Hepatitis C Virus Infection and Injection Drug Users: Prevention, Risk Factors, and Treatment

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Injection drug users (IDUs) are the largest group of persons infected with hepatitis C virus (HCV), with a prevalence of 50%–90%. The transmission of HCV is not the effect of the drug injected but of sharing contaminated equipment. For the sake of prevention, we have to know which factors are more likely to lead to HCV seroconversion and which particular situations and environments are risk factors for equipment sharing. As far as therapy is concerned, some studies have shown that treatment for HCV infection in IDUs during substitution treatment for drug dependency is as successful as is treatment of patients who are not IDUs. Screening and early treatment of IDUs could play an important role in controlling HCV infection. The rate of reinfection may not as high as supposed. All studies dealing with treatment for HCV infection in IDUs have stressed the necessity of collaboration among hepatologists and specialists in addiction medicine, social workers, and psychotherapists.

Injection drug users (IDUs) are the largest group of persons infected with hepatitis C virus (HCV) in the United States and in Europe. Among IDUs, 50%–90% are infected [1–8]. In the United States, injection drug use accounts for most cases of HCV transmission [1], and the long-term sequelae of chronic HCV-related hepatocellular carcinoma continue to increase, particularly in white men aged 45–54 years. This may be explained by the consequences of HCV infections acquired during the 1960s and 1970s [9]. Control of HCV infection in the United States therefore will require the development, testing, and implementation of effective prevention and treatment strategies for persons who inject drugs [10].

PREVENTION: INFORMING ABOUT RISK FACTORS FOR HCV INFECTION

Among IDUs, epidemics of malaria, tetanus, and other infectious diseases and of viral infections (e.g., HIV, hepatitis B virus [HBV], and HCV) have been reported [11–16]. The transmission of these infectious diseases is not an effect of, for example, heroin or cocaine but the result of sharing contaminated equipment [17–21]. However, needle exchange programs do not seem to prevent HCV infections as effectively as they do HIV infections [20, 22]. This is because HCV, in contrast to HIV, is detectable in high concentrations in other utensils for heroin injection, such as filters, spoons, and rinsing liquids. Therefore, not only the sharing of needles and syringes but also the sharing of the other utensils seems to be an important risk factor for HCV infection [23–28].

To be able to inform effectively, we have to know which other factors are more likely to lead to HCV seroconversion and which particular situations and environments are risk factors for equipment sharing. In different studies, the following risk factors were identified: intranasal consumption of cocaine, iv consumption of cocaine, former imprisonment, higher age, longer duration of cocaine use, higher frequency of injections, female sex, iv heroin injections by other persons or to other persons, and consumption of several different drugs [23, 29–32].

We investigated risk factors for HCV infection in a cohort of patients admitted to our detoxification unit
between April 1991 and April 1997. All subjects included in our study had to be admitted voluntarily and had to meet the current *International Classification of Diseases* (10th edition) diagnosis of opioid dependence. All subjects have previously injected heroin iv. One thousand forty-nine patients were included. By use of multiple logistic regression, we found that older age, longer duration of opioid use, living with other long-term drug users, history of imprisonment, history of inpatient abstinence-oriented psychotherapeutic therapy, and additional daily consumption of alcohol were independently associated with serologic test results positive for antibody to HCV (figure 1) [8].

### ADDICTION CARE NETWORK—POSSIBLE SETTINGS FOR TREATMENT OF HCV INFECTION IN IDUs

**Treatment for chronic HCV infection.** The treatment of somatic diseases in IDUs is reported to be difficult. To treat somatic diseases in IDUs successfully, collaboration between specialists for somatic diseases and addiction medicine is mandatory. Alternatively, physicians should be specialized in both addiction medicine and infectious diseases. However, not only physicians should collaborate. Interdisciplinary teamwork seems to be the best prerequisite for success: Social workers, psychologists, psychotherapists, and physicians should work together. Possible parts of an addiction care network are listed in table 1. A psychotherapeutic approach could be most suitable for the first contact between physician or therapist and IDU: It is important to establish a good physician-patient relationship and to win the confidence of IDUs. Physicians and therapists have to inform and educate how to inject safely and how to avoid sharing any injection equipment.

The common opinion about IDUs is that they are not compliant. Therefore, it could be helpful to look for settings that perhaps enhance compliance. A few studies have shown that treatment of chronic HCV infections in IDUs is effective (reviewed in [33]). A study from Oakland, California, reported a sustained virological response rate of 29% among 66 patients undergoing maintenance therapy with methadone who were treated with combination therapy with IFN-α and ribavirin [34]. This response rate was achieved despite the patients’ relatively higher age, longer duration of infection, more advanced liver disease, and predominance of HCV genotype 1—all of which are factors associated with reduced response rates [35]. In a recent prospective and controlled study [36], different HCV-infected psychiatric risk groups (i.e., methadone-treated patients, former addicts, and patients with depression or schizophrenia) were investigated. The rate of sustained virological response was 35% in the control group, 38% in the psychiatric group, 48% in the methadone group, 28% in the former drug user group [36] (figure 2). This poor result among former addicts is in contradiction to the current recommendations of the European Society for the Study of the Liver (EASL) [37], which require a drug-free period of 6–12 months before starting therapy for HCV infection. One reason for the unfavorable result could be that withdrawal symptoms and adverse effects of IFN are rather similar: sleeplessness, sweating, nausea, vomiting, fever, headache, and pain. It is well known that former addicts, when feeling discomfort in either mind or body, are in danger of having a drug relapse.

In the Munich study [38], we made the assumptions that, if we commence therapy for HCV infection during detoxification treatment, 1 of 4 different settings may apply: The patient continues to live drug-free at home after detoxification treatment; the patient continues to live drug-free at abstinence inpatient treatment after detoxification treatment; the patient continues to inject drugs after having had a drug relapse; or the patient is treated with methadone after having had a drug relapse.

**Table 1. Possible components of an addiction care network.**

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<tr>
<td>Counseling</td>
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<td>Emergency treatment for overdosed injection drug users</td>
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<td>Substitution treatment</td>
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<td>Abstinence-oriented treatment</td>
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<td>Psychotherapy</td>
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![Figure 1. Factors independently associated with positive results of serological testing for hepatitis C virus in drug users in Germany (n = 1049) in a multiple logistic regression analysis.](image-url)
As shown in our previous study [38], patients who had a drug relapse and entered a methadone treatment program reached a rate of sustained virological response of 53% (figure 3). The overall rate of sustained virological response was 36% (figure 3) [38]. Patients who were treated with IFN alone or in combination with ribavirin completed detoxification treatment as successfully as did nontreated patients [39]. A study in Italy [40] showed that, shortly after detoxification treatment, 17 of 47 patients dropped out of treatment for HCV infection. Of the remaining 30 patients, 27 (57%) achieved negative results for the presence of HCV RNA 8 weeks after the start of treatment for HCV infection [40].

To prove the good results of treatment for HCV infection during substitution treatment with methadone, we started an outpatient treatment study in 2001. All patients were allocated by the municipal allocation office, in case they could not be handled by practitioners because of the severity of the opioid dependency. The municipal allocation office is called “Clearingstelle.” Every practitioner or patient can call and ask for a free place in a substitution program. All patients were tested for antibody to HCV, and, if results were positive, they were tested for the presence of HCV RNA. Patients were also tested for antibody to HIV, and results were negative for all patients. In persons positive for HCV RNA, genotype and quantitative HCV RNA load were determined. Of 115 HCV-infected IDUs undergoing substitution treatment as outpatients at the hospital, treatment for HCV infection was commenced for 40 IDUs (35%). The mean age was 35 years (range, 19–56 years); 63% were men, and 37% were women. HCV genotype 1 was found in 48% of cases (figure 4). Figure 5 shows the interim results. To date, 14 patients (35%) have experienced a sustained virological response. Treatment for HCV infection is ongoing for 9 patients who had test results negative for the presence of HCV RNA at week 12. Five patients had test results negative for the presence of HCV RNA at the end of treatment. Twelve patients (30%) had either no response or rebound of HCV RNA. On the basis of this experience, we assume a rate of sustained virological response of ~50% of treated patients. A recent prospective trial showed that the rate of sustained virological response was 42% in the methadone group and 56% in the control group \( (P = .16) \) [41] Thus, for us, the best approach for treatment of HCV infection for IDUs has been initiation of antiviral treatment during detoxification or during methadone maintenance carried out by physicians specialized in both hepatology and addiction medicine.

**Acute HCV infection in IDUs.** In contrast to the diagnosis of hepatitis A virus (HAV) infection, the diagnosis of acute HCV infection is not confined to the presence of a certain antibody. The diagnosis of acute HCV infection thus is based either on seroconversion to antibodies to HCV and/or clinical and biochemical criteria and on the presence of HCV RNA as detected by RT-PCR in the first serum sample. Most studies of acute HCV infection focused on posttransfusion hepatitis, which has a clinically asymptomatic course in 50%–80% of patients. Although symptomatic acute HCV infections may have a better outcome, detailed information on the prognostic parameters and on the correlates of immunity are still lacking. Today, only a few patients with acute HCV infection are found incidentally, whereas the vast majority are discovered only if symptoms compatible with acute HCV infection are present or if an infection was suspected and follow-up examinations revealed elevation in levels of aminotransferases. The National Institutes of Health has recommended that all IDUs should be screened for HCV infection [42]. This will lead to more diagnoses of asymptomatic acute HCV infections in IDUs. Recent studies have shown that acute HCV infection could be treated very successfully with a rate of sustained virological response of >90% [43, 44]. Gerlach et al.
[44] showed that spontaneous clearance was observed in 52% of patients with acute symptomatic HCV infection, whereas all asymptotically infected patients went on to develop chronic HCV infection, indicating a reduced immune response in those patients. When treatment for HCV infection was started 3 months after the onset of acute HCV infection, it led to a sustained virological response in ∼80% of patients. When only those patients who remained HCV RNA–positive for >3 months after the onset of acute HCV infection were treated, induction therapy with IFN-α led to overall virus clearance (self-limited and treatment induced) in ∼91% of the patients. Among the patients with acute HCV infection, 25% (15/60) were active IDUs; 27% (7/26) of all treated patients were IDUs, and all reached a sustained virological response. A recent study showed that, in young men, acute infection with HCV genotype 3 leads more often to spontaneous clearance than does infection with HCV genotype 1 [45].

WHAT DO WE KNOW ABOUT REINFECTION?

The incidence of HCV infection among IDUs not previously infected with HCV has been reported to be as high as 10–40 cases/100 person-years [46–48]. In contrast to HAV or HBV, a lack of protective immunity against HCV is suggested [49–52]. A Scandinavian study reported 5-year follow-up evaluations of 27 IDUs who had cleared HCV RNA after receiving IFN therapy. Nine patients (33%) relapsed to drug use, but only 1 became reinfected, despite a total of 45 person-years of observation [53].

RECOMMENDATIONS AND CONCLUSIONS

The above-mentioned studies showed that, under specific conditions, treatment of HCV infection is both safe and efficient. These results and the conclusions of the workshop "Infectious Diseases in Injection Drug Users, Hepatitis C—An Interdisciplinary Challenge," which was held in October 2003 at the University of Hamburg (Hamburg, Germany) [54–60], led to the following recommendations:

• the first time that IDUs (active IDUs, methadone-treated patients, and former drug users) contact the addiction health care system, they should be screened for HAV, HBV,
• physicians should inform IDUs about what they can do to minimize the risk of becoming infected and to avoid transmitting infectious agents to others;
• if results of testing for antibody to HAV and/or HBV are negative, IDUs should be vaccinated;
• if results of testing for antibody to HCV are negative, IDUs should be screened yearly;
• if acute HCV infection is suspected, the presence of HCV RNA should be tested for by PCR;
• if IDUs are positive for antibody to HCV, the presence HCV RNA should be tested for by PCR;
• if HCV RNA is detected, the patient and physician need to decide whether treatment for HCV infection could be successful (if that is the case, virus load and genotype should be determined);
• partners of IDUs should also be screened, vaccinated, and informed; and
• interventions should be proposed, including contact tracing of IDUs.

Special recommendations for the treatment of HCV infections in IDUs include the following:
• the best time for treating HCV infection is during substitution treatment for drug dependency;
• in interdisciplinary units (e.g., specialists in hepatology, addiction medicine), therapy for HCV infection should be allowed to begin during detoxification treatment;
• active IDUs could be treated in a case-by-case decision, if active drug use is not recognizable;
• hepatologists and specialists in addiction medicine should collaborate, or physicians should be specialized in both addiction medicine and hepatology and should also collaborate with the addiction care network;
• conditions for therapy for HCV infection should include teaching about adverse effects and how to avoid infections, reinfections, and transmission to others and that alcohol consumption is harmful for treatment for HCV infection;
• it appears that a psychotherapeutic approach is necessary (strong physician-patient relationships);
• as seen before, a few studies have shown that patients undergoing methadone substitution treatment can be treated as successfully as nonaddicts and that patients beginning therapy for HCV infection during detoxification treatment can be treated as successfully as nonaddicts;
• screening is useful to discover acute HCV infection;
• rates of reinfection are not as high as supposed;
• we have to screen, inform, vaccinate, and treat IDUs;
• treatment for HCV infection during detoxification treatment and substitution treatment seems to be the best approach; and
• further studies with higher numbers of cases are needed.

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References