Medical Management of HIV–Hepatitis C Virus Coinfection in Injection Drug Users

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Several million people inject drugs of abuse and, as a result, are coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). The treatment of this coinfected drug-abusing population is fraught with many problems such that clinicians and other health care providers have to determine whether patients should be treated first for drug addiction, for HIV/AIDS, or for HCV infection or simultaneously treated. These proceedings present the incidence and prevalence of co-infections with HIV and HCV in high-risk populations and discuss the underlying pathophysiology of coinfections and the problems and strategies of managing the treatment of coinfections among people who also inject illicit drugs. In addition, the expert panel recommended further research to determine the best possible treatment regimens applicable to injection drug users coinfected with HIV and HCV.

Worldwide, an estimated 38 million people are living with HIV/AIDS, and an estimated 1 million of those with HIV/AIDS live in the United States [1]. In addition, an estimated 170 million people worldwide are living with hepatitis C virus (HCV) infection, ~4 million of them in the United States [2]. According to the 2003 National Survey on Drug Use and Health, ~110 million Americans aged ≥12 years (46%) used at least 1 illicit drug in their lifetime [3]. HIV and HCV infections are prevalent among substance abusers. For example, injection drug use directly and indirectly accounts for more than one-third (36%) of cases of AIDS; of the 42,156 new cases of AIDS reported in the United States in 2000, 11,635 (28%) were associated with injection drug use. An estimated 80%–90% of HIV-infected injection drug users (IDUs) are also infected with HCV [4]. IDUs may be treated with pharmacotherapeutic agents such as methadone or the newly approved buprenorphine; patients with HIV/AIDS may be treated with protease inhibitors, nonnucleoside reverse-transcriptase inhibitors, nucleoside reverse-transcriptase inhibitors, or HAART. Persons acutely infected with HCV may be treated with pegylated IFN (peg-IFN) and/or ribavirin. However, the treatment of IDUs infected with HIV alone or coinfected with HIV and HCV is fraught with many problems.

With these facts in mind, the National Institute on Drug Abuse, a part of the National Institutes of Health, organized a symposium concerning issues in the medical management of Coinfection with HIV and HCV in IDUs on 22 April 2004, at the 35th annual conference of the American Society of Addiction Medicine in Washington, DC. The symposium was devoted to the generation of a clinical and basic science research agenda for coinfection with HIV and HCV in the context of injection drug use. An international panel of clinicians and scientists discussed current issues and medical management practices for patients coinfected with HIV and HCV who have a history of substance abuse. Topics included epidemiology, prevention interventions, natural history of liver disease in HIV and HCV coinfection, virology, diagnosis and evaluation, clinical trials, management of care and treatment of substance use and viral infections, new therapies, and liver transplantation. A minisymposium on this topic also was presented at a meeting of the International Society of Addiction Medicine on 26 September 2003 in Amsterdam. Participants also made several recommendations for future research.

PRESENTATIONS

HCV infection is a major public health problem and one of the most important causes of chronic liver disease in the United States [5]. Furthermore, injection drug use is a major risk factor for both HIV and HCV infections, and IDUs constitute the largest group of persons infected with HCV. The prevalence of HCV infection...
among IDUs is estimated at 80%–90%, with the incidence ranging from 10% to 20%. As a result, coinfection with HIV and HCV is common, affecting ~1% of persons in the United States. Many IDUs coinfected with HIV and HCV are members of poor, ethnic minority populations with little access to medical care. Strader [6] emphasized that little information is available with regard to the epidemiological profile of and optimal therapy for coinfection with HIV and HCV among minority IDUs. Although improvements in HAART have led to decreased HIV-related mortality, liver-related morbidity and mortality have increased among coinfected patients [6].

Similarly, Garten et al. [7] reported rapid growth of HIV and HCV infections among IDUs in China, noting that young heroin users quickly switch from smoking drugs to injecting them. The HCV incidence among IDUs in China continues to be alarmingly high, at >30 cases/100 person-years. Although HIV infection is spreading at a slower incidence than HCV infection (incidence, ~7 cases/100 person-years), nearly one-fourth of the IDU population in China is infected. Almost all HIV-positive persons are coinfected with HCV. In addition, HCV infection among IDUs is marked, with low rates of clearance of HCV RNA and high genotype diversity. Preliminary data suggest that IDUs are susceptible to reinfection with HCV and that they can be concurrently infected with >1 HCV genotype. No current data are available with regard to the effect of infections with multiple genotypes on the pathogenesis of HCV. No treatments are available to IDUs in China for either HIV or HCV infection, which highlights the urgent need for both primary substance abuse prevention programs and programs to reduce the transition from oral to injection drug use.

The clearance of HCV infection, either alone or in the presence of HIV infection and drug addiction, is complex. A relatively small number of IDUs experience spontaneous clearance of acute HCV infection. According to Chung [8], persistent infection following acute reinfection with HCV is substantially reduced among IDUs who have been previously infected, which suggests that immunity to HCV infection may be partially protective. In persons who acquire symptomatic, acute HCV infection, spontaneous clearance appears to occur frequently among female patients who have jaundice. Among persons in whom acute HCV infection fails to clear, a relatively brief course of therapy with IFN-α, with or without ribavirin, is successful in producing sustained virological response in the majority (80%–98%) of cases. Thus, it is important to identify acute HCV infection early, because rates of sustained virological response and immune responses against HCV infection appear to decrease significantly after the first year of infection. It may be justified to wait for the first 12 weeks after the onset of symptoms and then resume treatment if viremia persists. On the other hand, the acquisition of acute HCV infection in chronically HIV-infected persons almost always leads to persistent infection and should prompt consideration of early antiviral therapy for HCV infection.

Koziel [9] stated that, although CD4+ and CD8+ T lymphocyte immune cell responses are important for recovery from acute HCV infection, the exact role of the cellular immune response in progression of liver disease during chronic HCV infection remains unclear. Classic models of HCV infection suggest that cellular immune responses promote liver injury, either through direct cytolysis of infected cells or by promoting inflammation. However, clinical evidence suggests that persons with impaired immune function, such as those with HIV infection, have more-rapid disease progression. Furthermore, although there are data on the effect of coinfection with HIV and HCV on the cellular immune response to HCV infection, further research might shed light on the pathogenesis of liver disease in both immunocompromised and nonimmunocompromised hosts [9].

The elegant studies of Ganju and colleagues show that hepatocytes exposed to HCV and HIV envelope proteins undergo apoptosis via an “innocent bystander” mechanism due to the cell surface binding of viral proteins independent of direct viral infection [10, 11]. The envelope proteins of HCV (E2) and HIV (gp120) cooperatively induce novel downstream signaling pathways that result in the apoptosis of hepatocytes, independent of direct infection. Thus, targeted inhibition of these signaling pathways might limit hepatic injury in hosts coinfected with HIV and HCV.

Coinfection with HIV and HCV is associated with medical (clinical) consequences that may include psychiatric and neurological complications, cognitive impairment, liver toxicity, and death from liver cancer. Coinfection with HIV and HCV is commonly seen in persons with HIV infection because of shared risk factors for transmission and is a leading cause of morbidity and mortality in this population. Hinkin and colleagues reported that the cognitive and psychiatric dysfunction is found in both HIV- and HCV-infected persons [12–14]. Only recently have investigators begun to focus on the neurocognitive and neuropsychiatric sequelae of coinfection with HIV and HCV, and preliminary results suggest the existence of a possible synergistic detrimental effect on global cognitive functioning that particularly affects reaction time and executive functioning. However, current data on the neuropsychiatric symptoms in persons coinfected with HIV and HCV are inconclusive and are complicated by important differences in study populations and severity of disease. On the other hand, Martin reported that examining neurocognitive functions among drug-dependent patients coinfected with HIV and HCV is a challenging, but by no means impossible, endeavor and that experiences from investigations of HIV and neurocognition may help in providing di-
directions for future investigations of HCV infection [15].

With regard to liver damage, it has been observed that improved survival in patients coinfected with HIV and HCV contributes to the development of long-term complications in comorbid conditions such as viral hepatitis and toxicity associated with HAART [16]. As a result, the incidence and prevalence of end-stage liver disease (ESLD) among HIV-infected patients with cirrhosis have markedly increased [17]. In selected populations, the primary cause of death in patients infected with HIV is ESLD [18]. Since 1996, hospital admissions because of chronic viral hepatitis in HIV-infected patients have increased from 9% to 16%, whereas mortality in HIV-infected patients with ESLD has increased from 9% to 45%. The treatment for selected cases of ESLD is orthotopic liver transplantation. However, many transplantation centers consider HIV infection to be a relative or absolute contraindication for orthotopic liver transplantation [19]. For IDUs who are coinfected with HIV and HCV, the sparse literature on antiviral therapy is a result of the current standard of care obligating all patients to refrain from the use of alcohol and other drugs while undergoing antiviral therapy. This resultant bias toward IDUs also is reflected in attitudes toward patients with end-stage organ disease and the requirement for abstinence from alcohol and other drugs for 6 months before transplantation, consulting by transplant mental health teams, and continued surveillance and drug testing before and after transplantation. Patients who do not adhere to these guidelines are removed from transplant lists. On the other hand, IDUs may respond to antiviral therapy despite their continued use of alcohol and other drugs [20]. Overall, IDUs with liver disease, with or without HIV infection, have limited therapeutic options if abstinence is not maintained [16].

As explained by McGovern [21], it appears that HCV infection has emerged as a formidable challenge in the management of the HIV-infected host in every aspect of care [22]. Multiple studies of patients with hemophilia and IDUs have confirmed that the natural history of HCV infection is accelerated in a background of HIV infection, with increased morbidity and mortality related to ESLD [23]. Underpinning these trends may be the fact that rates of progression of fibrosis appear to be high in patients coinfected with HIV and HCV, particularly those with advanced immunosuppression [24]. Underlying chronic, active viral hepatitis also complicates the administration of HAART because of the increased risk of hepatotoxicity. Although the rationale for treating HCV infection in HIV-infected patients is compelling, many obstacles to therapy still exist. The presence of more advanced histopathologic abnormalities, higher HCV RNA levels, and advanced immunosuppression at baseline are prognostic of less-than-optimal outcomes. Drug interactions, mental health issues, and substance abuse problems also complicate the delivery of care [22, 23]. McGovern also pointed out that only a few patients coinfected with HIV and HCV are treated for their underlying hepatitis because of ongoing substance abuse, severe depression, a chaotic lifestyle, hopelessness, and perceived nonadherence. Prisons house a large burden of infectious diseases, particularly persons infected with HIV and HCV. Prison-based medical care for HCV infection in HIV-infected patients enables clinicians to offer complicated therapy in a structured environment, in combination with substance abuse counseling programs. Adherence to and adverse effects from therapy can be monitored closely. Targeting underserved patients for treatment of HCV during incarceration is highly efficient and affords a “window of opportunity” for education, counseling, and screening.

Sherman discussed problems, such as drug interactions and toxicity, encountered when planning and conducting clinical trials of treatment for HCV [24]. He stated that future clinical trials will likely focus on novel therapies with different antiviral targets, such as helicase and polymerase inhibitors, that are now under way in both preclinical and early clinical trials. Despite reasonable initial concerns about drug-drug interactions and toxicity associated with HAART and HCV infection, studies have demonstrated that therapies that are safe for monoinfected patients are generally as safe for coinfected patients. It remains to be seen whether the lessons of the past decade will spur faster action and greater investment toward clinical trials in the coinfected population.

Both Cooper and de Vlaming discussed the merits of successfully using HAART for the treatment of coinfection with HIV and HCV in Canada. Cooper [25] noted that liver fibrosis and the clinical features of liver disease develop more rapidly in patients coinfected with HIV and hepatitis B virus or HCV than in HIV-seronegative patients with chronic viral hepatitis. Although patients coinfected with HIV and HCV may progress more rapidly to AIDS, this may be related to comorbid illness, substance abuse, and socioeconomic circumstances. In most cases, HAART represents the most beneficial initial pharmacological treatment intervention for coinfected patients. Although antiviral therapy for HCV is potentially organ- and life-saving, in most cases it should be reserved for patients who achieve suppression of HIV RNA and immune restoration from HAART or patients with nadir CD4+ T lymphocyte counts of >350 cells/µL. Cooper reported that HAART improved the health of patients coinfected with HIV and HCV and slowed the rate of liver fibrosis and that adherence to HAART was feasible among coinfected IDUs. Regimens with low pill counts and high dosing may be particularly advantageous in this population. However, Cooper stated that such medications as stavudine should be used cautiously, if at all, in coinfection with HIV and HCV and that efavirenz should be...
used cautiously in patients with depression. Methadone doses may need to be increased for patients receiving a protease inhibitor or a nonnucleoside reverse-transcriptase inhibitor. Cooper suggested that attention to these issues and careful monitoring of patients while they are undergoing therapy would maximize the benefits of HAART in this population [25].

de Vlaming also argued that, with the simplification and improved efficacy of HAART for the treatment of HIV infection and therapy with peg-IFN and ribavirin for the treatment of HCV infection, there is an opportunity to treat patients who have often been denied access to optimal care [26]. One approach to improving patient adherence to long-term medical therapy may be to combine addiction and medical management. This could be done through programs featuring directly observed therapy, which integrate the administration of methadone, HAART, HCV medications, and other anti-infective medications to address intercurrent conditions that do not acquire hospitalization, such as bronchitis, cellulitis, and community-acquired pneumonia. Over the past 4 years, Conway et al. [26] have implemented programs to treat HIV infection in populations showing levels of virological suppression similar to those reported in clinical trials. The current challenges include the expansion of such programs for the treatment of HCV infection and the design of strategies to engage patients not currently undergoing maintenance therapy with methadone.

The majority of prevalent and incident cases of HCV infection in the United States are associated with injection drug use [27]. However, there are limited data on treatment of HCV in this population and on the effect of such barriers as psychiatric disease and intervening drug use on outcomes of treatment for HCV [28–31]. Sylvestre [32] stated that the overall effect of barriers such as mental illness, limited abstinence, and drug use among these patients is relatively modest when patients are engaged in an outpatient setting that can address their special needs. Factors such as adherence, treatment efficacy, and reinfection have significant effect on effectiveness of therapy. A preexisting psychiatric diagnosis has a more significant negative effect on outcomes of treatment for HCV than does short abstinence or intervening drug use. Overall, data suggest that the duration of abstinence might be individualized; aggressive intervention to prevent a drug relapse from becoming regular drug use may preserve treatment outcomes and eliminate the need to discontinue treatment for HCV; and, although comorbid psychiatric conditions may reduce rates of response to treatment for HCV, addicted patients with a history of depression or other mental illness may be successfully treated as long as their condition is stabilized before initiating treatment for HCV [32]. Furthermore, improvements in outcomes of HCV infection in addicted patients may be expected by use of regimens that incorporate more effective peg-IFNs and as strategies for addressing IFN-mediated neuropsychiatric toxicity become better refined [32].

Kresina et al. [33] also pointed out that accessing and maintaining care for HIV and HCV among drug users presents special challenges to the health care team that require a nonjudgmental attitude, experience, and patience. Care for HCV, however, could be used as an instrument to engage drug-using persons in ongoing primary care relationships. Common elements to both care for HCV and primary care for HIV are HCV and HIV testing and counseling, substance abuse and mental health services, social support, and subspecialty referral. These elements, in particular substance abuse treatment, could be focal points for model care systems that provide integrative care for both HCV and HIV infections.

The clinical treatment of IDUs coinfected with HIV and HCV also is complicated by interactions between antiretroviral drugs and medications used for the treatment of drug addiction, such as methadone or buprenorphine, as pointed out by McCance-Katz [34]. She stated that methadone maintenance therapy has been the treatment of choice for opioid dependence in patients with HIV/AIDS. Clinically significant adverse drug interactions between methadone and HIV therapeutics that can contribute to nonadherence have been reported [35, 36]. Knowledge of drug interactions could be used to anticipate necessary clinical interventions. There have been pharmacokinetic interactions between buprenorphine, an opioid partial agonist, and the CYP3A4 inducer efavirenz but without pharmacodynamic interactions; therefore, simultaneous administration of these drugs is not associated with opioid withdrawal, as was seen with methadone [37]. This observation would simplify the treatment of opioid-dependent patients with HIV disease.

Finally, Bean [38] and Tedaldi [39] provided up-to-date information on new pharmacotherapeutic entities that are in various stages of development and on aspects of the viruses that new antiretroviral drugs could target. Bean [38] noted that, in recent years, progress had been seen in the treatment of HIV-related illness with HAART, resulting in improvements in prognosis and diminished opportunistic infections. Practically all of the compounds currently used as part of HAART are nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, or protease inhibitors, which target the intracellular, reverse transcription, and protease steps in the life cycle of the virus. Entry of HIV into target cells involves multiple stages, starting with interaction of a viral glycoprotein with the CD4 host receptor. This leads to conformational changes that expose a binding site in the viral glycoprotein, which then binds to the chemokine coreceptors (mainly CXCR4 or CCR5) and triggers release of the fusion domain of another viral protein. The hydrophobic N-terminus then is inserted into the host cell membrane to form a fusion pore, leading to entry of the virus. There-
fore, targeting the fusion peptide presents an attractive new method of inhibiting HIV infection and a novel addendum to the current range of drugs. In the case of HCV infection, Tedaldi [39] argued that current IFN-based therapy for HCV infection in coinfected patients is limited by incomplete virological response, poor adherence, and lack of tolerability. Thus, newer therapies for HCV infection might target viral replication (e.g., HCV serine protease inhibitors, helicase inhibitors, RNA interference, or HCV polymerase inhibitors). Other treatments will focus on viral translation (e.g., antisense molecules). Additions to IFN therapy that could modulate the immune response (e.g., thymosin, isatortine, or injectable histamine) might improve tolerability of treatment. Alternative forms of IFN are needed to minimize the inflammatory response by the liver (e.g., IFN-γ). Tedaldi related that some therapeutic vaccines are in the early stages of development. Drugs to replace or enhance ribavirin with IFN-based treatments were being studied. For patients who have received orthotopic liver transplantation, the risk of recurrent HCV infection is a concern. At least 2 approaches with a monoclonal antibody or HCV immunoglobulin are being evaluated in clinical trials. Tedaldi [39] suggested that researchers should encourage strategic treatment trials that address the sequencing of HCV and HIV therapies with current and future therapeutic agents and combination therapy and that orthotopic liver transplantation might be a viable option for patients with decompensation.

RECOMMENDATIONS FOR FUTURE RESEARCH

We make the following recommendations for future research:

- characterize those populations at elevated risk of acquiring both infections among IDUs,
- determine the incidence and prevalence of both HIV and HCV infections co-occurring in IDUs, with emphasis on IDUs who use a single illicit drug, such as opioids, stimulants (e.g., amphetamines and cocaine), or marijuana,
- study the effect of drug abuse on disease progression,
- determine the biomarkers of HCV infection that are especially suited for IDUs,
- develop noninvasive techniques (e.g., imaging) to diagnose acute and chronic HCV infection,
- develop methods to prevent recurrence of infection,
- develop pharmacotherapeutic and alternative therapy modalities for the treatment of coinfections in IDUs,
- determine drug-drug interactions among pharmacotherapeutics used in the treatment of infections and drug addiction,
- develop therapeutics that would interfere with viral replication and translation,
- develop therapeutic and preventive vaccines that would not be adversely affected by substance abuse, and
- evaluate strategies designed to increase adherence to treatment protocols.

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References


