

Overcoming Barriers to Prevention, Care, and Treatment of Hepatitis C in Illicit Drug Users

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Injection drug use accounts for most of the incident infections with hepatitis C virus (HCV) in the United States and other developed countries. HCV infection is a complex and challenging medical condition in injection drug users (IDUs). Elements of care for hepatitis C in illicit drug users include prevention counseling and education; screening for transmission risk behavior; testing for HCV and human immunodeficiency virus infection; vaccination against hepatitis A and B viruses; evaluation for comorbidities; coordination of substance-abuse treatment services, psychiatric care, and social support; evaluation of liver disease; and interferon-based treatment for HCV infection. Caring for patients who use illicit drugs presents challenges to the health-care team that require patience, experience, and an understanding of the dynamics of substance use and addiction. Nonetheless, programs are successfully integrating hepatitis C care for IDUs into health-care settings, including primary care, methadone treatment and other substance-abuse treatment programs, infectious disease clinics, and clinics in correctional facilities.

Injection drug users (IDUs) constitute the largest group of persons infected with the hepatitis C virus (HCV) in the United States, and most new infections occur in IDUs. The prevalence of HCV antibody in most studies of older IDUs is 80%–90% [1–3], and uninfected IDUs generally become infected at rates of 10%–20%/year [3–7]. Controlling the HCV epidemic, therefore, will require developing, testing, and implementing strategies for the prevention, care, and treatment of hepatitis C that will be effective for IDUs [8]. Substantial barriers to providing effective care and treatment for IDUs with hepatitis C stem from characteristics of the disease, patients, providers, and the health care system. As a result, although a large proportion of IDUs with hep-

atitis C express willingness to undergo treatment, a disproportionately low number of IDUs have actually received antiviral therapy for HCV infection [9]. Fortunately, clinicians undertaking hepatitis C care can draw upon a substantial body of research and clinical experience in the prevention and management of chronic viral diseases among IDUs [10, 11]. This article addresses the scope of hepatitis C care and the challenges and barriers faced by health-care providers and IDUs in the medical management of HCV infection.

INJECTION DRUG USE AND HEPATITIS C RISK BEHAVIOR

Drug use is a complex behavior with multidimensional determinants, including social, psychological, cultural, economic, and biological factors [11–13]. The 2002 National Survey on Drug Use and Health [14] reported that 3.7 million Americans >12 years have experimented with heroin use. An estimated 1.0–1.5 million Americans actively use illicit drugs by injection [15]. Bloodborne viral infections, including HCV, hepatitis

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B virus (HBV), and HIV, are transmitted when uninfected IDUs use injection equipment, especially syringes, that have previously been used by an infected person [15]. The transmission of HCV is estimated to be 10 times more efficient than that of HIV [16] and can probably result not only from the sharing of syringes but also from the sharing of other injection equipment, such as “cookers” (i.e., bottle caps, spoons, and other containers used to dissolve drugs) and “cottons” (i.e., filters used to remove particulate matter while drawing up the drug solution into a syringe) [3–5]. Transmission can probably also occur through minor instances of blood contact, such as when one person administers an injection to another [17].

The HIV epidemic led to significant changes in injection practices. Beginning in the 1980s, as IDUs learned of the risks of disease transmission through sharing syringes, behavioral norms changed, and rates of syringe sharing dropped dramatically [18–20]. HIV prevention programs, including needle exchange, outreach, and peer education, have strengthened and supported reductions in needle sharing while increasing the availability of sterile syringes and injection equipment. When given access to sterile syringes, IDUs readily made use of them, reducing needle sharing [18–20] and rates of disease transmission [15, 21, 22]. The sharing of other injection equipment, however, remains relatively common [19, 23], as does the practice of giving and receiving injections [24]. Historically, HCV was usually acquired very soon after a person began injecting drugs [2, 25]. Recent studies have shown, however, that, since the introduction of needle exchange and other HIV prevention interventions for IDUs, the prevalence and incidence of HCV infection among young IDUs and recent initiates have declined substantially [5, 6, 7, 22]. Thus, although the incidence of HCV infection among IDUs remains unacceptably high [3–7], the evidence suggests that prevention efforts can be successful.

NATURAL HISTORY OF HCV INFECTION

Infection with HCV may result in 1 of 3 outcomes: infection may spontaneously resolve during the acute phase and never progress to chronic infection, infection may become chronic without medical complications or end-organ disease, or infection may become chronic, with progressive medical complications, such as cirrhosis, hepatocellular carcinoma, or end-stage liver disease. The virus-host interactions that result in the resolution of HCV infection are not well understood [26], but it has been shown that treatment of acute HCV infection can result in high rates of successful clearance of the virus [27–29]. Thus, regular testing for HCV of uninfected persons at high risk for infection—particularly young IDUs and recent initiates to injection drug use—is an important strategy for secondary prevention of chronic HCV infection in persons who acquire the infection acutely. On the other hand, the long period of

clinical latency before chronic HCV infection causes severe liver disease and the low but variable proportion of infected persons who will develop severe liver disease make it impossible to predict the clinical sequelae of untreated HCV infection in any particular individual. This complicates the assessment of the benefits of treatment when counseling infected patients.

HEPATITIS C CARE FOR ILLICIT DRUG USERS

Care for hepatitis C is a vital component of a comprehensive health program for persons who use illicit drugs. Such care includes screening for transmission risk behavior, prevention counseling and education, testing for HCV antibody and RNA, vaccination against hepatitis A virus (HAV) and HBV, and evaluation for comorbidities, including HIV infection. IDUs who are found to have chronic HCV infection should be assessed for the presence and degree of liver disease and evaluated for treatment for HCV. This evaluation should include determining the need for substance abuse services, psychiatric care, and social support and an effort to engage the patient in primary care.

Patient-provider relationships. Caring for drug users presents special challenges to the health-care team and requires patience, experience, and tolerance. Comorbid psychiatric conditions are common, including major depression, anxiety disorders, posttraumatic stress disorder, and bipolar disorders. In addition, many drug users have had negative experiences with the health-care system and its providers [30, 31]. IFN therapy has a number of reversible neuropsychiatric adverse effects, including impairment in concentration, depression, insomnia, and irritability [32]. Successful treatment for hepatitis C requires a trusting relationship with a health care provider who can help patients anticipate, plan for, and endure the difficulties of therapy for HCV infection. Patients must work at adhering to the regimen, physicians must be responsive to patients' experiences of adverse effects, and both parties must be able to communicate openly about their expectations and frustrations. Physician-patient relationships that support this kind of collaboration are based on mutual trust and respect and take time to develop. Drug users often believe that the health care they receive is judgmental and condescending, unresponsive to their needs, and delivered without respect. For their part, persons actively using drugs may fail to follow through with medical advice, appointments, and prescribed medication [10, 11, 12, 33]. These problems can lead to a dynamic of mistrust and lack of cooperation between the patient and provider.

The extensive experience gained from treating IDUs for medical conditions, especially HIV infection, has led to the development of effective principles for engaging drug users in health-care relationships (table 1) [11, 34–36]. Successful programs invariably adopt a respectful approach to substance users, un-

Table 1. Principles for managing health-care relationships with substance-using patients.

Establish a climate of mutual respect
Maintain a professional approach that reflects the aim of enhancing patients' well-being; avoid creating an atmosphere of blame or judgment
Educate patients about their medical status, proposed treatments, and their adverse effects
Include patients in decision making
If possible, establish a multidisciplinary team consisting of primary care physicians, HIV specialists, psychiatrists, social workers, and nurses
Have a single primary care provider coordinate the care delivered by such a team, to maximize consistency and continuity
Define and agree on the roles and responsibilities of both the health-care team and the patient
Set appropriate limits and respond consistently to behavior that violates those limits
Minimize barriers to participation (e.g., allow flexibility in adherence to appointment schedules and allow drop-in visits, to the extent possible)
While recognizing that patients must set their own goals for behavior change, work with patients to achieve commitment to realistic goals for healthier behaviors
Acknowledge that abstinence is not always a realistic goal; emphasize measures to reduce risks for patients who continue to use drugs
Acknowledge that sustaining abstinence is difficult and that success may require several attempts
Be familiar with local resources for the treatment of drug users
Pitfalls to avoid
Unrealistic expectations
Frustration
Anger
Moralizing
Blame
Withholding therapy

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derstand the medical and behavioral sequelae of addiction, and refrain from moralistic judgments [10, 11, 35–37]. They use client-centered approaches and, often, multidisciplinary teams. Providers can be effective by working with clients individually to identify changes they are motivated to make to enhance their health and well-being. This client-centered approach recognizes that, when global behavior change (such as ceasing all drug use) is not possible or likely in the short term, many other measures can nevertheless reduce the harmful medical consequences of high-risk behavior [36, 38].

Education about prevention of HCV infection. Education and counseling aimed at reducing the transmission of HCV and other bloodborne pathogens are integral components of all health-care services for IDUs. The primary goal of prevention education and counseling for patients who continue to inject drugs is to support safer injection practices [39, 40]. IDUs

should be encouraged to use a new, sterile syringe for each injection and to avoid sharing injection equipment with other users, practices that can reduce the risk of acquisition of HCV by uninfected persons and help those who have received successful antiviral treatment to avoid reinfection. Health-care providers can also facilitate access to sterile syringes by prescribing syringes [41] and by referring patients to syringe exchange programs and pharmacies that sell syringes without a prescription [42, 43]. Physicians in at least 46 states are allowed by law to prescribe syringes to IDUs to reduce transmission of bloodborne infections [44]. A survey of knowledge and attitudes among health-care providers about prescription of syringes showed uncertainties about legal issues but substantial willingness to prescribe syringes to IDUs [45]. Prescribing syringes to patients who inject drugs can strengthen patient-provider relationships and facilitate retention in care.

Where possible, IDUs should also be referred to local syringe exchange programs and pharmacies that sell syringes without a prescription. Currently, there are >200 syringe exchange programs in >150 cities in 36 states in the United States. A majority of syringe exchange programs provide a range of ancillary services, including education, support groups, and case management. Pharmacies are more widely accessible than are syringe exchange programs, operating in more locations and for more hours. At present, pharmacies in 46 states may legally sell syringes without a prescription, because they either do not have laws requiring prescription for syringes [46, 47] or have recently amended them [42, 43, 48, 49].

Health-care professionals can provide education and support for safer injection practices at relatively little cost. Only a limited number of public health departments offer HCV education [50]. In addition, a recent report indicated that only 54% of treatment programs for substance abuse provide education about HCV to all of their patients [51]. Thus, there is a need to increase education about HCV for IDUs and other high-risk populations. Incorporating education initiatives regarding HCV into existing and widely available HIV prevention programs and substance-abuse treatment programs is an optimal and cost-effective strategy to address the growing need for education about HCV through the use of existing resources. Continuing education programs can help physicians and pharmacists, who have traditionally been trained to make every effort to keep syringes from being used for nonmedical purposes, recognize that providing access to sterile syringes and education about sterile injection methods can be lifesaving interventions [52].

Screening and testing for HCV infection. A comprehensive health care program for IDUs should include strong linkages with hepatitis C prevention services, including community-based programs of counseling and testing for HCV, so that IDUs infected with HCV can be identified and their entry into

care facilitated. Testing for HCV antibodies should be accompanied by client-centered counseling based on individualized behavioral risk assessments. Such services should be available either on-site or by referral [53] in all public programs and institutions serving illicit drug users, including public health clinics and hospitals, syringe exchange and HIV prevention programs, substance-abuse treatment programs, correctional institutions, programs for high-risk youth, HIV counseling and testing sites, sexually transmitted disease clinics, mental health clinics, and psychiatric hospitals. Regardless of where HCV testing occurs, counseling and testing provide a critical opportunity to connect IDUs to comprehensive medical and social services addressing other core issues, such as primary care, untreated mental health conditions, housing, and hunger.

Existing testing programs outside of medical facilities generally provide only testing for HCV antibody and do not offer tests for HCV RNA. HCV RNA testing is necessary to distinguish between persons with chronic infection and those who have cleared their infection spontaneously. Without HCV RNA testing, persons who have positive antibody test results do not learn whether they are actually infected, and many who are not infected may assume that they are [54]. Persons whose HCV infection resolved spontaneously during the acute phase are susceptible to reinfection [55, 56]. Therefore, programs of counseling and testing for HCV require strong referrals to medical care for confirmatory testing for HCV RNA and appropriate evaluation and follow-up. If negative HCV RNA test results reveal cleared infection, IDUs can be so informed, counseled on strategies to reduce the risk of reinfection, and referred to prevention services.

Vaccination against HAV and HBV. HAV and HBV are important public health concerns for IDUs infected with HCV, because of the increased risk of severe liver disease due to superimposed chronic HBV infection [57] or acute HAV infection [58]. Vaccinations against HAV and HBV are recommended for persons at high risk, including IDUs and persons with HCV infection [59]. Thus, vaccination strategies for HAV and HBV are an important component of hepatitis C care [60]. To maximize their effectiveness, vaccination strategies should take into account issues such as seroprevalence [61, 62], knowledge of immunity status [63], adherence to follow-up visits [64], vaccine schedule [65], current medical services [66], and the need for social services [65]. Targeted vaccinations for IDUs have been shown to be effective when done at methadone clinics [67], as part of infectious disease prevention services at a syringe prescription program [68], or in other community-based settings [69]. Of note, even if a vaccine series is not completed or not completed on schedule, partial protective immunity may still be conferred [59].

Substance-abuse treatment and hepatitis C care. Hepatitis C care also requires providing access to treatment for substance

use and abuse. Numerous treatment modalities for substance dependence have demonstrated effectiveness [70–72]. Therapy with opioid agonists, including methadone maintenance treatment, has been shown to diminish and often eliminate opioid use and reduce transmission of many infections, including HIV [73–75]. The recent approval of buprenorphine makes office-based pharmacotherapy for opioid addiction possible [72]. Physicians who complete a defined training [76] can apply for a waiver to the Drug Addiction Treatment Act of 2000 and prescribe buprenorphine to opioid-dependent patients. This new treatment modality not only expands the accessibility of pharmacotherapy for opioid dependence but also mitigates the stigma associated with receiving substance-abuse treatment by integrating it into routine general medical practice.

Care for hepatitis C must also address the risks of alcohol use. All patients with HCV infection should be counseled to refrain from the consumption of alcohol, because heavy alcohol intake [77] accelerates the progression of HCV-related liver disease and increases the risk of developing hepatocellular carcinoma [78, 79]. Blood levels of HCV RNA are commonly elevated in infected patients who regularly consume alcohol, presumably because of enhanced viral replication in hepatocytes, which has been observed in in vitro models [80–82]. Both the consumption of alcohol during treatment and higher baseline HCV RNA levels have been associated with a decreased rate of therapeutic response to IFN-based treatment regimens. Consumption of alcohol compromises the responses of endogenous IFN- α to HCV infection [82] and is associated with poor adherence to medications [79, 82, 83].

Brief interventions by medical providers focused on problem use of alcohol have been shown to produce positive results in a variety of settings [84–86]. This approach consists of delivering brief, client-centered counseling within the context of the medical relationship, by using reflective listening while assuming a nonjudgmental demeanor. Core elements of brief interventions include assessing current levels of consumption of alcohol, providing education regarding risks, assessing and facilitating motivation to alter alcohol consumption, problem solving and developing strategies for change, setting goals, and discussing progress during scheduled follow-up visits [87]. Although brief interventions in the medical context have usually been used to help patients reduce alcohol consumption, the approach can easily be adapted to address any number of potentially harmful behaviors, with the quality of the patient-provider relationship being a fundamental determinant of the approach's effectiveness.

Naltrexone and acamprosate are US Food and Drug Administration–approved pharmacotherapeutic modalities that have been shown to be safe and efficacious in treating alcohol addiction in an outpatient setting [88]. Acamprosate and naltrexone have different mechanisms of action and modify dif-

ferent behavioral aspects of addiction. Acamprostate is a long-acting agent that prolongs periods of abstinence by normalizing glutamateric neurotransmission, which is dysregulated during chronic consumption of alcohol and withdrawal. Naltrexone is a fast-acting opioid receptor antagonist that reduces heavy consumption of alcohol by decreasing the rewarding effects of ethanol. The safety and efficacy of combination treatment with both drugs for alcohol addiction has been demonstrated in double-blind studies, although no studies have addressed concurrent HCV infection or IFN-based antiviral treatment.

Antiviral treatment. Optimal antiviral regimens for HCV infection are discussed elsewhere [89, 90]. Not all IDUs will want or need antiviral therapy, given the toxicity and limited efficacy of current regimens and the variable natural history of untreated infection, but none should be denied therapy solely on the basis of their addiction. The 2002 National Institutes of Health Consensus Statement on the Management of Hepatitis C [89] and the 2004 Practice Guidelines for the Management of Hepatitis C endorsed by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America [90] recommended that decisions about treatment of hepatitis C in IDUs be made on a case-by-case basis and advised that drug use itself was not an absolute contraindication to antiviral therapy for HCV infection. Several groups have now reported success in providing antiviral treatment for HCV infection to IDUs, even those who were not abstinent from illicit drugs [91–99]. Correctional facilities provide an opportunity to offer treatment to a large number of persons with hepatitis C through existing infrastructure, as discussed elsewhere in this supplement issue of *Clinical Infectious Diseases* [100].

Successful treatment of IDUs with hepatitis C by means of IFN-based treatment regimens must be considered in the context of overall health care of IDUs and requires collaboration between experts in hepatitis, substance use and addiction, and mental health to create treatment models specifically designed for IDUs. An optimal multidisciplinary team would represent the perspectives of primary care physicians, hepatologists, nurse practitioners, nurses, psychiatrists, psychologists, addiction specialists, social workers, and drug counselors. Backmund et al. [91] demonstrated the success of this approach, which has been replicated by others. Particular efforts are needed to address the challenges faced by IDUs with respect to adherence to medications, psychological adverse effects, and the potential for reinfection [101, 102].

Adherence to treatment. Active use of psychoactive substances, particularly alcohol or stimulants, is often associated with reduced adherence to medical interventions [103, 104]. Individualized programs designed to address the particular needs of IDUs, however, can achieve rates of adherence as high as those in other patient populations [8, 91, 92, 96, 105, 106].

Adherence to medications can be optimized by integrating medical care and treatment for substance abuse [98]. Patients who are engaged in methadone maintenance treatment programs or have a history of injection drug use or psychiatric disorders show rates of discontinuation of treatment for HCV that are similar to those of control groups [91, 107]. Methadone maintenance treatment, coupled with multiple support interventions, improves rates of adherence to medications and reduces the risk of HIV infection [108].

The most effective interventions for improving adherence among IDUs are multidimensional and target several aspects of adherence behavior [109, 110]. In one study of HIV-positive IDUs, treatment with buprenorphine had a significant effect on adherence to treatment for HIV; 78% of IDUs receiving treatment with buprenorphine were adherent to therapy for HIV, compared with 65% of former IDUs and 42% of active IDUs [111]. Similarly, the identification and treatment of depression associated with injection drug use, whether comorbid or antecedent, has been associated with improved adherence to treatment [112]. Providing essential support services, such as case management and transportation, has also been shown to improve retention in care, a critical component of treatment for HIV [113]. Helping a homeless patient find housing can improve adherence.

Additional effective strategies for improving adherence include basic elements of good clinical care, such as establishing a consistent, trusting physician-patient relationship, providing clear information about intended effects and adverse effects of medication, and paying careful attention to perceived adverse effects. Individual counseling that addresses barriers to and facilitators of adherence may be of benefit. Specialized tools, such as electronic reminder systems, directly observed therapy, and cash incentives for attending scheduled medical appointments, have also been shown to improve adherence [106, 114–117]. Directly observed therapy is highly effective in improving rates of adherence to preventive treatment for tuberculosis among IDUs [118] and may have a place in the treatment of hepatitis C for IDUs, especially in combination with pharmacotherapy for substance dependence.

Mental health assessment, monitoring, and treatment. When considering treatment for IDUs with hepatitis C, particular attention must be paid to mental health conditions, which are associated with both hepatitis C and substance use and may be induced or exacerbated by treatment for hepatitis C [95, 119–122]. As a group, IDUs exhibit higher rates of comorbid psychiatric disorders than do the general population [31, 123]. IFN-based regimens for hepatitis C are often complicated by neuropsychiatric adverse effects, including depression, insomnia, and irritability [120–122]. Patients should be screened for depression and other mental health problems before beginning treatment with IFN, treated if necessary, and

monitored for these problems during treatment for HCV. Strong linkages with mental health services, whether on-site or within the community, are a vital component of comprehensive health programs for IDUs and are particularly important during treatment for hepatitis C. Past episodes of depression or other psychiatric disorders are not absolute contraindications to treatment for HCV infection. Persons with psychiatric histories may adhere to and complete treatment for HCV infection at rates as high as those of other patient groups [92, 93], if their mental health status is closely monitored and treated. Some authors have recommended prophylactic antidepressant therapy before beginning treatment for HCV in patients thought to have a high risk of depression [124].

Morbidity due to concurrent infectious diseases. HIV infection may complicate hepatitis C care. HIV infection modifies the natural history of HCV infection [125], reducing the ability of the host to clear or resolve HCV infection. Clearance of HCV viremia occurs less often in persons coinfecting with HIV than in HIV-uninfected persons and occurs less frequently in those with low CD4 lymphocyte counts. Patients coinfecting with HCV and HIV have higher levels of HCV RNA and more rapid progression of cirrhosis to end-stage liver disease and death than do HCV-monoinfected persons [126]. Liver disease due to HCV infection has become a major cause of morbidity and mortality among persons living with HIV infection. In addition, HCV coinfection increases the frequency of drug-induced hepatotoxicity in HIV-infected persons, thus complicating the medical management of HIV infection [127]. HIV-coinfecting patients are less likely than are HCV-monoinfected persons to achieve a sustained virological response to treatment for HCV infection, although combination therapy with pegylated IFNs and ribavirin have improved treatment outcomes in this population [128, 129]. HIV-infected IDUs with chronic HCV infection should be considered to be candidates for anti-HCV therapy, especially given their higher risk of progression to end-stage liver disease and the higher risk of liver toxicity after beginning antiretroviral therapy. However, this decision should be considered in the wider context of the patient's presentation, including stable antiretroviral therapy, ongoing psychosocial needs (nutrition, housing, and support), underlying psychiatric diagnoses, immunologic status (CD4 lymphocyte count), and the education and motivation of the patient. This is clearly an area in need of further study.

STRUCTURAL CHALLENGES TO PROVIDING CARE FOR IDUs WITH HCV INFECTION

Poverty, homelessness, addiction, mental health disorders, social marginalization, fear of arrest and prosecution, mistrust of the health-care system, and limited involvement in stable primary care relationships represent challenges to effective

hepatitis C care. Other barriers may include the social instability and comorbidities associated with drug use, insufficient access to expertise about HCV, and the high cost of comprehensive care and treatment. Physicians rarely receive meaningful training in addiction medicine or effective strategies for managing the difficulties often encountered in providing care for drug users. Consequently, unrealistic expectations, coupled with judgmental attitudes, can lead to frustration and resentment for both physician and patient. Drug users, similar to non-drug using patients, may fail to follow their physicians' advice, be reluctant to fully and truthfully disclose their lifestyles and behaviors, and/or experience difficulty keeping their appointments. Physicians caring for IDUs often experience this behavior as frustrating and specifically related to drug use and may respond with aversion, malice, or neglect [130]. Indeed, most physicians do not feel comfortable caring for IDUs, preferring to relegate this task to an addiction specialist or a drug treatment facility [131]. A growing number of programs are successfully integrating hepatitis C care into a variety of health-care settings, including primary care, methadone maintenance treatment programs and other substance-abuse treatment programs, infectious disease clinics, and clinics in correctional facilities. Better education of physicians and health-care providers about substance use and addiction, and exposure to models of compassionate care, are needed to improve their understanding of problematic substance use as a treatable disorder. Expanding the capacity of hepatitis specialists to manage care for substance users, and of addiction specialists to manage treatment of hepatitis C, will be necessary to overcome these challenges.

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