Case Report From the Field

Syphilis Negatively Influences the Response to Hepatitis C Virus Treatment in an HIV-Infected Patient

Ellen H. Nagami, BA, Arthur Y. Kim, MD, Rachel P. Baden, MD, and Barbara H. McGovern, MD

Syphilis is a chronic inflammatory disease caused by the sexually transmitted pathogen, *Treponema pallidum*.[1] Concomitant HIV and syphilis infections are prevalent among men who have sex with men (MSM).[2] Syphilis negatively impacts disease management in the HIV-infected host by causing substantial immune activation, as evidenced by precipitous declines of CD4+ cells and by increased levels of HIV RNA.[3,4] Syphilis has also been reported as a risk factor for hepatitis C virus (HCV) acquisition among MSM.[5] Whether intercurrent syphilis has any negative impact on HCV treatment response is unknown.

We report a case of an HIV/HCV-coinfected man who was treated with peginterferon alfa and ribavirin. He had a very slow attainment of HCV RNA suppression and a dramatic fall of CD4+ cell count in excess of what would be expected in response to HCV therapy. During HCV treatment, the patient was diagnosed with intercurrent syphilis and admitted to the use of methamphetamines; HCV treatment was subsequently discontinued at week 28. After drug rehabilitation and administration of benzathine penicillin for syphilis, the patient underwent retreatment for HCV with remarkably improved viral kinetics and a modest decline in CD4+ cell count. We propose that active syphilis infection may have been a key contributor to the patient's slow virologic response to his initial course of HCV treatment. Within this report we discuss the public health implications of this case.

Case Presentation

In 2007, Patient J, a 46-year-old HIV-infected white man with HCV genotype 1b infection, underwent a liver biopsy that demonstrated moderately active chronic hepatitis with evolving cirrhosis and moderate steatosis. Prior to HCV treatment, Patient J's baseline HCV viral load was 1.5 million IU/mL and his plasma HIV RNA level was undetectable on antiretroviral therapy. A baseline rapid plasma reagin (RPR) test was nonreactive for treponemal infection 6 weeks before starting HCV treatment.

Patient J was started on peginterferon alfa-2a (180 mcg subcutaneously weekly) and weight-based ribavirin (1000 mg daily for a weight of more than 75 kg). During treatment, the patient reported excellent adherence to both his antiretroviral and HCV medications. His major adverse effect related to HCV treatment was anemia requiring darbepoetin alfa supplementation; ribavirin dose was not reduced. At weeks 4 and 12 of treatment, Patient J's HCV viral load was 147,000 IU/mL and 3,208 IU/mL, respectively. HCV RNA suppression was not achieved until 21 weeks into treatment, consistent with a slow virologic response. Although HIV RNA remained suppressed, his pre-treatment CD4+ cell count dropped from 834/µL to 311/µL at the time of discontinuation of HCV therapy and his CD4+ cell percentages remained fairly constant at 26% and 29%, respectively (normal range, 29%-62%).

During his course of HCV therapy, Patient J presented with a maculopapular rash at week 17 and acknowledged that he had had unprotected anal intercourse. An RPR test was reactive with a titer of 1 to 64 and a confirmatory test was reactive for *Treponema pallidum* antibody (TPA). Cerebrospinal fluid analysis after a lumbar puncture was unremarkable. Patient J was treated with three doses of intramuscular injections of benzathine penicillin over a 3-week period with an appropriate titer decline to 1 to 16 after 6 weeks of follow-up.

At week 28 of HCV therapy, Patient J was hospitalized because of acute onset of a transient febrile episode with hypotension and was started on broad-spectrum antibiotics. At this time, his HCV treatment was discontinued. All blood cultures were negative and his antibiotics were stopped when no obvious source of infection was found. Patient J subsequently admitted to use of intravenous crystal methamphetamine a few days prior to his hospitalization. His clinicians surmised that his acute and transient febrile event with hypotension may have been related to endotoxemia since no infectious etiology was identified.

At the end of 2008, 2 months after completion of benzathine penicillin therapy for syphilis, Patient J requested retreatment for his HCV infection because he felt that he was in stable substance abuse recovery. At the time of his presentation to our clinic (1 month after discontinuation of HCV therapy), Patient J's HCV RNA level had rebounded

to 1,590,000 IU/mL, consistent with his pretreatment baseline viral load level. His CD4+ cell count had risen while off of peginterferon alfa-2a and ribavirin treatment to 861/μL (CD4+ percentage: 41%) and his HIV RNA level remained suppressed on antiretroviral therapy. Etiologies for his initial slow HCV viral suppression were explored, including insulin resistance, which was negative.

The patient continued to abstain from any illicit drug use and was restarted on peginterferon alfa-2a and ribavirin. The dosing of ribavirin was decreased to 400 mg twice daily based on his current weight. By week 4, his HCV RNA level was 121 IU/mL. At repeat HCV RNA testing at week 7, his HCV RNA level was below 5 IU/mL by HCV RNA quantitative polymerase chain reaction. Patient J attained a sustained virologic response (SVR) after completing 48 weeks of HCV treatment. Of note, the patient did not require darbepoetin alfa during this second course of therapy. Despite receiving the same dose of peginterferon alfa during his second course of HCV therapy, the decline in his CD4+ cell count was less dramatic (861/μL to 529/μL) and his CD4+ cell percentage remained relatively stable, 41% and 36%, respectively.

Discussion

End-stage liver disease is a leading cause of death among HIV-infected patients taking antiretroviral therapy.[6,7] HIV/HCV-coinfected patients have higher rates of liver-related and overall mortality than patients with HCV alone.[8] However, successful treatment of HCV infection is associated with decreased liver-related disease and improved survival.[9] Therefore, treatment of HCV infection in the setting of HIV is of paramount importance.

Unfortunately, response rates to HCV treatment are generally lower among HIV/HCV-coinfected patients, although this finding has not been directly linked to immunosuppression.[9] Pretreatment predictors of virologic failure in HIV/HCV-coinfected patients include high baseline HCV viremia, HCV genotype 1 infection, male sex, African American race, older age, unfavorable IL-28 genotype, insulin resistance, and advanced fibrosis stage.[9-14]

Regardless of HIV serostatus, the most powerful predictor of attaining SVR to HCV treatment is rapid viral clearance.[9,15] In studies of dual HCV therapy in HIV seronegative patients with HCV genotype 1 infection, a rapid virologic response (RVR) is associated with SVR rates ranging from 75% to 89%.[16,17] In studies of HIV/HCV coinfection, the same principles apply. In a posthoc analysis of 323 HIV/HCV-coinfected patients in the RIBAVIC treatment trial, RVR at week 4 had a positive predictive value of 97% for sustained virologic clearance.[18,19] However, the proportion of coinfected patients who achieve rapid virologic clearance on dual therapy is low.

Even with the recent introduction of HCV protease inhibitors, the best on-treatment predictor of virologic clearance remains rapid viral suppression.[20] Patients who attained an undetectable viral load at week 4 on telapravir, peginterferon alfa-2a, and ribavirin had an SVR rate of 88%.[20] In contrast, those who had a greater than $1 \log_{10}$ IU/mL decline in HCV RNA level after the 4 weeks of treatment had an SVR rate of 64%.[20,21] Similar trends were seen in the clinical trial evaluating boceprevir, peginterferon alfa, and ribavirin in treatment-naive patients.[22]

In this case report, we demonstrate that viral kinetics dramatically improved during the second course of HCV therapy after treatment of intercurrent syphilis infection. Such changes in viral kinetics have not been reported among patients undergoing retreatment for HCV with dual therapy.[23,24] In fact, retreatment with a different formulation of peginterferon alfa (switching from peginterferon alfa-2a to peginterferon alfa-2b or vice versa) has been largely unsuccessful. In a large study of patients with chronic HCV infection, only 9% achieved SVR after retreatment with peginterferon alfa and ribavirin for 48 weeks.[23]

During the first course of treatment, the patient described herein did not achieve an undetectable viral load until week 21 of HCV therapy. In contrast, during retreatment our patient attained a $4 \log_{10}$ decline in viremia by week 4 (to 121 IU/mL) and achieved complete viral suppression at 7 weeks, when he was next tested.

Several factors were explored to explain the dramatic differences in viral clearance. Patient J had no evidence of insulin resistance or hyperglycemia.[14] There were no changes in the interferon alfa formulation that he received between the first and second courses of therapy and his ribavirin dose was lower during retreatment (800 mg versus 1000 mg). Furthermore, during his first course of treatment, the patient had excellent adherence to both HCV and HIV therapies, evidenced by the development of anemia on ribavirin and maintenance of HIV RNA suppression.[9,11,25] Finally, there were no changes in his background antiretroviral regimen during this time frame, which could have potentially played a role in these differential treatment outcomes.[26]

Unfortunately, we do not have the original viral isolate and thus cannot rule out the possibility of HCV reinfection. However, it is unlikely that an HIV-infected patient with HCV genotype 1 infection and a high HCV RNA level would have achieved virologic eradication after only 28 weeks of treatment, especially since he attained late virologic suppression. In addition, after discontinuing the first course of treatment the patient's HCV RNA level returned to his pretreatment level. This is consistent with rebound viremia back to the viral setpoint.

Patient J's remarkable change in viral kinetics led us to question whether intercurrent syphilis may have modified the cytokine environment and negatively impacted his first course of treatment. Modulators of response to interferon alfa-based therapies include cytokines such as inducible protein-10 (IP-10) and interleukin 10 (IL-10).[27-31] In a study of 19 HIV/HCV-coinfected patients, pretreatment IP-10 levels were

statistically significantly lower among virologic responders (217 pg/mL; interquartile range [IQR], 181 pg/mL–301 pg/mL) than among nonresponders (900 pg/mL; IQR, 628 pg/mL–2048 pg/mL).[32] A similar inverse relationship has been described for IL-10. In a study of 79 patients with HCV genotype 1 infection, low baseline levels of IL-10 were strongly associated with high rates of virologic eradication.[31] Other factors predictive of HCV clearance include hepatic interferon-stimulated gene (ISG) expression levels. Patients who achieve rapid HCV clearance have strong up-regulation of ISGs in response to peginterferon alfa treatment. In contrast, HCV patients who do not respond have high levels of ISGs before therapy and are refractory to further stimulation.[33,34]

The role of cytokines in HCV treatment outcomes is pertinent when considering the possible negative impact of syphilis during our patient's first course of HCV therapy. *T pallidum* infection alters the balance of T helper cell 1 (T_H1) and T helper cell 2 (T_H2) CD4+ cell profiles of the host. Initially, *T pallidum* elicits vigorous inflammation characterized by a predominant T_H1 (cellular) response. This is followed by activation of T_H2 (humoral) responses that are thought to contribute to spirochete evasion of the host immune system and to the development of chronic infection, if left untreated. This switch to a T_H2 response is characterized by profound increases in IL-10 level, which may facilitate the persistence of various pathogens through interference with innate and adaptive immunity.[35-37] In a novel study of cytokine responses during syphilis infection in 36 HIV-infected patients, IL-10 levels increased substantially during primary and secondary stage syphilis, only to decline with penicillin therapy.[35] An attractive hypothesis is that early syphilis led to marked increases in IL-10 levels, which interfered with our patient's initial response to interferon alfa. Subsequent treatment of syphilis may have led to declines in IL-10 level, which facilitated clearance of HCV RNA in response to treatment.[31]

Interestingly, treatment response rates for acute HCV infection are generally lower among HIV/HCV-coinfected patients than among those who have HCV infection alone.[38,39] Although this lower response rate has been attributed to HIV-associated immunosuppression, an additional hypothesis is that undiagnosed intercurrent syphilis reduces treatment efficacy in a subset of patients.

We also suspect that our patient's dramatic decline in CD4+ cells during the first course of HCV therapy was related to several factors, including peginterferon alfa exposure and active syphilis. Treatment of HCV in HIV-infected patients is associated with substantial declines in the absolute CD4+ cell count, which resolve with discontinuation of peginterferon alfa therapy. In APRICOT (AIDS Pegasys Ribavirin International Coinfection Trial), which examined HCV treatment in the setting of HIV, the mean CD4+ cell decline was 157/μL.[9] However, Patient J had a dramatic drop of 523 cells/μL, which is much greater than would be expected with peginterferon alfa alone. This profound drop in CD4+ cell count is consistent with reports of immunologic changes seen in HIV-infected patients with primary or secondary syphilis, which may be attributed to increased cell turnover, apoptosis, and changes in T-cell homeostasis.[3,4,40] Generalized immune activation is associated with increased expression of CC chemokine receptor 5 (CCR5) and dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) receptors on human monocytes and dendritic cells, which enhances the cells' susceptibility to HIV infection.[1,3,41] Of note, syphilis has also been associated with increased HIV RNA levels in patients not on antiretroviral therapy.[3,4,40]

Overall incidence rates of primary and secondary syphilis have been on the rise since 2001, after decreasing throughout the 1990s.[42,43] Recent reports have shown an increasing incidence of syphilis specifically among MSM in the United States and Europe.[44,45] Between 2000 and 2004, the percent of cases of primary and secondary syphilis attributed to MSM in the United States rose dramatically from 7% to 64%.[43] Furthermore, the current syphilis epidemic among MSM has disproportionately affected those with HIV infection.[46] Many factors may have contributed to the resurgence of syphilis among HIV-infected MSM, including serosorting of sexual partners, initiation of higher-risk sexual activity due to a sense of security created by effective HIV therapeutics, and a longer lifespan of HIV-infected individuals.[46] Other risk factors associated with syphilis infection include underlying HIV infection and use of methamphetamines.[46]

A major obstacle to the diagnosis of syphilis is that many infected individuals are asymptomatic. In a cohort of 218 HIV-infected patients with newly detected and untreated syphilis, 60% were asymptomatic and, most likely, would have gone undiagnosed if not for annual screening.[2] A recent study in an Australian HIV clinic compared syphilis diagnoses in HIV-infected MSM before and after the implementation of syphilis serologic testing with every routine blood sample.[47] The proportion of asymptomatic HIV-infected MSM who tested positive for syphilis rose from 21% to 85% percent with the implementation of this routine screening intervention.[47] The Centers for Disease Control and Prevention and the United Kingdom National Screening and Testing Guidelines now recommend annual serologic testing for HIV and syphilis for sexually active MSM.[48,49]

The alteration of viral kinetics and the immunologic changes observed in Patient J support the possibility that intercurrent syphilis is a modulator of HCV treatment outcome. This would indicate that it is important to screen patients who are at risk for syphilis infection prior to initiating HCV antiviral therapy as well as counsel patients about the importance of safe sex. Syphilis screening may also be warranted among HCV-infected patients who demonstrate slow virologic clearance during HCV treatment, despite excellent adherence. Syphilis screening should also be considered among patients with dramatic CD4+ cell declines that exceed what is normally expected with peginterferon alfa therapy.

Acknowledgements and Disclosures

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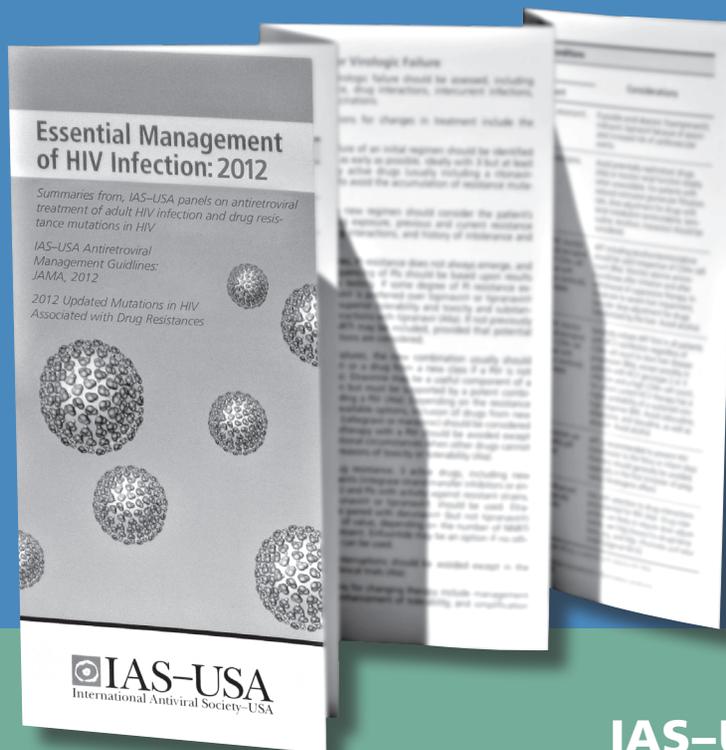1. Salazar JC, Cruz AR, Pope CD, et al. Treponema pallidum elicits innate and adaptive cellular immune responses in skin and blood during secondary syphilis: a flow-cytometric analysis. *J Infect Dis*. 2007;195(6):879-887.

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