

# Evaluating Persons with Substance or Alcohol Use Prior to Treatment of Hepatitis C

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Module 4: [Evaluation and Preparation for Hepatitis C Treatment](#)

Lesson 4: [Evaluating Persons with Substance or Alcohol Use Prior to Treatment of Hepatitis C](#)

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## Approach to HCV Treatment in Persons with Substance Use

The availability of direct-acting antiviral (DAA) medications has radically changed the assessment of substance use in HCV treatment decisions. Recommendations issued by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) HCV Guidance state that in the modern DAA treatment era recent or active injection-drug use should not be considered a contraindication to HCV treatment and requirements for pretreatment screening for illicit drug or alcohol use should be discontinued.[1] Substance use, which encompasses use of alcohol, marijuana, cocaine, amphetamines, opioids, and other drugs, may still be relevant to public health goals of HCV treatment, to adherence support, and to medication access. Substance use disorders are common in the United States, with 2015 data indicating that among persons 18 years of age or older, approximately 10% had used illicit drugs in the past month and approximately 51% had used illicit drugs in their lifetime.[2] The following discussion will address the impact of substance use on HCV disease and potential issues in HCV treatment.

### Prior and Active Substance Use and HCV Treatment

The approach to considering initiation of treatment of HCV for individuals with a prior history of substance use, including injecting drugs, should be the same as in patients with no history of drug use. Active substance use, in contrast, may result in payer barriers to accessing HCV treatment, but is not considered a contraindication to DAA-based HCV treatment, particularly when the DAA treatment regimen does not include peginterferon. Indeed, active substance use through injection is considered by many to be a direct indication for HCV treatment due to the potential benefit of reducing secondary HCV transmission.[3]

## Impact of Substance Use on HCV Treatment Decisions

### Adherence and Active Substance Use with Interferon-Based Therapy

Adherence studies among substance users have focused on interferon-based treatments and found a modest decrease in adherence among active substance users compared to others.[4] In one review, the overall rate of nonadherence was 6.8% among persons who inject drugs (PWIDs) with HCV treatment, compared with 4.9% of patients without drug use. A mean of 70.9% of PWIDs completed treatment compared to 79.4% of others; in studies treating only PWIDs, 62.6% completed treatment. Enrollment in agonist maintenance therapy, with methadone or buprenorphine, can substantially improve treatment completion: four of five studies found that PWIDs who were enrolled in methadone maintenance had rates of treatment completion similar to people who did not inject drugs. Again, these studies involved interferon-based treatment, which is in itself a substantial barrier to adherence. Stigma is also a major barrier and requires attention to the patient-provider relationship.

### HCV Treatment Outcomes among Drug Users with Interferon-Based Therapy

Treatment success rates with peginterferon and ribavirin have historically been comparable among current and former PWID,[5] with the exception that frequent drug use during treatment was associated with lower SVR rates than drug abstinence or occasional drug during treatment (Figure 1).[6] In a meta-analysis, Aspinall and coworkers evaluated HCV treatment outcomes in studies that included approximately 50% of participants with active injecting drug use during the HCV treatment; all studies in this meta-analysis were conducted prior to DAA-based therapy.[7] Overall, they concluded that patients had SVR rates that were slightly lower than seen in major clinical trials, but similar to reported rates outside of clinical trials. In a recent retrospective analysis from the University of California at San Diego,[8] SVR rates were evaluated across three different HCV treatment eras in HIV-infected persons seen in a clinic where active barriers to care, including drug or alcohol use were common. The SVR rates markedly increased in the DAA treatment era in this patient population (Figure 2).

### HCV Treatment with DAA Therapy in Persons who Inject Drugs

Despite the extensive data that have been generated with DAA-based therapies, relatively sparse data exists with the use of DAAs in patients with active drug use. Recently, however, the investigational agent grazoprevir-elbasvir was evaluated in the C-EDGE CO-STAR study as a treatment for PWID who were receiving Opiate Agonist Therapy (e.g. methadone or buprenorphine maintenance).[9] This phase 3 trial enrolled 301 HCV-treatment-naïve patients with chronic HCV genotype 1, 4, or 6 to receive either an immediate or deferred 12-week course of grazoprevir-elbasvir. On day 1 of the study, 58% of the subjects had a positive urine drug screen (excluding Opiate Agonist Therapy). Overall, when excluding patients who discontinued for non-treatment reasons, 95.1% of patients achieved an SVR12 (Figure 3). In addition, the SVR12 rates were excellent and similar with genotypes 1a and 1b, presence or absence of cirrhosis, and positive or negative baseline positive drug screen. Further, patients tolerated the regimen well and the overall adherence rates were very high (greater than 99% of patients took more than 90% of medication). This phase 3 study clearly shows that use of DAA-based therapy in PWID can result in very high SVR rates, comparable to those seen in persons who do not use drugs. There have been additional trial data with ledipasvir-sofosbuvir and sofosbuvir-velpatasvir in PWID that show comparable high SVR rates.[10,11]

### HCV Treatment Outcomes among Alcohol Users

The literature is mixed on whether alcohol use impacts treatment outcomes. Among a privately

insured cohort, pre-treatment alcohol consumption patterns were unrelated to SVR attainment or HCV relapse after interferon-based treatment.[12] A Swiss retrospective study also found no difference in SVR among 554 patients stratified by alcohol use .[13] In contrast, some studies suggest that active or heavy alcohol use during treatment with peginterferon plus ribavirin diminishes treatment responses.[14,15,16] In one French prospective study, investigators enrolled 73 patients with chronic hepatitis C (genotypes 1, 2, 3, or 4) who had varying degrees of alcohol consumption (abstinence, low-risk consumption and excessive consumption).[15] All patients received hepatitis C treatment with peginterferon and ribavirin. Abstinence referred to patients off alcohol during the entire treatment period. Low-risk consumption was defined as weekly consumption of no more than 21 standard drinks (10 g of pure ethanol) for men and no more than 14 drinks for women, and no more than 4 by drinking occasion. Excessive consumption was defined as drinking more than the limits defined for low-risk consumption on at least two occasions during the treatment period. Overall, 48% of the patients achieved a sustained virologic response (SVR). Patients with excessive alcohol use had lower SVR response rates than those who were abstinent or had low-risk ingestion (Figure 4). We do not currently have comparable data on how alcohol consumption impacts DAA outcomes.

## **Duration of Abstinence to Maximize Treatment Outcome**

Although some payers require 6 months or more of abstinence prior to HCV treatment, studies of both injection drug use and alcohol use have found no impact of duration of abstinence on likelihood of SVR.[4] There is no medical reason to ensure any duration of abstinence prior to HCV treatment.

## **Potential Reinfection with HCV among Persons who Inject Drugs**

In one study that clearly evaluated reinfection among treated PWIDs, the reinfection rate for those reporting ongoing injection after SVR was 5.3 per 100 person-years, suggesting a small ongoing risk comparable to that reported in one meta-analysis of late relapse or reinfection.[17] Although unstudied, detailed guidance on safer injection techniques may mitigate this risk (i.e. ensuring a source of sterile syringes and other injection equipment, as well as reviewing possible sources of HCV transmission such as cottons, cookers, water, alcohol pads, or any syringes used to divide, prepare or inject drugs).[18]

## **Impact of Treating active PWIDs on HCV Transmission**

Mathematical modeling, even assuming a reinfection rate equal to initial infection rates, has demonstrated that HCV treatment among active PWIDs would result in a reduction in HCV transmission.[19,20,21,22] Several recent studies utilizing mathematical modeling based on DAA regimens concluded that scaling up HCV treatment in PWIDs would have a major impact in reducing HCV incidence and prevalence in this patient population, even more so in the setting of robust access to sterile injection equipment and agonist maintenance services.[21] Further, scaling up and widespread treatment of HCV in PWID as a prevention tool has become a more realistic goal with the short-course, well-tolerated, interferon-free regimens.

## **Challenges with Treating Active Substance Users**

In clinical practice, treating active substance users may be complicated by coexisting social problems and barriers erected by payers, but clinical experience suggests that, with appropriate infrastructure and patient support including the treatment of substance use,[23] HCV treatment is feasible in this population.[6,15,24,25,26]

## Alcohol Consumption

### Impact on Liver Fibrosis in Patients with Chronic HCV

Several studies have shown that heavy alcohol consumption (at least 60 g/day in men and 40 g/day in women) clearly accelerates the progression of HCV-related hepatic fibrosis ([Figure 5](#)).[\[27,28\]](#) A typical alcohol drink (12 ounces of beer, 5 ounces of wine, and 1.5 ounces of whiskey) contains 12 g of alcohol. An estimated one-third of patients with chronic HCV infection have cirrhosis attributable to heavy alcohol consumption.[\[29\]](#) In a study in Alaska, investigators compared outcomes in persons who recovered from hepatitis C infection with those who had chronic hepatitis C and found heavy alcohol use (at least 50 grams of alcohol daily) was associated with the highest incidence of end-stage liver disease, regardless of whether the individual had recovered from hepatitis C or had chronic hepatitis C infection.[\[30\]](#) In addition, separate studies have shown that progression of liver disease may continue among heavy alcohol users even if SVR is achieved with treatment of HCV. Taken together, the available data suggest reducing alcohol use is critical to liver health. The effects of moderate alcohol consumption on liver health are not well characterized.

### Pretreatment Requirements

Although abstinence from alcohol is strongly encouraged for patients with HCV infection, requirements for abstinence from alcohol prior to HCV treatment are no longer recommended. Some payers may still require abstinence.

### Management Strategies

Discussing alcohol use results in reduced use for patients with chronic HCV infection. Alcohol consumption is discouraged in patients with chronic HCV infection due to the hepatotoxic effects of alcohol. Multiple pharmacologic agents are available for alcohol dependence, including naltrexone, acamprosate, and topiramate.[\[31\]](#) Among these, the most promising results have been seen with naltrexone given as a monthly injection. Brief counseling on alcohol has also shown reductions in use among patients with HCV infection. A multidisciplinary approach, involving personalized addiction care and case management, may provide further benefit in managing alcohol dependence.[\[15\]](#)

## Opioid Use

### Impact on Natural History of HCV

Opioid use by injection is a major driver of HCV transmission, but opioid use itself does not appear to speed progression of liver disease in persons with chronic HCV. Opioid analgesic use disorder is also a risk factor for HCV transmission, particularly as some users transition to illicit opioids or higher risk modes of administration.

### Pretreatment Requirements

There is no requirement for abstinence from opioids prior to HCV treatment. In contrast, some payers may require abstinence from non-prescribed opioids.

### Management Strategies

Multiple treatment options exist for opioid use disorders. Agonist maintenance therapy is the most effective known treatment and has been shown to reduce the risk of new HCV infection.[\[32\]](#) Data from interferon-based regimens demonstrate that patients receiving methadone or buprenorphine therapy respond to HCV treatment similar to non-drug using populations.[\[33,34,35\]](#) Injectable naltrexone is also approved for opioid dependence, although access and uptake can be limited. There are no known clinically significant interactions between opioid agonist therapies or naltrexone and currently approved DAA medications.[\[36,37\]](#)

## Stimulant Use

### Impact on HCV

Injection of cocaine or methamphetamine is another major driver of HCV transmission. Other routes of administration of stimulants, such as intranasal, may be associated with HCV transmission. In addition, prolonged stimulant abuse may result in cardiac and cerebrovascular toxicity.

### Pretreatment Requirements

There is no requirement for abstinence from stimulant use prior to HCV treatment. However, some payers may require abstinence.

### Management Strategies

Stimulant use is often more intermittent than opioid or alcohol use but can also be associated with periods of poor adherence to medical care. Pharmacologic options are limited, with multiple current trials underway for both methamphetamine and cocaine dependence.[\[38\]](#) Mirtazapine and possibly bupropion or modafinil have demonstrated some efficacy for reducing methamphetamine use among dependent persons, but there is no current standard of therapy for methamphetamine dependence at this time.[\[39,40,41\]](#)

## Other Drugs

### Marijuana

There is mixed evidence regarding marijuana use and fibrosis progression.[[42](#),[43](#),[44](#)] A longitudinal cohort study found no association between marijuana use and progression of liver fibrosis among patients coinfecting with HCV and HIV and at least one study found a positive association between marijuana use and good adherence with HCV treatment.[[42](#),[45](#)] Patients with HCV are generally advised to abstain from regular marijuana use, although ongoing marijuana use is not considered a contraindication for initiating HCV therapy.

### Tobacco

Smoking tobacco is a risk factor for development of hepatocellular carcinoma.[[46](#)] In addition, smoking is associated with reduced quality of life among persons with HCV, higher hepatic histologic activity,[[47](#)] and lower rates of SVR with interferon-based therapies,[[48](#)] although there are no data suggesting such a correlation for DAA-based therapy. Use of nicotine replacement therapies, bupropion, or varenicline is effective at promoting smoking cessation, more so when paired with behavioral support. Ongoing tobacco use is not a contraindication for initiating of hepatitis C therapy.

## Summary Points

- Active substance use or use disorder is not a contraindication to HCV treatment.
- It is important to talk to patients about their substance use not insofar as to determine treatment eligibility but to understand how best to support them through treatment and prevent reinfection.
- Treatment of persons actively injecting drugs may have public health benefits in terms of reduced secondary transmission.
- Patients should be aware that heavy use of alcohol may reduce the benefits of HCV treatment.
- Therapeutic approaches to substance use disorders are generally more effective when including a pharmacologic agent.
- Care should be taken to ensure that PWIDs are aware of specific drug use techniques to avoid reinfection.



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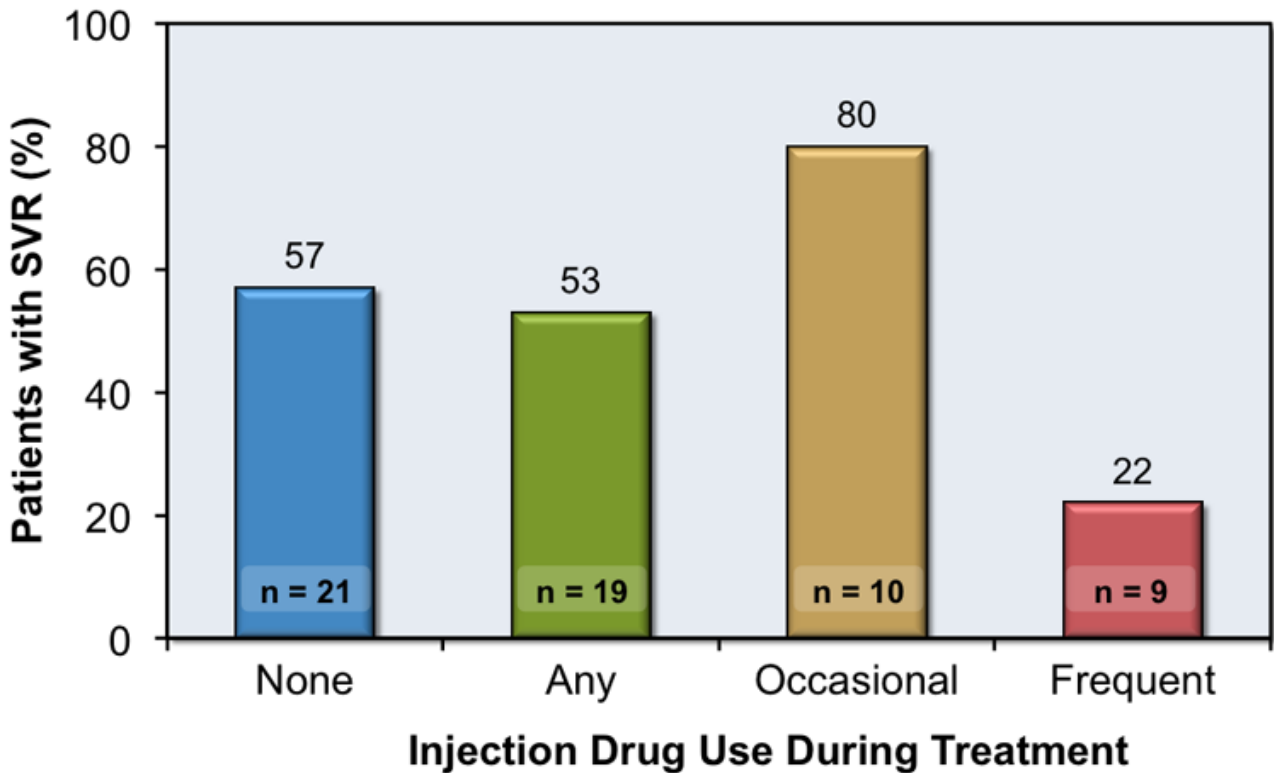
## Figures

**Figure 1 Impact of Injection Drug Use on HCV Treatment Response**

This study enrolled 40 patients with hepatitis C (genotypes 1, 2, or 3) and injection drug use who received treatment with peginterferon (or interferon) plus ribavirin. Among individuals with drug abstinence for longer than 6 months prior to treatment, 50% achieved a sustained virologic response (SVR), compared with 63% for those with drug abstinence for 6 months or less (data not shown). Overall, the SVR rates with any drug use during hepatitis treatment (53%) did not appear different than with no drug use during treatment (57%), with the exception that SVR rates were very low with frequent drug use during treatment (22%).

Source: Grebely J, Raffa JD, Meagher C, et al. Directly observed therapy for the treatment of hepatitis C virus infection in current and former injection drug users. *J Gastroenterol Hepatol.* 2007;22:1519-25.

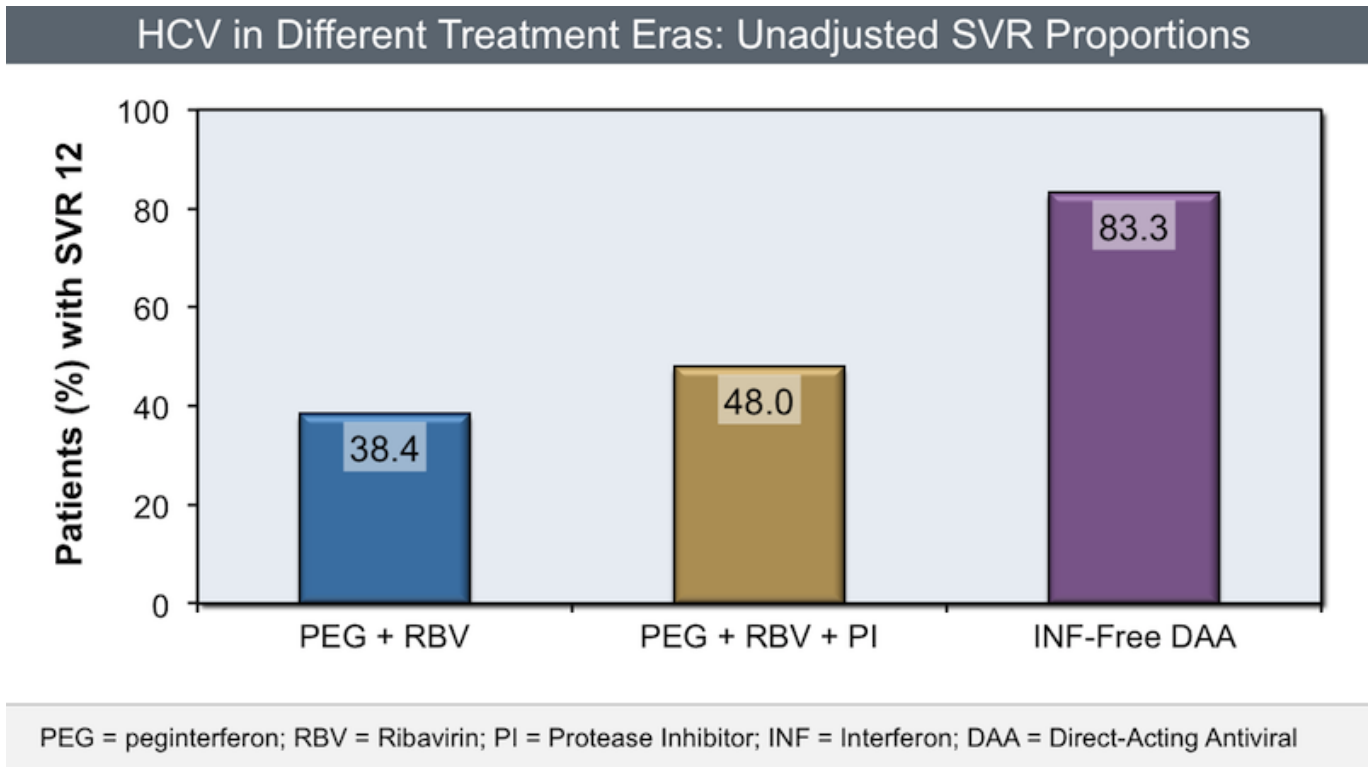
### Sustained Virologic Rates According to Drug Use During Therapy



**Figure 2 HCV Treatment Responses in 3 Treatment Eras in Patients with HIV Coinfection and Frequent Barriers to Care**

This graphic shows a retrospective comparison of SVR rates in three different HCV treatment eras in an urban HIV clinic where barriers to care, including drug and alcohol use were common.

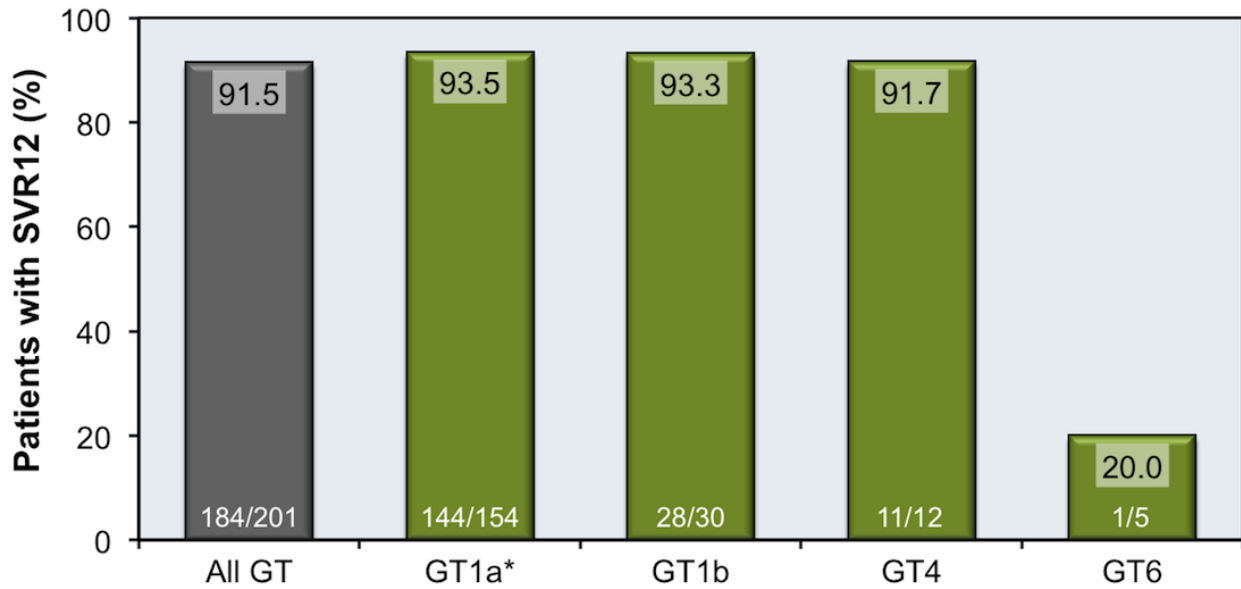
Source: Cachay ER, Wyles D, Hill L, et al. The Impact of Direct-Acting Antivirals in the Hepatitis C-Sustained Viral Response in Human Immunodeficiency Virus-Infected Patients With Ongoing Barriers to Care. *Open Forum Infect Dis.* 2015;2:ofv168.



**Figure 3 (Image Series) - Grazoprevir-Elbasvir in Persons who Inject Drugs: C-EDGE CO-STAR (Image Series) - Figure 3 (Image Series) - Grazoprevir-Elbasvir in Persons who Inject Drugs: C-EDGE CO-STAR  
Image 3A: SVR12 Results (Assumes Reinfections are Failures)**

Source:Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. Ann Intern Med. 2016;165:625-634.

C-EDGE CO-STAR: SVR12 Results (Assumes Reinfections are Failures)

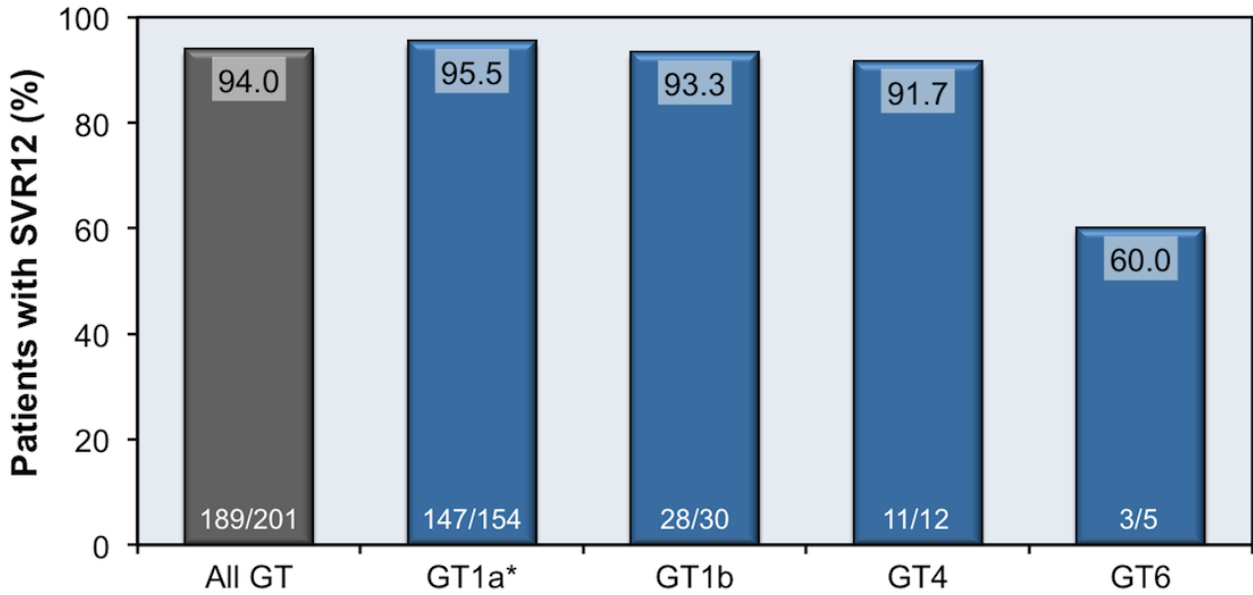




**Figure 3 (Image Series) - Grazoprevir-Elbasvir in Persons who Inject Drugs: C-EDGE CO-STAR**  
**Image 3B: SVR12 Results (Assumes Reinfections are Responses)**

Source: Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. Ann Intern Med. 2016;165:625-634.

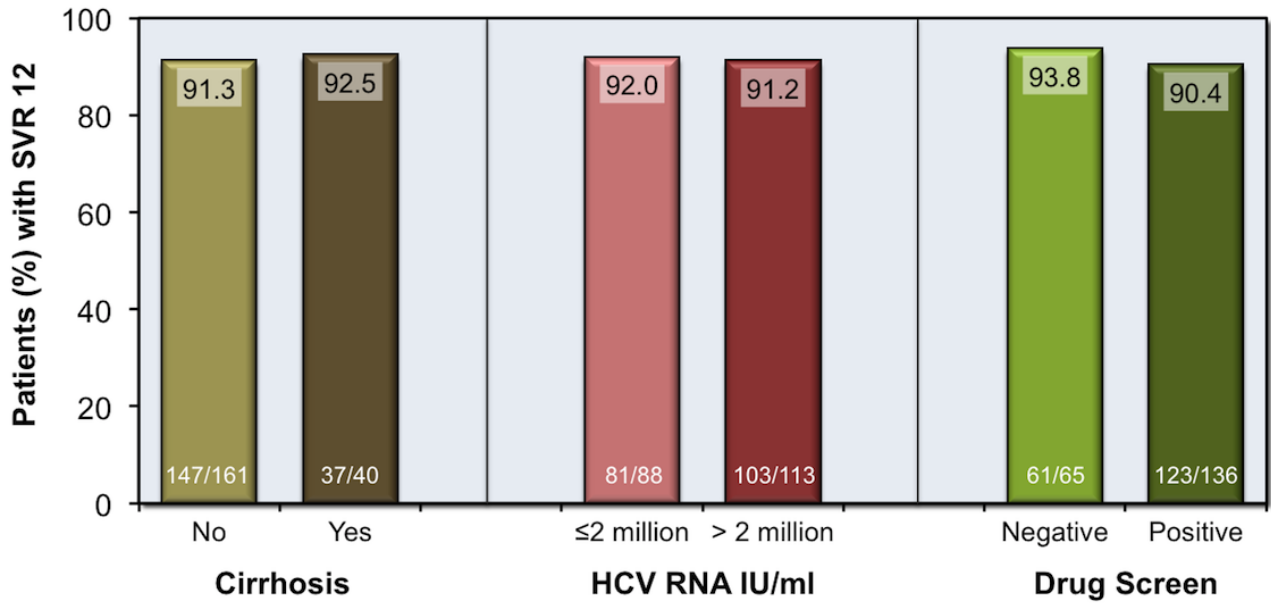
C-EDGE CO-STAR: SVR12 Results (Assumes Reinfections are Responses)



**Figure 3 (Image Series) - Grazoprevir-Elbasvir in Persons who Inject Drugs: C-EDGE CO-STAR**  
**Image 3C: SVR12 by Subgroups**

Dore GJ, Altice F, Litwin AH, et al. Elbasvir-Grazoprevir to Treat Source: Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med.* 2016;165:625-634.

**C-EDGE CO-STAR: SVR12 Results Subgroup Analysis**

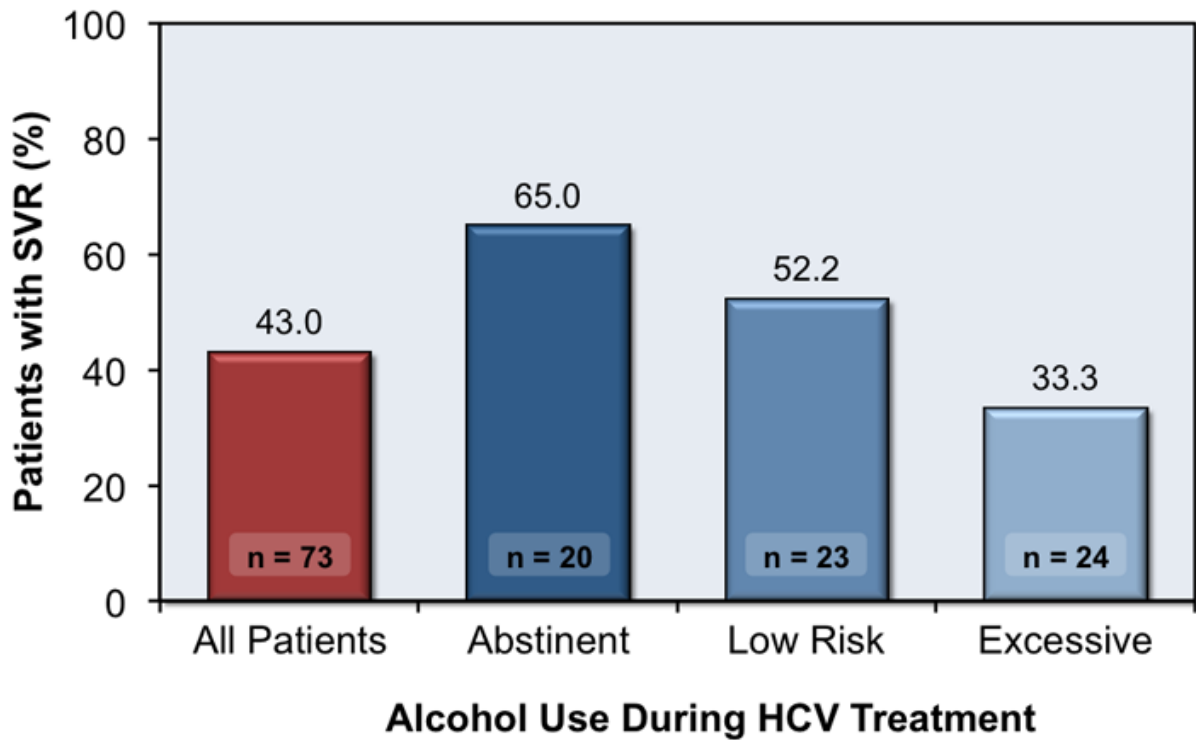


**Figure 4 Impact of Alcohol Consumption on HCV Treatment Response**

Investigators enrolled 73 patients with chronic hepatitis C (genotypes 1, 2, 3, or 4) who had ongoing alcohol consumption (or abstinence for less than 6 months) All patients received hepatitis C treatment with peginterferon and ribavirin. Abstinence referred to patients off alcohol during the entire treatment period. Low risk consumption was defined as weekly consumption of no more than 21 standard drinks (10 g of pure ethanol) for men and no more than 14 drinks for women, and no more than 4 by drinking occasion. Excessive consumption was defined as drinking more than the limits defined for low risk consumption on at least two occasions during the treatment period. Overall, 48% of the patients achieved a sustained virologic response (SVR). Patients with excessive alcohol use had lower SVR response rates than those who were abstinent or had low-risk ingestion.

Source: Le Lan C, Guillygomarc'h A, Danielou H, et al. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. *J Hepatol.* 2012;56:334-40.

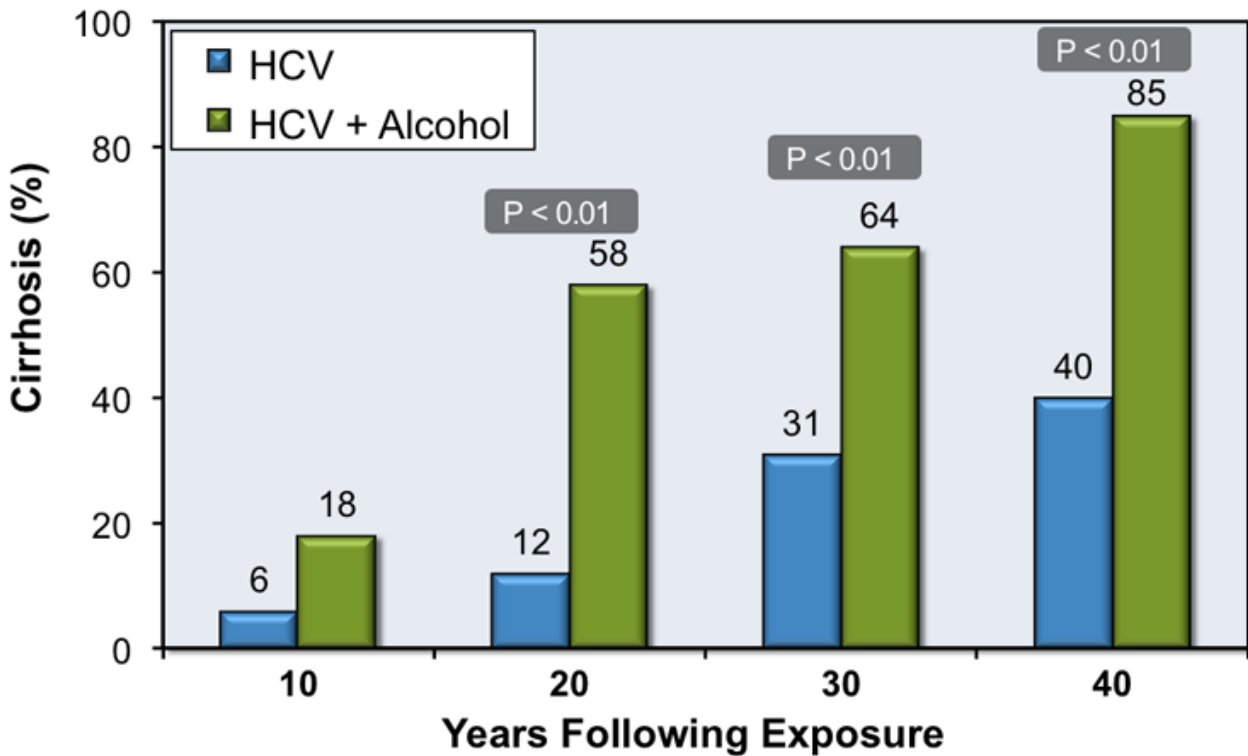
**Sustained Virologic Rates According to Alcohol Consumption During Therapy**



**Figure 5 Impact of Alcohol Consumption on HCV Treatment Response**

In this study, investigators examined the impact of excessive alcohol consumption on hepatic fibrosis in patients with chronic hepatitis C infection. Excessive alcohol consumption was defined as more than 60 g/day for men and more than 40 g/day for women. Throughout all times during the study it was clear that patients with excessive alcohol ingestion had greater risk of developing cirrhosis.

Source: Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology*. 1998;28:805-9.



\*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men