Hepatitis C Virus and the Infectious Disease Physician: A Perfect Match

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(See the Hepatitis Invited Article by Cooper, on pages 418–25.)

About a decade ago, I was attending a major research meeting on liver diseases when I overheard a well-known hepatologist say, “These patients do not respond well and should not be treated.” He was referring to a research poster showing low rates of hepatitis C virus (HCV) eradication in human immunodeficiency virus (HIV)–infected patients taking standard interferon and ribavirin. His words made me flush with a combination of anger, despair, and frustration. I knew from my own clinic experience that my patients with HIV/HCV coinfection were dying of end-stage liver disease at a frightening rate [1]. Yet, the researcher was pointing out an observation that was painfully correct; HIV/HCV coinfected patients had significantly lower treatment response rates than patients with HCV alone. These discordant rates of virologic cure continued to be apparent, despite the later introduction of the pegylated interferons [2, 3]. What followed was more than a decade of fractured care because few physicians felt comfortable taking care of both infections and fewer patients could successfully navigate all the barriers to HCV treatment [4]. But are the obstacles to virologic cure of HCV in the HIV-infected patient as monumental as they once were? Are HIV/HCV patients really somehow “different” in this new era of directly acting antiviral (DAA) agents?

Although the development of effective HIV therapeutics has spanned about 25 years to date, the HCV therapeutic armamentarium is galloping at lightning speed. Greatly benefiting from the HIV experience, multiple pharmaceutical companies are now developing a stunning array of HCV drugs in the race toward the optimum therapeutic regimen. Within just a few years, it seems certain that we will be able to prescribe an all-oral HCV treatment regimen with drugs of varying classes without any need for interferons [5]. With the advent of these antiviral agents, it seems certain that we will see comparable HCV cure rates in the HIV-infected host as in those with HCV alone. We can base this not-so-brash prediction on the success of antiretroviral therapy (ART) for HIV, which has led to viral suppression in the vast majority of patients. Furthermore, pharmaceutical attention to issues of coformulation and once-daily dosing has facilitated excellent drug adherence to ART. Similar principles are being applied to HCV drug development. The winners in the end will be the patients because virologic cure is associated with regression of liver disease and a reduced risk of cirrhosis and hepatocellular carcinoma [6]. One can even imagine a bright day in the future when HCV transmission rates will dramatically decline because the human reservoir of infection no longer exists.

In light of fast-paced developments in HCV therapy, infectious disease specialists should be asking themselves 1 question: Why shouldn’t I be treating HCV-infected patients? As infectious disease doctors, we construct complex antiviral combinations, interpret results of drug-resistance testing, devise salvage regimens, manage drug-drug interactions, and monitor patients on maintenance therapy over the course of a lifetime. Application of these same general principles would serve the HCV-infected patient well.

To start, we need to understand the similarities to HIV and where those similarities end. For example, it seems likely that combination antiviral therapy will be needed because resistance-associated variants (RAVs) emerge within days of mono-therapy with certain HCV-specific agents (eg, HCV protease inhibitors, NS5A inhibitors) [7]. As seen with HIV therapeutics, some HCV agents have a high genetic barrier to resistance (eg, the nucleoside polymerase inhibitors), whereas others have a lower barrier (eg, the protease inhibitors) [8, 9]. Knowledge of
specific mutations is important because resistance to 1 drug (eg, telaprevir) may lead to cross-resistance to another agent within the same class (eg, boceprevir). One key difference is that, whereas HIV is integrated into the host genome, HCV is found within the cytoplasm; thus, it is unknown if HCV-related drug resistance will be archived or if RAVs will revert to wild-type virus. Although preliminary resistance data suggest that the proportion of RAVs declines over time in the absence of drug pressure [10], the clinical implications are less clear. To date, knowledge of baseline drug-resistance mutations does not appear to influence virologic outcomes; thus, baseline drug-resistance testing is not recommended for HCV, as it is for HIV. Patient monitoring will be for the duration of HCV treatment, which will be as short as 6 months, or less, for the venerable cure.

Another major question is more historical in nature: Why has HCV treatment traditionally been under the jurisdiction of our hepatology colleagues?

First, the need for a liver biopsy for staging of disease has been a major impediment to the infectious disease community. The rationale for this prerequisite was driven by the historically low treatment response rates and the substantial toxicities associated with standard interferon/ribavirin therapy. With the emergence of the pegylated interferons and high cure rates for genotype 2– and 3–infected patients, the need for a liver biopsy was questioned by many experts. Now in the era of potent DAA agents, we are seeing HCV cure rates of 75%–85%, even in the difficult-to-treat patient with genotype 1 infection [11, 12]. These dramatic therapeutic advances have been coupled with the development of noninvasive fibrosis assays and novel imaging modalities (eg, elastography) [13]. Some opponents to noninvasive monitoring cite the suboptimal performance of these serum markers, as compared with liver biopsy. However, 1 comparative analysis demonstrated that the true accuracy of noninvasive markers will always remain underappreciated because the gold standard is flawed by its own limitations, such as sampling error [14]. In fact, noninvasive markers perform well when assessing important clinical developments, such as cirrhosis. Thus, the liver biopsy should no longer be a deterrent to greater involvement of the infectious disease community.

The other main reason HCV has remained in the hands of our hepatology colleagues is an obvious one: patients who are not given antiviral therapy, or who fail treatment, are at risk of developing decompensated cirrhosis with its attendant complications, such as esophageal bleeding, ascites, hepatic encephalopathy, and hepatocellular carcinoma. Each of these complications needs expert management by a hepatologist who has been thoroughly trained in these complex issues. Unfortunately, the number of patients developing end-stage liver disease has climbed over the past few decades, and HCV remains the leading indication for liver transplantation [15]. However, just as early initiation of treatment of HIV infection leads to better immunologic recovery compared with the treatment of late-stage AIDS, early treatment of HCV is preferred because overall efficacy rates are higher and the prevention of cirrhosis is highly desirable from the standpoint of the individual and overburdened healthcare systems worldwide. Furthermore, there are emerging data that suggest that viral eradication of HCV not only reduces liver-related mortality but also overall mortality [16]. These data are reminiscent of those that emerged from the HIV structured treatment interruption trials, which clearly demonstrated that the risk of mortality from common comorbidities (eg, cardiovascular, cancer, liver, kidney) increased in HIV-infected patients who discontinued ART [17]. From a simplistic viewpoint, it appears that having a chronic infection, whether it be HIV or HCV, is unhealthy for the overall host. But solutions to the overall problem are not simple because the HCV epidemic is daunting. Worldwide, an estimated 170 million people are infected with HCV, with some endemic areas having seroprevalence rates of 20% [18]. There are an estimated 5 million HCV-infected patients in the United States alone—about 5 times the number of HIV infections nationwide [19]. With the promise of therapeutic cure for the vast majority of patients, there have been calls for increased screening efforts for this “silent killer” because the majority of individuals are unaware of their infection. The Centers for Disease Control and Prevention in the United States is considering HCV screening based on birth cohort because persons born from 1945 to 1965 have a higher prevalence of HCV infection than other age groups [20, 21]. If these new guidelines are adopted, there will be a new unmet challenge of getting these patients into care. Hepatologists are already overwhelmed by the number of HCV patients who are seeking evaluation, with long waits for clinic appointments. Furthermore, the dazzling array of new drug combinations requires specialists who are at home with complicated antiviral therapies. Thus, the need for more HCV experts is great.

How can we expand the pool of HCV clinicians within the infectious disease community to meet this enormous challenge? Several possibilities can be considered. First, we need to have centers of excellence where infectious disease practitioners who are already expert in treating HCV can serve as role models for infectious disease fellows. These young physicians should be encouraged to learn all aspects of care of the HCV-infected patient as a way to improve their career opportunities. Joint fellowships incorporating the expertise of infectious disease and hepatology mentors would be mutually beneficial for fellows studying infectious diseases or gastroenterology. Second, a much-needed HCV task
force has been created within the Infectious Diseases Society of America (IDSA); its leadership has committed a significant amount of time at the annual IDSA meetings to clinical sessions devoted to HCV evaluation and management. Needed supplements to this avenue of education are one-day conferences/workshops tailored to the need of the infectious disease physician who will quickly understand emerging data on HCV drug resistance and viral kinetics but will need more guidance in the management of the compensated cirrhotic. Third, surveys of the IDSA membership should collect data on the barriers to HCV patient care so the perceived gaps can be addressed. Fourth, HCV treatment guidelines with real-time clinical updates will also be critical to patient care in the years to come.

Although HCV does not command the same media attention as for some emerging infectious diseases, advancing liver disease will be exacting a tremendous toll in morbidity and mortality in the decades to come if wider access to treatment is not realized in the near future. In fact, in 2007, deaths from HCV infection exceeded deaths from HIV in the United States [21]. Millions of HCV-infected patients will be depending on an expeditious response from the infectious disease community, as we have done for many other infections in the past. In preparation, we will need to improve our overall knowledge of the complications of liver disease and when to suspect underlying cirrhosis. We need to understand the clinical tightrope that these patients walk between compensated and decompensated disease. We must be cognizant of when we require the expert input of our hepatology colleagues, who understand the pathophysiology of liver disease better than the infectious disease specialist can ever hope to achieve. Timely referral to our hepatology colleagues is important for overall patient safety and management. We have learned over the past decades that our HIV-infected patients thrive when multidisciplinary care is rendered. Infectious disease physicians can help hepatologists contain the floodgates of cirrhosis and hepatocellular carcinoma in the years to come by curing patients of their viral infection at earlier stages of disease. There will hopefully be a subset of fully engaged infectious disease physicians who will take on this calling. Greater expertise in liver disease, which comes with managing many HCV-infected patients, will likely translate into better treatment outcomes, as has been noted in the past for HIV.

As part of our own contribution to this educational effort, Clinical Infectious Diseases will devote more space than ever before to the timely coverage of new developments in HCV. Within this issue, readers will see a concise synopsis of highlights from the American Association for the Study of Liver Disease (AASLD) annual meeting by Curtis Cooper, an infectious disease specialist in Canada who is also expert in HCV management. We will be publishing a series of articles and supplements devoted to different aspects of HCV management by ID/HCV specialists and our esteemed hepatology colleagues. Finally, we welcome critical feedback on this HCV initiative from our community of infectious disease specialists, with a special section on reader feedback in order to keep the conversation going. We look forward to your thoughts.

Note
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References