Addressing Viral Hepatitis in People With Substance Use Disorders

A Review of the Literature*

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*TREATMENT IMPROVEMENT PROTOCOL (TIP) SERIES

*This document is available online only (http://www.kap.samhsa.gov) and supports TIP 53, Addressing Viral Hepatitis in People With Substance Use Disorders.
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Section 1—A Review of the Literature

Overview

This literature review is Part II of the Substance Abuse and Mental Health Services Administration’s (SAMHSA’s) Treatment Improvement Protocol (TIP) 53, *Addressing Viral Hepatitis in People With Substance Use Disorders*. The TIP gives healthcare providers, treatment counselors, and administrators of drug treatment programs the information they need to help their clients with past or current substance use disorders (SUDs) receive counseling, screening, referral, and followup care for hepatitis. The literature review is available online only at http://www.kap.samhsa.gov.

Although several types of hepatitis viruses have been identified, the TIP (including this literature review) touches on the three types most common in the United States: hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). The TIP concentrates on hepatitis C because:

- People with SUDs are at high-risk of HCV infection.
- Hepatitis C usually becomes chronic and might progress to liver cancer and cirrhosis.
- There is no vaccination, and treatment is long and difficult for many patients.
- Treatment providers can help their clients learn how to reduce their exposure to HCV and support their clients living with this chronic condition.


The National Institutes of Health (NIH) first recommended hepatitis C treatment for people who have a history of injection drug use (IDU) in 2002. Most of the literature describing the counseling and management of this population has been published since that time. Furthermore, people who have a history of drug use were not included in the clinical trials of interferon for treatment of hepatitis until recently. The result is that much of the relevant literature on this population is recent and involves small samples. Although cultural differences in healthcare systems, approaches to SUD treatment, prejudice faced by people who have hepatitis and SUDs, and many other factors make drawing comparisons across national boundaries difficult, foreign studies written in English are included here to supplement the scant research on the topic that has been conducted in the United States. Where data from only the United States are relevant, or where the research is proportionate to that in other countries and does not differ in its conclusions, the literature review cites only U.S. data; in other cases, the country where the research was conducted is identified.

Status of HCV Services in Drug Treatment Facilities

SAMHSA endorses the development of community-based resources for hepatitis prevention and treatment, including the incorporation of hepatitis services in SUD treatment facilities (Kresina, Hoffman, Lubran, & Clark, 2007). However, services for hepatitis screening and treatment are not widely offered in SUD treatment facilities (Exhibit 1).
Exhibit 1 Types of Services Offered in U.S. SUD Treatment Facilities

<table>
<thead>
<tr>
<th>Service</th>
<th>Percentage of Facilities Offering Service (figures rounded)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient risk assessment</td>
<td>72</td>
<td>Brown et al., 2006</td>
</tr>
<tr>
<td>Hepatitis B screening</td>
<td>34</td>
<td><a href="http://wwdasis.samhsa.gov/webt/state_data/US08.pdf">http://wwdasis.samhsa.gov/webt/state_data/US08.pdf</a></td>
</tr>
<tr>
<td>Hepatitis C screening</td>
<td>29</td>
<td><a href="http://wwdasis.samhsa.gov/webt/state_data/US08.pdf">http://wwdasis.samhsa.gov/webt/state_data/US08.pdf</a></td>
</tr>
<tr>
<td>HAV/HBV vaccination</td>
<td>Disaggregated data not available</td>
<td></td>
</tr>
<tr>
<td>Provider education</td>
<td>63</td>
<td>Brown et al., 2006</td>
</tr>
<tr>
<td>Patient education</td>
<td>74</td>
<td>Brown et al., 2006</td>
</tr>
<tr>
<td>Treatment for chronic hepatitis</td>
<td>29</td>
<td>Brown et al., 2006</td>
</tr>
<tr>
<td>Medical monitoring</td>
<td>35</td>
<td>Brown et al., 2006</td>
</tr>
<tr>
<td>HCV counseling</td>
<td>59</td>
<td>Brown et al., 2006</td>
</tr>
</tbody>
</table>

Researchers noted that, overall, nonmedical services, such as counseling and support services for hepatitis, were offered more than medical services, such as biologic testing and treatment (Brown et al., 2006). In general, there are differences in service delivery between opioid treatment programs (OTPs) and nonmedical facilities. Researchers found that treatment programs with more medical personnel offered more types of services than nonmedical facilities (Astone-Twerell, et al., 2006; Brown et al., 2006). In addition, perhaps because of staffing patterns, OTPs tended to offer more medical services than nonmedical treatment programs; whereas nonmedical facilities tended to offer more social services. The authors observed that “although drug free programs provide fewer services for their HCV positive clients, they appear to provide more individualized and/or intensive services” for hepatitis (p. 299).

Other differences between OTPs and nonmedical treatment programs were observed (Astone-Twerell et al., 2006). Compared with OTPs, a greater percentage (figures rounded) of nonmedical treatment programs:

- Had clients who were on HCV medication (93 percent vs. 73 percent).
- Monitored client HCV medications (44 percent vs. 26 percent).
- Set up medical appointments for clients (56 percent vs. 34 percent).
- Had a greater proportion of clients accepting treatment referrals (71 percent vs. 43 percent).
In contrast, more OTPs:

- Referred clients to a healthcare provider for offsite treatment (94 percent vs. 84 percent).
- Obtained followup information (79 percent vs. 62 percent).

Brown et al. (2006) and Astone-Twerell et al. (2006) identify the following gaps in hepatitis service:

- Provider education (Astone-Twerell et al., 2006; Brown et al., 2006)
- Patient education (Brown et al., 2006)
- Patient counseling (Brown et al., 2006)
- Biologic testing (Brown et al., 2006)
- Patient monitoring/help adhering to antiviral therapy (Astone-Twerell et al., 2006)
- Obtaining medication (Astone-Twerell et al., 2006)

**Screening**

Many people who use drugs do not realize they have been exposed to hepatitis; they self-report infection rates that are lower than the prevalence demonstrated by serum testing (Schlicting et al., 2003; Weaver, Cropsey, & Fox, 2005). In a study of people in Alaska who inject drugs, Schlicting et al. (2003) compared self-reports of infection with hepatitis A, B, and C with the results of blood tests and found underreporting for all three types of hepatitis:

- Of 477 participants, 6.5 percent reported a past infection with HAV, but blood tests revealed a true prevalence of 32.5 percent.
- Of 550 participants, 14.9 percent reported a past infection with HBV, but blood tests revealed a true prevalence of 39.8 percent.
- Of 557 participants, 13.3 percent reported a past infection with HCV, but blood tests revealed a true prevalence of 52.7 percent.

In a study in five U.S. cities involving 1,033 people ages 15–30 who tested positive for HCV, only 28 percent knew their positive status; 72 percent were unaware that they tested positive for HCV (Hagan et al., 2006).

**Vaccination in People Who Use Drugs**

Vaccinations against HAV and HBV are effective, and CDC recommends both vaccinations for people who use drugs. Nevertheless, hepatitis vaccination rates among this population appear to be low.

Estimating rates of hepatitis B vaccination among people who use drugs is difficult in part because self-reports of vaccination tend to be unreliable. For example, in a study by Koblin et al. (2007) of 402 women in New York City who use noninjection drugs, 97 women (24.1 percent) indicated that they had been vaccinated, but only 38 showed serologic evidence of vaccination. Similarly, Kuo, Mudrick, Strathdee, Thomas, and Sherman (2004) found that more than half (52
percent) of 92 subjects ages 15–30 who used drugs and claimed to have been vaccinated against HBV were, in fact, susceptible.

Serologic tests among people who use drugs show vaccination rates of 3–17 percent (Altice, Bruce, Walton, & Buitrago, 2005; Koblin et al., 2007; Kuo, Mudrick, et al., 2004; Ompad et al., 2004). Numerous factors could explain the wide range of vaccination rates found by the different studies, including average age of study participants (younger participants are more likely to have been vaccinated), whether the study was conducted at a syringe exchange program (where participants are more likely to interact with medical professionals), and other reasons.

**Missed Opportunities**

Despite that CDC recommends HAV and HBV vaccinations for people who use drugs, many people are not offered these vaccines. Missed opportunities—times when people who used drugs interacted with medical professionals who were in a position to recommend vaccination but did not—are common. Some studies about people who use drugs and are susceptible to HBV infection found the following:

- Of 191 people in Baltimore, 161 (84 percent) had at least 1 missed opportunity and 53 percent had at least 2 missed opportunities (Kuo, Sherman, Thomas, & Strathdee, 2004).
- Of 210 women in New York City, 36.7 percent reported ever being offered HBV vaccinations (Koblin et al., 2007).
- Of 1,134 veterans with hepatitis C, 41 percent had not been asked about vaccination for hepatitis A or B (Hernandez, Hasson, & Cheung, 2009).

**Rates of Vaccination Uptake and Completion**

The HBV vaccination is a series of three injections usually given at 0, 1, and 6 months. Limited research shows that when people who use drugs are offered the HBV vaccine series, the majority are willing to get vaccinated. Altice et al. (2005) conducted a 4-year study of screening and vaccination uptake rates in New Haven, Connecticut, among people who inject drugs. Of 212 people screened, 134 were vaccination eligible, of whom 94 percent received the first injection. Of these, 77 percent completed at least two injections in the series, and 66 percent received all three injections. The researchers offered no monetary incentives for vaccination; however, onsite vaccinations were provided, client appointments were scheduled in advance, and outreach was conducted to remind clients of their appointments.

Other U.S. studies of vaccination uptake among people who have histories of drug use include the following:

- McLaughlin (2007) studied completion rates for combination HAV/HBV vaccination administered at an OTP in Hartford, Connecticut. Of 2,072 clients who received a first dose, 1,914 (92 percent) received the second dose and 1,433 (69 percent) completed the three-dose series.
- Ompad et al. (2004) screened 1,117 people in New York City who used drugs, including injection drugs, for hepatitis B. Of those screened, 610 were susceptible to
hepatitis B. To be offered a vaccination, participants had to return to the clinic and obtain their screening test results, and 466 did so. Of these, 251 agreed to receive at least one injection. These participants were escorted to a nearby, offsite clinic where injections were administered. They received counseling about HBV, HCV, and HIV and were paid $5 per dose as an incentive to complete the vaccination series. Of the 610 subjects eligible to be vaccinated, 98 completed all three doses. People who did not use injection drugs were more likely to complete the series compared with people who used injection drugs (44.4 percent compared with 24.4 percent, respectively).

- In a five-city study, Campbell et al. (2007) studied hepatitis A and B vaccination uptake among young adults who use drugs. Of 3,181 people, 83 percent indicated a willingness to be vaccinated, although fewer than half (43 percent) of these actually received the first dose. Uptake varied considerably by site, from 83 percent in Baltimore to 2 percent in Chicago. The opportunity to receive vaccinations immediately was crucial to uptake. Ninety-five percent of participants with immediate access to the vaccination accepted it.

Client motivations for starting or completing the vaccine series included:

- Convenience (Altice et al., 2005; Campbell et al., 2007; Hagan, Thiede, McGough, & Alexander, 2002; Koblin et al., 2007; McLaughlin, 2007; Ompad et al., 2004).
- Prevention of HBV infection (Koblin et al., 2007).
- Free counseling (Koblin et al., 2007; Ompad et al., 2004).
- Free vaccination (McLaughlin, 2007).

Barriers to vaccination included:

- Lack of awareness of a vaccine (Campbell et al., 2007).
- Needing three doses (Koblin et al., 2007).
- Side effects (Koblin et al., 2007).
- Fear of needles (Koblin et al., 2007).

A combined vaccine against HAV and HBV is available. The combined vaccine requires 3 injections given at 0, 1, and 6 months, but dosing can be accelerated to 0, 7, and 21 days, with a booster at 12 months. Altice et al. (2005) suggest that people who use injection drugs are more likely to complete the vaccine series on an accelerated dosing schedule. However, Brim, Zaller, Taylor, and Feller (2007) point out that the benefits of higher completion rates on the accelerated dosing schedule compared with the 6-month schedule must be weighed against a potential decrease in immunogenicity seen in accelerated dosing, but not evident in regular dosing.

Staff Knowledge of HCV

In a national survey of 434 treatment programs, 69 percent reported that most or all of their staff members had been educated about HCV (Astone, Strauss, Vassilev, & Des Jarlais, 2003). However, little is known about the extent and accuracy of staff knowledge of HCV. Strauss et al. (2006) administered a 20-item, true/false questionnaire on HCV to 104 staff members in two
methadone maintenance treatment (MMT) programs and two nonmedical treatment facilities in the New York metropolitan area. Participants included physicians, nurses, and other medically credentialed or noncredentialed staff members. The majority of participants answered 25 percent of the questions wrong. Medical staff across facilities averaged 14 correct answers, and these results did not differ significantly across sites. Nonmedical staff averages differed significantly across sites: MMT staff averaged 14 correct answers compared with an average of 9 correct answers among staff at the two nonmedical treatment programs. Across all sites, 61.5 percent of staff members had received HCV training, of whom 40.3 percent reported their HCV training took place more than a year before the questionnaire.

**Client Knowledge of HCV**

People who inject drugs have a poor understanding of hepatitis (Carey et al., 2005; Heimer, et al., 2002.) Astone et al. (2003) found that 54 percent of the treatment facilities they surveyed provided HCV education to all clients. However, surveys of people who use drugs reveal gaps in their knowledge about HCV and how to reduce risk. Examples follow (figures rounded):

- 50 percent of 200 patients at an MMT clinic reported that they knew risk factors for contracting HCV (Weaver et al., 2005).
- 49 percent of 334 people who inject drugs knew that hepatitis C can be transmitted by needles and syringes (Carey et al., 2005).
- 70 percent of 597 people who inject drugs knew that treatments are available for HCV (Mehta et al., 2008). Smaller studies by Carey et al. (2005), Walley, White, Kushel, Song, and Tulsky (2005), and Weaver et al. (2005) reported results of 37 percent, 34 percent, and 32 percent, respectively.
- 51 percent of 200 patients at an MMT clinic knew where to get HCV treatment (Weaver et al., 2005).
- 42 percent of 280 patients in a drug treatment program knew that HCV medications can be effective in people who actively use drugs (Strauss et al., 2007).

Weaver et al. (2005) asked clients in MMT how they would prefer to receive information on HCV. The majority (76 percent) preferred printed matter, 68 preferred video format, 65.2 percent wanted counseling (individual or group), and 58 preferred a referral to HCV treatment.

**Effect of HCV Education on Risky Transmission Behaviors**

Only one U.S. study within the parameters of this literature review attempted to ascertain the effects of HCV educational or motivational interventions on client behaviors. Zule, Costenbader, Coomes, and Wechsberg (2009) compared motivational interviewing and client educational interventions for people who inject drugs and who are not in a treatment program. The study measured the effects of these interventions on alcohol consumption, use of new syringe at last injection, and condom use. The study enrolled 851 people: 423 in the motivational group and 428 in the educational group. Participants were assessed at baseline and at 6 and 12 months after the intervention. Seventy-five percent ($n = 625$) completed the 6-month followup, and 72 percent ($n = 462$) completed the 12-month followup. The groups did not differ significantly demographically, and approximate numbers completed both followup interviews.
Both interventions consisted of six sessions. The educational sessions covered the three main types of hepatitis, risky behaviors, how drug equipment can become contaminated with HCV, and information on HIV and addiction. The motivational intervention began with information on hepatitis, transmission modes, and the like but primarily consisted of counseling participants on motivation to change. At baseline, 86 percent of participants in the educational group reported using a new syringe the last time they injected. This increased to 88 percent at the 6-month followup and dropped to 82 percent at the 12-month followup. Among participants in the motivational intervention group, 88 percent reported using a new syringe at baseline. This increased to 91 percent at 6 months and dropped to 89 percent at 12 months. None of the differences on syringe use within groups reached statistical significance. Between groups, participants exposed to motivational interventions were significantly less likely than participants in the educational group to use alcohol after 6 months. At 12 months, there were no significant differences between study groups on alcohol use. However, both groups showed lower alcohol use compared with use at baseline.

Two smaller, non-U.S. studies reported little success with educational interventions among people who inject drugs. One study in London randomized 52 people into educational counseling and 43 people into motivational counseling. A total of 62 subjects were available for followup 12 months later. There were no significant differences between groups in injecting behavior, needle exchange, or rates of seroconversion (Abou-Saleh et al., 2008).

Interviews with 60 people in Australia who inject heroin found that knowledge of possible consequences of IDU, including death by overdose, was not enough to change risky behaviors in people who were indifferent to or fatalistic about death (Miller, 2009).

**Effect of HCV Diagnosis on Risky Transmission Behaviors**

Evidence suggests that knowing one’s HCV status has only a modest effect on subsequent risky behavior.

Tsui et al. (2009) studied 112 people in San Francisco (predominately White males) younger than age 30 who tested negative for HCV at the start of the study but seroconverted during the study period. The study sought to determine whether knowledge of HCV status affected alcohol use, the use of non-injection drugs, sharing injection drug equipment, and condom use. After the HCV screening test, participants were given counseling that included information about the need to reduce drinking to prevent harm to the liver, how to decrease the likelihood of passing the virus to others, and medical evaluation and treatment modalities. Knowledge of positive HCV status was not associated with a significant reduction in IDU or in sharing equipment or in an increase of condom use. The authors conclude that “screening and providing post-test counseling for HCV in young [people who inject drugs] is insufficient for changing long-term behaviors” (p. 162).

Hagan et al. (2006) studied 3,004 people ages 15 through 30 (the majority were White and male) in 5 U.S. cities. They found that knowledge of HCV status made little difference in several injection risky behaviors, such as sharing syringes, cookers, and cotton filters. However, researchers found that participants who believed they were HCV negative were less likely to
share rinse water than those who believed they were HCV positive or did not know their serostatus.

A study in Denver of 197 people ages 15 through 65 who injected drugs (predominately White and male) compared subjects who knew they tested positive for HCV with subjects who were unaware of their HCV status before the study. Researchers found that participants who did not know their HCV status were more likely to have injected with a used needle and to have shared other drug paraphernalia (Kwiatkowski, Fortuin Corsi, & Booth, 2002).

Ompad, Fuller, Vlahov, Thomas, and Strathdee (2002) studied people younger than 30 in Baltimore (predominantly Black women) who inject drugs to determine whether knowledge of HCV status had an effect on risky behaviors. In this study, counselors provided pretest and posttest HCV counseling to 106 young people and interviewed them about risky behaviors before disclosing HCV status to participants. At 6-month followup, both those who tested positive and those who tested negative for HCV were continuing to share injection paraphernalia, including syringes and needles, and were continuing to engage in high-risk practices, such as backloading.

**Effect of HCV Diagnosis on Consumption of Alcohol and Marijuana**

High rates of alcohol use have been noted among people who have hepatitis C who inject drugs (Campbell et al., 2006; Ompad et al., 2002; Weaver et al., 2005). Heavy alcohol use in the presence of HCV infection carries increased risk of developing serious liver complications, including increased rates of fibrosis, cirrhosis, and hepatocellular carcinoma (Donato et al., 2002; Jamal & Morgan, 2003; Singal & Anand, 2007).

Research shows that, among people who inject drugs, knowing that they are infected with HCV can have a modest effect on their alcohol consumption. One study screened participants for HCV infection and provided education on HCV and the need to stop drinking alcohol if they had hepatitis C. Of the 132 participants who regularly drank one or more alcoholic drinks per week before their screening test, 27 percent decreased their alcohol consumption at followup, which occurred in 3 to 35 months (median 14 months) after the screening test (Mark, Murray, Callahan, & Gunn, 2007).

Tsui et al. (2007) surveyed 400 people who have HIV and a history of alcohol abuse about whether they were ever told they had hepatitis C. Results showed that a higher percentage of participants who were told they had hepatitis C abstained from alcohol (64 percent) compared with participants who were never told they had hepatitis C (52 percent).

Tsui et al. (2009) found an initial reduction in alcohol consumption in the 112 study subjects immediately after they learned they were infected with HCV, but their alcohol use increased over time.

Cannabis can also increase harm to the liver in people who have hepatitis C. Studies show that daily cannabis smoking is associated with severity of steatosis (“fatty liver”), moderate-to-severe fibrosis, and rate of fibrosis progression, suggesting that patients with chronic hepatitis C should be discouraged from using cannabis (Hézode et al., 2005, 2008; Ishida et al., 2008). No studies
have been identified that measure patient reduction in cannabis use with knowledge of HCV serostatus.

**Treatment Referral and Uptake**

Healthcare providers play a key role in determining whether a patient gets treatment for hepatitis C (Wagner & Ryan, 2005). A healthcare provider’s decision to recommend HCV treatment for a patient with SUDs takes into account the patient’s ability to adhere to treatment, psychiatric comorbidity (especially depression), and risk of reinfection. Providers might also consider whether drug use is ongoing or in the past, whether the patient injects drugs, the types of drugs injected, the frequency of IDU, whether the patient shares needles, whether HCV treatment is likely to cause relapse, and the like (Strader, Wright, Thomas, & Seeff, 2004). When determining whether to recommend hepatitis treatment, healthcare providers might also consider genotype, stage of disease, and other factors, as they do for people who do not have SUDs. NIH (2002) recommends making case-by-case decisions on treating hepatitis C in patients with SUDs.

When treatment is offered, few patients with histories of drug use accept. One study of patient uptake of HCV treatment in New York City found that 20 of 31 patients had been offered treatment for HCV, but only 2 agreed to treatment. The main reasons cited for declining treatment include having no symptoms, fear of liver biopsy, and fear of medication side effects. At followup, one of the two patients in treatment had discontinued, citing intolerable side effects (Schackman, Teixeira, & Beeder, 2007).

Mehta et al. (2008) report that, of 418 participants with hepatitis C, 86 (21 percent) reported that their healthcare providers discussed treatment options with them. Of those who had discussed treatment with their provider, 36 started treatment. Reasons for declining treatment included fear of antiviral treatment and lack of need for antiviral treatment.

Patients from 14 U.S. drug treatment programs reported that information from peers influenced their decisions to delay or to initiate antiviral treatment (Munoz-Plaza et al., 2008). Because peers are such a strong source of information (correct or incorrect), HCV support groups led by trained peers are encouraged in the literature. However, only 12 percent of nonmedical treatment programs and 30 percent of OTPs provide support groups for patients with hepatitis C (Strauss, Astone, Vassilev, Des Jarlais, & Hagan, 2003).

SUD treatment providers can play an important role in helping patients receive antiviral treatment. A survey of 233 treatment programs revealed that the majority of the programs kept a list of healthcare providers experienced with serving people in recovery and that accepted referrals for followup testing for clients who tested positive for HCV (Astone-Twerell et al., 2006). More than half (56 percent) of the nonmedication treatment programs had a policy to set up and provide transportation to medical appointments for clients. Approximately 71 percent of clients attending these programs accepted referrals for followup. Seventy percent of MMT programs also provided access to followup testing. This study did not measure how many clients underwent antiviral treatment after further assessment by a healthcare provider. However, when asked to speculate about why not all clients received antiviral medication, most treatment programs (36 percent) indicated that the client had not been abstinent long enough to start treatment. Lack of funding to cover treatment costs, client fear of side effects, and the negative
impact of antiviral treatment on client recovery from SUDs were other common reasons cited by treatment programs about why clients had not received HCV medication (Astone-Twerell et al., 2006).

**HCV Treatment in Patients Who Use Alcohol**

People who actively use alcohol should not be categorically denied hepatitis treatment (NIH, 2002); however, use of alcohol before or during antiviral treatment is associated with reduced response to treatment.

A study in 24 Department of Veterans Affairs hospitals evaluated treatment response in 726 patients with HCV infection (Anand et al., 2006). Researchers compared patients who were nondrinkers (they had stopped drinking at least 1 year before treatment), patients who drank moderately (fewer than 6 drinks a day), and patients who drank heavily (6 or more drinks a day) until beginning HCV treatment. Sustained virologic response (SVR) rates were 20 percent among nondrinkers, 15 percent among moderate drinkers, and 19 percent among heavy drinkers, but the differences were not statistically significant. Anand et al. (2006) found that recent drinkers discontinued antiviral treatment at a rate significantly higher than that of nondrinkers (40 percent and 26 percent, respectively).

Chang et al. (2005) assessed combination antiviral therapy for HCV in 98 patients who had a history of alcohol consumption. They found that patients who had consumed fewer than 30 grams of alcohol per day were more likely to achieve an SVR than patients who drank more.

**Adherence to and Success of HCV Treatment in Patients With Histories of SUDs**

The ability of people who have past or active SUDs to adhere to antiviral treatment is a concern when considering treatment for hepatitis C because adherence is associated with SVR. Adherence is typically understood to be taking at least 80 percent of the cumulative prescribed dose of each medication for at least 80 percent of the treatment duration. Evidence about HCV treatment completion rates among people who have a history of drug use varies. Some studies show higher rates of dropout for people who have a history of drug use than for others in HCV treatment (Mauss, Berger, Goelz, Jacob, & Schmutz, 2004; Neri et al., 2002; Schaefer et al., 2003). For instance, Neri et al. (2002) showed that people who used heroin who began antiviral treatment within 4 weeks of completing detoxification with methadone discontinued HCV treatment at higher rates than people who have no history of drug abuse. In this study, all 30 subjects in the control arm completed the study, but only 30 of 47 people who had used heroin did so. However, people who completed treatment had similar SVR rates, regardless of history of heroin use.

Sylvestre and Clements (2007) studied 71 patients receiving MMT who started antiviral treatment for HCV and tracked their reasons for discontinuing treatment. Fifteen participants were drinking at least some alcohol during the treatment period, and 42 used illicit drugs. Most \( n = 54 \) completed antiviral treatment, and 48 were adherent. Seventeen participants discontinued treatment early, the majority citing intolerable somatic side effects.
In contrast, in a study involving 454 subjects (98 of whom injected drugs), Robaeys et al. (2006) found that people who actively used or had used injection drugs completed treatment at similar rates as subjects who never injected drugs. Among people who used or had used injection drugs, no significant difference was noted between those on MMT and those who were not or between subjects actively injecting drugs and those who were not. In a review of seven studies from 1995 through 2003, Schaefer, Heinz, and Backmund (2004) report adherence to treatment ranging from 46 percent to 94 percent in patients with histories of IDU. In a review of studies from 1985 to 2004, Robaeys and Buntinx (2005) found similar adherence rates.

Few studies examine HCV treatment outcomes in patients with past or active drug use. Small enrollment, differences in HCV genotype, length of abstinence from substance use (if required for treatment), co-occurring physical and mental disorders (if noted), length of followup period, and other differences among studies make comparisons difficult. Two reviews of clinical trials on the effectiveness of HCV treatment in patients with past or active drug use conclude that these patients can obtain a SVR comparable with that of other patients if they are treated by healthcare providers knowledgeable about SUD and HCV (Robaeys & Buntinx, 2005; Schaefer et al., 2004).

Some studies show that people who have SUDs can be successfully treated for HCV while they are in drug treatment, and even during relapses to drug use, if they complete antiviral treatment (Backmund, Meyer, Von Zielonka, & Eichenlaub, 2001; Bruggmann, et al., 2008; Dalgard et al., 2002; Sylvestre, 2005). In their review of the literature published from 1985 to 2004, Robaeys and Buntinx (2005) found no difference in SVR between people who use substances and control groups.

### Adherence to and Success of HCV Treatment in Patients With Substance Use and Preexisting Mental Disorders

A study by Golub et al. (2004) measured moderate to severe depression in 56 percent (108/193) of people who have HCV and histories of IDU. Although severe mental disorders can contraindicate treatment for HCV (Schaefer et al., 2004), several studies suggest that prior depression, anxiety, or both are not contraindications to antiviral treatment.

In a study with 43 people who inject drugs, Guadagnino, Trotta, Carioti, Caroleo, and Antinori (2006) found that antiviral treatment did not worsen depression in patients who reported depression at baseline. Depression in patients did not affect early virologic response or discontinuation of treatment. However, high depression scores predicted somatic side effects, such as pain and fatigue.

Similarly, in a study of 176 patients, Martin-Santos et al. (2008) found that a history of depressive or anxiety syndromes, baseline anxiety, or use of antidepressants at the start of treatment did not predict an increase of psychiatric side effects of antiviral medication; however, high baseline depression scores were associated with an increase of psychiatric side effects during HCV treatment. In this study, although 79 percent of patients with depression, anxiety, or both adhered to treatment, adherence was higher (91 percent) in patients who did not experience psychiatric syndromes during treatment.
Sylvestre, Litwin, Clements, and Gourevitch (2005) found that patients with and without preexisting psychiatric comorbidities stopped HCV treatment at similar rates. (However, psychiatric side effects were the primary reason patients ended treatment prematurely.) In a later study, Sylvestre and Clements (2007) found that patients who reported a prior psychiatric condition were less likely than those who did not report such a condition to take antiviral treatment as prescribed (64 percent vs. 72 percent). However, the two groups discontinued treatment at similar rates: 26 percent of those who reported a prior psychiatric condition and 21 percent without a prior psychiatric condition discontinued treatment prematurely.

Studies of HCV treatment in patients with histories of substance use suggest that psychiatric comorbidity does not negatively affect SVR in patients who complete treatment. Alvarez-Uria, Day, Nasir, Russell, and Vilar (2009) studied people who have HCV genotype 2 or 3; their study included people who had psychotic disorders who also injected drugs. Patient subgroups included:

- 60 who formerly injected drugs, of whom 44 achieved an SVR.
- 10 who actively injected drugs, of whom 4 achieved an SVR.
- 34 who had a history of depression, of whom 20 achieved an SVR.
- 4 who had a chronic psychiatric disorder, of whom all 4 achieved an SVR.

Some researchers (Alvarez-Uria, Day, Nasir, Russell, & Vilar, 2009; Jeffrey et al., 2007; Schaefer & Mauss, 2008; Sylvestre, 2002) recommend premedicating MMT patients with antidepressants before HCV treatment and using aggressive interventions with antidepressants during treatment, as indicated.

**Psychiatric Side Effects of and Adherence to Treatment**

Psychiatric side effects, especially depression and anxiety, are common during hepatitis antiviral treatment, but studies suggest that psychiatric side effects do not occur more frequently in people who have histories of IDU. A study of 100 people, 50 in MMT and 50 with no IDU in the 5 years before starting antiviral treatment, showed that, at the start of treatment, 4 of 50 people on MMT and 2 of 50 people in the control group were receiving antidepressants. During the course of treatment, 15 of 50 people in MMT and 10 of 50 in the control group were prescribed antidepressants, but this difference was not significant ($p = .36$) (Mauss et al., 2004).

Schaefer et al. (2003) studied the relationships among the psychiatric side effects of antiviral treatment, adherence rates, and SVR rates. Of 81 participants at the start of treatment, 16 were identified as having psychiatric disorders, 21 were on MMT, 21 were formerly addicted to substances but not on MMT, and 23 were a control group reporting no prior drug addiction or psychiatric disorders. Among those in the psychiatric group:

- Six had major depression.
- One had general anxiety disorder.
- Two had schizoaffective disorder.
- Four had chronic schizophrenia.
- Three had severe borderline personality disorder.
In this study, most participants who discontinued treatment early had former addictions. Nobody with prior mental disorders dropped out as a result of psychiatric side effects. Overall, 22 percent of participants discontinued treatment and only 2 cited psychiatric side effects. Of the 16 patients in the psychiatric group, 3 discontinued treatment: 2 cited somatic side effects, and 1 could not comply with treatment. During treatment, 16 percent of participants developed new depressive symptoms; however, depression, whether it resulted from a side effect of treatment or was preexisting, did not predict dropout. Schaefer et al. (2003) also found that, among those with histories of addiction, time abstinent was not associated with dropout. SVR was 37 percent overall, and rates of SVR did not differ significantly among groups.

People who have a history of SUDs are more likely to leave antiviral treatment in the first 2 months, compared with other groups (Mauss et al., 2004; Schaefer et al., 2003). In a study of 50 patients on MMT and 50 with no IDU history, Mauss et al. (2004) found that half of the patients in the MMT group discontinued treatment prematurely; 22 percent left in the first 8 weeks, compared with 4 percent of patients in the control group who left during this period.

One explanation for early dropout is that psychiatric side effects develop early in antiviral treatment (Robaeys & Buntinx, 2005). In one study of 98 patients (Castera, Constant, Bernard, de Ledinghen, & Couzigou, 2006), 38 developed psychiatric side effects over the course of treatment, most (33) between baseline and week 12. The development of psychiatric side effects had no impact on adherence rates, and there was no significant difference in SVR between patients who experienced psychiatric side effects and those who did not. Early detection and treatment of these side effects are important ways to help patients adhere (Martin-Santos et al., 2008).

**Risk of Reinfection Among People Who Inject Drugs**

Because relatively few people who inject drugs have had HCV treatment, and because only some of them clear the virus, determining reinfection rates among this group is difficult. Three studies within the parameters of this literature review tracked reinfection among a subset of subjects who returned to IDU after HCV treatment (Exhibit 2).

**Exhibit 2 Reinfection Among People Who Inject Drugs**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number Reporting IDU Who Cleared HCV</th>
<th>Number Reporting IDU at Followup</th>
<th>Number Reinfected</th>
<th>Followup Period (months)</th>
<th>Incidence of Reinfection (per 100 person years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Backmund, Meyer, &amp; Edlin, 2004</td>
<td>18</td>
<td>9</td>
<td>2</td>
<td>39.8 (mean)</td>
<td>4.10</td>
</tr>
<tr>
<td>Currie et al., 2008</td>
<td>38</td>
<td>16</td>
<td>1</td>
<td>5.1 (median)</td>
<td>1.75</td>
</tr>
<tr>
<td>Dalgard et al., 2002</td>
<td>27</td>
<td>9</td>
<td>1</td>
<td>64 (median)</td>
<td>2.50</td>
</tr>
</tbody>
</table>
A few studies compared rates of reinfection among people who inject drugs who had cleared HCV with rates of new infections among people who inject drugs and had never had hepatitis C to gather information on whether clearing HCV lends partial immunity. Mehta et al. (2002) compared 164 people who had never been infected with HCV with 98 people who had cleared HCV. In their study, 35 subjects (21 percent) who had never had hepatitis C were infected during the study period, compared with 12 people (12 percent) who were reinfected. Grebely et al. (2006) also found that reinfection rates of people who spontaneously cleared HCV were lower than initial infection rates (9.2 percent vs. 18.6 percent). Researchers in these two studies conclude that people who have cleared HCV might be at lower risk of acquiring the virus in the future compared with people who have not had the virus, regardless of their risky behaviors.

In contrast, Aitken et al. (2008) and Micallef et al. (2007) found much higher incidences of reinfection. In a retrospective study in Australia, Micallef et al. (2007) reported that 9 of 18 subjects were probably reinfected, compared with 114 of 423 people who acquired a first-time infection. However, the difference did not reach statistical significance. In another Australian study, Aitken et al. (2008) found similar rates of reinfection: 23 of 50 people in their study were reinfected with HCV after having cleared the virus, compared with 10 of 55 cases of new infection. According to Aitken et al. (2008), the high incidence of reinfection measured in their study could be attributed to a shorter followup period and a definition of reinfection that included possible acute infection.
References


Miller, P. G. (2009). Safe using messages may not be enough to promote behaviour change amongst injecting drug users who are ambivalent or indifferent towards death. *Harm Reduction Journal, 6*(18), 1–8.


Appendix—Methodology

The series of comprehensive searches undertaken for this literature review was done by the University of Maryland’s Center for Substance Abuse Research (CESAR), starting in February 2007. The searches covered literature published in English from January 1999 through July 2009. All fields (including title, abstract, and key terms) were searched.

The initial search, done through the PubMed database of clinical and nursing journals and through the Cochrane Review, aimed to identify review articles, including meta-analyses, practice guidelines, reviews of the literature, and evaluation studies. The initial search, conducted by a professional librarian from CESAR, used the following terms:

- **Cochrane Review.** Hepatitis and selected relevant citations.

This search elicited very few documents. Therefore, the scope of the search was broadened to include overview articles on the management of hepatitis in people who have a history of substance use disorders. A followup search of the literature was conducted in July 2007 and again in May 2009. These searches used the following terms:

- **PubMed.** (hepatitis, viral human [main heading] OR hepatitis, chronic [main heading] OR hepatitis, toxic [main heading]) AND (substance-related disorders [main heading] OR substance abuse treatment centers [main heading]) AND date limits
- **CINAHL (Cumulative Index to Nursing & Allied Health Literature), PsycINFO, socINDEX, and Academic Search Premier.**
  - (viral hepatitis OR hepatitis C) [all text fields] AND (substance abuse OR drug abuse) [all text fields] AND reviews [text word] AND date limits
  - (viral hepatitis OR hepatitis C) [all text fields] AND (substance abuse OR drug abuse) [all text fields] AND (NOT reviews) AND, for PsycINFO only, (Drug and Alcohol Rehabilitation [classification 3383])

Supplemental searches were undertaken on specific targeted topics, such as the use of directly observed antiviral therapy among people in drug treatment settings. These supplemental searches, conducted in August 2007 and updated on May 26, 2009, used the following search paths:

**PubMed**

- viral diseases [main heading] AND directly observed therapy [main heading]
- hepatitis [main heading] AND case management [main heading]
- hepatitis, viral human [main heading] AND (the following terms, serially, limited to the United States):
CINAHL, PsycINFO, socINDEX, and Academic Search Premier

- directly observed therapy [all text fields]
- (viral hepatitis OR hepatitis C) [all text fields] AND serially, all the terms listed above under PubMed, from case management through sex workers OR prostitutes

Using the search strategy developed for the initial and followup literature searches, the literature review was updated in May 2009, January 2010, March 2011, and August 2011.

TIP writers reviewed abstracts for citations found. They eliminated citations that focused on preclinical research or on the specific medical treatment of hepatitis. They also excluded studies that did not clearly differentiate between hepatitis patients with a history of drug use and those without this history.

After references were selected using these search procedures, the bibliographies or citation lists from these references were reviewed to find older, seminal literature appropriate to this topic. Members of the TIP consensus panel suggested additional research that would be relevant to the TIP.
Section 2—Links to Select Abstracts


http://www.ncbi.nlm.nih.gov/pubmed/18166478


Section 3—Bibliography


Miller, P. G. (2009). Safe using messages may not be enough to promote behaviour change amongst injecting drug users who are ambivalent or indifferent towards death. Harm Reduction Journal, 6(18), 1–8.


