Background

Substance use disorders are common in the United States, with 2018 data indicating that nearly 1 in 5 persons 12 years of age or older used an illicit drug in the past year (Figure 1).[1] The availability and effectiveness of direct-acting antiviral (DAA) medications has radically changed the assessment and consideration of substance use in hepatitis C virus (HCV) treatment decisions. The AASLD-IDSA HCV Guidance states that recent or active injection-drug use or alcohol use should not be considered an absolute contraindication to HCV treatment and requirements for pretreatment screening for illicit drug or alcohol use should be discontinued.[2] Nevertheless, for persons with chronic HCV infection, substance use, either past or present, which encompasses the use of opioids, amphetamines, cannabis, cocaine, alcohol, and other drugs, may still be relevant to the individual's overall health and medication access. The following discussion will address the potential impact of substance use on HCV disease and HCV treatment and will provide current recommendations for the treatment of HCV in persons with substance use disorders.
Approach to HCV Treatment in Persons with Substance Use

HCV Treatment Eligibility

The AASLD-IDSA HCV Guidance recommends treatment for all persons with chronic HCV, except those with a short life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy.[2,3] The general 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 persons with no history of drug use. Persons with substance use disorder, including those with injection-drug use or alcohol use should have the same HCV pretreatment screening requirements as those without a substance use disorder.[2]

Abstinence Requirements

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 achieving a sustained virologic response (SVR) 12 weeks after completing DAA-based therapy SVR.[4] Thus, there is no medical reason to ensure abstinence (for any duration) prior to HCV treatment. Current AASLD-IDSA HCV Guidance recommendations state that current or prior substance use should not be a contraindication to HCV treatment.[2]

Impact of Comorbidities in Persons with Substance Use Disorder

In clinical practice, treating persons with an active substance use disorder 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 disorders, HCV treatment is feasible in this population.[5,6,7,8,9] Examples of patient support include directly-observed therapy and related approaches, patient navigation, and group treatment models, particularly in substance use disorder treatment settings.
HCV Treatment in Persons with Opioid Use

Impact of Opioid Use on Natural History of HCV

Opioid use by injection is a major driver of HCV transmission, but opioid use itself, either orally or by injection, does not appear to speed progression of liver disease in persons with chronic HCV.[10] Opioid analgesic use disorder is also a risk factor for HCV acquisition and transmission, particularly as some users transition from oral ingestion of prescribed opioids to illicit opioids, and potentially to higher risk modes of administration, such as injection.[11,12]

Impact of Treating People with Active Injection-Drug Use on HCV Transmission

Mathematical modeling, even assuming a reinfection rate equal to initial infection rates, has demonstrated that HCV treatment among persons with active injection-drug use would result in a significant reduction in HCV transmission.[13,14,15,16] Several recent studies utilizing mathematical modeling based on DAA regimens concluded that scaling up HCV treatment in people who inject drugs (PWID) 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 opioid agonist maintenance services.[15] Further, scaling up and widespread treatment of HCV in PWID as a prevention tool, akin to treating HIV to reduce community viral load, has become a more realistic goal with the short-course, well-tolerated, interferon-free regimens.

Impact of Opioid Use and HCV Treatment Adherence

Multiple studies that have enrolled persons with active or recent injection-drug use have shown excellent adherence with DAA-based HCV therapy (Figure 2).[17,18,19] Persons with opioid use disorder who receive opioid agonist maintenance therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone) during HCV treatment have excellent rates of adherence, treatment completion, and sustained virologic response (SVR) rates, all comparable to results of other study participants.[21,22]

HCV Treatment Outcomes with DAA Therapy in PWID

Despite the extensive overall data that have been generated with DAA-based therapies, only a moderate amount of data exists specific to the use of DAs in persons with active injection drug use. The following summarizes several key studies that have analyzed HCV treatment responses with DAA-based therapy in persons who inject drugs or who have previously injected drugs and were receiving opioid agonist therapy. Multiple studies clearly show that use of DAA-based therapy in persons with past or current injection-drug use results in high SVR rates, comparable to those seen in persons who do not use drugs.[17,20]

- **Elbasvir-Grazoprevir (C-EDGE CO-STAR):** In this phase 3, multinational study (C-EDGE CO-STAR), investigators evaluated HCV treatment with elbasvir-grazoprevir in 301 PWID who had also been receiving opioid agonist therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone maintenance) for at least 3 months prior to enrollment.[19] Participants with chronic HCV genotype 1, 4, or 6 were randomized to immediately receive a 12-week course of elbasvir-grazoprevir (immediate treatment group) or to receive the 12-week course of elbasvir-grazoprevir after a 16-week delay (deferred treatment group). On day 1 of the study, 58% of the subjects had a positive urine drug screen (excluding opiate agonist therapy). Overall, when excluding participants who discontinued for non-treatment reasons, 91.5% in the immediate treatment group and 89.5% in the deferred treatment group achieved an SVR12; the treatment responses were excellent regardless of cirrhosis status and baseline drug screening results (Figure 3).[19]

- **Glecaprevir-Pibrentasvir:** In a pooled analysis of 7 phase 3 studies that involved HCV treatment with 8 or 12 weeks of glecaprevir-pibrentasvir, investigators compared SVR12 rates among persons with recent drug use (use in the past 12 months), persons with former drug use (use more than 12 months ago), and persons who did not use drugs.[23] Overall, the SVR12 rates were high among all
groups: 93% in persons with recent drug use, 97% in those with former drug use, and greater than 99% in persons who did not use drugs.[23] A similar pooled analysis of 8 phase 2 and 3 trials of glecaprevir-pibrentasvir evaluated treatment outcomes among persons receiving opioid substitution therapy (OST).[24] In the intention-to-treat analysis, SVR-12 rates were 96.2% among persons receiving opioid substitution therapy and 97.9% in those not receiving opioid substitution therapy.[24]

- **Ledipasvir-Sofosbuvir (ION Trials):** In the ION trials, participants with chronic HCV genotype 1 infection received 8, 12, or 24 weeks of ledipasvir-sofosbuvir.[25] Investigators performed a pooled data analysis to compare HCV treatment response in participants receiving opioid substitution therapy during treatment (n = 70) with participants not receiving opioid substitution therapy (n = 1882).[25] The two groups had similar treatment completion, adherence, and SVR12 rates (Figure 4).[25] Among those receiving opioid substitution therapy, 94% (66 of 71) achieved an SVR12.[25] In addition, a pilot trial of ledipasvir-sofosbuvir among 31 persons with active injection-drug use randomized participants 1:1 to modified directly-observed treatment (mDOT) or unobserved dosing. All but one participant (in the mDOT arm) completed treatment, 96.8% achieved end-of-treatment response, and 89.7% achieved SVR-12.[26]

- **Sofosbuvir-Based Treatment in Phase 3 Trials:** In a pooled analysis of data from phase 3 trials using sofosbuvir-based regimens, investigators compared HCV treatment responses in participants receiving opioid substitution therapy during treatment (n = 194) with participants not receiving opioid substitution therapy (n = 4,549).[22] There were no significant differences in SVR12 rates (94% in those receiving opioid substitution therapy versus 97% for those not receiving opioid substitution therapy).[22]

- **Sofosbuvir-Velpatasvir (SIMPLIFY):** In this single-arm, open-label, phase 4 study, 103 participants with chronic HCV infection genotype 1, 2, 3, 4, 5, or 6 and recent (within 6 months) injection drug use were treated with a 12-week course of sofosbuvir-velpatasvir.[18] During the treatment course, 59% (61 of 103) participants were receiving opioid substitution therapy and 74% (76 of 103) had used injection drugs in the month prior to starting treatment.[18] A total of 97% (100 of 103) participants completed treatment; 2 were lost to follow-up and one person died from an accidental overdose. Overall, 97 (94%) of participants achieved an SVR12.[18]

- **Sofosbuvir-Velpatasvir (ASTRAL Trials):** In a subset analysis of the phase 3 ASTRAL trials, investigators compared treatment response to sofosbuvir-velpatasvir in persons receiving opioid substitution therapy during treatment (n = 51) compared with those who were not receiving opioid substitution therapy (n = 984).[21] Receipt of opioid substitution therapy did not impact treatment responses—96% of participants receiving opioid substitution therapy achieved an SVR12.[21]

**Pretreatment Requirements**

The AASLD-IDSA HCV Guidance does not have a requirement for abstinence from opioids prior to HCV treatment.[2] Indeed, active injection drug use in an individual with chronic HCV is considered by many to be a direct indication for HCV treatment, due to the potential benefit of reducing secondary HCV transmission.[27,28] In contrast to these expert recommendations, some payers may require abstinence from non-prescribed opioids. There are three FDA-approved treatments for opioid use disorder—buprenorphine, methadone, and extended-release naltrexone. While methadone access is limited to designated Outpatient Treatment Programs, the other medications can be prescribed in the context of routine medical care.

**Management Strategies**

For persons with a past or current history of opioid use disorder, treatment of HCV infection would ideally be performed in a multidisciplinary setting whereby HCV treatment and opioid use disorder can be addressed, as well as other comorbidities that may exist.[2] Multiple treatment options exist for opioid use. Agonist maintenance therapy is the most effective known treatment and has been shown to reduce the risk of new HCV infection.[29] Data from interferon-based regimens demonstrate that patients receiving methadone, buprenorphine, or buprenorphine-naloxone for opioid agonist therapy respond to HCV treatment similar to
populations not using drugs.\cite{30, 31, 32} In addition, data from the DAA era similarly indicate comparable SVR rates when comparing persons on opioid agonist therapy with those who do not use drugs.\cite{18, 19, 21, 22, 24, 25} Injectable extended-release naltrexone is also approved for opioid dependence, although access can be challenging and uptake can be limited. There are no known clinically significant interactions between opioid agonist therapies or naltrexone and currently approved DAA medications.\cite{33, 34} A detailed discussion of opioid agonist therapy is beyond the scope of this topic review.

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

Multiple studies have shown significant risk of HCV reinfection in persons cured with HCV therapy. Thus, it is essential that persons with past or active injection-drug use be counseled that they can become reinfected with HCV after achieving an SVR. This risk is significant in persons who inject drugs, but reinfection can also occur through sexual contact, particularly among men who have sex with men. In one study that clearly evaluated reinfection among treated PWID, the reinfection rate for those reporting ongoing injection after SVR was 5.3/100 person-years.\cite{35} Similarly, in a recent systematic review of 36 studies of HCV reinfection following successful HCV treatment in persons who inject drugs, the overall rate of HCV reinfection was 6.2 per 100 person-years among those who reported recent injection-drug use.\cite{36} In a pilot study among 31 persons with active injection-drug use treated with ledipasvir-sofosbuvir, the reinfection rate was 16.3/100 person-years (95% CI 5.3-50.5).\cite{26} Thus, it is important that programs for HCV treatment provide access to counseling for safe injection practices and opioid agonist therapy. Although unstudied, detailed guidance on safer injection techniques may mitigate the risk for HCV infection (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).\cite{37}
HCV Treatment in Persons with Stimulant Use

Impact of Stimulant Use on Natural History of HCV

Injection of cocaine or methamphetamine is another major driver of HCV transmission.[38,39,40] Other routes of administration of stimulants, such as intranasal, may also be associated with HCV transmission.[41] In addition, prolonged stimulant use may result in cardiac and cerebrovascular toxicity.

Pretreatment Requirements

There is no medical requirement for abstinence from stimulant use prior to HCV treatment, but some payers may require abstinence from methamphetamine prior to starting treatment.

HCV Treatment Outcomes in Persons with Stimulant Use

One study examined the impact of past or active methamphetamine use in persons with chronic HCV treated with interferon-based regimens and methamphetamine use did not appear to significantly impact treatment completion or SVR rates.[42] There are no published studies on the impact of methamphetamine use on DAA therapy.[42]

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.[43] In a double-blind, placebo-controlled, randomized trial conducted from 2012 to 2015, a 12-week course of extended-release naltrexone did not appear to reduce amphetamine use among dependent persons.[44] In a similar randomized, controlled trial, a 12-week course of aripiprazole, when given over a 12-week period, did not significantly reduce methamphetamine use.[45] Mirtazapine has demonstrated efficacy in reducing methamphetamine use in two separate trials.[46,47] Bupropion and modafinil have also demonstrated benefit in small trials.[48,49] A combination of high-dose bupropion plus high frequency extended-release naltrexone with intensive paid video directly-observed therapy for adherence support also demonstrated benefit in a trial of 403 participants.[50]
HCV Treatment in Persons who Consume Alcohol

Impact of Alcohol Use on Liver Fibrosis in Persons with Chronic HCV

Several studies have shown that heavy alcohol consumption (at least 60 grams/day in men and 40 grams/day in women) accelerates the progression of HCV-related hepatic fibrosis. A typical alcohol drink (12 ounces of beer, 5 ounces of wine, and 1.5 ounces of whiskey) contains 12 grams of alcohol. An estimated one-third of patients with chronic HCV infection have cirrhosis attributable to heavy alcohol consumption. In a study in Alaska, investigators compared outcomes in persons who recovered from HCV with those who had chronic HCV 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 HCV or had chronic HCV infection. 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 low or moderate alcohol consumption on liver health are not well characterized for persons with chronic HCV infection.

HCV Treatment Outcomes Among Persons with Alcohol Use

Most of the studies that have addressed whether alcohol use impacts treatment outcomes were performed in the pre-DAA treatment era and results from these studies were mixed.

DAA Treatment Era

- In the DAA treatment era, a large observational study out of the Veteran's Affairs (VA) healthcare system evaluated the impact of alcohol use on HCV DAA-based treatment outcomes. Of the 15,151 persons who initiated DAA therapy and had a documented AUDIT-C score, 68.5% were categorized as abstinent, 22.6% as low-level drinking, and 8.9% as unhealthy drinking. Overall SVR12 rates were high among all persons in the study, regardless of alcohol use, with no statistical difference between HCV genotype or by cirrhosis status. These findings support current recommendations to not exclude persons from HCV treatment based on their alcohol use.

Interferon and Peginterferon Treatment Era

- Among a privately insured cohort, pretreatment alcohol consumption patterns were unrelated to SVR attainment or HCV relapse after interferon-based treatment.
- A Swiss retrospective study also found no difference in SVR among 554 patients stratified by alcohol use.
- In one French prospective study, investigators enrolled 73 patients with chronic hepatitis C who were treated with peginterferon and ribavirin and had varying degrees of alcohol consumption: abstinence, low-risk consumption, and excessive consumption. Abstinence referred to persons 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 drinks per 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, individuals with excessive alcohol use had lower SVR rates than those who were abstinent or had low-risk ingestion.

Pretreatment Requirements

Although abstinence from alcohol is strongly encouraged for patients with chronic HCV infection, a requirement for abstinence from alcohol prior to HCV DAA treatment is no longer recommended. Some payers, however, may still require abstinence.
Management Strategies

Although abstinence from alcohol prior to HCV DAA treatment is no longer required, efforts should be made to ensure that ongoing alcohol use does not interfere with adherence or medical follow-up. Alcohol consumption is discouraged in patients with chronic HCV infection due to the hepatotoxic effects of alcohol and its acceleration in liver fibrosis. Multiple pharmacologic agents are available for alcohol use disorder, including naltrexone, acamprosate, and topiramate. Among these, the most promising results have been seen with naltrexone, particularly when given as a monthly injection. Brief counseling on alcohol has also shown reductions in use among persons with HCV infection. A multidisciplinary approach, involving personalized addiction care and case management, may provide further benefit in managing alcohol dependence. Following DAA-based therapy, one study that included 123 participants found provider-delivered, alcohol-related counseling during HCV treatment was successful in reducing alcohol consumption patterns both during and after treatment in individuals with harmful alcohol use.
HCV Treatment in Persons who Use Cannabis

There is mixed evidence regarding cannabis use and HCV-related hepatic fibrosis progression.[60,61,62] Two separate longitudinal cohort studies found no association between cannabis use and progression of liver fibrosis among patients coinfected with HCV and HIV.[60,63] In addition, one study found a positive association between cannabis use and good adherence with HCV treatment.[64] Although individuals living with HCV are generally advised to abstain from regular cannabis use, ongoing cannabis use is not considered a contraindication for initiating HCV therapy.
Summary Points

- Active substance use, substance use disorders, or injection-drug use, are not contraindications to HCV treatment.

- Treatment of HCV in persons with active injection drug use likely has major public health benefits in terms of reducing secondary HCV transmission.

- 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 lower the risk of reinfection.

- Persons with HCV should be aware that heavy use of alcohol may continue to cause damage to the liver.

- Therapeutic approaches to substance use disorders are generally more effective when including a pharmacologic agent.

- Care should be taken to ensure that PWID are aware of specific drug use techniques to avoid reinfection, particularly in the ways drugs are divided or prepared for injection.
Citations


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3. AASLD-IDSA. Recommendations for testing, management, and treating hepatitis C. Key populations: identification and management of HCV in people who inject drugs. [AASLD/IDSA Hepatitis C Guidance] -


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- Center for Behavioral Health Statistics and Quality (CBHSQ), Substance Abuse and Mental Health Services Administration (SAMHSA), and U.S. Department of Health and Human Services (HHS). Results from the 2015 National Survey on Drug Use and Health:Detailed Tables


[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -

[PubMed Abstract] -
Figures

Figure 1 Number of Persons Aged 12 or Older with Past Year Illicit Drug Use, United States, 2018

**Figure 2 Adherence with HCV Therapy in C-EDGE CO-STAR Trial**

In this trial, investigators evaluated HCV treatment with elbasvir-grazoprevir in 301 persons with a history of injection-drug use who were receiving opioid agonist therapy (e.g. methadone, buprenorphine, or buprenorphine-naloxone maintenance) for at least 3 months prior to enrollment. This graph shows excellent rates of adherence.

In this study, reinfections are considered as failures.


**C-EDGE CO-STAR: SVR12 Results Immediate-Treatment Group**

<table>
<thead>
<tr>
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<th>Patients with SVR12 (%)</th>
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<tr>
<td>GT1a</td>
<td>93.5</td>
</tr>
<tr>
<td>GT1b</td>
<td>93.3</td>
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<tr>
<td>GT4</td>
<td>91.7</td>
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<td>GT6</td>
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^Excludes patients who discontinued trial for non-treatment related reasons
*Includes one subject with mixed infection (GT 1a and 1b) who achieved SRV12
Figure 3 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR
Image 3B: SVR12 Results (Assumes Reinfections are Responses)


<table>
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<th>Patients with SVR12 (%)</th>
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<th>GT1b</th>
<th>GT4</th>
<th>GT6</th>
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<td>147/153</td>
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</tbody>
</table>

^Excludes patients who discontinued trial for non-treatment related reasons
*Includes one subject with mixed infection (GT 1a and 1b) who achieved SRV12
Figure 3 (Image Series) - Elbasvir-Grazoprevir in Persons who Inject Drugs: C-EDGE CO-STAR Image 3C: SVR12 by Subgroups


C-EDGE CO-STAR: SVR12 Results Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>SVR12 (%)</th>
<th>Patients with SVR12 (%)</th>
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<tbody>
<tr>
<td>Cirrhosis</td>
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<td>147/181</td>
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<td>HCV RNA IU/mL</td>
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<tr>
<td></td>
<td>91.2</td>
<td>103/113</td>
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<tr>
<td>Drug Screen</td>
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<td></td>
<td>90.4</td>
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Figure 4 Sustained Virologic Responses to Ledipasvir-Sofosbuvir in Persons Receiving Opioid Substitution Therapy: Phase 3 ION Trials

Abbreviations: OST = opioid substitution therapy This graph shows summary data in the phase 3 ION trials comparing SVR rates with ledipasvir-sofosbuvir for the small subset of persons enrolled in the trials who were receiving OST versus those not receiving OST.

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.


*Excessive alcohol defined as > 40 g/day for women and > 60 g/day for men
Figure 6 HCV SVR12 Rates Achieved with DAA-Based Treatment, by AUDIT-C Category and HCV Genotype, 2014–2015

Figure 7 HCV SVR12 Rates Achieved with DAA-Based Treatment, by AUDIT-C Category and Cirrhosis Status, 2014–2015

Figure 8 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) and were treated 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 for men and 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.