

# Follow-Up Studies of Treatment for Hepatitis C Virus Infection among Injection Drug Users

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Physicians are reluctant to treat chronic hepatitis C virus (HCV) infection in active injection drug users (IDUs). An important reason for this is concern about reinfection after successful treatment. However, little is known about this apparent risk; because of lack of protective immunity, reinfection with HCV seems possible. Here, I discuss several cases of probable reinfection in IDUs, 2 of which occurred during or after successful treatment for HCV infection. In a Norwegian trial, 69 IDUs who had abstained from drug use for  $\geq 6$  months were treated for HCV infection; of these, 27 tested negative for HCV RNA at 6 months of follow-up (sustained virological response). At 5 years of follow-up, 9 (33%) of the 27 IDUs with sustained virological response had returned to drug use, but only 1 case of reinfection was observed. In another study, 395 subjects with sustained virological response were followed with yearly testing for HCV RNA. Although injection drug use was the route of HCV transmission in 40% of the subjects, only 7 (2%) experienced a late relapse of HCV infection. It has not been determined whether any of these cases were actual reinfections. Available data suggest that the rate of long-term response to treatment for HCV infection is excellent in IDUs.

Injection drug use is a major route of hepatitis C virus (HCV) transmission in both Europe [1] and the United States [2]. In a population-based survey among 11,500 adult residents of Oslo, my group recently found that 80% of cases of HCV transmission among persons of Norwegian origin had occurred through injection drug use [3]. Although fairly effective treatment for HCV infection is available, physicians are reluctant to offer such treatment to active injection drug users (IDUs). Reasons for this may include anticipated difficulties with managing the adverse effects of treatment, such as depression and hematologic disturbances, and a perceived risk of reinfection after successful treatment [4]. The latter issue is discussed here.

## REINFECTION

It is reasonable to ask whether reinfection with HCV is possible at all. Attempts to develop an HCV vaccine

have highlighted the inability of the immune system to develop humoral or cellular protective immunity to HCV [5]. One explanation for this may be the ability of the virus to change surface proteins through a high frequency of mutation. Lack of protective immunity to HCV is also suggested by experiments that demonstrate the reappearance of HCV RNA in chimpanzees re-challenged with the same or a different strain of HCV after spontaneous convalescence from infection [6].

A few cases of probable reinfections with HCV in humans have been published. In one case, a French IDU received a diagnosis of acute infection with HCV genotype 1a [7]. She spontaneously cleared the virus, as demonstrated by the fact that alanine aminotransferase levels remained normal and that HCV RNA was undetectable by PCR for several months. After continued exposure to HCV through injection drug use, she presented again with acute hepatitis, and this time the genotype was determined to be HCV genotype 3a. She did not clear the virus and developed chronic HCV infection.

In another case, a 22-year-old woman had an infection with HCV genotype 3a that was treated with IFN- $\alpha$  [8]. At 6 months, HCV RNA was undetectable. Dur-

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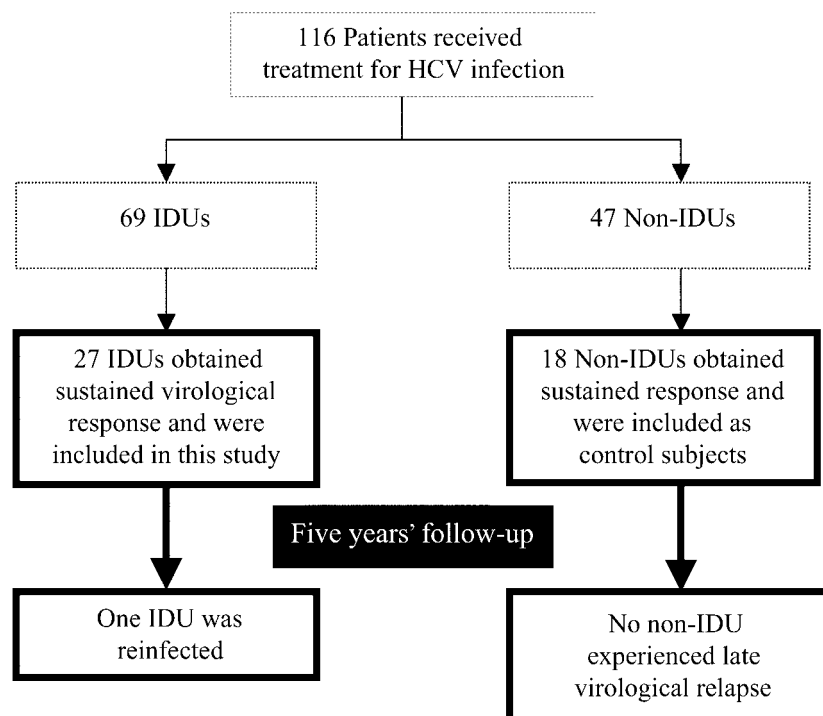
ing treatment, she developed acute hepatitis, and this time HCV genotype 1a was detected. Multiple infection with both genotypes 1a and 3a before treatment was ruled out by use of PCR with specific probes for genotypes 1 and 3.

## FOLLOW-UP AFTER TREATMENT FOR HCV INFECTION AMONG IDUs

Active IDUs only rarely receive treatment for HCV infection, and, to date, no follow-up studies of such patients have been published. However, my group reported the results of long-term follow-up after treatment for HCV of IDUs who had been abstinent from drug use for  $\geq 6$  months [9]. In that study, 116 patients (69 former IDUs and 47 non-IDUs) were treated with IFN- $\alpha$  alone or in combination with ribavirin (figure 1) [10, 11]. In total, 45 patients experienced a sustained virological response, defined as the absence of HCV RNA in serum, as determined by PCR ("in-house" detection limit of 800 virus copies/mL), 6 months after the end of treatment. Injection drug use was the route of HCV transmission for 27 patients with a sustained virological response, and 18 patients had other routes of HCV transmission. Of the 27 IDUs, 18 were classified as former regular drug users and 9 were classified as casual drug users. At long-term follow-up 13–82 months (median, 65 months) after the end of treatment, HCV RNA had reappeared in 1 of 27 IDUs with sustained virological response and in 0 of 18 non-IDUs ( $P = .41$ ). In the patient who was positive for

HCV RNA at follow-up, HCV genotype 1a had been identified before treatment, as opposed to HCV genotype 1b after treatment. He acknowledged returning to injection drug use and reported frequent needle sharing with a person positive for HCV antibody. I believe it probable that this patient was reinfected with HCV. However, it cannot be ruled out that he initially had a mixed infection with different genotypes and was not able to clear all genotypes during treatment. Although methods for demonstrating mixed infections with different HCV genotypes are unreliable, such infection was detected in as many as 11% in a study of patients with chronic HCV infection [12].

Return to injection drug use was common among the former IDUs in this trial [9]: 9 of the 18 former regular IDUs had reinitiated drug use, and 2 of these had died of overdose. The incidence of reinfection among all 27 IDUs was 0.8 cases/100 person-years at risk (95% CI, 0–5 cases/100 person-years at risk), and, among the 9 IDUs who returned to drug use, the incidence of reinfection was 2.5 cases/100 person-years at risk (95% CI, 0–14 cases/100 person-years at risk). In comparison, the incidence of HCV infection among IDUs not previously infected with HCV have been reported to be as high as 15–40 cases/100 person-years [13, 14]. The small sample size is clearly of concern for the interpretation of our finding, although a low incidence of reinfection could be explained by safer injection routines in the relatively experienced



**Figure 1.** Long-term follow-up of injection drug users (IDUs) who participated in a Norwegian treatment trial

IDUs who participated in our study. In Norway, needle exchange programs are readily available in all major cities. An incidence of only 4.3 cases/100 person years was seen among a group of IDUs who had injected for >2 years [15]. Another possibility suggested by our finding is that partial protective immunity may have developed. Such immunity was suggested by an incidence study among IDUs in Baltimore. This study revealed that IDUs positive for antibody to HCV but negative for HCV RNA were half as likely to develop new viremia as were IDUs without antibody to HCV [16].

McHutchison et al. [17] also found a low incidence of relapse of HCV infection after successful treatment. In that study, 395 patients with a sustained virological response from 3 large treatment trials [18–20] were followed-up with testing of serum for HCV RNA every 12 months. Injection drug use was the route of transmission in 40% of the subjects in those trials, but no information on drug use after treatment for HCV infection was reported. To date, relapse of HCV infection has been detected in only 7 (1.8%) of the 395 patients.

The high rate of return to drug use observed in our follow-up study is disturbing but in line with the findings of a Norwegian follow-up study of 200 IDUs who completed a drug treatment program. The study showed that more than half had returned to heavy drug use within 5 years [21].

## CONCLUSION

Reinfection after successful treatment for HCV infection is probably possible. After a period of abstinence during treatment for HCV infection, IDUs are prone to return to drug use. Despite this, the incidence of reinfection seems to be low.

## Acknowledgment

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