Epidemiology and Definitions

**Epidemiology of Acute HCV:** In the United States, the CDC estimates that during the 1980s, an average of 230,000 new HCV infections occurred each year. By 1989, however, the annual estimated number of new infections declined more than 80% to 36,000 and in 2013 there were approximately 30,000 new cases. Infection with hepatitis C virus (HCV) occurs among persons of all ages, but the highest incidence is found among persons 20 to 39 years of age. The most common risk factor for new HCV infections in the United States is injection drug use (IDU). In addition, acute HCV infections have been increasingly recognized among men who have sex with men, particularly when engaging in unprotected receptive anal intercourse in the setting of methamphetamine use. Among men who have sex with men, the rate of sexual acquisition of HCV is more than 5-fold higher in HIV-infected men than in HIV-uninfected men. The sexually transmitted HCV infections in the HIV-infected population have been associated with methamphetamine use, the practice of serosorting (according to HIV status), sexual practices that may involve mucosal trauma, multiple sexual partners, concurrent sexually transmitted infections, and CD4 cell count less than 500 cells/mm$^3$ in the person who becomes infected.

**Definition of Acute HCV Infection:** Most experts define acute hepatitis C infection as the 6-month time period following acquisition of hepatitis C virus. The definition of acute hepatitis C does not depend on the presence or absence of symptoms associated with the acute infection. The preferred accepted laboratory diagnosis of acute includes documentation of either of the two following criteria:

- A positive (detectable) HCV RNA in conjunction with a negative HCV antibody, or
- Positive HCV antibody with documentation of a negative HCV antibody in the past 12 months
Spontaneous Clearance of HCV following Acute Infection

Following acquisition of hepatitis C, an estimated 20 to 35% persons will have spontaneous clearance of HCV infection; a systematic review of 31 studies performed by Micallef and coworkers found a spontaneous clearance rate of 26%. Investigators have identified multiple factors that predict a higher likelihood of spontaneous clearance: female sex, IL28B CC genotype, presence of jaundice, and a significant decline in HCV RNA in the first four weeks after HCV diagnosis. In contrast, lower rates of spontaneous clearance occur in persons coinfected with HIV. Most studies have shown that if spontaneous clearance occurs, it typically happens within 6 months, with a median time of clearance of 16.5 weeks. Among patients with viremia at 6 months after infection, approximately 90% will go on to have chronic infection. Thus, failure to clear virus by 6 months is a strong predictor of chronic HCV infection. Persons with HIV infection may have delayed clearance of HCV. Since some patients who go on to have chronic HCV may have a transient period with an undetectable HCV RNA level, patients should have a repeat viral level checked if they are found to have an undetectable HCV RNA at any point in the follow-up monitoring; patients with two or more undetectable HCV RNA levels spaced weeks apart can be considered to have spontaneous clearance of HCV.
Acute HCV Treatment Data

Overall, treatment of acute HCV infection has been shown to result in high sustained virologic response (SVR) rates, even prior to the modern era of treatment with direct-acting agents. The SVR rates observed with interferon-based therapy of acute HCV contrasted with the much lower SVR rates observed in chronic HCV. The highest SVR rates have occurred in patients who received treatment within 16 weeks following HCV acquisition. Highly successful outcomes were seen even in typically more challenging populations, including injection drug users and persons with HIV infection. In acute HCV in patients with HIV infection, trials overall showed an SVR rate of 75% using peginterferon with and without ribavirin. There are limited data at this time on the use of newer direct-acting antiviral regimens for acute HCV infection. Several trials are ongoing examining the efficacy of interferon-free treatment in this setting. The following summarizes available data regarding the effectiveness of treatment regimens for persons with acute hepatitis C infection.

- **Interferon**: In this landmark trial, 44 patients with acute HCV infection were treated with standard interferon alpha-2b, 5 million units subcutaneously, daily for 4 weeks, followed by 3 times per week for 20 weeks. The SVR rate was 98%, with 43 of the 44 patients achieving an SVR (Figure 1). In this trial, however, most patients had symptomatic acute HCV, which has been associated with higher spontaneous clearance.

- **Peginterferon**: Studies of peginterferon alpha-2b monotherapy in intent-to-treat analyses showed SVR rates of 71 to 96%. A meta-analysis of 22 studies (n = 1076) using either standard interferon or peginterferon monotherapy reported an overall SVR rate of 78%. In one study involving a 12-week course of peginterferon alfa-2b, SVR rates were higher if treatment was started at week 8 or 12 versus week 20 (Figure 2); the higher SVR12 rate with earlier initiation of therapy may have resulted in part from additional cases of spontaneous clearance that occurred after week 8, but it is possible that patients have an enhanced response if virus is controlled through treatment very early following the acute infection.

- **Peginterferon and Ribavirin**: As the addition of ribavirin to peginterferon became widely used for treatment of chronic HCV, some clinicians used this combination for the treatment of acute HCV. Given the lack of clinical data supporting this combination for treatment of acute HCV, there remains no clear benefit for adding ribavirin to either interferon or peginterferon in patients with acute HCV.

- **Peginterferon and Ribavirin plus a Protease Inhibitor**: As part of the New York Acute Hepatitis C Surveillance Network, HIV-infected men with acute HCV genotype 1 were treated with peginterferon and ribavirin plus telaprevir for 12 weeks, with 16 (84%) of 19 patients achieving an SVR, as compared to historical patients from the same network previously treated with peginterferon and ribavirin with 30 (63%) of 48 obtaining an SVR. In the Dutch Acute HCV in HIV study (DAHHS), HIV-infected patients with acute genotype 1 HCV infection received treatment with a 12-week course of peginterferon and ribavirin plus boceprevir. Preliminary results showed an SVR12 in 21 (78%) of 27 patients; among those with a rapid virologic response at week 4, SVR12 was achieved in 18 (95%) of 19.

- **Sofosbuvir plus Ribavirin**: In an ongoing trial in Australia and New Zealand, DAA-based Therapy for Recently Acquired Hepatitis C II study (DARE C II), approximately 20 persons with recently acquired HCV infection will receive a 6-week course of sofosbuvir plus ribavirin to address the effectiveness of short-course regimens in this setting. In the SWIFT-C study, an estimated 44 HIV-infected persons with acute HCV are being randomized to treatment with either an 8-week or 12-week treatment course with sofosbuvir plus ribavirin.

- **Ledipasvir-sofosbuvir**: The HepNet Acute HCV IV study, which is underway in Germany, is investigating the effectiveness of a 6-week course of ledipasvir-sofosbuvir in an estimated 20 patients with acute HCV genotype 1 HCV infection.
Considerations before Initiating Treatment for Acute HCV

Multiple factors should be considered prior to initiating treatment of hepatitis C in persons diagnosed with acute hepatitis C.

- **Clinical Features**: Determine the date of illness onset, whether jaundice or other symptoms consistent with acute viral hepatitis were present, and the results of testing for hepatic aminotransferase levels. If possible, review prior laboratory studies (aminotransferase levels and hepatitis C antibody testing) to assess the likelihood that current symptoms are due to a newly acquired infection. The presence of new hepatic aminotransferase elevation and documented HCV antibody seroconversion should be explored.

- **Risk Factors for Infection**: All confirmed cases of acute hepatitis C should be interviewed to identify any risk factors for acquiring HCV infection during the 2 weeks to 6 months prior to illness onset. Knowledge of risk factor status is important from an epidemiology perspective and it can help identify individuals who may have high risk of HCV transmission. Assessment of HCV forward transmission risk could factor in when deciding whether to treat HCV in the acute infection setting.

- **Pregnancy Status of HCV-infected Women of Childbearing Age**: It remains unclear whether women with acute HCV infection during pregnancy are at greater risk of transmitting HCV infection to their child than women with chronic HCV infection. No post-exposure prophylaxis is available to prevent perinatal transmission of HCV. Children born to women who test positive for antibodies to HCV (anti-HCV) should be tested for HCV infection.

- **Counseling and Referral for Follow-Up**: Persons with acute Hepatitis C should receive counseling on how to reduce their risk of transmitting HCV to others, minimize exposure to any agents that are hepatotoxic, and the necessity of follow-up to determine the outcome of their infection. Those with ongoing injection drug use should have a referral to an addiction medicine specialist.

- **Assessment for Likelihood of Adherence**: If treatment during the acute period is being considered, it is important to assess the patient's understanding regarding the importance of adherence with therapy, as well as to address any barriers that may negatively impact adherence.

- **IL28B Genotype**: Patients with IL28B CC genotype are more likely to spontaneously clear the acute HCV than those with the CT or TT genotype. Nevertheless, it is unclear if knowledge of IL28B status would change the clinical approach to patients with acute HCV infection and existing guidelines do not include IL28B testing as part of the evaluation of patients with acute HCV infection.

- **Drug-Drug Interactions**: All persons who are being considered for treatment of acute HCV should have an evaluation of current medications to identify any potential for drug-drug interactions, particularly for HIV-infected persons on antiretroviral therapy.
Guidance for Treatment of Acute HCV Infection

In the era prior to the new highly effective direct-acting antiviral agents, treatment of acute HCV generated significantly higher SVR rates than with treatment of chronic HCV, particularly with genotype 1 infection. With the availability of highly effective and well-tolerated direct-acting antiviral agents, the major advantage of treating acute HCV infection versus chronic HCV (in terms of SVR response rates) no longer exists. The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) guidance on the Recommendations for Testing, Managing, and Treating Hepatitis C addresses the approach to patients with acute HCV infection in the Management of Acute HCV section. For a summary of the Recommendations for Management of Acute HCV Infection, see the Summary Box. The following summary highlights several key recommendations from the AASLD/IDSA guidance on managing patients with acute HCV infection.

- **Monitoring for Spontaneous Clearance**: All patients with acute HCV should have HCV RNA monitoring every 4 to 8 weeks for a minimum of 16 weeks. If the decision is made to delay treatment for a patient with acute HCV infection, then monitoring for spontaneous clearance should extend out to 6 to 12 months after infection. In either circumstance, if spontaneous clearance of HCV occurs, then treatment of acute HCV is not recommended. Note that because HCV RNA levels may fluctuate in acute HCV infection, a single negative HCV RNA is not considered adequate to document spontaneous clearance.

- **Approach to Patients with Acute HCV**: Two main treatment options exist when managing patients with acute HCV infection: (1) treat acute HCV but only after monitoring out to 12 to 16 weeks to allow the patient to have adequate time for spontaneous HCV clearance; or (2) defer any treatment decisions until after 6 months.

- **Patients with Potential Benefit for Treatment of Acute HCV**: The rationale for treatment in the acute period may include (1) to prevent transmission to others (injection-drug users or surgeons), (2) to minimize the risk of developing severe hepatic complications from acute infection, as may occur in persons with underlying cirrhosis, or (3) to capitalize on the treatment opportunity in a person who may become lost to follow-up.

- **Treatment Regimens for Patients with Acute HCV**: If the decision is made to treat a patient with acute HCV infection (within 6 months of the HCV infection), the same regimens should be used as recommended for the initial treatment of patients with chronic hepatitis C.

- **Treatment Regimens for Patients after 6 Months**: If treatment takes place after 6 months following infection, the patient should be considered to have chronic HCV infection and the treatment approach and regimens would be the same as when treating chronic HCV.
Summary Points

- Treatment of acute HCV infections has shown high SVR rates (71 to 98%) with the use of standard interferon or peginterferon, with and without ribavirin.
- The limited data on protease inhibitor-based treatment regimens for genotype 1 acute HCV suggest the main benefit may be in a shorter duration of therapy.
- Interferon-free regimens using all-oral direct-acting antiviral agents for acute HCV are currently under study in acute HCV infection. Two studies are using sofosbuvir plus ribavirin for durations of 6, 8 or 12 weeks. One study is examining the use of ledipasvir-sofosbuvir for 6 weeks.
- Since 20 to 35% of persons will spontaneously clear HCV in the first year after infection, all patients with acute HCV should have monitoring of HCV RNA levels every 4 to 8 weeks for a minimum of 12 to 16 weeks (if acute treatment initiated) and out to 6 to 12 months if acute treatment not initiated.
- If the decision to treat acute HCV infection is made, the AASLD/IDSA guidance recommends using the same regimens as for treatment of chronic HCV infection.
- In the current era, the early initiation of acute HCV treatment may pose less of an advantage for efficacy of viral clearance given the safety and very high efficacy of currently available direct-acting antiviral agents. The possible efficacy benefits of early acute HCV treatment and the potential public health benefits of reducing transmission must be balanced with the importance of avoiding unnecessary therapy in those individuals who will go on to clear virus spontaneously.
- If the decision to treat acute HCV infection is made, the AASLD/IDSA guidance recommends using the same regimens as for treatment of chronic HCV infection, with the exception that peginterferon (with or without ribavirin) is considered an alternative option in this setting.
- If treatment is initiated after 6 months, the AASLD/IDSA guidance recommends using the same treatment regimens as for chronic HCV.
References

- AASLD/IDSA. Recommendations for testing, management, and treating hepatitis C. Management of acute HCV infection. [AASLD/IDSA Hepatitis C Guidance]

- American Association for the Study of Liver Diseases, the Infectious Diseases Society of America, and the International Antiviral Society-USA. Recommendations for testing, management, and treating hepatitis C. [Hepatitis C Guidance]


- Hullegie SJ, Classen M, van den Berk GE, et al. SVR12 results after 12w Boceprevir + P/R in Dutch Acute Hepatitis C in HIV Study. [2015 CROI Conference] -


In this study, 44 patients with acute HCV infection received 5 million U interferon alpha-2b given subcutaneously daily for 4 weeks, followed by 3 times per week for 20 weeks. The graph shows the cumulative incidence of undetectable (lower limit 600 copies/ml) serum HCV levels during treatment and in follow-up. Hepatitis C virus levels were measured by reverse transcriptase polymerase chain reaction (RT-PCR). The mean baseline HCV RNA level was 420,000 copies/ml. Sixty-one percent of the patients had genotype 1A. The mean time from infection to the start of therapy was 89 days.

Figure 2 Peginterferon alfa-2b for 12 Weeks in Patients with Acute HCV

In this study, investigators treated patients with acute HCV infection with 1.5 mcg/kg of peginterferon alpha-2b given subcutaneously once weekly for 8 weeks. The treatment was initiated at either week 8, 12, or 20 after initial HCV infection. This graph shows SVR 12 responses. Patients who had spontaneous clearance after randomization but before initiation of treatment are not included in this graph.