TREATMENT OF CHRONIC HEPATITIS C IN ACTIVE DRUG USERS

It is currently estimated that between 2.7 million and 4.0 million persons in the United States have chronic hepatitis C virus (HCV) infection. Many of these persons have potentially progressive disease. Studies suggest that mortality and health care costs from complications of chronic hepatitis C and cirrhosis, such as hepatocellular carcinoma and liver failure, will increase dramatically over the next 10 to 20 years. Several reports indicate that this increase has already begun to occur. Thus, the development of more effective interferon-based treatments is particularly encouraging. A standard regimen of interferon and ribavirin results in sustained eradication of HCV in 40 percent of patients, whereas the combination of pegylated interferon and ribavirin results in a sustained response in 54 to 56 percent.

Injection-drug use has been the greatest risk factor for HCV infection since the early 1980s. Drug use currently accounts for 60 percent of newly acquired cases and 20 to 50 percent of cases of chronic infection. Among injection-drug users who share needles or other equipment, the risk of infection is phenomenally high; 50 to 80 percent of such persons become infected after one year of drug use, and nearly all become infected after eight years of use. The high risk is due, in part, to limited knowledge among drug users about infectivity and the routes of transmission of HCV. Furthermore, among patients with chronic hepatitis C, cirrhosis and associated complications are two to three times as likely to develop in those with chronic alcohol use, which is common among injection-drug users, as in those who do not drink. Thus, persons with current or past substance abuse should be informed about HCV infection and screened for it.

Most physicians who care for HCV-infected drug users withhold antiviral treatment until drug use has stopped. This practice is supported by the recommendations of three consensus conferences on the management of hepatitis C, held in the United States, Canada, and Europe. Specifically, it was recommended that such patients be referred for treatment of their addiction before they receive antiviral therapy. The justifications for this approach were that drug use poses a greater short-term threat to health than does hepatitis C, that it increases the risk of adverse events associated with antiviral treatment, and that it is likely to be a reason for poor compliance with treatment. The argument against this recommendation, made by patients and some clinicians, particularly those who specialize in the treatment of addiction, is that it denies active drug users access to potentially lifesaving treatment of HCV infection. Are the current recommendations justified by the data? Should antiviral treatment continue to be discouraged for patients who are drug users?

The National Institutes of Health (NIH) consensus conference did not establish strict treatment rules. Rather, it sought to standardize nomenclature, make data-based management and treatment recommendations, and identify areas in need of further research. Thus, the NIH recommendations are only guidelines and should not be used as the basis for withholding antiviral treatment if the physician believes that it is in the patient’s best interest to provide it. Indeed, treatment options and the standard of care have changed substantially since 1997, when the NIH recommendations were issued, because therapies have improved. Nonetheless, these recommendations were carefully considered and continue to be justified by the available data.

Interferon-based therapy has serious side effects and is especially problematic in patients with psychiatric disorders such as depression. In fact, a history of severe depression or other psychiatric conditions is considered to be a relatively strong contraindication to interferon-based therapy, since dose-dependent and reversible neuropsychiatric effects occur in 30 to 40 percent of patients during treatment, may be severe or may limit treatment in 10 to 20 percent, and are more common among persons with a history of a psychiatric disorder than among those without such a history. A survey has shown that up to 36 percent of HCV-infected patients do not receive antiviral treatment because they have psychiatric diagnoses other than substance-abuse disorders.

The lifetime prevalence rates for major depression, bipolar disorder, and anxiety disorders among adults with substance-abuse disorders are high and may be even higher among those who are also infected with HCV. Failure to treat these psychiatric conditions adequately may increase the risk that a patient will resume substance abuse and that antiviral treatment will fail. In addition, the availability of needles and syringes for the administration of interferon may pose a problem for patients who have previously been addicted to intravenous drugs. Indeed, there are anecdotal reports of relapses among former drug users, as well as overdoses, some of which have been fatal. Ho and colleagues reported that 68 percent of patients with a prior psychiatric diagnosis (68 percent of whom had a history of alcohol or drug dependence) had major psychiatric problems during monotherapy with interferon, as compared with 28 percent of those with no prior psychiatric diagnosis. In addition, the patients with a history of substance abuse were three times as likely to be lost to follow-up during the treatment period (20 percent vs. 7 percent).

A sustained virologic response to interferon-based therapy is less likely in HCV-infected patients with substance abuse than in other HCV-infected patients for several reasons. First, treatment must be modified...
or discontinued in a large portion of such patients.\(^6\)\(^,\)\(^20\) Second, approximately one fifth of patients do not comply with monitoring and are lost to follow-up before completing an adequate course of treatment.\(^3\)\(^1\) Third, both injection-drug use and chronic alcohol use have been reported to suppress cellular immunity.\(^2\)\(^5\) This effect may prevent a sustained response to treatment, since interferon-based therapy is thought to act, at least in part, by augmenting the response of type 1 helper T cells to the virus.\(^2\)\(^6\) Alcohol also decreases the cellular effects of interferon.\(^2\)\(^7\) Finally, regular alcohol intake increases HCV levels and reduces the virologic response to treatment.\(^2\)\(^8\),\(^2\)\(^9\) Taken together, these factors make a sustained response to treatment unlikely in patients with active substance abuse.

One concern about treating HCV infection in active injection-drug users is that those in whom the virus is cleared may become reinfected. HCV infection, even when it is cleared spontaneously or with antiviral treatment, does not confer protective immunity, and cases of reinfection have been reported.\(^2\)\(^0\),\(^3\)\(^1\) Therefore, persons who continue to be exposed to the virus are at risk for reinfection, and the risk is probably the same as that for drug users who have never been infected.\(^1\)\(^2\) In at least half of patients with active injection-drug use, clearance of HCV after treatment with interferon-based therapy is likely to be followed by reinfection within one year.

The costs associated with HCV infection in injection-drug users are considerable.\(^3\)\(^2\) Since injection-drug use is the most common cause of chronic hepatitis C, it accounts for most of the costs of antiviral treatment and management of liver failure and associated complications. A typical 12-month regimen of interferon-based therapy costs about $16,000 for medications, plus the cost of office visits and laboratory tests to monitor for side effects. Antiviral treatment may have a limited benefit in drug users, given the likelihood that only a small proportion of such patients will be able to complete treatment and that more than half will die at a younger age than they would have if they had not used drugs.\(^3\)\(^3\),\(^3\)\(^4\) The death rate among active drug users is 3 to 14 times as high as that in the general population, and most of these deaths are related to drug use.\(^3\)\(^4\) Indeed, studies of the cost effectiveness of identifying and treating HCV-infected drug users have been difficult to design and the results inconclusive because of the uncertainty of assumptions about treatment efficacy and survival.\(^3\)\(^5\)

Despite the many valid arguments against the treatment of HCV infection in active drug users, an individualized approach is best. Most such patients will not be appropriate candidates for interferon-based therapy because of psychological contraindications, coexisting conditions, or problems with compliance. However, antiviral treatment should be considered for patients with ongoing drug use who are likely to comply with the treatment regimen and who do not have psychological or other contraindications. It has been suggested that among HCV-infected drug users, those enrolled in a methadone-maintenance program are the best candidates for antiviral treatment, because participation in such a program increases the likelihood of compliance with the antiviral regimen. However, a substantial number of such patients continue to use drugs while receiving methadone, and their risk of exposure to HCV is therefore not necessarily reduced.\(^3\)\(^6\)

All potential candidates for antiviral treatment should undergo a comprehensive psychological assessment. Careful monitoring is important for all patients receiving treatment for HCV infection, but it is critical for those who are drug users. There should be close collaboration between a physician who is experienced in treating HCV infection and an expert in the assessment and treatment of substance abuse. Together, they can provide services that will promote adherence to the antiviral regimen, treat coexisting conditions, and implement strategies to prevent relapse.

With such a collaborative approach, at least some HCV-infected drug users can be successfully treated.

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**REFERENCES**


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