

# Update on Hepatitis C Virus and HIV Coinfection

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## Abstract

Chronic hepatitis C virus (HCV) infection has historically been difficult to treat in the HIV-infected population, owing to generally poor responses to interferon-based therapies. The recent rapid development of directly acting antiviral agents (DAAs) against HCV has the potential to revolutionize treatment of this infection in the HIV population by improving tolerability and outcome, and, ultimately, reducing the significant burden of liver-related morbidity and mortality in this population. Clinical trials to address the safety and efficacy of novel DAAs in the HCV/HIV coinfecting population are ongoing, and show much promise. The rapidity of current drug discovery in the field of HCV is both impressive and daunting for clinicians who will have to master these drugs. Going forward, the inclusion of individuals from this large and growing patient population in clinical trials will be of paramount importance.

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## Introduction

The advent of effective combination antiretroviral therapy (ART) nearly two decades ago has resulted in a gradual transition in HIV treatment, with more HIV-infected patients receiving therapy earlier in the course of disease. This, in turn, has resulted in non-HIV-related comorbidities becoming a greater contributor to mortality in this population. Perhaps the most striking of these HIV-related non-AIDS conditions (HANA) is liver disease, largely secondary to viral hepatitis. In 2006, the landmark SMART (Strategies for Management of Antiretroviral Therapy) trial demonstrated increased morbidity and mortality secondary to HANA conditions, such as liver disease, renal disease, and cardiovascular disease, in

patients receiving intermittent ART with subsequent fluctuations in viral load and CD4 counts.<sup>1</sup> These findings, coupled with data from large cohort studies, led to sequential changes in national guidelines recommending treatment initiation at higher CD4 counts.<sup>2,3</sup>

Chronic hepatitis C virus (HCV) infection has historically been difficult to treat in the HIV-infected population, owing to generally poor responses to interferon (IFN)-based therapies. The recent rapid development of directly acting antiviral agents (DAAs) against HCV has the potential to revolutionize treatment of this infection in the HIV population, improving tolerability and outcome, and ultimately reducing the significant burden of liver-related morbidity and mortality in this population.

## Epidemiology of Hepatitis C Virus and HIV Coinfection in 2013

It is estimated that around 170 million people around the world are infected with HCV, and 40 million with HIV. A national survey in the USA, the National Health and Nutrition Examination Survey (NHANES), conducted in 1999–2002, showed an HCV prevalence of 1.6% and an estimated 3.1 million people having chronic HCV infection.<sup>4</sup> Another recent NHANES revealed an HCV seroprevalence of 1.68%.<sup>5</sup> HCV/HIV coinfection is common because these viruses share similar routes of transmission. Similar to HIV infection, HCV can be transmitted efficiently through contaminated blood/blood products and needles. Unscreened blood transfusions and unsafe injection practices are the main routes of HCV transmission in developing countries, whereas transmission in developed countries is primarily identified in injection drug users (IDUs). Approximately 25% of the 1.2 million HIV-infected individuals in the USA have HCV infection.<sup>6</sup> Studies have also demonstrated HCV seroprevalence to be as high as 75% in HIV-infected IDUs.<sup>7</sup>

The majority of the 3.1 million individuals infected with HCV are not aware of their infection, and, hence, do not receive any medical treatment or care. Individuals who were born between 1945 and 1965 carry an HCV prevalence of about 4%, and comprise around two-thirds of the total infected population in the USA.<sup>4</sup> Based on this, the Centers for Disease Control and Prevention (CDC) recently recommended a single anti-HCV antibody test for individuals born between 1945 and 1965, the “baby boomer” generation.<sup>8</sup> All individuals who are found to have HCV infection through this screening process should be screened for HIV infection. Baseline screening for HCV is recommended as part of the standard of care for HIV-infected individuals.

A recent population surveillance study conducted in Massachusetts during the time period 2006–2009 demonstrated increases in rates of newly reported HCV infection

**Keywords:** Hepatitis C; HCV; HIV; Coinfection; Antiretroviral therapy; ART; Drug interaction.

**Abbreviations:** ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CPC, Child-Pugh Class; CPS, Child-Pugh Score; DAAs, directly-acting antiviral agents; DHHS, Department of Health and Human Services; DILI, drug-induced liver injury; EASL, European Association of the Study of the Liver; FDC, fixed dose combination; HANA, HIV-related non-AIDS conditions; HCV, hepatitis C; IDU, injection drug users; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; NHANES, National Health and Nutrition Examination Survey; NNRTI, non-NRTI; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitors; PegIFN/RBV, pegylated interferon and ribavirin; RGT, response guided therapy.

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since 2002 among adolescents and young adults in the 15–24 year age group. It was also noted that IDU was the most common risk factor for HCV transmission.<sup>9</sup> This increased incidence of HCV among young injection drug users could represent a population at particularly high risk for HCV/HIV coinfection in the future.

Global outbreaks of new HCV infection and increased sexual transmission of HCV have occurred in HIV-infected individuals in recent years. There have been HCV outbreaks among HIV-infected men who have sex with men (MSM) in the USA and western Europe.<sup>10</sup> These epidemics resulted from an aggregation of several risk factors, notably non-IDU and high risk sexual behavior.<sup>11,12</sup>

### Clinical Considerations

The deleterious effects of HIV infection on the rate of progression of liver disease in individuals with chronic HCV underscore the need for adequate control of HIV infection, as well as renewed commitment to identifying feasible and effective treatment for HCV in this population.<sup>6</sup> Patients who are dually infected with HCV and HIV may experience more rapid development of liver fibrosis and cirrhosis, leading to higher rates of hepatocellular carcinoma and end stage disease.<sup>13,14</sup> It has been similarly demonstrated that coinfecting patients diagnosed with hepatocellular carcinoma tend to have more advanced and aggressive liver disease at younger ages, associated with significantly higher mortality rates.<sup>15</sup>

These effects may be curtailed in part by adequate virologic suppression, although it seems clear that the effects of HIV infection of the liver have more to do with immune activation and triggering of harmful cellular pathways (including induction of transforming growth factor  $\beta$ 1 and lipopolysaccharide release<sup>16</sup>) than with immune deficiency. Virologic suppression using effective ART has been associated with decreased incidence of liver-related morbidity and mortality.<sup>17</sup>

It is less well documented as to what effects, if any, chronic HCV infection has on HIV. Most of the available data indicate a higher likelihood of encountering drug-induced liver toxicity from antiretrovirals (ARVs) in patients with chronic HCV infection, correlated with the degree of underlying fibrosis.<sup>6,18</sup> Chronic HCV infection and its therapies may also compound metabolic dyscrasias associated with ART, such as insulin resistance and diabetes. In addition, exacerbation of neurologic or psychiatric disorders may lead to more erratic adherence and increased risk of virologic failure.<sup>19</sup>

Liver biopsy has classically been considered the gold standard for the staging of HCV-related liver disease in both monoinfected and coinfecting patients. In recent years, several non-invasive methods have been developed to estimate the degree of liver fibrosis, some of which have been studied in the HCV/HIV coinfecting population. A primary concern in the coinfecting population is the potential of certain ART-associated effects (one example is hyperbilirubinemia associated with atazanavir) to alter the results of certain tests. One study demonstrated the reliability of certain biomarkers (hyaluronic acid, aspartate aminotransferase (AST) to platelet ratio index, and FIB-4) in predicting liver-related mortality in chronic HCV, with or without HIV coinfection.<sup>20</sup> Transient elastography is an ultrasonography-based rapid and non-invasive technique to estimate liver stiffness, recently approved by the FDA for use in the USA. Its

efficacy in HCV/HIV coinfecting patients is under investigation, but shows considerable promise as a future option to aid in the staging of liver disease in these patients prior to, during, and after antiviral therapy.<sup>21</sup>

### Current Standard of Care for HCV/HIV Coinfection

Despite the availability and widespread use of DAAs in HCV-monoinfected patients, the current standard of care for the treatment of HCV infection in patients coinfecting with HIV remains a 48-week course of pegylated IFN and ribavirin (PegIFN/RBV). The Hepatitis-HIV Spanish Group identified predictors of response in HIV-infected patients with chronic hepatitis C after 12 months of IFN treatment. The CD4 count, expressed as either an absolute number or a percentage, and baseline HCV viral load levels were strong predictors of response to IFN treatment. Female patients responded more frequently than male patients to IFN treatment, but this difference was not statistically significant (Table 1).<sup>22</sup> Unfortunately, rates of virologic response to PegIFN/RBV in coinfecting patients have historically been low, with patients having certain unfavorable characteristics (genotype 1, IL28B non-CC genotype, high baseline viral load, cirrhosis, African-American ethnicity), having even lower response rates. These poor response rates, along with the perception of intolerable side effects, and the frequency of comorbid conditions that are common in the HIV-infected population, such as active substance abuse and psychiatric illness, have resulted in very limited numbers of coinfecting patients receiving treatment for HCV.

The FDA has yet to approve any DAA for coinfecting patients, although recent data suggest significantly better response rates to PegIFN/RBV in combination with one of the two currently available NS3/4A protease inhibitors (PI), telaprevir and boceprevir.<sup>23</sup> Both PIs were approved in 2011 for the treatment of HCV genotype 1 mono-infection. Although clinical trials are ongoing, phase II data have been presented, leading to the provision of preliminary guidelines from the Department of Health and Human Services (DHHS) on the use of these agents in patients coinfecting with HIV and HCV genotype 1.<sup>2</sup> In the C110 study, 60 patients coinfecting with HIV and HCV genotype 1 were randomized to receive either telaprevir (n=38) or placebo (n=22) in addition to PegIFN/RBV for 12 weeks, followed by 36 weeks of PegIFN/RBV alone. A strategy of response-guided therapy (RGT), as utilized for HCV-monoinfected patients, was not employed in this study.<sup>24</sup> Patients received either no ART, or one of two ART regimens: tenofovir and emtricitabine in fixed dose combination with either efavirenz or ritonavir-boosted atazanavir. Telaprevir was given as 750 mg orally three times daily, except for those patients receiving efavirenz, who received 1125 mg every 8 hours (see section on "Drug-Drug Interactions"). Most patients were male, and infected with genotype 1 subtype a (1a), with relatively high median CD4 cell counts (514–675 cells/mm<sup>3</sup>). Rates of sustained virologic response (SVR) at 12 weeks after therapy completion (SVR12) were 74% in patients who received triple therapy with telaprevir, compared with 45% in those receiving standard PegIFN/RBV. There were no significant differences in response rates between groups stratified by ART regimen. Overall, safety and tolerability were similar in this population of coinfecting patients to those found in HCV-monoinfected patients receiving PI-based triple therapy,

**Table 1. Rates of response in HIV-infected patients with chronic hepatitis after 12 months of IFN therapy<sup>22</sup>**

Characteristics	Total no. of patients with indicated characteristic	No. (%) who responded	95% CI	P value
Gender				
Male	57	15 (26.3)	0.99–3.34	0.063
Female	23	11 (47.8)		
Mean age in years				
<30	45	16 (35.6)	0.41–1.55	0.508
>30	35	10 (28.6)		
CD4 count ( $\times 10^6/L$ )				
<500	35	7 (20.0)	1.00–4.45	0.035
>500	45	19 (42.2)		
Percentage of CD4				
<25	29	4 (13.8)	1.19–8.19	0.007
>25	51	22 (43.1)		
Histological evidence of liver damage (Knodell's score)				
<10	41	15 (36.6)	0.45–1.72	0.704
>10	28	9 (32.1)		
Unknown	11	2 (18.2)		
Baseline HCV viremia level (copies/ml)				
> $10^7$	22	4 (18.2)		
< $10^7$	31	15 (48.4)	1.02–6.94	0.024
Unknown	27	7 (25.9)		

with anemia, rash, and anal pruritis being the most common side effects. The hyperbilirubinemia associated with atazanavir therapy was also exacerbated in some patients on telaprevir.<sup>25</sup>

Week 12 interim analysis of the phase III INSIGHT trial was presented at The Liver Meeting<sup>®</sup> in November 2013 in Washington, DC.<sup>26</sup> Patients were on stable ART, consisting of a nucleoside backbone of tenofovir plus emtricitabine or abacavir plus lamivudine, with either raltegravir, efavirenz (requiring higher dosing of telaprevir), etravirine, rilpivirine, darunavir/ritonavir or atazanavir/ritonavir, and received 12 weeks of triple therapy with telaprevir and PegIFN/RBV. PegIFN/RBV was then continued for up to 36 additional weeks, based on RGT principles as previously described. The currently available data include rates of virologic suppression at 12 weeks in 128 patients who completed telaprevir therapy, and demonstrated rates of 72% undetectable HCV RNA. A majority of patients had genotype 1a (64%), and 30% had known bridging fibrosis or cirrhosis. Rates of suppression were highest in patients with previous partial response (83%), and lowest in those with a history of null response (57%). Patients with little to no fibrosis on biopsy fared better than those with significant fibrosis or cirrhosis (77 vs 62%, respectively). No HIV viral breakthroughs were observed, although mean absolute CD4 count dropped on triple therapy by nearly 300 cells/mm<sup>3</sup>. Interestingly, mean CD4 cell percentage actually increased on therapy, by 5.2%, suggesting that the drop in absolute count is probably transient, and of questionable clinical consequence. Overall, safety and observed tolerability were similar to previous findings with this regimen in monoinfected patients, with

rash, pruritis, and fatigue being among the most common. Serious adverse events were rare (6%), and the degree of anemia observed was lower with a reduced dose (800 mg) of ribavirin.<sup>26</sup>

The use of boceprevir-based therapy was similarly examined, and a report presented at the 47<sup>th</sup> European Association of the Study of the Liver (EASL) Conference in Barcelona. The design of this phase IIa trial was similar to the aforementioned C110 study, in that all patients were IFN-naïve, male, and infected with HCV genotype 1a.<sup>27</sup> In the study, 98 patients were randomly assigned in a 2:1 fashion to receive a standard 4-week lead-in with PegIFN/RBV, followed either by placebo or by boceprevir plus PegIFN/RBV for an additional 44 weeks. In this trial, patients were receiving primarily HIV protease inhibitor-based therapy, including ritonavir-boosted atazanavir, darunavir, or lopinavir. Again, median CD4 cell counts were relatively high (577–586 cells/mm<sup>3</sup>). SVR12 rates were significantly higher for boceprevir treatment compared with placebo (60.7% vs. 26.5%), although notably lower than those seen in the telaprevir phase II trial. Adverse events were common, and were similar to those observed in HCV mono-infection trials, including anemia, neutropenia, pyrexia, dysgeusia, diarrhea, and vomiting.<sup>23</sup>

Of note, pharmacodynamic data demonstrating significant interactions between antiretroviral agents and HCV PIs became available after enrollment in these phase II studies. Despite this, little adverse impact on virologic parameters was noted in either study.

The above data led to interim guidance from the DHHS, suggesting that practitioners should take the following into

account when considering HCV PI treatment of coinfecting patients: (i) if minimal fibrosis is present, consider deferral of therapy in anticipation of the release of more tolerable and effective agents in the near future; (ii) consider treatment with the standard PegIFN/RBV regimen if favorable prognostic characteristics are present, such as IL28B CC genotype; (iii) if feasible based on HIV treatment history, consider switching ART to agents with little to no known interaction with PIs, such as raltegravir; (iv) consider using telaprevir rather than boceprevir, given the shorter duration of PI dosing and fewer drug–drug interactions with ART.<sup>2</sup>

Data on the treatment of acute HCV infection in patients coinfecting with HIV was also presented recently. In the study, 75 HIV-infected MSM who were identified as having acute HCV infection were treated with PegIFN/RBV as part of ongoing cohort studies.<sup>28</sup> Risk factors for failure to achieve SVR were assessed in 57 patients; median CD4 count in this group was quite high at 559 cells/mm<sup>3</sup>. Although a decrease in CD4 count by 100 cells/mm<sup>3</sup> conferred a significant risk of failure to achieve SVR in univariate analysis (OR=1.31,  $p=0.053$ ), this was not borne out in multivariate analyses, which found only IL28B genotype and high baseline HCV RNA level (greater than 10<sup>6</sup>) to be predictive. Overall, SVR rate in this cohort of patients was reported to be 68%. Subsequently, the addition of telaprevir to PegIFN/RBV to treat acute HCV in the HIV-infected population was studied, and data were presented at The Liver Meeting<sup>®</sup> in November 2013. In this small pilot study, 84% (16/19) patients achieved SVR12 after receiving triple therapy for 12 weeks. Small sample size precluded statistical analysis, but the three non-responders had IL28B genotypes other than CC; no data on association with CD4 count were reported.<sup>29</sup> These data inform the recommendation in this population of acutely infected individuals that identification of poor prognostic factors, such as non-CC IL28B genotype and high baseline HCV RNA level, should prompt consideration of adding telaprevir to PegIFN/RBV.<sup>28,29</sup>

### New Agents for the Treatment of Hepatitis C and Their Potential for Use in HCV/HIV Coinfection

Several novel agents for the treatment of HCV infection are in various stages of development, and are under investigation in ongoing clinical trials to evaluate their roles in the treatment of HCV/HIV coinfecting patients. Sofosbuvir and simeprevir have been submitted to the FDA for approval in the treatment of HCV mono-infection.

Sofosbuvir is a uridine analog nucleotide with potent antiviral activity across all HCV genotypes, along with a high barrier to resistance and a good safety profile.<sup>25</sup> In the phase I PHOTON (All-Oral Therapy With Sofosbuvir Plus Ribavirin For the Treatment of HCV Genotype 1, 2, and 3 Infection in Patients Co-infected With HIV) study, 19 HIV/HCV coinfecting individuals on ART received sofosbuvir 400 mg once daily for 1 week. The patients tolerated the drug well, with maximal reductions in serum HCV RNA of 4 log IU/ml.<sup>30</sup> In Phase II, coinfecting patients were given sofosbuvir and RBV without IFN; results are not yet available.<sup>30</sup> Another pilot study is underway to examine the efficacy and safety of once-daily sofosbuvir in combination with 12 weeks of PegIFN and RBV in the naïve HCV/HIV coinfecting patients. Preliminary results showed a high SVR4 (83%), with the therapy being well tolerated without evidence of HIV viral breakthrough or changes in CD4 T cell percentages.<sup>31</sup>

Simeprevir is a second-generation HCV protease inhibitor that is under evaluation by the FDA for the treatment of HCV mono-infection. Study C212 evaluated 24 or 48 weeks of triple therapy with simeprevir and PegIFN/RBV in 106 HCV/HIV coinfecting patients; 93% of the patients were on ART and had favorable CD4 counts and undetectable HIV-RNA. Preliminary outcomes showed that 66% of the patients had undetectable HCV RNA at week 4. Better results were seen in HCV treatment-naïve and relapsed subjects than in previous partial or null responders. SVR rates of 77% were noted in 13 IFN-naïve and relapsed patients who had completed at least 12 weeks of triple therapy.<sup>32</sup>

Faldaprevir is another investigational second-generation HCV protease inhibitor with favorable dosing, higher potency, and fewer drug interactions than first-generation inhibitors.<sup>25</sup> The STARTVerso 4 trial is evaluating faldaprevir with PegIFN/RBV in 308 HCV/HIV coinfecting patients. In the trial, 78% of the patients had genotype 1a HCV, and 17% had cirrhosis. Nearly 90% of the patients were on ART with raltegravir, efavirenz, darunavir or atazanavir. Preliminary results showed that 80% of the patients had undetectable HCV RNA at weeks 4 and 12 of therapy. The SVR data are not yet available. Hyperbilirubinemia was the most common side effect associated with faldaprevir treatment.<sup>33</sup>

Daclatasvir is the first investigational NS5A inhibitor to be developed. The combination of daclatasvir, the protease inhibitor asunaprevir, and the non-nucleoside NS5B inhibitor BMS-791325 has been shown to be efficacious in an IFN/RBV-free treatment regimen.<sup>34</sup> An ongoing trial is investigating the safety and efficacy of the triple combination of PegIFN/RBV and daclatasvir in HCV/HIV coinfecting individuals, and the preliminary data are expected in late 2013.<sup>25</sup>

### Drug–Drug Interaction Considerations in HCV/HIV Coinfection

Although the potential for drug interactions between the standard antivirals for HCV/HIV coinfection and antiretroviral agents is well described, the addition of HCV PIs has complicated the treatment landscape immensely. As telaprevir and boceprevir are both substrates and inhibitors of CYP3A4/5 enzymes, both may interact with various ART agents metabolized by the same pathway.<sup>35</sup> As always, the unique aspects of the coinfecting patient must be considered in risk stratification for initiation of HCV treatment, including their immune status, stability of HIV infection, antiretroviral regimen, presence of cirrhosis, and risk of drug-induced liver injury (DILI). Most experts agree that patients coinfecting with HCV and HIV should receive ART irrespective of baseline CD4 count, given the more rapid progression of liver disease in the presence of poorly controlled HIV infection, and the potential deleterious effects of abnormal immune activation on the liver.<sup>2</sup>

HCV/HIV coinfecting patients are likely to be at higher risk for DILI on exposure to ART, and several agents require dose modification or are contraindicated in the presence of significant liver disease.<sup>2,18</sup> Certain ART agents from nearly every available class require dose modification and careful clinical and laboratory monitoring of the patient while on therapy, underscoring the importance of practitioner awareness of these drug effects. Some examples include abacavir, a nucleoside reverse transcriptase inhibitor (NRTI), which is contraindicated in patients with a Child–Pugh Score (CPS) of

**Table 2. Dosing recommendations of commonly prescribed antiretroviral agents in patients with liver disease<sup>2</sup>**

Antiretroviral agent	Class	Recommendation in liver disease
Abacavir	NRTI	Contraindicated CPS >6
Nevirapine	NNRTI	Contraindicated for CPC B or C
Atazanavir	PI	Not recommended for CPC C; dose 300 mg daily for CPC B
Darunavir	PI	Not recommended in severe impairment
Fosamprenavir	PI	CPS 5–6: dose 700 mg BID + ritonavir 100 mg once daily; CPS 7–9: dose 450 mg BID + ritonavir 100 mg once daily; CPS 10–15: dose 300 mg BID + ritonavir 100 mg once daily
Lopinavir/ritonavir	PI	Use with caution
Tipranavir	PI	Contraindicated for CPC C
Elvitegravir/cobicistat/tenofovir/emtricitabine	INSTI	Not recommended in severe impairment

>6, and nevirapine, a non-NRTI (NNRTI), which is contraindicated in patients in Child–Pugh Class (CPC) B or C. Several HIV PIs either require dose adjustment or are not recommended in moderate to severe hepatic impairment; elvitegravir, an integrase strand transfer inhibitor (INSTI), is not recommended in severe hepatic insufficiency.<sup>2</sup> Table 1 reviews the dosing recommendations of commonly prescribed antiretroviral agents in patients with liver disease. As with any new ART regimen, safety investigations, including complete blood counts, blood chemistries, and full liver function panels should be monitored approximately 1 month after the change, and quarterly thereafter. Significant elevations in alanine aminotransferase and/or AST levels in the absence of alternative causative factors should prompt consideration of ART discontinuation.

Several interactions are known or suspected between current standard HCV/HIV therapies, PegIFN/RBV, and the NRTIs. For example, zidovudine coadministration with PegIFN/RBV is not recommended, given its propensity to cause bone marrow suppression.<sup>36</sup> Ribavirin has been shown in several *in vitro* experiments to decrease azidothymidine levels and effectiveness. The mechanism responsible for this antagonism is possibly attributable to inhibition of azidothymidine phosphorylation by ribavirin.<sup>37</sup> Similarly, administration of didanosine with ribavirin is contraindicated because of the increased risk of severe mitochondrial toxicities, including lactic acidosis and hepatic steatosis.<sup>38</sup> The same is likely to be true of other nucleoside analogs, such as stavudine. Other

potential interactions with ARVs include exacerbation of hyperbilirubinemia associated with atazanavir therapy when coadministered with PegIFN/RBV<sup>39</sup> and exacerbation of central nervous system or psychiatric effects of efavirenz when taken together with PegIFN.<sup>40</sup> All of the above are relevant to the forthcoming discussion of interactions between ARVs and the HCV PIs, as the current standard of care requires these PIs be administered along with PegIFN/RBV.

Both of the available HCV PIs, boceprevir and telaprevir, are metabolized in part by CYP3A4, leading to serious potential for interaction with a multitude of ARVs. HIV PIs, such as lopinavir, darunavir, and ritonavir, inhibit CYP3A4, while the NNRTIs efavirenz, etravirine, and nevirapine induce the same enzyme.<sup>35</sup> Ritonavir also inhibits several uptake and efflux transporters, such as P-glycoprotein. Boceprevir also inhibits P-glycoprotein enzymes, and is a substrate and inhibitor of CYP3A4. Data from a single-center, randomized study in healthy volunteers indicated several important interactions between boceprevir and HIV PIs.<sup>41</sup> Maximum and mean trough concentrations of ritonavir-boosted atazanavir, darunavir, and lopinavir were all significantly reduced when administered with boceprevir. Interestingly, boceprevir pharmacokinetics were minimally altered by exposure to atazanavir, while mean concentrations of boceprevir decreased in the presence of darunavir or lopinavir. Such reduced concentrations of both HCV and HIV PIs raise concern about potential virologic breakthrough of either or

**Table 3. Recommendations regarding coadministration of available HCV PIs and ARVs based on existing data<sup>2</sup>**

	Concomitant use appropriate	Coadministration not recommended
<b>Boceprevir</b>	Raltegravir (INSTI) Etravirine (NNRTI) Tenofovir (NRTI)	Elvitegravir/cobicistat (INSTI) Efavirenz (NNRTI) Atazanavir/ritonavir (PI) Darunavir/ritonavir (PI) Lopinavir/ritonavir (PI)
<b>Telaprevir</b>	Raltegravir (INSTI) Efavirenz (NNRTI; increase telaprevir dose) Tenofovir (NRTI; monitor for toxicity) Atazanavir/ritonavir (PI)	Elvitegravir/cobicistat (INSTI) Darunavir/ritonavir (PI) Lopinavir/ritonavir (PI) Fosamprenavir/ritonavir(PI)

both viruses. It must be noted, however, that data extracted from healthy volunteers without notable liver disease may not be indicative of potential effects on patients coinfecting with HCV and HIV. Interestingly, although the aforementioned phase 2 studies took place before the availability of such pharmacokinetic data, they nevertheless demonstrated significantly improved virologic responses in patients receiving these HIV PIs. Additional information is necessary in order to clarify the clinical importance of these drug interactions in the coinfecting population.

Data on boceprevir administration with other ARV classes reveal little to no significant effect of boceprevir on the INSTI raltegravir, or the NRTI tenofovir.<sup>41,42</sup> Efavirenz concentrations were generally increased, and etravirine concentrations decreased in the presence of boceprevir.<sup>41,43</sup>

Telaprevir administration with various ARVs has been similarly studied in healthy volunteers.<sup>44</sup> These data, along with information from phase 2 and 3 trials in coinfecting patients<sup>24,45</sup> indicate minimal pharmacokinetic interaction between telaprevir and raltegravir. In the presence of ritonavir-boosted HIV PIs, telaprevir concentrations are significantly decreased, and coadministration of other drugs, with the exception of atazanavir, is generally not recommended. Telaprevir concentrations are lower in the presence of efavirenz as well, but this can be overcome by increasing the telaprevir dose to 1125 mg every 8 hours.<sup>13</sup> Tenofovir levels are elevated in the presence of telaprevir, requiring more vigilant monitoring for toxicities, in particular renal insufficiency<sup>2</sup> (Table 2).

Although data are very limited regarding the use of investigational agents such as simeprevir, faldaprevir (both HCV PIs), sofosbuvir (polymerase inhibitor) and daclatasvir (NS5A inhibitor) in HCV/HIV coinfection, preliminary information on certain agents is available from recent international meetings. A small study in healthy subjects indicated that administration of daclatasvir with tenofovir, efavirenz, or ritonavir-boosted atazanavir is appropriate, with dose modifications of the latter two required.<sup>46</sup> Interactions between the HCV PIs, simeprevir and faldaprevir, and ARVs, including efavirenz and HIV PIs, have been identified, although more definitive data are forthcoming. Phase 1 study data have revealed significantly increased concentrations of simeprevir in the presence of ritonavir-boosted darunavir, and decreased concentrations in the presence of efavirenz. No significant interactions were noted between simeprevir and either raltegravir, rilpivirine, or tenofovir. In similar pharmacokinetic studies in healthy volunteers, faldaprevir concentrations were increased by ritonavir-boosted darunavir, and decreased by tenofovir and efavirenz, which may ultimately require dose adjustments of the HCV PI in the presence of certain ARVs.<sup>36,39</sup> Increased bilirubin levels were also noted with simeprevir administration, so coadministration with atazanavir will probably require additional caution.<sup>47</sup>

## Conclusions

Chronic HCV infection in the setting of HIV infection represents a major cause of morbidity and mortality. Given the current state of HIV medicine, with many effective, increasingly available, and well-tolerated antiretrovirals, liver disease from chronic HCV infection is becoming one of the more prominent, yet preventable causes of death in HIV-infected individuals. New HCV infections are on the rise in MSM and young adults because of high risk sexual behavior and IDU,

respectively. The need for safe and effective HCV treatment regimens in the management of HCV/HIV coinfecting individuals has never been more apparent. Although not yet approved by the FDA for use in HIV-infected patients, boceprevir or telaprevir, together with PegIFN/RBV, offer hope of increased response rates, despite the challenges these regimens pose, including drug interactions with ARVs and adverse effects. Clinical trials to address the safety and efficacy of novel DAAs in the HCV/HIV coinfecting population are ongoing, and show much promise. The rapidity of current drug discovery in the field of hepatitis C is both impressive and daunting for clinicians who will have to master these treatments. Going forward, the inclusion of individuals from this large and growing patient population in clinical trials will be of paramount importance.

## Conflict of interest

None

## Author contributions

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