Treatment of Acute HCV Infection

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Section 6: Treatment of Key Populations and Unique Situations
Topic 1: Treatment of Acute HCV Infection

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Background

Epidemiology of Acute HCV

In the United States, during the 1980s, an estimated average of 230,000 new hepatitis C virus (HCV) infections occurred each year.[1] After 1989, however, the annual estimated number of new infections steadily declined until 2005, followed by a leveling off between 2006-2010, and then a steady increase from 2011 to 2016 (Figure 1).[1,2] The Centers for Disease Control and Prevention data shows new annual HCV infections in the United States increased approximately 4-fold from 2005 to 2016, with a peak of 41,200 new infections in 2016 (Figure 2).[1] New HCV infections have the highest incidence among persons 20 to 39 years of age. The current opioid epidemic in the United States is the predominant force driving the increase in new HCV infection.[3,4] In addition, an increase in acute HCV infections has been recognized among men who have sex with men, particularly men living with HIV infection who engage in condomless anal intercourse and use methamphetamine.[5]

Definition of Acute HCV Infection

Most experts define acute HCV infection as the 6-month time period following acquisition of HCV.[6,7,8] The definition of acute HCV infection does not depend on the presence or absence of symptoms associated with the acute HCV infection. The preferred accepted laboratory diagnosis of acute HCV infection 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

Risk Factors for Recent Acute HCV Acquisition

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 factors is important from an epidemiology perspective and can help identify individuals who may be at high risk of transmitting HCV to others. Assessment of ongoing HCV transmission risk may need to be considered in the decision to treat HCV in the acute infection setting.

Differentiating Acute HCV infection from HCV Reinfection

Although reinfection with HCV after SVR is uncommon, it can occur, especially for persons who continue or resume activities that place them at risk for acquiring HCV.[9,10] Individuals with HCV infection who achieve an SVR will have a permanently positive HCV antibody test. Therefore, for persons with HCV who achieved an SVR (at 12 weeks or later after completing HCV treatment), a diagnosis of HCV reinfection is based on the new presence of HCV RNA.[11] It is important to

distinguish reinfection from relapse following an undetectable HCV RNA at the end-of-treatment; when relapse occurs, it almost always occurs within the first 12 weeks after completing therapy. Therefore, if an individual has an SVR at 12 weeks or later after completing treatment and subsequently has detectable HCV RNA, a diagnosis of HCV reinfection should be suspected. In this situation, an HCV genotype should be ordered and compared to genotype of HCV in the initial HCV infection. The finding of distinct genotypes confirms reinfection. Note, however, that persons can become reinfected with the same genotype and thus finding the same HCV genotype does not rule out reinfection. Viral sequence analysis can differentiate HCV infections that are the same genotype, but this test is not routinely performed for clinical purposes.[11]

Spontaneous Clearance of HCV Following Acute Infection

Following acquisition of hepatitis C, an estimated 20 to 35% of persons will have spontaneous clearance of HCV infection.[12,13,14] Investigators have identified multiple factors that predict a higher likelihood of spontaneous clearance: female sex, IL28B CC genotype, white race, presence of jaundice, and a low peak HCV RNA level during early HCV infection.[12,15,16,17] In contrast, lower rates of spontaneous clearance occur in persons of black race and those coinfected with HIV.[15,18] Studies have shown that if spontaneous clearance occurs, most have clearance within 6 months—failure to clear HCV by 6 months is a strong predictor of chronic HCV infection, except in persons with HIV coinfection, who often have delayed clearance of HCV.[18]

Comprehensive Clinical Care during Workup for Acute HCV

Additional Laboratory Evaluation

During the initial evaluation for possible acute HCV infection, all persons should also have the following tests performed:

- Testing for HIV infection, (even if previously negative)
- Testing for acute HBV infection (HBsAg, HBcAb IgM, HBcAb IgG), unless previously documented to have a positive and sufficient hepatitis B surface antibody titer
- Comprehensive testing for sexually transmitted diseases if their risk factor for acute HCV was sexual activity

Consideration for HIV Preexposure Prophylaxis

Regardless of whether a patient suspected of acute HCV infection does or does not have HCV, they should be evaluated and considered for HIV preexposure prophylaxis (PrEP), since persons engaging in activities that place them at risk for acquiring acute HCV will also have risk for acquiring HIV infection.

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 antiviral (DAA) medications. Studies of peginterferon alpha-2b monotherapy in intent-to-treat analyses showed SVR rates of 71 to 96%.[19,20] A meta-analysis of 22 studies (n = 1,075) using either standard interferon or peginterferon monotherapy reported an overall SVR rate of 78%.[19] The SVR rates observed with interferon-based therapy of acute HCV are significantly higher than SVR rates observed with interferon- or peginterferon-based treatment of chronic HCV. With interferon-based therapy, the highest SVR rates in the acute infection setting have occurred in persons who received treatment within 12 weeks following acute HCV diagnosis.[20,21] Highly successful outcomes were seen even in typically more challenging populations, including injection drug users and persons with HIV infection. There are limited data at this time on the use of newer DAA regimens for treatment of acute HCV infection. The following summarizes available data regarding the effectiveness of treatment regimens for persons with acute HCV infection.

DAA Regimens for the Treatment of Acute and Recent HCV

- **Sofosbuvir plus Ribavirin (DARE-C II)**: In an open-label trial in Australia and New Zealand, investigators enrolled 19 participants with recent HCV infection (defined duration of infection less than 12 months) to receive a 6-week treatment course of sofosbuvir plus ribavirin.[22] Of those enrolled, (74%) had HIV coinfection and 68% had HCV genotype 1 infection. The median baseline HCV RNA level for participants was 252,000 IU/mL. Only 6 of 19 (32%) subjects achieved an SVR12 and treatment outcome correlated with HIV status and baseline HCV RNA level (Figure 3).[22]
- **Sofosbuvir plus Ribavirin (SWIFT-C)**: This open-label trial enrolled 17 men living with HIV who developed acute HCV infection.[23] All subjects received a 12-week course of sofosbuvir plus ribavirin for treatment of acute HCV.[23] Most subjects (88%) had HCV genotype 1. Overall, only 10 of 17 (59%) subjects achieved an SVR12 and all treatment failures resulted from virologic relapse (Figure 4).[23] Among those enrolled, the median baseline HCV RNA level was 2,280,000 IU/mL.
- **Ledipasvir-Sofosbuvir (HepNet Acute HCV IV)**: This prospective, single-arm study enrolled 20 individuals in Germany with acute HCV genotype 1 monoinfection.[24] All subjects enrolled received ledipasvir-sofosbuvir for 6 weeks and 20 of 20 (100%) achieved an SVR12 (Figure 5).[24] At baseline, 15 of 20 (75%) subjects had HCV RNA levels less than 100,000 IU/mL and only 2 had HCV RNA levels greater than 1 million IU/mL.[24]
- **Ledipasvir-Sofosbuvir**: In this open-label, single arm study, 26 men living with HIV in Germany or England who were diagnosed with acute HCV genotype 1 or 4 infection were treated with a 6-week course of ledipasvir-sofosbuvir.[25] Overall, 20 of 26 (77%) study participants achieved an SVR12 (Figure 6).[25]
- **Ombitasvir-Paritaprevir-Ritonavir and Dasabuvir (TARGET-3D)**: This open-label, single arm study enrolled 30 persons in Australia, England, and New Zealand with recent (duration less than 12 months) HCV infection to receive treatment with an 8-week course of ombitasvir-paritaprevir-ritonavir and dasabuvir.[26] Most (77%) of the participants had HIV coinfection and 93% had genotype 1a HCV infection.[26] Overall, 29 of 30 (97%) persons achieved an SVR12; the one failure occurred in a participant who withdrew from the study after 2 weeks of therapy. The median baseline HCV RNA was approximately 510,200 log IU/mL and 13 of 30 (43%) participants had a baseline HCV RNA greater than 1,000,000 IU/mL.[26]

Clinical Trials for the Treatment of Acute or Recent HCV

- **Elbasvir-Grazoprevir (DAHHS-2 II)**: In this phase 3, open-label trial, Dutch investigators plan to evaluate the efficacy of an 8-week course of elbasvir-grazoprevir in 86 adults living with HIV who develop acute HCV genotype 1 or 4 infection (NCT02600325).

- **Elbasvir-Grazoprevir (SAHIV)**: In this phase 2, open-label trial, French investigators plan to is evaluate the efficacy of an 8-week course of elbasvir-grazoprevir in 30 adults living with HIV who develop acute HCV genotype 1 or 4 infection (NCT02886624).
- **Glecaprevir-Pibrentasvir (TARGET-3D Part II)**: In this phase 3, open-label study, investigators plan to enroll 30 adults with recent HCV infection (acquired within 12 months) to receive treatment with a 6-week course of glecaprevir-pibrentasvir (NCT02634008).
- **Glecaprevir-Pibrentasvir (TARGET-3D Part III)**: In this phase 3, open-label trial, investigators plan to enroll 30 adults with recent HCV infection (acquired within 12 months) to receive treatment with a 4-week course of glecaprevir-pibrentasvir (NCT02634008).
- **Sofosbuvir-Velpatasvir (REACT)**: In this phase 3, randomized, international study, investigators plan to enroll 250 adults who inject drugs who are diagnosed with recent HCV infection to receive treatment with sofosbuvir-velpatasvir for either 6 or 12 weeks (NCT02625909).

Treatment of Acute HCV with Interferon-Based Therapy

- **Interferon**: In this trial, 44 adults 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.[27] Overall, an SVR occurred in 43 of 44 (98%) of persons who received treatment (Figure 7).[27] Note that most participants had symptomatic acute HCV, which has been associated with higher spontaneous clearance.[27]
- **Peginterferon**: In a 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 8).[28] 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 an enhanced SVR response rate occurs if HCV is controlled through treatment very early following the acute infection.[28]
- **Peginterferon and Ribavirin plus Telaprevir**: As part of the New York Acute Hepatitis C Surveillance Network, men with HIV infection who developed acute HCV genotype 1 were treated with peginterferon and ribavirin plus telaprevir for 12 weeks, with 16 of 19 (84%) participants achieving an SVR12, as compared to 30 of 48 (63%) in historical controls who were treated with peginterferon and ribavirin.[29]
- **Peginterferon and Ribavirin plus Boceprevir:** In the Dutch Acute HCV in HIV study (DAHHS), persons with HIV infection who developed acute genotype 1 HCV infection received treatment with a 12-week course of peginterferon and ribavirin plus boceprevir.[30] Preliminary results showed an SVR12 in 21 of 27 (78%) participants; among those with a rapid virologic response at week 4, an SVR12 was achieved in 18 of 19 (95%).

AASLD-IDSA Guidance for Management of Acute HCV Infection

In the era prior to the new highly effective direct-acting antiviral agents, treatment of acute HCV generated markedly higher SVR12 rates than with treatment of chronic HCV.[27,28,31] With current DAA therapy, however, SVR12 rates are generally greater than 95% in persons with chronic HCV [32,33] Thus, the prior advantage of treating acute HCV infection versus chronic HCV (in terms of SVR12 rates) no longer exists. For these reasons, most experts recommend waiting at least 6 months after HCV acquisition to allow adequate time for spontaneous HCV clearance. The most compelling reason for immediate treatment is to impact HCV transmission risk in a person imminently likely to transmit HCV to others. The American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD-IDSA) Hepatitis C Guidance addresses the approach to treating individuals with acute HCV infection.[8] The following summary highlights key recommendations from the AASLD-IDSA guidance on managing persons with acute HCV infection.[8]

- **Monitoring for Spontaneous Clearance**: Persons with acute HCV should have HCV RNA monitoring every 4 to 8 weeks for 6 to 12 months to determine if spontaneous HCV clearance occurs. Note that HCV RNA levels may fluctuate in acute HCV infection, and a single negative HCV RNA is not considered adequate to document spontaneous HCV clearance.
- **Approach to Persons with Spontaneous HCV Clearance**: Persons who spontaneously clear HCV do not require treatment of HCV.
- **Treatment Approach to Persons with Acute HCV:** The main HCV treatment options for managing persons with acute HCV infection are: (1) defer any HCV treatment decisions until at least 6 months to see if spontaneous HCV clearance occurs, or (2) treat during the acute HCV infection period after monitoring for 12 to 16 weeks to allow time for possible spontaneous HCV clearance. Unless extenuating circumstances exist (as outlined below), the recommended approach is to defer treatment decisions for at least 6 months after HCV acquisition. Treatment should only be initiated in persons with persistently positive HCV RNA levels.
- **Circumstances that May Warrant Early Treatment**: Situations that may warrant treatment in the acute infection period (prior to 6 months of waiting for possible spontaneous clearance) include: (1) to prevent transmission to others (e.g. person who injects drugs, a surgeon, or a man coinfected with HIV who has sex with other men), (2) to minimize the risk of developing severe hepatic complications from acute infection, as may occur in persons with underlying cirrhosis who become acutely infected with HCV, or (3) to capitalize on the treatment opportunity in a person who may become lost to follow-up.
- **Treatment Regimens for Persons with Acute or Recent HCV**: If the decision is made to treat a patient in the acute infection period (within 6 months) or in the 6-12 month after HCV acquisition, the recommended DAA regimens and duration of therapy are the same as those recommended for the initial treatment of individuals with chronic HCV.
- **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.

Summary Points

- Since 20 to 35% of persons will spontaneously clear HCV in the first year after infection, persons with acute HCV should have monitoring of HCV RNA levels every 4 to 8 weeks for a minimum of 6 to 12 months, unless extenuating circumstances warrant earlier treatment.
- Individuals undergoing workup for acute HCV infection should also be evaluated for acute or new HBV and HIV infection; if their risk for acquiring HCV was through sexual contact, the evaluation should also include comprehensive testing for sexually transmitted infections.
- Persons with ongoing activities that place them at risk for acquiring HCV infection also are at risk of acquiring HIV infection and thus should be carefully considered for HIV PrEP.
- If the decision to treat acute or recent HCV infection is made, the AASLD-IDSA guidance recommends using the same regimens as for initial treatment of chronic HCV infection.
- In the current DAA era, the early initiation of acute HCV treatment provides no real advantage with regard to SVR12 rates.
- 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 or recent HCV infection is made, the AASLD-IDSA guidance recommends using the same regimens as for initial treatment of chronic HCV infection.

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Figures

Figure 1 New HCV Infections in United States, 1982-2016

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.

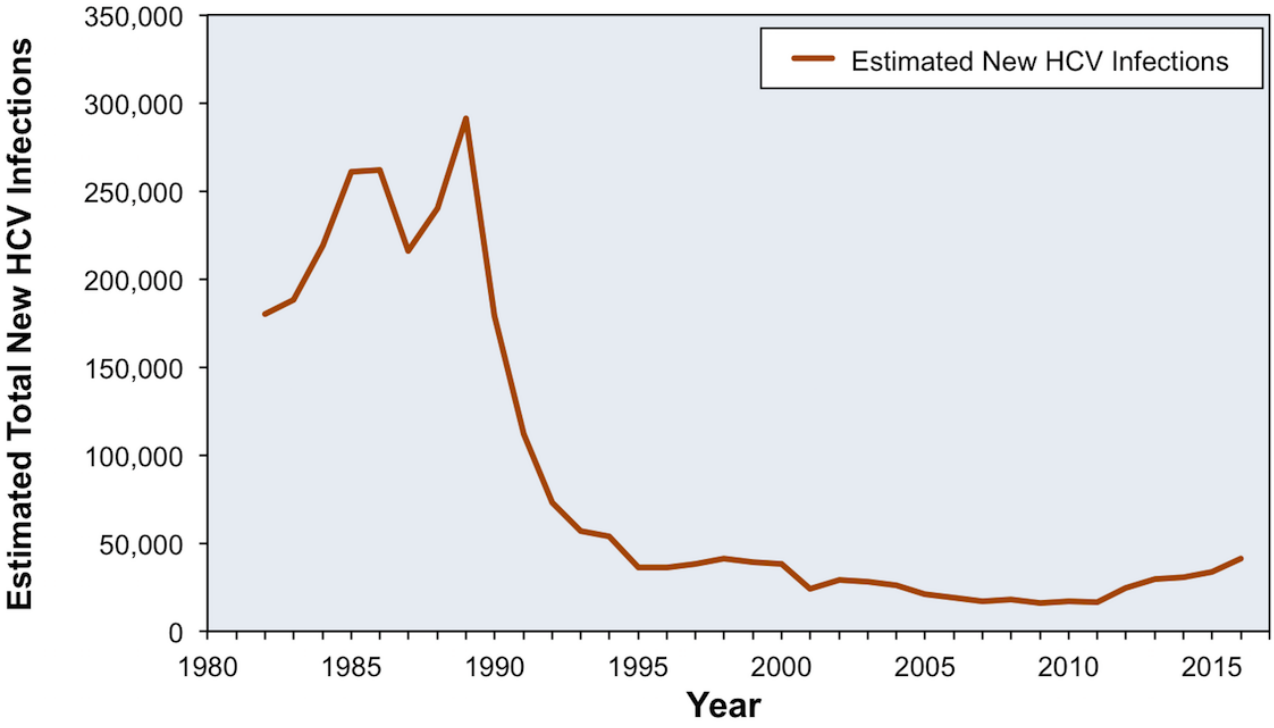

Figure 2 New HCV Infections in United States, 2005-2016

Source: Centers for Disease Control and Prevention. Division of Viral Hepatitis. Statistics and Surveillance.

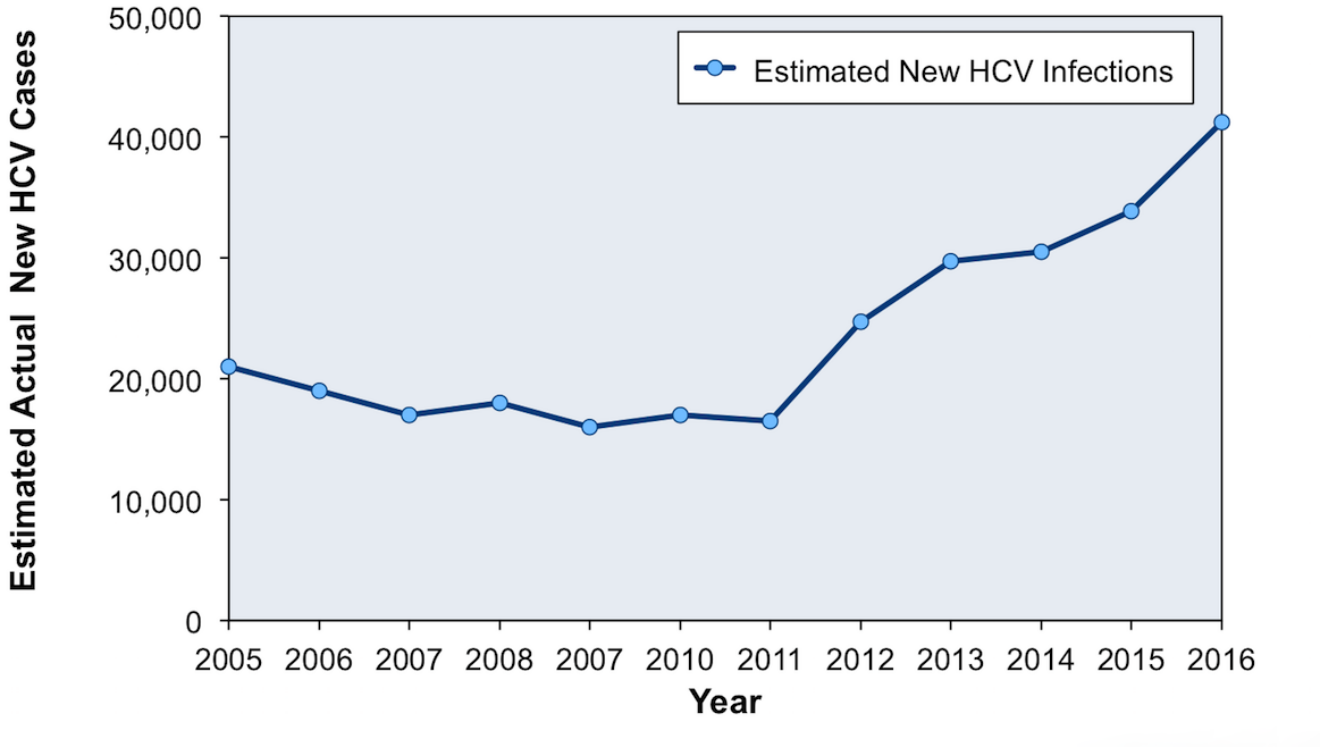

Figure 3 Sofosbuvir plus Ribavirin for 6 Weeks in Adults with Acute HCV

This graph shows overall poor overall SVR12 rates in persons with acute HCV infection treated with a 6-week course of sofosbuvir and ribavirin. The treatment responses correlated with HIV status and baseline HCV RNA levels.

Source: Martinello M, Gane E, Hellard M, et al. Sofosbuvir and ribavirin for 6 weeks is not effective among people with recent hepatitis C virus infection: The DARE-C II study. Hepatology. 2016;64:1911-1921.

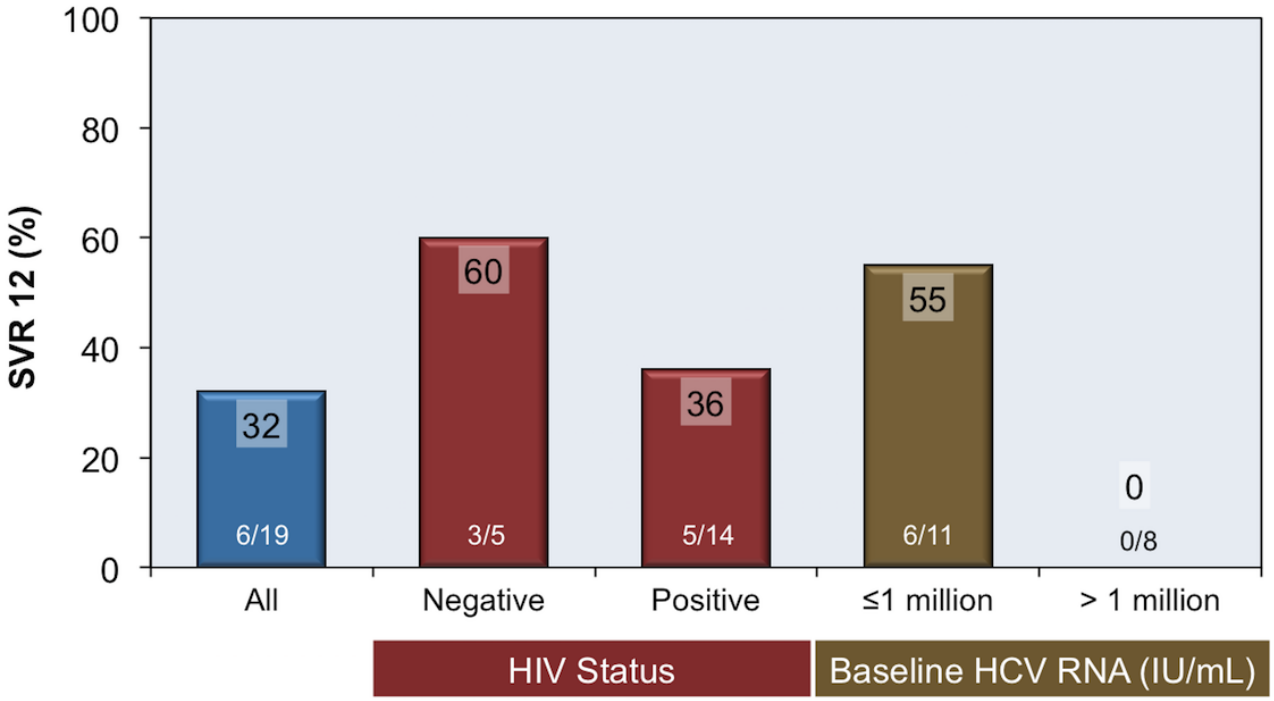

Figure 4 Sofosbuvir plus Ribavirin for 12 Weeks in Adults with Acute HCV

This graphic shows that all sofosbuvir plus ribavirin treatment failures occurred due to virologic relapse.

Source: Naggie S, Marks KM, Hughes M, et al. Sofosbuvir Plus Ribavirin Without Interferon for Treatment of Acute Hepatitis C Virus Infection in HIV-1-Infected Individuals: SWIFT-C. Clin Infect Dis. 2017;64:1035-1042.

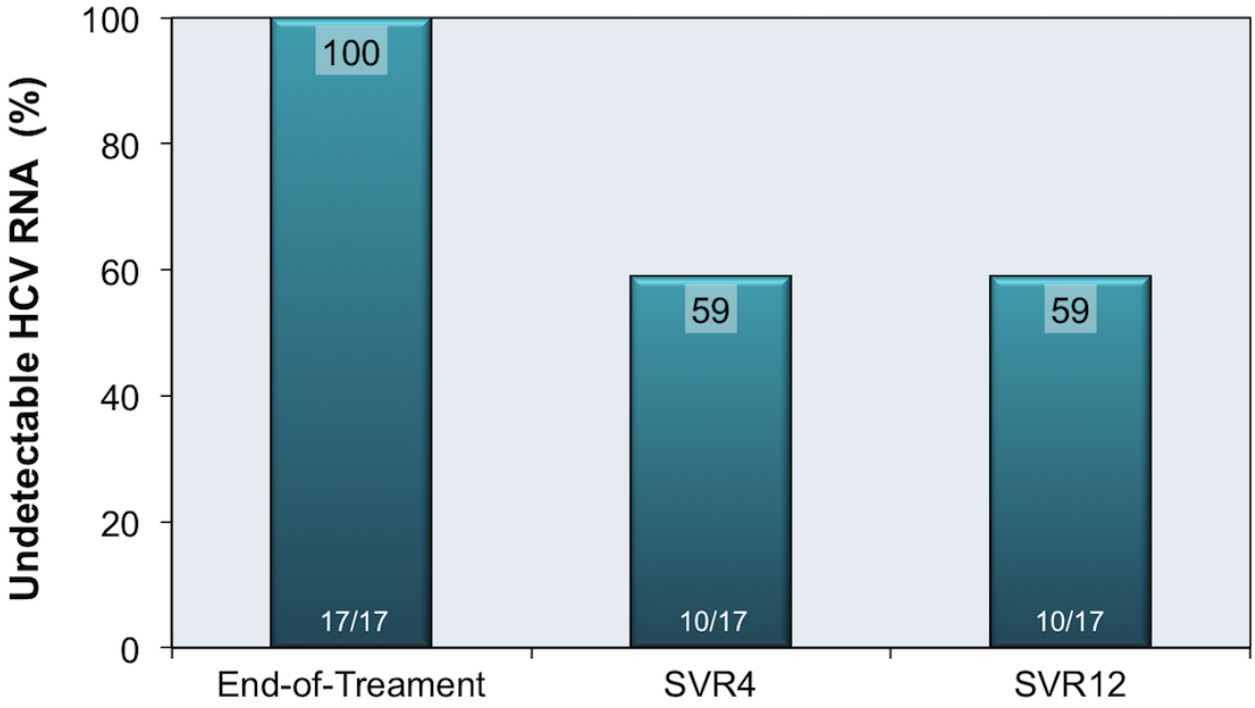

Figure 5 Ledipasvir-Sofosbuvir for 6 Weeks in Adults with Acute HCV

All participants in the study achieved an SVR12. At week 4 of treatment, the 6 participants who had detectable HCV RNA had very low levels (Less than 15 IU/mL)

Source: Deterding K, Spinner CD, Schott E, et al. Ledipasvir plus sofosbuvir fixed-dose combination for 6 weeks in patients with acute hepatitis C virus genotype 1 monoinfection (HepNet Acute HCV IV): an open-label, single-arm, phase 2 study. Lancet Infect Dis. 2017;17:215-222.

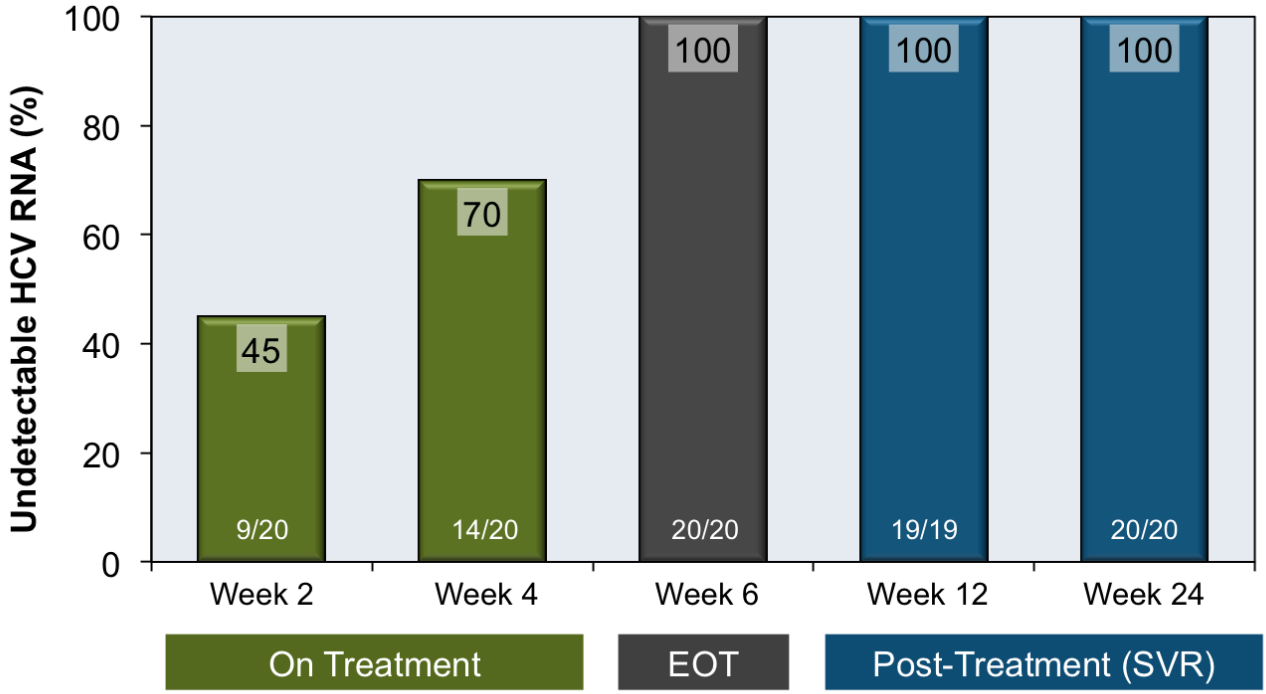

Figure 6 Ledipasvir-Sofosbuvir for 6 Weeks in Adults with Acute HCV and Chronic HIV Infection

Source: Rockstroh JK, Bhagani S, Hyland RH, et al. Ledipasvir-sofosbuvir for 6 weeks to treat acute hepatitis C virus genotype 1 or 4 infection in patients with HIV coinfection: an open-label, single-arm trial. Lancet Gastroenterol Hepatol. 2017;2:347-353.

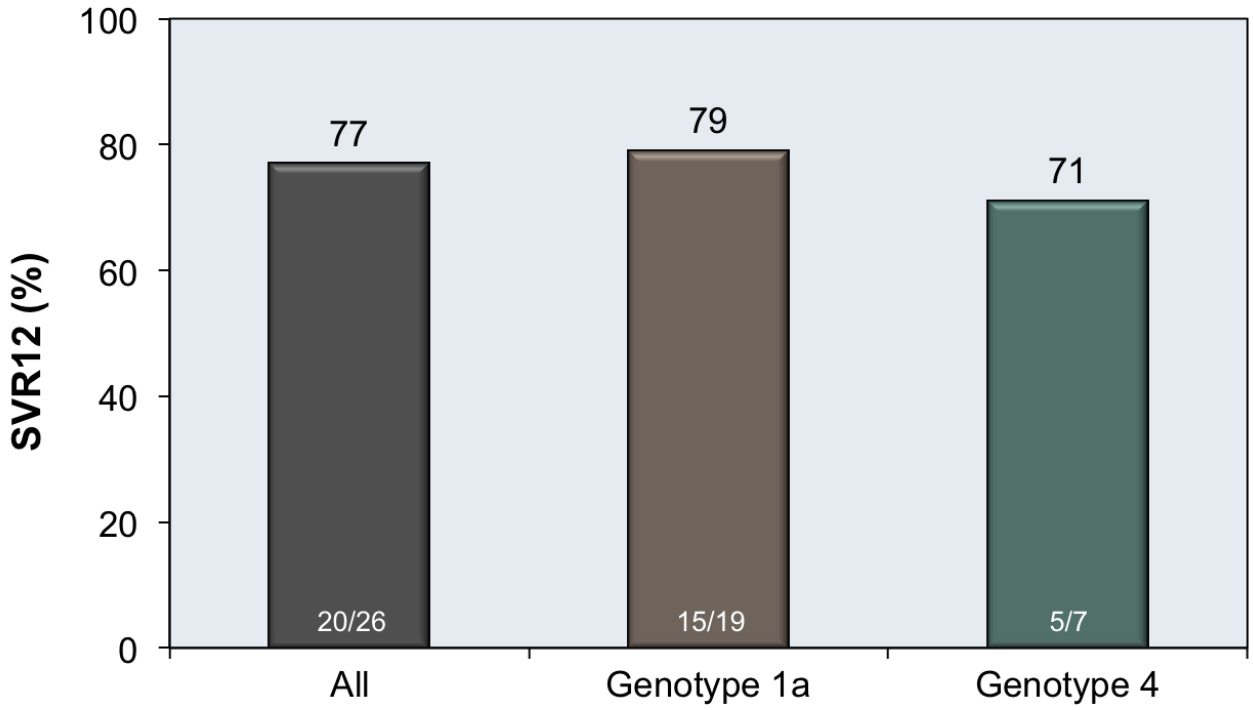

Figure 7 Interferon alfa-2b for 24 Weeks in Adults with Acute HCV Infection

In this study, 44 adults 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.

Source: Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. N Engl J Med. 2001;345:1452-7. Reproduced with permission from the Massachusetts Medical Society. Copyright © 2001 Massachusetts Medical Society. All rights reserved.

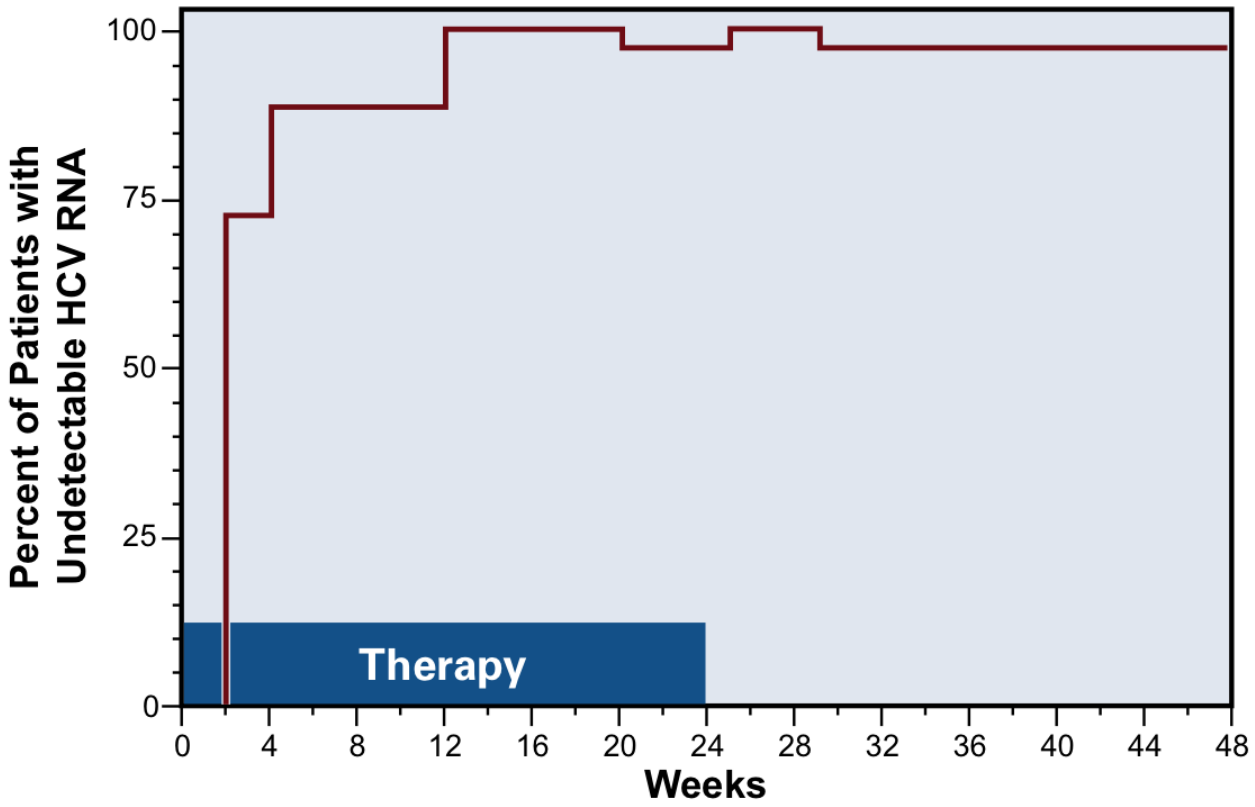

Figure 8 Peginterferon alfa-2b for 12 Weeks in Adults with Acute HCV

In this study, investigators treated adults 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 rates. Individuals who had spontaneous clearance after randomization, but before initiation of treatment, are not included in this graph.

Source: Kamal SM, Fouly AE, Kamel RR, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology. 2006;130:632-8.