

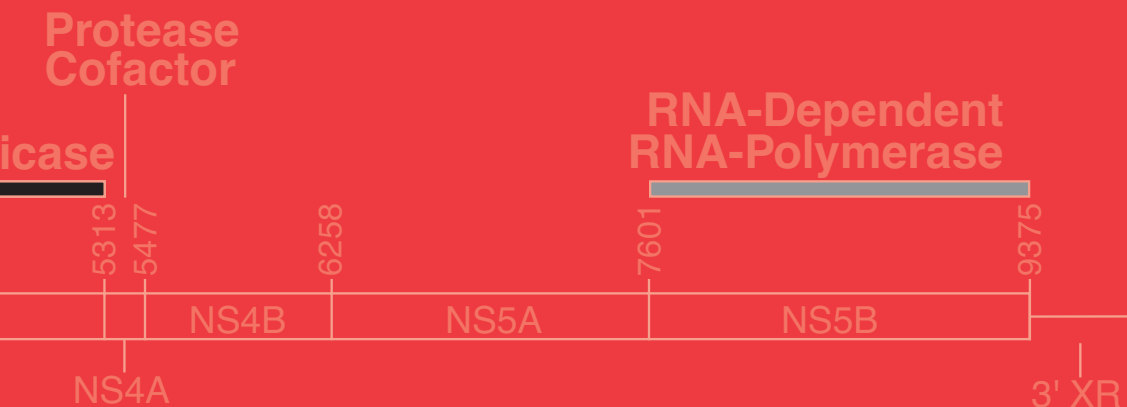


# Research & Policy Recommendations for Hepatitis C Virus (HCV)/HIV Coinfection

Critical Issues from TAG's forthcoming  
HCV/HIV Coinfection Report, version 2.0

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by Tracy Swan



## Credits

**Tracy Swan** is the author of TAG's upcoming Hepatitis C/HIV Coinfection Report, version 2.0. She is delighted to have the opportunity to bring together her experience in direct service, advocacy, education, program development, policy, and research for TAG. She created a Hepatitis C Program at Cambridge Health Alliance for active and recovering drug users, developed a curriculum for the Massachusetts Department of Public Health, provided HIV and HCV treatment education, and is a member of the Adult AIDS Clinical Trials Group's Community Constituency Group, as representative to the Liver Disease Subcommittee and the Immunology Research Agenda Committee.

**The Treatment Action Group (TAG)** fights to find a cure for AIDS and to ensure that all people living with HIV receive the necessary treatment, care, and information they need to save their lives. TAG focuses on the AIDS research effort, both public and private, the drug development process, and our nation's health care delivery systems. We meet with researchers, industry, and government officials, and resort when necessary to acts of civil disobedience, or to acts of Congress. We strive to develop the scientific and political expertise needed to transform policy. TAG is committed to working for and with all communities affected by HIV.

**Contact us.** TAG welcomes feedback and comments on this report and inquiries on our work. To comment directly on this report, please contact Tracy Swan by email at [tracyswan9@aol.com](mailto:tracyswan9@aol.com).

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# INTRODUCTION

The unfolding epidemic of hepatitis C virus (HCV) infection is a serious and growing problem. An estimated 170 million people around the world are infected. In the United States, at least four million people have been exposed to HCV, and 2.7 million of them have developed chronic hepatitis C. Chronically infected persons can either remain asymptomatic, progress very slowly, maintain mild to moderate liver scarring or develop serious liver damage, such as cirrhosis or hepatocellular carcinoma (HCC). Hepatitis C-related liver damage has become the chief cause for liver transplantation in this country, and ten to twelve thousand people die each year from HCV-associated end-stage liver disease (ESLD). HCV disease is a particularly severe problem for HIV-positive people. Up to a quarter of all people with HIV in the U.S. may be coinfecting with HCV. The progression of hepatitis C is accelerated in HIV-positive individuals, and HCV-related ESLD has become a leading cause of death in those with HIV.

The current state of research on HCV infection lags far behind that on HIV. For example, it is not yet possible to grow infectious hepatitis C virions in tissue culture, and there is still no adequate animal model for HCV infection or disease. These limits have seriously hampered the understanding of HCV's replication cycle and have impeded development of new treatments. The best current combination therapy for hepatitis C (pegylated interferon and ribavirin) fails at least half those who undergo treatment, and the range and severity of its side effects can seriously affect patients' quality of life, adherence, and chances for a successful outcome. Clearly more and better treatments are needed.

Although millions of Americans are infected and at risk for progression to serious disease, there is no federally funded infrastructure to coordinate education, prevention, testing, care, and treatment for HCV infection. The lack of a comprehensive plan to reduce HCV incidence—particularly through increasing access to sterile syringes—means that existing prevention programs have scattered and limited impact. Many individuals lack access to

costly HCV treatment, including the underinsured and uninsured, while cash-strapped AIDS Drug Assistance Programs (ADAPs) are in most cases unable to add expensive HCV care to their already overburdened portfolios. Prisoners, among whom hepatitis C is endemic, have had to resort to litigation to obtain treatment. Projections of HCV-related morbidity and mortality in mono- and HIV coinfecting individuals forecast a significant upsurge in health care costs, illness, and loss of life over the next twenty years. The time to step up action to address gaps in research and policy is now.

TAG's first hepatitis report, by Michael Marco and Jeffrey Schouten, released in July of 2000, was written to provide affected individuals, clinicians, researchers, educators and policy makers a detailed overview of hepatitis C and HIV/HCV coinfection. The report concluded with a set of research and policy recommendations (see Appendix A). In the spring of 2003, TAG will publish a new version of The Hepatitis C/HIV Coinfection Report that will include a revised and expanded set of research and policy recommendations for HCV and HIV/HCV coinfection research, prevention and care programs. These draft recommendations have been developed following a comprehensive literature review of more than 500 journal articles, abstracts from conferences on HCV and HIV/HCV, updated treatment guidelines, and interviews with HCV and HIV/HCV coinfecting individuals, researchers, physicians, harm reduction experts, health educators, public health officials, and activists and advocates from both the HCV and HIV communities.

The growing voice of HCV advocacy and the increasing attention given to HCV coinfection by HIV activists suggest that the timing is right for a broad-based coalition to press for a comprehensive research agenda and increased access to treatment. With these recommendations, TAG is hoping to broaden dialogue and collaboration among activists, policy makers, researchers, funders, educators and, especially, people with HCV and HIV/HCV coinfection.

# **EXECUTIVE SUMMARY: RESEARCH & POLICY RECOMMENDATIONS**

TAG's recommendations fall into six categories: 1) Epidemiology, Transmission, & Prevention; 2) Pathogenesis & Natural History; 3) Diagnostics; 4) Care & Treatment; 5) Key Treatment Questions in HIV/HCV Coinfection; and 6) Basic Research & Drug Development.

## **1. Epidemiology, Transmission & Prevention**

- 1a. Implement national surveillance for chronic hepatitis C infection.
- 1b. Increase access to sterile injection equipment.
- 1c. Provide HCV education for high-risk and high-prevalence populations.
- 1d. Clarify the risk of non-injection drug use (e.g., snorting or smoking) associated HCV transmission.
- 1e. Clarify routes and risks of sexual HCV transmission.
- 1f. Increase the focus on mother-to-child HCV transmission.
- 1g. Institute the CDC's recommendations for preventing HCV transmission at hemodialysis facilities.
- 1h. Develop and implement prevention strategies for the developing world.

## **2. Pathogenesis & Natural History**

- 2a. Establish prospective, longitudinal cohort studies of the natural history of HIV/HCV coinfection in the HCV treatment/HAART era.
- 2b. Investigate the role of genetic and ethnic factors in susceptibility to HCV infection, disease progression, and response to treatment.
- 2c. Investigate the role of sex differences in HCV disease progression.
- 2d. Investigate the influence of light-to-moderate alcohol consumption on HCV disease progression.

## **3. Diagnostics**

- 3a. Educate primary care providers about HCV infection, diagnosis, prevention, and treatment.
- 3b. Continue research on non-invasive testing methods to replace or reduce the need for liver biopsy.
- 3c. Identify and validate prognostic markers and effective screening methods for early diagnosis of hepatocellular carcinoma (HCC).

## **4. Care & Treatment**

- 4a. Develop integrated, multidisciplinary systems of care for individuals with multiple co-morbidities (HCV, HIV, mental illness, addiction).
- 4b. Develop guidelines for the care and treatment of coinfecting individuals.
- 4c. Promote screening and vaccination for hepatitis A and hepatitis B among individuals infected with HCV or coinfecting with HIV/HCV.
- 4d. Develop strategies to enhance HAV and HBV vaccine immunogenicity in HIV-positive individuals.
- 4e. Increase research on treatment safety and efficacy in understudied populations.
- 4f. Provide full access to hepatitis C care and treatment for all those in need.
- 4g. Provide full access to hepatitis C prevention, care and treatment services for incarcerated individuals.
- 4h. Increase research on strategies to manage side effects of HCV treatment.
- 4i. Identify optimal dosing strategies.

## **5. Key Research Questions in HIV/HCV Coinfection**

- 5a. Investigate sequencing of treatment for HIV and HCV.
- 5b. Establish a universal definition of hepatotoxicity and characterize its severity.
- 5c. Explore pharmacokinetics and drug levels in coinfecting individuals.
- 5d. Support access to and research on liver transplantation for HIV-positive individuals.

## **6. Basic Research & Drug Development**

- 6a. Support and intensify research into the molecular biology and immunopathogenesis of HCV infection.
- 6b. Support and accelerate the development of new therapeutic strategies.
- 6c. Include HIV/HCV coinfecting individuals in early-phase HCV treatment trials.
- 6d. Establish a hepatitis C clinical research network.

# 1. EPIDEMIOLOGY, TRANSMISSION & PREVENTION

## 1a. Implement national surveillance for chronic hepatitis C infection.

Hepatitis C virus (HCV) was identified in 1988, and the development of an antibody test soon followed (Choo 1989; Kuo 1989). 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 four million people—have been infected with HCV; 2.7 million remain chronically infected. Data from NHANES III may significantly underestimate the true prevalence of HCV infection 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 must include high-risk and high-prevalence populations to obtain accurate estimates of hepatitis C prevalence.

### United States HCV Prevalence

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

Alter 1999

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. The recommendations from CDC's Guidelines for Viral Hepatitis Surveillance and Case Management should be implemented (CDC 2002).

### **1b. Increase access to sterile injection equipment.**

Although the 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 injection drug users (IDUs) is estimated at 70% to 90% (Alter 1998; Donahue 1991; Garfein 1996; Thomas 1995). More than half of new hepatitis C infections are acquired through drug injection using shared, unsterilized equipment (Kim 2002). There is ample potential for HCV transmission among new IDUs via shared syringes and other injection drug equipment (Thorpe 2002; Vidal-Trecan 2002).

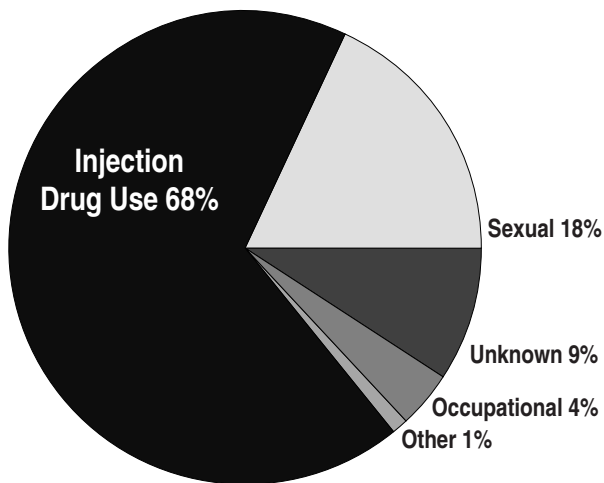
Although CDC recommends that syringes and injection equipment never be shared or used more than once, its Guidelines for Prevention and Control of Hepatitis C Virus Infection (1998) and Guidelines for the Prevention of Opportunistic Infections among HIV-Infected Persons (2002) state that shared injection equipment should be cleaned with bleach and water. The efficacy of bleach for neutralizing HCV has not been established (Hagen 2001).

Access to sterile syringes and injection equipment is vital to hepatitis C prevention. Research on the efficacy of bleach and identification of optimal disinfection practices for injection drug equipment is necessary as well. Policies that create barriers to risk reduction must be changed. Inadequate access to sterile syringes and injection equipment, restrictive one-for-one syringe exchange policies, limited access to methadone, and the unavailability of

drug treatment on demand continue to fuel both the HCV and HIV epidemics. 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 federal ban on 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 insure that pharmacy sale of syringes is accessible and affordable.

### Sources of HCV Infection 1995-2000

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Alter 2002

#### **1c. Provide HCV education for high-risk and high-prevalence populations.**

More than three million people in the United States are injection drug users; 94,000 are between the ages of twelve and seventeen (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 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 coinfecting, active and recovering drug users, the homeless, and others who are infected or at risk. Public health funding must be made available to support education, and state-contracted agencies must provide these services.

**1d. Clarify the risk of non-injection drug use (e.g., snorting or smoking) associated HCV transmission.**

Conflicting data have emerged about the risk of HCV infection from intranasal (i.e., snorting or sniffing) drug use (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; however they were not specifically asked if they had ever injected drugs. Because drug-taking modes—snorting or smoking versus injecting—were not recorded in NHANES III, no estimate of the actual incidence of HCV transmission via intranasal drug use can be made from that data. A study of HCV-infected blood donors revealed a significant reluctance to disclose even one-time use of injection drugs. Forty-two percent (103) of 248 HCV-positive donors who disclosed intravenous drug use during a self-administered questionnaire about recreational drug use had denied any intravenous drug use during their initial blood donation screening (Conry-Cantilena, 1996).

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.

### **1e. Clarify routes and risks of sexual HCV transmission.**

HCV can be sexually transmitted, although the relative risk of sexual transmission, and by what means, remain controversial. Several 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 coinfecting individuals (Alter 1988; Alter 2002; Bodsworth 1996; Buchbinder 1994; Eyster 1991). Most research on sexual HCV transmission 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 as well as individual decision-making about risk reduction to prevent HCV transmission.

### **1f. Sharpen the focus on mother-to-child HCV transmission.**

Worldwide, 35% of those infected with hepatitis C are women in childbearing years. Infection through mother-to-infant transmission of HCV occurs in approximately 5% of children born to mothers with HCV (Yeung 2001). The risk of HCV transmission increases if the mother is coinfecting with HIV or is a current or former injection drug user (Thomas 1998; Yeung 2001). At present, no interventions have been identified to prevent mother-to-infant transmission of HCV. Screening pregnant women for hepatitis C is not a routine part of prenatal care. 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.

Voluntary testing and counseling for hepatitis C should be offered as part of routine prenatal care. Standardized diagnostic guidelines for mothers and infants are necessary both in clinical practice and in research settings. Further research to elucidate factors involved in mother-to-infant transmission of HCV is needed to identify risk-reduction and prevention strategies.

**1g. 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, the CDC issued recommendations for preventing transmission of pathogens among chronic hemodialysis patients; they 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.

**1h. 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 (WHO 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 parts of the developing world, injection drug use is also a major mode of HCV transmission. In some regions, it is estimated that 2.3 to 4.7 million new HCV infections occur each year as a result of unsafe injections (Kane 1999).

Prevention of new HCV infections must be a priority in resource-poor settings. 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); and 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.

## **2. PATHOGENESIS & NATURAL HISTORY**

### **2a. Establish prospective, longitudinal cohort studies of the natural history of HIV/HCV coinfection in the era of HCV treatment and HAART.**

It is estimated that 16–25% of HIV-positive individuals in the United States are coinfecting with HCV, with substantially higher rates of coinfection among HIV-positive injection drug users (Thomas 2002; Sherman 2002). In the era of highly active antiretroviral therapy (HAART), HIV-related mortality has decreased significantly while HCV-related morbidity and mortality have become prominent in coinfecting individuals. End-stage liver disease from HCV is now a leading cause of death in coinfecting individuals (Bica 2001; Martín-Carbonero 2001; Monga 2001; Quintana 2002).

Pre-HAART-era data from cohorts of coinfecting hemophiliacs and injection drug users indicate that coinfection with HIV produces an accelerated course of HCV disease (Eyster 1993; Rockstroh 1996; Sánchez-Quijano 1995; Telfer 1994). In the HAART era, new questions and conflicting data about the efficacy of HAART in coinfecting individuals have emerged (Greub 2000; Law 2002; Sulkowski 2002). We need to increase our understanding of the complex interrelationship between these two viruses, as well as the impact of HAART and immune restoration. So far, most studies that have examined the effect of HCV on responses to HAART and clinical progression of HIV disease have not collected information about the progression or severity of underlying HCV disease. Without data on actual liver histology, it is impossible to determine

the severity of HCV disease, which may in turn affect an individual's ability to respond to HAART.

Well-designed, prospective longitudinal cohorts will be essential to follow infected populations, define prognostic factors and other cofactors for progressive disease, observe changing treatment outcomes over time, and generate productive hypotheses for pathogenesis, prevention, and treatment studies. Because treatment modalities for HIV and HCV will continue to evolve, cohort studies must be large enough and long enough to measure and account for variations in treatment, as well as other cofactors such as access to health care, drug use, ethnicity, and gender. Barriers to enrollment such as invasive needle biopsies can be addressed by being restricted to intensified substudies, if necessary. In any case, full participation of coinfecting persons and advocates will be essential in planning and implementing such cohort studies.

**2b. Investigate the role of genetic and ethnic factors in susceptibility to HCV infection, disease progression, and response to treatment.**

Hepatitis C infection is twice as prevalent among black Americans as white Americans. The highest observed prevalence of hepatitis C in the United States—a shocking 9.8%—occurs among black males aged 40 to 49 (Alter MJ 1999). African-Americans appear less likely to achieve spontaneous viral clearance of HCV (Thomas 2000; Villano 1999). In addition, race appears to have a substantial impact on the efficacy of interferon. Significantly lower treatment response rates have been observed in blacks than in whites, Latinos, or Asian-Americans (Jeffers 2002; McHutchison 2000; Reddy 1999). Research is needed to understand the mechanisms that account for these disparities and to identify strategies to improve treatment response.

**2c. Investigate the role of sex differences in HCV disease progression.**

High rates of spontaneous viral clearance have been observed in two cohorts of premenopausal women, and some evidence suggests that the course of hepatitis C disease in this population may be

less severe (Benhamou 1999; Kenny-Walsh 1999; Poynard 1997; Weise 2000). No research has explored why female sex appears to be a favorable prognostic factor. The role of hormones, immunological differences between males and females, lower body mass, and socioeconomic factors all warrant further investigation.

## **2d. Investigate the influence of light-to-moderate alcohol consumption on HCV disease progression.**

A large body of data has confirmed that alcohol consumption of more than 50 grams per day accelerates the progression of HCV-related liver disease (Harris 2002; Poynard 1997; Thomas 2000). The effect of light-to-moderate alcohol consumption on hepatitis C disease progression is unknown. Without more specific information, most clinicians simply recommend abstinence from alcohol; data to support or modify recommendations of abstinence are needed.

## **3. DIAGNOSTICS**

### **3a. Educate primary care providers about hepatitis C infection, diagnosis, prevention, and treatment.**

Acute hepatitis C infection is clinically silent for most infected people, with only 15% to 20% of individuals developing symptoms (Koretz 1993). Symptoms, when they occur—low-grade fever, fatigue, appetite loss, abdominal pain, nausea, and vomiting—are typical of many common viral infections. Chronic hepatitis C infection is also often asymptomatic, and both acute and chronic hepatitis C infections may go undiagnosed by physicians who fail to ask about the risk factors (Shehab 2001; Shehab 2002; Villano 1999).

Additionally, many physicians are unaware of the proper procedures for diagnosing hepatitis C (Shehab 1997). HIV-positive individuals (especially those with fewer than 200 CD4 cells), injection drug users, and transplant recipients may harbor occult hepatitis C infection (Beggren 2001; Beld 1999; Busch 2001; Lin 2002; Thomas 1995). Performing HCV RNA testing in these populations, even when an antibody test result is negative, can sometimes

identify infections that might otherwise go undiagnosed. Professional educational programs, cross-disciplinary training, and public health initiatives are needed to increase knowledge of hepatitis C transmission, prevention, diagnostics, care, and treatment among health care providers at all levels.

### **3b. Continue research on non-invasive testing methods to replace or reduce the need for liver biopsy.**

Liver biopsy is still the only way to assess the condition of liver tissue. Information from liver biopsy is used to assess the degree of inflammation, gauge hepatic cell death and damage, identify other causes of liver injury, and guide treatment decisions. Although fatalities from biopsy are extremely rare (0.01–0.1%), liver biopsy can be painful, and occasional complications such as hemorrhage or puncture of adjoining organs may occur. The risk of complications and the potential pain of the procedure have made liver biopsy unpopular with many patients. Sampling errors and variations among observers may result in serious diagnostic errors (Bejarno 2001). Providing sedation during the procedure can reduce associated pain, while using ultrasound to guide the biopsy reduces the risk of complications and sampling errors (Cadranell 2000; Pokorny 2002; Soyer 1993).

Alternatives to liver biopsy using panels of serum biochemical markers have been proposed and are under investigation. Although these tests may serve as substitutes when biopsy is contraindicated or refused, the information they yield is far less precise. The identification, development, and validation of a non-invasive, cost-effective replacement for liver biopsy would be an important breakthrough. In the meantime, to reduce the risk of pain, complications, and sampling errors, experienced physicians guided by ultrasound should perform liver biopsy, and pain management should be provided to those undergoing biopsy. A standardized and simplified system for evaluating the results of liver biopsy in research and clinical care settings should be instituted, and biopsies should be read by pathologists who are skilled at reviewing liver biopsies.

### **3c. Identify and validate prognostic markers and effective screening methods for early diagnosis of hepatocellular carcinoma (HCC).**

Hepatocellular carcinoma (HCC) is a known complication of hepatitis C. In the United States, the incidence of HCC in the general population has increased from a rate of 1.4 cases per 100,000 in 1976–1980, to 2.4 cases per 100,000 during the period 1991–1995 (El-Serag 1999). This rise may reflect an epidemic of increased HCV transmission that occurred decades earlier. The annual incidence of HCC in hepatitis C-infected cirrhotics ranges from 1% to 4% (Di Bisceglie 1997; Lauer 2001).

HCC can be identified by measuring alpha-fetoprotein (AFP) levels and by ultrasound imaging, but the value of these tests for early detection of HCC in cirrhotic individuals has not been sufficiently demonstrated. The sensitivity and specificity of AFP levels in the detection of HCC varies considerably (from 39–64% and from 76–91%) in different studies (Collier 1997). Some research has shown that ultrasound surveillance increases early detection of HCC, but without reducing mortality (Larcos 1998; Solmi 1996). HCC mortality is extremely high, with five-year survival rates of less than 5% (El-Serag 1999). Better interventions to facilitate the early diagnosis of HCC and reduce the high fatality rate are urgently needed.

## **4. CARE & TREATMENT**

### **4a. Develop integrated, multidisciplinary systems of care for individuals with multiple co-morbidities (HCV, HIV, mental illness, addiction).**

Individuals with hepatitis C are often grappling with other issues: HIV coinfection, the stress involved with illicit drug use, maintaining recovery from addiction, severe, debilitating fatigue, poverty, homelessness, or incarceration. HCV is more prevalent among the mentally ill; moreover, individuals with HCV have a greater prevalence of depression (Zdilar 2000).

Our health care system is not prepared to accommodate the needs of active users or dually and triply diagnosed individuals. Multidisciplinary systems of care have been proven successful in treating active users, coinfecting individuals with addiction and psychiatric co-morbidities, and individuals in a methadone maintenance program (Backmund 2001; Schwartzapfel 2002; Sylvestre 2002). Cross-disciplinary care should become an integral part of the care and treatment of people living with HCV and HIV/HCV coinfection.

#### **4b. Develop guidelines for the care and treatment of coinfecting individuals.**

No one has yet integrated the recommendations from the Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents (USPHS 2002) and the National Institutes of Health's 2002 Consensus Statement on the Management of Hepatitis C (NIH 2002). Some infectious disease doctors providing care for both HIV and HCV may be more focused on HIV disease. Referral to a gastroenterologist is not always feasible and, if available, the gastro-enterologist may not be well informed about the clinical management of HIV. Adapting, integrating, and updating existing recommendations from the HIV-HCV International Panel under the aegis of an ongoing guidelines panel of the U.S. Public Health Service could address these concerns. Such guidelines would provide an essential resource for clinicians, treatment educators, treatment advocates, and coinfecting individuals.

#### **4c. Promote screening and vaccination for hepatitis A and hepatitis B among individuals infected with HCV or coinfecting with HIV/HCV.**

Individuals infected with HCV are at risk for severe, potentially fatal disease if they become coinfecting with hepatitis A (Koff 2001; Pramoolsinsap 1999; Vento 1998; Vento 2000). Coinfection with hepatitis B may accelerate progression of an existing hepatitis C infection or even cause liver failure and death (Koff 2001; Liaw 2000). Because of these risks, CDC recommends vaccination against HAV and HBV for all individuals infected with or at risk for HCV infection. Yet many are not receiving vaccinations. A survey

of primary care physicians found that only 1.6% of their HCV patients were vaccinated against HAV and only 3% had been vaccinated against HBV (Nicklin 1999).

Physicians, health educators, and direct service staff need to be educated about the importance of vaccination against HAV and HBV. Screening and vaccination initiatives are needed. Vaccination should be available in correctional facilities and outside of clinic and hospital-based settings, especially in venues such as syringe exchange programs, substance abuse treatment programs, shelters, and methadone maintenance clinics, where high-prevalence and high-risk groups receive services. Screening and vaccination should be provided free of charge. Public health funding must be available for these services.

#### **4d. Develop strategies to enhance HAV and HBV vaccine immunogenicity in HIV-positive individuals.**

Although vaccinations for hepatitis A and B are safe in HIV-positive individuals, vaccine immunogenicity is decreased, especially those with low CD4 cell counts (Bruguera 1992; Hess 1995; Neilson 1997; Puoti 2002). The CDC estimates that only 66–75% of HIV-positive individuals develop protective antibody responses after vaccination for HAV. The efficacy of HBV vaccination in HIV-positive individuals is unclear, and an optimal strategy to enhance immunogenicity is needed. Response testing after vaccination and use of additional doses have been proposed as possible interventions to improve HBV vaccine response in people with HIV (CDC 1993).

Research on interventions to enhance the immunogenicity of HAV and HBV vaccines in HIV-positive persons should be prioritized.

#### **4e. Increase research of treatment safety and efficacy in understudied populations.**

Most of the studies of HCV treatment efficacy and safety have focused on populations with favorable prognostic factors. Individuals with medical and psychiatric co-morbidities have been excluded from the pivotal studies of peg-interferon and ribavirin, and results from these trials may not be applicable to a majority of

individuals with HCV infection. More research is urgently needed on the safety, efficacy, and optimal dosing and duration of HCV treatment in HIV-positive individuals, cirrhotics, African-Americans, active drug users, individuals on methadone maintenance, the mentally ill, transplant recipients, individuals with renal disease, individuals with autoimmune conditions, the elderly, young children, adolescents, and non-responders and relapsers after prior HCV treatment.

**4f. Provide full access to hepatitis C care and treatment for all those in need.**

Current treatments for HCV can cost up to \$40,000 per year. The uninsured, underinsured, and those ineligible for patient assistance and entitlement programs go untreated, even when treatment is urgently needed. Cash-strapped AIDS Drug Assistance Programs (ADAPs) are unable to offer the latest HCV treatments; fewer than ten of them have the resources available to provide pegylated interferon and ribavirin.

Advocacy efforts to increase access to HCV treatment must continue. Entitlement programs and private insurers should cover the costs of HCV treatment, including laboratory monitoring and medications to manage its side effects. ADAPs must receive the necessary funding from Congress to cover HCV treatment. Strategies must be developed to provide coverage for HCV therapy among the uninsured who do not qualify for entitlements or patient assistance programs.

**4g. Provide full access to hepatitis C prevention, care and treatment services for incarcerated individuals.**

In the United States, 1.8 million individuals are incarcerated. HCV infection is endemic among prisoners; a 1994 study of HCV prevalence among 4,513 inmates (87% male; 13% female) in the California correctional system reported that 39.4% of the males and 53.5% of the females were HCV-antibody-positive (Ruiz 1999). The need for HCV treatment remains largely unmet in correctional systems. Policies about HCV treatment in prison differ in every state, and incarcerated individuals do not have uniform

access to treatment for HCV. Some inmates have had to resort to legal action to obtain treatment. This is an unacceptable situation. State and national advocacy efforts to demand access to HCV treatment for inmates must be intensified.

CDC's new guidance document on Prevention and Control of Infections with Hepatitis Viruses in Correctional Settings is a useful tool for advocates. CDC recommends medical evaluation of all inmates who are HCV antibody-positive and establishment of criteria for HCV treatment based on current treatment guidelines, and that treatment should be conducted in consultation with a specialist familiar with treatment regimens for HIV and HCV (CDC 2003).

#### **4h. Increase research on strategies to manage side effects from HCV treatment.**

The side effects of treatment for hepatitis C range from the uncomfortable to the life threatening. In a recent 1,100-person phase III trial of peg-interferon alfa-2a (with placebo or ribavirin) versus interferon alfa-2b, the rate of treatment discontinuation due to adverse events and/or laboratory abnormalities was 10% in the peg-interferon/ribavirin arm and 11% in the standard interferon arm. Dose reductions were necessary for 32% of the individuals in the peg-interferon/ribavirin arm (Fried 2002a). Significant dose reductions may have an impact on the response to treatment (Fried 2002a; McHutchison 2002).

A report on adverse events from a recent trial comparing peg-interferon alfa-2b and ribavirin to interferon alfa-2b and ribavirin found that more than 20% of participants in each arm experienced fatigue, headache, fever, muscle aches and stiffness, insomnia, nausea, hair loss, irritability, joint pain, loss of appetite and weight loss, depression, and injection site reactions (Manns 2001). The list of serious adverse events associated with interferon treatment, although occurring in fewer than 1% of individuals studied so far, is daunting and includes severe neuropsychiatric complications and suicidal ideation, as well as skin, kidney, blood, liver, heart, and autoimmune diseases and sensory organ disorders (Fried 2002b).

Research to increase the tolerability of, and adherence to, HCV treatment is a priority. More research is needed to identify the proper threshold to initiate the use of growth factors to treat anemia and neutropenia, and to study their impact on HCV treatment efficacy. Interventions to decrease neuro-psychiatric side effects are a priority: the instruments used to screen for depression—both prior to initiation of HCV treatment and during treatment—have not been validated for this purpose. More exploration of the instruments used to diagnose depression and evaluation of the efficacy, side effects, and indications of selective serotonin reuptake inhibitors (SSRI), other antidepressants, and anti-anxiety agents is needed to optimize individual side effect management strategies.

#### **4i. Identify optimal dosing strategies.**

The two available pegylated interferons—peg-interferon alfa-2a (Pegasys, manufactured by Roche) and peg-interferon alfa-2b (Peg-Intron, manufactured by Schering-Plough)—use different types of PEG molecules to prolong the half-life of the interferon. Pegasys is premixed and given at a fixed dose, while Peg-Intron is dosed by weight and mixed prior to injection. Despite the lack of a head-to-head comparison, and despite the different methods of dosing, similar efficacy of the two products has been demonstrated. The overall rate of sustained virological response to treatment with Pegasys and Peg-Intron, combined with ribavirin, is 54% vs. 56%, respectively (Di Bisceglie 2002a).

Recent information from a pivotal study of Pegasys found that individuals with genotype 2 or genotype 3 responded to 24 weeks of therapy and a lower dose of ribavirin (800 mg) as well as those who received higher doses of ribavirin over 48 weeks. Individuals with genotype 1 obtained better responses with 48 weeks of treatment and a higher dose of ribavirin (1,000–1,200 mg) (Hadziyannis; unpublished data). With Peg-Intron, the recommended dose of ribavirin is 800 mg; this may be too low for individuals with genotype 1 and viral loads over 2,000,000 copies. The recommended duration of therapy (48 weeks) for Peg-Intron may be unnecessarily long for individuals with genotypes 2 and 3.

The full range and upper limit for weight-based dosing of Peg-Intron have not been adequately defined. Obese individuals typically have lower response rates, but it is unclear whether this is due to inadequate dosing of peg-interferon and ribavirin or to other poor prognostic factors, viral resistance, or a combination of these elements. For some, peg-interferon dosing may be too high, and dose reduction may be necessary to reduce hematologic problems.

In the absence of more effective and less toxic therapies for hepatitis C, questions about dosing variability must be addressed. More research needs to be conducted on optimal dosing and duration of therapy in other understudied populations, including individuals with acute hepatitis C infection, those with renal disease, advanced liver disease, non-responders to prior HCV treatment, those who have relapsed after treatment, children, individuals with autoimmune disorders, and transplant recipients.

## **5. KEY RESEARCH QUESTIONS IN HIV/HCV COINFECTION**

### **5a. Investigate sequencing of treatment for HIV and HCV.**

It is still unclear when antiretroviral therapy should be initiated in coinfecting individuals. Some studies have found a blunted immune response to HAART in coinfecting individuals (Greub 2000; Law 2002). Earlier initiation of HAART may help to preserve immune function. End-stage liver disease (ESLD) occurs more frequently in individuals with low CD4 cell counts (Goedert 2002; Ragni 2001). Thus, for coinfecting individuals, it is now critical to investigate whether earlier initiation of HAART—possibly earlier than today's recommended thresholds of 200-350 CD4 cells—will decrease the incidence and progression of ESLD among coinfecting individuals. Alternatively, since it may be possible to eradicate HCV in people who experience a sustained virological response (SVR) to therapy, early initiation of HCV treatment in HIV-positive individuals should also be explored. Preemptive treatment of HCV—even if an SVR is not achieved—may improve toleration of antiretroviral agents. Answering these questions will require allocation of resources for long-term treatment strategy studies.

## **5b. Establish a universal definition of hepatotoxicity and characterize its severity.**

Coinfected individuals often have elevated liver enzyme levels, which may be due to liver disease, the hepatotoxicity of anti-HIV medications, or both (Staples 1999). A universal definition of hepatotoxicity for research and clinical practice is needed to increase the consistency and interpretability of results from clinical trials, to guide antiretroviral treatment decisions and to enable the collection of consistent adverse event data.

Hepatitis C coinfection significantly increases the risk of hepatotoxicity from HAART (Lana 2001; Nunez 2001). Some individuals must discontinue HAART altogether because of liver toxicity; in other instances, only one drug must be switched. Hepatotoxicity has multiple causes, such as underlying liver diseases unrelated to HCV, fatty liver, alcohol consumption, genetic variation, antiretrovirals, or other medications. We need more research to understand if HAART-related hepatotoxicity worsens HCV disease, and to differentiate between transient elevations in liver enzymes and clinically significant indications of clinical progression.

## **5c. Explore pharmacokinetics and drug levels in coinfecting individuals.**

Up to 90% of HIV-positive individuals receive at least one hepatotoxic drug (Orenstein 2002). The potential for drug interactions in HIV-positive individuals is abundant even without hepatitis C coinfection; often, these individuals may be taking lipid lowering agents, methadone, anti-anxiety medications, prophylaxis against opportunistic infections, vitamins, herbs, supplements, and antiretrovirals.

Several important antiretrovirals are metabolized by the liver. HCV-related liver damage may diminish the liver's ability to metabolize these drugs. Drug levels may be elevated in individuals with liver disease, increasing side effects, interactions, and toxicities. The incidence of complications from antiretroviral therapy among coinfecting individuals needs further investigation and documentation. The contribution of specific classes and drugs to interactions, side

effects, and complications needs further study.

#### **5d. Support access to and research on liver transplantation for HIV-positive individuals.**

Although HAART has significantly increased the survival of HIV-positive individuals, their risk for end-stage liver disease remains significant. Some evidence has emerged in the HAART era indicating that HIV-positive individuals have post-transplantation outcomes equivalent to HIV-negative individuals (Gow 2001; Kuo 2001; Prachalias 2001; Ragni 1999). UNOS, the United Network for Organ Sharing, does not consider HIV infection to be a contra-indication for organ transplantation. Despite the emerging reports of favorable outcomes in HIV-positive individuals, insurers have sometimes denied reimbursement for transplants when HIV is involved, deeming it “experimental”. Expanding an indication to include people with HIV does not transform an established procedure into an “experiment”. Transplantation must be reimbursable for HIV-positive individuals.

Prospective studies of transplantation in HIV-positive individuals will provide vitally important information about the specific risks for those undergoing transplantation, as well as help to identify the optimal clinical management strategies for improved and extended survival of HIV-positive organ recipients.

### **6. BASIC RESEARCH & DRUG DEVELOPMENT**

#### **6a. Support and intensify research into the molecular biology and immunopathogenesis of HCV.**

The initial identification of hepatitis C (Choo 1989) ushered in a decade of productive virology and immunology research, as scientists began investigating the genetic structure of the virus, the role of viral proteins in HCV replication, the immune response to HCV, and how HCV causes disease. During the 1990s, researchers made significant inroads into understanding the structure and genetics of HCV. Scientists cloned the genome of various HCV strains (Choo 1991; Kato 1990; Takamizawa 1991) and characterized

the morphology of HCV through isolation of virions using electron microscopy (Kaito 1994; Li 1995; Shimizu 1996). Researchers also discovered the crystal structure of the key viral proteins serine protease (Kim 1996; Love 1996), helicase (Cho 1998; Kim 1998; Yao 1997), and RNA-dependent RNA polymerase (Ago 1999). Immunologists identified major epitopes recognized by HCV-specific cytotoxic T lymphocytes (Battegay 1995; Cerny 1995; Kita 1993; Koziel 1993; Koziel 1995), cells which are believed to play a key role in liver injury and cell death. Other groups made preliminary attempts at developing a cell culture system to model the HCV replication cycle using infectious complementary DNA clones (Kholykhalov 1997; Yanagi 1997) and subgenomic RNA replicons (Lohmann 1999).

In recent years, researchers have provided detailed evaluations of cell-mediated immune responses to HCV (Day 2002; Godkin 2002; Lauer 2002; Penna 2002; Rosen 2002a) and further clarified the viral replication cycle and viral-host cell interactions (Bartenschlager 2002; Shirota 2002; Spahn 2001; Takikawa 2000; Tellinghuisen 2002; Walewski 2001). Researchers still lack an efficient, reproducible cell culture system that can support viral replication and infection. However, the refinement of cell culture models, including more robust replicon systems (Blight 2000; Ikeda 2002), as well as a surrogate tissue culture system using GBV-B in tamarin hepatocytes (Beames 2000), enables the examination of the expression and function of viral proteins. Replicon systems have facilitated drug development efforts by allowing researchers to screen compounds for activity against viral proteins involved in the replication cycle, with the significant limitation that these replicons cannot infect new cells. While chimpanzees are the only other animals aside from human beings known to support HCV replication, progress has been made towards making a viable chimeric mouse model of hepatitis C infection (Mercer 2001). Despite these advances, numerous challenges remain. Key aspects of HCV pathogenesis and the viral replication cycle are not fully understood, and further work on cell culture systems and animal models remains an urgent priority.

Continued elucidation of the pathogenesis of HCV will be critical in leading to new therapies. Researchers have not conclusively

determined the receptors involved in HCV's entry into cells, though the roles of CD81 (Meola 2000; Roccasecca 2003; Takikawa 2000), the low-density lipoprotein receptor (LDL-R) (Germi 2002; Hennig 2002; Wunschmann 2000), and most recently the asialoglycoprotein receptor (ASGP-R) (Saunier 2003), have been explored. The potential roles of HCV proteins—particularly the core protein and NS5A—in the pathogenesis of fibrosis progression, hepatic steatosis, and hepatocellular carcinoma require investigation (Gimenez-Barcons 2001; Shi 2002; Tsutsumi 2002; Yoshida 2001). Key foci in immunology research include clarifying the correlates of the protective immune responses that enable clearance of acute infection as well as defining mechanisms of long-term virological control in chronic infection (Bassett 2001; Major 2002; Shata 2002; Thomson 2003). Immunologists should also continue to explore the associations between HCV disease progression, cytokines such as IL-10 and TNF-alpha, and genetic polymorphisms (Rosen 2002b; Tokushige 2003; Yee 2001), and further investigate the possible contributions of interactions among HCV and gamma-delta T cells, NK cells, and dendritic cells to pathogenesis and immune evasion (Tseng 2001; Crotta 2002; Tseng 2002; Auffermann-Gretzinger 2001; Bain 2001).

Finally, efforts must be made to increase the utility of the mouse model and enhance the efficiency and reproducibility of in vitro cell culture systems. The chimeric mouse model incorporating human hepatocytes shows promise, though further work is necessary to better mimic the human immune response to HCV in this model. The National Institute of Allergy and Infectious Diseases (NIAID) Division of Microbiology and Infectious Diseases (DMID) “Request for Proposals for the Hepatitis Animal Model Network” (RFP-NIH-NIAID-DMID-99-19) provides a good vehicle for supporting small animal model studies and should be expanded to prioritize HCV research. DMID must also update its “Framework for Progress on Hepatitis C” (NIAID 1997) and increase its commitment to funding intramural and extramural basic research.

### **6b. Support and accelerate the development of new therapeutic strategies.**

The standard HCV treatment using pegylated interferon and

ribavirin has limited efficacy, suboptimal tolerability, and significant expense. New treatment options that are more potent, less toxic, and effective in those who relapse or do not respond to current regimens are desperately needed. Anecdotal reports suggest that many people with HCV are choosing—often based on the advice of their doctors—to defer treatment due to the limitations of interferon and ribavirin. The complicated calculus of when and whether to initiate HCV treatment begins with an assessment of one's current disease state and risk of disease progression. However, for many, these considerations are superseded by the difficulties of managing treatment (including the duration of treatment, the necessity of injecting interferon, the risk of depression, and the potential impairment of quality of life) as well as the lower likelihood of a sustained virological response (SVR) among those with genotype 1, high viral loads, and HIV coinfection. New and better treatments could mitigate many of these concerns and make therapy for HCV more widely acceptable and, ultimately, more successful.

The mechanisms of action of interferon and ribavirin as treatment for HCV—as well as the causes of viral resistance and treatment failure—are not fully understood, and most likely involve multiple immunomodulatory and antiviral effects (Gretch 2001; Lau 2002; Taylor 2001). Researchers and drug companies are exploring several new viral targets and drug candidates informed by a substantial body of basic research into the molecular biology of HCV. Progress here has been delayed by the lack of standard tools to screen potential drugs—an efficient, reproducible cell culture system that can sustain viral replication and infection of new cells, and a small animal model. Chimpanzees, the only other animal model known to support HCV replication, have been used to study pathogenesis and immune response, yielding data that may inform efforts at finding a vaccine against HCV. However, chimpanzee research is prohibitively expensive and ethically challenging, and the supply of chimpanzees is extremely limited (Grakoui 2001; Lanford 2001; Lanford 2002).

Current drugs in development include those targeting translation initiation (antisense oligonucleotides and synthetic ribozymes), viral enzymes (serine protease and helicase), and inhibitors of

RNA synthesis (RdRp inhibitors and IMPDH inhibitors), as well as antifibrotic compounds and immunomodulators (Di Bisceglie 2002b; Tan 2002). Most of these drugs are in very early stages of preclinical or clinical development. Vaccine development has not advanced beyond a few animal studies (Himoudi 2002; Matsui 2002; Pancholi 2003). During the 1990s, some drug and vaccine studies were delayed by lawsuits initiated by Chiron against other companies, claiming that their drug development programs infringed Chiron's patents related to HCV (Cohen 1999). While these issues appear to be largely resolved for now, the potential inhibitory effect of intellectual property disputes on the development of new drugs and diagnostics calls for scrutiny and vigilance.

Speeding the development of new therapeutic strategies for HCV will require a coordinated effort involving government, industry, research institutions, private foundations supporting biomedical research, and HCV advocates, especially people infected with hepatitis C. A strategic partnership between public and private sectors could support exploration of new targets and a better understanding of viral-host interactions through techniques such as microarray analysis (Aizaki 2002; Bigger 2001), an intensive research and development program on tools for rapid and high-throughput screening of candidate compounds, preclinical research, and the establishment of a network to facilitate the recruitment of patients into clinical trials.

NIAID's new Partnerships for Novel Approaches to Controlling Infectious Diseases, a collaboration between government, industry, and academia, has begun to focus on hepatitis B and should be expanded to address HCV. Increased leadership and coordination from the National Institutes of Health's NIAID and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in concert with advocacy from HCV and HIV organizations, will be necessary to ensure progress on these fronts.

### **6c. Include HIV/HCV coinfecting individuals in early-phase HCV treatment trials.**

Preliminary data suggest a poorer response rate to HCV treatment in coinfecting persons (Chung 2002; Perronne 2002). Because

HCV is more aggressive in HIV-positive individuals, the need for new, more effective treatments is particularly urgent. Research on the safety and efficacy of HCV treatment in coinfecting persons has lagged; usually, patients and clinicians must wait for a couple of years before these data are available to them. Coinfecting individuals must be offered the opportunity to participate in clinical trials of new agents as soon as it is safe to do so. A good benchmark here would be to ensure enrollment of coinfecting persons as soon as a safe and virologically active dose is defined.

#### **6d. Establish a hepatitis C clinical research network.**

The National Institutes of Health's 2002 Consensus Statement on the Management of Hepatitis C calls for the establishment of a Hepatitis Clinical Research Network examining natural history, prevention, and treatment (NIH 2002). Such a network would fill a void in current research efforts, providing better data regarding pathogenesis, natural history, long-term clinical outcomes, and determinants of variations in response rates to current treatment. A clinical research network could also provide a mechanism to test new therapies alone and in combination with the standard of care. A well-designed network should support investigation into optimizing the use of current treatments in understudied populations, including injection drug users, cirrhotics, and people with a history of depression. A new network could systematically address many of the research recommendations in this document, specifically those in sections 1d and 1e (research on transmission routes); all of section 2 (Pathogenesis & Natural History); sections 3b and 3c (biopsy alternatives and HCC screening); sections 4e, 4h, and 4i (research on treatment in understudied populations, side effects, and dosing strategies); and all of section 5 (Key Research Questions in HIV/HCV Coinfection).

Much current knowledge on HCV and HIV/HCV coinfection has come from clinic-based cohort studies with relatively homogenous patient populations and treatment follow-up rates generally limited to five years at most. The existing multicenter networks that have studied HCV have a narrow focus or limited capacity for large-scale, long-term research. For instance, the Adult AIDS Clinical Trials Group (AACTG) and the American Foundation for AIDS

Research (amfAR) have sponsored studies on HIV/HCV coinfection, while the industry-sponsored Hepatitis Research Network's Clinical Trials Group has focused on treatment strategies. NIAID's Division of Microbiology and Infectious Diseases (DMID) has begun to develop research networks, including the Hepatitis C Research Recovery Network and the Hepatitis C Cooperative Research Centers. This work should be supported and expanded, given the pressing need for increased resources, strong leadership, and strategic direction.

## **APPENDIX A: The 2000 Recommendations**

Recommendations from TAG's 2000 Hepatitis Report are listed below, with progress on achieving them and comments on their place in the current recommendations.

**1. CDC should further investigate the role of HCV sexual transmission in MSM.**

See recommendation 1e (Clarify routes and risks of sexual HCV transmission).

**2. CDC should update its 1998 recommendations to suggest HCV testing for all persons with HIV/AIDS.**

HCV testing has been recommended by CDC for all persons with HIV; also, see recommendation 3a (Educate primary care providers about HCV infection, diagnosis, prevention, and treatment).

**3. More research should be conducted to completely understand the immunologic responses associated with control of HCV infection.**

This is still an important recommendation; see recommendations 5a and 6a (Investigate sequencing of treatment for HIV and HCV and support and intensify research into the molecular biology and immunopathogenesis of HCV).

**4. The NIAAA (National Institute on Alcohol Abuse and Alcoholism) should commence studies on the effects of alcohol in patients with HCV. The findings should be widely distributed to patients and community physicians in a timely manner.**

See recommendation 2d (Investigate the influence of light-to-moderate alcohol consumption on HCV disease progression).

**5. Large natural history studies should be initiated to determine the current natural history of HIV/HCV coinfecting individuals in the era of HAART.**

This remains an important issue; see recommendation 2a (Establish prospective, longitudinal cohort studies of the natural history HIV/HCV coinfection in the era of HCV treatment and HAART).

**6. NIH's ICDs (Institutes, Centers, and Divisions) [i.e., NIAID (National Institute of Allergy and Infectious Diseases), NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases), NHLBI (National Heart, Lung, and Blood Institute)] should issue multiple RFAs for cross-training of fellows in hepatology and infectious disease/HIV research.**

Although this is a good idea, it may not be necessary—a hepatitis C clinical research network may be able to bring hepatologists and infectious disease researchers together. The AACTG has an integrated Liver Disease Subcommittee that allows for cross-disciplinary collaboration. See recommendation 6d (Establish a hepatitis C clinical research network).

**7. NIH's Office of AIDS Research should make available some of its discretionary funding for basic and clinical research on HIV/HCV coinfection.**

OAR has included research on HCV coinfection in its strategic plan. Funding will be addressed in Version 2.0 of the full Hepatitis C/HIV Coinfection Report.

**8. The NIH should explore the desirability and feasibility of a Hepatitis Clinical Trials Network. The network would carry out phase I to phase IV clinical studies with nested basic science research.**

See recommendation 6d (Establish a hepatitis C clinical research network).

**9. Future HCV treatment trials should stratify for HIV serostatus and enroll both HIV-positive and HIV-negative people in order to gather these critical data.**

See recommendation 6c (Include HIV/HCV coinfecting individuals in early-phase HCV treatment trials).

**10. HCV treatment should be mandated in all state and federal prison systems.**

Access to HCV treatment should be mandated; see recommendation 4g (Provide full access to hepatitis C care and treatment for incarcerated individuals).

**11. Transplant centers in the U.S. should consider HIV-positive people for liver transplantation.**

There have been successful liver transplants in HIV-positive recipients in the U.S; we are moving towards research to establish safety, efficacy, and the development of a standard of care for transplantation in HIV-positive individuals. See recommendation 5d (Support access to and research on liver transplantation for HIV-positive individuals).

**12. HCV patients must have access to their HCV RNA levels at timely intervals (e.g., week 24) while on HCV treatment studies.**

This is an important concern; new data about 12-week early stopping rules in individuals with HCV mono-infection, and the longer half-life of HCV virions in HIV/HCV coinfecting individuals should be considered in study design and reimbursement.

**13. Schering-Plough must unbundle Rebetron® so that ribavirin can be purchased separately.**

Unfortunately, this has not made HCV treatment more financially accessible unless individuals are purchasing their ribavirin from a compounding pharmacy. See recommendation 4f (Provide full access to hepatitis C care and treatment for all those in need).

**14. Research should be conducted to determine the lowest effective dose of ribavirin to minimize unnecessary toxicity.**

Although issues about ribavirin dosing have been fairly well resolved, issues about the dosing of peg-interferon remain. See recommendations 4h and 4i (Increase research on strategies to manage side effects from HCV treatment; and Identify optimal dosing strategies).

**15. All 50 U.S. states should add ribavirin to their Medicaid and ADAP formularies.**

Currently, Medicaid programs in all 50 states cover ribavirin and Schering's Peg-Intron®; however, serious access problems remain. See recommendation 4f (Provide full access to hepatitis C care and treatment for all those in need).

**16. Industry should conduct drug interaction studies of anti-HIV drugs in HIV/HCV coinfecting people while drugs are in development so that potential hepatotoxicity and drug interactions are defined prior to approval.**

See recommendations 5b, 5c, and 6c (Establish a universal definition of hepatotoxicity and characterize its severity; Explore pharmacokinetics and drug levels in coinfecting individuals; and Include HIV/HCV coinfecting individuals in early-phase HCV treatment trials).

**17. FDA should grant Hoffmann-La Roche's PEG-IFN NDA (new drug application) a "priority review" because of the unmet need for therapies for HCV patients with cirrhosis.**

Roche's Pegasys® was approved in October of 2002.

**18. HCV-treating physicians should fully explain the risk and benefits of IFN/RBV combination therapy with their patients as well as estimates of treatment response according to host and viral characteristics.**

See recommendation 3a (Educate primary care providers about HCV infection, prevention, and treatment).

**19. Industry must actively recruit African-Americans in all phases of HCV clinical trials. These studies should have the statistical power to assess racial differences in viral clearance and response rates.**

NIH is currently funding a study on HCV treatment responses in African-Americans; Roche has an ongoing safety and efficacy study as well. See recommendation 2b (Investigate the role of genetic and ethnic factors in susceptibility to HCV infection, progression, and response to treatment).

**20. Hepatitis treatment advocates should be included in all facets of NIH decision-making about hepatitis clinical and basic science research, including protocol development, scientific agenda committees, and grant reviews.**

See recommendations 6a and 6d (Support and intensify research into the molecular biology and immunopathogenesis of HCV infection; and Establish a hepatitis C clinical research network).

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