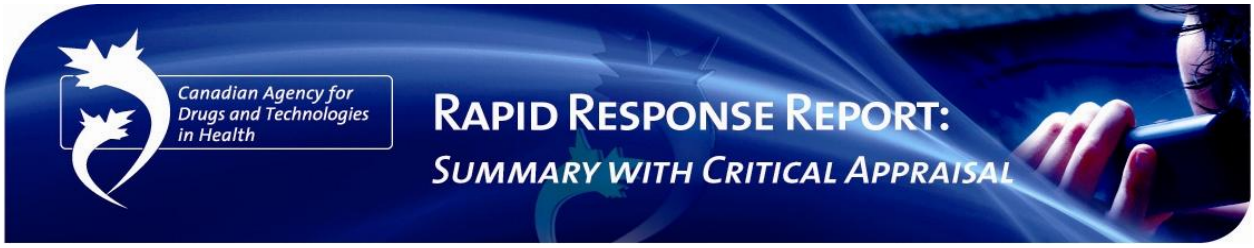


TITLE: Protease Inhibitor Use for Chronic Hepatitis C infection in Special Populations: A Review of the Clinical Evidence and Guidelines

DATE: 8 March 2012

CONTEXT AND POLICY ISSUES

Chronic hepatitis C (CHC) infection is a major co-morbidity seen in HIV patients.[1] CHC infection adds to the burden of disease for the patient, and its treatment adds to the pill burden and adverse effects already experienced by the patient, as well as additional cost. Additionally, there is the potential for drug interactions, with a number of the antiretrovirals demonstrating pharmacokinetic interactions with other agents. With the advent of the NS3/4A protease inhibitors (PI) boceprevir and telaprevir, there is a need to assess the efficacy and safety/tolerability of PI-peginterferon-ribavirin (PR) triple therapy for CHC infection in patients who have HIV. It should be noted that, according to the product monographs for boceprevir and telaprevir, the safety and efficacy of these agents has not been established in patients with HIV co-infection.[2,3]

The addition of protease inhibitors to the established PR regimen may provide another opportunity for patients with CHC infection who have not achieved sustained virological response (SVR) with prior PR therapy. The most challenging CHC patients to re-treat are those who have had a null response to prior therapy, meaning that they had minimal to no reduction in viral load.[4] It is therefore important to ascertain the efficacy of PI-PR triple therapy in this population.

The question of when to initiate therapy for CHC infection is a key issue associated with this condition. With PR therapy, SVR rates were typically higher in patients with minimal or no fibrosis, and decreased as patients progressed to cirrhosis.[5,6] The dilemma in CHC is that not all patients will progress to serious complications such as cirrhosis or hepatocellular carcinoma.[6,7] With the addition of protease inhibitors to PR therapy, it is important to determine whether response rates to triple therapy are impacted by baseline fibrosis status.

This report was reviewed by a clinical expert in hepatology.

RESEARCH QUESTIONS

1. What is the evidence for the clinical benefit and harm of using boceprevir or telaprevir in patients with chronic hepatitis C infection who are co-infected with HIV?

2. What are recommendations from evidence-based guidelines on treatment of HIV co-infected patients with chronic hepatitis C infection with boceprevir or telaprevir?

3. What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

4. What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients with CHC infection and Metavir scores of F0 or F1?

KEY MESSAGE

At present, there is insufficient evidence to determine the clinical benefit and harm of adding boceprevir or telaprevir to PR in patients with CHC co-infected with HIV. CHC patients who are null responders to previous PR therapy may benefit from telaprevir-PR, although the response rate is expected to be lower than in the general CHC population. There are no RCT data on this population for boceprevir-PR. Similar to the overall trial populations in the included studies, patients with CHC infection and metavir scores of F0 or F1 (telaprevir) or F0-F2 (boceprevir) achieved higher SVR rates with protease inhibitors added to PR over PR alone. Response rates with PI-PR were generally higher at earlier stages of fibrosis compared with later stages in treatment-naïve patients, but not in treatment-experienced patients.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including MEDLINE, PubMed, EMBASE, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents. The search was not limited by publication date. The search was run on January 4, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to the selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1, Q2: Patients with chronic hepatitis C infection coinfected with HIV Q3: Patients with chronic hepatitis C infection who are classified as null responders on prior PR therapy Q4: Patients with chronic hepatitis C infection with Metavir scores of F0 or F1
Intervention	PR plus Protease inhibitor (boceprevir or telaprevir)
Comparator	PR alone
Outcomes	Clinical benefit-SVR, morbidity, mortality Clinical harms- antiviral resistance, drug interactions, adverse effects
Study Designs	Health technology assessments, systematic reviews and meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines Emerging evidence (e.g. conference abstracts)

Exclusion Criteria

Health technology assessments, systematic reviews and meta-analyses published prior to 2010 were excluded, as were duplicate publications of the same study. Studies that were included in selected systematic reviews were also excluded.

Critical Appraisal of Individual Studies

The quality of the included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.[8] The adequacy of randomization, allocation concealment, blinding (of patients, clinicians or health care providers, data collectors and outcome assessors), loss to follow-up, early stopping of trial, and description of intention-to-treat (ITT) analysis were considered in the critical appraisal of the included randomized controlled trials (RCTs). The AGREE II (Appraisal of Guidelines for Research and Evaluation) instrument was used to assess the included guidelines.[9]

Critical appraisal of emerging evidence was not performed due to the limited study information available for this type of evidence.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 567 citations. Upon screening titles and abstracts, 556 citations were excluded and 11 potentially relevant articles were retrieved for full-text review. One additional report was identified in the grey literature. Of the 12 potentially relevant reports, five did not meet inclusion criteria. Seven studies and one evidence based guideline are included in this review, including three pieces of emerging evidence. The study selection process is outlined in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart (Appendix 1).

No systematic reviews were identified for inclusion in this report.

One phase 3 study that featured telaprevir triple therapy (REALIZE [N=662 randomized 2:2:1]) enrolled prior null responders.[4] There were no controlled trials of boceprevir in prior null responders.

Two phase 3 studies that featured telaprevir triple therapy (REALIZE [N=662 randomized 2:2:1] and ADVANCE [N=1088 randomized 1:1:1]) and reported subgroup data by Metavir score were identified.[4,10] Three double blind RCTs featuring boceprevir met the inclusion criteria for this review, however only two studies reported subgroup data by Metavir score.[11,12] SPRINT-2 randomized 1099 patients 1:1:1 to boceprevir-PR, boceprevir-PR response guided therapy (RGT) or placebo all on a background of peginterferon alpha 2b plus ribavirin (PR). RESPOND-2 randomized 404 patients 2:2:1 to boceprevir-PR, boceprevir-PR RGT or placebo-PR, respectively, all on a PR background.

One recently (2011) published guideline related to HIV/HCV co-infection that provided information specific to use of hepatitis C virus protease inhibitors in patients with HCV/HIV co-infection was identified.[13]

Emerging evidence

Three pieces of emerging evidence were identified. Two RCTs were identified pertaining to the use of protease inhibitors in patients with chronic hepatitis C virus infection co-infected with HIV, one published only as a conference abstract, and the other published as part of a review of clinical guidelines.[14,15]

There was one single arm study that was identified relating to treatment of prior null responders to PR; the PROVIDE study (N=48) is an ongoing rollover study for patients in the Phase 2 and 3 studies of boceprevir that were null responders in the placebo-PR arms.[16]

Summary of Study Characteristics

Details of the characteristics of the included RCTs are provided in Appendix 2.

<u>What is the evidence for the clinical benefit and harm of using boceprevir or telaprevir in patients with chronic hepatitis C infection who are co-infected with HIV?</u>

No health technology assessments, systematic reviews, or RCTs were identified regarding the use of boceprevir or telaprevir in patients with chronic hepatitis C infection co-infected with HIV.

Emerging evidence

A conference abstract by Sherman reported interim results from a phase 2 RCT (N=60) that compared telaprevir-PR with placebo-PR in HIV co-infected patients.[14] The study was divided into two parts, and patients in each part were randomized to either telaprevir-PR or placebo-PR. Patients in the telaprevir-PR group received telaprevir 750 mg every 8 hours plus peginterferon 180 µg/week and ribavirin 800 mg/day for 12 weeks followed by 36 weeks PR. The placebo group received placebo-PR for 48 weeks. In Part A (N=13) of the study, patients had no concurrent antiretroviral therapy (ART), and in Part B (N=47), patients were on stable predefined ART with either an efavirenz or an atazanavir/ritonavir based regimen.

An ongoing study is being conducted with boceprevir-PR in HCV/HIV co-infected patients. Patients are receiving a 4 week lead-in of PR, followed by addition of either boceprevir (800 mg three times daily) (N=64) or placebo (N=34) for an additional 44 weeks.[13,15] Patients were excluded if they were on zidovudine, didanosine, stavudine, efavirenz, etravirine, or nevirapine, but raltegravir and ritonavir-boosted protease inhibitors were permitted.

What are recommendations from evidence-based guidelines on treatment of HIV co-infected patients with chronic hepatitis C infection with boceprevir or telaprevir?

The single guideline identified[13] was published by an American group and included information specific to patients with chronic hepatitis C virus infection co-infected with HIV.

What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

REALIZE was a multicentre study sponsored by the manufacturer of telaprevir. The primary outcome was sustained virologic response, defined as maintenance of undetectable viral load 24 weeks after completion of therapy. Patients were typically about 50 years of age, on average, and the majority were male. Approximately half of all patients had previously experienced a relapse on PR therapy, approximately one-quarter were null responders, and about 20% were partial responders. Approximately one-quarter of patients in REALIZE had cirrhosis at baseline.

Patients in the two telaprevir groups received telaprevir for 12 weeks. However, one of the two groups began the first four weeks of the study on placebo-PR before switching to telaprevir-PR for the next 12 weeks ('delayed start'), while the other group began treatment with telaprevir-PR.

Emerging evidence

PROVIDE was a rollover study that included patients from the Phase 2 and 3 studies of boceprevir that were treated with placebo-PR and who had failed to achieve SVR. Of these, 48 patients met the criteria for a null response (<2 log decrease in HCV RNA by week 12), and these patients were re-treated with a 4 week lead-in of PEG-IFN alpha-2b (1.5 mcg/kg/week) and ribavirin (600-1400 mg/day), followed by the addition of boceprevir (800mg three times daily) for 44 weeks.[16]

What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients with CHC infection and Metavir scores of F0 or F1?

ADVANCE enrolled patients who were treatment naive, while patients in REALIZE and RESPOND-2 were treatment experienced. All studies were multicentre and were sponsored by the manufacturer of the PI studied. The primary outcome of all studies was a sustained virologic response, defined as maintaining undetectable viral load 24 weeks after completion of therapy.

Across the studies of telaprevir, patients were typically about 50 years of age, on average, and the majority were male. In REALIZE, which featured a treatment-experienced population, approximately half of all patients had previously experienced a relapse, approximately one-quarter were null responders, and about 20% were partial responders. Approximately one-quarter of patients in REALIZE had cirrhosis at baseline, while in ADVANCE only about 6% of patients had cirrhosis.

In REALIZE, patients in the two telaprevir groups received telaprevir for 12 weeks. However, one of the two groups began the first four weeks of the study on placebo-PR before switching to telaprevir-PR for the next 12 weeks ('delayed start'), while the other group began treatment with telaprevir-PR.

RESPOND-2 and SPRINT-2 were the included studies of boceprevir. RESPOND-2 randomized patients who were non-responders (decrease in HCV RNA but not to undetectable levels) or relapsers (undetectable HCV RNA at end of treatment but detectable during follow up). Prior null responders (< 2 log10 decline in HCV RNA at Week 12 of prior therapy) were excluded from RESPOND-2. Patients in SPRINT-2 were treatment-naive, and had to have a minimum HCV RNA level of 10000 IU/ml. Patients in SPRINT-2 were slightly younger than patients in RESPOND-2 (mean age 50 versus 53 years). The majority of patients were male in each of SPRINT-2 (60%) and RESPOND-2 (67%) and most patients were Caucasian in SPRINT-2 (82%) and in RESPOND-2 (86%).

Summary of Critical Appraisal

A summary of the strengths and limitations of individual included RCTs is provided in Appendix 3. A summary of the guideline strengths and limitations is provided in Appendix 4.

What is the evidence for the clinical benefit and harm of using boceprevir or telaprevir in patients with chronic hepatitis C infection who are co-infected with HIV?

Only emerging evidence was identified. A thorough critical appraisal was not possible, as both reports provided very limited information about the included studies.

What are recommendations from evidence-based guidelines on treatment of HIV co-infected patients with chronic hepatitis C infection with boceprevir or telaprevir?

Using the AGREE II instrument, a few limitations of the guidelines were identified, however many pertained to methods for implementation rather than the recommendations within.

What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

The REALIZE trial was randomized and double-blinded. Randomization appeared to be centralized, and measures were taken to maintain adequate allocation concealment. Loss to follow-up rates were small and ITT analysis was employed.

Emerging evidence

PROVIDE was a single arm study, therefore it was neither blinded nor randomized. Only minimal information was available regarding study design, and there was too little information available to perform further critical appraisal.

What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients with CHC infection and Metavir scores of F0 or F1?

The phase 3 trials of boceprevir and telaprevir were all randomized and double-blinded. Randomization appeared to be centralized in all studies, and measures were taken to maintain

adequate allocation concealment. Loss to follow-up rates were low and ITT analysis was employed in all studies.

Summary of Findings

The main findings of the included RCTs are described in Appendix 5.

What is the evidence for the clinical benefit and harm of using boceprevir or telaprevir in patients with chronic hepatitis C infection who are co-infected with HIV?

Emerging evidence

In the telaprevir study, sixty patients received at least one dose of study medication. Because it was an interim analysis, no SVR data were reported. Overall, a larger proportion of telaprevir-PR treated patients achieved undetectable viral load at week 24 compared with placebo-PR (74% versus 55%). Patients treated with efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) were more likely to have undetectable HCV RNA at week 24 with telaprevir-PR versus placebo-PR (75% versus 50%). However, patients treated with ritonavir-boosted atazanavir/ tenofovir/ emtricitabine (ATV/r /TDF/FTC) had numerically lower responses with telaprevir-PR versus placebo-PR (67% versus 75%). The greatest difference in proportion of responders between telaprevir-PR and placebo-PR was in the small cohort (N=13) that received no antiretrovirals (86% versus 33%). However none of these subgroup comparisons were adequately powered to detect differences between groups.

In the boceprevir study, SVR data were not available for the interim analysis of this study in HCV/HIV co-infected patients. At week 24, HCV was undetectable in 70.5% of boceprevir-PR and 34.4% of placebo-PR patients. Treatment was discontinued due to an adverse event in 14% of boceprevir-PR and 9% of placebo-PR patients.

What are recommendations from evidence-based guidelines on treatment of HIV co-infected patients with chronic hepatitis C infection with boceprevir or telaprevir?

In provisional guidance published in 2011, the authors made the following observations:[13]

- Liver fibrosis progression is more rapid and PR less effective in patients co-infected with HCV-HIV;
- Safety and efficacy of hepatitis C virus PIs are largely unproven in HCV-HIV
- Knowledge about drug-drug interactions is limited
- Additional anti-HCV medications are being developed
- Price of PIs may add to the cost of PR

The authors of these guidelines stated that some co-infected HCV/HIV patients should be treated with PI-PR. They also noted that the benefits of PI-PR are most likely to outweigh the risks in patients with advanced liver fibrosis (i.e., Metavir fibrosis score >1). They acknowledged that efficacy of HCV treatment is better if initiated earlier in the course of the disease, although some believe that it is safer to monitor patients with little/no fibrosis for evidence of progression while waiting for additional efficacy and safety information on the use of boceprevir or telaprevir in patients co-infected with HIV. However, during the production of this review, these guidelines were temporarily withdrawn pending revision to accommodate new information.

What is the clinical evidence on sustained virological response rates with the protease inhibitors in patients who are classified as null responders on prior PR therapy?

In the REALIZE Study, SVR rates were lower in patients who were prior null responders compared to patients who were prior partial responders, or compared to the results in the study population as a whole. For example, in the group that received 12 weeks telaprevir and 48 weeks PR, SVR rates were 64% overall versus 29% in the subgroup identified as null responders. SVR rates among prior null responders were, however, still statistically higher with telaprevir-PR than with placebo-PR (29% versus 5%). Similar results were seen in the telaprevir group that had a 'delayed start' of telaprevir. Subgroup data for prior null responders were not reported for any of the other outcomes.

Emerging evidence

In PROVIDE, of the 42 patients who completed treatment and follow-up, 38% achieved an SVR. Relapse occurred in 16% of patients.

What is the clinical evidence on sustained virological response rates with the protease inhibitors for patients with CHC infection and Metavir scores of F0 or F1?

Subgroup analyses by baseline fibrosis score were only reported for SVR rates, the primary outcome of all studies.

Treatment-naïve patients

For telaprevir-based triple therapy, subgroup analysis in ADVANCE (treatment-naïve CHC) was presented for patients according to the descriptor 'no or minimal fibrosis', which corresponds to Metavir scores of 0 or 1. SVR response rates in this subgroup as well as patients with portal fibrosis (Metavir 2) were higher in both telaprevir-PR and placebo-PR groups than in the two subgroups demonstrating more advanced fibrosis at baseline. In patients with Metavir 0/1, SVR responses were 81% with telaprevir-PR versus 46% with placebo-PR, and this difference was statistically significant. In contrast, SVR rates were 62% versus 33%, respectively, in each of the subgroups with Metavir scores of 3 and 4.

For boceprevir-based triple therapy in SPRINT-2, the publication grouped scores of 0, 1, and 2. Patients on triple therapy with these lower fibrosis scores had higher SVR rates than patients with Metavir scores of 3 or 4, while responses to placebo-PR appeared unaffected by baseline Metavir scores. SVR rates were 67% in each of the boceprevir-PR groups (regular regimen and response guided therapy) and 38% with placebo-PR among patients with baseline Metavir scores 0-2. These differences between groups were statistically significant.

Treatment experienced

The publication for the REALIZE study did not report a subgroup analysis by baseline Metavir score.

As in the SPRINT-2 trial, Metavir scores of 0, 1, and 2 were grouped in the RESPOND-2 trial. Patients treated with boceprevir-PR had similar SVR rates across Metavir subgroups (0-2 vs. 3-4) (SVR of 68% versus 23% in placebo-PR arm at Metavir 0-2, $P < 0.05$; 68% versus 13% at Metavir 3 or 4, $P > 0.05$ (NS)).

Limitations

There is currently only one study for each of boceprevir and telaprevir in HCV-HIV co-infected patients. These studies potentially lack the statistical power needed to detect differences between groups, and they have not been published in a peer reviewed publication.

The evidence based guidelines relating to treatment of CHC infection in HIV co-infected patients are limited by the lack of evidence. As provisional guidance in a rapidly changing field, they are also subject to revision. During the production of this review, the guidelines were temporarily withdrawn pending revision to accommodate new information.

The trials of boceprevir did not enroll a previous null responder population. Only emerging (i.e., non-peer reviewed) evidence from a single arm study were available for this agent. Therefore all of the comparative evidence for the efficacy of protease inhibitor-PR therapy versus PR alone in prior null responders is for telaprevir, and it is not clear whether this would be generalizable to boceprevir.

Subgroup analysis of efficacy and harms results by baseline Metavir scores were only reported for treatment naïve patients in the studies of telaprevir. Although subgroup data by fibrosis score were available for both treatment-naïve and treatment experienced patients in the studies of boceprevir, a wider range of fibrosis scores (Metavir 0-2) were combined.

Chronic hepatitis C is a slowly progressive condition that does not inevitably lead to serious complications such as cirrhosis and/or hepatocellular carcinoma.[6,7] A limitation of the identified studies is that they were not designed to detect differences in hard clinical outcomes such as morbidity and mortality, relying instead on SVR rates as the key measure of efficacy.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is limited evidence assessing the effects of boceprevir or teleprevir in HCV/HIV co-infection, thus no conclusions regarding efficacy and safety can be drawn in this population. Evidence based guidelines tend to reflect this lack of evidence. It is noteworthy that higher doses of boceprevir or telaprevir may be required when co-administered with certain antiretroviral agents (e.g., efavirenz) due to pharmacokinetic interactions,[2,3] potentially increasing the cost of PI-PR therapy.

Although SVR rates for prior null responders to PR therapy are significantly lower than those seen in the general CHC population, there is a statistically significant treatment effect of telaprevir-PR over placebo-PR in this population. There are no comparative data for boceprevir in the null responder population.

For both telaprevir- and boceprevir-based triple therapy, there is evidence that the addition of protease inhibitor to PR confers a statistically significant increase in SVR rates over PR alone in patients with earlier stages of fibrosis (Metavir 0 or 1 with telaprevir, and Metavir 0-2 with boceprevir). Response rates among patients with earlier stages of fibrosis (Metavir scores 0-1 or 0-2) tended to be higher in treatment-naïve patients, but not in treatment-experienced patients.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Buxton JA, Yu A, Kim PH, Spinelli JJ, Kuo M, Alvarez M, et al. HCV co-infection in HIV positive population in British Columbia, Canada. BMC Public Health [Internet]. 2010 [cited 2012 Feb 15];10:225. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2868820

2. e-CPS [Internet]. Ottawa: Canadian Pharmacists Association. Victrelis™; 2011 Jul 27 [cited 2012 Feb 29]. Available from: https://www.e-therapeutics.ca Subscription required.

3. Highlights of prescribing information: Incivek™ (telaprevir) film coated tablets [Internet]. Cambridge (MA): Vertex Pharmaceuticals Incorporated; 2011 May. [cited 2012 Feb 29]. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf

4. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment of HCV infection. N Engl J Med. 2011 Jun 23;364(25):2417-28.

5. Muir AJ, Bornstein JD, Killenberg PG, Atlantic Coast Hepatitis Treatment Group. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. N Engl J Med. 2004 May 27;350(22):2265-71.

6. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology. 2009 Apr;49(4):1335-74.

7. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. Hepatology. 2008 Aug;48(2):418-31.

8. Shea BJ, Bouter LM, Peterson J, Boers M, Andersson N, Ortiz Z, et al. External validation of a measurement tool to assess systematic reviews (AMSTAR). PLoS ONE [Internet]. 2007 [cited 2012 Feb 8];2(12):e1350. Available from: http://dx.plos.org/10.1371/journal.pone.0001350

9. The AGREE Next Steps Consortium. Appraisal of guidelines for research & evaluation II: AGREE II instrument [Internet]. [Hamilton (ON)]: The AGREE Research Trust; 2009 May. [cited 2012 Feb 15]. Available from: http://www.agreetrust.org/index.aspx?o=1397

10. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. N Engl J Med. 2011 Jun 23;364(25):2405-16.

11. Bacon BR, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1207-17.

12. Poordad F, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, et al. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

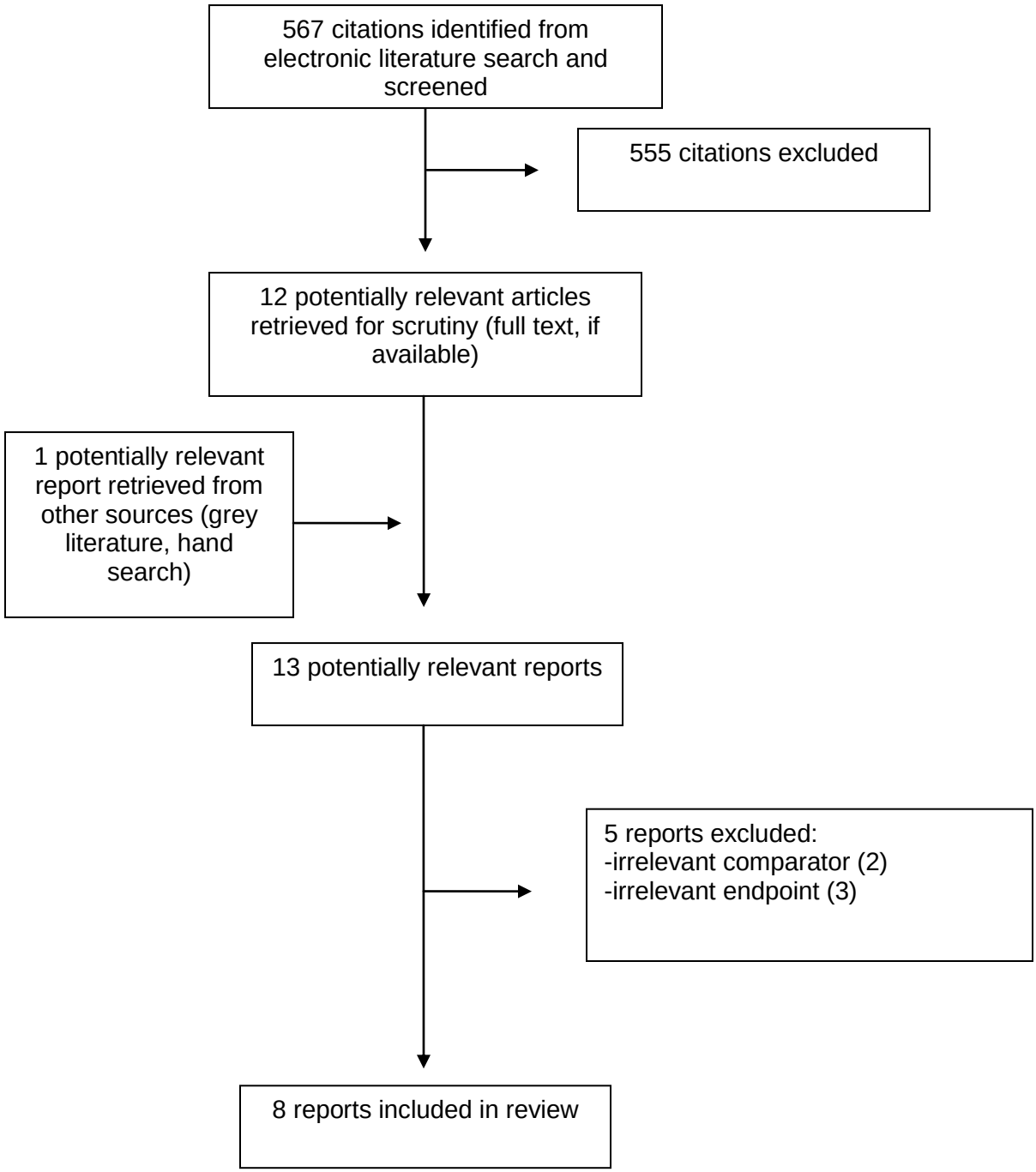
13. Thomas DL, Bartlett JG, Peters MG, Sherman KE, Sulkowski MS, Pham PA. Provisional guidance on the use of hepatitis C virus protease inhibitors for treatment of hepatitis C in HIV-infected persons. Clin Infect Dis. 2011 Dec 14. Epub ahead of print.

14. Sherman KE, Rockstroh JK, Dieterich DT, Soriano V, Girard PM, McCallister S, et al. Telaprevir combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfected patients: 24-week treatment interim analysis [abstract]. Hepatology. 2011 Oct;54 Suppl:1431A. (Presented at 62nd Annual Meeting of the American Association for the Study of Liver Diseases: The Liver Meeting 2011, San Francisco; 2011 Nov 4-8).

15. Sulkowski M, Pol S, Cooper C, Fainboim H, Slim J, Rivero A, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: interim on-treatment results [Internet]. Abstract presented at: 49th Annual Meeting of the Infectious Diseases Society of America (IDSA); 2011 Oct 22; Boston. [cited 2012 Feb 22]. Available from: http://idsa.confex.com/idsa/2011/webprogram/Paper33020.html

16. News release: Boceprevir based therapy cleared the hepatitis C virus in 38 per cent of patients who had failed to respond to previous treatment [Internet]. Montreal: Merck; 2011 Nov 7. [cited 2012 Feb 22]. Available from: http://www.merck.ca/newsroom/ca_en/product-news/AASLD_News_Release_Nov_7_2011_en.pdf

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Randomized Controlled Trials

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
Zeuzem 2011[4] REALIZE	DBRCT Multicentre	CHC genotype 1 with HCV RNA level ≥1000 IU/mL, treatment failure with at least one prior course of PR therapy n=662	TP + PR for 12 weeks then PL + PR for 4 weeks then PR for 32 weeks PL + PR for 4 weeks then TP + PR for 12 weeks then PR for 32 weeks	PL + PR for 16 weeks then PR for 32 weeks
Jacobson 2011[10] ADVANCE	DBRCT Multicentre	CHC genotype 1 with HCV RNA level ≥1000 IU/mL, treatment naïve without contraindications to receiving peginterferon or ribavirin n=1095	TP for 8 weeks then PL for 4 weeks + PR for 24 weeks (T8/PR24) TP for 12 weeks + PR for 24 weeks (T12/PR24)	PL for 12 weeks + PR for 48 weeks (PL/PR48)
Poordad 2011[12] SPRINT-2	DBRCT Multicentre	Chronic infection with HCV genotype 1 Plasma HCV RNA level of 10,000 IU per milliliter or greater No previous treatment for HCV infection N=1099	Boceprevir 800 mg TID x 44 weeks (N=367) Boceprevir 800 mg TID x 24 weeks (RGT) (N=368) Peginterferon alfa-2B SC 1.5 µg/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided	Placebo X 44 weeks (N=364) Peginterferon alfa-2B SC 1.5 µg/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)
			doses	
Bacon 2011[11] RESPOND-2	DBRCT Multicentre	Chronic infection with HCV genotype 1, and either Non-response or Relapse on prior PR therapy (minimum duration 12 weeks): -Non-response (decrease in the HCV RNA level of at least 2 log10 IU/mL by week 12 but detectable HCV RNA during the therapy period) -Relapse (i.e., undetectable HCV RNA level at the end of treatment, without subsequent attainment of sustained virologic response during follow up period).N=404	Boceprevir 800 mg TID x 44 weeks (N=162) Boceprevir 800 mg TID x 32 weeks (RGT) (N=162) Peginterferon alfa-2B SC 1.5 µg/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses	Placebo X 44 weeks (N=80) Peginterferon alfa-2B SC 1.5 µg/kg once weekly; and weight-based oral ribavirin 600 to 1400 mg per day in divided doses
HCV=hepatitis C virus; **IFN**=interferon; **PEG**=pegylated; **RIBA**=ribavirin; **RCT**=randomized controlled trial; **SVR**=sustained virologic response				

Appendix 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Zeuzem 2011[4] REALIZE	• Centralized randomization • Double blind design	• Follow up too short to assess clinical outcomes such as mortality/morbidity
Jacobson 2011[10] ADVANCE	• Centralized randomization • Double blind design	• Follow up too short to assess clinical outcomes such as mortality/morbidity
Poordad 2011[12] SPRINT-2	• Centralized randomization • Double blind design	• Follow up too short to assess clinical outcomes such as mortality/morbidity
Bacon 2011[11] RESPOND-2	• Centralized randomization • Double blind design	• Follow up too short to assess clinical outcomes such as mortality/morbidity

Appendix 4: Summary of Guideline Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Thomas 2011[13]	Objective stated Health questions defined Population defined Target users defined Methods for formulating recommendations described Benefits and risks of therapy taken into account Recommendations and evidence linked Guideline externally reviewed Specific recommendations provided Different management options provided Key recommendations easily identified Conflicts of interest reported	Methods for literature search not described Not clear whether patient groups were involved No specific procedure for updating provided No tools for application provided Organizational barriers in applying not discussed Resource implications not described Monitoring and/or audit criteria not described

Appendix 5: Summary of Main Study Findings and Author Conclusions

First author, publication year	Main findings	Author conclusions
Randomized controlled trials		
Zeuzem 2011[4] REALIZE	SVR: T12PR48: 64% T12(DS)PR48: 66% PR48: 17% Relapses: T12PR48: 27% T12(DS)PR48: 25% PR48: 60% SAE: Pooled Telaprevir: 12% PR48: 5%	"Telaprevir combined with peginterferon plus ribavirin significantly improved rates of SVR in patients with previously treated HCV infection, regardless of whether there was a lead-in phase." (p. 2417)
Jacobson 2011[10] ADVANCE	SVR: T12PR: 75% T8PR: 69% PR44: 44% Relapses: T12PR: 9% T8PR: 9% PR44: 28% SAE: T12PR: 9% T8PR: 9% PR44: 7%	"Telaprevir with peginterferon-ribavirin as compared with peginterferon-ribavirin alone, significantly improved rates of sustained virologic response in patients with HCV genotype 1 infection who had not received previous treatment, with only 24 weeks of therapy administered in the majority of patients" (p. 2405)
Poordad 2011[12] SPRINT-2	SVR: BOC-PR48: 66% BOC-PR-RGT: 63% PR48 (control): 38% Relapses: BOC-PR48: 9% BOC-PR-RGT: 9% PR48 (control): 22% SAE: BOC-PR48: 12% BOC-PR-RGT: 11% PR48 (control): 9%	"The addition of boceprevir to standard therapy with peginterferon-ribavirin, as compared with standard therapy alone, significantly increased the rates of SVR in previously untreated adults with chronic HCV genotype 1 infection. The rates were similar with 24 weeks and 44 weeks of boceprevir." (p. 1195)
Bacon 2011[11] RESPOND-2	SVR: BOC-PR48: 66% BOC-PR-RGT: 59%	"The addition of boceprevir to peginterferon-ribavirin resulted in significantly higher rates of sustained

First author, publication year	Main findings	Author conclusions
	PR48 (control): 21% Relapses: BOC-PR48: 12% BOC-PR-RGT: 15% PR48 (control): 32% SAE: BOC-PR48: 14% BOC-PR-RGT: 10% PR48 (control): 5%	virologic response in previously treated patients with chronic HCV genotype 1 infection, as compared with peginterferon-ribavirin alone." (p. 1207)

BOC=boceprevir; **DS**=delayed start; **HCV**=hepatitis C virus; **PR**=peginterferon/ribavirin; **RD**=risk difference; **RGT**=response guided therapy; **RR**=relative risk; **SAE**=serious adverse events; **SVR**=sustained virologic response