EDITORIAL

Hepatitis C and HIV Co-infection
Closing the Gaps

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Hepatitis C virus (HCV) infection causes substantial morbidity and mortality, but patients with human immunodeficiency virus (HIV) co-infection are 3 times more likely to develop cirrhosis or liver decompensation than those infected with hepatitis C alone.[1] Unlike the treatment of HIV, for which the goal is viral suppression, treatment of hepatitis C is finite in duration, and the goal is to achieve a sustained virologic response (SVR), which is a lack of detectable HCV RNA at least 12 weeks after completion of treatment. Clinically, SVR is considered to represent eradication of hepatitis C infection, although reinfection is possible. Achieving SVR is associated with a significant decrease in subsequent decompensation of liver function, liver cancer, and all-cause mortality in persons with HIV co-infection.[2] However, treatment of hepatitis C in patients with HIV co-infection has been limited by the reluctance of many HIV clinicians to use interferon alfa and the hesitation of many hepatologists to treat persons with HIV.

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Two studies in this issue of *JAMA* suggest solutions to this clinical conundrum. In the TURQUOISE-I trial, Sulkowski and colleagues[3] studied the oral combination of paritaprevir (a protease inhibitor) pharmacokinetically enhanced by ritonavir (also used in regimens to treat HIV), plus ombitasvir (an NS5A inhibitor), and dasabuvir (a nonnucleoside NS5B polymerase inhibitor) (collectively referred to as 3D) and ribavirin for 12 or 24 weeks in patients with HIV and HCV co-infection. These patients either had not received prior HCV treatment (treatment naive) or did not achieve SVR with previous pegylated interferon alfa (pegIFN) plus ribavirin and had compensated cirrhosis or milder liver fibrosis. In all patients, HIV was virologically suppressed because of the concern about development of HIV resistance given receipt of ritonavir monotherapy. The authors reported SVR in 29 of 31 patients (94%) who received 12 weeks of 3D-plus-ribavirin therapy and 29 of 32 patients (91%) who received 24 weeks of therapy.

In another report in this issue of *JAMA*, Osinusi and colleagues[4] studied a more narrowly defined group of patients with HIV and HCV co-infection without prior HCV treatment and also without cirrhosis. These patients received the combination of ledipasvir (an NS5A inhibitor) plus sofosbuvir (a nucleotide NS5B polymerase inhibitor) for 12 weeks. Some patients were not receiving antiretroviral treatment for their HIV (unlike ritonavir, ledipasvir plus sofosbuvir does not have anti-HIV activity). Forty-nine of 50 patients (98%) achieved SVR.

No patients discontinued study drugs because of adverse events in either study. However, 10% of patients receiving the 3D-plus-ribavirin regimen had to reduce their doses of ribavirin because of anemia, underscoring the need for close monitoring of hemoglobin levels for patients treated with these agents. Two patients in the study by Sulkowski et al[3] and 1 patient in the study by Osinusi et al[4] experienced virologic failure. The 2 patients who had virologic failure while receiving 3D plus ribavirin both had cirrhosis and had previously not responded to pegIFN plus ribavirin. Patients with these clinical characteristics were excluded from the trial of sofosbuvir plus ledipasvir. Of note, both patients had variants associated with resistance to all 3 classes of direct antiviral agents (DAAs) contained in 3D plus ribavirin. The clinical significance of these variants for re-treatment of HCV remains unknown.

These 2 studies leave many questions unanswered, but details in each reinforce the transformative nature of new treatment regimens of all-oral DAAs. One key observation is that DAA-containing regimens result in equivalent SVR rates in patients co-infected with HIV/HCV compared with HCV-monoinfected patients. In the era of pegIFN plus ribavirin, the SVR rate for patients co-infected with HIV and genotype 1 HCV was 27% compared with 41% in an HCV monoinfection study.[5,6] In contrast, studies that include a DAA have closed this gap. This is reflected in current practice guidelines. The Guidelines for the Use of Antiviral Agents in HIV-1 Infected Adults and Adolescents[7] refers readers to the HCV guidance for HCV antiviral therapy recommendations. The HCV guidance states, "HIV/HCV-co-infected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications."[8] The Food and Drug Administration–approved product label for the combination of ledipasvir plus sofosbuvir (Harvoni) used the data from a clinical trial among patients with HIV/HCV co-infection (PHOTON-1) to support an indication for the combination of sofosbuvir plus ribavirin in patients infected with genotype 1 who were interferon ineligible, including those with HCV monoinfection. Because the data generated from trials involving HCV monoinfection and HIV/HCV co-infection are being treated as interchangeable from a clinical and regulatory standpoint, it is time to integrate patients with HIV/HCV co-infection into trials with patients with HCV monoinfection once appropriate antiretroviral drug interaction studies are complete.

Another important observation from these 2 reports is the closure of the gap in SVR rates between black patients and white patients with HCV infection. Black patients are disproportion-

ately affected by hepatitis C, with an estimated 1 of 12 black men in the United States who were born from 1945 through 1965 being infected.[9] The Viral Resistance to Antiviral Therapy of Chronic Hepatitis C (VIRAHEP-C) study found that black patients who were treated with pegIFN plus ribavirin had a 28% SVR rate compared with a 52% rate among white patients.[10] A subsequent discovery suggested that persons of African descent are more likely to have genetic polymorphisms near the *IL28B* gene that confer innate resistance to the antiviral actions of interferon alfa.[11] Initial studies of DAAs did not close this gap in SVR rates. In one of the phase 3 studies of the protease inhibitor boceprevir, black patients were studied as a separate cohort from nonblack patients and had a 53% SVR rate with 44 weeks of boceprevir plus pegIFN plus ribavirin compared with 68% in nonblack patients.[12] In the studies by Sulkowski et al[3] and Osinusi et al,[4] 57 of 133 patients (50%) were black. Because only 3 patients across both studies experienced virologic failure, the present results help extend the opportunity for high cure rates with non–interferon-containing regimens to black patients with hepatitis C infection.

A sobering finding in the study by Sulkowski et al[3] was that for 2 of the 3 patients who did not achieve SVR in the 24-week group, reinfection with a new strain of HCV occurred within 12 weeks after completion of treatment. Both patients reported unprotected intercourse with a sexual partner after treatment. A meta-analysis of studies examining HCV reinfection found that persons with HIV/HCV co-infection had a 23.6% reinfection rate.[13] Individuals who are most at risk for reinfection will need to be cured to achieve decreases in the incidence of HCV infection, an idea termed "cure as prevention." Clinicians who treat patients with hepatitis C must facilitate harm reduction measures as well as provide antiviral treatment to achieve the ultimate goal of eradication of hepatitis C. Cost-effectiveness studies that model the value of cure as prevention are needed to demonstrate that resources are well spent in treating persons with a high risk of reinfection.

Liver disease represents the second leading cause of death in persons infected with HIV.[14] The high SVR rates in these 2 studies suggest that future barriers to prevention of unnecessary deaths due to HCV may be related to failures of the health care system. Clinicians who care for patients with HIV infection are already skilled at selecting regimens, managing drug-drug interactions, optimizing adherence, and providing harm reduction counseling. These skills are exactly what is needed to treat patients with hepatitis C and to ensure that the successes seen in research trials are replicated in clinical practice. Many clinicians also have experience advocating for their patients, and this skill may be as valuable now as it was in the early days of HIV. With the current concern about the high price of these regimens, it is critical that the patients who are living with hepatitis C and the value of treating this disease remain front and center.

ARTICLE INFORMATION

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REFERENCES

1. Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis*. 2001;33(4): 562-569.

2. Limketkai BN, Mehta SH, Sutcliffe CG, et al. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfected with HIV/HCV. *JAMA*. 2012;308 (4):370-378.

3. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *JAMA*. doi:10.1001/jama.2015.1328.

4. Osinusi A, Townsend K, Kohli A, et al. Virologic response following combined ledipasvir and sofosbuvir administration in patients with HCV genotype 1 and HIV co-infection. *JAMA*. doi:10.1001 /jama.2015.1373.

5. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al; APRICOT Study Group. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004;351(5): 438-450.

6. McHutchison JG, Lawitz EJ, Shiffman ML, et al; IDEAL Study Team. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med*. 2009;361(6):580-593.

7. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Dept of Health and Human Services. http://aidsinfo.nih.gov /contentfiles/lvguidelines/AdultandAdolescentGL .pdf. Accessed February 7, 2015.

8. Unique patient populations: patients with HIV/HCV coinfection. http://www.hcvguidelines.org /full-report/unique-patient-populations-patients -hivhcv-coinfection. American Association for the Study of Liver Diseases, Infectious Diseases Society of America, International Antiviral Society-USA. Accessed February 7, 2015.

9. Smith BD, Morgan RL, Beckett GA, et al; Centers for Disease Control and Prevention. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep*. 2012;61 (RR-4):1-32.

10. Conjeevaram HS, Fried MW, Jeffers LJ, et al; Virahep-C Study Group. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology*. 2006;131(2):470-477.

11. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature*. 2009; 461(7262):399-401.

12. Poordad F, McCone J Jr, Bacon BR, et al; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med*. 2011;364(13):1195-1206.

13. Hill A, Saleem J, Heath KA, et al. Effects of sustained virological response (SVR) on the risk of liver transplant, hepatocellular carcinoma, death and re-infection: meta-analysis of 129 studies in 23,309 patients with hepatitis C infection. Presentation at: American Association for the Study of Liver Diseases Liver Meeting; November 7-11, 2014: Boston, MA.

14. Weber R, Sabin CA, Friis-Møller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med*. 2006;166(15):1632-1641.