Eligibility for Treatment of Hepatitis C Virus Infection among Young Injection Drug Users in 3 US Cities

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(See the editorial commentary by Edlin and Cardin on pages 673–6)

Among 404 injection drug users aged 18–35 who tested positive for hepatitis C virus (HCV) RNA, 96% had conditions that are potentially unwarranted contraindications for HCV treatment (e.g., problem drinking, moderate-to-severe depression, and recent drug injection). Restrictive eligibility criteria may deny treatment to a large proportion of patients who could benefit from it.

Globally, the prevalence of hepatitis C virus (HCV) infection among injection drug users (IDUs) ranges between 40% and 95%, depending on the underlying characteristics of the sample population, such as time at risk and relative frequency of exposure to HCV through unsafe injection [1]. Successful treatment of chronic HCV infection has steadily advanced in recent years; in 2005, approximately half of HCV-infected patients will recover after receiving combination therapy with pegylated interferon and ribavirin [2].

Treatment of IDUs for HCV infection has been controversial. The principal concerns are that drug use may interfere with their ability to adhere to treatment or that it may increase the risk of reinfection after they have recovered [3]. Interferon treatment is associated with acute depression, and symptoms of depression are highly prevalent among IDUs [4, 5]. Heavy alcohol use is related to severe liver disease in HCV-positive patients, and it can reduce the effectiveness of anti-HCV treatment [6]. Polydrug use, including heavy alcohol consumption, is also relatively common among IDUs [7]. Altogether, IDUs may face a number of obstacles to anti-HCV treatment, and anti-HCV treatment may be received less often by IDUs than by other patient groups [8, 9]. In 2002, the National Institutes of Health consensus on medical management of HCV infection reversed a previous judgment from 1997 [10], and recommended that practitioners "determine on an individual basis whether patients who use drugs or alcohol may be offered treatment" [11, p. 12]. This represented an important step toward providing treatment for HCV infection to a greater proportion of infected persons, but many individual practitioners still choose to apply restrictive criteria, including abstinence from ongoing illicit drug use for 6 months prior to treatment [8, 12]. Previous studies have not examined the potential impact of multiple screening criteria on IDUs' access to treatment. This article assesses eligibility of a sample of young, HCV RNA–positive IDUs for anti-HCV treatment—an important population because young age (defined here as aged 18–35) is associated with higher likelihood of successful treatment outcome [13].

Methods. The Study to Reduce Intravenous Exposures (STRIVE) was a trial of a randomized, controlled, behavioral intervention that aimed to reduce HCV transmission risk behavior and increase health care utilization among HCV-positive, young IDUs in Baltimore, New York, and Seattle. Enrollment occurred from June 2002 to February 2004. To be eligible, participants had to have used injection drugs in the past 6 months, had to test positive for antibodies against HCV, and test negative for antibodies against HIV, and had to be aged 18–35 years. Participants were recruited by referral from other studies that had screened them for antibodies against HCV. At baseline, participants completed questionnaires via computer-assisted self-interview. Depression was measured using the Beck Depression Inventory [14]; a score of >19 indicates moderate-to-severe depression symptoms. Alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT) [15]; an AUDIT score of >8 indicates problem drinking. We defined current IDUs as those who had used an injection drug in the 30 days prior to study enrollment. Blood samples were tested for antibodies against HCV with either HCV EIA 3.0 (Ortho)

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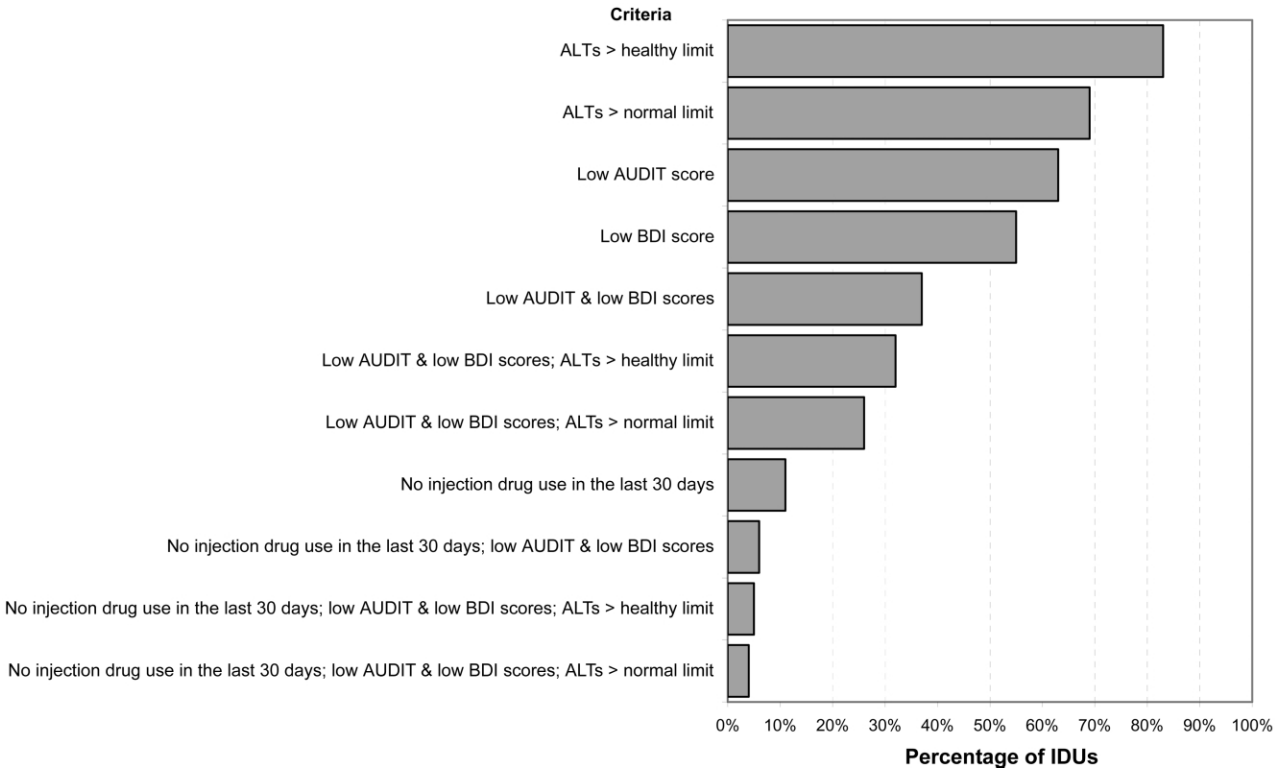

Figure 1. The incredible shrinking patient: the diminishing percentage of injection drug users (IDUs) who test positive for hepatitis C virus (HCV) RNA and are eligible for HCV treatment when various criteria are applied. A low Alcohol Use Disorders Identification Test (AUDIT) score is defined as <8, and a low Beck Depression Inventory (BDI) score is defined as <19. ALT, alanine aminotransferase level. (The figure title was inspired by the title of a graph that appears in a book by Edward Tufte [22].)

or HCV EIA 2.0 (Abbott), and alanine aminotransferase (ALT) levels and HCV RNA levels were determined with the Cobas Amplicor assay (Roche Diagnostic Systems). The reference ranges used by the 3 local laboratories that performed the tests were used to establish the upper limit of normal for ALT levels. However, because the accepted upper limit of normal may not be a sensitive measure of hepatic injury, Prati et al. [16] have proposed that the "healthy" upper limit of normal for ALT levels be revised as 0.75 times the upper limit of normal for men and 0.63 times the upper limit of normal for women. Therefore, we report the proportion of subjects with elevated ALT levels, showing both the percentage of those whose levels are above healthy limits and the percentage of those whose levels are above normal limits. This analysis estimates the proportion of HCV RNA–positive subjects that may be considered eligible for treatment of HCV infection, assuming that problem drinking, depression, or current drug injection may be used to screen patients, and that some clinicians may only treat patients with elevated ALT levels. These criteria were selected because they appear to reflect general practice; with the exception of alcohol use, none of the criteria have been systematically studied to assess their impact on treatment outcome. This study was approved by institutional review boards at each of the study sites.

Results. There were 632 eligible subjects enrolled in STRIVE; 404 (64%) were HCV RNA–positive and included in this analysis. Seventy-eight percent were men, and 60% were white. The median age was 26 years (interquartile range, 23–29 years). Heroin injected alone or with cocaine was the injected drug mainly used by subjects. The median number of years since first injection was 6 (interquartile range, 4–9 years). Eighty-four percent of the subjects had never been incarcerated, and 70% had never been in drug treatment of some type. Only 23% reported they were currently enrolled in a drug treatment program. Most participants (65%) injected drugs daily. Two hundred twenty-two (55%) of 404 IDUs scored <19 on the Beck Depression Inventory, and 255 (63%) of 404) scored <8 on AUDIT. Forty-four (11%) of 44/404 had not injected drugs in the previous 30 days.

Figure 1 shows the percentage of IDUs who may be deemed eligible for treatment of HCV infection, as multiple criteria are applied. Three hundred thirty-five (38%) of 404 had ALT levels above the healthy limit, and 279 (69%) of 404 had ALT levels above the normal limit. Thirty-seven percent had low Beck

Depression Inventory and AUDIT scores; including only those with elevated ALT levels, this reduced the percentage of eligible subjects to 26%–32%. Of the 11% who had not injected drugs in the previous 30 days, only half would be considered eligible for treatment of HCV infection if the presence of problem alcohol use or depression was also used in screening. Only 4% of all subjects in the study would be considered eligible for anti-HCV therapy on the basis of having ALT levels above normal limits, low AUDIT and Beck Depression Inventory scores, and having not injected drugs in the past 30 days.

Discussion. In this sample of HCV RNA–positive IDUs aged 18–35 years, there was a high prevalence of conditions that represent potentially unwarranted contraindications for anti-HCV treatment. In particular, most subjects (89%) had injected drugs recently, and 63% had symptoms of either depression or problem drinking. Thus, the application of multiple exclusion criteria to this population may deny treatment to the vast majority—perhaps 96%—of IDUs with HCV infection.

Considering the degree to which these criteria may restrict access to treatment, there is remarkably little evidence to support their use in screening patients for eligibility. A review of anti-HCV treatment experiences among active or former IDUs reported that studies have consistently shown low rates of reinfection, and treatment completion rates among IDUs are comparable to the rates in other patient populations [8]. Other studies have shown that it may be unnecessary to withhold HCV treatment from patients with symptoms of moderate or severe depression, and pretreatment with antidepressants and monitoring for signs of acute depression may improve treatment safety [17]. A relatively large proportion of IDUs with HCV infection (50%–80%) may be willing to undergo treatment [18], which suggests that patient reluctance is not a major barrier. Heavy alcohol use may represent a more important contraindication to HCV treatment, because it appears to decrease response to therapy, but the effect of moderate alcohol use is less clear [19]. Thus, the number of IDUs treated for HCV infection may increase substantially if only those factors empirically shown to affect treatment outcome are considered. Particularly because younger patients are more likely to respond to treatment of HCV infection, factors used in screening for treatment eligibility in this group should be limited to those that clearly reduce the effectiveness of treatment or increase toxicity.

In addition to increasing the likelihood of a sustained virologic response to HCV therapy, treating young patients may have other important public health and individual benefits. Early treatment may substantially shorten the period of infectiousness and, if carried out on a large scale, lower the prevalence of IDUs who are infectious HCV carriers to a meaningful degree. In addition, anti-HCV pharmacotherapy requires regular medical visits over a long-term period—a regimen that may permit the integration of primary medical care or office-based treatment of opiate addiction with buprenorphine [20]. Clearly, cost-benefit analyses of anti-HCV treatment for IDUs should include any health care cost savings due to averted infections and early treatment of other conditions, including substance abuse.

Limitations to the study include the possibility that the patient sample may not be representative of the underlying population of younger, HCV RNA–positive IDUs. Although the sample included a relatively large proportion of white males and may not be representative of IDUs in all US cities, the use of several different recruitment strategies, including targeted street outreach and participant-driven referrals, would tend to reduce recruitment bias. Social desirability bias may have influenced the reporting of alcohol use, although the interviews were administered using computer-assisted self-interview technology. The elevated ALT levels in a large proportion of patients in our sample may have been a consequence of alcohol use rather than an indication of the effects of HCV infection. However, the use of elevated ALT levels to select individuals with a higher probability of response to treatment has been brought into question by recent studies of HCV virologic kinetics [21]. We also did not perform liver biopsies or other tests to determine medical eligibility for treatment, and the single ALT test may not be particularly informative in determining whether active hepatitis infection is present. None of the young IDUs we screened for recruitment were ineligible to join the study because they had not injected drugs in the past 6 months. However, if 6 months' abstinence were a requirement, even fewer than 4% of young IDUs may be eligible for HCV treatment.

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ERRATUM

In an article in the 1 March 2006 issue of the journal (Hagan H, Latka MH, Campbell JV, Golub ET, Garfein RS, Thomas DA, Kapadia F, Strathdee SA, for the Study to Reduce Intravenous Exposures Project Team. Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities. Clin Infect Dis 2006; 42:669–72), an error appeared in the sixth sentence of the Results section. The sentence should read "Eighty-four percent of the subjects had ever been incarcerated, and 70% had ever been in drug treatment of some type" (*not* "Eighty-four percent of the subjects had never been incarcerated, and 70% had never been in drug treatment of some type"). The journal regrets this error.

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