Volume I. Clinical Science

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EXECUTIVE SUMMARY

Hepatitis C is a serious global health problem. Worldwide, an estimated 170 million people have been infected with the hepatitis C virus (HCV). In the United States, an estimated 4 million people have been infected with HCV; 2.7 million of them have developed chronic hepatitis C. The U.S. estimate may be low, as many high-prevalence populations were excluded from HCV surveillance. Up to one quarter of HIV-positive individuals in the U.S. are coinfected with HCV.

Since viral inactivation procedures and effective donor screening have almost completely eliminated the risk of hepatitis C infection from blood transfusions and blood products, the majority of new HCV infections occur via injection drug use with shared, unsterilized equipment. HCV is prevalent among current and former injection drug users; up to 90% have been infected.

Many questions about HCV transmission remain unanswered. HCV can be transmitted through sex, from mother to infant, and via dialysis at centers with inadequate infection control procedures. Men who have sex with men, sex workers, people with multiple sex partners, and partners of HIV/HCV-coinfected persons have higher-than-average HCV prevalence rates, yet the routes and risks of sexual transmission are unclear. The risk of HCV transmission from mother to infant is about 5%; the risk increases if the mother is HIV/HCV coinfected. Interventions to reduce the risk of mother-to-infant transmission have yet to be identified. While it has been speculated that HCV may be transmitted from shared tubes used for intranasal drug use and from crack pipes, the risk of HCV transmission from non-injection drug use has not been quantified. Current HCV prevention strategies for injection drug users are inadequate, and education about HCV transmission and prevention is lacking.

Recommendations:

- **Implement national surveillance for chronic HCV infection.**
- **Provide HCV testing and education for high-risk and high-prevalence populations.**
- **Increase access to sterile injection equipment.**
- **Increase access to drug treatment and methadone maintenance programs.**
- **Institute CDC's recommendations for prevention of HCV transmission in hemodialysis facilities.**
- **Clarify routes and risks of HCV sexual transmission.**
- **Clarify the risk of non–injection drug use behaviors associated with HCV transmission, such as smoking or sniffing.**
- **Research mechanisms and interventions to decrease mother-to-infant transmission.**
- **Develop protocols for HCV counseling and testing for pregnant women, and offer voluntary HCV counseling and testing to pregnant women.**
- **Develop and implement HCV prevention strategies for the developing world.**

Hepatitis C is not invariably chronic; 15% to 45% of those infected achieve spontaneous viral clearance. Chronic HCV infection can result in fibrosis (mild liver scarring) and cirrhosis (serious liver scarring). Symptoms may include fatigue, depression, and confusion ("brain fog").

The course of chronic HCV varies widely and depends on a number of factors, including age, race, sex, and alcohol consumption. People living with HCV and their health care providers need better information about prognostic factors and risk of disease progression to make informed decisions about care and treatment. The most serious clinical consequences of HCV infection are cirrhosis, hepatocellular carcinoma, and hepatic decompensation (liver failure). HCV-related end-stage liver disease is the leading indication for liver transplants in the United States, where there is a critical shortage of donor livers. Potentially life-saving vaccinations for hepatitis A and B are recommended by CDC, but have not yet been universally incorporated into HCV care.

Recommendations:

- **Investigate the role of genetic and ethnic factors in susceptibility to HCV infection, disease progression, and response to treatment.**
- **Investigate the role of sex differences in HCV disease progression.**
- **Investigate the role of light-to-moderate alcohol consumption on HCV disease progression.**
- **Identify possible causes of and interventions for HCV-related "brain fog."**
- **Promote screening and vaccination for hepatitis A and hepatitis B among individuals infected with HCV or coinfected with HIV/HCV.**
- **Create an "opt-out" system for organ donation in the United States and include discussion of organ donation as part of school health education programs and regular medical care.**

Acute HCV is usually asymptomatic and often goes undiagnosed. A series of blood tests is available to diagnose chronic HCV infection, predict and monitor the effects of treatment, and measure other complications of HCV infection. Liver biopsy is still considered the "gold standard" for assessment of liver damage and determining the need for treatment, although it is expensive, invasive, unpopular with patients, and subject to substantial interpretive variation. Hepatocellular carcinoma (HCC) occurs in 1–4% of cirrhotics annually. Current surveillance techniques are suboptimal for early diagnosis of hepatocellular carcinoma.

Provider education on HCV is limited. Many high-risk and high-prevalence populations lack access to regular medical care. Outreach strategies for diagnosis of HCV and linkage of newly diagnosed HCV-infected persons to care programs are needed.

Recommendations:

- **Educate primary care providers about diagnosis of acute and chronic HCV infection.**
- **Develop and market oral fluid test kits for HCV-antibody testing.**
- **Promote use of a standardized system for evaluation of liver biopsy.**
- **Continue research on non-invasive testing methods to replace or reduce the need for liver biopsy.**
- **Identify and validate prognostic markers and more effective screening methods for early diagnosis of hepatocellular carcinoma.**

Treatment for HCV—a 6-to-12 month course of pegylated interferon and ribavirin—has many drawbacks, including potentially severe side effects. On average, treatment eradicates HCV in about half of patients, but various factors can dramatically increase or decrease the likelihood of a sustained virological response. Initial reports suggest that HCV treatment may be particularly effective during acute infection. Treatment may also improve the condition of the liver, even in people who do not have a sustained virological response.

Primary care providers often do not receive adequate information about efficacy and side effects of HCV treatment. Moreover, even for expert clinicians, numerous questions about treatment remain: Can treatment success rates be improved by optimizing dosing regimens? Is treatment safe and effective across all populations with high HCV rates—especially drug and alcohol users and people with psychiatric co-morbidities, who have often been excluded from clinical trials? Is there a role for treatment even in people who don't clear the virus? Can improvements in the management of side effects make treatment more tolerable? When and how should people acutely infected be treated? How effective are herbs such as milk thistle as complementary and alternative therapies for HCV? These questions are relevant not only for HCV monoinfection but also for HCV/HIV coinfection.

Recommendations:

- **Increase knowledge of treatment and care for hepatitis C patients among primary care providers.**
- **Identify optimal dosing strategies.**
- **Increase research on treatment safety and efficacy in understudied populations.**
- **Increase research on strategies to manage side effects of HCV treatment.**
- **Identify when and in whom treatment for acute HCV should be initiated; optimal regimen; and duration of treatment.**
- **Establish prospective, long-term follow-up studies to assess the durability and clinical benefit of histological responses in virological responders, relapsers, and non-responders.**
- **Investigate safety and efficacy of alternative therapies for HCV infection.**

In 1999, CDC added hepatitis C infection to the list of opportunistic infections (OIs) associated with HIV. HIV accelerates HCV disease progression, and HCV-related end-stage liver disease has become a leading cause of death among HIV-positive people. Although potent antiretroviral therapy has significantly increased survival, some studies have reported a blunted immune response to antiretroviral therapy among HCV-coinfected individuals. HCV coinfection increases the risk of hepatotoxicity from antiretroviral therapy. Vaccination for HAV and HBV may be less immunogenic in individuals with advanced HIV disease.

HCV treatment is less effective for HIV/HCV-coinfected people, and they tend to experience more severe side effects. Although promising data have emerged on the survival of coinfected liver recipients, restrictive policies at transplant centers and refusal to reimburse for transplantation have limited access to transplantation for HIV-positive candidates. For these reasons, people coinfected with HIV and HCV and their health care providers face complicated decisions about care and treatment for both infections.

Recommendations:

- **Establish prospective, longitudinal cohort studies of the natural history of HIV/HCV coinfection in the era of HCV treatment and HAART.**
- **Develop guidelines for the care and treatment of coinfected individuals.**
- **Establish a universal definition of hepatotoxicity and characterize its severity.**
- **Explore pharmacokinetics and drug levels of antiretroviral agents and other drugs commonly used by coinfected individuals.**
- **Include HIV/HCV-coinfected individuals in early-phase HCV treatment trials.**
- **Explore strategies to optimize HCV treatment for HIV/HCV-coinfected persons.**
- **Support access to and research on liver transplantation for HIV-positive and HCV/HIV-coinfected individuals.**

HCV is prevalent among African Americans, the incarcerated, the poor, current and former injection drug users, people with psychiatric disorders, and HIV-positive persons. These groups face significant barriers to care and treatment. Incarcerated individuals have had to resort to legal action to obtain HCV treatment, and most still do not receive it. Inadequate, decreasing funding of AIDS Drug Assistance Programs (ADAPs) has limited access to HIV and HCV treatment for HIV-positive individuals. Expected cuts in Medicaid threaten access to HCV treatment for many more.

Recommendations:

- **Provide full access to hepatitis C care and treatment for all of those in need.**
- **Do not withhold treatment from active drug users; decisions should be made on an individualized basis.**
- **Strengthen linkages among substance abuse treatment programs, methadone maintenance programs, medical and mental health providers, and HIV/HCV prevention programs.**
- **Increase capacity to provide individualized medical care and treatment to coinfected active drug users.**
- **Develop integrated, multidisciplinary systems of care for individuals with multiple co-morbidities (HIV, HCV, psychiatric disorders, addiction).**

It is in this environment that TAG is releasing Hepatitis C and HIV/HCV Coinfection: A Critical Review of Research and Treatment. This report is meant to serve as a blueprint for activism as well as a source of information.

TAG's Coinfection Project closely monitors new data on the epidemiology and natural history of HIV/HCV coinfection, as well as the development of new diagnostics, prophylaxes, and treatments for hepatitis C in both the pre- and postmarketing stages. We advocate for the expeditious development, proper clinical research and regulation, ease of access, and optimal use of these drugs. We work with the pharmaceutical companies, NIH, FDA, researchers, and other treatment activists to achieve these objectives. TAG also educates members of the HIV community about coinfection with hepatitis C.

INTRODUCTION

TAG's Hepatitis C and HIV/HCV Coinfection Report is a comprehensive review of basic and clinical science accompanied by recommendations for research and policy. It was written for people living with hepatitis C or HIV/HCV coinfection, clinicians, researchers, activists, educators, and advocates.

The Hepatitis C and HIV/HCV Coinfection Report reflects my experience. I have worked for more than ten years as a direct service provider to people at risk for, or living with, HCV and HIV, which has contributed to my understanding of their needs. While I was writing this report, I reviewed more than a thousand journal articles and hundreds of conference abstracts, and interviewed researchers, clinicians, coinfected individuals, and advocates.

TAG's original hepatitis report was released in July of 2000. Since then, HCV-related end-stage liver disease has been recognized as a leading cause of death among people with HIV. For people with HCV monoinfection, liver-related deaths are projected to increase by 180% over the next 20 years. Meanwhile, a more effective therapy, pegylated interferon, has been approved for treatment of HCV, and researchers are moving closer towards an understanding of HCV pathogenesis. The Hepatitis C and HIV/HCV Coinfection Report is a synthesis of current knowledge; key issues are highlighted in the Recommendations section at the end of each chapter.

Despite advances in treatment, many barriers to optimal care and treatment of people with HCV and HIV/HCV remain. As with HIV, HCV is a lens that magnifies the intersection of medical and social inequities. In the U.S., both viruses disproportionately affect African Americans and other groups who have traditionally had poor access to care and treatment, including the incarcerated, the poor, people with psychiatric disorders, and injection drug users. Up to 90% of injection drug users are infected with HCV. Injection drug users in particular are regarded with an astounding degree of contempt by most of society. Draconian drug laws and inadequate access to sterile syringes have created penalties for drug use that exceed incarceration alone by costing people their health and, ultimately, their lives. Until we acknowledge that HCV is a disease that is prevalent among injection drug users and demand expansion of needle exchange programs, universal availability of syringes through legalized pharmacy sale, access to methadone maintenance therapy, and drug treatment upon request, we will not be able to mitigate the spread of hepatitis C.

Access to care and treatment is not just an issue for injection drug users. In the United States, access to health care for the poor is restricted; more than 43 million Americans are uninsured. Cuts in federal funding for programs such as AIDS Drug Assistance Programs and Medicaid threaten access to health care for the more than 42 million Americans who rely on them. Drug prices are exorbitant; the 48-week course of treatment for HCV costs as much as $40,000.

Even individuals with access to health care suffer from the constraints of managed care and a lack of provider and patient education about HCV; these factors collectively make it difficult to insure that people with HCV receive optimal care. Many clinicians work in health care settings ill-suited to providing care for dually or multiply diagnosed individuals. Successful models of service delivery to injection drug users and people with psychiatric co-morbidities must be imported into the

clinic. Clinicians must take a proactive approach to managing drug-related adverse events by educating people about them before initiating treatment, providing options to ameliorate them and offering access, where indicated, to mental health care. While pressuring the medical system to meet these needs, people must receive clear and direct education about transmission, prevention, diagnostics, care, and treatment of HCV and HIV/HCV.

Preparation and implementation require resources. Very little funding is specifically designated for HCV prevention and education services, nor are there any validated and established models for such programs. HCV prevention and education must be integrated into programming at AIDS service organizations and available to staff and participants at methadone clinics, syringe exchanges, detoxification facilities, residential drug and alcohol treatment programs, homeless shelters, and correctional facilities. Information and services must reach those who need them most, not merely those who are the easiest to reach.

Progress toward new treatments and improvements in efficacy of existing HCV therapy has been hampered by the absence of a coordinated research agenda for hepatitis C. HCV research is currently spread across different NIH institutes without the oversight that exists for HIV research from the NIH Office of AIDS Research (OAR). Currently, there is no mechanism for meaningful community participation in the development of a research agenda for HCV.

The current situation demands intensified, focused action: members of the HCV and HIV communities need to work together to advocate for prevention initiatives, broadened access to care and treatment for HCV and HIV/HCV, and a comprehensive research agenda.

I. Epidemiology and Transmission of Hepatitis C

Summary

Hepatitis C is the most common bloodborne infection in the United States. The Centers for Disease Control's Third National Health and Nutrition Examination Study (NHANES III), conducted from 1988 to 1994, estimated that 1.8% of the non-institutionalized United States population, or 4 million people, have been infected with HCV. Liver damage resulting from HCV infection is the leading cause of liver transplants in the United States (CDC 1998). End-stage liver disease (ESLD) and hepatocellular carcinoma (HCC; liver cancer) resulting from HCV infection cause between 10,000 and 12,000 deaths per year in the United States. Global HCV infections are estimated at 170 million, or 3% of the world's population (World Health Organization 1999).

Decades before the hepatitis C virus (HCV) was identified, many transfusion recipients developed a post-transfusion viral hepatitis infection that was not caused by the hepatitis A or hepatitis B viruses. Non-A, non-B (NANB) hepatitis was originally thought to be a mild infection, but over the years doctors began to notice that some NANB hepatitis patients developed serious liver damage.

In 1988, a small RNA virus, designated hepatitis C, was identified, and an antibody test was quickly developed (Choo 1989; Kuo 1989). Testing of stored blood samples revealed that 70% to 90% of NANB hepatitis infections were hepatitis C infections.

Approximately one-third of the estimated 900,000 HIV-positive people in the United States are coinfected with HCV. The rate of coinfection is much higher among people who acquired HIV from injection drug use. HCV infection rates in injection drug users (IDUs) range from 70% to 90% (M. J. Alter 1998; Donahue 1991; Garfein 1996; Mao 2001; Mendel 1995; Sherman 2002a; Sulkowski 2002; Thomas 1996).

Most new HCV infections in the United States are from injection drug use with shared, unsterilized equipment. People who are on kidney dialysis are at risk for HCV infection if dialysis centers do not practice proper infection control procedures. The other two main sources of HCV infection, blood transfusions and contaminated blood products, have been almost completely eliminated (Donahue 1992). Viral inactivation techniques for clotting factors were introduced in 1985 (Factor VIII) and 1987 (Factor IX). Effective screening for HCV in the United States blood supply began in July 1992 and has improved steadily since then.

Mother-to-infant transmission of HCV occurs among approximately 5% of infants born to mothers with HCV. The risk of HCV transmission increases if the mother is coinfected with HIV (Thomas 1998; Yeung 2001).

HCV can be sexually transmitted, but so far research has yielded conflicting results about how likely sexual transmission of HCV actually is, and exactly how it takes place. HCV is more prevalent among men who have sex with men, people with multiple partners, sex workers, and partners of HIV/HCV coinfected individuals (M. J. Alter 1988; M. J. Alter 2002; Bodsworth 1996; Buchbinder 1994; Eyster 1991).

Tattooing with shared needles and/or ink receptacles may result in HCV infection, though incidence is low and data are scarce.

It has been speculated that HCV infection can be spread by sharing tubes for intranasal (snorting or sniffing) drug use as well as sharing personal implements with infected blood on them (such as nail clippers, manicure sets, razors, and toothbrushes). Again, however, incidence is low and data are scarce.

Epidemiology of Hepatitis C

Hepatitis A and hepatitis B have long been known, and vaccines have been developed to prevent infection with both viruses.

In 1965, Baruch S. Blumberg discovered an antigen that was later named hepatitis B (HBV). In 1968, the hepatitis B antigen was associated with post-transfusion hepatitis (Sherlock 1984). More than 350 million people worldwide are infected with hepatitis B; the Centers for Disease Control and Prevention (CDC) estimates that 4.9% of Americans have been infected with HBV; 1.25 million have developed chronic HBV infections. A vaccine to prevent infection with hepatitis B has been available since 1982 (W. M. Lee 1997). Since 1991, the American Council on Immunization Practices has recommended universal hepatitis B vaccination of newborns and adolescents.

In 1973, hepatitis A (HAV) was first identified; by 1979 it could be grown in tissue cultures (Sherlock 1984). In 1995, the Food and Drug Administration (FDA) licensed a vaccine to prevent infection with hepatitis A. In 2001, FDA approved a combined vaccine to protect against infection with hepatitis A and hepatitis B. Hepatitis A infection is endemic in many parts of the world; CDC has estimated that 31% of Americans were infected with HAV during their lives. Once a person is infected with HAV, re-infection does not occur, but acute HAV can be fatal among people with chronic HBV or HCV infections.

Before the hepatitis C virus was definitively identified, hepatitis infections were frequently seen in recipients of blood transfusions. Screenings for hepatitis A were negative, and only about 25% of transfusion-associated hepatitis infections were caused by hepatitis B (H. J. Alter 1999). The remaining 75% of these infections were attributed to a virus designated non-A, non-B (NANB) hepatitis, which was initially thought to be fairly harmless. Although most NANB infections were identified by liver enzyme elevations as high as 21 times the upper limits of normal soon after infection, only a small group of people developed symptoms during acute infection (M .J. Alter 1992; Koretz 1993). These symptoms—fatigue, low-grade fever, appetite loss, nausea, vomiting, and jaundice (yellowed skin and eyes)—resolved in a few weeks.

Over time, physicians became alert to the possibility of more serious consequences as they began to see many NANB patients with persistently elevated liver enzymes and some with serious liver damage.

In 1988, a group of researchers at Chiron identified an RNA virus (from the flaviviridae family) that they suspected might be the agent causing NANB infections. The virus was named hepatitis C

(Choo 1989). An antibody test was rapidly developed (Kuo 1989). When researchers at the National Institutes of Health (NIH) tested the new antibody on archived blood samples, they discovered that 70% to 90% of NANB hepatitis cases were actually HCV infections.

Hepatitis C Infection in the United States

Early epidemiological studies did not provide an accurate picture of HCV prevalence in the general population because most participants were volunteer blood donors who had already been screened for infectious diseases. The CDC's Third National Health and Nutrition Examination Survey (NHANES III) provided the best available estimate of HCV infection in the United States, finding that 1.8% of Americans, or roughly 4 million people, have been infected with HCV; 2.7 million of them remain chronically infected (see Chapter II, Natural History of Hepatitis C). Hepatitis C is the most common bloodborne infection in the United States.

In NHANES III, blood samples from 21,241 people were screened for antibodies to hepatitis C. Samples with a positive antibody test result were then tested for HCV RNA (viral load) to distinguish between chronic and resolved (past) HCV infections. Three-quarters (74%) of the antibody-positive samples were also HCV-RNA-positive, indicating chronic HCV infection (M. J. Alter 1999). The NHANES III data have been widely cited in media reports and policy discussions; however, there are several limitations to the study. It may significantly underestimate the true prevalence of HCV in the United States, because NHANES III did not survey incarcerated or homeless persons. Between 30% and 40% of the 1.8 million people incarcerated in the U.S. are infected with HCV (Reindollar 1999). A 1994 study of HCV prevalence among 4,513 inmates (87% male; 13% female) in California revealed that 39.4% of the men and 53.5% of the women were HCV-antibody-positive (Ruiz 1999). HCV is prevalent among the homeless; in one study almost 42% of 597 homeless veterans were anti-HCV positive (Cheung 2002).

Limitations also exist with the NHANES III data on drug use; although participants were asked about their drug-use history, they were not asked if they had ever injected drugs. A multivariate analysis revealed that the strongest factors independently associated with HCV infection were drug use (defined as the use of marijuana more than 100 times, or any cocaine use ever) and, in the absence of drug use, "high-risk" sexual behavior (more than 50 sexual partners and/or early age at first intercourse). Because marijuana use does not involve blood-to-blood contact, it presumably serves here as a proxy for other drug use or sexual behaviors. On the other hand, intranasal cocaine use with shared straws or other implements might involve contact with infected blood. Yet because modes of administration—snorting vs. injecting—among cocaine users in NHANES III is unknown, the incidence of HCV transmission via intranasal drug use could not be assessed.

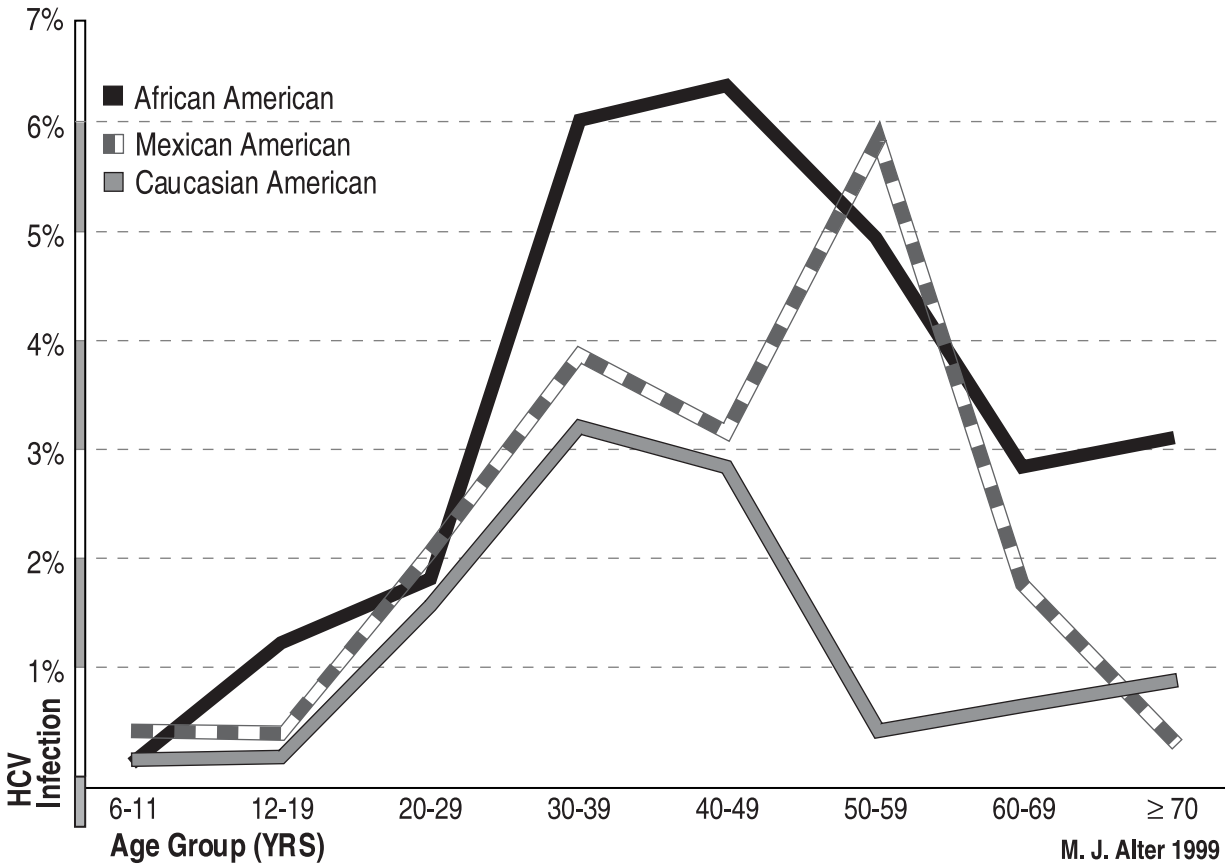
Sixty-five percent of HCV infections identified in NHANES III were found in persons between the ages of 30 and 49. The highest observed prevalence was among black males aged 40 to 49—a shocking 9.8%. This is especially alarming in light of data indicating a poorer response to HCV treatment in African Americans (see Chapter V, Hepatitis C Treatment).

Table 1. Prevalence of Antibody to HCV (Anti-HCV+) According to Demographic Characteristics in NHANES III

Characteristic	N tested	HCV+ %	Nationwide estimate
All Subjects	**21,241**	**1.8%**	**3,875,000**
Non-Hispanic White	7,965	1.5%	2,359,000
Non-Hispanic Black	6,119	3.2%	762,000
Mexican American	6,268	2.1%	261,000
Other	889	2.9%	493,000
Male	10,076	2.5%	2,586,000
Female	11,165	1.2%	1,289,000

M. J. Alter 1999

Figure 1. Prevalence of HCV infection by age and race/ethnicity United States, 1988-1994



Veterans and Hepatitis C Infection

Several studies have found shockingly high rates of HCV among United States veterans. In March of 1999, the Veteran's Health Administration (VHA) did a one-day serosurvey to estimate HCV prevalence in order to forecast future health care costs. Blood was drawn from 26,102 veterans. HCV antibodies were detected in 1,724 (6.6%) veterans. The mean age among HCV antibody-positive individuals was 53.8 years. Most were male (97.4%) and served during the Vietnam era (58.7%); 29% identified themselves as black, non-Hispanic, and 46% identified themselves as white, non-Hispanic (Roselle 2002).

A study of 1,032 veteran outpatients at San Francisco's Veteran's Affairs Medical Center reported an HCV seroprevalence rate of 17.7% (Briggs 2000). Study participants were screened for HCV and given a detailed questionnaire on sociodemographic information and risk factors. Over 90% of veterans surveyed had at least one risk factor not directly related to military service. Risk factors related directly to military service included rank (enlisted vs. officer), exposure to blood during combat, combat job as a medical worker, and history of a needlestick during military deployment.

A retrospective analysis of blood samples and risk histories provided by 597 homeless veterans admitted to a VA shelter found an HCV seroprevalence of 41.7%; intravenous drug use was identified by multivariate analysis as an independent risk factor (Cheung 2002).

A 2001 study found a low HCV prevalence among active-duty personnel in the U.S. military—just five of one thousand troops (0.5%). HCV prevalence increased with age to 3.0% among troops over 40 years old, a prevalence rate similar to that of a matched age cohort (Hyams 2001).

Gathering Data: Hepatitis C Surveillance

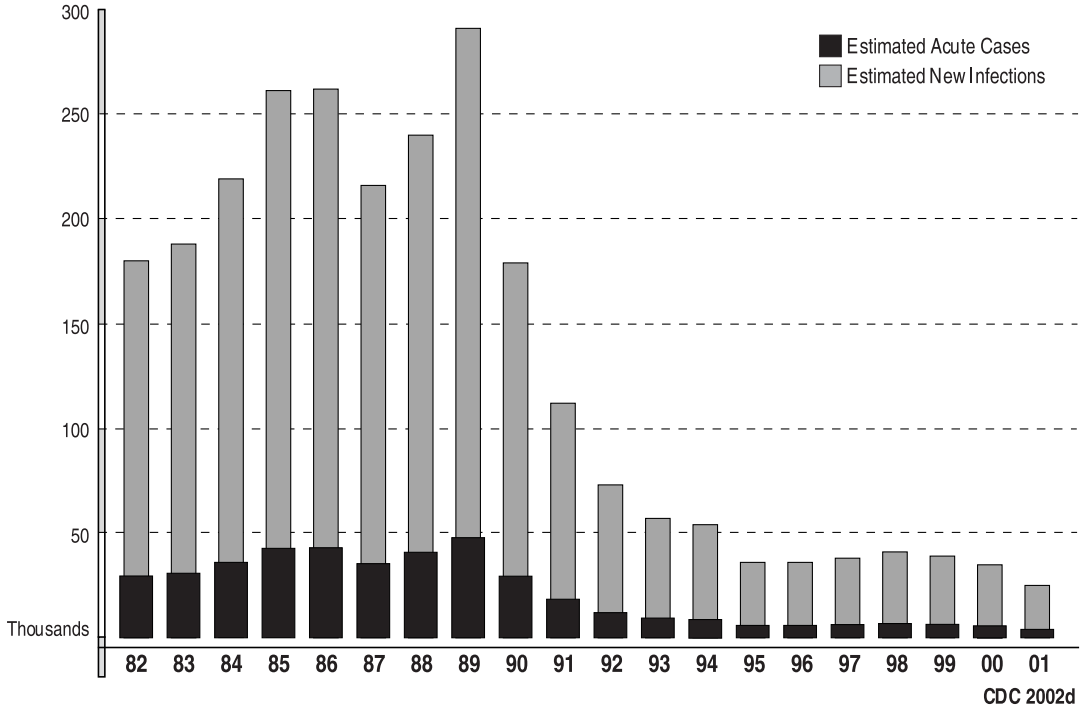
The yearly incidence of hepatitis C infections rose from approximately 45 per 100,000 in the early 1960's to 100–200 per 100,000 in the late 1980's, when they reached their peak (Armstrong 2000). Age-specific prevalence data have been used to identify transmission patterns in the United States (Wasley 2000). Because HCV prevalence is highest among people 30 to 49 years of age, HCV incidence is thought to have peaked among young adults 10 to 30 years ago.

According to CDC estimates, new HCV infections have decreased by 80% (M. J. Alter 1998). CDC estimated that 291,000 new HCV infections occurred in 1989; the estimate of new infections for 2001 dropped to 25,000 (CDC 2002d). The extent of this drastic reduction in new HCV infections is questionable, although effective screening of blood products and the blood supply and saturation of HCV infection among injection drug users shrunk the pool of vulnerable people. Most acute HCV infections are not picked up by surveillance systems because the majority of acutely infected people are asymptomatic (Di Bisceglie 1998; Hagan 2002).

Acute hepatitis C is subject to mandatory reporting requirements by the Council of State and Territorial Epidemiologists (CTSE). The acute hepatitis C surveillance system is inherently limited due to lack of a single, definitive test for acute vs. chronic HCV infection and inadequate resources at state health departments to test for both HCV antibodies and HCV RNA. Some people will achieve spontaneous viral clearance of acute hepatitis C, although they remain antibody-positive,

thus some reported cases of acute HCV may be false positives. In addition, it is not possible to distinguish how recent an HCV infection actually is. Surveillance data are corrected for underreporting and asymptomatic infections, although the method/s of correction is/are unspecified.

Figure 2. Acute Hepatitis C Infections in the United States 1982–2001



Only acute cases of hepatitis C are reported, although a small, pilot program—sentinel surveillance of physician-diagnosed chronic liver disease—has begun tracking both acute and chronic hepatitis C infections. The updated CDC case definition for acute hepatitis C includes clinical and laboratory criteria. Laboratory criteria include ruling out hepatitis A and B; alanine aminotransferase (ALT; a liver enzyme) levels over seven times the upper limits of normal; and confirmatory HCV-RNA testing if HCV antibody testing is reactive. Accurate identification of acute HCV infections will increase by combining laboratory reports of reactive HCV-antibody tests, ALT levels, and clinical information. Chronic hepatitis C infections can be distinguished from acute infections by laboratory reporting of reactive HCV-antibody tests and confirmatory antibody testing by RIBA or HCV-RNA (viral load) detection by RT-PCR. Reporting of HCV infections includes demographic and risk information.

CSTE is considering inclusion of chronic and resolved HCV infections in reporting systems. In June 2002, CDC issued guidelines for viral hepatitis surveillance and case management (CDC 2002). Two different surveillance systems, the National Notifiable Disease Surveillance System and the Viral Hepatitis Surveillance Program have been consolidated into the National Electronic Telecommunications System for Surveillance (NETSS). Upcoming changes in the structure and function of NETSS, will increase the capacity for surveillance of both acute and chronic hepatitis C infections, but must be supported by funding for adequate staffing and laboratory resources.

Global Hepatitis C Prevalence

Although prevalence data are not available from every country, it is estimated that 170 million people are infected with HCV worldwide (WHO 1999). The true number may be much higher due to missing data and differing data collection and interpretation methods.

Table 2. Global Hepatitis C Prevalence

WHO Region	Population (Millions)	HCV Prevalence	Infected Pop. (Millions)	# Countries Not Counted
Africa	602	5.30%	31.9	12
America	785	1.70%	13.1	7
Eastern Mediterranean	466	4.60%	21.3	7
Europe	858	1.03%	8.9	19
SouthEast Asia	1,500	2.15%	32.3	3
Western Pacific	1,600	3.90%	62.2	11
Total	**5,811**	**3.10%**	**169.7**	**57**

WHO 1999

The HCV epidemic in the developing world is largely driven by transfusions, unsterilized medical and dental equipment, unsterilized instruments used for circumcision, scarification, tattooing, traditional medicine, and, in some regions, injection drug use.

The World Health Organization (WHO) developed conservative estimates of the transmission of bloodborne pathogens (hepatitis B, hepatitis C, and HIV) via unsafe injections. This model estimates that 2.3–4.7 million new HCV infections may result from unsafe injections annually (Kane 1999).

Hutin and colleagues estimated the safety and frequency of injection practices at healthcare facilities in ten regions comprised of developing and transitional countries by reviewing literature, including unpublished data from WHO. They reported that at least 16 million injections were administered annually; unsterilized injection equipment was reused in approximately one of three injections (Hutin 2003). Based on this data, Hauri and colleagues estimated that there were two million HCV infections—40% of all new infections—from unsafe injection practices in health care settings in the year 2000 (Hauri 2004).

HIV/HCV Coinfection Prevalence in the United States

CDC estimates that 800,000–900,000 people in the United States are HIV-positive; about 16–25% of them are also infected with HCV (Sherman 2002a; Tedali 2003b; Thomas 2002). Coinfection rates vary according to mode of transmission; 50–90% of HIV-positive people infected from shared injection equipment are coinfected with HCV (Sulkowski 2000). Over 50% of HIV-positive people with hemophilia are HCV coinfected due to receiving clotting factor concentrates before viral inactivation procedures were initiated in 1985.

A cross-sectional analysis of 213 Adult AIDS Clinical Trials Group (AACTG) study participants found an overall HCV seroprevalence of 16.1% (Sherman 2002a). Participants were divided into an at-risk group (those with a history of drug use or people with hemophilia) and a low-risk group. Those in the at-risk group had an HCV seroprevalence of 72.7%. HCV seroprevalence in the low risk group was 3.5%—nearly twice what NHANES III found in a broader population sample.

The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) assessed HCV prevalence among 2,705 HIV-positive trial participants. Data were collected from September 1998 through September 2001. Antibodies to HCV were detected in 16.6% of participants (449/2,705). A subgroup analysis of an all-male cohort found a significantly greater odds ratio for coinfection among males with a history of IDU (OR, 69.77; 95% CI, 43.93–110.81; $P<0.001$) and IDU plus male-male sex (OR, 11.86; 95% CI, 7.28–19.32; $P<0.001$) (Tedali 2003b).

A serosurvey of HIV-positive patients receiving care in the San Francisco Community Health Network found that 39.4% of 2,859 people tested were anti-HCV-positive (Hare 2002). Another study reported that 28% (394) of 1403 HIV-positive patients from an urban clinic in Richmond, Virginia, were coinfected with HCV (Tsogas 2002).

A serosurvey of 557 active and former injection and non-injection drug users in New York City found HCV RNA in blood samples from 74.2% (170/229) of HIV-positive participants (Klein 2003).

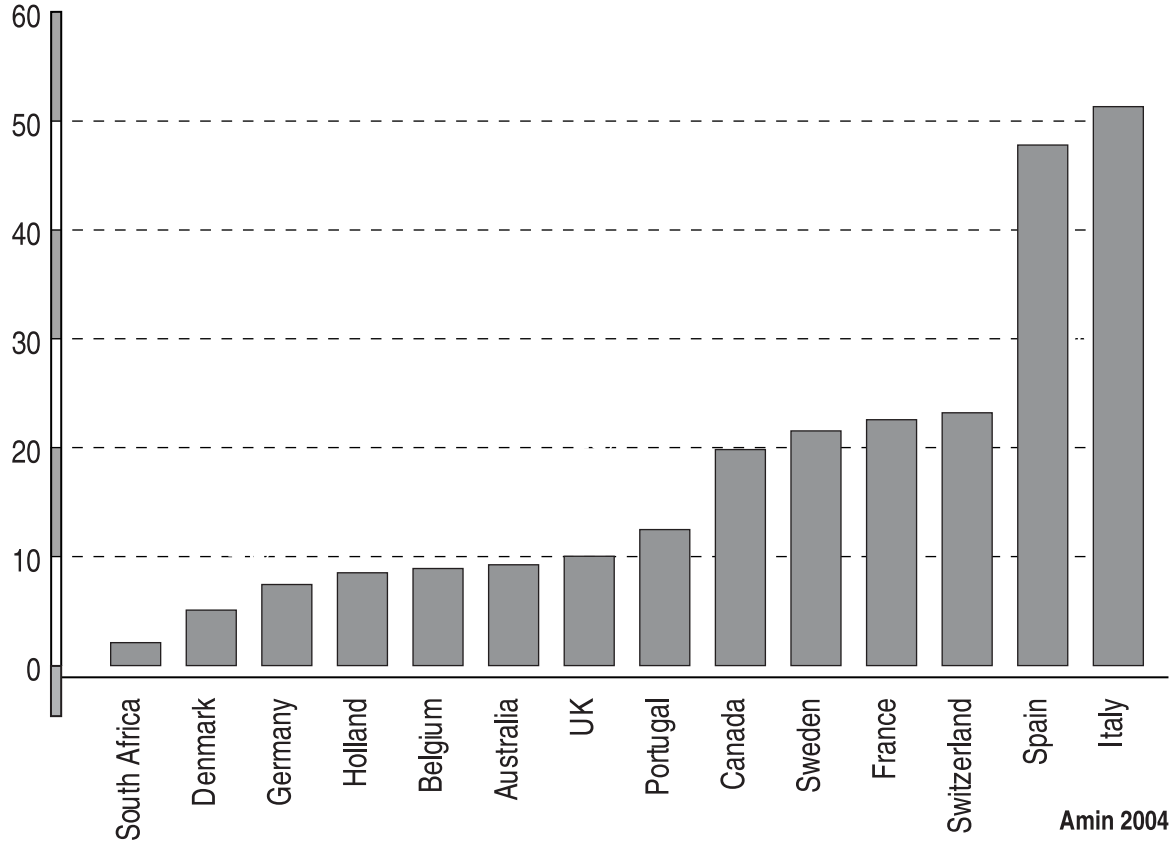
HIV/HCV Coinfection Prevalence in Europe

EuroSIDA is a prospective observational cohort study of more than 9,800 HIV-positive persons from 26 European Countries and Argentina. HCV prevalence was assessed in a subset of 4,957 EuroSIDA cohort participants. Overall, 34% (1685/4.957) were anti-HCV-positive (Rockstroh 2004). Viksna and colleagues assessed regional differences—including HCV serostatus—among a subset of 5,708 EuroSIDA participants from Eastern Europe (907), Southern Europe (1580), Central Europe (1583), Northern Europe (1538) and Argentina (100). Anti-HCV positivity was most prevalent in Eastern Europe (41%), followed by Southern Europe (34%), Argentina (24%), Central Europe (20%) and Northern Europe (13%) (Viksna 2003).

Table 3. Coinfection Prevalence from Five European Studies

Study	Cohort	HIV+	HIV+ & HCV+	% Coinfection
Soriano 2000	Euro SIDA	4,034	1,350	33.5%
Greub 2000	Swiss HIV	3,111	1,157	37.2%
Pailoux 2000	France	1,746	465	27.0%
Mendel 1995	Normandy, France	161	55	34.2%
J. Martín 2001	Madrid, Spain	902	649	72.0%

Figure 3. Prevalence of HCV coinfection by country: CAESAR study



Transmission of Hepatitis C

Transfusion and Blood Products

HCV is most efficiently transmitted through transfusion of infected blood, transplantation of infected organs, and sharing injection drug equipment (M. J. Alter 1994).

In 1985, screening of donor blood for antibodies to HIV, hepatitis A (HAV), and hepatitis B (HBV) was instituted. A study of 912 people who received transfusions between 1985 and 1991 found that the risk for HCV infection was 0.45% per unit transfused before donor blood screening began (Donahue 1992); after screening for HIV, HAV, and HBV was instituted, the risk dropped to 0.19% per unit. The U.S. blood supply has been screened for HCV antibodies since May 1990. This screening has reduced the risk per unit to 0.03%, or about 3 per 10,000 units transfused. The risk of HCV infection from a blood transfusion has continued to decrease since July 1992, when the EIA-2 antibody test replaced the less sensitive EIA-1.

Additional advances in screening technology have further reduced the risk from transfusions; the EIA-2 was replaced by the EIA 3.0 in 1996. HCV nucleic acid amplification (RNA) testing was introduced in April 1999 and approved by FDA in February 2002 (Glynn 2000). Because nucleic

acid amplification testing measures viral RNA rather than antibody, the "window" (the amount of time between infection and detection) for HCV donor blood is reduced from an average of 82 days to 25 days (FDA 2002). It is estimated that 90% of HCV infections due to transfusions result from donations made during the "window" period (CBER 2002). Thus, by shortening the window period, nucleic acid amplification testing will decrease the likelihood of HCV infection from transfusions and blood products. The incidence of HCV infection from a blood transfusion in the U.S., before widespread implementation of nucleic acid amplification testing, was estimated to be about 1 in 103,000 (Schreiber 1996). It is estimated that the use of nucleic acid amplification testing reduces the risk of HCV infection from donor blood by an additional 27–72%.

Before 1985, clotting factor concentrates made from pooled donor blood infected up to 90% of the hemophiliacs who had used them with HCV. Effective viral inactivation techniques were instituted in 1985 with Factor VIII and in 1987 with Factor IX. Viral inactivation procedures have almost completely eliminated the risk of infection with HCV, HIV, and other viral infections from clotting factors.

Since December 1994, all immunoglobulin products made in the U.S. are either screened for HCV or put through a viral inactivation procedure.

Organ donors are screened for HCV antibodies.

Hemodialysis

In a December 2000 study, dialysis recipients at 40% of U.S. dialysis centers were tested for HCV antibody; 8.4% were antibody-positive (Tokars 2002). Other studies of dialysis recipients have reported anti-HCV prevalence of 10–36% among adults and 18.5% among children (CDC 2001).

A majority of these hepatitis C infections result from inadequate infection control procedures at hemodialysis centers. In April of 2001, CDC issued recommendations for preventing transmission of infections among chronic hemodialysis patients which include stricter infection-control practices and regular monitoring of ALT levels and HCV testing of dialysis recipients.

Occupational Exposures

The NHANES III study did not detect a difference in the anti-HCV prevalence of health care workers (1–2%) and that of the general population (1.8%) (H. J. Alter 1991). A serosurvey examining a group of dentists and oral surgeons found anti-HCV in 2.0% of the oral surgeons and 0.7% of the dentists (Thomas 1996). A five-year surveillance program in Italy followed 245 health care workers with occupational exposures to blood. Health care workers and source patients were tested for HCV antibody and RNA. Although 27.8% of the source patients had HCV, there were no seroconversions (development of antibodies in the blood) among the health care workers (Baldo 2002). One review of prospective studies of health care workers has estimated that the risk of HCV infection after a needlestick exposure from an HCV-infected source patient is about 1.8%, with a range of 0–7% (Beltrami 2000). Other studies found risks ranging from 1% to 6% (Lamphear 1994; Puro 2001). It is possible that the risk of needlestick infection increases with higher HCV viremia (McDonald 1996). Needle size, inoculum amount, and inoculation depth may influence

the likelihood of HCV infection. A crude estimate of the comparative risks of transmission from needlestick uses the rule of threes: HBV is transmitted in 30% of exposures, HCV in 3%, and HIV in 0.3% (Lauer 2001).

Injection Drug Use

Because viral inactivation techniques have dramatically reduced the risk of HCV infection from transfusions and the use of clotting factors in the United States, the majority of new HCV infections result from injection drug use (IDU). Before 1990, 60% of HCV infections were attributed to IDU and 10% to blood transfusions. Since 1995, newly acquired HCV infections from transfusions have become extremely rare, while HCV infections from IDU increased to 68% (M. J. Alter 2002). A seven-year CDC surveillance program of acute HCV infections in four counties showed a drop in HCV incidence among transfusion recipients from 17% to 6%, while infections in IDUs rose from 21% to 42% (M. J. Alter 1990).

Hepatitis C is very efficiently transmitted via contaminated syringes. Shared injection equipment, such as cookers, cotton filters, and water can also be a source of infection (Hagan 2001; Thorpe 2002; Vidal-Trecan 2002). Although CDC does not recommend that syringes or injection equipment ever be used more than once, or shared, their *Guidelines for Prevention and Control of Hepatitis C Virus Infection* (1998) and *Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Persons* (2002) recommend that shared injection equipment should be cleaned with bleach and water. The efficacy of this intervention, however, is not certain; Hagen and colleagues found no difference in the incidence of HCV infection between individuals who almost always used bleach to clean their syringes and those who reported inconsistent or no use of bleach (Hagen 2001). Between 70% and 90% of injection drug users may be infected with HCV (M. J. Alter 1998; Donahue 1991; Garfein 1996; Thomas 1995). Because 55–85% of HCV infections become chronic and remain infectious, there is constant and abundant potential for HCV transmission via shared injection drug equipment.

Although HCV prevalence increases with duration of IDU, new injectors have a higher rate of HCV infection than longer-term IDUs. Garfein and colleagues found that 64.7% of a cohort with less than one year of injection drug use were anti-HCV-positive, and anti-HCV prevalence among a cohort of long-term users increased to 85%. Daily use of injection drugs and cocaine injection was associated with an increased risk of HCV infection. In the same cohorts, the rate of HIV infection during the first year of injection drug use was 13.9%, rising to 20.9% in long-term IDUs (Garfein 1996).

It is difficult to estimate the number HCV infections that result from IDU. A study of blood donors with HCV infection revealed a significant reluctance to disclose even one-time use of injection drugs. Forty-two percent (103) of 248 HCV-positive donors disclosed IDU during a self-administered questionnaire about recreational drug use, although they had denied any injection drug use during their initial blood donation screening (Conry-Cantilena 1996).

In the United States, 9% of HCV infections are from unknown sources, also referred to as sporadic transmission (M. J. Alter 2002).

Other Drug Use

Many people have speculated about the risk of HCV infection from sharing straws for intranasal drug use. In one study of HCV-infected blood donors, HCV infection was significantly linked by multivariate analysis to intranasal cocaine use (Conry-Cantilena 1996). Intranasal cocaine use—but not injection drug use—was reported by 68% of HCV-positive blood donors. Further follow-up of 137 donors reporting intranasal cocaine use found that 115 (84%) shared straws, 60 (44%) used intranasal cocaine more than three times per day, and 40 (29%) had nosebleeds during cocaine use. The authors hypothesized that HCV transmission could result from infected blood in a shared straw entering "denuded nasal mucosa."

An alarming study of female non-injection drug users in East Harlem, New York, found HCV antibodies among 26% (18/70) of heroin users and 11% (11/101) of crack and powder cocaine users (Tortu 2001). The same study reported that 61% of women with a history of IDU had antibodies to HCV. Study participants were screened for past IDU by a detailed questionnaire and an examination of their arms for track marks. Unfortunately, the study did not provide any information about HIV status, number of sexual partners, history of sexually transmitted diseases, or specific sexual practices.

Conflicting data on the likelihood of HCV infection from intranasal drug use has come from the Retrovirus Epidemiology Donor Study (REDS). The REDS has gathered infectious disease and demographic data from blood donors in five urban centers since 1990. After controlling for injection drug use, the REDS found no association between intranasal drug use and HCV infection (E. L. Murphy 2000). According to the CDC's *Guidelines for Prevention and Control of Hepatitis C Virus Infection*: "Currently, the strength of the association between intranasal cocaine use and HCV infection does not support routine testing based solely on this factor." (CDC 1998).

Miscellaneous Exposures to Blood

According to data from NHANES III, three percent of reported acute hepatitis C cases were attributed to "household contact." Murphy and colleagues reported an odds ratio of 1.6 (95% CI, 1.0–2.5) from sharing a toothbrush or razor; although biologically plausible, these are unlikely modes of HCV transmission (E. L. Murphy 2000).

Acute HCV surveillance by CDC over the last 20 years has found that less than one percent of reported acute HCV infections were associated with tattooing. According to CDC, "no data exist in the United States indicating that persons with exposures to tattooing alone are at increased risk for HCV infection" (CDC 2001).

Sexual Transmission of HCV

HCV can be sexually transmitted. Hepatitis C virus RNA has been detected in semen, vaginal fluid, and cervical smears (Caldwell 1996; Gameiro 2001; Leruez-Ville 2000; Manavi 2002; Nyamathi 2002; Pasquier 2003; Tang 1996). Questions about the likelihood of sexual transmission of HCV continue to bedevil researchers, public health educators, doctors, epidemiologists and, most importantly, HCV-infected people, their partners, and sexually active individuals. The risk

associated with specific sexual acts, and the role of possible cofactors that may facilitate sexual transmission of HCV, have not been fully explored. Unfortunately, many of the existing studies have failed to question people in sufficiently extensive detail about their sexual behaviors. Specific sexual practices may have a greater influence on HCV transmission than we are currently aware.

The National Institute of Health's *Consensus Development Conference on Management of Hepatitis C* estimates that the prevalence of HCV is between two to three percent among long-term, monogamous sexual partners of HCV-infected individuals; the estimated risk of transmission is 0–0.6% annually, though in heterosexual couples the risk of male-to-female transmission is three-fold greater. They suggest that "because of the low risk of HCV transmission, [these heterosexual] couples need not use barrier protection (condoms); however, couples should be advised that the use of condoms may decrease the risk of HCV transmission." Because HCV prevalence is higher among people with multiple sex partners, men who have sex with men and sex workers, condom use is "advised…to prevent transmission of HCV and other sexually transmitted diseases."

Studies of long-term, monogamous serodiscordant heterosexual partners have shown a low rate of male-to-female HCV transmission. Three of 106 women (2.7%) from a cohort of long-term sex partners of anti-HCV-positive male hemophiliacs were anti-HCV-positive (Brettler 1992). However, these three women had other potential exposures to HCV: one had a former partner who was an injection drug user; another had jaundice and a prior blood transfusion; the third had worked as a nurse.

In the late 1970s, a group of Irish women were infected with hepatitis C from a batch of anti-D immunoglobulin. In March 1994, they were notified. Since then, two studies of these women and their male partners have examined the possibility of female-to-male sexual transmission of HCV. Neither study found any cases of female-to-male HCV transmission (Meisel 1995; Sachithanandan 1997).

Sometimes, HCV infections from other sources can be attributed to sexual transmission. Zylberberg and colleagues studied 24 HCV-infected couples. All 48 participants provided risk information and blood samples that were tested for HCV RNA, genotype, and in some cases, phenotype. Twelve pairs of partners had matching genotypes; virus from the other twelve couples differed in genotype between partners. A phylogenetic analysis of virus from seven couples showed that four pairs were infected with different viral strains, suggesting that each partner had acquired HCV independently. The remaining three couples with similar strains each had at least one other parenteral risk factor (Zylberberg 1999).

Certain factors may increase the risk of sexual transmission of HCV. A study of the presence and predictors of HCV RNA in semen from 80 men reported that higher HCV virus loads in blood were associated with the presence of HCV RNA in semen, as well as current use of alcohol (Nyamathi 2002). NHANES III found an association among HCV infection and sexual intercourse prior to age 18, multiple sex partners (especially more than 50 partners), and herpes simplex infection. Fifteen percent of acute HCV infections in the U.S. between 1992 and 1995 were attributed to sexual risk factors—a rate that has increased to 18% since 1995 (M. J. Alter 1998; M. J. Alter 2002).

Sexual Transmission of HCV from an HIV-Coinfected Partner

A cross-sectional study at ten hemophilia centers evaluated HCV and HIV transmission rate from 231 male hemophiliacs to their female sex partners. Just 2.6% of the female partners were HCV-antibody positive. No woman with an HCV monoinfected partner had antibodies to HCV. Every anti-HCV-positive female partner had an HIV/HCV coinfected partner. In contrast, 12.8% of the women with HIV-positive male partners and 13% of those with HIV/HCV coinfected partners were also HIV-positive (Eyster 1991). Although sexual transmission of HCV is less efficient than sexual transmission of HIV, coinfection with HIV may increase the risk of sexual transmission of HCV.

Another study found an almost two-fold greater increase in HCV transmission from coinfected partners. Nine of 98 (9.2%) individuals with coinfected partners were anti-HCV-positive; anti-HCV prevalence dropped to 2 of 49 (4.1%) among partners of individuals with HCV alone (P=0.2) (Lissen 1993). Higher HCV RNA levels may increase the risk of HCV transmission. HCV RNA levels increase after HIV infection, and may remain up to ten times higher than in HCV mono-infection (Bonacini 2000, Collier 1998).

One study has looked at factors influencing the presence of HCV RNA in the semen of 35 HIV/HCV coinfected men. HCV RNA was detectable (intermittently) in the semen of 25.7% (9). No correlation between the presence of HCV RNA in semen and the amount of HCV RNA in blood was found, nor was there any correlation with the presence of seminal HCV RNA and duration or treatment of HIV infection, CD4 cell count, HIV viral load, or presence of HIV RNA in semen (Pasquirer 2003).

The Multicenter Hemophilia Cohort study found a three-fold increase in HCV viral load of coinfected men, although there was no significant association between higher HCV RNA levels and sexual transmission. One of 42 males with HCV monoinfection transmitted hepatitis C to his female partner; 20 of the 343 coinfected men transmitted HCV to their female partners (2.3% vs. 5.8%). While HCV viral load was significantly higher among coinfected men, men with HCV-positive partners did not have significantly higher HCV viral loads than those with HCV-negative ones. Each one-log increase in HIV viral load increased HIV transmission risk by 1.37-fold, although higher HCV viral loads were not significantly associated with increased risk of HCV transmission (Hisada 2000).

The presence of other sexually transmitted diseases (STDs) may be a possible cofactor for HCV transmission. An analysis of non-IDU patients at an STD clinic found HCV antibodies among 7% of men and 4% of women. Females with an HCV-positive male sex partner were 3.7 times more likely to be positive than those with HCV-negative male sex partners (Thomas 1995). The presence of HCV antibodies was associated with greater numbers of sex partners and with other STDs (HIV and trichomonas).

Sexual Transmission Among Men Who Have Sex With Men (MSM)

Higher-than-average HCV prevalence has been documented among men who have sex with men (MSM) in a number of studies, but controversy about the risk of sexual transmission due to specific sexual acts remains unresolved, as information about particular sexual acts was not collected

consistently or with sufficient detail. More detailed information on sexual behavior is needed to help guide prevention initiatives and risk-reduction strategies for MSM.

One study associated specific sexual practices with HCV infection in a group of MSM. Craib and colleagues studied blood samples and self-administered questionnaires from 662 MSM. The questionnaires were completed between 1982 and 1985, and the serum samples were collected between 1982 and 1998—therefore, some of the samples were collected years after the completion of questionnaires, and may not have reflected changes in sexual behaviors over time. HCV antibodies were detected in 39 (5.9%) study participants. HIV-positive men were significantly more likely to have HCV antibodies than HIV-negative men (31/352, or 8.8% vs. 8/310, or 2.6%; $P<0.001$). Nineteen HCV-positive MSM reported no history of IDU. Questionnaire data from these 19 men was compared to data from 589 HCV-antibody negative men with no IDU history. Oral-anal contact (rimming) and insertive fisting were significantly associated with HCV ($P=0.029$ for rimming; $P=0.012$ for insertive fisting) (Craib 2001).

Other studies failed to significantly correlate specific sexual acts or number of sex partners and HCV infection. Bodsworth and colleagues studied 1,075 homosexual or bisexual men in Sydney, Australia, and found a 7.6% HCV seroprevalence. Although more HIV-positive men had HCV antibodies than HIV-negative ones (OR, 3.14; $P<0.0001$), no significant difference was reported in the number of sex partners between HCV-negative and HCV-positive men. HCV-negative men reported engaging in anal receptive intercourse without ejaculation, unprotected oral-anal sex (rimming), and insertive fisting more frequently than HCV-positive men. The only factors significantly associated with anti-HCV-positivity were IDU in the previous six months (OR, 7.24; $P<0.001$) and HIV infection (Bodsworth 1996).

Buchbinder and colleagues recruited 435 homosexual men from an STD clinic in 1983–1984. When stored plasma samples were tested for anti-HCV antibodies and behavioral data were analyzed, a history of IDU was the only variable independently associated with anti-HCV-positivity. After controlling for IDU, no significant association was found between sexual practices and anti-HCV-positivity. Overall HCV seroprevalence was 9.2%; among men with a history of IDU it was 25%, vs. just 5% among non-IDUs, making it harder to assess sexual risk factors due to the small sample size.

Donahue and colleagues found HCV seroprevalence of 1.6% in a cohort of 926 homosexual men. There was no association between anti-HCV seroprevalence and the number of sex partners, anal or oral receptive sex, HIV status or history of STD infection. The only associations found were with history of IDU and prior hepatitis A infection (Donahue1991).

Danta and colleagues identified 23 cases of acute HCV in a group of HIV-positive MSM between 2001 and 2003. All had engaged in unprotected anal intercourse; 70% identified fisting and group sex as risk factors and 43% had other sexually transmitted infections, while only 17% had injected drugs (Danta 2003).

Sexual transmission of HIV between men is far more efficient than male-to-male sexual transmission of HCV. A cohort analysis of European homosexual men estimated a cumulative incidence of anti-HCV positivity of 4.1% between 1981 and 1984, with no seroconversions between 1984 and

1989 (Melbye 1990). In the same cohort, the cumulative incidence of HIV from 1981 to 1984 went from 8.8% to 24%; between 1984 and 1989, incidence rose to 30.1%.

Mother-to-Infant Transmission

One hundred and seventy million people worldwide are infected with hepatitis C; of these, 35% are women in childbearing years. Using a conservative estimate of the likelihood of mother-to-infant transmission, with an annual fertility rate of 2%, between 10,000 and 60,000 babies will be infected with HCV each year (Yeung 2001). Mother-to-infant transmission rates vary widely; in their meta-analysis of 77 mother-to-infant transmission studies, Yeung and colleagues found HCV transmission rates ranged from zero to 35.3%. Roberts and colleagues found higher weighted rates of mother-to-infant transmission among viremic Japanese and Italian mothers (6.9% and 5.6%, respectively) than among other viremic women studied (3.1%) (Roberts 2002).

Careful follow-up and repeat testing of babies born to mothers with HCV infection is necessary to ensure proper diagnosis or exclusion of HCV infection. Maternal antibodies to HCV can be found in uninfected infants for up to 18 months after birth, and RNA levels can seesaw from undetectable to detectable while liver enzymes stay normal (Thomas 1999). In an analysis of 441 HCV-positive mothers and their infants, 50% of the uninfected infants became anti-HCV-negative by eight months, and 95% were anti-HCV-negative by 13 months. PCR sensitivity increased with age; in the infant's first month, sensitivity was 22%; after one month of age, sensitivity rose to 97% (Gibb 2000).

The specific mechanisms involved with mother-to-infant transmission are unclear; studies suggest that multiple factors may be involved. Maternal HCV transmission may occur in utero, intrapartum, or postpartum. Resti and colleagues found that 6 of 13 infants who acquired HCV infection had detectable HCV RNA directly after birth, which argues for in utero transmission of HCV (Resti 1998). The presence of HCV RNA in cord blood is difficult to interpret because of potential contamination with maternal blood; therefore it cannot be interpreted definitively as evidence of mother-to-infant transmission in utero. Although HCV RNA has been detected in amniotic fluid, its presence does not offer de facto proof of in utero HCV transmission (Delamare 1999). Azzari and colleagues have observed a greater likelihood of mother-to-infant transmission when active viral replication in peripheral blood mononuclear cells (PBMCs) is present. Replicating HCV was found in PBMCs from 5 of 13 mothers who had HCV-infected infants; none was detected in the mothers who had uninfected infants ($P=0.0001$) (Azzari 2000).

The effect of mode of delivery remains controversial. Some research has found a greater likelihood of mother-to-infant transmission of HCV with vaginal delivery; other research has failed to support this conclusion (Conte 2000; Granovsky 1998; Okamoto 2000; Paccagnini 1995; Resti 1998; Roberts 2002; Tajiri 2001). Delivery via elective caesarean section may lower the risk of mother-to-infant transmission of HCV. In a meta-analysis of 363 cases of mother-to-infant transmission, the rate of HCV transmission was 4.3% for vaginal deliveries vs. 3.0% for elective caesarean deliveries (Yeung 2001).

The single factor that has been linked to mother-to-infant transmission across many studies is the level of maternal HCV RNA. Although there is no known transmission threshold for HCV RNA,

a lower viral load should reduce the likelihood of transmission. A meta-analysis of 77 mother-to-infant transmission studies, using consistent criteria for identification of infected infants, identified a rate of transmission of 1.7% for mothers with antibodies to HCV; when this analysis was restricted to viremic mothers, the rate rose to 4.3% (Roberts 2002). A study of 105 HCV-infected mothers and their infants found a 6.6% rate of transmission; only viremic mothers transmitted HCV (Dal Molin 2002). Other mother-to-infant transmission studies of 63, 30, and 22 HCV-monoinfected women reported that all infected infants had viremic mothers (Sabatino 1996; Spencer 1997; Resti 1995). In an examination of potential risk factors among seven HCV-infected infants, Ohto and colleagues found that non-transmitting mothers had lower HCV titers than transmitting mothers (Ohto 1994). HCV RNA levels may increase during the second and third trimesters of pregnancy (Gervais 2000; Paternoster 2001).

Women coinfected with HIV generally have higher HCV RNA levels, which are associated with a greater risk of mother-to-infant transmission of HCV (Okamoto 2000; Roberts 2002; Tajiri 2001; Yeung 2001). In a meta-analysis of eight studies on HCV transmission among mothers with and without HIV, the rate of hepatitis C transmission from coinfected mothers to their infants was 19.4% vs. just 3.5% in mothers with HCV alone (Yeung 2001). The Women and Infants Transmission Study (WITS) followed 155 infants born to HIV/HCV coinfected mothers for 36 months after birth. Overall, 8.4% (13) of the infants were infected with HCV. The incidence of HCV infection among the HIV-positive infants was 3.2-fold higher than that of HIV-negative infants. While 17% (7/41) of the HIV-positive infants were coinfected with HCV, only 5% (6/112) of the HIV-negative infants were infected with HCV (Thomas 1998). In the Mothers and Infants Cohort Study, incidence of mother-to infant transmission of hepatitis C was 4% among HCV-infected mothers and 7% among HIV/HCV coinfected mothers (Granovsky 1998).

The hepatitis C virus has been detected in genital secretions from HIV/HCV coinfected women (Nowicki 2003; Rakela 2003); this may be involved with mother-to-infant transmission of hepatitis C. Rakela and colleagues found HCV RNA in the cervicovaginal lavage (CVL; a washing technique) from 18/62 (28%) HIV/HCV coinfected women. The presence of HCV RNA in CVL was significantly associated with the presence of HIV RNA in CVL ($P=0.03$) (Rakela 2003).

Researchers have found an increased risk of mother-to-infant transmission among women with a history of IDU or current IDU. In an analysis of six studies which included mothers with and without past or current IDU, the rate of HCV transmission among mothers with a history of IDU was 8.6% vs. 3.4% among mothers with no IDU history (Roberts 2002). A multisite study of 1,372 HCV-infected mothers and their infants found increased rates of mother-to infant transmission in current and former IDUs; no difference in the rate of hepatitis C transmission by HIV status was observed. The overall rate of mother-to-infant transmission of HCV was 7.1% (98/1,372). Among a subgroup of 1,178 HIV-negative mothers, transmission from those with a history of IDU was 10.8% (33/305) vs. 4.8% (42/873) from those without. A few mothers were active IDUs during pregnancy (23/ 461); 13% of this group transmitted HCV to their infant (Resti 2002). In another study, Resti and colleagues followed 403 mother-infant pairs for over two years. Transmission rates were significantly lower among women with no known risk for hepatitis C than women with a history of transfusion or IDU ($P=0.0063$). Mother-to-infant transmission of hepatitis C occurred in 8% of infants born to women with a history of IDU and 10% born to mothers who had received a transfusion, vs. 1% transmission from mothers with no known risk.

Although HCV RNA has been found in breast milk and colostrum, breastfeeding does not appear to pose a significant risk for mother-to-child transmission of HCV, so long as the mother's nipples are intact (Kumar 1998; Roberts 2002). In an analysis of ten studies of mother-to-infant transmission of HCV, the rate of transmission among breast-fed infants was 3.7% vs. 3.9% for non-breast-fed infants (Yeung 2001). The risk of mother-to-infant transmission from breastfeeding may increase when mothers have higher virus loads or postpartum flares of hepatitis C.

There are no known interventions to decrease the risk of mother-to-infant HCV transmission. Elective caesarean sections may slightly decrease mother-to-infant transmission of HCV, but this remains controversial. Treatment of HCV during pregnancy is contraindicated. Ribavirin is known to be teratogenic. Interferon is contraindicated in infants less than two years old because of neuro-toxicity. A large observational study utilizing state-of-the-art, standardized diagnostic guidelines for mothers and infants is needed to identify routes of transmission and risk reduction strategies. In addition, all pregnant women should be offered HCV testing as part of their routine prenatal care.

Recommendations

Implement national surveillance for chronic hepatitis C infection.

The Center for Disease Control's (CDC's) Third National Health and Nutrition Examination Study (NHANES III), conducted from 1988 to 1994, estimated that 1.8% of the United States population—or 4 million people—have been infected with HCV; 2.7 million remain chronically infected. NHANES III may have significantly underestimated the true prevalence of HCV infections in the United States since incarcerated and homeless individuals were not included in the populations surveyed. HCV prevalence among this country's 1.8 million incarcerated persons is estimated at 30% to 40% (Reindollar 1999). A 2002 survey of 597 homeless veterans found an HCV seroprevalence of 41.7% (Cheung 2002). Epidemiological studies need to include high-risk and high-prevalence populations to obtain accurate estimates of hepatitis C prevalence.

The CDC's Sentinel Counties Study of Viral Hepatitis provides data on the incidence of acute HCV infections. At present, only a pilot program—sentinel surveillance for physician-diagnosed chronic liver disease—tracks both acute and chronic HCV infections. National surveillance of chronic hepatitis C infections is necessary to forecast disease burden and provide a sound basis for planning allocation of adequate resources for prevention, education, care, and treatment programs. Funding for implementation of the CDC's 2002 *Guidelines for Viral Hepatitis Surveillance and Case Management* must be allocated by Congress and the Administration.

Clarify the risk of non-injection drug use behaviors associated with HCV transmission.

Conflicting data have emerged about the risk of HCV infection from intranasal drug use (i.e., snorting or sniffing)(Conry-Cantilena 1996; Murphy, 2000). There has also been speculation about HCV transmission from shared crack pipes, since frequent users often have burned or split lips from heated glass crack pipes. NHANES III participants were asked about drug-use history, although they were not specifically asked whether they had ever injected drugs. Because drug-taking modes—snorting or smoking vs. injecting—were not recorded in NHANES III, no estimate of the actual incidence of HCV transmission via intranasal drug use can be made from those data.

Research on the risk of intranasal drug use must clarify questions about this mode of drug administration as a potential route of transmission. Further investigation of the risk of HCV infection from smoking crack or other drugs is also needed. Studies must be designed to elicit accurate information about drug use. Pending more definitive data, educators and medical providers should incorporate appropriate and responsible messages on intranasal transmission risk. The National Institutes of Health and the Centers for Disease Control must fund research on HCV transmission from non-injection drug use.

Clarify routes and risks of sexual HCV transmission.

HCV can be sexually transmitted, although the relative risk and mechanism of sexual transmission remain controversial. A number of studies have documented higher-than-average anti-HCV prevalence among men who have sex with men (MSM), sex workers, individuals who have had multiple partners, and partners of HIV/HCV-coinfected individuals (M. J. Alter 1988; M. J. Alter

2002; Bodsworth 1996; Buchbinder 1994; Eyster 1991). Most research on sexual transmission of HCV has not collected information about specific sexual acts.

Research on HCV transmission must employ direct questions about sexual behaviors. Mucosal transmission by oral, penile, vaginal, and anal routes must be investigated as well as sexual practices that may involve the exchange of blood. Information about the risk associated with specific sexual practices is needed to inform prevention program messages and individual decision-making about risk reduction to prevent HCV transmission. NIH and CDC must fund research on routes and rates of sexual transmission of HCV among MSM, individuals with multiple partners, and partners of HIV/HCV-coinfected individuals.

Research mechanisms and interventions to decrease the rate of mother-to-infant HCV transmission.

If 35% of the 170 million people infected with hepatitis C worldwide are women in childbearing years with an annual fertility rate of 2%, 10,000–60,000 newborns will be infected with HCV each year (Yeung 2001). At present, no interventions have been identified to prevent mother-to-infant transmission of HCV, although some data suggest that transmission may be reduced by elective caesarean (Okamoto 2000; Paccagnini 1995; Yeung 2001). Well-designed studies using standardized diagnostic guidelines for mothers and infants will elucidate factors involved in mother-to-infant transmission of HCV and assist in development of strategies for risk reduction and prevention of mother-to-infant transmission. This research should be funded by NIH and CDC.

Develop and implement HCV prevention strategies for the developing world.

Globally, an estimated 170 million people, or 3% of the world's population, may be infected with hepatitis C (World Health Organization in collaboration with the Viral Hepatitis Prevention Board 1999). HCV infections in the developing world are mainly acquired from unscreened, contaminated blood transfusions, unsterilized medical and dental equipment, and unsterilized instruments used for circumcision, scarification, tattooing, and traditional medicine. In some regions, injection drug use is also a major mode of HCV transmission. In developing and transitional countries, approximately 16 million injections are given each year in formal and informal medical settings; one-third are with reused, unsterilized injection equipment (Hutin 2003). An estimated 2.3 to 4.7 million new HCV infections occur each year in the developing world as a result of unsafe injections (Kane 1999).

In resource-poor settings, prevention of new HCV infections must be a priority. This will include implementing screening of donor organs, blood, and blood products; offering training on viral inactivation techniques, infection control procedures, and proper methods of sterilizing medical equipment (including injection equipment); promoting harm reduction; and providing access to sterile injection equipment for injection drug users. Prevention interventions need to be adapted to specific regions, cultures, and settings.

As antiretroviral scale-up occurs, strategies for prevention and treatment of HCV should be implemented in regions where HCV is prevalent, such as the former Soviet Union. The World Health Organization (WHO) must fund HCV prevention initiatives.

Provide HCV testing and education for high-risk and high-prevalence populations.

Less than half of United States city and county health departments provide hepatitis C counseling, and only 23% provide testing for HCV (National Association of City and County Health Officers. Hepatitis C/HIV Needs Assessment 2000). CDC must provide funding to make free, voluntary HCV testing available to high-risk and high-prevalence populations through city and county health departments.

In the United States, 94,000 injection drug users are between the ages of 12 and 17 (National Household Survey on Drug Abuse, 2000 and 2001). The incidence of HCV infection is highest among new injectors, with an estimated 50% to 80% of injection drug users (IDUs) becoming infected within a year of initiating injection drug use (Garfein 1996). Education about HCV transmission must be provided to young people before they become sexually active or begin injecting drugs. Information about prevention, transmission, diagnosis, natural history, and treatment of HCV must be provided and integrated within program activities for staff and clients of detoxification facilities, drug treatment programs, shelters, methadone maintenance programs, correctional facilities, and AIDS service organizations. Hepatitis C advocacy organizations can provide HCV educational materials and information; AIDS service organizations can be an important source of HIV-related information for clients of hepatitis C organizations. Collaboration among these entities will benefit people with HCV, the coinfected, active and recovering drug users, the homeless, and others who are infected or at risk. Public health funding from Congress and the Administration must be made available to support education, and state-contracted agencies must provide these services.

Institute CDC's recommendations for prevention of HCV transmission in hemodialysis facilities.

People receiving kidney dialysis are at risk for acquiring HCV infection when dialysis centers do not practice proper infection control procedures. A study that screened dialysis recipients for HCV antibodies at 40% of U.S. dialysis centers during December of 2000 reported that 8.4% tested positive (Tokars 2002). Other studies of dialysis recipients have reported anti-HCV prevalence ranging from 10% to 36% among adults and 18.5% among children (CDC 2001).

In April of 2001, CDC issued recommendations for preventing transmission of pathogens among chronic hemodialysis patients that included stricter infection control practices, regular monitoring of ALT levels, and HCV testing of dialysis recipients (CDC 2001). All dialysis facilities must implement these recommendations and be monitored by the appropriate licensing and regulatory bodies.

Increase access to sterile injection equipment.

More than three million people in the United States are injection drug users (National Household Survey on Drug Abuse, 2000 and 2001). Although a majority of new HCV infections in the United States result from drug injection using shared, unsterilized equipment, it has not been widely and openly acknowledged that hepatitis C is a disease of drug users. HCV prevalence among IDUs is estimated at 70% to 90% (M. J. Alter 1998; Donahue 1991; Garfein 1996; Thomas 1995). There is

ample potential for HCV transmission among new IDUs via shared syringes and other injection drug equipment (Thorpe 2002; Vidal-Trecan 2002).

Inadequate access to sterile syringes and injection equipment and restrictive one-for-one syringe exchange policies continue to fuel both the HCV and HIV epidemics. Federal, state and local barriers to syringe exchange programs must be removed; program expansion will require an increased commitment of resources and hence the overturning of the laws against syringe exchange funding. Legislation must be enacted to legalize pharmacy sale of syringes in the remaining states that prohibit over-the-counter sales without prescriptions, and all state and local public health programs must ensure that pharmacy sale of syringes is accessible and affordable.

Research on the efficacy of bleach as a disinfectant and identification of optimal disinfection practices for injection drug equipment should be funded by NIH and CDC.

Increase access to drug treatment and methadone maintenance programs.

Policies that create barriers to risk reduction must be changed. Currently, access to methadone is limited; of an estimated 810,000 opiate-dependent persons, only about 40,500 are known to be receiving methadone maintenance treatment (MMT) (Office of National Drug Control Policy 2000). According to the 1997 NIH Consensus Statement, *Effective Medical Treatment of Opiate Addiction*, "Of critical importance in improving MMT of opiate dependence is the recognition that, as in every other area of medicine, treatment must be tailored to the needs of the individual patient. Current Federal regulations make this difficult if not impossible. However well intended the FDA's treatment regulations were when written in 1972, they are no longer helpful. We recommend that these regulations be eliminated."

Methadone should be available by prescription to all those who need it, and coverage should be provided by private and public insurers.

In 2001, 6,096,000 Americans needed treatment for drug addiction, yet only 17.3% (1,054,000) received treatment at a facility specializing in addiction (National Household Survey on Drug Abuse 2001). Drug treatment must be available on demand.

Develop protocols for HCV counseling and testing for pregnant women, and offer voluntary HCV counseling and testing to pregnant women.

Infection through mother-to-infant transmission of HCV occurs in approximately 5% of children born to mothers with HCV (Yeung 2001). Screening pregnant women for hepatitis C is not a routine part of prenatal care, yet some pregnant women want to be tested for hepatitis C. The draft guidelines from the National Institute of Health's *Consensus Development Conference on Management of Hepatitis C: 2002* do not offer any guidance for HCV testing of infants or pregnant women. We urge CDC to develop guidelines for voluntary HCV counseling and testing of pregnant women and to recommend their incorporation as a routine part of prenatal care.

List of Terms Used in This Chapter

Anti-HCV: antibodies to hepatitis C.

Anti-HCV negativity: no antibodies to hepatitis C detected in the blood.

Anti-HCV-positivity: antibodies to hepatitis C detected in the blood.

Anti-HCV prevalence: the percentage of a population or group that has antibodies to hepatitis C at a given time.

Genotype: the genetic makeup of an organism.

HCV-negative: no antibodies to hepatitis C detected in the blood.

HCV-positive: antibodies to hepatitis C detected in the blood.

Incidence: the rate of occurrence of new cases of a particular disease in a population or group being studied.

Phenotype: visible characteristics of an organism created by the interaction of the genotype and the environment.

Phylogenetic: the evolutionary history of a virus.

Prevalence: the number of individuals with a condition in a specific population or group.

Seroprevalence (also HCV seroprevalence): the frequency of individuals in a population or group that have a particular element (antibodies to hepatitis C) in the serum of their blood.

Serostatus: the presence or absence of antibodies to an organism.

Serodiscordant: having a different serostatus than another person; used to describe a couple in which one person is anti-HCV positive and the other is anti-HCV negative.