chronic hepatitis C. Blood 2002; 99:4588–91.
- Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology 2017; 66:371–8.
- 100. Wirth S, Rosenthal P, Gonzalez-Peralta RP, et al. Sofosbuvir and ribavirin in adolescents 12-17 years old with hepatitis C virus genotype 2 or 3 infection. Hepatology 2017; 66:1102–10.
- 101. Kuncio DE, Newbern EC, Fernandez-Viña MH, Herdman B, Johnson CC, Viner KM. Comparison of risk-based hepatitis C screening and the true seroprevalence in an urban prison system. J Urban Health 2015; 92:379–86.
- 102. Waruingi W, Mhanna MJ, Kumar D, Abughali N. Hepatitis C virus universal screening versus risk based selective screening during pregnancy. J Neonatal Perinatal Med 2015; 8:371–8.
- 103. Fernandez N, Towers CV, Wolfe L, Hennessy MD, Weitz B, Porter S. Sharing of snorting straws and hepatitis C virus infection in pregnant women. Obstet Gynecol 2016; 128:234–7.
- 104. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. Ann Intern Med 2017; 166:775–82.
- 105. Koneru A, Nelson N, Hariri S, et al. Increased hepatitis C virus (HCV) detection in women of childbearing age and potential risk for vertical transmission— United States and Kentucky, 2011–2014. MMWR Morb Mortal Wkly Rep 2016; 65:705–10.
- 106. Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. Hepatitis C virus infection among women giving birth—Tennessee and United States, 2009–2014. MMWR Morb Mortal Wkly Rep 2017; 66:470–3.
- 107. Watts T, Stockman L, Martin J, Guilfoyle S, Vergeront JM. Increased risk for mother-to-infant transmission of hepatitis C virus among Medicaid recipients— Wisconsin, 2011–2015. MMWR Morb Mortal Wkly Rep 2017; 66:1136–9.
- 108. Varan AK, Mercer DW, Stein MS, Spaulding AC. Hepatitis C seroprevalence among prison inmates since 2001: still high but declining. Public Health Rep 2014; 139:187-95.
- 109. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. Hepatology 2015; 62:1353-63
- 110. Macalino GE, Vlahov D, Sanford-Colby S, et al. Prevalence and incidence of HIV, hepatitis B virus, and hepatitis C virus infections among males in Rhode Island prisons. Am J Public Health 2004; 94:1218–23.
- 111. Rich JD, Allen SA, Williams BA. Responding to hepatitis C through the criminal justice system. N Engl J Med 2014; 370:1871–4.

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