

IDSA GUIDELINES

Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection

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The Infectious Diseases Society of America and the American Association for the Study of Liver Diseases have collaboratively developed evidence-based guidance regarding the diagnosis, management, and treatment of hepatitis C virus (HCV) infection since 2013. A panel of clinicians and investigators with extensive infectious diseases or hepatology expertise specific to HCV infection periodically review evidence from the field and update existing recommendations

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or introduce new recommendations as evidence warrants. This update focuses on changes to the guidance since the previous 2020 published update, including ongoing emphasis on recommended universal screening; management recommendations for incomplete treatment adherence; expanded eligibility for simplified chronic HCV infection treatment in adults with minimal monitoring; updated treatment and retreatment recommendations for children as young as 3 years old; management and treatment recommendations in the transplantation setting; and screening, treatment, and management recommendations for unique and key populations.

Keywords: HCV screening; direct-acting antivirals; HCV guidance; HCV treatment; HCV prevention

The Infectious Diseases Society of America (IDSA) and the American Association for the Study of Liver Diseases (AASLD) collaboratively initiated the hepatitis C virus (HCV) guidance project in 2013 to provide clinicians with evidence-based, unbiased, timely guidance regarding diagnosis, treatment, and management of HCV infection. The project includes the web-based HCV guidance platform (www.hcvguidelines.org) to enable rapid, accessible dissemination of new and/or updated information and recommendations in response to the latest data from the field. The HCV guidance website (hereafter the HCV guidance) has been highly successful. From the launch of the HCV guidance in January 2014 through April 2022, the site has been accessed by more than 2 million unique users generating more than 4 million pageviews. In 2021, the site had more the 194,000 unique users from 201 countries and territories with most visits originating from the United States (US), India, Russia, Canada, and Pakistan. Under the umbrella of the HCV guidance, the AASLD-IDSA HCV guidance panel (hereafter the guidance panel) also issues regular, periodic published updates to review new or updated data and recommendations as well as an overview of the ever-changing landscape of the HCV epidemic.

Recognizing viral hepatitis poses a public health threat on par with human immunodeficiency virus (HIV), malaria, and tuberculosis, in June 2016, the World Health Organization (WHO) published its first global health sector strategy setting forth the goal of elimination of viral hepatitis as a major public health threat by 2030 [1]. Specific HCV elimination targets include a 90% reduction in incidence and prevalence, treatment of 80% of eligible persons with chronic infection, a 65% reduction in HCV-related deaths, and universal access to key prevention and treatment services [1]. In response to the WHO's call to action, the National Academies of Sciences, Engineering, and Medicine developed a US strategic plan for viral hepatitis elimination [2]. The US Centers for Disease Control and Prevention (CDC) [3] and the US Department of Health and Human Services (DHHS) [4] subsequently developed national implementation strategies and targets commensurate with those set forth by the WHO. Notably, the new and updated recommendations highlighted and discussed in this update both independently and collectively support, promote, and advance accomplishment of HCV elimination.

Major changes in the HCV guidance since the previous 2020 publication [5] featured in this update include: an ongoing emphasis on universal HCV screening; new recommendations

addressing the management of incomplete treatment adherence; updated recommendations regarding simplified treatment with minimal monitoring and expanded eligibility; management and treatment recommendations for solid organ transplant recipients; newly expanded treatment and retreatment recommendations for children and adolescents; and screening, management, and treatment recommendations for unique and key populations. In addition, we highlight key issues critical to HCV management especially with the mission of HCV elimination in mind. See Figure 1 for key points in this HCV guidance update.

PROCESS

The HCV guidance was developed and is regularly updated by a volunteer panel of more than 30 infectious diseases and hepatology clinicians and investigators with HCV expertise representing IDSA and AASLD, respectively. Four co-chairs (2 from each society) oversee the work of the guidance panel. The HCV guidance undergoes major biannual updates based on a rigorous literature review that encompasses peer-reviewed, published literature and relevant abstracts from national and international scientific conferences. The data are reviewed by section leads, with points of discussion resolved during section and full panel remote meetings.

New or updated recommendations are evaluated using a modified scale adapted from the American College of Cardiology and the American Heart Association practice guidelines [6, 7] (see the [HCV guidance](#) for further details). All new or updated recommendations are reviewed and approved by the IDSA and AASLD governing boards prior to online release or print publication.

TESTING, EVALUATION, AND MONITORING

Implementation of Universal HCV Screening

The guidance panel first recommended universal HCV screening for all adults aged ≥ 18 years in 2019 [5], concomitant with congruous draft recommendations from the US Preventive Services Task Force (USPSTF) and the CDC. The USPSTF subsequently recommended universal HCV screening for adults aged 18 to 79 years in March 2020 [8]. In April 2020, the CDC recommended HCV screening at least once in all adults aged ≥ 18 years and for all pregnant persons during each pregnancy, except in settings where HCV prevalence is $< 0.1\%$ [9]. The rationale for universal HCV screening includes cost-effectiveness [10-13]; improved HCV case finding [8, 9]; shifting epidemiology of HCV infection with incident infections occurring primarily in young adults [14-16]; and the availability of safe, cost-effective direct-acting antiviral (DAA) treatment [17]. Universal screening is a crucial and necessary component of any HCV elimination strategy [1-4] because it is the entry point into the HCV continuum of care [18, 19]. For initial HCV testing, the guidance panel recommends HCV antibody screening with

reflex HCV RNA testing to establish the presence of active infection (as opposed to spontaneous or treatment-induced viral clearance).

Recommendations without rigorous implementation, however, are ineffectual. HCV screening, diagnosis, and treatment were significantly adversely affected by the COVID-19 pandemic [20]. The number of HCV antibody and HCV RNA tests processed by a large US, multicenter, commercial clinical laboratory decreased precipitously beginning in mid-March 2020 [21] coincident with the US federal government declaring a national state of emergency due to COVID-19 [22]. HCV RNA positive test results decreased 62% in March 2020 and remained 39% below baseline in July 2020, with a concomitant decline in the number of DAA prescriptions dispensed [21]. Investigators who conducted a similar study in Ontario, Canada reported comparable decreases in HCV antibody screening and confirmative HCV RNA testing during each of the first 3 waves of the COVID-19 pandemic [23]. The reduced level of HCV testing negatively affecting initiation of HCV treatment appears corroborated by findings from a US national, retrospective study wherein only 23% of people on Medicaid with a positive HCV RNA test between January 30, 2019 and October 31, 2020 initiated treatment DAA within 360 days of diagnosis [24]. A survey conducted among European Association for the Study of the Liver members representing 48 clinical centers also demonstrated decreased HCV testing, diagnosis, and treatment in 2020 compared with 2019 (prepandemic) [25]. Collectively, these findings underscore the critical importance of ongoing, rigorous, universal HCV screening for case identification and linkage to care. In addition, monitoring the proportion of persons meeting steps in the HCV cascade of care will be critical to assessing the quality of HCV care.

Management of Incomplete DAA Adherence

Incomplete medication adherence is well-known, even in the highly structured clinical trial setting [26, 27]. Recognizing that incomplete DAA treatment may occur in clinical practice and potentially contribute to treatment failure, the HCV guidance includes a new algorithm for the management of incomplete adherence as part of DAA treatment monitoring (see Figure 2). The algorithm is applicable only to DAA treatment-naïve persons and, generally, the same patient populations who are eligible for the simplified treatment algorithms described in the following section. Excluded persons with incomplete adherence should be managed in consultation with a specialist in HCV management.

Although there are few studies examining incomplete medication adherence in the DAA era, data suggest that it is relatively common, occurring in 11% to 40% of persons on treatment [28-31]. Most episodes of nonadherence appear short lived. One study demonstrated that 61% of nonadherent episodes lasted 1 to 2 days [31]. These short periods of nonadherence were not associated with virologic failure. Sustained virologic response (SVR) 12 weeks after the completion of treatment (SVR12) was 94% among both adherent and nonadherent participants, where nonadherence was defined as taking <90% of the total prescribed dosage [31]. Longer periods of nonadherence, however, may adversely affect SVR. Investigators examining the

relationship between premature discontinuation of DAA therapy and SVR found that among study participants with F0 to F3 liver disease, SVR12 was 50% in persons who received <4 weeks of DAA therapy compared with 99% SVR12 in those who received ≥ 4 weeks of treatment [32]. Among participants with compensated cirrhosis, SVR12 rates were 83% and 95% in those who completed <8 weeks of DAA therapy compared with ≥ 8 weeks of treatment, respectively [32].

Based on these limited findings and the expert consensus of the guidance panel, a management algorithm that considers the timing and duration of the nonadherence as well as specific patient factors (ie, genotype 3 infection and presence of compensated cirrhosis) is recommended (see Figure 2). Additional large-scale studies in clinical practice settings that examine the relationship of DAA adherence and SVR12 — including the threshold level of adherence below which SVR12 is adversely affected — are sorely needed.

INITIAL TREATMENT

Simplified HCV Treatment for Treatment-Naive Adults

The guidance panel continues to strongly recommend universal DAA treatment for all people with acute or chronic HCV infection (except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy). A key aspect of facilitating the implementation of this recommendation/goal is expanding the pool of clinicians providing HCV treatment, thereby boosting accessibility and delivery of care. Accordingly and coincident with the accumulation of real-world data and experience with the pangenotypic DAA regimens, the HCV guidance first introduced the simplified treatment algorithms for treatment-naive persons (without cirrhosis or with compensated cirrhosis) in 2019 [5]. The current update to the simplified treatment algorithms features reduced pretreatment and on treatment clinician intervention and expanded eligibility of persons who can be treated using these approaches.

Recent data from a global sample of persons undergoing DAA treatment for chronic HCV infection suggest that a minimal on treatment monitoring approach is safe, effective, and leads to an SVR rate comparable to that realized with standard monitoring [33]. The minimal monitoring (MINMON) approach was examined in an international, phase 4, open-label, single-arm trial. Four hundred treatment-naive participants aged ≥ 18 years with active HCV infection were enrolled from 38 sites in Brazil, South Africa, Thailand, Uganda, and the US. Participants included persons with compensated cirrhosis and HIV coinfection. Key exclusion criteria were pregnancy, breastfeeding, and chronic hepatitis B virus (HBV) infection (hepatitis B surface antigen [HBsAg] positive; due to possible risk of HBV reactivation). However, participants with resolved HBV infection (hepatitis B core antibody [anti-HBc] positive, with or without hepatitis B surface antibodies [anti-HBs]) were eligible. Of the 400 enrolled participants, 399 initiated a planned 12-week course of once daily sofosbuvir (400 mg)/velpatasvir (100 mg). At entry, 42%

(166) were living with HIV, 9% (34) had compensated cirrhosis, and 32% (121/374) with an available HBV panel had resolved HBV infection. The 4 components of minimal monitoring included: (1) no pretreatment genotyping; (2) dispensing the entire treatment course at entry; (3) no scheduled on-treatment visits or laboratory monitoring; and (4) remote contact at week 4 to assess DAA adherence, and at week 22 to schedule SVR assessment at week 24. SVR was achieved by 95% (379/399) of those who initiated treatment. Fourteen participants experienced a serious adverse event between treatment initiation and week 28; none were treatment related or led to treatment discontinuation or death [33].

Given the findings of this minimal monitoring study, treatment-naive persons with HIV/HCV coinfection are newly eligible for a simplified HCV treatment approach. Figure 3 shows the eligibility and exclusion criteria for the simplified HCV treatment approaches. Figure 4 provides an overview of the simplified HCV treatment algorithm for treatment-naive adults without cirrhosis. Figure 5 reviews the simplified treatment algorithm for HCV treatment-naive adults with compensated cirrhosis.

The inclusion of persons living with HIV in the simplified HCV treatment algorithm is consistent with the DHHS Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV [34]. In this guidance, the decision to expand eligibility to include persons living with HIV was informed by the comparable SVR12 rates in those with and without HIV coinfection in the MINMON study [33], the availability of integrase strand transfer inhibitor-based antiretroviral regimens that mitigate concerns of drug-drug interactions between HIV and HCV medications, and the need to expand treatment access, particularly in the COVID-19 pandemic era.

Initial treatment regimens

In the current DAA era of hepatitis C treatment, therapy is safe, effective, of relatively short duration, and curative in most people [1, 17]. Widespread use of recommended initial treatment regimens has the potential to substantially reduce hepatitis C prevalence. Given the many benefits of virologic cure — including reduced risk of cirrhosis, hepatocellular carcinoma, liver-related mortality [35], and all-cause mortality [35-37] — expanded use of DAA treatment and the associated probable cure has the capacity to reduce HCV-related disease burden at individual, national, and potentially global levels.

Since the last published update [5], genotypic activity has been added to the hierarchical ranking of treatment regimens (in addition to recommended or alternative, evidence level, and alphabetical order). Table 1 presents a summary of initial treatment recommendations for treatment-naive adults. Shortening of the duration of glecaprevir/pibrentasvir therapy to 8 weeks for persons with compensated cirrhosis is a notable change. The updated recommendation is supported by the findings from the international, single-arm, open-label, phase 3b EXPEDITION-8 clinical trial [38]. Investigators enrolled 343 treatment-naive participants aged

≥18 years with chronic HCV infection (genotypes 1 through 6) and compensated cirrhosis. Key exclusion criteria included coinfection with HIV and/or HBV, or a history of hepatic decompensation. Participants received an 8-week course of once daily glecaprevir (300mg)/pibrentasvir (120 mg). SVR12 was 98% (335/343) in the intention-to-treat (ITT) population. Seven participants experienced a serious adverse event, only 1 of which was treatment related. One participant who had low baseline leukocyte and neutrophil counts experienced grade 3 leukopenia and neutropenia that presented on posttreatment day 29, which the investigator considered treatment related. No adverse event led treatment discontinuation or death [38].

Another significant change is the recommendation that sofosbuvir/velpatasvir/voxilaprevir may be used as an alternative regimen for persons with genotype 3 infection and compensated cirrhosis. This new recommendation is based on findings from the international, open-label, randomized, phase 3 POLARIS-3 clinical trial and acknowledges limited access to resistance associated substitution (RAS) testing in some settings [39]. Investigators enrolled 220 DAA treatment-naïve participants with genotype 3 infection and compensated cirrhosis who were randomized to 8 weeks of once daily sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of once daily sofosbuvir (400 mg)/velpatasvir (100 mg). SVR12 was 96% in both treatment arms [39].

Initial treatment using elbasvir/grazoprevir for genotype 1a infection was changed from a recommended to an alternative regimen because of the need for baseline RAS testing. Additionally, several regimens are no longer recommended because the therapeutics are either no longer available in the US and/or the regimens have inferior SVR rates compared with currently recommended DAA regimens. These include sofosbuvir and daclatasvir, sofosbuvir and ribavirin, paritaprevir/ritonavir/ombitasvir/dasabuvir, and sofosbuvir, telaprevir, or boceprevir with pegylated interferon and ribavirin.

RETREATMENT

Although DAA therapy is curative for most persons [1, 17], the small percentage of those in whom treatment fails to result in SVR12 require retreatment. Updated retreatment recommendations focus on DAA treatment failures, specifically, sofosbuvir-based regimen failure; glecaprevir/pibrentasvir failure; and multiple DAA failure, including sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir plus glecaprevir/pibrentasvir (see Table 2). Retreatments recommendations for sofosbuvir-based or HCV nonstructural protein 5A (NS5A) inhibitor-based treatment failures in persons with decompensated cirrhosis are also noted in Table 2.

Sofosbuvir-based regimen failure

Generally, persons who have experienced treatment failure with a sofosbuvir-based regimen should be retreated with 12 weeks of sofosbuvir/velpatasvir/voxilaprevir. The exception is persons with genotype 3 infection and compensated cirrhosis for whom the addition of weight-based ribavirin to the regimen is recommended. This recommendation is supported by data from clinical trials [40, 41] and real-world cohorts [42-45]. Glecaprevir/pibrentasvir for 16 weeks can be used as an alternative retreatment regimen [46-48]. This regimen, however, has not been evaluated in persons with genotype 3 infection and prior sofosbuvir/NS5A inhibitor exposure and is, therefore, not recommended for these individuals.

Glecaprevir/pibrentasvir failure

For persons with a prior glecaprevir/pibrentasvir treatment failure, retreatment with glecaprevir/pibrentasvir plus ribavirin and sofosbuvir is a recommended retreatment option. This recommendation is supported by findings from the MAGELLAN-3 clinical trial [49]. This open-label, phase 3b study evaluated the efficacy and safety of once daily glecaprevir (300 mg)/pibrentasvir (120 mg) plus sofosbuvir (400 mg), and twice daily weight-based ribavirin for retreatment of persons with a prior glecaprevir/pibrentasvir treatment failure. Participants with non-genotype 3 infection without cirrhosis and naive to HCV nonstructural protein 3-4A (NS3/4A) protease inhibitors and NS5A inhibitors received 12 weeks of treatment. Those with genotype 3 infection and/or compensated cirrhosis, and/or prior exposure to NS3/4A protease inhibitors and/or NS5A inhibitors received 16 weeks of treatment. SVR12 was 96% (22/23) in the ITT population. One patient experienced a serious adverse event unrelated to treatment. No treatment discontinuations or deaths occurred [49].

Treatment with sofosbuvir/velpatasvir/voxilaprevir for 12 weeks is another recommended option in the setting of prior glecaprevir/pibrentasvir treatment failure. Findings from a prospective, nonrandomized, observational study support this recommendation. Investigators enrolled 31 participants with a history of virologic failure with glecaprevir/pibrentasvir therapy. Participants with compensated cirrhosis were included; those with HBV and/or HIV coinfection were excluded. SVR12 was 94% (29/31) with 12 weeks of once daily sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg). Two participants relapsed at week 4 after completion of therapy. No serious adverse events, treatment discontinuations, or deaths occurred [50]. Although the addition of ribavirin was not evaluated in this study, based on prior studies of DAA failures, addition of weight-based ribavirin to the regimen is recommended for persons with compensated cirrhosis.

Multiple DAA Failures, Including Sofosbuvir/Velpatasvir/Voxilaprevir or Sofosbuvir Plus Glecaprevir/Pibrentasvir

The MAGELLAN-3 clinical trial demonstrated the efficacy (96% SVR12; 22/23) of glecaprevir/pibrentasvir plus sofosbuvir and weight-based ribavirin for heavily DAA-experienced patients, although no sofosbuvir/velpatasvir/voxilaprevir failures were included

[49]. Among patients with a prior sofosbuvir/velpatasvir/voxilaprevir treatment failure, 16 weeks of glecaprevir/pibrentasvir plus sofosbuvir and weight based ribavirin is recommended based on the improved resistance profile of pibrentasvir and high response rate seen with this duration of therapy among genotype 3 infected participants in the MAGELLAN-3 trial [49]. Extension to 24 weeks or longer with this regimen should be considered for persons with factors that may reduce the likelihood of achieving SVR (eg, genotype 3 infection with cirrhosis or prior treatment failure with glecaprevir/pibrentasvir plus sofosbuvir). While there are case report data using this treatment duration [51-54], no clinical trial data are available to support such an approach.

A 24-week course of sofosbuvir/velpatasvir/voxilaprevir plus weight-based ribavirin is also recommended for persons with a prior sofosbuvir/velpatasvir/voxilaprevir treatment failure. Although there are currently no published clinical trial data examining retreatment with sofosbuvir/velpatasvir/voxilaprevir for patients in whom initial therapy with the same regimen failed, a small retrospective, observational study of persons with an initial DAA treatment failure and a subsequent retreatment failure with sofosbuvir/velpatasvir/voxilaprevir included 4 persons who received 24 weeks of sofosbuvir/velpatasvir/voxilaprevir rescue therapy (1 with the addition of ribavirin). SVR12 was 100% (4/4) in this small group of extensively DAA-experienced patients [53]. The recommendation to extend duration of therapy to 24 weeks in conjunction with weight-based ribavirin when retreating with the same DAA regimen (sofosbuvir/velpatasvir/voxilaprevir) is predominantly based on extrapolation from prior studies showing benefit with this strategy in different populations [55].

Retreatment in Patients With Decompensated Cirrhosis

Retreatment of persons with decompensated cirrhosis and a history of DAA-based treatment failure is limited by the inability to use an NS3/4A protease inhibitor (eg, glecaprevir, grazoprevir, voxilaprevir) in the setting of decompensated cirrhosis. Recommendations to retreat with a 24-week course of either sofosbuvir/velpatasvir plus weight-based ribavirin or ledipasvir/sofosbuvir plus weight-based ribavirin are based on the relatively favorable SVR rates (91% to 100%) with these regimens among patients with compensated cirrhosis and prior DAA failure [55-57].

MANAGEMENT OF UNIQUE AND KEY POPULATIONS

The HCV guidance stresses the importance of addressing the special considerations and unmet needs of unique and key populations to achieve significant reductions in the burden of HCV-related disease. This approach aligns with the WHO strategy for achieving hepatitis C elimination targets, which also emphasizes the importance of focusing efforts on populations disproportionately affected by HCV infection, specifically HIV/HCV coinfecting persons, people who inject drugs (PWID), men who have sex with men (MSM), and incarcerated persons [1]. The HCV guidance additionally focuses on the special considerations and unmet needs of other

unique or key populations, namely individuals with acute HCV infection, pregnant persons, children and adolescents, and solid organ transplant recipients. Recommendations for these populations aim to maximize the potential benefits of often missed opportunities to reduce hepatitis C infection incidence and prevalence, personal and societal disease burden, and HCV-related morbidity and mortality.

Hiv/hcv coinfection

Treatment-naive persons living with HIV/HCV coinfection (without cirrhosis or with compensated cirrhosis) are newly eligible for DAA therapy using a simplified treatment algorithm (see Figure 4 and Figure 5). This recommendation is supported by findings from the MINMON clinical trial. Among the 166 HIV/HCV coinfecting study participants, 95% (157/166) achieved SVR12 [33]. Given that people living with HIV are disproportionately affected by HCV infection [58], reducing treatment barriers benefits the affected individuals while furthering the goal of HCV elimination.

Acute hcv infection

The guidance panel reiterates the recommendation that persons with confirmed acute HCV infection (HCV RNA positive) should be treated the same as those with chronic HCV infection without awaiting possible spontaneous clearance (ie, a test-and-treat approach). Given that the incidence of acute hepatitis C in the US increased 124% from 2013 through 2020 [59], treatment of this key population is critical to both HCV prevention and elimination.

Findings from studies evaluating the efficacy of an abbreviated 6 weeks of therapy for acute HCV infection with various DAA regimens, including ledipasvir/sofosbuvir [60, 61], glecaprevir/pibrentasvir [62], and sofosbuvir/velpatasvir [63], have demonstrated largely inferior response rates compared with standard of care. As such, an abbreviated course of DAA therapy is not recommended for acute HCV infection.

HCV in Pregnancy

Following the 2018 HCV guidance recommendation for universal hepatitis C screening during pregnancy [64], the USPSTF and CDC issued largely concurrent recommendations in 2020 [8, 9]. In May 2021, the American College of Obstetricians and Gynecologists issued a practice advisory recommending hepatitis screening for all pregnant persons during each pregnancy [65]. The Society for Maternal-Fetal Medicine endorsed that practice advisory and published a concurring recommendation in September 2021 [66]. Given that the DHHS viral hepatitis national strategic plan specifies expanded implementation of universal hepatitis C screening during pregnancy as an important strategy for actualizing HCV elimination [4], the coalescence of screening recommendations for this key population is an important step toward achieving that goal. Treatment recommendations during pregnancy are largely unchanged from the previous update [5]. Although there have been no published large-scale clinical trials evaluating the safety

of DAA therapy during pregnancy, smaller studies and case series have not demonstrated any safety concerns [67-71]. The guidance panel suggests that DAA treatment may be considered during pregnancy on a case-by-case basis after a discussion of potential risks and benefits.

HCV in Children

Strategies to reduce the burden of HCV-related disease have historically focused on the adult population [72]. Data from a recent modeling study indicate that at least 3.26 million children and adolescents (aged ≤ 18 years) are living with HCV infection worldwide [73]. National hepatitis C incidence and prevalence data among children and adolescents in the US are sparse and/or outdated [73]. However, with the recent increase in HCV infection among women of childbearing age [15, 74-78] comes a coincident risk of increased cases of mother-to-child transmission [76], the primary route of HCV transmission in children [79, 80].

Treatment for HCV infection in children has been revolutionized in recent years, beginning with the US Food and Drug Administration approval of the first DAAs for adolescents in April 2017 [81, 82] to the June 2021 approval of 2 pangenotypic regimens (glecaprevir/pibrentasvir and sofosbuvir/velpatasvir) for children as young as 3 years old [83, 84]. Efficacy and safety data from therapeutic DAA clinical trials conducted in children are largely comparable to those conducted in adults [85-90]. As such, the guidance panel reaffirms its recommendation to treat all HCV-infected children and adolescents aged ≥ 3 years with an approved DAA regimen regardless of disease severity. Treatment and retreatment recommendations for children are shown in Tables 3 and 4, respectively.

Management of HCV After Solid Organ Transplantation

Clinical trial and real-world data provide robust evidence supporting the safety and efficacy of HCV DAA treatment in patients who have undergone solid organ transplantation [91-95]. Discussion of specific clinical scenarios follows. Table 5 shows HCV treatment recommendations posttransplantation.

Treatment of Recurrent HCV Infection Post Liver and Kidney Transplantation

The phase 3, single-arm, open-label MAGELLAN-2 trial evaluated a 12-week course of once daily glecaprevir (300 mg)/pibrentasvir (120 mg) for the treatment of HCV infection (genotypes 1 through 6) among patients without cirrhosis who had undergone liver or kidney transplantation and were ≥ 3 months posttransplantation. Those whose immunosuppressive regimen included cyclosporine $>100\text{mg/d}$ or prednisone $>10\text{mg/d}$ were excluded. Treatment-naïve and -experienced (genotypes 1, 2, 4, 5, 6; prior treatment with interferon-based therapy or sofosbuvir plus ribavirin with or without pegylated interferon) participants were included. Treatment-experienced persons with genotype 3 infection were excluded. Overall SVR12 was 98% (98/100). No treatment-related serious adverse events were reported [91].

Sofosbuvir-based regimens have also shown efficacy in persons who have undergone liver or kidney transplantation [93-96]. Investigators who conducted a real-world observational study evaluating the efficacy and safety of DAA therapy in 179 liver, kidney, or dual liver and kidney transplant recipients reported an SVR12 of 94% (169/179) among participants treated with ledipasvir/sofosbuvir. Adverse events, including acute cellular rejection, were rare [93]. A phase 2, open-label study that evaluated 12 weeks of daily sofosbuvir (400 mg)/velpatasvir (100 mg) in 79 HCV-infected (genotypes 1, 2, 3, 4) liver transplant recipients demonstrated a similar response rate with an SVR12 of 96% (76/79). No treatment-related serious adverse events, transplant rejection episodes, or deaths occurred during the study period [94].

Important drug-drug interactions unique to the posttransplant setting should be addressed prior to initiation of DAA therapy. Cyclosporine significantly increases the area under the curve of elbasvir/grazoprevir [97, 98] as well as sofosbuvir/velpatasvir/voxilaprevir [99] and should not be coadministered with these regimens. Coadministration of glecaprevir/pibrentasvir and cyclosporine >100mg/d is also not recommended [83].

Treatment of HCV-Uninfected Transplant Recipients Receiving Organs from HCV-Viremic Donors

A large disparity persists among people in need of solid organ transplantation and available deceased donor organs [100]. Given that available data support the safety and efficacy of DAA therapy in the posttransplant setting, many transplant centers have begun utilizing solid organs from HCV-positive donors for HCV-negative recipients to increase the pool of available organs [101-106]. The pool of HCV-positive donors includes both HCV-viremic donors (ie, HCV RNA positive) and HCV-seropositive donors (ie, HCV antibody positive, HCV RNA negative [nonviremic]). The use of HCV-positive organs has been shown to be an effective strategy for increasing access to transplantation and reducing wait list time and overall mortality [107-110].

Timing and Treatment of HCV-Viremic Liver Grafts in Nonviremic Recipients

Emerging data supports HCV treatment as early as possible when transplanting an HCV-viremic liver graft into an HCV-seronegative recipient [111]. In a recent multicenter prospective study, 34 HCV-seronegative liver transplant patients underwent transplantation using organs from HCV-positive donors (20 viremic, 14 nonviremic). All recipients of grafts from HCV-viremic donors became viremic by day 3 posttransplantation. DAA treatment was initiated in these graft recipients a median of 27.5 days after transplantation. SVR12 was 100% (20/20). One patient developed acute HCV-related membranous nephropathy on postoperative day 18 (prior to initiation of DAA therapy), ultimately resulting in end-stage renal disease requiring dialysis despite achieving SVR12 [112]. This case highlights the importance of early initiation of DAA therapy posttransplantation to avoid HCV-related complications. The guidance panel recommends initiating therapy at least within 2 weeks after transplantation but preferably within 1 week when the patient is clinically stable.

An abbreviated duration of DAA therapy is currently not recommended for recipients of organs from HCV-viremic donors due to lack of data demonstrating efficacy. The large reservoir of HCV in a transplanted liver graft may be responsible for the lack of efficacy.

Timing and Treatment of HCV-Viremic Non-Liver Grafts in Nonviremic Recipients

HCV treatment should occur as early as possible in HCV-seronegative patients who undergo transplantation with a non-liver graft from an HCV-viremic donor. This strategy reduces the likelihood of hepatic and extrahepatic HCV-related complications in the immediate posttransplant period. The phase 4, open-label, multicenter MYTHIC clinical trial evaluated the efficacy and safety of 8 weeks of once daily glecaprevir (300 mg)/pibrentasvir (120 mg) in 30 HCV-negative kidney transplant recipients who underwent transplantation using a graft from an HCV-viremic donor [113]. Treatment initiation occurred 2 days to 5 days posttransplantation (target was 3 days). All 30 participants achieved SVR12; no HCV-related serious adverse events were reported [113]. Based on this study and others showing benefit(s) associated with early HCV treatment [113-116], use of a prophylactic (immediately prior to transplantation or day 0 posttransplantation) or preemptive (day 0 to day 7 posttransplantation; as soon as the patient is clinically stable) strategy for initiation of DAA treatment is recommended for HCV-negative recipients of a non-liver solid organ graft from an HCV-viremic donor. Note that neither approach requires demonstration of HCV viremia in the transplant recipient.

Shorter durations of DAA-based therapy in this setting are currently under investigation with promising results. These practices, however, are currently not recommended outside of a clinical trial [115, 117, 118].

Outcomes and Process in Transplantation Using HCV-Viremic Donor Grafts in HCV-Seronegative Recipients

Data evaluating longer term patient outcomes after transplantation with an HCV-viremic donor organ have shown encouraging results. Among 51 dual heart/kidney transplant recipients undergoing transplantation with organs from HCV-viremic donors, 1-year survival was comparable to those who received organs from nonviremic donors [119]. Another study that evaluated outcomes among multiorgan transplant recipients (heart/kidney, heart/lung, heart/liver) demonstrated similar 1-year survival among recipients of organs from HCV-viremic donors compared with those who received organs from HCV-negative donors [106].

In an analysis of the United Network for Organ Sharing database, HCV-negative liver transplant patients who received the graft from an HCV-positive donor (viremic and nonviremic) were shown to have superior 1-year graft survival rates compared with those who received a graft from an HCV-negative donor [120]. Notably, HCV-positive donors were statistically significantly younger than their HCV-negative counterparts. Multivariate analysis demonstrated that donor age — but not donor HCV status — was an independent predictor of 1-year graft survival [120].

Extensive informed consent as recommended by the American Society of Transplantation consensus panel [121] and shared decision-making between the patient and clinical team should occur prior to transplantation of an HCV-viremic organ into an HCV-negative recipient. Patients should understand the risk of HCV infection, risk to caregivers from needlestick exposures, as well as success rates and risks of DAA-based therapy [115, 121-125]. Given the breadth of safety and efficacy data now available, institutional review board approved protocols are no longer required. However, based on the unique factors noted, transplant centers should have a specific HCV consent and follow-up process in place.

People who inject drugs

Injection drug use (IDU) is the most common risk factor for HCV infection in North America and Europe. The HCV seroprevalence among PWID ranges from 18% to 88%, depending on geographic location [126] and duration of IDU exposure [127, 128]. IDU accounts for approximately 70% of new HCV infections [59]. Thus, the growing opioid epidemic has become an important force in the perpetuation of the HCV epidemic [1, 2, 4, 14, 16, 59]. Consequently, achieving the goal of HCV elimination depends heavily on diagnosing and treating HCV infection in PWID, and implementing harm reduction strategies to prevent future infections [1, 2, 4, 122, 129-132]. Data from Australia support the efficacy of the treatment as prevention approach among PWID. After implementation of unrestricted access to DAA therapy in 2016, the proportion of PWID diagnosed with active HCV infection who were treated increased from 3% to 47% while the proportion of those with HCV viremia declined from 44% to 17% [133].

Annual HCV testing is recommended for PWID with ongoing IDU regardless of either no prior testing or past negative testing. Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV antibody testing with confirmatory HCV RNA testing and linkage to care for those determined to be HCV infected [132, 134]. PWID with HCV infection should be counseled about measures to reduce the risk of transmission to others and offered linkage to harm reduction services, including intranasal naloxone, needle/syringe service programs, medications for opioid use disorder, and other substance use disorder treatment programs.

Clinical trials and observational studies of PWID reporting current IDU at the start of HCV treatment and/or continued use during therapy demonstrate SVR12 rates approaching 95% [135-140]. The guidance panel strongly asserts that active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment. At least annual HCV RNA testing is recommended for PWID with recent IDU after they have spontaneously cleared HCV infection or have been successfully treated [141-144].

Hiv-uninfected men who have sex with men

While the increased risk of HCV infection among MSM living with HIV is well known [145], acute HCV infections have also been reported among HIV-uninfected MSM presenting for HIV

pre-exposure prophylaxis (PrEP) [146, 147]. HCV testing at HIV PrEP initiation and at least annually thereafter (while on PrEP) is recommended for HIV-uninfected MSM. All MSM should be counseled about the risk of sexual HCV transmission with high-risk sexual and drug use practices, and educated about measures to prevent HCV infection or transmission [148, 149].

Antiviral treatment for HCV-infected MSM should be coupled with ongoing counseling about the risk of HCV reinfection, and education about methods to reduce HCV reinfection risk after cure [150]. At least annual (and risk-based, if indicated) HCV RNA testing is recommended for all high-risk sexually active MSM after successful treatment or spontaneous clearance of HCV infection [151, 152].

Persons in Correctional Settings

Recent cross-sectional surveys suggest that the HCV seroprevalence among incarcerated populations in the US ranges from 3.0% to 34.6% [153], which exceeds the 1.7% HCV seroprevalence in the general population [154]. More than 90% of these persons are eventually released and re-enter the general population, where they can contribute to HCV spread in the community [155, 156] and may have little contact with the healthcare system [157, 158]. Given the high HCV prevalence among persons in the US correctional system, the success of the US HCV elimination effort depends on identifying infected individuals in jails and prisons, linking these persons to medical care for HCV management, and providing access to antiviral treatment [2, 159]. Jails and prisons should therefore implement opt-out HCV testing consisting of HCV antibody testing followed by confirmatory HCV RNA testing if antibody positive. Universal opt-out testing of incarcerated persons for chronic HCV is highly cost-effective and has been shown to reduce ongoing HCV transmission and the incidence of advanced liver disease [160].

DAA treatment for chronic HCV infection is feasible within jail and prison settings and would aid the HCV elimination effort [161, 162]. Chronically infected persons residing in jails should receive counseling about HCV infection and be provided linkage to follow-up community healthcare for evaluation of liver disease and treatment upon release [163-166]. Those whose jail sentence is sufficiently long to complete a recommended course of DAA therapy should receive that treatment while incarcerated [161]. Chronically infected individuals in prison should receive DAA therapy according to AASLD-IDSA guidance while incarcerated [162, 167]. Jails and prisons should facilitate continuation of HCV therapy for persons on HCV treatment at the time of incarceration. HCV treatment in correctional settings is cost-effective because DAAs halt progression of HCV-related liver disease and decrease the risk of cirrhosis, hepatic decompensation, and hepatocellular carcinoma, offsetting future healthcare costs from liver and nonliver complications [168].

Upon release from a correctional facility, HCV-infected persons with advanced hepatic fibrosis or cirrhosis should be provided linkage to community healthcare for surveillance for HCV-related complications. To prevent HCV reinfection and reduce the risk of progression of HCV-

associated liver disease, correctional facilities should provide harm reduction and evidence-based treatment for underlying substance use disorders [169]. Addressing hazardous alcohol use among persons with chronic HCV in a correctional setting may help slow liver disease progression, decrease HCV transmission, and might reduce recidivism.

Funding

The work of the hepatitis C guidance project is supported exclusively by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America.

Acknowledgments

The panel thanks the able staffs of IDSA and AASLD, particularly Jon Heald, Genet Demisashi, Elizabeth Durzy, Audrey Davis-Owino, and Sheila Tynes for project management and administrative support of the HCV guidance project, and Dr. Tina M. St. John for technical and editorial support of the HCV guidance project, and manuscript preparation assistance.

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Potential conflicts of interest. A.I.A has no conflict. D.B. was awarded research grants, paid to her institution, from Gilead Sciences Inc. V.L. has no conflict. J.C.P was awarded research grants, paid to her institution, from Gilead Sciences Inc and Merck & Co Inc. Spouse has interest in stock that is independently managed in AbbVie Inc, Bristol Myers Squibb Co, Johnson & Johnson, and Merck & Co Inc. J.J.F. serves as a scientific consultant to AbbVie Inc, Bluejay Therapeutics Inc, Deep Genomics Inc, Gilead Sciences Inc, GSK Plc, and Janssen Pharmaceutical Companies of Johnson & Johnson; was awarded research grants, paid to his institution, from AbbVie Inc, Alexion AstraZeneca Rare Disease, Altimmune Inc, Eiger Biopharmaceuticals Inc, Enanta Pharmaceuticals Inc, Gilead Sciences Inc, GSK Plc, Janssen Pharmaceutical Companies of Johnson & Johnson, and Fujifilm Wako Chemicals Corp. S.C.G. was awarded research grants, paid to his institution from AbbVie Inc, Gilead Sciences Inc, and Merck & Co Inc. T.H. has no conflict. R.J. participates in the Advisory Board for AstraZeneca/Sanofi, is an Expert Panel Member for Moderna, is a Advisory Board member/Consultant for Seqirus (Flu vaccine), is a Consultant for AstraZeneca (Flu vaccine), is a Consultant for Dynavax (Hep B vaccine), receives royalties from UpToDate (HCV chapter), receives an editorial stipend from PIDS (EiC of JPIDS), and receives a research grant from GSK (rVZV vaccine). M.M.J. served as a scientific consultant (pediatric HCV advisory board) to Gilead Sciences Inc (ceased as of June 2021); was awarded research grants, paid to her institution, from AbbVie Inc, Gilead Sciences Inc, F. Hoffmann-La Roche AG (ceased as of June 2021), and Merck & Co Inc. J.J.K. was awarded research grants, paid to her institution, from Gilead Sciences Inc. B.P.L. has no conflict. T.R.M. was awarded research grants, paid to his institution, from AbbVie Inc, Genfit, Gilead Sciences Inc, and Merck & Co Inc. K.R.R. serves on scientific advisory boards for Spark

Therapeutics, Novo Nordisk, Genfit, BioVie, Mallinckrodt, Served on DSMB-Novartis, Astra

Zeneca; was awarded grants, paid to his institution, from Bristol Myers Squibb Co, Exact Sciences Corp, Grifols, Intercept Pharmaceuticals, Inc, BioVie, Mallinckrodt Pharmaceuticals, Merck & Co Inc, and Sequana Medical Co, HCC-TARGET, NASH-TARGET. A.R.'s organization was awarded educational grants from AbbVie Inc and Gilead Sciences Inc. J. D. S. has personal financial relationships with Gilead Sciences Inc and Premera Blue Cross. G.S.'s organization was awarded grants from AbbVie Inc., Gilead Sciences Inc, and Merck & Co Inc. P.S. has no conflict. N.A.T. has served on the data safety monitoring board of Moderna Inc (ceased as of April 2022); was awarded research grants, paid to her institution, from Gilead Sciences Inc, GSK Plc, Helio Health Group, and F. Hoffmann-La Roche AG (Genentech). E.C.V. serves on an advisory board of Gilead Sciences Inc; was awarded research grants, paid to her institution, from Salix Pharmaceuticals Inc. J.B.W. is a member of the United States Preventive Services Task Force (USPSTF); article does not necessarily represent the views and policies of the USPSTF. A.E.W. has no conflict. K.W. was awarded research grants, paid to her

institution, from Gilead Sciences Inc. D.L.W. was awarded research grants, paid to his institution, from Gilead Sciences Inc. J.P. received grant support, paid to her institution, from AbbVie, Zydus, and Genentech.

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TABLES

Table 1. Recommendations for initial treatment of HCV-infected adults

Regimen	Genotypes	Classification	Duration	Rating	Caveats and Other Considerations
Treatment naive, without cirrhosis or with compensated cirrhosis					
Glecaprevir/pibrentasvir	1 - 6	Recommended	8 weeks	I, A ^a	
Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	I, A ^b	For genotype 3 infection with compensated cirrhosis, NS5A RAS testing is recommended. If baseline NS5A RAS Y93H is present, add weight-based ribavirin or choose another recommended regimen.
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 weeks	I, A ^c	Not recommended for genotype 6e infection if subtype is known.

	1 without cirrhosis	Recommended	8 weeks	I, B	Applicable to patients without cirrhosis who are HIV-uninfected and whose HCV RNA is <6 million IU/mL.
Elbasvir/grazoprevir	1b, 4	Recommended	12 weeks	I, A ^d	
	1a	Alternative	12 weeks	I, A	For genotype 1a infection, NS5A RAS testing is recommended. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), another recommended regimen should be used.
Sofosbuvir/velpatasvir + weight-based ribavirin	3	Alternative	12 weeks	IIa, A	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.

Sofosbuvir/velpatasvir/voxilaprevir		Alternative	12 weeks	IIa, B	Applicable to genotype 3 infection with compensated cirrhosis and baseline NS5a Y93 RAS.
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Treatment naive with decompensated cirrhosis

Sofosbuvir/velpatasvir + weight-based ribavirin	1 - 6	Recommended	12 weeks	I, A ^e	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
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Sofosbuvir/velpatasvir	1 - 6	Recommended	24 weeks	I, A ^e	Applicable to patients who are ribavirin ineligible.
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Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	12 weeks	I, A ^f	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
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Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	24 weeks	I, A ^f	Applicable to patients who are ribavirin ineligible.
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Recommendations are listed by recommended versus alternative, and by genotypic activity, evidence level, and alphabetically.
Abbreviations: CTP, Child-Turcotte-Pugh score; HIV, human immunodeficiency virus; NS5A, hepatitis C virus nonstructural protein 5A; RAS, resistance associated substitution.

- ^a The level of evidence rating is I, B for persons with compensated cirrhosis.
- ^b The level of evidence rating is I, B for persons with genotype 5 or 6 infection.
- ^c The level of evidence rating is IIa, B for persons with genotype 5 or 6 infection, and those with genotype 4 infection and compensated cirrhosis.
- ^d The level of evidence rating is IIa, B for persons with genotype 4 infection and compensated cirrhosis.
- ^e Only available data for genotype 6 infection are in persons with compensated cirrhosis.
- ^f Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

Table 2. Recommendations for retreatment of HCV-infected adults by prior exposure

Regimen	Genotypes	Classification	Duration	Rating	Caveats and Other Considerations
Sofosbuvir-based treatment failure, without cirrhosis or with compensated cirrhosis					
Sofosbuvir/velpatasvir/voxilaprevir	1 - 6	Recommended	12 weeks	I, A	For genotype 3 infection with compensated cirrhosis, add weight-based ribavirin if there are no contraindications.
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Alternative	16 weeks	I, A	Not recommended for patients with

prior exposure to an NS5A inhibitor
plus NS3/4A protease inhibitor
regimen (eg, elbasvir/grazoprevir).

Glecaprevir/pibrentasvir treatment failure, without cirrhosis or with compensated cirrhosis

Glecaprevir/pibrentasvir +
sofosbuvir + weight-based ribavirin

1 - 6 Recommended 16 weeks IIa, B

Sofosbuvir/velpatasvir/voxilaprevir

1 - 6 Recommended 12 weeks IIa, B

For patients with compensated
cirrhosis, addition of weight-based
ribavirin is recommended (rating IIa,
C).

Sofosbuvir/velpatasvir/voxilaprevir or sofosbuvir + glecaprevir/pibrentasvir treatment failure, without cirrhosis or with compensated cirrhosis

Glecaprevir/pibrentasvir +
sofosbuvir + weight-based ribavirin

1 - 6 Recommended 16 weeks IIa, B

Extension to 24 weeks should be
considered in extremely difficult cases

(eg, genotype 3 infection with compensated cirrhosis) or failure following sofosbuvir + glecaprevir/pibrentasvir therapy.

Sofosbuvir/velpatasvir/voxilaprevir + weight-based ribavirin	1 – 6	Recommended	24 weeks	IIa, B
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Sofosbuvir- or NS5A inhibitor-based treatment failure with decompensated cirrhosis

Sofosbuvir/velpatasvir + weight-based ribavirin	1 - 6	Recommended	24 weeks	II, C ^a	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
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Ledipasvir/sofosbuvir + weight-based ribavirin	1, 4, 5, 6	Recommended	24 weeks	II, C ^b	Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
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Recommendations are listed by recommended versus alternative, and by genotypic activity, evidence level, and alphabetically.

Abbreviations: CTP, Child-Turcotte-Pugh score; NS3/4A, hepatitis C virus nonstructural protein 3-4A; NS5A, hepatitis C virus nonstructural protein 5A.

^a Only available data for genotypes 5 or 6 infection are in a small number of persons with compensated cirrhosis.

^b Only available data for genotype 6 infection are in persons with compensated cirrhosis.

Table 3. Recommendations for initial treatment of HCV-infected pediatric patients, without cirrhosis or with compensated cirrhosis

Regimen	Genotypes	Classification	Duration	Rating
Glecaprevir/pibrentasvir	1 - 6	Recommended	8 weeks	I, B
Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	I, B
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 weeks	I, B

Recommendations are listed by genotypic activity, evidence level, and alphabetically.

Table 4. Recommendations for retreatment of HCV-infected pediatric patients, by prior exposure and cirrhosis status

Regimen	Genotypes	Classification	Duration	Rating	Cirrhosis Status
Interferon-based regimen (\pmribavirin) and/or sofosbuvir treatment failure without NS3/4A protease inhibitor or NS5A inhibitor exposure					
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Recommended	8 weeks	I, C	No cirrhosis
Glecaprevir/pibrentasvir	1, 2, 4, 5, 6	Recommended	12 weeks	I, C	Compensated cirrhosis

Glecaprevir/pibrentasvir	3	Recommended	16 weeks	I, C	Without cirrhosis or with compensated cirrhosis
Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	I, C	Without cirrhosis or with compensated cirrhosis
Sofosbuvir/velpatasvir + weight-based ribavirin	1 - 6	Recommended	12 weeks	I, C	Decompensated cirrhosis
NS3/4A protease inhibitor treatment failure without NS5A inhibitor exposure					
Glecaprevir/pibrentasvir	1 - 6	Recommended	12 weeks	I, C	Without cirrhosis or with compensated cirrhosis
NS5A inhibitor treatment failure without NS3/4A protease inhibitor exposure					
Glecaprevir/pibrentasvir	1 - 6	Recommended	16 weeks	I, C	Without cirrhosis or with compensated cirrhosis

Interferon (\pm ribavirin) plus an HCV protease inhibitor treatment failure

Ledipasvir/sofosbuvir	4, 5, 6	Recommended	12 weeks	I, C	Without cirrhosis or with compensated cirrhosis
Ledipasvir/sofosbuvir	1	Recommended	12 weeks	I, C	No cirrhosis
Ledipasvir/sofosbuvir	1	Recommended	24 weeks	I, C	Compensated cirrhosis

Recommendations are listed by genotypic activity, evidence level, and alphabetically.

Abbreviations: NS3/4A, hepatitis C virus nonstructural protein 3-4A; NS5A, hepatitis C virus nonstructural protein 5A.

Table 5. Recommendations for HCV Treatment Posttransplantation

Regimen	Genotypes	Classification	Duration	Rating	Caveats and Other Considerations
Recurrent HCV Post Liver Transplant Without Cirrhosis					
Glecaprevir/pibrentasvir	1 - 6	Recommended	12 weeks	I, B	
Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	I, B	
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 weeks	I, B	

Recurrent HCV Post Liver Transplant With Compensated Cirrhosis

Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	I, B
Glecaprevir/pibrentasvir	1 - 6	Recommended	12 weeks	I, C
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 weeks	I, A

Recurrent HCV Post Kidney Transplant Without Cirrhosis or With Compensated Cirrhosis

Glecaprevir/pibrentasvir	1 - 6	Recommended	12 weeks	I, A ^a IIa, C ^b	
Sofosbuvir/velpatasvir	1 - 6	Recommended	12 weeks	IIa, C	
Ledipasvir/sofosbuvir	1, 4, 5, 6	Recommended	12 weeks	I, A	
Elbasvir/grazoprevir	1, 4	Alternative	12 weeks	I, B	Limited to patients without baseline NS5A RASs for elbasvir.

HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors

Glecaprevir/pibrentasvir	1 - 6	Recommended	12 weeks	I, C	Timing: Initiate treatment within the first 2 weeks posttransplant, preferably within the first week.
Sofosbuvir/velpatasvir	1 – 6	Recommended	12 weeks	I, C	Timing: Initiate treatment within the first 2 weeks posttransplant, preferably within the first week.

HCV-Uninfected Recipients of Non-Liver Solid Organs from HCV-Viremic Donors

Glecaprevir/pibrentasvir	1 - 6	Recommended	8 weeks ^c	I, C	Timing: Initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible. Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.
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Sofosbuvir/velpatasvir	1 – 6	Recommended	12 weeks	I, C	Timing: Initiate treatment prior to HCV RNA results, immediately pretransplant or day 0 posttransplant, if possible. Otherwise, begin on day 0 to within the first week posttransplant when clinically stable.
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Recommendations are listed by genotypic activity, evidence level, and alphabetically.

Abbreviations: HCV, hepatitis C virus; HCV RNA, hepatitis C virus ribonucleic acid; NS5A, hepatitis C virus nonstructural protein 5A; RAS, resistance associated substitution.

^a Rating is based on evidence for persons without cirrhosis.

^b Rating is based on evidence for persons with compensated cirrhosis.

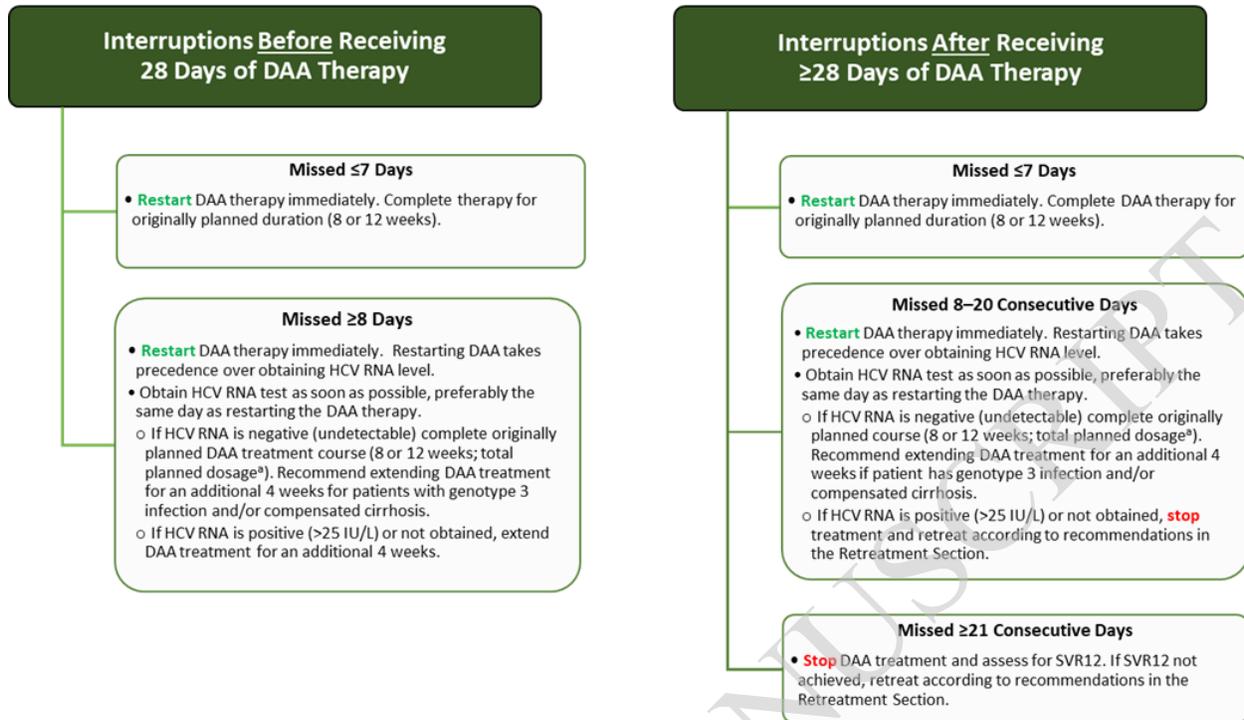
^c If treatment initiation is delayed beyond the first week after transplant, treatment should be extended to 12 weeks.

Figure 1. Key Points Summary

Key Points in Hepatitis C Guidance
<ul style="list-style-type: none">• Universal HCV screening is recommended.• The simplified HCV treatment algorithm now includes persons living with HIV.• A new algorithm for incomplete treatment adherence is included, with a key recommendation for persons who have missed ≤ 7 days of DAA therapy.• HCV treatment is recommended for infected persons residing in jail or prison.• Emerging data highlight the safety and efficacy of HCV DAA treatment in persons who have undergone solid organ transplantation.

Abbreviations: DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

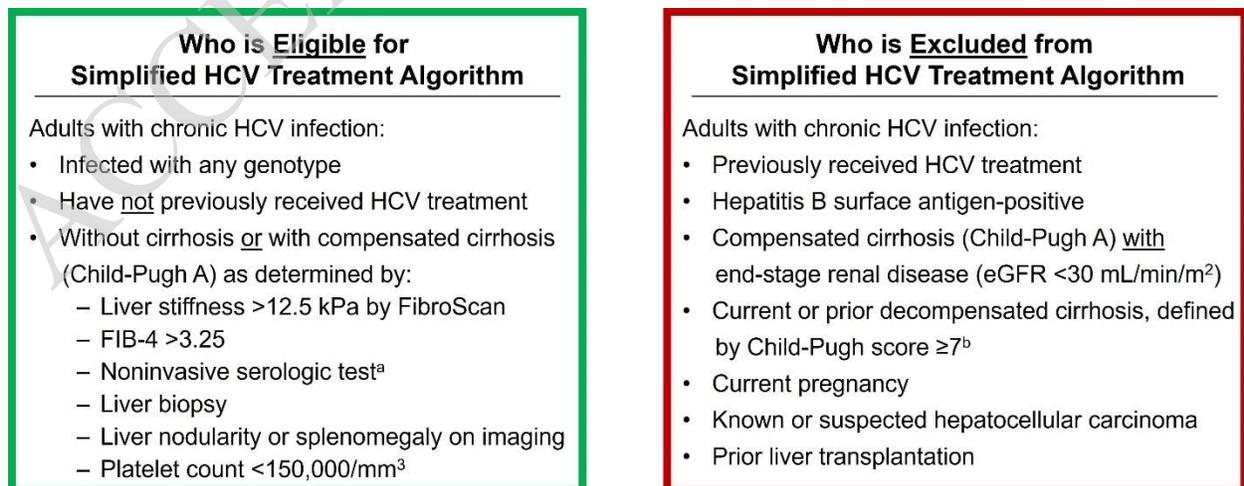
Figure 2. Recommended Management of DAA Treatment Interruptions for Treatment-Naive Patients, Without Cirrhosis or With Compensated Cirrhosis, Receiving Glecaprevir/Pibrentasvir or Sofosbuvir/Velpatasvir



Abbreviations: DAA, direct-acting antiviral; HCV RNA, hepatitis C virus ribonucleic acid; SVR12, sustained virologic response 12 weeks after completion of therapy.

^a Extend duration of therapy such that the patient receives the total planned dosage (ie, the total number of daily pills). For example, if a patient missed 10 days of a planned 8-week course of therapy, treatment would be extended to 8 weeks plus 10 days.

Figure 3. Inclusion and Exclusion Criteria for Simplified HCV Treatment Algorithm

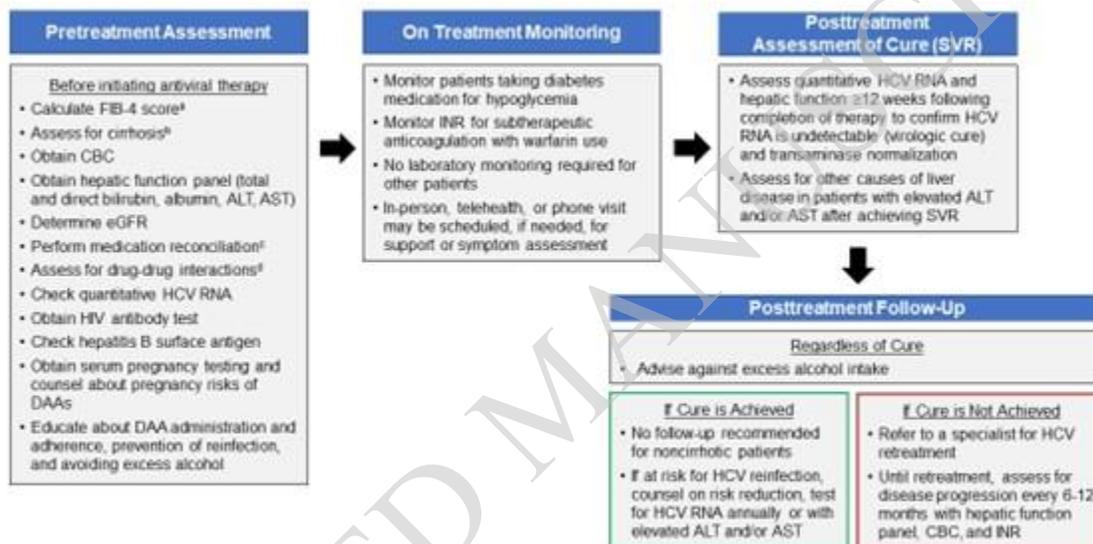


Abbreviations: eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus.

^a Noninvasive serologic tests include HCV FibroSure or Enhanced Liver Fibrosis test.

^b Child-Pugh score based on presence of ascites, hepatic encephalopathy, total bilirubin >2.0 mg/dL, albumin ≤3.5 g/dL, or INR ≥1.7.

Figure 4. Simplified algorithm for HCV treatment among HCV treatment-naive adults without cirrhosis.



Recommended DAA regimens for this simplified treatment approach include either 8 weeks of glecaprevir (300 mg)/pibrentasvir (120 mg) taken with food, or 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg). More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found on the [HCV guidance website](#).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus; HCV RNA, hepatitis C virus ribonucleic acid; INR, international normalized ratio; SVR, sustained virologic response.

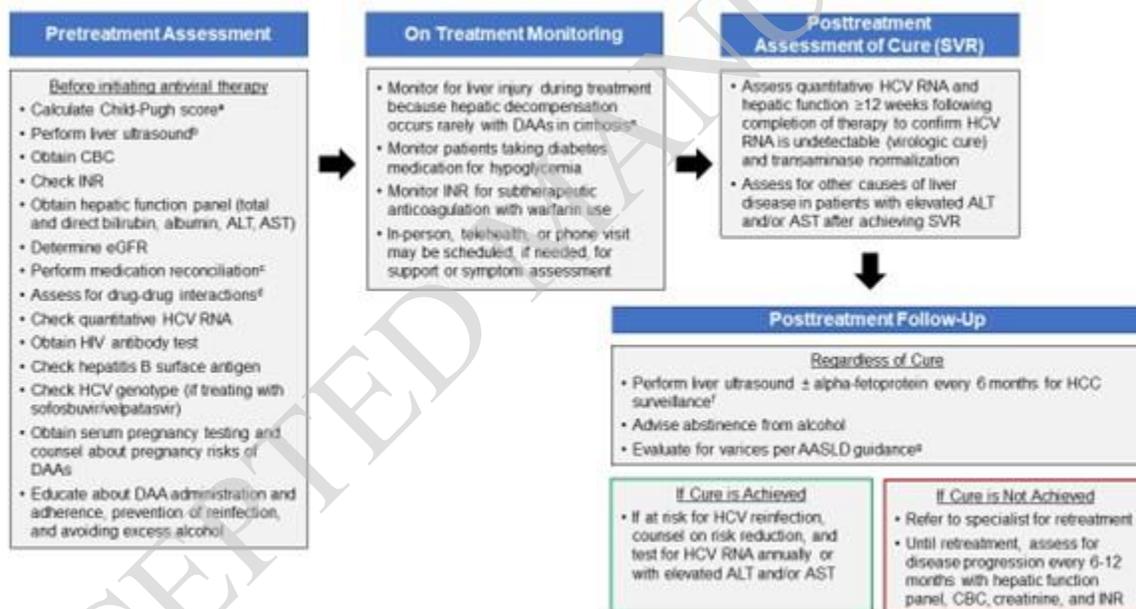
^a FIB-4 is a noninvasive measure of hepatic fibrosis that is calculated by: (age [years] x AST [U/L]) ÷ (platelet count [10⁹/L] x (ALT^{1/2} [U/L])).

^b A patient is presumed to have cirrhosis if they have a FIB-4 score >3.25 or if they any of the following from a previously performed test: (1) transient elastography indicating cirrhosis (ie, liver stiffness >12.5 kPa); (2) noninvasive serologic test above the proprietary cutoff indicating cirrhosis (eg, FibroSure, Enhanced Liver Fibrosis Test); (3) clinical evidence of cirrhosis (eg, liver nodularity and/or splenomegaly on imaging, platelet count <150,000/mm³); or (4) prior liver biopsy showing cirrhosis.

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

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

Figure 5. Simplified algorithm for HCV treatment among HCV treatment-naïve adults with compensated cirrhosis.



Recommended DAA regimens for this simplified treatment approach include either 8 weeks of glecaprevir (300 mg)/pibrentasvir (120) mg taken with food for genotypes 1 through 6, or 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotypes 1, 2, 4, 5, or 6. More detailed descriptions of the patient evaluation process and antivirals used for HCV treatment can be found on the [HCV guidance website](#).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; DAA, direct-acting antiviral; eGFR, estimated glomerular filtration rate; HCC,

hepatocellular carcinoma; HCV, hepatitis C virus; HCV RNA, hepatitis C virus ribonucleic acid; INR, international normalized ratio; SVR, sustained virologic response.

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

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

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

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

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

^f Ultrasound surveillance for hepatocellular carcinoma (with or without alpha-fetoprotein testing) every 6 months is recommended for patients with cirrhosis, in accordance with AASLD guidance.

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