

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

David L. Thomas,¹ John G. Bartlett,¹ Marion G. Peters,² Kenneth E. Sherman,³ Mark S. Sulkowski,¹ and Paul A. Pham¹

¹Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; ²Department of Medicine, University of California, San Francisco School of Medicine; and ³Department of Medicine, University of Cincinnati School of Medicine, Ohio

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 37 [70%]) was substantially greater in the TVR arms than with placebo (1 of 22 [5%]). 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

Received 20 June 2011; accepted 21 October 2011.

Correspondence: David L. Thomas, Chief, Division of Infectious Diseases, Johns Hopkins School of Medicine, Rm 437, 1830 Monument St, Baltimore, Maryland 21205 (junk7900@verizon.net).

Clinical Infectious Diseases

© The Author 2011. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cir882

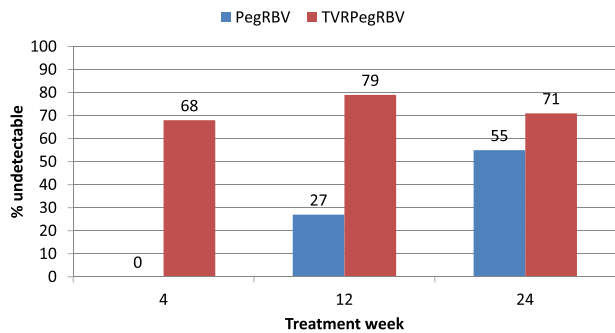


Figure 1. Higher percent hepatitis C virus (HCV) undetectable in human immunodeficiency virus (HIV)/HCV coinfected persons taking telaprevir (TVR), peginterferon (Peg), and ribavirin (RBV) compared to Peg/RBV and placebo [3, 12].

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

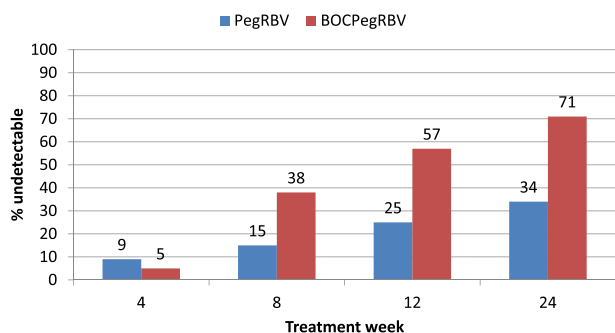


Figure 2. Higher percent hepatitis C virus (HCV) undetectable in human immunodeficiency virus (HIV)/HCV coinfected persons taking boceprevir (BOC), peginterferon (Peg), and ribavirin (RBV) compared to Peg/RBV and placebo [4].

(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.

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 coinfecting 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-coinfecting 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-coinfecting 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 $>500/\text{mm}^3$ 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).

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 but have detectable HCV RNA at treatment week 24 should also discontinue peginterferon/ribavirin.

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

TVR Dose	ARV	TVR AUC _{tau}	TVR C _{min}	ARV AUC _{tau}	ARV C _{min}	Comments
TVR 750 mg every 8 h	ATV/r 300/100 qd	↓20%	↓15%	↑17% (NS)	↑85%	Dose TVR 750 mg every 8 h + ATV/r 300/100 mg qd
	DRV/r 600/100 mg bid	↓35%	↓32%	↓40%	↓42%	Avoid coadministration
	FPV/r 700/100 mg bid	↓32%	↓30%	↓47%	↓56%	Avoid coadministration
	LPV/r 600/100 mg bid	↓54%	↓52%	↑6% (NS)	↑14% (NS)	Avoid coadministration
TVR 1125 mg every 8 h	EFV 600 mg qhs (with TDF)	↓18%	↓25%	↓18%	↓10%	Dose: TVR 1125 mg every 8 h + EFV 600 mg qhs
	TDF 300 mg qd (with EFV)			↑10%	↑17%	Dose: TDF 300 mg qd
TVR 750 mg every 8 h	TDF 300 mg qd	No change	↑3% (NS)	↑30%	↑41%	Dose: TVR 750 mg every 8 h + TDF 300 mg qd
TVR 750 mg every 8 h	RAL 400 mg bid	↑7% (NS)	↑14%	↑31%	↑78%	Dose: TVR 750 mg every 8 h + RAL 400 mg bid

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.

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. A ritonavir-boosted PI or raltegravir plus tenofovir/emtricitabine 1 tab once daily with BOC 800 mg every 7–9 hours with food.
- iii. Until research demonstrates safety, BOC should NOT be used with efavirenz, etravirine, or nevirapine.
- iv. 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.

5. 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 coinfecting 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 via CYP3A4/5 [10]. Boceprevir trough concentrations are decreased 44% with EFV coadministration, and BOC concentrations are also decreased by 19% with low-dose ritonavir at steady state (100 mg twice daily) [11]. 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-coinfecting persons, the benefits of including these medications will outweigh the risks for some individuals. In the future, HIV/HCV-coinfecting 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.

Notes

Financial support. This research was supported in part by US Public Health Service grants (R01016027 to D. T. and K24DK070528 to K. E. S.).

Potential conflicts of interest. M. P. has served as an advisor to Roche, Merck, and Vertex. K. E. S. has served as an advisor for Merck, Vertex, Genentech, Bristol-Myers Squibb (BMS), Regulus, GlaxoSmithKline, SciClone, and Boehringer Ingelheim, and has institutionally contracted research associations with Merck/SPRI, Vertex, Genentech, BMS, SciClone, Boehringer Ingelheim, Anadys, and Gilead during the last 12 months. M. S. S. has served as an advisor for Merck, Vertex, Roche, BMS, Boehringer Ingelheim, Pharmasset, Gilead, and Abbott and has institutionally contracted research (paid to Johns Hopkins University) with Merck, Vertex, Roche, BMS, Boehringer Ingelheim, Pharmasset, Gilead, and Abbott. D. T. has served as an advisor for Merck and has received support for National Institutes of Health-funded clinical trials from Merck and Gilead. All other authors report no potential conflicts.

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

1. Poordad F, McCone J, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* **2011**; 364:1195–206.
2. Jacobson IM, McHutchison JG, Dusheiko G, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* **2011**; 364:2405–16.
3. Sulkowski M, Dieterich DT, Sherman KE, et al. Interim analysis of a phase 2a double-blind study of TVR in combination with pegIFN-a2a and RBV in HIV/HCV co-infected patients [abstract 146LB]. In: 18th Conference on Retroviruses and Opportunistic Infections. Boston, **2011**.
4. Sulkowski M, Pol S, Cooper C, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV coinfecting patients: interim on-treatment results [Abstract LB-37]. In: Programs and abstracts of the 49th Annual Meeting of the Infectious Diseases Society of America. Boston, MA.
5. Sulkowski MS, Mehta SH, Torbenson MS, et al. Rapid fibrosis progression among HIV/hepatitis C virus-co-infected adults. *AIDS* **2007**; 21:2209–16.
6. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* **2004**; 292:2839–48.

7. van Heeswijk R, Garg V, Boogaerts G, et al. The pharmacokinetic interaction between telaprevir and raltegravir in healthy volunteers [abstract A1-1738a]. In: Interscience Conference on Antimicrobial Agents and Chemotherapy. Chicago, **2011**.
8. Telaprevir package insert. Incivek[package insert]. Cambridge, MA: Vertex Pharmaceuticals incorporated, 2011.
9. van Heeswijk R, Vandevorde A, Boogaerts G, et al. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor TVR in healthy volunteers [abstract 119]. In: 18th Conference on Retroviruses and Opportunistic Infections. Boston, **2011**.
10. Boceprevir package insert.
11. Kasserra C, Hughes E, Treitel M, Gupta S, O'Mara E. Clinical pharmacology of BOC: metabolism, excretion, and drug-drug interactions [abstract 118]. 18th Conference on Retroviruses and Opportunistic Infections. Boston, **2011**.
12. Sherman KE, Rockstroh JK, Dieterich DT, et al. Telaprevir in combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfecting patients: a 24-week treatment interim analysis [abstract LB-8]. In: 62nd Annual Meeting of the American Association for the study of Liver Disease. San Francisco, CA, 2011.