

## HCV/HIV Coinfection: A New Treatment Paradigm

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Comment on:

Sulkowski MS, Naggie S, Lalezari J, et al. Sofosbuvir and ribavirin for hepatitis C in patients with HIV coinfection. *JAMA* 2014;312:353–361.

It is estimated that 7 million people are co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in the world (*J Hepatol* 2006;44:S6–9). HIV infection accelerates the progression of HCV, with higher rates of histologic fibrosis and cirrhosis, decompensated liver disease, and death. Until recently, treatment of HCV required the use of interferon-based regimens with long durations of therapy and significant side effects to achieve meaningful sustained virologic response (SVR; *N Engl J Med* 2006;355:2444–2451). Historically, HCV infection has been more challenging to treat in patients coinfecting with HIV owing to the hematologic effects of the therapy, the immune compromised host, and the drug–drug interactions with the first-generation protease inhibitors. It is estimated that 70% of individuals with HIV/HCV coinfection are not eligible for interferon-based therapies (*Clin Infect Dis* 2013;56:718–726). Owing to the natural history of HIV/HCV and an accelerated fibrosis rate, the current American Association for the Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA) guidelines recommend priority treatment for HCV/HIV coinfecting patients, regardless of liver fibrosis stage. Historically, SVR rates have been lower in the HIV/HCV coinfecting population and they have been thus considered a special population. In 1 study involving 711 patients treated with interferon and ribavirin, an overall SVR rate of 31% was achieved with the SVR rate being 18% for genotypes 1 and 4 and 50% for genotypes 2 and 3. This is markedly lower than non-HIV-infected SVR rates in patients with similar genotypes (*Hepatology* 2009;50:407–413). In 2011, the first direct-acting antiviral agents (DAAs), NS3/4A serine protease inhibitors, boceprevir and telaprevir were approved for HCV treatment in conjunction with pegylated interferon and ribavirin. The addition of telaprevir or boceprevir to pegylated interferon and ribavirin improved SVR rates to 74% and 63%, respectively, in genotype 1 HIV/HCV-infected individuals who were eligible for interferon-based therapy (*Ann Intern Med* 2013;159:86–96; *Lancet Infect Dis* 2013;13:597–605). Achieving SVR is important because coinfecting patient who achieve SVR have a significant decrease in incidence rates per 100 years of overall mortality, liver-related mortality, and liver decompensation (*Hepatology* 2009;50:407–413).

In 2013, 2 new DAAs were approved for treatment of HCV. Simeprevir, a protease inhibitor, was approved for patients with genotype 1 in combination with pegylated interferon and ribavirin for 24–48 weeks based on treatment response (*Lancet* 2014;384:403–413). Sofosbuvir, a nucleotide polymerase inhibitor, was also approved in 2013 in combination with pegylated interferon and ribavirin for 12 weeks for patients with genotypes 1 and 4 and with ribavirin alone for 12–24 weeks in genotypes 2 and 3. The overall SVR rate with triple combination was 90% among patients with predominantly genotype 1 and 4 at 12 weeks (*Lancet* 2014;384:403–413). Genotypes 2 and 3 may achieve SVR rates of approximately 90% with 12 or 24 weeks of sofosbuvir and ribavirin and do not require interferon (*N Engl J Med* 2013;368:1878–1887; *N Engl J Med* 2014;370:1993–2001).

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In the PHOTON-1 trial, the efficacy of an all oral, interferon-free regimen for HCV genotypes 1, 2, and 3 patients coinfecting with HIV was evaluated. This was a multicenter, open-label, nonrandomized, uncontrolled phase III trial involving 34 academic, private practice, and community health centers in the United States and Puerto Rico (JAMA 2014;312:353–361).

A total of 224 patients were included with 115 genotype 1 treatment-naïve patients assigned to receive sofosbuvir and ribavirin for 24 weeks, 68 treatment-naïve patients with genotype 2 or 3 assigned to receive sofosbuvir with weight-based ribavirin for 12 weeks, and 41 patients treatment experienced patients with HCV genotype 2 or 3 assigned to receive sofosbuvir and ribavirin for 24 weeks. The SVR rate in the genotype 1 treatment-naïve group was 76%. Treatment-naïve patients with HCV genotypes 2 and 3 achieved SVR12 of 88% and 67% with 12 weeks of treatment. Patients with treatment experienced genotype 2 and 3 achieved SVR12 rates of 92% and 94% after receiving treatment for a total of 24 weeks.

The PHOTON-1 study provides a glimpse at the future of HCV therapy for coinfecting individuals as SVR rates were comparable with or superior to interferon-based therapies for genotypes 1, 2, and 3, with an all oral regimen free of interferon for 12–24 weeks. The inclusion criteria for this study was markedly broader owing to the lack of drug–drug interactions with sofosbuvir compared with other classes, such as protease inhibitors, and included regimens containing emtricitabine–tenofovir in combination with atazanavir ritonavir, darunavir, ritonavir, efavirenz, raltegravir, or orilpivirin. This lack of interaction of sofosbuvir with the cytochrome P450 3A4 metabolized drugs allowed the administration of this therapy in combination without dose adjustment or adjustment of frequency of dosing which is a major advance of the treatment of HCV in those coinfecting with HIV. In the genotype 1 population, the SVR rate of 76% was comparable with the SVR rate reported with pegylated interferon–based therapies with first-generation protease inhibitors and occurred in one-half the duration (24 weeks). Moreover, this SVR rate was achieved in a population that had contraindications to interferon, including psychiatric illnesses, seizure disorders, autoimmune disorders, and other comorbidities that had historically excluded patients from interferon-based therapies for HCV. The SVR rates in genotypes 2 and 3 treatment-naïve and treatment-experienced populations were similar to the SVR rates reported with sofosbuvir and ribavirin when given in non–HIV-infected populations and superior to those reported with interferon-based therapies. Moreover, patients did not require erythropoietin or other support, and the rate of completion in this study was markedly greater than noted in those receiving interferon-based therapies with or without DAAs owing to the excellent safety profile of sofosbuvir, as well as the high barrier to resistance. Indeed, with both telaprevir- and boceprevir-based therapies, therapy was discontinued owing to adverse events as well as development of resistance-associated variants. In the PHOTON-1 study, the resistance-associated variant S282T was not identified in any subject who failed to achieve SVR and those who developed breakthrough had undetectable levels of sofosbuvir, suggesting noncompliance. For genotypes 2 and 3, greater SVR rates were seen when treatment was extended to 24 weeks in the treatment-experienced group, but importantly the therapy was well-tolerated with an additional 12 weeks conferring no increase in adverse events. Patients with genotype 3 treated for 12 weeks showed lesser SVR rates of 67% as expected given the recommended treatment duration of 24 weeks in those without HIV coinfection.

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The genotype 1 SVR rates for this population still lag behind what has been reported for non-HIV coinfecting HCV patients where SVR rates of >95% have been reported using combinations of DAAs with and without ribavirin (N Engl J Med 2014;370:1483–1493; N Engl J Med 2014;370:1889–1898; N Engl J Med 2014;370:1594–1603; N Engl J Med 2014;370:1604–1614; N Engl J Med 2014;370:1973–1982). This study did not include patient with treatment experienced genotype 1, although it is likely that higher rates of SVR will be seen when multiple DAA classes are combined. The PHOTON-1 results have been confirmed in the PHOTON-2 study where SVR rates were 85%, 88%, 89%, and 84% among patients with genotype 1, 2, 3, and 4, respectively. This was observed in a population that included genotype 1 nonresponders (Molina et al, Program and Abstracts of the 20th International AIDS Conference, 2014) and safety of this regimen of sofosbuvir and ribavirin for 24 weeks was again confirmed. Even with these high SVR rates, preliminary data using the combinations of DAAs in HIV/HCV-coinfecting individuals suggest that SVR rates will be comparable with those achieved without HIV coinfection (Molina et al, Program and Abstracts of the 20th International AIDS Conference, 2014; J Hepatol 2014;60:S7). The CORAL-1 study demonstrates that the combination of paritaprevir, ombitasvir, and dasabuvir with ribavirin may be given to genotype 1–infected HIV patients with an overall SVR rate of 93% in those receiving atazanavir- or raltegravir-based antiretroviral. A small study has reported high SVR rates with combination of sofosbuvir/ledipasvir in HIV/HCV coinfecting individuals receiving tenofovir/emtricitabine plus efavirenz or raltegravir or rilpivirine (97%) or no antiretroviral therapy (100%; Hepatology 2014;60:236A–241A).

#### Comment

The PHOTON-1 study heralds the era where special populations, such as HIV/HCV coinfecting individuals, will be able to experience the same high SVR rates as those without HIV coinfection. It is likely that sofosbuvir and ribavirin will not be the first line therapy for coinfecting individuals, because combinations of DAAs will prove to be more effective. Removing interferon from the therapy is a dramatic leap forward for this population, who can now experience SVR rates higher than ever seen in the interferon era across all genotypes. However, the elimination of ribavirin is also a worthwhile goal, and preliminary data suggest that this too is on the horizon. Finally, although these high SVR rates are encouraging for all clinicians who treat the HIV/HCV-coinfecting population, access to therapies worldwide will also be important. This requires a collaborative effort including physicians, governments and policy makers, drug developers, and insurers. Nonetheless, the future of therapy for HIV/HCV coinfecting individuals has arrived, and we are on the verge of moving one of the largest special populations of HCV-infected individuals worldwide into the not-so-special category.

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