Interferon-Containing and Interferon-Free HCV Therapy for HIV-Infected Patients

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Abstract

In the era of effective treatment for human immunodeficiency virus (HIV) infection, coinfection with hepatitis C virus (HCV) is an important cause of morbidity and mortality. Similar to other observations made in other HCV-infected patient populations, treatment of chronic HCV infection that results in sustained virologic response or eradication of the hepatitis infection has been strongly associated with decreased likelihood of end-stage liver disease and/or hepatocellular carcinoma and improved overall survival in HIV-infected patients. However, the effectiveness of HCV treatment has been limited due to frequent contraindications to interferon-α (INFα) and prior to the advent of HCV direct acting antivirals, relatively low rates of sustained virologic response. Since 2011, the efficacy of HCV treatment in coinfected patients has improved substantially with the addition of HCV direct-acting antivirals to INFα-based regimens. Based on these observations, there is mounting optimism that INFα-free, oral HCV treatments will further improve efficacy, and more importantly, increase access to treatment for many coinfected patients.

Keywords
► human immunodeficiency virus
► hepatitis C virus interferon
► direct-acting antivirals
► protease inhibitors
► polymerase inhibitors
► NS5A inhibitors

Due to shared modes of transmission, hepatitis C virus (HCV) infection is common in persons living with human immunodeficiency virus (HIV) infection.1,2 Increasingly, liver disease due to chronic HCV is a major cause of morbidity and mortality in this population and represents a leading cause of death in many settings.3,4 Current guidelines recommend that patients with HIV/HCV coinfection undergo HCV treatment with the combination of peginterferon (PegIFN) and ribavirin (RBV).5,6 Indeed, on the basis of large randomized controlled trials, the combination of PegIFN α-2a and RBV is approved for the treatment of hepatitis C in HIV-infected patients in the United States and other countries.7–9 More recently, data from several large prospective longitudinal HIV cohort studies have provided strong evidence that HCV treatment that results in sustained virologic response or cure of chronic HCV infection is associated with decreased risk of end-stage liver disease, hepatocellular carcinoma, and liver-related death.10,11

Despite the high burden of HCV disease and the availability of antiviral treatment that has been shown to improve clinical outcomes, few persons with HIV/HCV coinfection have been treated with PegIFN/RBV and even fewer have achieved sustained virologic response.12–14 For example, less than 10% of HIV/HCV coinfected patients receiving care in the United States Veterans Affairs system have received PegIFN based HCV treatment; in the Johns Hopkins HIV clinic, only 15% of patients treated with PegIFN/RBV achieved a sustained virologic response.10,15 The reasons for the limited effectiveness of PegIFN based HCV treatment in this population include (1) high prevalence of medical (e.g., anemia, acquired immunodeficiency syndrome [AIDS]) and psychiatric (e.g., depression) comorbid conditions in patients with HIV/HCV coinfection that may prevent the safe administration of PegIFN; (2) higher levels of HCV RNA in the blood in patients with HIV infection compared with those without HIV infection; (3) blunted antiviral response to PegIFN in HIV/HCV coinfected patients relative to HCV monoinfected patients; (4) relatively high incidence of treatment related-adverse effects that impair the ability of HIV/HCV coinfected patients to adhere to prolonged course of IFN and limit the willingness
of coinfected patients and their HIV care providers to initiate HCV treatment with this drug.\textsuperscript{16–18} Accordingly, more effective and better tolerated HCV treatment regimens represent an important unmet medical need for patients with HIV/HCV coinfection.

The expectation is that this urgent medical need will be addressed by many of the multitude of novel HCV antivirals that are in late-stage clinical development. In 2011, the first of these direct-acting antivirals (DAAs), telaprevir and boceprevir, were approved for the treatment of chronic HCV genotype 1 infection in combination with PegIFN/RBV.\textsuperscript{19,20} These oral drugs directly inhibit the HCV NS3/4A protease, leading to potent inhibition of HCV replication. In 2013, sofosbuvir, a once daily, oral DAA that inhibits the active site of the HCV NS5B polymerase, and simeprevir, a once daily, oral DAA that inhibits the HCV NS3/4A protease, were approved in combination with PegIFN/RBV for the treatment of HCV genotype 1 infection; in addition, sofosbuvir was approved in combination with RBV for the treatment of HCV genotype 2 and 3 infections, heralding the advent of IFN-free therapy for this subset of patients.\textsuperscript{21,22} Further, by 2015, potent, INF-free, combinations of DAAs are expected to become available for the treatment of patients infected with HCV genotypes 1 and 4.\textsuperscript{23,24}

Although these IFN-free regimens promise to transform the management of HCV infection, important questions about their effectiveness in HIV/HCV coinfected patients remain to be answered: 1) Will the antiviral efficacy of these regimens be blunted by HIV infection? 2) Will unanticipated adverse effects emerge in HIV/HCV coinfected patients? 3) Will clinically important drug interactions exist between antiretroviral drugs used to treat HIV infection and direct acting antivirals used to treat HCV infection?

**Limited Effectiveness of Interferon Based HCV Treatment in Patients with HIV Infection**

Interferon-\(\alpha\) (INF\(\alpha\)) has been used extensively in persons with HIV infection. Prior to the advent of targeted anti-HIV medications, INF\(\alpha\) was used to treat HIV infection. In vitro, HIV replication can be inhibited by type I IFNs through the induction of proteins with anti-HIV-1 activity. For example, Kane and coworkers recently demonstrated that myxovirus resistance 2 (Mx2) is an IFN-induced inhibitor of HIV-1 infection that may act by inhibiting capsid-dependent nuclear import of subviral complexes.\textsuperscript{25} In vivo, clinical trials have consistently demonstrated modest anti-HIV activity of INF\(\alpha\). In 1990, clinical trials demonstrated that IFN alfa alone or in combination with zidovudine could decrease HIV-1 isolation and slow HIV disease progression.\textsuperscript{26} More recently, Asmuth and colleagues from the AIDS Clinical Trials Group A5192 team found that weekly PegIFN \(\alpha-2a\) (180 mcg) led to a median plasma HIV viral load decrease of 0.61 \(\log_{10}\) copies/mL (90% confidence interval: 0.20–1.18 \(\log_{10}\) copies/mL).\textsuperscript{27}

While the role of INF\(\alpha\) remains under investigation in the effort to cure chronic HIV infection, its utility in the treatment of chronic HCV infection has been limited by multiple factors including (1) Adverse effects that restrict patient eligibility for its use in all patient populations, and (2) impaired antiviral response in patients with HIV/HCV coinfection compared with those with HCV alone. First, at doses used to treat hepatitis C infection, INF\(\alpha\) is associated with fatigue, depression, and bone marrow suppression, leading to lymphopenia and neutropenia as well as a myriad of other side effects.\textsuperscript{28} Not unexpectedly, many patients with HIV/HCV coinfection have medical and/or psychiatric contraindications to the use of INF\(\alpha\). For example, in an examination of the United States Veterans Affairs Clinical Case Registry, only 35\% of HCV-infected patients were deemed eligible for IFN-based treatment and only ~7\% of HIV/HCV coinfected patients had received treatment.\textsuperscript{14,15} Second, INF\(\alpha\) therapy appears to be less effective for the treatment of HCV in patients with HIV infection compared with those with HCV alone. In studies of HCV kinetics with INF\(\alpha\) therapy, Sherman and colleagues found that after 48 weeks of treatment HCV RNA level was undetectable at 72 weeks in 25\% and 40\% of HIV/HCV coinfected and HCV monoinfected patients, respectively.\textsuperscript{29} The researchers reported that HIV infection was associated with prolonged viral clearance and that the basis of this delayed HCV clearance was due primarily to higher levels of HCV RNA at baseline in coinfected patients compared with monoinfected patients.

The observation that HIV-infected patients have higher levels of HCV RNA than HIV-uninfected patients is well established. Indeed, as early as 1994, Oyster and coworkers observed that HCV RNA levels increased in men with hemophilia following HIV seroconversion and multiple studies of patients with chronic HCV infection have demonstrated that those with HIV coinfection have higher levels of hepatitis C viremia compared with those without HIV.\textsuperscript{30–32} Recently, Balagopal and colleagues demonstrated that the level of HCV RNA decreased following the initiation of antiretroviral therapy in 19 patients with untreated HIV infection who had a median (range) CD4\(^+\) T lymphocyte count and HIV RNA level at baseline were 425 cells/\(\mu\)L (219–690) and 4.27 \(\log_{10}\) cp/mL (2.91–5.44), respectively. The researchers observed two distinct phases. In the first 12 weeks following initiation of antiretrovirals, HCV RNA levels increased in 18 of 19 patients (94.7\%) by a median of 0.28 \(\log_{10}\) IU/mL. However, after a median of 175 days of antiretroviral therapy, HCV RNA levels decreased to a level below baseline in 16 of 19 (84.2\%). The absolute within-individual decline from baseline in HCV RNA was modest (median change in HCV RNA, -0.21 \(\log_{10}\) IU/mL).

Interestingly, the decline in HCV RNA was closely associated with change in expression of several hepatic IFN-sensitive genes (ISGs) including among others, IFIT1 and IFIT2.\textsuperscript{33} This observation points toward a direct or indirect effect of HIV infection on the mechanism for control of HCV replication and support treatment with antiretroviral therapy in most HIV/HCV coinfected patients.

While interesting, the effect of HIV treatment on HCV RNA levels is modest and the impact of high HCV RNA on response to INF\(\alpha\) therapy is also well established in patients taking concurrent antiretroviral therapy. In the APRICOT study, HIV/HCV coinfected patients were treated with PegIFN \(\alpha-2a\) and a fixed dose of RBV (800 mg/d) for 48 weeks. Coinfected
patients with HCV RNA levels greater than 800,000 copies/mL prior to treatment had a sustained virologic response rate of 18% (23 of 130 patients); in contrast, those with HCV RNA levels less than 800,000 copies/mL prior to treatment had a sustained virologic response rate of 61% (28 of 46 patients). 7

By comparison, in the study by Hadziyannis and colleagues, HCV monoinfected patients were treated with the same regimen, PegIFN α-2a and fixed-dose RBV (800 mg/d) for 48 weeks. Monoinfected patients with HCV RNA levels greater than 800,000 copies/mL prior to treatment had a sustained virologic response rate of 36%; in contrast, those with HCV RNA levels less than 800,000 copies/mL prior to treatment had a sustained virologic response rate of 55%. 34 In this cross-study comparison of patients with high HCV RNA levels, the efficacy of PegIFN-based therapy was markedly lower in patients with HIV/HCV coinfection (18%) compared with HCV monoinfected (36%) (Fig. 1).

**Table 1** Sustained virological response for oral direct-acting antiviral regimens for the treatment of HCV genotype 1 infection in HIV-infected adults

<table>
<thead>
<tr>
<th>Direct acting antiviral agent (Oral)</th>
<th>Peginterferon (Subcutaneous injection)</th>
<th>Ribavirin (Oral)</th>
<th>Regimen duration</th>
<th>Sustained virological response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telaprevir 750 mg every 8 h 36</td>
<td>Alfa-2a 180 μg/wk</td>
<td>1000 or 1200 mg/d</td>
<td>48 wks (telaprevir for the initial 12 wks only)</td>
<td>74% (28 of 38)</td>
</tr>
<tr>
<td>Boceprevir 800 mg every 8 h 35</td>
<td>Alfa-2b 1.5 μg/kg/wk</td>
<td>Ribavirin 600–1400 mg/d</td>
<td>48 wks (48 wks for peginterferon and ribavirin; 44 wks for boceprevir)</td>
<td>63% (40 of 64)</td>
</tr>
<tr>
<td>Simeprevir 150 mg once daily 37</td>
<td>Alfa-2a 180 μg/wk</td>
<td>1000 or 1200 mg/d</td>
<td>24 or 48 wks based on HCV RNA response at treatment week 4 (simeprevir for the initial 12 wks only)</td>
<td>79% (42 of 53)</td>
</tr>
<tr>
<td>Sofosbuvir 400 mg once daily 40</td>
<td>Alfa-2a 180 μg/wk</td>
<td>1000 or 1200 mg/d</td>
<td>12 wks (all drugs)</td>
<td>89% (17 of 19)</td>
</tr>
<tr>
<td>Sofosbuvir 400 mg once daily 41</td>
<td>None</td>
<td>1000 or 1200 mg/d</td>
<td>24 wks (all drugs)</td>
<td>76% (87 of 114)</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

**Fig. 1** Sustained virological response rate with peginterferon alfa-2a 180 μg weekly plus ribavirin 800 mg per day in human immunodeficiency virus-infected 7 and uninfected patients 34 with hepatitis C virus (HCV) genotype 1 infection and high levels of HCV RNA level prior to treatment (> 800,000 copies/mL). 7

Taken together, low rates of INFα eligibility and reduced efficacy have led to markedly limited effectiveness of IFN-based therapies in HIV/HCV coinfected patients. For example, in the Johns Hopkins HIV clinic, less than 1% of ~845 HIV/HCV coinfected patients engaged in HIV care had achieved sustained virologic response.12 As such, strategies with antiviral agents that directly target the hepatitis C virus are urgently needed to increase the rate of sustained virologic response. Although the removal of INFα will be necessary to increase the proportion of HIV/HCV coinfected patients who are willing and able to undergo HCV treatment, the addition of highly active, oral HCV direct acting antivirals to PegIFN plus RBV in an important step toward IFN-free regimens.

**Similar Antiviral Contribution of Oral Direct Acting Antivirals to Peginterferon/Ribavirin in Patients with and without HIV Infection**

Antiviral agents that directly target HCV have shown great promise for the treatment of HIV/HCV coinfected patients (Table 1). To date, multiple studies have been reported for the treatment of HCV genotype 1 infection in HIV-infected patients with PegIFN plus RBV in combination with a single direct acting antiviral agent, including NS3/4A protease inhibitors such as telaprevir, boceprevir, simeprevir, and the nucleotide analogue NS5B polymerase inhibitor, sofosbuvir.35,36 Although in some cases, these data are preliminary in nature, the observed sustained virologic response rates in patients with HIV infection are similar to those observed in patients without HIV infection who were treated with the same HCV regimen. In the study of telaprevir plus PegIFN and RBV for the treatment of HCV genotype 1 infection in patients with HIV infection, sustained virologic response occurred in 74% (28 in 38 patients).36 In a separate study of telaprevir plus PegIFN and RBV for the treatment of HCV genotype 1 infection in patients without HIV infection, sustained virologic response occurred in 74% (28 in 38 patients).
response occurred in 75% (271 of 365 patients).

Similarly, for the regimen of boceprevir in combination with PegIFN and RBV, the sustained virologic response rate in patients with HCV genotype 1/HIV coinfection was 63% (40 of 64 patients). In the study of boceprevir plus PegIFN and RBV by Poonad and colleagues, the corresponding sustained virologic response rate in persons with HCV genotype 1 infection alone was 68% (213 of the 311 patients).

The combination of simeprevir plus PegIFN and RBV has also been investigated in patients with and without HIV infection. In a study of 106 patients with HIV and HCV genotype 1 coinfection treated with this regimen, the overall sustained virologic response rate was 74% and, among those who had not undergone prior HCV treatment (naïve), the efficacy was 79%.

In two studies of HIV-uninfected persons with HCV genotype 1 infection who were treatment naïve, the regimen of simeprevir plus PegIFN and RBV led to sustained virologic response in 80% of patients.

Finally, in a small study of sofosbuvir plus PegIFN and RBV conducted by Rodriguez-Torres and coworkers in the Commonwealth of Puerto Rico, 23 patients with HIV and HCV genotype 1 (n = 19), 2 (n = 1), 3 (n = 2), and 4 (n = 1), coinfection was treated with this regimen for 12 weeks. The overall rate of sustained virologic response was 91%, including 17 of 19 (89%) of patients infected with HCV genotype 1.

This regimen of sofosbuvir plus PegIFN and RBV was also studied by Lawitz and colleagues in HIV-uninfected patients in the NEUTRINO study; in patients with HCV genotype 1 infection, the sustained virologic response rate was 89%.

Although the studies of a single DAA plus PegIFN and RBV are relatively small and do not directly compare the efficacy in patients with or without HIV coinfection, the HCV treatment regimens have achieved similar efficacy in both patient populations. Indeed, the regulatory approvals in the United States and Europe of the nucleotide analogue NS5B polymerase inhibitor, sofosbuvir, provide labeling for the use of this agent in patients with HIV coinfection. Similarly, the regulatory approval in the United States (pending in Europe) of the HCV NS3/4A protease inhibitor, simeprevir, provides specific recommendations for drug interactions of this drug and commonly prescribed antiretroviral agents. Further, these data provide strong support for the hypothesis that oral, DAA will have similar anti-HCV efficacy in the setting HIV infection and that the ability of the host to eradicate chronic HCV infection during antiviral treatment is not adversely impacted by the direct or indirect effects of HIV infection. Based on these promising results with INFs, the removal of INFα from combination HCV treatment regimens is expected to increase patient eligibility for treatment as well as result in greater efficacy in the setting of high levels of HCV RNA.

**Encouraging Preliminary Data for Interferon-Free, Oral Direct Acting Antiviral Therapy in HIV-Infected Patients**

Adequate tests of the hypothesis that efficacy will be similar in patients with and without HIV infection will require large, adequately powered studies in both patient populations; at this time, many such studies have been initiated (Table 2). To date, the PHOTON-1 study is the only IFN-free study to report sustained virologic response data. In this study, sofosbuvir and weight-based RBV were administered to 114 treatment-naïve patients with HCV genotype 1 for 24 weeks and 68 treatment-naïve patients with HCV genotype 2 or 3 for 12 weeks. Among treatment-naïve patients with HIV infection, the sustained virologic response rates were 76% for patients with genotype 1 infection, 88% for patients with genotype 2 infection, and 67% for patients with genotype 3 infection.

This same regimen, sofosbuvir plus weight based RBV for 12 or 24 weeks, has also been studied in HIV-uninfected patients in two different studies. Similarity, in the FISSION study, Lawitz and colleagues reported that 68% of patients treated with sofosbuvir and weight-based RBV for 24 weeks achieved sustained virologic response.

Similarly, in the FISSION study, Lawitz and colleagues reported that sustained virologic response occurred in 97% of patients with genotype 2 and in 56% of those with genotype 3 treated with sofosbuvir and weight-based RBV for 12 weeks.

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**Table 2** Clinical trials of Interferon-free, oral direct-acting antiviral regimens for the treatment of HCV infection in HIV-infected adults

<table>
<thead>
<tr>
<th>HCV treatment regimen</th>
<th>ClinicalTrials.gov identifier</th>
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<tbody>
<tr>
<td>NS5A inhibitor</td>
<td></td>
</tr>
<tr>
<td>NS5B nucleotide analogue polymerase inhibitor</td>
<td></td>
</tr>
<tr>
<td>NS5B non-nucleoside analogue polymerase inhibitor</td>
<td></td>
</tr>
<tr>
<td>Ribavirin</td>
<td></td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>NCT01878799</td>
</tr>
<tr>
<td>Ledipasvir</td>
<td>NCT02032888</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td></td>
</tr>
<tr>
<td>ABT267</td>
<td></td>
</tr>
<tr>
<td>ABT333</td>
<td>1000 or 1200 mg/d</td>
</tr>
<tr>
<td>MK-5172</td>
<td>NCT01717326</td>
</tr>
<tr>
<td>MK-8742</td>
<td>NCT01939197</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.
Additional studies of IFN-free, oral DAAs for the treatment of HCV in HIV-infected patients are underway. At the National Institute of Allergy and Infectious Diseases (NIAID), the combination of sofosbuvir and the HCV NS5A inhibitor, ledipasvir, is being evaluated in 100 patients with HIV and HCV genotype 1 infection who are not being treated for HIV infection (CD4 > 500 cells/mm³) or who have suppressed HIV-1 RNA on antiretroviral therapy regimens consisting of medications from the following: tenofovir, emtricitabine, efavirenz, raltegravir, and rilpivirine (ClinicalTrials.gov Identifier: NCT01878799). Similarly, in the ALLY-2 study, HIV-infected patients who are chronically infected with HCV genotype 1, 2, 3, 4, 5, or 6 are being treated with the combination of the sofosbuvir and the HCV NS5A inhibitor, daclatasvir, for 8 or 12 weeks (ClinicalTrials.gov Identifier: NCT02032888). Also underway is the TURQUOISE-I study, which will evaluate the safety and efficacy of the coformulated ritonavir-boosted HCV NS3/4A protease inhibitor, ABT-450, and the HCV NS5A inhibitor, ABT-267 (ABT-450/rt/ABT-267), in combination with the HCV NS5B nonnucleoside polymerase inhibitor, ABT-333, and RBV in HIV-infected patients with HCV genotype 1 infection (ClinicalTrials.gov Identifier: NCT01939197). Lastly, the C-WORTHY study is evaluating the safety and efficacy of the two-drug combination of the second-generation HCV NS3/4A protease inhibitor, MK-5172, plus the second-generation HCV NS5A inhibitor, MK-8742, with or without RBV in HCV genotype 1 infected patients with and without HCV coinfection (ClinicalTrials.gov Identifier: NCT01717326). Interesting, the C-WORTHY study is enrolling both patient populations—HIV-infected and uninfected patients—in the same HCV study protocol. This study design underscores the emerging recognition that HIV-infected patients may not be unique in terms of the effectiveness of oral, IFN-free DAA regimens.

Conclusions

Multiple IFN-free clinical trials are underway in persons with HIV/HCV coinfection; these studies are anticipated to demonstrate that oral, DAAs for HCV have similar efficacy in patients with and without HIV coinfection, lending additional support to the hypothesis that HIV coinfection does not adversely impact the effectiveness of these highly active HCV treatments. If, as expected, these studies yield high rates of sustained virologic response with acceptable safety and tolerability profiles, the remaining challenge to the management of HCV infection in persons with HIV coinfection will be the need to carefully consider the potential drug interactions between the patient’s antiretroviral drug regimen and the HCV DAA drug regimen. For some patients’ and some drug regimens, this may represent the combination of as many as 10 unique antiviral drugs each with a different mechanism of action to inhibit HIV or HCV or to block antiviral drug metabolism through inhibition of the patient’s cytochrome P450 pathways with pharmacologic enhancers, such as ritonavir or cobicistat.

Full understanding of the potential for drug interactions between highly active drug regimens for the treatment of HCV and HIV is required before these regimens can be safely combined for routine use in clinical practice. Indeed, due to complex drug interactions with some antiviral agents, the expectation is that not all antiretroviral regimens will be able to be safely combined with all HCV DAA regimens; as such, clinicians who treat patients with HIV/HCV coinfection will need to carefully select the most appropriate HIV and HCV treatment regimens for each patient. However, it is important to recognize that HCV treatment is finite, leading to cure of the chronic HCV infection. Further, the anticipated duration of HCV treatment with oral DAAs will be only 12 or 24 weeks for most HCV/HCV coinfected patients. Accordingly, complex drug interactions will not be an insurmountable barrier to HCV eradication for patients with HIV coinfection. Of course, the availability of safe and effective oral HCV DAAs is merely the first step toward controlling HCV disease in HIV-infected patients; comprehensive strategies to effectively and economically deliver these HCV treatments to the nearly 5 million patients with HIV/HCV coinfection worldwide will be critical to effectively address this curable, life-threatening infection.

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