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## IS IT JUSTIFIABLE TO WITHHOLD TREATMENT FOR HEPATITIS C FROM ILLICIT-DRUG USERS?

**Brian R. Edlin, M.D., Karen H. Seal, M.D., M.P.H., Jennifer Lorvick, Alex H. Kral, Ph.D., Daniel H. Ciccarone, M.D., M.P.H., Lisa D. Moore, Dr.P.H., and Bernard Lo, M.D.**

*University of California, San Francisco San Francisco, CA 94143*

APPROXIMATELY 3 million Americans are thought to be infected with hepatitis C virus (HCV).<sup>1</sup> HCV causes chronic infection in about 85 percent of infected persons, and cirrhosis may develop in as many as 20 percent of those with chronic infection.<sup>2</sup> HCV infection results in 8000 to 10,000 deaths annually and is the most common reason for liver transplantation in the United States. The rates of morbidity and mortality from HCV infection are increasing, and this trend is expected to continue in the coming decades.<sup>1</sup> Treatment with interferon, with or without ribavirin, for 6 to 12 months results in viral clearance in up to 40 percent of patients and histologic improvement, possibly, in more.<sup>3</sup> Side effects of this regimen, however, include depression, emotional lability, and hemolytic anemia.

Injection-drug users constitute the largest group of persons in the United States who are infected with HCV and account for the majority of new infections.<sup>1</sup> Of the 15 million Americans who currently use illicit drugs, an estimated 1.0 to 1.5 million inject them,<sup>4</sup> and some 80 to 95 percent of injection-drug users have been infected with HCV.<sup>5,6</sup> In a consensus statement on the management of hepatitis C, however, the National Institutes of Health recommended in 1997 that persons who use illicit drugs not be offered treatment for HCV infection until they had stopped all such use for at least six months.<sup>7</sup> Other national and international guidelines have reiterated this policy.<sup>8,9</sup>

Illicit-drug users are a stigmatized group with disproportionately high rates of many medical conditions.<sup>10</sup> A recommendation to withhold medical treatment from a stigmatized class of persons raises questions about fairness and discrimination.<sup>11</sup> Groups issuing guidelines that include such a recommendation can provide reassurance that the policy is warranted by clearly articulating the rationale for it, making sure that it is based on evidence and is consistent with policies for other, similar conditions, and ensuring that less restrictive alternative policies have been explored. In this article, we argue that guidelines for the treatment of HCV infection have, unfortunately, met none of these criteria. Published guidelines provide little explanation for the current policy.<sup>7-9</sup> We are unaware of studies that have reported results of attempts to treat HCV infection in active drug users. After examining the rationale for excluding drug users from treatment of HCV infection in the light of available clinical data, ethical guidelines, and accepted medical and public health practices, we propose a less restrictive alternative policy.

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## ARGUMENTS FOR WITHHOLDING TREATMENT FROM ILLICIT-DRUG USERS

In this article, we consider four possible reasons for the policy of withholding treatment of HCV infection from drug users: poor adherence to treatment regimens, side effects of treatment, the risk of reinfection with HCV, and the lack of urgency regarding the initiation of treatment for HCV infection.

### Adherence to Treatment

Treatment regimens for HCV infection are difficult to endure and require a serious commitment on the part of the patient. Adherence to treatment regimens among illicit-drug users is often thought to be poor. Some might therefore argue that treating drug users for HCV infection is futile.

Clinical data, however, do not support this view. In some studies, drug users were less likely than other persons to adhere to medical therapy,<sup>12-14</sup> whereas in other studies, the adherence of drug users was similar to that of other patients.<sup>15-17</sup> It is difficult to make generalizations about drug users because they differ with regard to the drugs they use, the extent and frequency of use, the degree of their dependence, the stability of their lives, and many other factors. For example, regular users may be more impaired than occasional users, and persons who use stimulant drugs or who binge may have more chaotic lives and poorer adherence than those who have used opiates consistently for many years.<sup>18</sup> Studies have shown that 40 percent to more than 80 percent of drug users adhere to treatment regimens, depending on the treatment, the study population, and the setting.<sup>12-21</sup> These rates of adherence are typical of those reported for patients receiving treatment for various medical conditions (30 to 70 percent).<sup>22,23</sup>

Drug use is only one of many characteristics of patients that are associated with poor adherence. Other characteristics include depression, psychological stress, unstable housing, and lack of social support.<sup>22,23</sup> Additional predictors of adherence include characteristics of clinicians, the quality of the clinician—patient relationship, the treatment regimen, and the clinical setting — many of which can be modified.<sup>23,24</sup> Effective strategies for improving adherence range from basic clinical practices — such as establishing a consistent, trusting relationship with the patient, providing clear information about the intended effects and possible side effects of medication, and paying careful attention to perceived side effects — to special strategies such as electronic reminder systems, directly observed therapy, and cash incentives.<sup>20-25</sup> Adherence can also be improved by simplifying complex treatment regimens, treating depression, or helping homeless patients find housing. For example, it is much easier to adhere to a regimen of peginterferon alfa-2a, which is administered once per week,<sup>26</sup> than to regimens that require more frequent administration. When treatment strategies for drug users take into account the circumstances of their lives, the rate of adherence can exceed 80 percent.<sup>12-21</sup>

Data on predictors of adherence have been used more effectively to design strategies that increase adherence rates than to identify subgroups of patients to exclude from therapy.<sup>21-25</sup> Withholding treatment from patients belonging to groups whose adherence is predicted to be poor is neither a just nor an effective strategy for improving adherence. It is unjust because it denies potentially beneficial treatment to patients. It is ineffective because it is not possible to predict accurately which patients will adhere to a treatment regimen.<sup>18,23</sup>

### Side Effects of Treatment

Interferon may have severe psychological side effects<sup>27</sup> in patients with or without preexisting psychiatric disorders.<sup>28,29</sup> Major depression is generally considered a contraindication to

interferon therapy, although patients with psychiatric disorders can be treated with interferon if they are monitored carefully.<sup>30,31</sup> Sixteen to 30 percent of persons who inject opiates may have a major depressive illness.<sup>32</sup> To our knowledge, however, there are no data on the risk of psychological side effects among active drug users treated for HCV infection. Moreover, 24 to 30 percent of patients with HCV infection who do not use illicit drugs may be depressed.<sup>33</sup> Thus, it is important to assess the mental health of all patients before they begin interferon treatment. A study of treatment with interferon and ribavirin in patients who were receiving methadone maintenance therapy, a substantial proportion of whom had serious preexisting psychiatric disorders, showed that the safety and tolerability, as well as the rate of adherence to the regimen, were similar to those in other groups of HCV-infected patients.<sup>34</sup>

### Reinfection with HCV

Illicit-drug users who do not inject drugs have a low risk of reinfection with HCV, and the risk is therefore not a reason to deny treatment to such persons. Those who inject drugs while receiving effective treatment for HCV infection can avoid reinfection by using a new sterile syringe for each injection and by not sharing their injection equipment with other users. There are 174 needle-exchange programs in the United States (in 120 cities in 34 states), and the number has increased yearly, although many injection-drug users are still not reached by these programs. Most drug users who participate in needle-exchange programs do not share needles.<sup>4,35</sup> For drug users without access to such programs, physicians in at least 46 states are allowed by law to prescribe syringes so that their patients can avoid acquiring and transmitting bloodborne infections.<sup>36</sup> When given access to sterile syringes, injection-drug users readily make use of them, reducing their high-risk behavior,<sup>35,37</sup> and as a result, rates of disease transmission are reduced.<sup>4,38</sup> HCV may be more readily transmitted than the human immunodeficiency virus (HIV) through the sharing of injection equipment other than syringes, such as “cookers” (bottle caps, spoons, and other containers used to dissolve drugs) and “cottons” (filters used to draw up the drug solution into a syringe).<sup>39</sup> Thus, it is particularly important for physicians to instruct their patients not to share these items.<sup>40,41</sup>

### Timing of Treatment

In patients who have chronic HCV infection but who do not have advanced hepatic fibrosis, delaying therapy for HCV infection while drug use is being treated is unlikely to be detrimental. For patients who want to stop using illicit drugs, treatment of HCV infection may be more likely to succeed after recovery from drug abuse has been established,<sup>18</sup> although we are unaware of studies that have examined the treatment of HCV infection before, during, and after the treatment of drug use.

Delaying therapy in drug users makes sense, however, only when there is a plan for the treatment of drug use. If there is no such plan, deferring therapy amounts to a tacit decision to withhold it indefinitely. Many persons who use illicit drugs are not willing or able to stop doing so. For those who are, the availability of treatment programs falls far short of the demand. Methadone-maintenance programs, for example, can accommodate only about 15 to 20 percent of the estimated number of heroin users in the United States.<sup>10</sup> A policy of deferring the treatment of HCV infection indefinitely for patients who do not have access to drug treatment programs effectively abandons those most affected by the HCV epidemic.

It is important to note that in two groups of patients, delaying treatment could be detrimental for additional reasons. One group is patients with acute HCV infection, who may have a greater benefit from immediate treatment than from treatment given during a later phase of infection.<sup>7,9,42</sup> The other group is patients with relatively advanced hepatic fibrosis, in whom progression to cirrhosis is imminent.<sup>2,43</sup>

## MEDICAL AND PUBLIC HEALTH PRACTICES

Excluding drug users from treatment for HCV infection departs from standard medical and public health practices in situations involving adherence to treatment regimens, contagion, and reinfection. If poor adherence were a contraindication to therapy, most medical conditions would go untreated.<sup>22,23</sup> Low rates of adherence are common, for example, among patients with hypertension, asthma, and diabetes. Nor are patients whose behavior could cause a recurrence of a condition generally denied treatment in other settings. Smokers are not denied coronary-artery bypass surgery or treatment for emphysema. Persons with alcoholic liver disease are not denied treatment for gastrointestinal bleeding or ascites. Commercial sex workers and others who engage in high-risk sexual practices are not denied treatment for sexually transmitted infections because of the risk of reinfection; rather, they are specifically targeted for treatment in order to prevent the transmission of disease. The cost, complexity, and expected duration of antiretroviral regimens for HIV infection exceed those of regimens for HCV infection. Nevertheless, the withholding of HIV therapy from all persons who use illicit drugs has never been recommended.<sup>24,44,45</sup>

## AN ALTERNATIVE POLICY

We propose that decisions about the treatment of HCV infection in patients who use illicit drugs be based on individualized risk—benefit assessments, just as they are for other patients. Patient and physician should make decisions about treatment together, after a thorough discussion of the need for adherence to the treatment regimen and the risks of adverse effects and reinfection. The patient's current and previous adherence to medical regimens and his or her mental health and risk of depression should be considered, as should access to safe injection equipment and knowledge of safe injection practices.

In many cases, such discussions may not lead to treatment for injection-drug users. For some patients, poor adherence to treatment regimens, uncontrolled depression, or unsafe injection practices may remain obstacles to therapy. Others may decline treatment when they learn that the side effects can be severe, that a sustained response is uncertain, and that the disease will not progress in most untreated patients.

Even though factors weigh against therapy in some drug users, however, this does not mean that it should be withheld from all drug users. For patients considering treatment, adherence and tolerance can be assessed individually through a trial of therapy. Depression can be assessed and treated before antiviral therapy is started. Physicians can help patients improve their adherence, offer referrals to drug treatment programs, inform patients about safe injection methods and sources of safe injection equipment, prescribe syringes if it is legal and appropriate to do so,<sup>36</sup> and otherwise provide patients with support in reducing the risk of reinfection.<sup>4,38</sup> Developing a strong physician—patient relationship requires patience, promotion of trust, and an incremental approach to behavioral change.<sup>46-49</sup> In our experience, helping a patient who uses drugs adhere to a complex medical regimen can support an upward spiral of self-esteem and the adoption of healthier practices.

Ethical guidelines suggest that physicians offer treatment to persons who might benefit from it, take steps to improve the likelihood of a benefit, base treatment decisions on only those characteristics of patients that are clinically relevant, and respect the patient's informed decision to accept or decline treatment.<sup>50</sup> It may be difficult to make predictions about adherence, toxic effects, and reinfection in individual patients, but such assessments are likely to be more accurate, and more ethical, than the assumption that therapy is futile in all patients who use illicit drugs. Individualizing treatment decisions is standard medical practice in situations in which characteristics of the patient substantially influence the balance between risks and benefits.

## CONCLUSIONS

In an article on medical care for HIV-infected drug users, O'Connor et al. stated, "Despite evidence that treatment for drug abuse is effective, many physicians view addicted patients as incurable and morally culpable. As with other 'hateful' patients, physicians may come to view addicts as manipulative, unmotivated, and undeserving of care. . . . Although the physicians' frustration is understandable, such attitudes contribute to the unwarranted withholding of treatment and to mutually unsatisfactory patient—physician interactions."<sup>46</sup> We are concerned that the unwarranted withholding of effective therapy may have become codified in treatment guidelines.

The difficulties of caring for drug users should not be underestimated.<sup>46,47</sup> Drug users engage in practices, often daily, that society defines as illegal. They may fail to keep appointments or to take medicines as directed. Sensing the discomfort or disapproval of their health care providers, drug users may resist ongoing relationships with them and may be unable or unwilling to plan ahead and make systematic changes in their lifestyles.

Drug users, however, often need medical treatment. Moreover, they can be engaged in efforts to address their health care needs.<sup>12-21,46-49</sup> Successful programs invariably adopt a respectful approach to drug users, understand the medical and behavioral sequelae of addiction, and refrain from making moralistic judgments. Active injection-drug users are the source of most cases of HCV transmission in the United States.<sup>1</sup> Control of HCV infection requires the provision of treatment to persons who use illicit drugs. We believe that treatment guidelines must be based on evidence, tolerance, and compassion if this goal is to be accomplished.

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