Epidemiology and Natural History of Hepatitis C Virus Infection in Injection Drug Users: Implications for Treatment

Mark S. Sulkowski and David L. Thomas

Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland

Effective methods to diminish the burden of hepatitis C virus (HCV) infection among injection drug users (IDUs) require consideration of the epidemiology and natural history of both hepatitis C and drug use. Most HCV infections are due to injection drug use, and most IDUs have HCV infection. In addition, HCV infection often occurs with other medical problems, such as human immunodeficiency virus infection and depression, which may complicate its recognition and management. Infection with HCV can be fatal, but usually not until years later, and persons may be unaware of the infection, allowing an individual to infect many others. Effective treatment is available for HCV infection; however, the therapy is prolonged, involving both weekly injections and daily oral medication, and is typically associated with significant adverse effects, such as fatigue, depression, and, rarely, life-threatening complications. Although clearly some IDUs want their HCV infection to be treated, many are unwilling or unable to initiate or sustain treatment with currently available therapies, and IDUs who are treated require considerable, multidimensional support. Solutions to the problem of HCV infection among IDUs must account for these facts.

IMPLICATIONS OF THE EPIDEMIOLOGY OF HEPATITIS C INFECTION

Injection drug use is the most important route of HCV transmission. Data from the Centers for Disease Control and Prevention indicate that at least two-thirds of new HCV infections in the United States are associated with illicit drug use [1]. As transmission via transfusion has virtually been eliminated, the proportion of cases due to injection drug use has increased. Furthermore, in almost every setting worldwide, the prevalence of HCV infection among IDUs is >50%, and, in some settings, it approaches 95% [2–7]. One explanation for this observation is that infection with HCV typically occurs within months of initiating the use of injected drugs. In one cohort, 80% of subjects acknowledging ⩾2 years of injection drug use were infected with HCV, a prevalence that was substantially higher than that of HIV or hepatitis B virus (HBV) infection (figure 1) [2, 8].

However, among many IDUs, HCV infection is only one of several important medical problems. Because HCV is ~10 times more infectious than HIV through percutaneous blood exposures, IDUs who acquire HIV infection usually already have HCV infection. As a result, the prevalence of HCV infection among persons who acquired HIV from injection drug use approaches 90% (figure 2) [9]. Although HIV infection is not a contraindication to treatment for HCV, IDUs coinfected with HIV may be less tolerant of and less responsive to current treatments for HCV infection. Furthermore, many HCV-infected IDUs also have major depression or other psychiatric disorders. In one study, almost half of HCV-infected young, new initiates into injection drug use had moderate-to-severe depression [10]. Although depression probably antedates drug use, the conditions are synergistic, leading to decreased adherence to medical care and increased conduct of high-risk behaviors. The current treatment for HCV infection, IFN-α, can cause depression, especially in persons

Reprints or correspondence: Dr. David L. Thomas, Johns Hopkins School of Medicine, Div. of Infectious Diseases, 1503 E. Jefferson St., Ste. 104, Baltimore, MD 21231.

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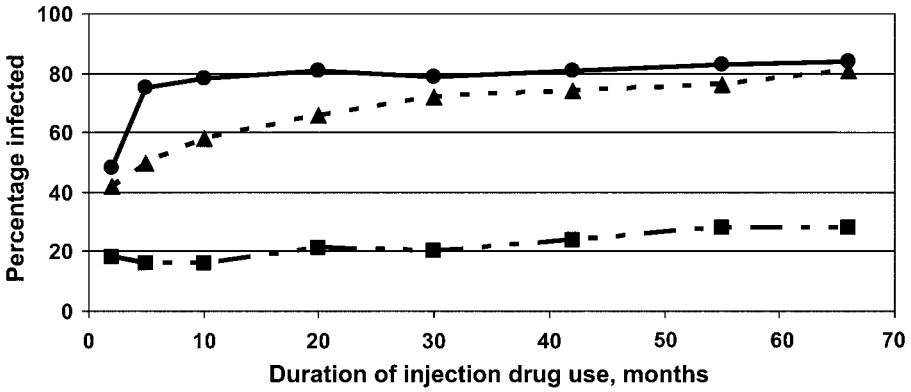

Figure 1. Prevalence of hepatitis C virus (●), hepatitis B virus (▲), and HIV (■) infection among injection drug users in Baltimore, according to duration of injection drug use. Adapted from Garfein et al. [8] and reprinted with permission from the American Public Health Association.

who have experienced it before, and suicides have been reported in association with the use of IFN-α. Because untreated or severe depression is a contraindication to the use of IFN-α, the overlay of epidemiology of HCV infection and psychiatric disease represents a formidable challenge to the medical treatment of HCV in IDUs.

Other factors can also complicate medical treatment of HCV infection in IDUs. The first step toward the medical management of HCV infection in IDUs is detection of active HCV infection. Although the HCV screening test (the EIA for HCV antibodies) is highly sensitive and specific and is relatively inexpensive, many HCV infections are not diagnosed, especially among IDUs. In addition, although it is difficult to obtain reliable estimates, a substantial fraction of persons with recognized active HCV infection are not receiving care for it. Although some public assistance programs cover HCV therapy, a barrier to treatment for HCV infection is cost; the medications alone typically cost $30,000–$40,000 over an 11-month course. When these costs are combined with those for medical visits and laboratory testing, the expense of treatment of HCV infection represents a serious obstacle to providing treatment for IDUs, especially those who are underinsured.

Finally, IFN-α is given by sc injection, raising concerns that the use of needles and the development of depressive side effects might predispose persons who have stopped injection drug use to relapse. Although anecdotes demonstrate that this can occur, it is not known how extensive this problem will be and whether persons likely to experience it can be identified. Furthermore, if persons recover spontaneously from acute HCV infection, they can be reinfected by continued high-risk injection practices [11]. This observation has raised the question of whether persons who are cured by treatment with IFN-α and ribavirin can be reinfected by continued or relapsed drug use, thus negating any benefits achieved after nearly 1 year of potentially toxic treatment. This potential concern has made some authorities recommend against treatment of HCV infection in persons with ongoing injection drug use and, given the high rate of early relapse, withholding of treatment for HCV until drug use has been discontinued for >6 months [12]. This policy has been questioned by many, and in our experience, concern of reinfection following curative therapy is rarely an important consideration in the discussion of potential risks and benefits of treatment for HCV for an individual patient.

IMPLICATIONS OF THE NATURAL HISTORY OF HCV INFECTION

HCV infection can spontaneously resolve, but it usually becomes persistent, as indicated by ongoing presence of HCV RNA in blood [13–16]. Although persistent HCV infection typically leads to hepatic inflammation and necrosis, the major medical consequences of persistent HCV infection are related to the expansion of hepatic fibrosis, which may progress to life-threatening cirrhosis and may greatly increase the risk of de-

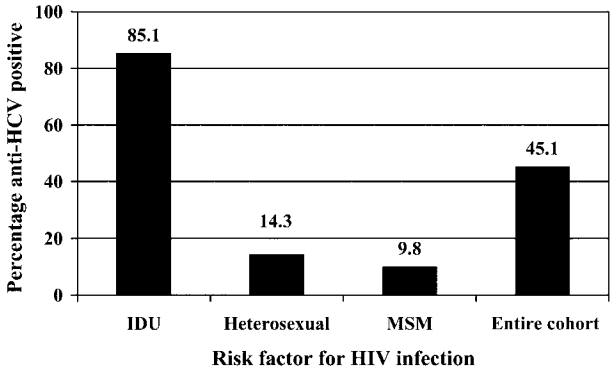

Figure 2. Prevalence of antibodies to hepatitis C virus (anti-HCV) in HIV-infected persons receiving medical care in the Johns Hopkins HIV clinic (Baltimore, MD) (n = 1955), according to self-reported HIV exposure risk category. IDU, injection drug use; MSM, men who have sex with men. Reprinted from Sulkowski and Thomas [9] with permission from the American College of Physicians.

veloping hepatocellular carcinoma. These potentially fatal complications generally occur >20 years after the onset of infection, though more rapid progression has been reported [17, 18]. Although the likelihood that cirrhosis will occur during the first 2 decades of persistent infection varies considerably in different studies (5%–25%) [18–23], a consistent trend is the low rate of disease progression reported among persons infected at young ages (<40 years old), including IDUs [14, 23–25]. In 1 cohort of 1667 HCV-infected IDUs who were infected with HCV for an estimated average of 14 years, the incidence of liver-related mortality was 3 cases/1000 person-years [14]. In addition, liver biopsies were performed for a random sample of 210 members of this cohort, and only 10% had evidence of serious liver disease, defined as evidence of bridging fibrosis or cirrhosis [26]. Studies of posttransfusion hepatitis, which often occurred in persons of older age, have reported higher rates of cirrhosis [17, 18]. Once cirrhosis develops, the rates of progression to liver failure (decompensation) and hepatocellular carcinoma are ~2%–4%/year and 1%–7%/year, respectively [27–29].

Because chronic HCV infection generally does not cause symptoms or easily recognized signs, it is difficult, in the absence of histological assessment, to assess the incremental progression of liver disease before clinical manifestation of decompensated cirrhosis. Staging of hepatic fibrosis by liver biopsy may provide important prognostic information for persons with chronic HCV infection. On the basis of fibrosis stage in a single biopsy and an estimation of duration of HCV infection for 2235 persons, Poynard et al. [30] estimated the median rate of progression of fibrosis per year to be 0.133 "fibrosis units," on a semiquantitative scale of 0–4 units, in which 4 fibrosis units represents cirrhosis. However, because the factors associated with progression of fibrosis, such as alcohol use, vary over time, it is unclear whether such estimates, which are based on the assumption of linear progression of fibrosis, can be used to predict future disease risk in a particular infected person. Moreover, there is considerable variability in severity of the disease among individual patients, and, although some factors associated with progression to cirrhosis have been identified, much of the interindividual variability remains unexplained.

The leading environmental determinant of cirrhosis is ingestion of alcohol [31–35]. Although excessive ingestion of alcohol and HCV infection independently may cause cirrhosis, combined exposure has a synergistic effect [14, 32, 34, 36]. This is especially true with very heavy ingestion of alcohol (>50–125 g/day), which, in one study, increased the risk of cirrhosis by ~100-fold [32]. Similarly, HIV coinfection increases the level of HCV viremia and is associated with more rapid progression of liver disease in most studies [37–42]. Overall, in a meta-analysis, Graham et al. [43] estimated that HIV coinfection increases the risk of cirrhosis by 2-fold. However, cirrhosis may develop in the absence of such recognized risk factors, and determination of the liver fibrosis stage by use of liver biopsy provides the most reliable means of assessing an individual person's disease risk. On the other hand, liver biopsy is an invasive procedure that may be difficult to undertake in many settings in which IDUs are encountered, and it can misrepresent the amount of disease because of variability in sampling and interpretation [44–46].

SOLUTIONS TO THE PROBLEM OF HCV INFECTION

Effective paradigms to treat HCV infection among IDUs will require a multidimensional and multidisciplinary approach. Drug use itself is a heterogeneous condition that affects persons of all socioeconomic strata and varies in many respects, including whether use is ongoing or is an event of the distant past; whether illicit drug use is occasional or is an uncontrollable daily need; whether heroin, cocaine, or other substances are used; and whether use is by injection or by other modes. In addition, persons frequently transition between these drug use stages. Thus, although treatment paradigms can be discussed, we first emphasize that it is impossible to make categorical recommendations for all settings.

Three critical elements are needed to improve treatment for HCV among IDUs: detecting infection, detecting disease, and delivering care (figure 3). Given the adverse events associated with the current treatments for HCV infection, the slow natural history of HCV infection, and the limited available resources,

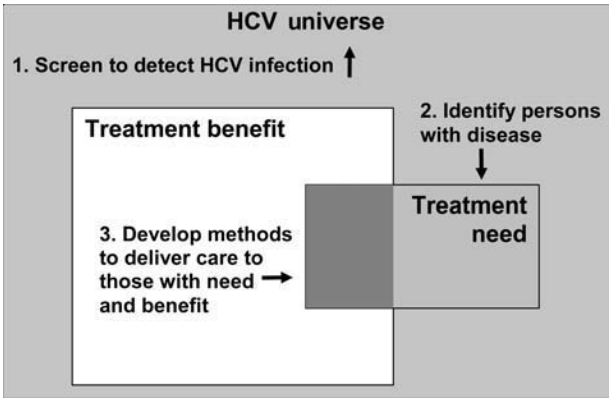

Figure 3. Treatment paradigm for hepatitis C virus (HCV) infection. Step 1 involves universal screening for antibodies to HCV of all persons actively engaged in or with a history of injection drug use. Step 2 involves identification of HCV-infected injection drug users (IDUs) who need treatment (i.e., those with significant liver disease). Step 3 involves delivery of treatment for HCV infection to IDUs with significant liver disease and no contraindications to HCV therapy, ideally focusing this treatment on those who are most likely to benefit from or respond to treatment. Current technology allows for effective HCV screening; work is needed to improve methods to implement this screening and to develop strategies to accomplish steps 2 and 3.

the optimal approach does not treat all HCV-infected persons. Similar to the treatment paradigm adopted for the management of HIV infection, treatment for HCV infection should be focused on those for whom the expected benefits outweigh the risks [47]. This paradigm is an extension of the approach for treatment of HCV infection recommended by the National Institutes of Health Consensus Panel, American Association for the Study of Liver Disease, and Infectious Diseases Association of America [12, 48].

Screening to detect infection. Although hard data are elusive, conventional wisdom (and our experience) suggests that many who acquired HCV infection through injection drug use do not know that they are infected. Thus, the first stage of any program to treat HCV infection must be detection of infection through screening. Indeed, guidelines published by the Centers for Disease Control and Prevention, American Association for the Study of Liver Disease, Infectious Diseases Association of America, and US Public Health Service call for screening of all persons who have ever injected illicit drugs [1, 47].

Fortunately, the HCV EIA is an ideal screening test because it is easy to use and inexpensive and has high sensitivity and specificity [49, 50]. The positive predictive value for ongoing or prior HCV infection among IDUs is >80%. Although the screening test to detect HCV infection is widely available, greater identification of infected persons requires more healthcare providers to question patients about prior injection drug use, as well as increased funding to provide HCV screening in alternative settings, such as prisons, emergency departments, sexually transmitted diseases clinics, and methadone treatment clinics.

Screening to detect disease. Among HCV antibody–reactive persons, confirmation of active HCV infection and the potential need for treatment requires additional testing for HCV RNA (e.g., RT-PCR), which is considerably more expensive and less accessible than HCV antibody testing. Once active HCV infection is identified, it is important to ascertain whether treatment is urgent or can be safely postponed. HCV load is not helpful in this regard, because the magnitude of viremia does not correlate with clinical or histological outcomes. According to existing guidelines, the liver biopsy is currently the only way to make this decision [12, 47]. The liver biopsy provides important information about 4 distinct HCV-related processes: periportal necrosis (piecemeal necrosis), parenchymal injury, portal inflammation, and fibrosis [51–53]. Standardized grading systems have been proposed [51, 54, 55]. The extent or stage of fibrosis is likely to be the most important finding about patients with chronic HCV infection.

However, histological staging has several important limitations. Although biopsy is the best available method for determining the type and extent of liver injury, there may be differences in histological appearance in samples from different sections of the liver; interobserver variance also has been described [56–58]. Complications such as serious bleeding and, rarely, death may also occur [56, 57]. The histological "snapshot" of the current state of inflammation and fibrosis also does not always predict the future course of disease. In addition, liver biopsy is an expensive medical procedure that is rarely undergone by IDUs who are not receiving targeted care for HCV infection. Thus, there is a need for an alternative method of identifying liver disease among HCV-infected IDUs.

There is substantial interest in developing blood markers of hepatic fibrosis [59–61]. A large number of serum fibrosis markers have been considered, ranging from liver-related enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyl transferase (GGT); direct and indirect measurements of molecules made or processed by the liver, such as the prothrombin time, platelet count, and levels of serum albumin, bilirubin, γ-globulin, and apolipoprotein A-I; and markers of inflammation, fibrinolysis, fibrogenesis, or stellate cell activation (e.g., hyaluronic acid and procollagen III N-peptide).

Determination of liver enzyme levels is inexpensive, readily available, and the most studied method [26, 62, 63]. In one community-based study of IDUs, among whom the prevalence of serious liver disease was low, normal levels of liver enzymes had a high negative predictive value for disease (97%) [26]. Longitudinal trends in ALT and AST levels may improve their correlation with histological disease [26, 64, 65]. In addition, a change in the ratio of AST to ALT has been reported to be a reliable indicator of the development of cirrhosis [66, 67]. Among other routine laboratory test results, decreased platelet count, reversal of the ratio of AST to ALT, and prolonged prothrombin time are the earliest indicators of cirrhosis [68, 69]. However, in most instances, these tests are not sufficiently sensitive or specific to play a major role in clinical decision making. The European MULTIVIRC group found that use of a combination of 6 markers (i.e., α_2-macroglobulin, haptoglobin, ALT, apolipoprotein A-I, GGT, and total bilirubin) achieved relatively high negative and positive predictive values [70]. However, although this assay is commercially available in the United States and other countries, the high negative and positive predictive values required scores that pertained to only 12% and 34% of subjects, respectively, and the data need to be confirmed.

Given the limitations of current therapy for HCV infection, accurate, inexpensive, and noninvasive tools are needed to identify IDUs for whom the potential risks of treatment outweigh the potential benefits and, thus, for whom therapy may be safely deferred. Such tools must also accurately identify IDUs with significant liver fibrosis for whom treatment for HCV infection is indicated. Accurate staging of liver disease in HCV-infected IDUs will allow the provision of medical care to those with the

greatest need while avoiding iatrogenic toxicity in those with low risk of significant liver disease.

PROGRAMS TO DELIVER MEDICAL CARE

After detection and staging, multidisciplinary and multidimensional programs must be in place to deliver care to IDUs who need treatment (i.e., those with significant liver fibrosis) and are eligible for treatment (i.e., the absence of contraindication to treatment). On the other hand, HCV-infected IDUs for whom the potential risks of treatment outweigh the potential benefits also have important medical needs, which will vary depending on the individual person's risk-benefit assessment. For IDUs with minimal liver disease (and, therefore, less potential benefit from treatment for HCV), efforts and resources must focus on prevention of progression of liver disease, including programs to promote abstinence from alcohol, vaccination of susceptible persons to prevent hepatitis A virus and HBV infection, and other harm reduction measures to improve health outcomes.

Conversely, the needs of IDUs for whom the prospect of treatment for HCV poses both potential benefits (i.e., those with significant fibrosis) and risk (i.e., those with medical or psychiatric disease) are expected to be more extensive. The care of such persons should focus on the correction of modifiable barriers to treatment for HCV infection. For example, persons with untreated major depression or other psychiatric disease should have temporally and geographically contiguous access to mental health care. Similarly, the evaluation and management of comorbid medical conditions will necessitate access to medical doctors, diagnostic testing, and treatment of significant conditions.

Furthermore, although active drug and/or alcohol use is no longer considered to be an absolute contraindication to treatment for HCV infection, and has never been a contraindication to treatment for HIV infection, there is convincing evidence that active substance abuse severely limits the delivery and effectiveness of medical care; among HIV-infected patients, switching from nonuse to substance abuse was strongly associated with worsening of HIV treatment response and disease, compared with remaining free of substance abuse [71]. More important, switching from substance abuse to nonuse was strongly associated with improvements in the delivery and effectiveness of antiretroviral therapy. Although such elegant data are not available for hepatitis C, interventions that lead to reduction or cessation of substance abuse will improve the delivery and effectiveness of treatment for HCV infection. Finally, in addition to internists, psychiatrists, and addiction specialists, health-care providers with expertise in the management of hepatitis C are needed to ensure the safe delivery of IFN-α and ribavirin. Unfortunately, in the United States, the demand for such experts exceeds their supply, and programs are needed to train additional providers to meet the needs of HCV-infected IDUs.

Because the development of such programs will undoubtedly require a considerable amount of time and money and because the current discussion is based on the delivery of IFN-based therapy, the potential effect of new therapies for HCV infection must be addressed. Undoubtedly, treatment for HCV infection will evolve over the next 3–7 years with the clinical development of small molecule inhibitors of the HCV polymerase and protease, as well as other therapeutic targets [72]. However, novel agents may be used to complement, rather than replace, existing therapies, and IFN-α may be part of management of hepatitis C for the foreseeable future. Furthermore, as efficacy of treatments for HCV infection increases, the impetus to deliver them to HCV-infected IDUs will increase as well. At the same time, the consequences of inappropriate delivery of treatment for HCV infection will intensify, because the improper administration of selective antiviral agents may lead to viral mutations, conferring drug resistance. Thus, any programs developed and implemented to deliver current care for HCV infection are expected to be increasingly important as treatments for HCV infection evolve.

CONCLUSION

Because of relatively efficient transmission, the prevalence of chronic hepatitis C among IDUs in the United States is substantial, and most new cases of hepatitis C occur among IDUs. However, the provision of care for hepatitis C is complicated by the high prevalence of other medical problems, such as depression or coinfection with HIV, which affect the safety and effectiveness of current treatment for HCV infection. Nonetheless, this potentially toxic treatment may also cure hepatitis C in some infected IDUs. Accordingly, the management of hepatitis C requires careful assessment of the potential risks and benefits of treatment for each individual IDU. Because chronic HCV infection generally does not cause symptoms and because some, but not all, HCV-infected IDUs will develop life-threatening liver disease, the identification of IDUs who are at risk for the development of cirrhosis is essential. Although liver biopsy is the best available method to determine the risk of significant liver disease and the need for treatment, noninvasive, inexpensive, and easily accessible blood markers of fibrosis are urgently needed.

In the context of the adverse effects of treatment for HCV infection and limited available resources, the epidemiology and slow natural history of HCV infection dictate that the optimal approach to treatment for HCV infection does not treat all HCV-infected IDUs. Developing effective paradigms for the provision of treatment for HCV infection to IDUs requires a multidimensional and multidisciplinary approach to detect in-

fection, determine liver disease, and deliver treatment for HCV infection.

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