Co-occurring Hepatitis C, Substance Use, and Psychiatric Illness: Treatment Issues and Developing Integrated Models of Care

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ABSTRACT *Hepatitis C virus (HCV) infection is transmitted by injection drug use and associated with psychiatric conditions. Patients with drug use or significant psychiatric illness have typically been excluded from HCV treatment trials noting the 1997 National Institutes of Health Consensus Statement on HCV that indicated active drug use and major depressive illness were contraindications to treatment of HCV infection. However, the 2002 NIH Consensus Statement recognized that these patients could be effectively treated for HCV infection and recommended that treatment be considered on a case-by-case basis. Treating HCV infection in these patients is challenging, with drug use relapse possibly leading to psychosocial instability, poor adherence, and HCV reinfection. Interferon therapy may exacerbate preexisting psychiatric symptoms. Co-occurring human immunodeficiency virus or hepatitis B virus provide additional challenges, and access to ancillary medical and psychiatric services may be limited. Patients with co-occurring HCV infection, substance use, and psychiatric illness can complete interferon treatment with careful monitoring and aggressive intervention. Clinicians must integrate early interventions for psychiatric conditions and drug use into their treatment algorithm. Few programs or treatment models are designed to manage co-occurring substance use, psychiatric illness, and HCV infection and therapy. The National Institute on Drug Abuse convened a panel of experts to address the current status and the long-range needs through a 2-day workshop, Co-occurring Hepatitis C, Substance Abuse, and Psychiatric Illness: Addressing the Issues and Developing Integrated Models of Care. This conference report summarizes current data, medical management issues, and strategies discussed.*

KEYWORDS *Comorbidities, HIV, HCV, Psychiatric illness, Treatment.*

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Current surveillance data indicate that acute hepatitis C virus (HCV) infection has diminished in the United States partly because of enhanced prevention and testing efforts among injection drug users (IDUs) and blood donors.² HCV transmission continues primarily through injection drug use (approximately 65%–70% of cases), sex with infected or multiple partners (approximately 15%–20% of cases), or occupational exposure (approximately 5% of cases). The prevalence of HCV infections in the United States is high, with approximately 3 to 4 million Americans estimated to be infected.

Chronic HCV infection is the leading cause of cirrhosis and hepatocellular carcinoma in the United States and the dominant reason for liver transplantation.² Studies demonstrated that up to 20% of chronically infected patients will develop cirrhosis over a 20-year period, and these patients are at risk for hepatocellular carcinoma. Persons at special risk for progression include those older at the time of infection, alcoholic, or co-infected with human immunodeficiency virus (HIV) or hepatitis B virus. Conversely, individuals infected at a younger age have a far lower rate of disease progression.

Clinical trials showed that the combination of interferon (IFN) and ribavirin was more effective than IFN alone for any genotype, but that the greatest therapeutic yield came with the use of pegylated IFN plus ribavirin.² Genotype 1, the most common HCV variant in the United States, is less responsive to treatment than genotypes 2 and 3. A sustained virologic response (SVR) is also less common in patients with higher HCV ribonucleic acid (RNA) levels or more advanced stages of fibrosis, especially cirrhosis, and in individuals with HIV/HCV co-infection.³ Persons with genotype 1 who fail to achieve an early virologic response (<2 log decrease in HCV RNA at week 12 of treatment) rarely develop an SVR.⁴ Initial studies of combination therapy in IDUs, patients with comorbid psychiatric illness, and children indicated that an SVR can be achieved in these populations.

Although the incident data for acute HCV infection in drug users has declined, drug use incidence has not. The prevalence of heroin use has grown over the past decade, with increasing numbers of users presenting for substance use treatment. The National Institute on Drug Abuse and the Community Epidemiology Work Group,⁵ using ethnographic research, focus groups, and community-based sources, reported that heroin abuse indicators increased nationally in 2002, particularly among young Caucasian and suburban populations. Primary heroin treatment admissions increased in Chicago, Illinois; San Diego, California; Boston, Massachusetts; and Newark, New Jersey, and continued to account for a large proportion of admissions in Baltimore, Maryland; Los Angeles, California; and New York City. In Denver, Colorado, and Dallas, Texas, heroin-related calls to the regional poison control center increased, heroin-related deaths were reported in Detroit, Michigan; Honolulu, Hawaii; Newark; Minneapolis/St. Paul, Minnesota; San Diego, California; and Seattle, Washington. Opiate-related deaths surpassed cocaine deaths in Washington, DC, and Minneapolis/St. Paul.

National seroprevalence studies have shown that exposure to HCV occurs in up to 90% of IDUs.⁶ For IDUs in methadone maintenance treatment, as many as 96% of tested individuals were seropositive for HCV antibody, and 62% were positive for HCV RNA.⁷ This compares to prevalence data from cohort studies of drug users who do not inject drugs, with the highest prevalence data reported at approximately 40% for individuals with more than 21 years of drug use.⁸ Studies have shown that HCV seroconversion in IDUs can occur rapidly in the initial 1–3 years of drug use.⁹ Thus, the prevalence of HCV infection in IDUs remains high.

Psychiatric disorders are also associated with HCV infection and injection drug use. Recent studies have shown that many patients with HCV infection also have diagnoses of depression, posttraumatic stress disorder (PTSD), psychosis, or anxiety.¹⁰⁻¹³ Compared to the overall population, individuals with chronic HCV infection have a higher prevalence of psychiatric disorders. For example, in a sample of 931 persons receiving treatment at inpatient and outpatient public health settings in four Eastern states, the prevalence of HCV infection was 19.6%, or 11 times greater than the rates observed in the general population. Injection drug use and use of crack cocaine were risk factors for HCV infection, and a lifetime history of injection drug use was associated with a 31-fold increased risk of HCV infection. Similarly, there is a 6% to 44% prevalence of preexisting depression among HCV-infected patients.^{14,15}

Taken together, these reports indicated that substance use and psychiatric disorders in patients with HCV infection are common and could be significant barriers to treatment of HCV infection. In the following sections, strategies for addressing the issues of co-occurring HCV, substance abuse, and psychiatric illness are presented. Although IFN can lead to severe neuropsychiatric side effects, the published evidence suggested that many patients with psychiatric or substance use diagnoses can be treated safely and effectively. Figure 1 provides a flow diagram that illustrates the comanagement and integration of care for patients with HCV, substance use disorders, and psychiatric illnesses.

FIGURE 1. Comanagement of patients with substance abuse, hepatitis, and psychiatric illness. PCR, polymerase chain reaction; STD, sexually transmitted disease.

SCREENING AND ASSESSMENT OF PSYCHIATRIC, SUBSTANCE USE, AND NEUROCOGNITIVE DISORDERS

Substance users have a high frequency of co-occurring psychiatric illness. Psychiatric screening and consultation should be considered prior to initiating IFN therapy. For the purposes of screening and monitoring patients for depression before and during IFN therapy, a number of self-rated or clinician-rated scales are available and are listed in the Table. Commonly used self-rated instruments are the Zung Self-Rating Depression Scale,³⁶ the Beck Depression Inventory (BDI),³⁷ and the self-rated version of the Montgomery Asberg Depression Rating Scale.²⁵ A recent report³⁸ examined the sensitivity and specificity of the BDI and other instruments for predicting eventual psychiatric and antidepressant treatment during IFN therapy. The BDI performed best in this analysis and is now the preferred screening tool at Veterans Affairs Medical Centers. These cost-effective tools can provide increased accuracy in assessing

TABLE. Screening/monitoring instruments for psychiatric, substance use, and neuropsychological disorders

Rating Scales	Purpose	Reference/resource material
AASE	Monitor alcohol cravings	16
ASI	Assess attitudes toward changing problem behaviors related to substance use	17
ASSIST 2.0	Lifetime and current substance use-related risk	18
AUDIT	Screen for alcohol use	19–22
AUDIT-C	Detect alcohol abuse/dependence	23, 24
BDI, BDI-II	Monitor depressive symptoms	25, 26, www.psychcorp.com
BPRS	Identify and monitor severity of psychiatric symptoms (i.e., delusions, anxiety, depression, hallucinations, and thought disorders)	27, www.psychrehab.com
CAGE	Detect alcohol abuse/dependence	28–30
CAGE-AID	Detect alcohol and other drug abuse/dependence	30
DAST	Detect drug abuse/dependence	31
MADRS	Monitor symptoms of depression	25
MAST	Detect alcohol abuse/dependence	29, 32
PCL-M or PCL-C	PTSD Checklist-Military or -Civilian	33
PSQ	Patient Screening Questionnaire	www.portland.med, va.gov/Mood-Disorders-center
TICS	Detect alcohol and other drug abuse/dependence	34
YMRS	Monitor symptoms of mania for patients with bipolar disorders	35
Zung Self-Rating Depression Scale	Monitor symptoms of depression	36, www.fpnotebook.com/psy85.htm

AASE, Alcohol Abstinence Self-Efficacy Scale; AUDIT, Alcohol Use Disorders Identification Test; ASI, Addiction Severity Index; BDI, Beck Depression Inventory; BPRS, Brief Psychiatric Rating Scale; CAGE, questionnaire focusing on cutting down, annoyance by criticism, guilty feeling, and eye-openers; CAGE-AID, CAGE Adapted to Include Drugs; DAST, Drug Abuse Screening Test; MADRS, Montgomery Asberg Depression Rating Scale; MAST, Michigan Alcohol Screening Test; PCL, PTSD Checklist; YMRS, Young Mania Rating Scale.

patient depressive symptomatology as well as improved objective measurement of changes in mood states during IFN therapy.³⁹

Gender-specific definitions of levels of hazardous alcohol consumption have been established,²⁸ but are not specific to HCV infection or treatment with IFN. However, heavy alcohol is a key factor in disease progression for both HCV infection and HIV/HCV co-infection. Thus, screening for alcohol consumption in multimorbid patients is imperative. The CAGE questionnaire, focusing on cutting down, annoyance by criticism, guilty feeling, and eye-openers, or the Michigan Alcoholism Screening Test (MAST) can be utilized. However, the Alcohol Use Disorders Screening Test (AUDIT) and the abbreviated version, the AUDIT-C, are best for identifying hazardous use or alcohol use disorders and can be used for stratification of risk to guide prevention and treatment strategies.^{19,20,23,29} Because of minimization and denial, the AUDIT-C does not measure actual alcohol exposure. Biomarkers of alcohol use have been used, such as carbohydrate-deficient transferrin, hemoglobin-associated aldehyde, and fatty acid ethylesters (in hair),^{40,41} but there are no sensitivity, specificity, or risk-level standards for HCV-infected populations.

Brief screens for other drug use problems, including the Drug Abuse Screening Test (DAST), CAGE Adapted to Include Drugs (CAGE-AID), and the Two-Item Conjoint Screen (TICS) and tests for drugs in urine, blood, or saliva focus on end-stage problems (consequences rather than use) and have no specific focus on tobacco or injection drug use. The ASSIST 2.1 (Alcohol, Smoking, and Substance Involvement Screening Test)¹⁸, developed by World Health Organization for primary care screening, assesses (1) lifetime use of 10 drug “classes,” (2) substance-specific recent use, (3) substance-specific severity, (4) current global risk, and (5) injection drug risk and shows reliability in international trials. However, its limitations include self-report, length, frequency assessment of alcohol use, and the need for further validation with biomarkers. The Patient Screening Questionnaire (PSQ) has been developed to identify psychiatric and substance use disorders prior to the start of antiviral therapy. This 10-item instrument screens for psychotropic medication use, past psychiatric in- and outpatient care, as well as past substance use.⁴²

Analog scales have been used to assess substance use, psychiatric disease, and cognitive performance. In an ongoing study to assess the combined effects of methamphetamine, HIV infection, and neurocognitive functioning, the individuals who were co-infected with HCV showed higher levels of cognitive impairment and markers of immune activation than those who were HCV seronegative. In this study, individuals with impaired memory also had higher HCV plasma RNA levels. Although no HCV RNA was found in cerebrospinal fluid (CSF), higher plasma HCV RNA correlated with a higher CSF HIV viral load. Currently, one individual with HIV/HCV co-infection treated with IFN alone showed a decline in the CSF HIV viral load. This is consistent with possible additive or interactive HCV and HIV contributions to neurocognitive impairment in these co-infected substance-using patients. Additional screening tools may be required to assess the individual and combined neurocognitive comorbidities caused by (1) HIV infection, (2) progression of liver disease, and (3) chronic alcohol consumption.

For patients with co-occurring illnesses, there is also the need for assessing function in areas such as driving, employment, self-care, risky behaviors, and adherence. Lessons learned from HIV-infected patients in these areas suggested that neuropsychological (NP) impairment is associated with lower employment percentage and decreased probability of receiving antiretroviral treatment. NP test results can be used to monitor response to treatment.⁴³ For HCV infection, autopsy and imaging

studies are providing evidence of HCV viral replication in the brain and abnormal metabolites consistent with central nervous system inflammation in the striatum and white matter,¹³ suggesting an extrahepatic manifestation of HCV infection that may contribute to neurocognitive impairment. On standard NP tests, HCV-infected patients showed defects of mental and motor speed, “complex” attention (sustained or divided), and short-term working memory, but not IQ or episodic memory.⁴⁴ This is similar to results found in other patients with cirrhotic or noncirrhotic liver disease, but there are indications that problems emerge earlier among patients with HCV infection.⁴⁵

The cognitive functioning of HCV-infected drug users has not been characterized. Studies with this population of patients need to consider drug use patterns, level of sobriety or withdrawal when tested, and the lack of test norms that reflect race, ethnicity, socioeconomic status, and frequent comorbidities of drug use (head trauma, learning disorders, malnutrition, HIV, other central nervous system infections, depression, antisocial personality disorder, PTSD). Moreover, classical NP tests such as the Trail-Making Test may provide evidence of impairment without localization or etiology. Computerized tests based on developments in cognitive neuroscience and mapping neuropathology have been useful with HIV-positive patients and may be applicable to those with HCV infection.⁴⁶ Such tests address (1) verbal working memory (with circuitry including the dorsolateral prefrontal cortex and striatum); (2) decision-making parameters such as risk, impulsivity, and delayed versus immediate reward; (3) mental speed; and (4) divided attention. These tests showed significant correlations with HIV infection and, in the case of verbal working memory, cytokine activity in polydrug users. Data from drug users grouped by HCV infection and HIV serostatus using a reaction time version of the Stroop task to evaluate the integrity of the prefrontal cortical systems mediating response inhibition showed greater Stroop interference in the co-infected group compared with those without infection.⁴⁷ In addition, the HCV monoinfected patients responded more slowly than did those who were HCV negative. However, studies are needed in HCV-infected drug users whose drug/use history and many comorbid conditions are well characterized to develop practice, brief, and informative assessment of neurocognitive function in patients with HCV infection and co-occurring illnesses.

HEPATITIS C VIRUS TREATMENT AND SUBSTANCE USERS: MANAGEMENT CHALLENGES

Most care providers withhold IFN-based treatment for active drug users who are chronically HCV infected.⁴⁸ However, calls for an individualized approach to treating HCV-infected patients^{2,49,50} are based on a limited number of studies that revealed HCV treatment efficacy in drug-using cohorts. A study of 50 heroin addicts enrolled in an inpatient methadone detoxification unit showed an overall SVR of 36%, even though half of the patients relapsed to heroin injection.⁵¹ Although the SVR was lower (24%) in the drug users, outcomes were not statistically different from those who maintained sobriety. Only 2 of the 50 patients developed IFN-induced severe depression.

The impact of a history of psychiatric and substance use disorders on HCV treatment was studied in 33 veterans; 19 had a history of psychiatric disease, 5 of the 14 nonpsychiatric patients had a remote history of injection drug use, and 13 of the 19 psychiatric patients reported a history of drug or alcohol dependence.⁵² Psychiatric diagnoses included PTSD, depression, schizoaffective disorder, obsessive-compulsive disorder, anxiety, and mixed personality disorder. Although patients

with psychiatric disease were more likely to develop neuropsychiatric adverse events caused by IFN-based treatment, their dropout rate and SVR were equivalent to those without psychiatric disease. However, virological response rates were low in both groups, and only 30% completed a year of IFN therapy. Overall, 5 patients (2 in the nonpsychiatric cohort and 3 in the psychiatric cohort) developed neuropsychiatric side effects requiring treatment discontinuation.

In a more recent study⁵³ of HCV treatment in 50 methadone patients, 62% (46% depression, 12% anxiety, 2% obsessive compulsive disorder, and 2% schizophrenia) reported a preexisting psychiatric diagnosis, and the end-of-treatment response (ETR) rate was 64%. Of the subjects, 30% were sober for less than 6 months, and 36% relapsed to hard drug use during the study. Pretreated with antidepressants was given to 47% of patients, and 88% were taking antidepressants by the end of IFN therapy. There was no significant difference in ETR between subjects with short sobriety compared to those whose sobriety was more lengthy, and relapse to drug use overall did not lead to a significant reduction in treatment outcomes. Although the dropouts in the study had a modestly higher prevalence of preexisting psychiatric disease than the entire study population (73% vs. 62%, respectively), there was no statistically significant correlation of psychiatric illness with treatment discontinuation.

Furthermore, a long-term follow-up of 27 former IDUs⁵⁴ treated for HCV infection indicated a limited likelihood of HCV reinfection because of recidivism. Although 33% of the patients returned to injection drug use, only 1 became reinfected, with a defined risk factor of sharing equipment. Taken together, these data warrant the use of the current standard of care, pegylated IFN, for drug users and methadone patients in clinical trials to expand the outcome data of these preliminary studies.

HEPATITIS C VIRUS TREATMENT, EVALUATION, AND MANAGEMENT OF PSYCHIATRIC AND SUBSTANCE USE COMORBIDITY

A growing number of studies provided preliminary support for the use of IFN-based therapy for patients with HCV infection who have active psychiatric illnesses and substance use disorders.^{38,49,51,53–55} These studies showed that patients with current and past histories of significant psychiatric illness, including substance use disorder, can successfully complete a course of IFN therapy, and that SVR rates were similar to those without such difficulties. Furthermore, patients with a past history of major depressive disorder or substance use may not be at increased risk for the development of IFN-induced depression.⁵⁶ Further studies are needed to detail definitively the treatment efficacy of IFN-based treatments for patients with HCV, substance use disorders, and psychiatric illnesses.

Given the very high frequency of co-occurring psychiatric and substance use disorders among patients with HCV infection and that antiviral therapy may exacerbate symptoms of psychiatric illness, psychiatric screening strategies for all patients represent optimal care (see Screening and Assessment of Psychiatric, Substance Use, and Neurocognitive Disorders; Table). Regular monitoring of psychiatric symptoms during IFN therapy is also important. The Department of Veterans Affairs Medical Center treatment recommendations for individuals with HCV infection state that patients not exhibiting depression before IFN therapy should be evaluated for depression at least monthly. Patients with depression scores on the BDI, for example, indicating moderate-to-severe depression should be considered for antidepressant treatment and preferably followed by a mental health professional.⁵⁷

For patients with a history of substance use disorders, regular monitoring using rating scales such as the Addiction Severity Index (ASI) or Alcohol Abstinence Self-Efficacy Scale (AASE) and coordination of care with addiction specialists are also recommended. In patients with co-occurring HCV infection and substance use disorders, possible IFN-induced drug cravings and the risk for drug relapse could seriously compromise their treatment and recovery (see Neurochemistry of the Addicted, Psychiatrically Ill, and Hepatitis C Virus-Infected Patient). A comanagement model of care that uses frequent psychiatric and substance use symptom monitoring and early intervention for reemergence or development of neuropsychiatric side effects and substance use is advocated (Fig. 1).

Several reports suggest that antidepressants, primarily selective serotonin reuptake inhibitors (SSRIs), are efficacious in ameliorating IFN-induced major depression in patients with HCV infection.^{56,58–60} SSRIs can alleviate IFN-induced depression, fatigue, and anxiety as well as cognitive and behavioral slowing.^{61,62} Importantly, increased depression following IFN therapy is related to the depletion of serum serotonin (Fig. 2) thus, SSRIs may act on the specific neurochemical targets (particularly serotonin), mediating these depressive side effects (see Neurochemistry of the Addicted, Psychiatrically Ill, and Hepatitis C Virus-Infected Patient). However, there are currently no large, placebo-controlled studies that have investigated the use of antidepressant treatment for IFN-induced depression in patients with HCV infection. In addition to using antidepressant treatment to manage preexisting and IFN-induced depression, the use of antidepressants in conjunction with IFN therapy may also serve to decrease relapse potential in patients with substance use disorders. Although the literature is not in complete agreement, treatment with antidepressant medications has been shown to reduce the risk of drug relapse in patients with a history of substance use disorders.^{63–65}

Additional studies are needed to understand better the effects of substance use and psychiatric illness on IFN treatment outcomes in patients with HCV infection.

FIGURE 2. Tryptophan metabolic pathway. Interferon (IFN) triggers the induction of IDO (indoleamine 2,3-dioxygenase) and results in more tryptophan being metabolized along the kynurenine pathway and correspondingly less being available for conversion to 5-HT (5-hydroxytryptophan). AA, amino acid; BH4, tetrahydrobiopterin (cofactor); 5-HTP, 5-hydroxytryptamine; TH, tryptophan hydroxylase.

To improve access to antiviral therapy for patients with co-occurring HCV infection and psychiatric and substance use disorders, future research should identify behavioral and pharmacological interventions that will enhance adherence to antiviral therapy and reduce the reemergence of psychiatric symptoms and substance use.

NEUROCHEMISTRY OF THE ADDICTED, PSYCHIATRICALY ILL, AND HEPATITIS C VIRUS-INFECTED PATIENT

The majority of cases of HCV infection occur in IDUs, a substantial fraction of whom have current neurocognitive dysfunction or a history of psychiatric illness. The development of addiction, which has a neurochemical basis and is characterized by states of drug craving and extended abstinence, has an impact on several separate, yet interrelated neurobiological processes.⁶⁶ In animal models of addiction, changes in dopaminergic neurotransmission within a highly limited band of structures, including specific parts of the nucleus accumbens, amygdala, and prefrontal cortex, typically underlie the motivational effects associated with dependence.^{67–70} Changes in the signals mediated by several neurotransmitters, including dopamine, opioid peptides, and corticotropin-releasing factor, and in the regulation of transcription factors within the neurons of this reward circuit may underlie the vulnerability to relapse that characterizes addiction in humans.^{68,71,72} In addition, alterations in gene expression appear to be involved in the long-term neuroadaptive changes associated with the motivational aspects of drug dependence.⁷³

Overlapping and additive neurochemical mechanisms validate the concern that IFN-based treatment of HCV infection may exacerbate preexisting depression or drug use behaviors. In animal models and human studies, there is a direct role for proinflammatory cytokines in the development of depression. Specifically, current literature favors the hypothesis that a relative serotonin depletion plays a central role in IFN-induced depression.^{74,75} As shown in Fig. 2, the neurochemical events that mediate IFN-related depression are a metabolic increase in the catabolism of tryptophan, specifically through IFN stimulation of the enzyme indoleamine 2,3-dioxygenase, leading to the peripheral depletion of tryptophan, a serotonin precursor.^{76,77} Thus, the etiology of IFN-induced depression may derive partly from the antiserotonergic effects of IFN, which is consistent with the large body of evidence pointing to a general link between serotonin and depressive disorders, as well as the efficacy of SSRI antidepressants in treating IFN-induced depression (see HCV Treatment, Evaluation, and Management of Psychiatric and Substance Use Comorbidity). However, the mechanism by which IFN produces depression remains unclear and is most probably multifactorial.

IFN also modulates neurochemical pathways of other cytokines, the hypothalamic-pituitary-adrenal (HPA) axis, and hypothalamic-pituitary-thyroid axis as well as dopaminergic, nonadrenergic, and cholinergic neurotransmission.^{78–81} IFN increases interleukin 6 (IL-6) production, which correlates with symptoms of depression and anxiety.⁸² IFN enhances levels of IL-1 and tumor necrosis factor- α (TNF- α), which influences noradrenergic activity. IL-1, IL-6, and TNF- α are also potent stimulators of the HPA axis.^{84,85} These neurochemical changes may occur in the presence of elevated glucocorticoid concentrations, and immune activation is associated with a decrease in the sensitivity of the glucocorticoid receptors in patients with major depression, thus contributing to altered regulation of the HPA axis.⁸⁵

Taken together, these observations suggested that IFN-mediated alterations in the HPA axis and perturbations in neurotransmission, especially those related to dopamine or serotonin, may have an additive impact on drug users with depression

who are treated for HCV infection. However, whether these neurological events will lead to disproportionately destabilizing neurochemical changes or increase the vulnerability to reinstitution of drug taking remains unclear.

INTEGRATING HEPATITIS C VIRUS TREATMENT INTO HEALTH CARE VENUES

The medical management of HCV infection in multimorbid patients necessitates the integration of IFN-based treatment into health care settings that care for substance-using and psychiatrically ill patients (Fig. 1). The panel identified the following as venues to address IFN-based treatment of HCV through clinical trials and health services research.

Methadone Clinics

Former IDUs comprise a population that has a high prevalence of HCV infection. Seroprevalence rates range from 67% to 96%, with noninjection (opium smokers) populations exhibiting significantly lower seropositive prevalence rates. Although studies have begun to test the safety, tolerability, and efficacy of antiviral treatment for HCV infection in patients on methadone maintenance, they have excluded active drug users and individuals with severe psychiatric illness or decompensated liver disease. Methadone clinics represent a unique resource to provide screening for HCV infection and psychiatric illness, thereby identifying potential candidates for treatment of substance use and HCV comorbidities.

Prisons

No national surveillance and no systematically collected national data are available regarding HCV among inmates. Based on Centers for Diseases Control and Prevention estimates, assuming needle sharing as the primary risk factor, between 17% and 21% of current inmates are infected with HCV.⁸⁶ Medical care for inmates is episodic and not given in the context of public health. Therefore, there is no consistent consensus on the treatment of HCV in correctional settings. Some prison systems have developed guidelines for the management of HCV that are not necessarily implemented. Incarcerated individuals, who exhibit drug addiction and psychiatric illness, can be effectively treated for HCV infection with IFN-based therapies. On release, the HCV-infected individual has an impact on the community in terms of disease transmission, costs for medical care, and recidivism. Prevention and treatment interventions would benefit inmates, their families, their partners, and the public health of communities to which inmates return.

Walk-In Clinics

A unique group model that operates as a walk-in clinic for addiction-related HCV has been operating in Oakland, California, since 1998. It was specifically structured to reduce barriers to HCV diagnosis and treatment in less-stable drug users. The clinic is held three times weekly, and its focus is on peer support and interactive education about HCV diagnosis and the treatment process. Attendees are offered on-site blood testing, referrals for biopsy, and comprehensive HCV treatment for interested participants as warranted. To date, over 1,500 low-income addicts have been screened in this cost-effective program, and over 200 have been treated; treatment outcomes appear to be only modestly lower than for nonaddicted patients despite the complexities of the patients served.

Community Mental Health Clinics and Psychiatric Hospitals-

The HCV treatment for persons with severe mental illness (SMI) in public mental health settings presents unique challenges and opportunities, including medical, psychosocial, housing, daily living, legal, and vocational services. Models of care that integrate mental health and substance use treatment can be effective,^{87,88} but are not routinely implemented because of limited financial and human resources.²⁴ Guidelines to treat HCV in persons with SMI are not available, and there are no national HCV guidelines for persons receiving treatment at community mental health centers or state psychiatric hospitals. Care practices vary greatly by state and community, and HCV-related service needs are not uniformly addressed.

Models of care developed for community-based psychiatric care of persons with SMI, including assertive community treatment (ACT) and intensive case management, can provide a valuable framework for treating HCV in public mental health settings. ACT teams provide a range of services, such as sexual education, reproductive counseling, and medication support services.⁸⁹ These programs can be expanded to include services related to HCV. Intensive case management can also be utilized to monitor symptoms and provide integration of psychiatric and medical teams.

One community model in a mental health clinic setting utilizes a service team, comprised of a nurse, an infectious disease specialist, a psychiatric specialist, and an administrator, who provide education and assist in the development of services, including best practices outlined by the Centers for Disease Control and Prevention for HCV care: screening, testing, immunization, risk reduction counseling and referral, and support for medical care.

SUMMARY AND DIRECTIONS FOR FUTURE RESEARCH

There are vast gaps in the understanding of the optimal management of HCV treatment in substance users and patients with comorbid psychiatric illness. Clinical research and trials are needed to understand further how to select patients who can successfully undergo therapy and to define better the impact of intervening drug use, the minimally appropriate length of sobriety, and the impact and management of the spectrum of preexisting psychiatric conditions. Information is needed on interventions when relapse to substance use occurs and whether different drugs of abuse present unique outcomes. Clinical research is needed for a better understanding of the individual and cumulative impact of the potential barriers to HCV treatment in patients with co-occurring HCV, substance abuse, and psychiatric illness, as well as for new approaches to the medical management of these patients and novel interventions that promote a SVR to HCV treatment.

Existing data suggest that selected substance users can be candidates for HCV treatment, even in the setting of psychiatric disease and relapse to drug use. In light of the vast impact of HCV in this population and their limited access to HCV treatment and life-saving liver transplantation, the urgent need for further clinical study is clear.

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