

# Defining the Standard of Care: Randomized Controlled Trials for the Treatment of Hepatitis C in the HIV-infected Person

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In the last decade, the treatment of both hepatitis C and human immunodeficiency virus (HIV) infection improved dramatically with the advent of combination antiviral drug regimens, namely interferon alfa/ribavirin therapy and highly active antiretroviral therapy (HAART), respectively. Among HIV-infected persons, HAART led to remarkable decreases in morbidity and mortality related to acquired immunodeficiency syndrome (AIDS) and prolonged life expectancy.<sup>1</sup> Ironically, this unparalleled success awoke a sleeping giant among persons living with HIV/AIDS: chronic hepatitis C. While earlier studies had documented high rates of hepatitis C virus (HCV) among HIV-infected persons, the impact of HCV-related liver disease was overshadowed by the devastation of AIDS. However, in the HAART era, the clinical significance of chronic hepatitis C became evident as increased rates of HAART-associated hepatotoxicity and rates of liver-related hospitalization and death were observed among coinfecting patients.<sup>2-4</sup> Consequently, the 1999 United States Public Health Service Guidelines for the Prevention of Opportunistic Infections in Persons Infected with HIV recognized that HIV infection adversely affects the outcome of hepatitis C, leading to increased viral persistence following acute infection, higher levels of viremia, and accelerated progression of HCV-related liver disease, and they recommended universal screening for HCV infection as well as consideration of HCV treatment for the coinfecting.<sup>5</sup> While this recommendation was reinforced by the 2002 National Institute of Health Consensus Panel on the Management on Chronic Hepatitis C, there has been little data from randomized, controlled clinical trials regarding the efficacy, safety, and tolerability of interferon/ribavirin ther-

apy for the treatment of hepatitis C in HIV-infected persons.<sup>6</sup> Thus, despite the rapid evolution of the standard of care for the management of hepatitis C for monoinfected persons, some of the most basic questions regarding the risks and benefits of HCV therapy in HIV-infected persons have remained unanswered.

The study by Bräu and colleagues in this issue provides some insight into the difficult issues related to the management of hepatitis C in this population.<sup>7</sup> To address the efficacy and safety of ribavirin, the researchers randomized subjects with stable HIV disease to receive standard interferon alfa-2b (3 million units thrice weekly) plus ribavirin (800 mg/day) or placebo. While at the time of study initiation, combination therapy was already the standard of care for the treatment of HCV monoinfected persons, HIV care providers were concerned about the risk of severe ribavirin-induced anemia and drug-drug interactions with antiretroviral agents (*e.g.*, zidovudine and didanosine). Nonetheless, recognizing that subjects receiving placebo may be at increased risk for treatment failure, those with detectable HCV RNA after 12-weeks of therapy crossed over to receive ribavirin for the remainder of the study period. Herein lies the first major limitation of the study: Neither interferon monotherapy nor standard interferon/ribavirin represent the current standard of care for the treatment of hepatitis C, and few clinicians would prescribe the regimens studied by Bräu et al. to their coinfecting patients.

This major limitation notwithstanding, the study by Bräu and coworkers offers several important observations. First, enrollment into this clinical trial was challenging. The researchers intended to enroll 200 subjects at 21 HIV and gastroenterology centers across the U.S. Despite an enrollment period that spanned nearly 3 years, recruitment was halted at 110 subjects because of slow accrual. While there are many potential explanations, including investigator inexperience with coinfection and the desire of patients to avoid placebo, the enrollment experience is consistent with the observation in some studies that the majority of HIV/HCV coinfecting patients are not eligible for HCV therapy. For example, Fleming and coworkers found that only 30% of patients referred to specialty clinics staffed by infectious disease and hepatology specialists were eligible for HCV treatment, and less than half of those eligible actually received interferon/ribavirin therapy.<sup>8</sup>

*Abbreviations: HIV, human immunodeficiency virus; HAART, highly active antiretroviral therapy; AIDS, acquired immunodeficiency syndrome; HCV, hepatitis C virus; SVR, sustained virologic response.*

*From the Johns Hopkins Medical Institutions, Baltimore, MD.*

*Address reprint requests to: Mark S. Sulkowski, M.D., Johns Hopkins Medical Institutions, 18030 East Monument St., Room 448, Baltimore, MD 21205. E-mail: msulkows@jhmi.edu; fax: 410-614-5138.*

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As expected, barriers to HCV therapy included missed clinic visits, active psychiatric illness, and active drug or alcohol use. While the drug treatment regimen used in the study by Bräu et al. may no longer be relevant, these barriers to care clearly are relevant to therapy with peginterferon/ribavirin. Accordingly, efforts to effectively deliver HCV therapy to HIV-infected patients must include innovative strategies to increase patient eligibility and access to care.

The second important finding of the study is confirmation that the eradication of hepatitis C can be achieved in persons infected with HIV. However, the sustained virologic response (SVR) rate observed (11%) among these HIV-infected subjects was marked lower than the rate achieved with a similar regimen among HIV-uninfected subjects (42%-46%).<sup>9,10</sup> Although cross-study comparisons are problematic due to inconsistencies in study design and populations, these data suggest that HCV therapy may be substantially less effective for HIV-infected patients compared with HIV-uninfected patients, even among the carefully selected subjects with well-controlled HIV disease and good immune function. The key question raised by this observation is: Can the effectiveness of HCV therapy be improved in HIV-infected patients? Undoubtedly, the answer is that yes, treatment outcomes will improve. Based on studies in HIV-negative patients and preliminary data in HIV-positive patients, clinicians can safely anticipate that the SVR rate will be significantly higher with peginterferon/ribavirin therapy. The question of how much higher will be definitively answered with final data from 3 large, randomized controlled trials evaluating the safety and efficacy of peginterferon alfa-2a (APRICOT, 868 subjects; AACTG 5071, 134 subjects) and peginterferon alfa-2b (RIBAVIC, 408 subjects) plus ribavirin, compared with standard interferon plus ribavirin. However, preliminary reports from two of these studies suggest that the effectiveness of peginterferon/ribavirin among HIV-infected patients will also be lower than the rate previously documented among HIV-uninfected patients (54% -56%). For example, after 24 weeks of therapy in the study, Chung and colleagues found that HCV RNA was undetectable in 44% of the peginterferon/ribavirin group.<sup>11</sup> Similarly, at the end of treatment in the study, Perronne and coworkers reported that HCV RNA was undetectable in 38% of the peginterferon/ribavirin recipients.<sup>12</sup> Thus, while HIV-infected patients and their health care providers anxiously await the final data from these important trials, it is apparent that even with peginterferon alfa/ribavirin, SVR rates will be lower in HIV-positive patients compared with those rates previously reported in HIV-negative patients.

In addition to the type of interferon used, other host and treatment factors undoubtedly contributed to the relatively low SVR rates observed in this study. The third central finding of Bräu and coworkers—the relatively poor tolerability of HCV treatment—highlights another major obstacle to effective therapy in this population and, more importantly, provides a roadmap to improved treatment outcomes. Remarkably, Bräu et al. reported that more than half of all subjects discontinued therapy prematurely due to adverse events (21%), nonadherence (5%), patient decision (4%), and relapse into substance use (4%). However, it is important to note that the nature of the adverse events was similar to that observed in HIV-uninfected patients. Moreover, no adverse impact was detected on markers of HIV disease (*e.g.*, opportunistic infections) or on the safety and efficacy of HIV treatment, including among those subjects taking drugs with the potential for adverse interactions with ribavirin (*e.g.*, zidovudine and didanosine).

In addition, anemia, one of the major treatment-limiting toxicities, may be correctable or even preventable. Despite the use of only 800 mg/day of ribavirin and a high baseline hemoglobin level, Bräu and colleagues reported that nearly one third of subjects underwent ribavirin dose reduction due to anemia. While difficult to quantify, the low initial dose of ribavirin (800 mg/day) and the high rate of dose reduction may have contributed substantially to the relatively low SVR rate observed in this study. Proactive strategies to prevent and treat anemia such as the discontinuation of zidovudine prior to HCV therapy, and the early initiation of erythropoietin may allow clinicians to use higher ribavirin doses (*e.g.*, 1000-1200 mg/day), which have been associated with higher SVR rates among genotype 1-infected patients.<sup>13</sup> Furthermore, strategies to aggressively manage psychiatric complications and to improve adherence, such as directly administered peginterferon injections, may also lead to more effective HCV care. Accordingly, the development and implementation of on-site multidisciplinary programs combining the expertise of HIV specialists, hepatologists, gastroenterologists, psychiatrists, and addiction specialists should improve HCV treatment outcomes.

Thus, although some patients and clinicians may be disappointed by the relatively low SVR rate reported by Bräu and colleagues, they must recognize that this study represents an important first step on a steep learning curve to define the standard of care for the management of hepatitis C in the HIV-infected person. These early lessons point to the immediate need for more potent treatment regimens, such as peginterferon alfa and higher initial and sustained doses of ribavirin, and the need for aggressive programs to prevent toxicity and improve ad-

herence. While such pragmatic steps can be implemented today, additional research is needed to further define the standard of care. Arguably, the most urgent of these priorities is the validation of the negative predicative value of early virologic response patterns among HIV-infected patients, since the early identification of nonresponders would permit the discontinuation of therapy, avoiding toxicity and cost.<sup>14</sup> In addition, given the anticipated high rates of virological failure and the increasing burden of advanced liver disease, clinical trials of maintenance therapy with peginterferon to prevent histological and clinical progression represent a major research priority. Nonetheless, while many important questions regarding the risks and benefits of HCV therapy remain unanswered, data from this and future randomized, controlled trials will provide the critical evidence needed to more effectively confront the growing problem of HCV-related liver disease in HIV-infected persons.

MARK S. SULKOWSKI, M.D.  
*Johns Hopkins Medical Institutions  
 Baltimore, MD*

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