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PHOTON-2: Light at the end of the tunnel for those with HIV/HCV co-infection

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About 4-5 million people are chronically infected with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) globally.¹ Compared to those with HCV infection alone, patients with HIV/HCV co-infection have higher rates of cirrhosis, hepatocellular carcinoma, and hepatic decompensation, which can be prevented by use of antiviral agents to achieve clinical cure defined as sustained virologic response (SVR).² This more rapid progression of natural history and historically low SVR rates to interferon based therapies led the Food and Drug Administration (FDA) to identify HIV/HCV co-infection as an unmet medical need.³ The first two direct acting antivirals (DAA) approved by the FDA in 2011, telaprevir and boceprevir, were not approved in HIV-infected patients, limiting access in many jurisdictions. For those with access to this first wave of DAAs, drug interactions and continued need for interferon complicated treatment of this high-risk population. To meet the significant need for better treatment options for this population, the development of sofosbuvir, a first-in-class potent NS5B nucleotide analogue with activity against all genotypes, limited pharmacologic interactions and excellent safety profile lent hope that HIV-infected patients might stand upon even ground with those without HIV.

The PHOTON studies represented the phase 3 program for sofosbuvir in combination with ribavirin in HIV-infected patients, and uniquely, an interferon-free regimen was pursued for all major genotypes, capitalizing on the pan-genotypic activity of sofosbuvir.^{4, 5} Following on the heels of PHOTON-1, PHOTON-2 was optimized based not only on its predecessor, but also registration trials in HCV mono-infection.^{4, 6, 7} Key differences were inclusion of patients infected with genotype 4 and extension of treatment from 12 to 24 weeks for treatment naïve patients with genotype 3 HCV infection, who responded poorly to 12 weeks in those trials. Investigating 12 weeks of therapy in treatment naïve genotype 2 infection and 24 weeks in all other groups, PHOTON-2 confirmed the pan-genotype potential of sofosbuvir, reporting SVR in 84-89% of all patients. The PHOTON studies were critical to the approval of sofosbuvir for HIV-infected patients, the first DAA to achieve this milestone,

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and they support use of sofosbuvir and ribavirin for genotype 2 and 3 infection in this population.

PHOTON-2 adds to a growing literature that challenges the dogma from the interferon-ribavirin era that those with HIV respond less well to anti-HCV treatment than their HIV negative counterparts. While not head-to-head trials, phase 3 DAA studies in HIV co-infected patients have produced similar SVR rates to HCV mono-infected studies. For instance, addition of simeprevir to pegylated interferon and ribavirin resulted in almost identical SVR when treatment-experience and other predictors of treatment success are considered, as well as similar safety profiles.⁸ Preliminary studies in co-infected patients suggest that similar efficacy and safety can be expected from other interferon-free regimens, such as the recently FDA-approved ledipasvir/sofosbuvir fixed-dose combination and the combination of paritaprevir/ritonavir/ombitasvir with dasabuvir.^{9, 10} With HIV seemingly no longer on the list of negative predictors for successful anti-HCV therapy, the expectation of similar efficacy rates has led to recommendations to utilize the same regimens as used for monoinfection in guidelines for the United States and Europe.^{11, 12}

What barriers remain for this goal of “equal eradication”? Firstly attention must be paid to drug interactions between novel anti-HCV medications and antiretrovirals. The sofosbuvir/ribavirin regimen utilized in PHOTON-2 remains the standard of care for genotype 2 and 3 infections and has few limitations with antiretrovirals. Recently approved combinations of DAAs with higher efficacies against genotypes 1 and 4 exhibit increased potential of drug interactions, complicating treatment for patients with multiple co-morbidities including HIV.^{13, 14} In our brief experience applying these new combination regimens, some patients will be able to maintain their current antiretrovirals while others will require careful substitutions and/or close monitoring. In this turbulent world of DAA pricing and exclusivity agreements, it remains unclear whether providers and patients will maintain autonomy with antiretroviral management decisions if choices for anti-HCV regimens are restricted.

The PHOTON-2 study should be viewed as an advance for HIV-infected patients, furthering the body of literature that supports efficacy and safety of DAA regimens in this population. As we eagerly await results from phase 3 trials of combination therapies in HIV/HCV patients we must also prepare for challenges ahead. It is not yet clear whether effectiveness and impact on mortality will be similar for these regimens in the “real world”, especially for patients with additional psychosocial barriers. While there is renewed hope that together we can work towards eradication of HCV and reducing the burden of liver-disease for co-infected patients, it is tempered by the disparity of access to DAA regimens across the globe. Although the disparity in treatment response is a barrier HIV patients are overcoming, we must work to ensure that these “rays of hope” from the PHOTON studies are realized for all.

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