The Natural History of Hepatitis C Virus Infection
Host, Viral, and Environmental Factors

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HERE ARE AN ESTIMATED 170 MILLION persons worldwide and 3.9 million in the United States who have been infected with hepatitis C virus (HCV). Hepatitis C virus infection may be self-limited (viral clearance) or persist. Viral clearance occurs in approximately 15% of persons and is assumed to have occurred when HCV RNA cannot be detected in multiple blood samples from someone with HCV-specific antibodies (anti-HCV) or in whom acute infection was observed. In a recent analysis of 43 new HCV infections, we discovered that viral clearance was less common in blacks than whites. However, these findings have not been confirmed, and there is little additional information regarding other determinates of viral clearance.

Context Hepatitis C virus (HCV) infection may resolve (viral clearance), persist without complications, or cause end-stage liver disease (ESLD). The frequency and determinants of these outcomes are poorly understood.

Objective To assess the incidence and determinants of viral clearance and ESLD among persons who acquired HCV infection from injection drug use.

Design and Setting Community-based prospective cohort study with enrollment in 1988-1989 and a median follow-up of 8.8 years.

Subjects A total of 1667 persons aged 17 years or older with a history of injection drug use and an HCV antibody–positive test result during follow-up.

Main Outcome Measures Viral clearance was assessed in a subset of 919 patients and defined as failure to detect HCV RNA in at least 2 consecutive samples collected 5 or more months apart. End-stage liver disease was assessed at semiannual visits and by review of medical records and death certificates and defined by the presence of ascites, esophageal varices, or hepatic encephalopathy, or when ESLD was stated as a cause of death.

Results Viral clearance was observed in 90 persons who were compared with 722 with persistent viremia, while the viremia of 107 was not resolved. Viral clearance occurred more often in nonblacks (adjusted odds ratio [OR], 5.15; 95% confidence interval [CI], 2.60-10.17) and those not infected with human immunodeficiency virus (HIV) (adjusted OR, 2.19; 95% CI, 1.26-3.47). Forty cases of ESLD were observed throughout follow-up (incidence, 3.1 per 1000 person-years). In a multivariate model, risk of ESLD was higher for persons aged 38 years or older at enrollment (adjusted relative incidence, 3.67; 95% CI, 1.96-6.88) and who reported ingestion of more than 260 g of alcohol per week (adjusted relative incidence, 3.60; 95% CI, 1.73-7.52). Of 210 patients without ESLD randomly selected for biopsy, only 2 had cirrhosis.

Conclusions Our results indicate that although HCV infection can be self-limited or associated with ESLD, the majority of adults have persistent viremia without clinically demonstrable liver disease. Further research is needed to explain the less frequent clearance of HCV infection among black persons and to improve utilization of treatment for those infected in the context of injection drug use.

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After 10 to 30 years, persons with persistent HCV infection may experience a wide spectrum of symptoms ranging from none to end-stage liver disease (ESLD), expressed as ascites, esophageal varices, or encephalopathy.8-17 The marked differences in the outcome of persistent infection and potential adverse effects of treatment underscore the importance of predicting the risk of ESLD for individual persons. Unfortunately, estimated rates of ESLD vary substantially, and there is little consensus on disease cofactors and laboratory markers of progression. For example, although regular, heavy alcohol use is perhaps the most consistent correlate of cirrhosis, there are few data regarding the safety of moderate intake.16,18-20 In addition, with other chronic viral illnesses such as human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections, the quantity of virus in blood correlates well with disease outcome.21-23 However, an association between viral load and disease has been inconsistently found in cross-sectional studies of HCV infection.5,24-27

Higher rates of cirrhosis typically are reported from referral centers and in persons infected at older ages from blood transfusions.8 However, in developed nations, most HCV infections occur at young ages from injection drug use, and because of difficulties with follow-up, the natural history of infection is even more poorly understood in this setting. Since 1989, we have followed a cohort of 1667 persons who acquired HCV infection in the context of injection drug use. In this community-based study, we assess the frequency of viral clearance and ESLD and evaluate putative cofactors of both outcomes.

**METHODS**

**Study Participants**

Between 1988 and 1989, 2946 persons who acknowledged injection drug use within 10 years were screened for participation in a study of the natural history of HIV and other infections that affect drug users, as previously described.28 All participants were older than 17 years, free of the acquired immunodeficiency syndrome (AIDS), and consented to semiannual follow-up that included administration of a questionnaire, blood collection, release of medical information, and testing for infectious diseases.

**Measurements**

A standardized questionnaire, which was administered at enrollment and in a modified form at each visit, elicited information on demographics, medical care encounters, and use of injection drugs, tobacco, and alcohol. Alcohol use was asked as the average number of drinks per week (1 drink equaled 10 g equivalent of alcohol) and proportion of days when alcohol was ingested. Antibody testing for HIV and HCV was done on serum specimens collected at enrollment and at each semiannual visit until a positive result was obtained, as previously described.29 Liver enzyme testing began in 1995.

At each semiannual visit, participants were questioned about medical care received, and medical records were reviewed for any care related to hepatitis or liver disease. Data related to liver disease were abstracted onto standardized forms by a single study nurse. In addition, death certificates were obtained from the State of Maryland Department of Vital Records for all known deaths, and each year a National Death Index search was performed for members of the cohort who had been missing for at least a year.

**Laboratory Testing**

Anti-HCV was evaluated in stored serum specimens by first-, second-, and third-generation enzyme immunoassay (EIA) and recombinant immunoblot (RIBA) tests (Ortho Diagnostics, Raritan, NJ). Assessment of HCV RNA was done by 3 commercially available assays according to the manufacturers’ specifications and by an “in-house” assay. Initially, the second-generation branched DNA (bDNA) assay (Chiron Corporation, Emeryville, Calif) was used to screen for possible clearance in previously unthawed, stored serum specimens collected between January 1993 and March 1996.30 Serial serum specimens from subjects with at least 1 bDNA result below the linear range (200,000 mE/mL) were tested using the qualitative COBAS AMPLICOR assay (Roche Diagnostic Systems, Branchburg, NJ), which amplifies HCV RNA by polymerase chain reaction. The quantity of HCV RNA was assessed with respect to subsequent development of ESLD using the COBAS AMPLICOR MONITOR (Roche Diagnostic Systems). The HCV genotype was assessed by restriction fragment-length polymorphism analysis of an “in-house” polymerase chain reaction amplicon, as described elsewhere.31 Laboratory methods used for HIV, HBV, and liver enzyme testing are described elsewhere.26,32-33 Liver enzyme testing was done on serum specimens within 24 hours of collection. Hepatitis B surface antigen (HBsAg) testing was performed at enrollment and repeated on an aliquot of the same serum specimens assessed for HCV clearance (that is, after January 1995) on all who were either initially HBsAg positive or negative for other markers. Hematoxylin-eosin and trichrome stains of liver biopsy specimens were evaluated and ranked at a single session in each of 4 categories as proposed by Knodell et al.34

**Outcome Definitions**

**HCV Infection.** Participants were considered HCV infected if anti-HCV was detected in a serum sample by any generation EIA test. In this cohort, 99.5% (955/960) of serum specimens found to be positive by first-generation EIA were also positive by a second test (a later generation EIA, RIBA, or RNA test).

**HCV Clearance.** Hepatitis C virus clearance was defined as the presence of anti-HCV (by both EIA and RIBA) without HCV RNA in serum specimens from at least 2 consecutive study visits (>5 months apart).35 HCV RNA was undetectable by the qualitative COBAS AMPLICOR assay in serum specimens from at least 1 of the 2 visits.
End-Stage Liver Disease. End-stage liver disease was defined clinically by documentation of esophageal varices, ascites, or hepatic encephalopathy on medical records, a death certificate, or both. Persons were also considered to have ESLD if “liver failure” or “ESLD” was written on the certificate as the principal or contributing cause of death. However, subjects were not classified as having ESLD if liver failure was attributed to sepsis (n=8).

Other clinical information regarding liver function was also evaluated including evidence of thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, and hyponprothrombinemia. However, these laboratory findings were not used to define ESLD because they were not uniformly ascertained (eg, HIV-positive persons had more laboratory testing) and were not accurate indicators of ESLD in this cohort. End-stage liver disease was considered to have occurred when first documented.

To assess if substantial histologic liver disease was missed by this clinical ascertainment of ESLD, 209 liver biopsies were performed (1996-1998) for study participants selected from 3 groups defined according to 2 consecutive alanine aminotransferase levels (both normal, both >1.5 times the upper limit of the laboratory, vs the remainder). Subjects who were infected with HIV and had CD4 lymphocyte counts less than 200 X 10^9/L were excluded from the biopsy protocol. Others gave informed consent using a protocol approved by Community Advisory Board and the Johns Hopkins School of Medicine Institutional Review Board and were referred to their own or a study physician for further evaluation.

Duration of HCV Infection. In prior analyses, more than 80% of participants acquired HCV infection within 2 years of the initiation of injection drug use. Thus, time from first injection drug use was used as a surrogate of duration of HCV infection.

Statistical Analyses
For these analyses, age and time from first injection drug use initially were examined after categorization into quartiles, then for multivariate analyses, as dichotomous variables classified where differences were observed. For alcohol intake and intravenous drug use, summary measurements were created using data up to the date of outcome ascertainment for viral clearance (January 1995) and date of censoring for ESLD (defined below). Viral clearance was examined as a dichotomous outcome using the χ² test and Fisher exact test as indicated. The independence of factors associated with viral clearance was assessed by multivariate logistic regression that included all factors for which P<.10 on univariate analysis.

For analysis of ESLD, anti-HCV-positive subjects with ESLD were compared with all anti-HCV-positive subjects without recognized ESLD. The following censoring rules were used: (1) persons who developed ESLD were considered free of ESLD from enrollment until first recognition; (2) others were considered free of ESLD from enrollment until the final study visit prior to the censoring date (December 31, 1997) or death from another cause, whichever came first; (3) HCV seroconverters did not contribute observation time until after anti-HCV was detected; and (4) for 264 HCV seroconverters, observation time was calculated separately before and after HIV infection. The relative incidence of ESLD was assessed by Poisson regression analysis, and the independence of these associations further examined by multivariate Poisson regression.

A nested case-control analysis was conducted to assess the association of HCV RNA level, HCV genotype, and ESLD. Each anti-HCV-positive subject with ESLD was matched to 2 controls without recognized disease based on HIV status, race, sex, and age (within 5 years), which were previously associated with HCV RNA level.

RESULTS
Of the 2946 persons who were initially screened for enrollment, 2226 returned for at least 1 semiannual visit and were candidates for the HCV natural history study. From these, 440 were excluded because their anti-HCV status was not known, 1 was excluded because he was lost to follow-up after becoming anti-HCV positive, 106 were excluded because they remained HCV seronegative, and 12 were excluded because the cause of death was not established, leaving 1667 anti-HCV–positive participants for this investigation. Among the 1667 participants at enrollment, the median age was 34 years, 94% were black, 78% were male, and 33% were HIV positive (TABLE 1). Compared with 1279 individuals who were originally screened but not analyzed, these 1667 HCV-positive members were more likely to be older, black, female, HIV positive, to have used injection drugs in the 6 months before enrollment, and to have a longer time since initiation of injection drug use (data not shown).

Viral Clearance
Viral clearance was assessed in a subset of 919 participants who had study visits between January 1995 and March 1996, when routine screening was done. After testing for each patient a median of 5 serum samples collected over 85 months (interquartile range, 5-6 samples over 61-92 months), viral clearance was demonstrated in 90 participants. Viral persistence was confirmed in 722 participants, and 107 had unresolved status (eg, intermittent viremia or possible reinfection). Compared with the 722 with viral persis-
tence, the 90 patients with viral clearance were more likely to be nonblack (odds ratio [OR], 4.66; 95% confidence interval [CI], 2.44-8.90), female (OR, 1.58; 95% CI, 0.98-2.54), and have HBsAg-positive serum specimens (OR, 2.48; 95% CI, 0.97-6.33). Persons with viral clearance were less likely to be HIV positive, especially with low CD4 lymphocyte counts (≥500×10⁹/L: OR, 0.60, 95% CI, 0.26-1.36; 200-499×10⁹/L: OR, 0.64, 95% CI, 0.36-1.14; and <200×10⁹/L: OR, 0.31, 95% CI, 0.13-0.73). No statistical association was detected between viral clearance and age, weekly alcohol use, and the frequency of injection drug use (data not shown). In a multiple logistic regression model, the associations of viral clearance with nonblack race (adjusted OR, 5.15; 95% CI, 2.60-10.17) and HIV-negative status (adjusted OR, 2.19; 95% CI, 1.26-3.47) remained (Table 2). In this model, viral clearance was marginally associated with age younger than 45 years and ongoing HBV infection.

END-STAGE LIVER DISEASE

The 1667 anti-HCV–positive participants were followed up for a total of 12,737 person-years, with a median 8.8 years per subject (interquartile range, 6.1-9.4 years). At enrollment, the median time from first injection drug use was 13.7 years (interquartile range, 6.9-19.3 years). Using time from first injection drug use as a proxy, the estimated median duration of HCV infection at the end of follow-up was greater than 15 years for 75% of subjects. During follow-up, only 1 person reported any treatment for HCV infection.

End-stage liver disease was detected in 40 persons (ESLD rate, 3.1 per 1000 person-years), and by the end of follow-up, 1 of these subjects had received a liver transplant while 35 others had died. Among 21 participants, the specific clinical manifestation of ESLD was available on death certificate and/or medical records: esophageal varices were present in 10 persons, ascites in 15, and encephalopathy in 8 (some had more than 1 condition).

The 35 patients who died with ESLD comprised less than 10% of the 409 deaths among study subjects, 40% of which were due to complications of HIV infection, 19% due to drug overdose, 12% due to bacterial infections (sepsis, pneumonia, or endocarditis), and the remaining due to miscellaneous causes (eg, homicide, suicide, accidental trauma, cardiac, stroke).

Liver Histology and Laboratory Markers

Liver biopsies were performed on a subset of 210 participants who did not have evidence of ESLD as determined by a hepatopathologist. The median total histologic activity index was 4 (range, 1-13). Cirrhosis was found in only 2 subjects and the median fibrosis score was 0 (range, 0-4). Autopsy reports were reviewed for 71 consecutive subjects dying of drug overdose. Five subjects without previously recognized ESLD (7%) had microscopic and/or macroscopic evidence of cirrhosis at autopsy.

Of 1627 subjects without ESLD, 299 had a serum albumin level less than 32 g/L, a serum total bilirubin level above 51.3 µmol/L, or a platelet count less than 120×10⁹/L on at least 1 occasion. Of 39 subjects with at least 1 such abnormal test result who later had a liver biopsy, none had cirrhosis and only 3 had septal fibrosis (Knodell fibrosis score of 3).

Table 2. Correlates of Hepatitis C Virus Clearance After Adjustment by Multivariate Logistic Regression

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%) Clearance</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>729 (9.3)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Nonblack†</td>
<td>44 (36.4)</td>
<td>5.15 (2.60-10.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HIV status (CD4 cell count)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>420 (13.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Positive (≥500×10⁹/L)</td>
<td>72 (8.3)</td>
<td>0.58 (0.24-1.42)</td>
<td>.23</td>
</tr>
<tr>
<td>Positive (200-499×10⁹/L)</td>
<td>162 (8.6)</td>
<td>0.54 (0.29-1.02)</td>
<td>.06</td>
</tr>
<tr>
<td>Positive (0-199×10⁹/L)</td>
<td>119 (5.0)</td>
<td>0.33 (0.14-0.80)</td>
<td>.01</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥45</td>
<td>193 (7.8)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>&lt;45</td>
<td>580 (11.9)</td>
<td>1.81 (0.98-3.33)</td>
<td>.06</td>
</tr>
<tr>
<td>HBsAg status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>746 (10.5)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>27 (22.2)</td>
<td>2.75 (1.00-7.59)</td>
<td>.05</td>
</tr>
</tbody>
</table>

*Age was considered as the upper quartile vs others since that was the only stratum that appeared to differ on univariate analysis. This multivariate model was performed on those who had complete information on all variables, which included 773 of the 812 considered in univariate analysis. CI indicates confidence interval; HIV, human immunodeficiency virus; and HBsAg, hepatitis B surface antigen.† Includes 34 white, 3 white Hispanics, 5 Asians, and 6 of other racial background.

Host and Environmental Correlates of ESLD

Compared with those younger than 30 years, the relative incidence of ESLD was 4.46 times higher in persons older than 38 years at enrollment (P<.001). No differences were detected in the ESLD incidences among subjects in the lower 3 age quartiles, younger than 30, 30 to 33, and 34 to 37 years (relative incidences <2.0, P > .10). The relative incidence of ESLD increased according to the time from first injection drug use. Compared with those starting less than 7 years before, relative incidences were 0.57, 2.00, and 2.26 for those starting drug use 7 to 13, 14 to 18, and more than 18 years before, respectively; P = .02 for trend. The incidence of ESLD was higher in persons who reported more alcohol use. Compared with those who drank less than 90 g per week, relative incidences were 1.57 and 3.60 for those who drank 90 to 260 and more than 260 g per week, respectively; P = .002 for trend. The relative incidence also increased in those who reported more frequent injection drug use. Compared with those injecting less than 50% of visits, rela-

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tive incidences were 1.21 and 2.75 for those reporting injecting 50% to 99% of visits and those reporting injecting at all study visits, respectively; \( P = .02 \) for trend. The relative incidence of ESLD was lower in females (relative incidence, 0.28; \( P = .01 \)). No increased risk was detected for HIV-positive participants (relative incidence, 1.00; \( P > .20 \)), blacks (relative incidence, 0.43; \( P = .11 \)), and HBsAg-positive persons (relative incidence, 1.87; \( P = .16 \)).

In a multivariate Poisson regression model, the adjusted incidence of ESLD remained higher in those who were older and acknowledged heavy alcohol use (equivalent of more than 260 g per week averaged over follow-up) (TABLE 3). Time from first injection drug use was also independently associated with ESLD, but too highly correlated with age to be included in the same model. A statistically significant increased risk of ESLD was not detected for participants with moderate alcohol use, whether measured as the estimated total weekly ingestion (shown) or the proportion of visits alcohol was consumed (data not shown).

**Virologic Correlates of ESLD**

No difference was detected in the HCV RNA levels of 37 subjects with ESLD (median, \( 2.6 \times 10^5 \) copies/mL, collected a median of 4.8 years prior to ESLD) and 72 controls without ESLD (median, \( 4.1 \times 10^5 \) copies/mL, collected a median of 8.9 years prior to their last study visit). No differences were detected in the relative occurrence of HCV genotypes of persons with ESLD when compared with the cohort as a whole or a subset of 54 controls without ESLD who were matched for the viral load analysis: persons with ESLD, 66% genotype 1a, 33% genotype 1b; cohort without ESLD, 62% genotype 1a, 26% genotype 1b, 12% other; selected controls, 69% genotype 1a, 31% genotype 1b.

**COMMENT**

In this investigation, the 2 principal outcomes of HCV infection, viral clearance and ESLD, were longitudinally examined in a large, community-based cohort of persons infected in the context of injection drug use. Discovery of a lower probability of HCV clearance in blacks confirms the prior finding made in this cohort among a subset of 43 participants with incident HCV infections and the finding of Alter et al.\(^3,4\) Interestingly, less frequent HCV clearance in blacks has also been found after interferon alfa therapy.\(^3,7\) Although the basis for this racial difference is unknown, the magnitude of the association and its independence from other factors suggest host genetics may be important in the outcome of acute hepatitis C.

It is impossible to speculate about the correlation of HCV clearance with ongoing hepatitis B or the inverse association with HIV infection, since the relative sequence of the 3 infections is not known. However, in this cohort, HCV infection usually occurs before HIV infection.\(^29,36\) Thus, the immune suppression associated with HIV infection might not be expected in many individuals during the first 2 years of HCV infection, when clearance is believed to occur.\(^4,5\) Reciprocal relationships between HCV and HBV have also been found in other studies.\(^37-39\)

There are several factors that could have contributed to the low incidence of ESLD reported in this study. Since a restrictive, clinical definition of ESLD was used, persons with laboratory results that could have represented cirrhosis were not considered to have ESLD without other indication. This decision was supported by the absence of cirrhosis in liver biopsy specimens obtained for 39 individuals with this type of possible laboratory evidence of liver disease and the multiple other clinical explanations for such findings in this setting. Nonetheless, we cannot exclude the possibility that serious liver disease was present among some of the other 260 subjects with abnormal laboratory results but no liver biopsy.

Competing mortality may have reduced the observed ESLD incidence and prevented some cases from being detected by our liver biopsy protocol. Since 40% of fatalities in the cohort were AIDS-related and because an increased incidence of ESLD has been reported in HIV-HCV coinfected persons, HIV-related mortality is important to consider.\(^30,41\) However, although their medical records were carefully scrutinized for evidence of ESLD, the incidence of ESLD was not increased in HIV-infected participants in this cohort. With use of highly active antiretroviral therapy, the relative incidence of ESLD may increase among HIV-infected members of this cohort in future years, if liver failure occurs more often than expected by prolonged survival. Drug overdose accounted for 19% of deaths in this cohort, and autopsy data from subjects dying of drug overdose revealed a greater than expected prevalence of cirrhosis. However, even if 20% of subjects who had overdose deaths ultimately developed ESLD (twice what was observed), the estimated incidence would remain low.
The ESLD incidence could also be low if the duration of infection were too short for disease to manifest. However, if as some studies have suggested, 15% of persons will develop cirrhosis within 15 years of HCV infection, the overall duration of infection in the cohort should have been sufficient to detect liver disease. More than 75% of participants were observed for at least 14 years after the estimated onset of HCV infection, and for 456 persons (27%), the estimated duration of infection was 27 or more years.

It is also possible that persons with serious disease would not have enrolled in a community-based cohort study because of being too ill or having already died of ESLD, thus lowering the observed disease incidence. The extent of survival bias cannot be estimated. However, in another recent large community-based study that followed women in Ireland after exposure to HCV-contaminated anti-D immune globulin (no survival bias), there were no instances of ESLD after approximately 17 years. Low incidences of ESLD have also been reported recently in long-term follow-up of anti-HCV positive army recruits and children infected by blood transfusion. The young ages of persons in these studies could be especially important given the more than 4-fold increase in ESLD incidence observed among those in this study who were 38 years or older at enrollment.

Thus, the observed incidence of ESLD in this study may underestimate the overall extent of serious liver disease caused by HCV infection, and data should not be generalized to other settings, especially for persons infected at older ages. However, these data are consistent with the conclusion reached from other community-based studies that HCV infection persists in many persons for decades without causing clinically apparent liver disease. In this study, the incidence of ESLD was higher in subjects who consumed the equivalent of 3 or more drinks daily. However, despite following up more than 1000 anti-HCV–positive individuals, a statistically significant increased relative incidence was not observed for those with more moderate use. If confirmed by other studies, this finding might suggest the combined risk to the liver of HCV and alcohol chiefly relates to daily use of large amounts.

Use of interferon alfa or a combination of interferon alfa and ribavirin has been associated with a reduced risk of cirrhosis, hepatocellular cancer, and ESLD. Therefore, it was disappointing that from 1989 to December 1997, interferon alfa therapy was only acknowledged by 1 of 1667 anti-HCV–positive persons in this cohort. The reasons that interferon was not received were not investigated. However, since more than two thirds of HCV infections occurring in the United States are related to injection drug use, further research is needed among inner-city populations, particularly among current and former injection drug users to develop alternative treatments and improve the provision of medical care for HCV infection.

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**REFERENCES**

There are in fact four very significant stumbling-blocks in the way of grasping the truth, which hinder every man however learned, and scarcely allow anyone to win a clear title to wisdom, namely, the example of weak and unworthy authority, longstanding custom, the feeling of the ignorant crowd, and the hiding of our own ignorance while making a display of our apparent knowledge.

—Roger Bacon (c 1220-1292)