Interventions for HIV and Hepatitis C Virus Infections in Recreational Drug Users

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Recreational drug use and infections are 2 of the major problems in the world today. Both cause serious health problems, such as immunologic impairment leading to opportunistic infections and medical comorbidity, including medical complications associated with, for example, human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infections. Effective and safe interventions (prevention and pharmacologic treatment) are possible for drug-dependent patients with single or dual infections with HIV and HCV if patients in drug treatment programs are closely monitored for adherence and compliance to treatment regimens.

Recreational drug use disorders and subsequent infections are among the most significant problems in the world today. This review presents the health problems of recreational drug use and co-occurring infections with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), as well as the related issue of interventions (prevention and treatment). Literature on HIV and HCV infections in substance users was identified using the National Library of Medicine’s PubMed database. Articles were reviewed for data on the prevention and treatment modalities used for treating substance users with single or dual infections with HIV and HCV.

Worldwide drug use is extremely prevalent. It is estimated that nearly 172 million to 250 million people used an illicit drug (eg, cocaine, opiates, amphetamines, or cannabis) at least once in the past year; of these, somewhere between 18 million and 38 million persons in the age range of 15–64 years were most likely drug dependent in 2007 [1]. In the United States, an estimated 20.1 million Americans 12 years and older (8%) used at least 1 illicit drug in the month before the survey (known as current users) [2]. In addition, an estimated 180 million people worldwide (3% of the world population) are living with HCV infection [3], and 33.4 million are living with HIV infection [4]. In 2007, injection drug use was the third most frequently reported risk factor for HIV infection in the United States [5]. During 2004–2006, ~40% of injection drug users (IDUs) with diagnosed HIV infection were deemed to have been given their HIV diagnoses late during their infections [5, 6]. Factors such as ongoing drug use, lifestyle correlates associated with drug use (such as risky sexual practices), issues of drug access, and adherence to treatment for drug use affect the onset and course of HIV disease. Injecting illicit drugs is a major risk factor for dual infections that significantly affect each disorder’s progression [7]. As an example, from 1966 through 2003 an estimated 1.0 million to 1.5 million people injected drugs and were at significant risk of contracting HIV and HCV infection, with IDUs accounting for 60% of new HCV cases and 25% of new HIV cases. The rate of sexual transmission of HCV is low [8], but HIV and HCV have common routes of transmission and risk factors. Approximately 4 million persons in the United States (1.8% of the US population) are infected with HCV, and an estimated 50%–90% of HIV-infected IDUs may also be coinfected with HCV [9]. Worldwide, ~1 million individuals die each year of liver disease and/or liver cancer. In the United States, an estimated 2% of persons with chronic HCV infection (8000–10,000) die of liver cancer annually [10, 11].

MANAGEMENT OF HIV AND AIDS IN DRUG-USING PATIENTS

Substance use and co-occurring HIV infection are associated with serious adverse medical morbidity and mortality affecting almost every physiologic and biochemical system. Interventions for HIV and AIDS consist of preventive and treatment mo-
dalities, including lifestyle and behavioral changes, promoting the use of sterile injection equipment, safer sexual practices (ie, not engaging in risky sexual behaviors or practices, such as not using condoms), discouraging the use of illicit drugs, and use of pharmacologic tools, all of which should slow the spread of HIV infection. Treatment during acute HIV infection produces a strong HIV-specific response consisting of CD4 cells and undetectable RNA [12], resulting in patients with fewer opportunistic infections and reduced disease progression to AIDS [13]. Currently, new effective medications are available. These medications are collectively known as highly active antiretroviral therapy (HAART) and consist of various combinations of nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, protease inhibitors [14], entry inhibitors [15], and a CCR5 receptor blocker [16]. Their use is further discussed in the recent guidelines for HIV and AIDS [14]. The goal of HAART is to induce long-standing viral suppression, restore and preserve immunologic function, improve quality of life, and decrease HIV-related morbidity and mortality. The best virologic response is seen when 3 or more drugs are used [17]. The risk for opportunistic infections, such as with Pneumocystis jirovecii, Toxoplasmosis gondii, or Mycobacterium avium complex, increases as the CD4 cell count declines to below 200, 100, or 50 cells/µL, respectively, the levels at which primary and secondary prophylaxes should be instituted. HAART has profoundly lowered the morbidity and mortality associated with HIV infection and AIDS [18, 19]. However, the effectiveness of therapy is negatively affected by poor adherence, risky sexual practices, use of illicit drugs, adverse effects (eg, hypersensitivity and mitochondrial toxicity [hepatic steatosis, lactic acidosis, neuropsychiatric symptoms, and metabolic abnormalities]) [14], and drug-drug interactions.

Treatment of HIV infection in IDUs poses a greater challenge to clinicians because of reported poor adherence to treatment regimens, engagement in risky and unsafe sexual behaviors, and continued injection drug use. Methadone treatment is effective in decreasing opiate use, needle sharing among opiate addicts, the number of sex partners, the practice of exchanging sex for drugs or money [20, 21], and lowering the incidence and prevalence of HIV infection among opiate injectors [22–24]. Post-exposure prophylaxis against acute HIV infection [25] is safe and effective for HIV-infected IDUs successfully enrolled in methadone maintenance treatment (MMT) programs [26], to further prevent the spread of infection. Further treatment for drug addiction improves adherence to antiretroviral therapy and prevents the development of drug resistance. Thus, substance abuse treatment must become an integral part of HIV management [27, 28], for which compliance to treatment is also significant. However, adverse pharmacokinetic and pharmacodynamic drug interactions could occur between antiretroviral medications and opioid agonists, such as methadone [29]. This subject has been reviewed recently [29–32].

**MANAGEMENT OF HCV INFECTION IN DRUG USERS**

Injection drug use is a major factor for acquiring HCV infection. Approximately 50%–90% of HIV-infected IDUs may also be infected with HCV. HCV can be transmitted via the sexual route [33], with an increased risk among HIV-infected men who have sex with men [34]. Although the risk of HCV infection in children via prenatal transmission is <5% [35], coinfection with HIV and HCV increases the risk of perinatal transmission of both viruses. The acute phase of HCV infection may last for ~6 months and is difficult to diagnose because of its asymptomatic nature. When symptoms occur, they tend to be mild or nonspecific and may include malaise and nausea. About 75%–85% of these patients may then become chronically infected, with detectable RNA. The chronic phase of HCV infection is also characteristically asymptomatic but may last several decades; thus, there is a need to develop algorithms. Alcohol use, advanced age, HIV infection, and marijuana use accelerate HCV-associated liver fibrosis [36]. Approximately 20% of patients with chronic HCV disease develop liver cirrhosis within 20 years, and 1%–5% will die of HCV-related liver cancer. Spontaneous clearance of HCV varies with its genotype [37] but may be independent of the duration of injection drug use, although disease may progress aggressively in patients >40 years of age [38]. The predictive factors for HCV seroconversion among IDUs are the exchange of contaminated syringes and cotton sharing [39]. HCV subtype distribution may vary among IDUs, with most (48%) having HCV subtype 1a and 16% having subtype 1b, with no difference in HIV subtypes [40]. HCV genotype 3a was prevalent in 65% of IDUs, whereas genotype 1b was predominant among patients who had received blood transfusions [41].

No vaccine or postexposure prophylaxis is available for HCV infection. Thus, its management must focus on providing primary prevention efforts, such as safer blood supplies in the developing world, encouraging safe injection practices in health care and other situations, and decreasing injection drug use [42]. Clinical management of HCV infection may consist of pretreatment, treatment during the acute and chronic stages of infection, encouraging lifestyle changes, and discontinuing injection of drugs of abuse. Programs such as physician referral of drug-dependent coinfected patients to drug treatment programs for clinical management and facilitation of access to health care and social services, with emphasis on ethnic and racial minorities (especially women), should be developed to slow or halt the spread of infection [43]. Early pharmacologic treatment of HCV infection appears to have a higher rate of sustained virologic response. During the
chronic phase, when the patient has persistently detectable RNA, moderate inflammation, and fibrosis or necrosis on biopsy specimens, pharmacotherapy may consist of pegylated interferon in combination with ribavirin, resulting in sustained viral response. Frequent injection drug use, opportunistic infections, and risky behaviors could hasten disease progression and negatively affect the effectiveness of treatment [44]. However, drug users chronically infected with HCV who are in an MMT program can be successfully treated with pegylated interferon and ribavirin [45]. Adverse effects related to treatment may include fatigue, headache, fever, myalgia, bone marrow suppression with pancytopenia, hemolytic anemia, depression, suicidal ideation, and suicide. About 10%–40% of patients taking interferon develop adverse neuropsychiatric complications that are serious enough to warrant discontinuation of therapy [46]. The neuropsychiatric complications can be further exacerbated by injection drug use [47, 48]. Therefore, patients taking interferon alone or in combination with ribavirin should be monitored regularly [49]. For further information on HCV treatment, see the American Association for the Study of Liver Diseases guidelines [50].

MANAGEMENT OF HIV/HCV COINFECTION IN DRUG USERS

HIV/HCV coinfection is an important and frequent scenario, with prevalence rates reaching 50%–90% among IDUs. Among IDUs worldwide, HIV prevalence varies from <5% to >80%, with an annual HIV incidence between <1% and 50%. More consistency is shown in HCV prevalence (50%–90%) and incidence (10%–30% per year) [9]. Because both HIV and HCV have common transmission pathways, dual infections are frequent, with the prevalence of HCV infection among HIV-infected IDUs being as high as 90% in some countries in Central, South, and Southeast Asia and in Eastern Europe [51–53]; 33% in St. Petersburg, Russia [54]; and 50%–55% in Australia [55, 56]. Higher levels of HIV and HCV infections are often associated with longer duration and higher frequency of injecting drugs of abuse, incarceration, sharing of drug injection equipment, and lack of access to needle exchange programs. Dually infected patients are less likely to be receiving HAART and are frequently hospitalized with higher CD4 cell counts for non-HIV-related medical problems, including complications of liver disease [57]. HAART reduces mortality among HIV-infected patients. However, rates of survival can vary because of HCV infection and drug use. Treatment of dually infected patients with HAART should be optimized to achieve the maximal benefits that have been observed among other individuals receiving HAART [58]. In MMT programs, the overall seroprevalence of those tested was 67% for HCV and 29% for HIV-1. Coinfection was present in 26% of patients. However, rates of infections varied with age. The prevalence of HCV reached 92% in the 45–49-year-old group (n = 53). The greatest HIV-1 prevalence (45%) was in patients in the 35–39-year-old group (n = 33). A linear relationship was found between infection seroprevalence and age at admission into an MMT program [59].

The clinical course of HIV and HCV infections may include a number of adverse health effects. Backus et al [60] reported that HIV/HCV-coinfected patients had high rates of comorbid conditions that complicated both pharmacotherapy and the clinical course of infections. For example, compared with patients infected with HIV alone (37%), HIV/HCV-coinfected patients were older men, were African American or Hispanic, reported intravenous drug use, and had depression and substance-dependence problems. The authors suggested that optimal models of integrated care should be developed for populations with single or dual infections and for those who also need treatment for substance dependence or mental health care [60]. Neuropsychiatric consequences of multiple infections among the IDUs may include emotional stress, psychological and coping problems, less fighting spirit, hopelessness, and anxious preoccupation toward illness. Overall, the neuropsychiatric impact of HCV is significant among those who also have advanced HIV infection and AIDS [61]. Routine assessment of psychosocial variables and coping mechanisms should be integrated into all HCV and HIV services, especially for patients with substance abuse dependence and those at risk for life-threatening physical illness, such as HCV and HIV infections [62]. The morbidity and mortality associated with HIV and HCV infections are significant, with a wide range of medical complications, including cardiovascular disease; dyslipidemia; post-HCV hepatic failure; bacterial infections; cancers of the lungs, rectum, liver, and uterus; non-Hodgkin lymphoma; suicide; and deaths from non-AIDS conditions [63]. The most frequent cause of death was liver disease and AIDS among HIV/HCV- and HIV/HBV-coinfected patients [64]. Nearly half of the patients who died of liver disease had CD4 cell counts >200 cells/μL. The risk of death from liver disease was highest in patients coinfected with HCV and HBV.

Coinfection with HIV worsens the outcome of chronic HCV infection, increasing both the level of serum HCV RNA and liver damage and decreasing the sustained viral response to interferon therapy. Alcohol consumption of >50 g per day (~4–5 drinks) is a risk factor for liver disease progression among patients with HIV/HCV coinfection [65]. Interferon therapy has a protective effect against HCV-related cirrhosis regardless of the patient’s HIV status [66]. HIV infection that is not treated early is associated with higher HCV viremia and more severe liver injury in IDUs with chronic hepatitis C [67]. In HIV-positive patients, the CD4 cell count does not influence the histologic response. In HIV/HCV-coinfected patients treated with interferon, liver improvement is similar to that observed in HIV-negative patients. Such beneficial effect of interferon
therapy supports early treatment of chronic HCV infection in HIV-infected patients [68]. HCV infection does not influence HIV RNA level but may be associated with poor immunologic outcome in HIV-infected persons and may act as a direct cofactor for HIV disease progression. Thus, treatment of chronic HCV infection might indirectly benefit HIV disease [69]. However, the poor immunologic outcome was not seen by Sulkowski et al [70] and Chung et al [71]. Chronic HCV infection accelerates the course of liver disease in HIV-infected IDUs, leading to cirrhosis and liver failure in a short period. According to Soriano et al [72], HCV alone or in combination with other hepatotropic viruses was involved in 93 patients (88.6%) admitted for chronic virus-related liver disease, resulting in hospital admissions and deaths in HCV-infected drug users that were primarily for non–AIDS-defining infections and complications of injection drug use.

TREATMENT SETTING: INTEGRATED AND NONINTEGRATED CARE

Clinical management of a single infection is relatively simple with a multitude of anti-infective agents (antibiotics against bacterial infections or antiviral agents against viral infections). However, the clinical management of dual infections with HIV and HCV poses a problem when patients are addicted to multiple drugs of abuse, are homeless, and have comorbid psychiatric or other medical complications. At a 1997 National Institutes of Health consensus conference on the management of HCV, it was recommended that IDUs have a period of abstinence from illicit drug use for 6–12 months before HCV treatment [73]. By 2002, the National Institutes of Health consensus panel recommendations had shifted; now, individuals with active injection drug use could be considered for HCV treatment [74, 75]. These recommendations were later reinforced by the American Association for the Study of Liver Disease practice guidelines for the diagnosis, management, and treatment of HCV [76], which stated that treatment of HCV infection should not be withheld from IDUs or those following an MMT program regimen provided they wish to take HCV treatment, are able to maintain close monitoring, and practice contraception. The recent studies by Edlin et al [77] and Sylvestre [78], discussed by Kresina et al [79], further show that drug-dependent patients infected with multiple viruses can be successfully treated.

In general, drug abusers face many challenges in gaining access to health care, including distrust of the health care system, cost of therapy, poor adherence to therapy, physician prejudice, and potential for reinfection or possible superinfection from injection drug use [80]. Compared with others, IDUs or HIV-infected patients are less likely to receive pretherapeutic evaluation and appropriate antiviral therapy, even after evaluation [81]. Adherence is important, but drug use itself does not necessarily predict lack of adherence. HCV-infected IDUs can be stabilized with methadone (or buprenorphine) and treated successfully with pegylated interferon alone or in combination with ribavirin and with adjunct drug addiction services, such as behavioral therapy [45]. Taylor et al [82] also report that HIV/HCV-coinfected persons with the common comorbidities of polysubstance dependence and psychiatric illness may effectively and safely undergo pharmacotherapy for HCV infection with the appropriate support. Lozano Polo et al [83] also report that HCV-infected drug users in an MMT program can be successfully treated with methadone or naltrexone without any adverse impact on levels of serum transaminases. Similarly, Huber et al [84] reported that antiviral therapy was feasible, safe, and effective for HCV-infected IDUs in an MMT program. Thus, strategies to improve access to HCV treatment for current and recovering IDUs should include the following: drug-dependency treatment education; training for infectious diseases physicians, hepatologists, and other HCV treatment physicians; HCV treatment education and training for addiction medicine physicians; development of multidisciplinary clinics; and peer-based education and support for patients considering and receiving HCV treatment [56].

Despite drug users being at high risk for HCV infection, many are uninformed or misinformed about the virus and its associated consequences. Strauss et al [85] found that, compared with drug-free programs, MMT programs cover a significant number of HCV-related and other specific topics (eg, how to avoid HCV transmission, the importance of testing for HCV, treatment options for HCV-positive individuals). In general, drug treatment programs need to educate patients about the proactive steps they could take to deal with HCV, provide critically needed HCV services, and encourage patients to make full use of these services. Programs should be established to educate patients about the dangers of substance use and co-occurring infections; health care professionals, infectious disease specialists, and hepatologists about drug addiction; and psychiatrists and others about infections [85–87].

CONCLUSION

Millions of people who use recreational drugs are coinfected with HIV and HCV. As a result, they develop serious morbidity that includes immunologic, neuropsychiatric, and hepatic complications and usually die of chronic liver disease and cancer. There was an earlier perception among infectious disease clinicians and/or hepatologists that drug-using patients with co-occurring infections with HIV and HCV are difficult to treat. Significant barriers to treatment exist at the level of the treatment system, the treating physician, and the infected patient. However, current research shows that drug-using patients enrolled in drug treatment programs using methadone maintenance or buprenorphine can be successfully treated with expensive but effective and safe antiretroviral therapies if they are...
closely monitored for adherence and compliance to treatment regimens.

Acknowledgments


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