Delivering Care to Injection Drug Users Coinfected with HIV and Hepatitis C Virus

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Injection drug use has fueled the epidemic of human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection in the United States. Nevertheless, drug dependence is among the main reasons that coinfectected persons are not being treated for HCV infection. This report describes the development and progress of an HIV clinic program (funded by the Ryan White Comprehensive AIDS Resources Emergency Act) to deliver care for HCV infection to HIV-seropositive injection drug users. To optimize safety and adherence, pegylated interferon is directly administered to patients in the context of integrated addiction, psychiatric, and HIV and HCV therapy. Ribavirin is packed weekly in pill boxes for patients to take at home. Thus far, adherence to weekly visits for treatment with interferon has been 99%. No one has had to stop treatment for HCV infection because of ongoing drug use, addiction relapse or exacerbation, or psychiatric complications. Presented here is a work in progress, rather than a finished research project or definitive model of care.

Persons coinfectected with HIV and hepatitis C virus (HCV) are arguably those most in need of treatment for HCV infection, for numerous reasons. HCV infection may be considered an opportunistic infection in persons coinfectected with HIV, because the prevalence of HCV infection is increased and the disease course is accelerated among HIV-seropositive persons [1, 2]. In the era of HAART, HCV has become a leading cause of morbidity and mortality among persons with HIV [3–6]. Infection with HCV can complicate treatment for HIV infection by increasing the risk of hepatotoxicity caused by antiretroviral agents [7–9]. Some data suggest that HCV infection hastens the HIV disease course and blunts the immune response to HAART [10]. Principles regarding treatment for HCV infection that are applicable to HCV-monoinfected patients are, for the most part, relevant for HCV-HIV–coinfected patients, and current medications are reasonably effective and safe for coinfectected persons [2, 11–14].

Nonetheless, disappointingly low rates of eligibility for treatment and enrollment into treatment for HCV protocols have been reported among HIV-seropositive persons [15–17]. Among the main reasons that coinfectected persons in the United States are not being treated for HCV infection is concomitant drug use [15–17], even though injection drug use is the major cause of acquisition of HCV infection in the United States [18, 19].

BARRIERS TO TREATMENT

Drug users in general face many challenges in gaining access to health care, including logistical hardships (e.g., lack of transportation) and distrust of the health-care system [20]. Prejudice and inexperience in treating drug users may contribute to physicians’ reluctance or limited ability to provide adequate care [21, 22]. Obstacles specific to treatment for HCV infection for persons engaging in substance use may include cost of HCV medications, incomplete understanding of HCV, or fear of the adverse effects of medications. Physicians’ concerns about treating drug users for HCV infection include poor adherence, the potential for reinfec tion after treatment, relapse or exacerbation of drug use, and psychiatric decompensation [23–25].

Although adherence is important, substance use itself does not necessarily predict lack of adherence [26–28]. Programs designed to meet the unique needs of sub-
stance users can optimize adherence, as shown in studies of treatment for latent tuberculosis [29, 30]. Physicians’ assumptions about patient adherence are often incorrect [31, 32]. Fears about reinfection with HCV are understandable, but this is not common. There are few confirmed cases of patients having reinforced themselves by drug injection after successful treatment for HCV infection [33–35].

IFN, the mainstay of therapy for HCV infection, has previously been considered to be contraindicated for persons with active substance use [18, 36, 37]. Trials of IFN-α and pegylated IFN (peg-IFN) have excluded persons who inject illegal drugs, drink alcohol, or are prescribed methadone [38]. Data about treatment of persons with addiction disorders are scant. Recent experience reveals comparable efficacy and safety of treatment for HCV infection among injection drug users (IDUs) with appropriate support [39–41].

Guidelines that recommended excluding persons who have used illicit drugs in the prior 6 months were developed despite a lack of supporting data [36]. Because addiction is a chronic, relapsing illness, 6 months of abstinence does not predict continued abstinence, just as 6 months of drug use does not preclude future abstinence [42]. A recent study suggests that duration of abstinence does not affect discontinuation of treatment for HCV infection because of drug relapse [41].

Persons with addictive disorders and HIV or HCV infection are at increased risk for mental illness, which was also previously considered to be a contraindication to treatment with IFN [43–46]. Most data about IFN-induced depression and other psychiatric symptoms are derived from trials among persons without preexisting psychiatric disease. Studies of patients with depression or other psychiatric diagnoses taking IFN demonstrate that many can be successfully treated, some with adjunctive therapy, including selective serotonin reuptake inhibitors and supportive care [39, 47–51].

Given current information on the feasibility, efficacy, and safety of treating IDUs and the potential for stemming the HCV epidemic by targeting IDUs, in 2002 the National Institutes of Health removed injection drug use from its list of contraindications and recommended coupling addiction services with treatment for HCV infection for IDUs [14]. Offering therapy for HCV infection to patients with substance use disorders should be viewed as a challenge, not an impossibility. Devising strategies to do so is imperative. For coinfected populations, the inexperience of hepatologists and gastroenterologists in treating HIV-infected patients, the HIV expertise of infectious diseases specialists, the lack of state and federal funding for treating HCV infection, and the streamlining of medical care form the basis for integrating HCV care into existing HIV practices.

MODELS OF CARE

Modified directly observed therapy with HAART and approaches to treatment for HCV infection in the Rhode Island prison system provided the rationale for our intervention for treatment for HCV infection for coinfected patients with drug dependence. Directly observed therapy (i.e., supervision of all medication doses) and modified directly observed therapy (i.e., supervision of some medication doses) improve access and adherence to HAART among substance users [52–54]. In Rhode Island’s modified directly observed therapy pilot program, near-peer outreach workers meet participants in the community to deliver antiretroviral medications. Adherence to medical appointments and mean CD4 cell counts increased, whereas mean plasma HIV loads decreased [52]. This pilot has since been expanded to a randomized, controlled trial, which is ongoing.

Successful treatment for HCV infection in the Rhode Island prison system provides an example, albeit an extreme one, of the value of observed medication dosing, close monitoring, and multidisciplinary care for a population with a high prevalence of addictive and psychiatric disorders [55]. Nurses administer IFN injections and dispense ribavirin in a highly structured environment, with adherence exceeding 90%. To receive anti-HCV medications, prisoners either agree to treatment for substance abuse or must have a 1-year period of sobriety. Persons with a history of depression or other psychiatric disease undergo psychiatric evaluation, and those determined to be stable are carefully monitored while taking IFN. Of the first 93 inmates treated, none discontinued for psychiatric reasons, and efficacy has been comparable to that reported in the community [55].

Many authors have written about the potential benefits of a multidisciplinary model to treat the intertwined diseases of addiction and HCV and HIV infection [15, 24, 38]. We describe here such an approach. This pilot incorporates direct administration of peg-IFN; integrated care for HIV and HCV infection, addiction, and psychiatric problems; peer support; and intensive home-based case management.

THE IMMUNOLOGY CENTER HIV/HCV COINFECTION CLINIC

Overview. The HIV/HCV Coinfection Clinic is part of The Miriam Hospital Immunology Center in Providence, Rhode Island, a clinical and research center for HIV-seropositive persons (funded by the Ryan White Comprehensive AIDS Resources Emergency Act) that is an integral component of Brown University’s Center for AIDS Research. The Immunology Center provides care for ∼1000 HIV-seropositive patients, 43% of whom are coinfected with HCV. Individual HIV physicians managed patients’ HCV infection on a case-by-case basis with
the support of a consulting gastroenterologist until January 2001, when a Coinfection Clinic was established.

Coinfection Clinic is held 2 times/month at the Immunology Center, in the same office where patients receive care for HIV infection, primary care, and gynecologic care. A physician specializing in HIV and HCV, a consulting hepatologist, a coinfection nurse, and a clinic coordinator with a bachelor’s degree are based at the Immunology Center. A collaborating community-based mental health agency, Family Service of Rhode Island, provides coordinated psychiatric care, counseling, addiction treatment and referral, and intensive home-based case management. Brown University gastroenterology and infectious disease fellows, residents, and medical students rotate through to advance their training. The goals of the clinic are education regarding HCV, medical evaluation, treatment with peg-IFN and ribavirin, evaluation of and treatment for drug dependence, evaluation of and treatment for psychiatric disease, and clinical research on HIV and HCV as medical complications of injection drug use.

Education. All patients are screened for HCV (as well as for hepatitis A and B viruses) at their initial visit to the Immunology Center. Physicians provide posttest counseling and refer HCV-seropositive patients to the clinic. Entry occurs through participation in an education session about HCV. This element was incorporated when it was realized that most patients presented with such limited knowledge of HCV infection that they could not make informed decisions about further evaluation or treatment. Topics discussed include transmission of HCV; prevention or harm reduction; role of the liver; hepatic damage due to HCV infection; alcohol reduction and cessation; differences between HCV, hepatitis A virus, and hepatitis B virus; liver biopsy and other components of medical evaluation; potential goals and adverse effects of treatment with peg-IFN and ribavirin; and importance of adherence to treatment with peg-IFN and ribavirin. Patients who prefer not to attend or do not speak English may schedule individual meetings with a translator if necessary. A coinfection pamphlet developed by clinic staff, written at the sixth-grade reading level, is available in English and Spanish. Patients are urged to attend the education group as often as they wish and schedule a clinic appointment.

Medical evaluation. Medical evaluation includes history and physical examination for signs and symptoms of liver disease, review of results of baseline serum and urine tests (as outlined elsewhere [25, 56]), appraisal of comorbid conditions such as cardiac disease, addiction and psychiatric history, and assessment of HIV disease and HCV status. Most patients undergo liver biopsy to gauge the extent of fibrosis, which aids in determining whether treatment for HCV infection will be encouraged or deferred. Miriam Hospital interventional radiologists perform percutaneous liver biopsies within 3 weeks.

Medication lists are reviewed for potential drug-drug interactions, such as didanosine and ribavirin. A team of specialists with experience in and commitment to caring for coinfected patients is available for consultation to stabilize relative contraindications such as thyroid disease, permitting treatment for HCV. Neither history of psychiatric illness nor suicide attempt is necessarily an impediment to treatment for HCV. The major consideration is current stability. A wide range of medications is used to stabilize psychiatric symptoms before therapy with peg-IFN, with primary use of selective serotonin reuptake inhibitors to treat depression.

Consideration for treatment with peg-IFN and ribavirin is based on review of all assessments and is in accordance with current standards [25, 56]. However, our goal is to move beyond conventional criteria for treatment of patients with drug dependence. Neither recent nor current use limits access to treatment for HCV infection. Whether a person wants and is able to follow through with evaluation is a greater consideration than simply whether drug use exists.

The message to patients is that there are no exclusion criteria based on addiction. Development and implementation of treatment plans for substance use occurs if and when patients are ready. Ideally, substance use is stabilized before therapy with IFN. However the definition of “stable” is patient dependent. For example, for some opiate-dependent persons, this means beginning maintenance therapy with methadone. For other patients, this means ensuring safe injection practices to avoid spread of disease, overdose, and other complications of drug injection, which may place them at more immediate risk than does HCV infection. For patients who are unwilling or unable to discontinue illicit drug use, ongoing discussion of substance use and treatment continues. Patients consuming alcohol are considered on a case-by-case basis. It is explained that alcohol cessation is more beneficial than IFN. Patients who are willing to address alcohol use to any degree are not denied access to treatment with peg-IFN and ribavirin. The goal of this approach is to address addiction realistically as a chronic, relapsing disease to be treated along with HIV and HCV infection. The only requirements are that patients are able to reasonably adhere to medical appointments and be willing to undergo psychiatric evaluation and engage in a psychiatric care plan as part of treatment for HCV infection.

Pilot intervention for coinfected patients with drug dependence. The primary goal of the pilot adherence and safety intervention is to extend treatment for HCV infection to HIV-infected persons with coexisting drug dependence. A secondary goal is to provide services for persons not stable for or not choosing treatment for HCV infection, to move them toward eventual treatment for HCV infection. The foundation of the intervention is direct administration of peg-IFN. The
hypothesis is that administering peg-IFN to patients maximizes safety, tolerability, adherence, and efficacy and minimizes adverse effects and treatment discontinuations through aggressive management of any adverse effects on a weekly basis.

The coinfection nurse sees patients weekly to administer peg-IFN and any accompanying growth factors, assess and manage routine adverse effects, and review adherence to ribavirin and other medications. The coinfection physician manages more-severe adverse effects, adjusts medication doses, and prescribes growth factors as needed. Serum and urine values are monitored in accordance with current standards [56]. Phlebotomy is coordinated with nursing visits and coinfection support group, so that patients are able to attend this peer-driven group while awaiting examination and injections.

Because no funding was available to hire staff for an on-site multimodality team, collaboration with a community-based mental health agency was initiated in January 2002. The purpose of this partnership is to combine medical expertise of the Immunology Center with integrated substance abuse, mental health, and support services. Available services include psychiatry, psychotherapy, medical case management, and addiction counseling and referral. Intensive home-based case management includes, but is not limited to, transportation or accompaniment to appointments and assistance with housing, vocational training, and financial matters.

New patients are presented at team meetings held twice per month, after initial evaluation at the clinic. Over the next several weeks, psychiatric, addiction, environmental, and family health needs are assessed, and a support team, termed the community-based support team (CBST), is assigned. Individualized care plans are fashioned according to each patient’s needs and lifestyle. Some patients require no further psychiatric involvement, whereas others begin treatment with an antidepressant or other psychoactive medication(s) or have existing medications adjusted. Patients who are too unstable to receive treatment with peg-IFN work with the CBST toward achieving stability.

Once treatment with peg-IFN and ribavirin is initiated, patients are provided with continuing education regarding their course of and response to treatment. Providers communicate frequently with regard to adverse effects, medical and mental status, necessary supports, and response to care. The care plan is adjusted accordingly. Coordinated appointments with physicians and members of the CBST continue during and for 6 months after treatment. Patients may continue with the CBST after treatment for HCV infection is complete.

For patients with preexisting relationships with a psychiatrist, methadone counselor, or health-care workers from other agencies, a team including these providers is assembled. Any gaps in service are filled by the CBST. If these relationships are relatively new or inconsistent, patients may transfer their care to the CBST.

Progress report. A total of 146 patients have been referred to the Coinfection Clinic. Of these patients, 92 have been seen at least once, for a total of 186 appointments. One hundred six additional appointments were not kept. Of the 92 patients, 97% have a history of addiction, and 43% reported current drug use. Eighty-five percent have a history of non–substance-based psychiatric diagnosis, primarily major depressive disorder. Other diagnoses include generalized anxiety disorder, post-traumatic stress disorder, schizophrenia, bipolar disease, and personality disorders. Sixty-nine patients have had liver biopsies. Seventy-four percent have at least stage 2 fibrosis [57], and 26% have cirrhosis. Of the 83 patients whose HCV genotype has been checked, 69% are infected with HCV genotype 1. Seventy-five persons have attended the group education session, and 31 have engaged in an individual session.

Thus far, 17 patients are in an intensive pretreatment phase, and 17 have been treated for HCV infection (table 1). The mean length of time from first consultation until start of treatment was 7 months (range, 1–20 months). Preparation for treatment with peg-IFN and ribavirin was slowed by such difficulties as patient reluctance to see a psychiatrist or take psychoactive medications, trouble finding an effective and tolerable antidepressant, poor compliance with appointments because of psychosocial instability, and needing to alter HAART before beginning treatment with peg-IFN and ribavirin.

Of the 17 persons treated for HCV, 9 are women. Their mean age is 46 years; 100% have a history of addiction, and 94% have a history of injection drug use. Ninety-four percent have a non–substance-based psychiatric diagnosis. Adherence to weekly visits has been 99%, with a total of 3 missed peg-IFN doses. Three additional doses were held for psychiatric symptoms, but no patient has had to stop treatment or be hospitalized because of psychiatric complications. At the beginning of treatment for HCV infection, drug use was ongoing for 6 patients. Of the remaining 11 patients, 2 relapsed during treatment. No one has had to stop treatment because of ongoing drug use, addiction relapse, or exacerbation.

Of the 17 treated patients, 7 completed a course of therapy, 5 continue to receive therapy, and 5 did not finish therapy. Of the 7 patients who completed treatment, 2 were treated for 48 weeks; 1 achieved a sustained virological response, and the other did not achieve a sustained virological response (cirrhotic with HCV genotype 1). Five patients had treatment discontinued at 24 weeks because of lack of virological response. Because these patients all had unfavorable HCV genotypes and advanced fibrosis, none was treated with the goal of virological clearance. Of those currently receiving treatment, 2 are at week 46 and have no detectable serum HCV RNA; the other 3 have not yet completed 24 weeks of treatment.

Of the 5 patients who did not complete treatment, 1 developed nausea and abdominal pain at week 16 and was found
Table 1. Characteristics of treated patients at start of treatment for hepatitis C virus (HCV) infection.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
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<tr>
<td>Age, median (range), years</td>
<td>46 (34–56)</td>
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<tr>
<td>Race</td>
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<tr>
<td>Black</td>
<td>4 (24)</td>
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<tr>
<td>White</td>
<td>7 (41)</td>
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<tr>
<td>Other</td>
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<tr>
<td>Ethnicity</td>
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<tr>
<td>Hispanic</td>
<td>6 (35)</td>
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<tr>
<td>Non-Hispanic</td>
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<tr>
<td>Female</td>
<td>9 (53)</td>
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<tr>
<td>Substance use and psychiatric history</td>
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<tr>
<td>Substance use history</td>
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<tr>
<td>Any substance use</td>
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<tr>
<td>Illicit drug use</td>
<td>16 (94)</td>
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<tr>
<td>Injection drug use</td>
<td>16 (94)</td>
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<tr>
<td>Excessive alcohola</td>
<td>11 (65)</td>
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<tr>
<td>Psychiatric history</td>
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</tr>
<tr>
<td>Depression</td>
<td>16 (94)</td>
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<tr>
<td>Anxiety</td>
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<tr>
<td>Personality disorder</td>
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<tr>
<td>Schizophrenia</td>
<td>1 (6)</td>
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<tr>
<td>Attempted suicide</td>
<td>4 (24)</td>
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<tr>
<td>HCV-related clinical values</td>
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<tr>
<td>Biopsy stageb</td>
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<tr>
<td>Stage 1–2 or 2</td>
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<tr>
<td>Stage 2–3 or 3</td>
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</tr>
<tr>
<td>Stage 3–4 or 4</td>
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<tr>
<td>HCV genotype</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (65)</td>
</tr>
<tr>
<td>3</td>
<td>5 (29)</td>
</tr>
<tr>
<td>4</td>
<td>1 (6)</td>
</tr>
<tr>
<td>HIV-related clinical values</td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count, mean (range), cells/mm³</td>
<td>387 (98–543)</td>
</tr>
<tr>
<td>Undergoing HAART</td>
<td>14 (88)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects, except where noted.
a Based on patient self-report and/or subjective determination by the attending physician of excessive alcohol use.
b Biopsy stages are defined elsewhere [57].

to have symptomatic hyperlactatemia without acidosis but nevertheless achieved sustained virological response. Two others had Child-Pugh class A cirrhosis [58] and CD4 cell counts of <100 cells/mm³, despite receiving optimal HAART; 1 patient had treatment discontinued at week 19 because of severe thrombocytopenia, and the other developed encephalopathy at week 6. Two patients dropped out, 1 because of extreme fatigue at week 44 (a mother of young children who also worked outside the home) and the other because of loss to follow-up at week 15 after home confinement ended.

Seventy-six percent of patients have been supported with the use of at least 1 growth factor—either erythropoietin-α, filgrastim, or low-dose oprelvekin (IL-11)—to avoid reduction in dosage or termination of treatment because of cytopenias.

CONCLUSION

Directly administering peg-IFN and providing adherence support for ribavirin, along with integrated care for HIV and HCV infection, cross-discipline collaborations, close monitoring, and community-based care can optimize safety, adherence, and tolerability for coinfected persons with drug dependence, many of whom have psychiatric comorbidities. Whether use of these strategies translates into improved sustained virological response and clinical outcomes will be determined with more patients treated and further study. Exporting these tactics to the setting of methadone treatment programs may allow for greater reproducibility of this model. Further research is needed into more inclusive treatment for HCV infection for HIV-infected drug users.

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