Provisional Guidance on the Use of Hepatitis C Virus Protease Inhibitors for Treatment of Hepatitis C in HIV-Infected Persons

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In May 2011, hepatitis C virus (HCV) protease inhibitors (PIs) were approved by the US Food and Drug Administration to treat persons with genotype 1 chronic hepatitis C virus (HCV) infection, but not those dually infected with human immunodeficiency virus (HIV). Although critical safety and efficacy data are lacking, the availability of the drugs and substantial medical need justify the off-label use of HCV PIs in select HIV/HCV-coinfected persons. Pending results of ongoing investigations, this article represents provisional guidance on the use of HCV PIs in HIV-infected persons.

On 13 May 2011 and 23 May 2011, boceprevir (BOC) and telaprevir (TVR), respectively, were approved by the US Food and Drug Administration to be used with peginterferon and ribavirin for treatment of genotype 1 chronic hepatitis C virus (HCV) infection. Use of these NS3/4A serine protease inhibitors (PIs) with peginterferon and ribavirin improves sustained virologic response by 25%-31% in human immunodeficiency virus (HIV)–uninfected persons [1, 2]. These efficacy data and drug availability raise the question of whether HCV PIs should be used in HIV/HCV-coinfected persons pending final results of ongoing phase 2 and subsequent phase 3 clinical trials of both BOC and TVR. Lacking the relevant data on HIV/HCV-coinfected persons, clinical and policy decisions must be made largely on data from HIV-uninfected persons. The following opinions were provided to the Maryland AIDS Assistance Program and may be useful to others.

HIV/HCV PHASE 2 DATA

Telaprevir

In the only data available in the public domain, HIV/HCV-coinfected individuals taking no antiretroviral therapy (ART) with well-controlled HIV infection (n = 13) or taking tenofovir/emtricitabine with either efavirenz (n = 24) or ritonavir-boosted atazanavir (n = 22) were randomized to peginterferon and ribavirin for 48 weeks or TVR plus peginterferon and ribavirin for the first 12 weeks, followed by the continuation of peginterferon and ribavirin for 36 additional weeks [3]. Notably, shortened durations of treatment with response-guided therapy to TVR are not currently being evaluated in HIV/HCV-coinfected patients. Baseline HCV RNA was >800 000 IU/mL for 83%; 69% of patients were white, and only 2 had cirrhosis. Telaprevir was given 750 mg every 7–9 hours with food with $20 g of fat (or 1125 mg every 7–9 hours if also taking efavirenz). The proportion of persons with undetectable HCV RNA at week 4 (26 of 38 [68%]) was substantially greater in the TVR arms than with placebo (0 of 22 [0%]). Likewise, at the planned week 12 evaluation, virologic responses were superior in the TVR arm (Figure 1). There were no unexpected adverse events reported through week 12. There were no instances of HIV breakthrough, but 2 patients...
experienced HCV breakthrough that is typically associated with resistance. In the TVR group, there were more skin and gastrointestinal complaints and 2 patients discontinued due to adverse events (jaundice and anemia). Complete safety and efficacy data to register TVR with peginterferon and ribavirin for use in HIV/HCV-coinfected individuals are not anticipated before 2013.

Boceprevir

A phase 2 trial of BOC in combination with peginterferon and ribavirin in HIV/HCV-coinfected persons is ongoing. In this study, 99 HIV/HCV-coinfected patients with stable HIV disease are being treated with an initial 4 weeks of peginterferon plus weight-based ribavirin (lead-in), then randomized 2:1 to the addition of BOC 800 mg every 7–9 hours or placebo to peginterferon alfa and ribavirin for an additional 44 weeks (total therapy, 48 weeks). Subjects were excluded if they were on zidovudine, didanosine, stavudine, efavirenz, etravirine, or nevirapine. Raltegravir and ritonavir-boosted PIs were permitted. An interim analysis was presented for 98 patients (34 placebo and 64 boceprevir) [4]. Baseline HCV RNA was >800 000 IU/mL for 88%; 82% were white; and 5% had cirrhosis. The proportion of persons for whom HCV RNA was undetectable at treatment week 8 (4 weeks of boceprevir vs placebo) was higher in those taking BOC (24 of 64 [37.5%]) than in those taking placebo (5 of 34 [14.7%]) (Figure 2). Likewise, at treatment week 24, HCV was undetectable in 43 of 61 patients (70.5%) in the BOC arm compared with 11 of 32 (34.4%) in the placebo arm. Treatment was discontinued due to an adverse event in 3 (9%) and 9 (14%) of the patients in the placebo and BOC arms, respectively. Complete safety and efficacy data to register BOC with peginterferon and ribavirin for use in HIV/HCV-coinfected individuals are not anticipated before 2013.

Figure 1. Higher percent hepatitis C virus (HCV) undetectable in human immunodeficiency virus (HIV)/HCV coinfected persons taking telaprevir (TVR), peginterferon (Peg), and ribavirin (RBV) compared to Peg/RBV and placebo [3, 12].

Figure 2. Higher percent hepatitis C virus (HCV) undetectable in human immunodeficiency virus (HIV)/HCV coinfected persons taking boceprevir (BOC), peginterferon (Peg), and ribavirin (RBV) compared to Peg/RBV and placebo [4].

PROVISIONAL RECOMMENDATIONS

Pending more conclusive data and regulatory approval, decisions to use or withhold HCV PIs in HIV/HCV-coinfected persons must take into account multiple related factors. On the one hand, liver fibrosis progression is more rapid and peginterferon and ribavirin treatment is less effective in HIV/HCV-coinfected persons than in those without HIV, and liver transplantation is neither widely available nor highly successful in HIV/HCV-coinfected persons [5]. On the other hand, the safety and efficacy of HCV PIs are largely unproven in HIV/HCV-coinfected persons, data regarding drug-drug interactions are limited, additional anti-HCV medications are being developed, and the price of HCV PIs may add to the cost of the peginterferon and ribavirin treatment regimen. At current cost levels used by the Maryland AIDS Administration and dosing used in phase 2 studies, a full course of BOC would add $51 116, while a full course of TVR would add $51 957 or $77 936 (for the additional pill required for coadministration with efavirenz [EFV]). The collective cost of HCV medications could detract from funds available for other medications, and the cost-effectiveness of treatments for HCV has not been rigorously compared with treatments already being supported for HIV.

Until additional data or alternative treatments are available, some experts believe that HCV PIs should be used in combination with peginterferon and ribavirin in certain HIV/HCV-coinfected persons. Since AIDS drug assistance programs will need to consider the provision of HCV PIs alongside other competing priorities, the following interim information was provided by an expert panel in June 2011 to the Maryland AIDS Drug Assistance Program regarding the use of HCV PIs in HIV/HCV-coinfected persons:

1. Peginterferon and ribavirin remain the standard of care for treatment of HCV infection in patients with HCV genotype 2, 3, or 4 HCV infection or in patients for whom
pharmacokinetic interactions between these HCV PIs and other necessary medications, including ART, cannot be confidently eliminated or managed (see Pharmacokinetics below) or in patients for whom HCV PIs are not available.

2. For some coinfected patients with chronic genotype 1 HCV infection, HCV PIs should be used with peginterferon and ribavirin. Use of HCV PIs alone (or with peginterferon but not ribavirin) is contraindicated because HCV PI-resistant viruses are rapidly selected if the medications are used without both peginterferon and ribavirin. Accordingly, persons with contraindications for peginterferon and ribavirin (eg, pregnancy, didanosine use, or severe, uncontrolled psychiatric or medical disease) also have contraindications for HCV PI-inclusive therapy. HCV PIs and/or peginterferon and ribavirin treatment should not be used for persons with liver failure (decompensated cirrhosis) because there is evidence that peginterferon and ribavirin may exacerbate liver disease in such patients [6]. The benefits of HCV PIs plus peginterferon and ribavirin treatment are most likely to outweigh the risks for individuals with significant liver fibrosis (often defined as greater than METAVIR fibrosis stage 0–1 or the equivalent). Although HIV/HCV-coinfected persons have more rapid progression of liver disease than HIV-uninfected persons and HCV treatment is more efficacious at a lower disease stage, some experts believe that it is safer to monitor patients with little or no fibrosis for evidence of progression while awaiting additional safety and efficacy data in HIV/HCV-coinfected persons, as well as additional new antiviral agents.

3. When possible, HIV infection should be controlled before treatment with HCV PIs and peginterferon/ribavirin. HIV control is often defined in persons off ART as CD4 cell count >500/mm³ and HIV RNA <20 000 copies/ml or in those on ART as HIV RNA <50 copies/mL. Importantly, HCV PIs should not be used with some medications that have proven or suspected pharmacologic interactions, while dosing adjustments may be required with other combinations (Table 1). Because of limited data, HIV RNA levels should be monitored closely when HCV PIs are used with antiretroviral therapies.

4. Before use in any patient, package inserts for the specific HCV PI should be consulted for a list of contraindicated drug combinations and details of multiple other drug-drug interactions.

Telaprevir option:

a. Telaprevir plus peginterferon/ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 36 weeks (total therapy, 48 weeks) plus:

i. No ART with controlled HIV disease.

ii. Ritonavir-boosted atazanavir (ATV/r) 300/100 mg once daily plus tenofovir/emtricitabine 1 tab once daily with TVR 750 mg every 7–9 hours with food with ≥20 g of fat.

iii. Although there are no clinical data with TVR plus raltegravir, coadministration does not appear to affect TVR pharmacokinetics, and the 31% increase in raltegravir is not considered significant enough to affect dosing [7]. Thus, some experts endorse the use of raltegravir 400 mg orally twice daily, tenofovir/emtricitabine 1 tab once daily, and TVR 750 mg every 7–9 hours with food (with ≥20 g of fat) in patients unable to take ATV/r, or to prevent the added cost and pill burden of using a higher TVR dose with EFV (see below).

iv. EFV 600 mg daily at bedtime plus tenofovir/emtricitabine 1 tab once daily with increased TVR dose to 1125 mg every 7–9 hours with food (with ≥20 g of fat).

v. To minimize the risk of selecting for TVR resistance, patient adherence should be high. TVR should be stopped if there is HCV rebound (>1 log increase in HCV RNA). Treatment with peginterferon, ribavirin, and TVR should be stopped if HCV RNA is not suppressed <1000 IU/mL at treatment weeks 4 and 12. Individuals who meet these week 4 and 12 milestones

### Table 1. Interactions Between Telaprevir and Antiretroviral Therapies [7, 8]

<table>
<thead>
<tr>
<th>TVR Dose</th>
<th>ARV</th>
<th>TVR AUC$_{tau}$</th>
<th>TVR C$_{min}$</th>
<th>ARV AUC$_{tau}$</th>
<th>ARV C$_{min}$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TVR 750 mg every 8 h</td>
<td>ATV/r 300/100 qd</td>
<td>↓20%</td>
<td>↓15%</td>
<td>↑17% (NS)</td>
<td>↑85%</td>
<td>Dose TVR 750 mg every 8 h + ATV/r 300/100 mg qd</td>
</tr>
<tr>
<td></td>
<td>DRV/r 600/100 mg bid</td>
<td>↓35%</td>
<td>↓32%</td>
<td>↓40%</td>
<td>↓42%</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td></td>
<td>FPV/r 700/100 mg bid</td>
<td>↓32%</td>
<td>↓30%</td>
<td>↓47%</td>
<td>↓56%</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td></td>
<td>LPV/r 600/100 mg bid</td>
<td>↓54%</td>
<td>↓52%</td>
<td>↓16% (NS)</td>
<td>↑14% (NS)</td>
<td>Avoid coadministration</td>
</tr>
<tr>
<td>TVR 1125 mg every 8 h</td>
<td>EFV 600 mg qhs (with TDF)</td>
<td>↓18%</td>
<td>↓25%</td>
<td>↓18%</td>
<td>↓10%</td>
<td>Dose: TVR 1125 mg every 8 h + EFV 600 mg qhs</td>
</tr>
<tr>
<td></td>
<td>TDF 300 mg qd (with EFV)</td>
<td>↑10%</td>
<td>↑17%</td>
<td></td>
<td></td>
<td>Dose: TVR 300 mg qd</td>
</tr>
<tr>
<td>TVR 750 mg every 8 h</td>
<td>TDF 300 mg qd</td>
<td>No change</td>
<td>↑3% (NS)</td>
<td>↑30%</td>
<td>↑41%</td>
<td>Dose: TVR 750 mg every 8 h + TDF 300 mg qd</td>
</tr>
<tr>
<td>TVR 750 mg every 8 h</td>
<td>RAL 400 mg bid</td>
<td>↑7% (NS)</td>
<td>↑14%</td>
<td>↑31%</td>
<td>↑78%</td>
<td>Dose: TVR 750 mg every 8 h + RAL 400 mg bid</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; ATV, atazanavir; AUC$_{tau}$, area under plasma concentration curve; C$_{min}$, minimum concentration; bid, twice a day; DRV, darunavir; EFV, efavirenz; FPV, fosamprenavir; LPV, lopinavir; NS, not significant; qd, once a day; qhs, at bedtime; r, low-dose ritonavir; RAL, raltegravir; TDF, tenofovir; TVR, telaprevir.
but have detectable HCV RNA at treatment week 24 should also discontinue peginterferon/ribavirin.

**Boceprevir option:**

b. Peginterferon/ribavirin for 4 weeks, followed by BOC plus peginterferon/ribavirin for 44 weeks (total therapy, 48 weeks) plus:

i. No ART with controlled HIV disease.

ii. Raltegravir plus tenofovir/emtricitabine 1 tab once daily with BOC 800 mg every 7–9 hours with food.

iii. Avoid using boceprevir with ritonavir-boosted lopinavir, atazanavir, or darunavir.

iv. Until research demonstrates safety, BOC should NOT be used with efavirenz, etravirine, or nevirapine.

v. To minimize the risk of selecting for BOC resistance, patient adherence should be high. BOC should be stopped if there is HCV rebound (>1 log increase in HCV RNA). Treatment with peginterferon, ribavirin, and BOC should be stopped if HCV RNA is > 100 IU/mL at treatment week 12. Individuals who meet the week 12 milestone but have detectable HCV RNA at treatment week 24 should also discontinue peginterferon/ribavirin.

6. To ensure that the benefits of treatment are sustained and outweigh the risks, persons should be judged to have a limited risk of reinfection.

6. Peginterferon, ribavirin, and HCV PI therapy is expected to be less efficacious in persons who did not clear HCV RNA with prior peginterferon and ribavirin treatment (so-called partial responders or nonresponders) and/or those with cirrhosis, unfavorable IL28B genotype, or African ancestry. Data regarding use of these agents in HCV treatment-experienced patients are lacking. However, triple therapy response is higher in re-treated patients than in patients treated with peginterferon and ribavirin alone, and guidelines for use similar to that in treatment-naive patients should be applied pending availability of additional data.

7. Since data are needed to answer many remaining questions, when available, clinical trials should be considered for HIV/HCV coinfected persons considering treatment.

**PHARMACOKINETICS**

Telaprevir is a P-glycoprotein and CYP3A4 substrate and inhibitor [8]. Blood concentrations are reduced by ritonavir-boosted fosamprenavir, darunavir, lopinavir, and, to a lesser extent, atazanavir (Table 1) [9]. Efavirenz also reduces blood concentrations of TVR, an effect that can, in part, be offset by using a higher TVR dose (1125 every 8 hours). TVR use significantly reduces the concentrations of darunavir and fosamprenavir. Boceprevir is primarily metabolized by aldo-keto reductases, and to a lesser extent, may undergo oxidative metabolism and excretion via CYP3A4/5, other complex enzymes, and drug transporters (Table 2) [10, 11]. In healthy volunteers taking both medications, BOC AUC concentrations are decreased 19%, 32%, 45%, with EFV, DRV/r, and LPV/r, respectively.

Likewise, coadministration is associated with a reduction in AUC of ATV, DRV, and LPV of 33%, 43%, 32%, respectively.

Similar to TVR, BOC is an inhibitor of CYP3A4 that increases concentration of substrates such as midazolam, tacrolimus, and atorvastatin.

**SUMMARY**

Approvals of boceprevir and telaprevir for treatment of HCV infection are major advances for the care of persons with chronic genotype 1 HCV infection. Although the medications are not approved by the US Food and Drug Administration for treatment of HIV/HCV-coinfected persons, the benefits of including these medications will outweigh the risks for some individuals. In the future, HIV/HCV-coinfected persons should be included at earlier stages in drug development so that practice guidelines can be based more on data and less on expert opinion.

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Table 2. Interaction Between Boceprevir and Antiretroviral Therapies (Source: Merck)

<table>
<thead>
<tr>
<th>Boceprevir dose</th>
<th>ARV</th>
<th>BOC AUC&lt;sub&gt;tau&lt;/sub&gt;</th>
<th>BOC C&lt;sub&gt;min&lt;/sub&gt;</th>
<th>ARV AUC&lt;sub&gt;tau&lt;/sub&gt;</th>
<th>ARV C&lt;sub&gt;min&lt;/sub&gt;</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>ATV/r 300/100mg qd</td>
<td>↓15% (NS)</td>
<td>↓18%</td>
<td>↓33%</td>
<td>↓49%</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>LPV/r 400/100mg bid</td>
<td>↓45%</td>
<td>↓57%</td>
<td>↓32%</td>
<td>↓43%</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>DRV/r 600/100mg bid</td>
<td>↓32%</td>
<td>↓35%</td>
<td>↓43%</td>
<td>↓59%</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 400 mg every 8 h</td>
<td>RTV 100 mg bid</td>
<td>↓19%</td>
<td>↓14% (NS)</td>
<td>—</td>
<td>—</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>EFV 600 mg qhs</td>
<td>↓19%</td>
<td>↓44%</td>
<td>↓20%</td>
<td>—</td>
<td>Avoid co-administration</td>
</tr>
<tr>
<td>BOC 800 mg every 8 h</td>
<td>TDF 300 mg qd</td>
<td>↑18%</td>
<td>↑18% (NS)</td>
<td>↑5%</td>
<td>—</td>
<td>Dose: BOC 800 mg every 8 h + TDF 300 mg qd</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; ATV, atazanavir; AUC<sub>tau</sub>, area under plasma concentration curve; BOC, boceprevir, Cmin minimum concentration; bid, twice a day; DRV, darunavir; EFV, efavirenz; LPV, lopinavir; NS, not statistically significant; qhs, at bedtime, /r, low-dose ritonavir; TDF, tenofovir
Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References