

Infrequent Reinfection after Successful Treatment for Hepatitis C Virus Infection in Injection Drug Users

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We followed-up 18 injection drug users for a mean of 33.8 months (range, 4–55 months) after successful treatment for hepatitis C virus (HCV) infection. Fifteen (83%) of the patients remained HCV RNA–negative, 1 patient was not tested, and 2 patients had test results positive for HCV RNA. The estimated rate of reinfection as a result of injection drug use was 0–4.1 cases per 100 person-years (cumulative incidence, 0%–12.6% at 48 months after completion of treatment). Of 50 patients originally treated, 15 (30%) were HCV RNA–negative 3 years later.

Injection drug users (IDUs) constitute the largest group of persons infected with the hepatitis C virus (HCV) in the United States and Europe, and most HCV transmission occurs among IDUs [1–7]. Controlling hepatitis C, therefore, will require prevention and treatment strategies that will be effective for persons who inject drugs [8–10]. Until 2002, treatment for HCV infection was not recommended for patients who were injecting illegal drugs [11, 12], on the grounds that adherence to therapy would likely be poor and the risk of reinfection would be high if they continued to inject drugs. Since 1997, knowledge of hepatitis C has increased dramatically, leading to the need to reexamine approaches to management and treatment [13].

Several studies in the United States and Europe have now shown that treatment of chronic HCV infection in IDUs is effective, with sustained virologic response (SVR) rates of 28%–36% [14–19]. In our own earlier study [14], performed in Munich, 50 IDUs began HCV treatment during opiate detoxification; the SVR rate was 36% overall and 53% among patients

who relapsed to using opiates and began methadone maintenance therapy while receiving treatment for HCV infection. The success rate of detoxification treatment among patients who were treated with IFN was similar to that among other patients [20].

Nonetheless, reinfection can occur after successful completion of treatment for HCV infection [21–23]. Little is known, however, about the incidence of reinfection among IDUs who have undergone successful treatment for HCV infection. A Scandinavian study [24] reported 5-year follow-up of 27 IDUs who had cleared HCV RNA from the blood after receiving IFN therapy. Nine patients (33%) relapsed to injection drug use, but only 1 patient became reinfected during a total of 40 person-years of observation. In this study, we present data on the 3-year follow-up of the 18 patients (36%) from our earlier study [14] who attained SVR after starting treatment for HCV infection during opiate detoxification.

Patients and methods. In 1997, we began a prospective study to investigate whether opiate-dependent IDUs with chronic HCV infection could be treated successfully with IFN. Fifty inpatients were enrolled in the study during detoxification treatment. All patients were taught how to avoid bloodborne infections in case they returned to using injection drugs. Patients received IFN α -2a monotherapy for 48 weeks (through 1998) or IFN α -2a and ribavirin for 24–48 weeks, according to HCV genotype (starting in 1998). SVR was defined by a test result negative for plasma HCV RNA at 24 weeks after the end of treatment. Eighteen patients (36%) achieved SVR [14] and were included in the present study. Patients were seen at follow-up intervals of \sim 1 year. They were asked by their physician about the use of drugs by injection and of syringes that had previously been used by another person. Plasma samples were tested for HCV RNA by PCR (Cobas Amplicor Hepatitis C Virus Test, version 2.0; Roche Diagnostics). If a test result was positive for HCV RNA, the HCV genotype was determined. The rate of reinfection was estimated using person-time methods, starting from the date of the HCV RNA test with a negative result (performed 24 weeks after the end of treatment) and assuming that reinfection occurred midway between the date of the last negative test result and the date of the first test result positive for HCV RNA. Kaplan-Meier survival methods were used to estimate the cumulative probability of reinfection after 48 months of follow-up.

Results. The median age of the 18 patients was 32.1 years (range, 20–40 years); 11 (61%) of the patients were men, and 7 (39%) were women. The patients were followed-up for 10–

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61 months (mean, 39.8 months) after completing treatment or for 4–55 months (mean, 33.8 months) after achieving SVR (table 1). Fifteen patients (83%; 9 men and 6 women) remained HCV RNA–negative. One patient died of an overdose before follow-up testing for HCV RNA was performed. Two patients tested positive for HCV-RNA. Patient 42, the only patient infected with HCV genotype 1b, was found to be positive for HCV RNA 4 months after attaining SVR and again had infection with HCV genotype 1b. Patient 31, who had been infected with HCV genotype 3a, developed infection with HCV genotype 1a after a needlestick injury sustained as a health care worker 42 months after achieving SVR. She denied any illicit drug use since receiving treatment for HCV infection. Both patients remained persistently HCV RNA–positive for ≥ 6 months on follow-up testing. Overall, of the 50 patients originally treated, 15 (30%) were alive and HCV RNA–negative 3 years after completing treatment.

We do not know whether patient 42 had a late viral relapse or became reinfected through continued injection drug use, nor do we know whether patient 31 became reinfected through undisclosed injection drug use or through her occupational injury. The number of reinfections attributable to injection drug use, therefore, was estimated to be 0–2. The estimated rate of reinfection due to injection drug use among the 18 patients was 0–4.1 cases per 100 person-years (95% CI, 0.5–

14.9). The estimated cumulative incidence of reinfection 48 months after SVR was 0%–12.6% (95% CI, 3.3%–41.9%) (figure 1).

Of the 18 patients, 9 (50%) injected illicit drugs during the follow-up period (table 1). The number of times they injected drugs during follow-up ranged from <10 (for 2 patients) to >100 (for 2 patients). None reported using syringes previously used by another person. Eight patients—1 of whom (patient 27) occasionally injected heroin during the follow-up period—are living drug-free at the time of writing, with neither methadone nor heroin dependence. One patient (patient 18) was readmitted to a detoxification unit after having experienced a relapse of injection drug use and is now in an inpatient abstinence-oriented drug treatment program. Of the 7 patients being treated with methadone, 5 also use heroin at least occasionally.

Discussion. The possibility of reinfection has been cited by the National Institutes of Health (NIH) [10] and the European Association for the Study of the Liver [11] as a reason not to administer therapy for HCV infection to active IDUs. We followed-up 18 active IDUs who were successfully treated for HCV infection, 9 of whom injected drugs during the follow-up period. No more than 2 (and possibly as few as none) of the patients became reinfected as a result of illicit injection drug use after treatment for HCV infection. Patient 42 might have

Table 1. Follow-up of 18 injection drug users with sustained virologic response (SVR) after treatment for hepatitis C virus (HCV) infection.

Patient	HCV genotype	Follow-up period, months after SVR	HCV RNA test result (genotype)	Any injection drug use during follow-up?	Current injection drug use status
1	3a	9	Negative	No	Receiving methadone treatment
3	1a	41	Negative	No	Receiving methadone treatment
5	3a	33	Negative	No	Drug free
7	1a	27	Negative	Yes	Receiving methadone treatment
10	3a	55	Negative	Yes	Receiving methadone treatment
12	1a	54	Negative	Yes	Receiving methadone treatment
18	3a	43	Negative	Yes	Enrolled in residential treatment program
21	3a	50	Negative	Yes	Receiving methadone treatment
26	1a	45	Negative	No	Drug free
27	3a	38	Negative	Yes	Drug free
30	3a	8	Negative	Yes	Receiving no treatment
31	3a	42	Positive (1a)	No	Drug free
33	3a	21	Negative	No	Drug free
35	3a	46	Negative	No	Drug free
42	1b	4	Positive (1b)	Yes	Receiving methadone treatment
46	1a	6	ND	Yes	Deceased ^a
49	3a	40	Negative	Unknown	Drug free
50	1a	47	Negative	No	Drug free

NOTE. Patients are derived from the cohort described in [14]. SVR was defined by a test result negative for plasma HCV RNA at 24 weeks after the end of treatment for HCV infection. ND, not done.

^a Patient 46 died of a drug overdose.

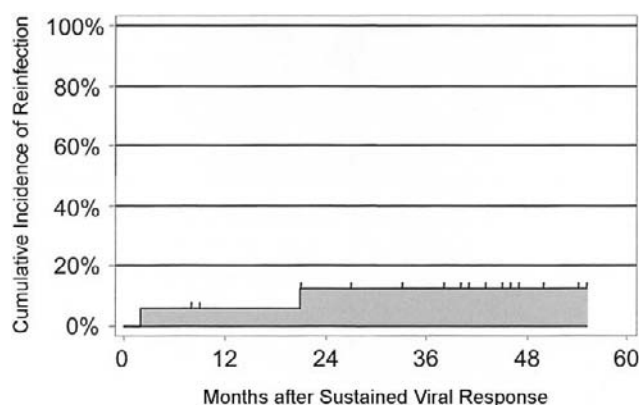


Figure 1. Estimated cumulative incidence of reinfection due to recurrent injection drug use after successful treatment for HCV infection among 18 injection drug users (*shaded area*). Kaplan-Meier plot shows the maximum estimated incidence. Estimated cumulative incidence at 48 months after achievement at sustained viral response was 0%–12.6% (95% CI, 3.3%–41.9%). Sustained virologic response was defined by a test result negative for plasma HCV RNA at 24 weeks after the end of treatment for HCV infection.

become reinfected, but the virus appeared only 4 months after SVR and had the same genotype as the virus responsible for the previous infection (genotype 1b, which was uncommon in our population). Late relapse may occur in 4%–10% of patients with SVR [25–27]. Patient 31 reported an occupational needle stick injury and denied any illicit drug use during the 4 years since being treated for HCV infection. Although we could not document the truthfulness of her report, we have no reason to suspect that she had used injection drugs. She had worked stably and productively as a nurse for 4 years. The genotype of the virus responsible for her second infection (1a) is uncommon among IDUs in Munich but is common among other individuals with HCV infection [8, 28–30]. Thus, we estimate that the rate of reinfection among our patients was between 0–4.1 cases per 100 person-years. These findings are consistent with a Norwegian study [24] that found a reinfection rate of 2.5 cases per 100 person-years among former IDUs (1 case of reinfection in 40 person-years of follow-up).

During treatment, the patients in our study were taught how to avoid bloodborne infections, in case they returned to using injection drugs. Addiction is a chronic, relapsing condition. Most patients entering treatment do not immediately and permanently stop using injection drugs. Relapse must be anticipated and should be planned for. Drug users may avoid acquiring and transmitting bloodborne infections when they inject drugs by using sterile injection equipment and safe injection techniques [31]. Physicians can help IDUs to avoid acquiring HCV infection and to avoid reacquiring it after successful treatment for HCV infection by helping them to un-

derstand safe injection techniques and to gain access to sterile syringes [13].

One of our patients died as the result of a drug overdose. In Germany, the mortality rate among IDUs in the first year after completion of detoxification treatment is 2.8%–10% [32, 33]. During methadone maintenance therapy, the mortality rate is 1.4%–2.7%, and treatment with higher doses of methadone seems to be protective [34, 35]. Among our patients who were successfully treated for HCV infection during the first year after detoxification, the mortality was 5.5% (95% CI, 0.1%–27.3%). These data underscore the importance of overdose prevention, which is always a critical component of the care of current and former IDUs [36, 37].

In conclusion, our data suggest that IDUs can be reinfected after treatment for HCV infection, but the reinfection rate is not so high as to jeopardize the potential benefit for most patients. Overall, 15 (30%) of the 50 IDUs we originally treated for HCV infection remained alive and HCV RNA–negative 3 years after the end of treatment. Our sample population was small; further studies with larger numbers of patients are needed. In the meantime, however, it appears that therapy for HCV infection is successful in a substantial proportion of IDUs [14–19], and reinfection appears to be uncommon, even among those who inject drugs after achieving SVR. Thus, therapy for HCV infection should not be categorically withheld from IDUs [9]. The new NIH recommendations of 2002 reflect this new standard [13]. In our experience, the best approach for treatment of HCV infection in IDUs has been to start treatment during detoxification or methadone maintenance, with supervision by physicians specialized in both hepatology and addiction medicine.

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